Intravenous acetaminophen (IV A) is the leading prescribed injectable analgesic in the European Union for the short-term treatment of pain and fever in adults and children, with approximately 440 million 1000-mg units distributed since its first European approval under the brand name of Ofirmev. Approximately 65 million patients had been treated with this drug by April 2010. It is now available in more than 60 countries around the world, including many in Europe, Asia-Pacific, the Middle East, and Africa. Acetaminophen (or paracetamol, as it is known outside the United States) has been well known as an effective analgesic and antipyretic for more than a century. The safety profile of oral acetaminophen is well understood, and acetaminophen is the most widely used analgesic and antipyretic currently in use in the United States. Acetaminophen is a first-line choice for pain in the World Health Organization1 step-ladder approach to pain treatment. This review will provide the reader with a critical prospective on the use of intravenous acetaminophen in the acute pain setting.

Indications

For Postoperative Analgesia

IV A is capable of statistically significant and clinically relevant analgesia by the end of the 15-minute infusion.2 IV A achieves a
In some patients with mild to moderate pain, IVA can eliminate the need for opioid treatment altogether.

To Reduce Total Perioperative Opioid Dose

In placebo-controlled trials in PO settings, IVA has produced statistically significant reductions in rescue-opioid consumption (range from 33% to 78%) while also producing statistically significant improvements in pain response (pain intensity and relief). In some patients with mild to moderate pain, IVA can eliminate the need for opioid treatment altogether, as evidenced by randomized, controlled trial (RCT) data and reports in the medical literature. In these RCTs, IVA was used after minor outpatient procedures including tonsillectomy and endoscopic sinus surgery. It should be noted that IVA alone may not be sufficient for pain control in some patients and opioids should still be readily available for analgesia.

IVA does not have any approved FDA indication for patients with chronic pain.

Dosage and Administration

For adults and adolescents weighing 50 kg or more, the recommended dosage of IVA is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of 1 g, a minimum

Tmax 30 minutes faster than that observed with equivalent oral (PO) doses, resulting in rapid central nervous system (CNS) levels and, therefore, rapid therapeutic effectiveness.

The continuing education activity in Topics in Pain Management is intended for clinical and academic physicians from the specialties of anesthesiology, neurology, psychiatry, physical and rehabilitative medicine, and neurosurgery as well as residents in those fields and other practitioners interested in pain management.

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dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day. For adults and adolescents weighing less than 50 kg, the recommended dosage of IVA is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of IVA of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

**Contraindications**

IVA is contraindicated in patients with severe hepatic impairment, severe active liver disease, or with a known allergy to acetaminophen. Acetaminophen should be used with caution in patients with the following conditions: alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment.

**IVA does not undergo first-pass hepatic metabolism because, unlike the oral route, it bypasses the liver with IV administration.**

**Adverse Effects**

The overall incidence of adverse events (AEs) was similar in the IVA and placebo groups. Minor observed differences in AE rates seemed to be largely the result of the PO setting or due to preexisting underlying medical problems. The incidence of treatment-related, serious, and severe AEs and AEs leading to discontinuation were similar between the IVA and placebo groups.

AEs were not different from placebo in several studies. The most common adverse reactions in patients treated with IVA were nausea, vomiting, headache, and insomnia in adult patients, and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients. An important consideration is that the antipyretic effects of IVA may mask fever in patients treated for postsurgical pain—that is, it may mask the signs of PO infection and sepsis.

**Metabolism**

IVA does not undergo first-pass hepatic metabolism because, unlike the oral route, it bypasses the liver with IV administration.

In both children and adults, acetaminophen is metabolized by the liver via 3 major pathways: glucuronidation (approximately 60%), sulfation (approximately 25%), and oxidation (approximately 10%). In neonates and infants, sulfation is the major metabolic pathway due to delayed maturity in the glucuronidation pathway. Minor metabolic pathways for acetaminophen include hydroxylation, methoxylation, and hydrolysis.

It is important to note that within the therapeutic dosage range, small amounts of N-acetyl-p-benzoquinone imine (NAPQI), a toxic intermediate, are produced by the cytochrome P450 CYP2E1 enzyme. Normally, this NAPQI is then conjugated with intracellular glutathione to produce a nontoxic thiol metabolite, which is excreted in the urine. When a supratherapeutic dose is taken or when there is significant depletion of glutathione stores, NAPQI is produced in larger amounts, which can result in hepatotoxicity.

**Clearance**

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted unchanged in the urine as unconjugated acetaminophen. More than 90% of a single dose is excreted within 24 hours.

**IVA seems to produce analgesia by elevation of the pain threshold through effects on a number of pathways and receptors.**

**Mechanism of Action**

IVA is a centrally acting analgesic and antipyretic agent. Although the exact site and mechanism of action is not clearly defined, IVA seems to produce analgesia by elevation of the pain threshold through effects on a number of pathways and receptors, including inhibition of the nitric oxide pathway, inhibition of central prostaglandin production, and modulation of serotonin (5HT), cannabinoid, N-methyl-D-aspartate, endogenous opioids, and substance P. Acetaminophen penetrates rapidly through an intact blood-brain barrier and enters the CNS via an active process. Levels are detectable in the CNS within 5 minutes of administration.

**Complications**

Seeff et al first described the interaction between acetaminophen and alcohol in 1986. They treated 6 patients with chronic alcoholism and identified an additional 19 reported in the literature who developed severe hepatotoxicity from acetaminophen taken in apparently moderate doses. The clinical disease in these 25 patients had a characteristic pattern: mild to moderate jaundice, mild to severe coagulopathy, and strikingly abnormal aminotransferase levels—values inconsistent with either acute alcoholic hepatitis or viral hepatitis.

The possible causes for the injury from ostensibly nontoxic drug levels seem to be either the induction by chronic alcohol intake of the cytochrome P450 system responsible for converting acetaminophen to a toxic metabolite, or the effect of alcoholism and the associated malnutrition in reducing the glutathione concentration, responsible normally for preventing hepatotoxicity by conjugation with the toxic metabolite.

The authors concluded: “Despite the low frequency of ethanol-potentiated acetaminophen hepatotoxicity, alcoholics should be cautioned about the use of acetaminophen while they persist in heavy consumption of alcohol.” In modern practice, a current history of alcoholism is a contraindication to the use of acetaminophen.

**Incidence of Hepatotoxicity of IVA in European Postmarketing Surveillance**

IVA is an incredibly safe drug. Extensive postmarketing surveillance revealed that the number of “hepatic events” after more
than 65 million patient exposures was approximately 3 cases per million exposures. Mortality was 0.3 per million exposures, and drug-induced liver injury was approximately 0.6 per million exposures.

**Cardiovascular Safety in Contrast to Nonsteroidal Anti-inflammatory Drugs**

In 2007, the American Heart Association provided a scientific statement on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as an update to physicians in the wake of the concerns regarding cardiovascular events with cyclo-oxygenase (COX)-2 selective agents, and noted that acetaminophen should be considered among first-line pharmacologic therapies for management of musculoskeletal symptoms in patients with known cardiovascular disease or those at risk for ischemic heart disease. There is no evidence that acetaminophen causes significant cardiotoxicity or cardiovascular problems when used in therapeutic doses. For example, Hillis, in his review of the impact of various classes of analgesics on the cardiovascular system, notes that:

“[Acetaminophen] provides no signal for risk of cardiovascular adverse events, and it should be considered as “first-line” therapy in patients with cardiovascular disease. This is in contrast to NSAIDs and the cyclo-oxygenase (COX)-2 selective agents.”

**Oral acetaminophen, IV propacetamol, and IVA all have produced transient hypotension in critically ill patients with fever.**

Transient blood pressure effects have been observed with oral and IV acetaminophen. Oral acetaminophen, IV propacetamol, and IVA have all been demonstrated to produce transient hypotension in critically ill patients with fever, presumptively due to removing the stimulus for the sympathetic drive associated with the fever. The reductions in blood pressure were generally mild to moderate, measurable within 15 to 30 minutes after the start of an infusion, and with maximal hypotension occurring between 1 and 2 hours after dosing. On the basis of this limited number of case series, it does seem that critically ill patients being treated for fever may sometimes be dependent on elevated sympathetic tone to support adequate blood pressure.

**Pregnancy Category C**

There are no studies of IVA in pregnant women; however, epidemiologic data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IVA, and it is not known whether IVA can cause fetal harm when administered to a pregnant woman. IVA should be given to a pregnant woman only if clearly needed. The results from a large population-based prospective cohort, including data from 26,424 women with live-born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared with a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects, compared with 4500 children in the control group.

**Nursing Mothers**

Although studies with IVA have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration. On the basis of data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1% to 2% of the maternal dose.

**Pediatric Use**

The safety and effectiveness of IVA for the treatment of acute pain and fever in pediatric patients age 2 years and older is supported by evidence from adequate and well-controlled studies of IVA in adults.

In a consensus statement of the assessment and management of acute pain in infants, children, and adolescents, the American Academy of Pediatrics Committee on Psychological Aspects of Child and Family Health (AAP Committee) and the American Pain Society Task Force on Pain in Infants, Children, and Adolescents (APS Task Force) have recommended that pediatricians should “anticipate painful experiences” and “use a multimodal approach to pain management.” They noted that the use of nonopioid analgesics, such as acetaminophen and NSAIDs, in combination with opioids can reduce the amount of opioids required to achieve adequate analgesia. In the view of the AAP Committee/APS Task Force, the goal of acute pain treatment is “to control the pain as rapidly as possible;” and when the child needs immediate pain relief, IV administration is indicated.

**Geriatric Use**

Of the total number of subjects in clinical studies of IVA, 15% (153 subjects) were age 65 years and older, whereas 5% (51 subjects) were age 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

**Patients With Renal Impairment**

In cases of severe renal impairment (creatinine clearance [CrCl] ≤ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be necessary to prevent accumulation.

**The addition of an NSAID to paracetamol may confer additional analgesic efficacy compared with paracetamol alone.**
Comparative Efficacy

Hyllestøl et al12 conducted a quantitative review of PO pain management, which demonstrated that the number of patients needed to treat for 1 patient to achieve at least 50% pain relief (NNT) is 2.7 for ibuprofen (400 mg) and 4.6 for paracetamol (1000 mg), both compared with placebo. However, direct comparisons between paracetamol and NSAIDs have not been extensively reviewed. They sought to compare the analgesic and adverse effects of paracetamol with those of other NSAIDs in PO pain, to compare the effects of combined paracetamol and NSAIDs with those of either drug alone, and to discuss whether the adverse effects of NSAIDs in short-term use are justified by their analgesic effects, compared with paracetamol.

NSAIDs were clearly more effective in pain from dental surgery, whereas the efficacy of NSAIDs and paracetamol seemed without substantial differences in major and orthopedic surgery, although firm conclusions could not be made because the number of studies was limited. The addition of an NSAID to paracetamol may confer additional analgesic efficacy compared with paracetamol alone, and the limited data available also suggest that paracetamol may enhance analgesia when added to an NSAID, compared with NSAIDs alone.

Remy et al13 conducted a systematic review of 7 RCTs, which demonstrated that PO acetylsalicylic acid combined with patient-controlled analgesia delivered as morphine provides a statistically significant morphine-sparing effect but does not decrease the incidence of morphine-related adverse effects.

Most of the studies in this meta-analysis included patients scheduled for orthopedic surgery. In these patients, a modest (though statistically significant) reduction in morphine dose resulted in a nonsignificant difference in the incidence of opioid adverse effects. It is this small effect that is touted as “morphine-sparing.” The morphine-sparing effect of acetaminophen seems to be weaker than the one documented with NSAIDs. Acetaminophen failed to decrease morphine-related adverse effects. Most of the studies included in the Remy et al13 meta-analysis demonstrated a morphine-sparing effect but not a decrease in morphine adverse effects. In the largest trial including 550 patients, morphine adverse effects in patients receiving acetaminophen were similar to those in patients not receiving it, despite a decrease in morphine requirements in the acetaminophen group.

Acetaminophen could have a ceiling effect at IV doses of 5 mg/kg, which is lower than previously suggested.

However, the subcutaneous morphine doses administered were low. Indeed, the median subcutaneous dose of morphine was 10 mg in the control group. Also, adverse effects such as PO nausea and vomiting (PONV) are only partly attributable to opioids.

The analgesic effect of acetaminophen depends on the rate and amount of active drug reaching the CNS, and several authors have recently recommended the use of a loading dose and/or a larger dose of acetaminophen to achieve therapeutic concentrations more rapidly and more completely. However, it has recently been demonstrated that acetaminophen could have a ceiling effect at IV doses of 5 mg/kg, which is lower than previously suggested. Therefore, increasing the single dose of acetaminophen for the treatment of acute PO pain was not associated with a decrease in the NNT.

IV Versus Oral

Peacock et al14 describe a study comparing the pharmacokinetics of IVA with a rapid-release oral liquid formulation of acetaminophen. This was an open-label, randomized, 4-period, crossover study, which compared the pharmacokinetics, pharmacodynamics, and safety of oral and IV acetaminophen (1000 mg every 4 hours or every 6 hours for a total of 8 doses in each 48-hour treatment period) in 32 healthy adult men (aged 18–48 years) over 48 hours. The mean Cmax and Tmax for IVA in this study occurred at the end of the 15-minute infusion.

This study demonstrates that IVA produces approximately a 70% higher mean Cmax and a mean Tmax that is approximately 30 minutes earlier than this rapid-release oral formulation. Of note, the higher Cmax of IVA did not result in clinically meaningful differences in the safety profile or the production of glutathione conjugates, compared with PO acetaminophen.

Pettersson et al15 compared IVA with an equivalent dose of oral acetaminophen (Panadol tablets) and compared opioid rescue requirements, the incidence of PONV, and pain scores between groups in 77 patients admitted to the intensive care unit after coronary artery bypass grafting. The IVA group demonstrated a 21% reduction in opioid consumption compared with the oral acetaminophen group (17.4 mg vs 22.1 mg, P = 0.016), with no difference in the incidence of PNOV and visual analog scale pain scores between groups.

Although rectal acetaminophen delivery may be considered, rectal bioavailability can be poor, and absorption is delayed.

IV Versus Rectal Administration of Acetaminophen

The rectal route of administration for acetaminophen is sometimes considered when oral administration is contraindicated or impractical, particularly in the pediatric population. Rectal acetaminophen has differing pharmacokinetic properties compared with oral acetaminophen,16 having poorer bioavailability of approximately 76%, and wide variability in pharmacokinetic parameters. Although the rectal route for acetaminophen delivery may be considered an alternative to IVA, rectal bioavailability can be poor, and absorption is delayed. For example, The
Harriet Lane Handbook\(^6\) notes that a loading dose up to 45 mg/kg (3 times the oral or IV maximum dose of 15 mg/kg) may be considered for rectal dosing in children. However, a higher loading dose also increases the risk of excessive hepatic exposure in children who absorb well. Although the rectal loading dose approach may overcome absorption limitations, the \(T_{\text{max}}\) is still delayed.

Montgomery et al\(^{18}\) demonstrated that with a 45-mg/kg rectal acetaminophen dose, the mean \(T_{\text{max}}\) was nearly 200 minutes and the mean \(C_{\text{max}}\) was 13 \(\mu\text{g/mL}\) (range, 7–19). Penetration into the CNS takes even longer. Therefore, although the high rectal loading dose in children seems to produce levels of acetaminophen equivalent to an oral acetaminophen dose of 10 to 15 mg/kg or an IVA dose of 5 to 10 mg/kg, the onset of action is likely to be markedly delayed. Furthermore, in adults, a 1000-mg rectal dose of acetaminophen has been demonstrated to produce subtherapeutic levels in nearly all patients.

**Average Sales Price and Wholesale Acquisition Cost**

IVA 1000 mg is sold in cases of twenty-four 100-mL vials at a wholesale acquisition cost price of $258.00 ($10.75 per vial). This should be compared\(^{19}\) with generic ketorolac, which costs $9.13 per dose, and ibuprofen for injection (Caldolor), which costs $9.20 per dose. In contrast, oral forms of these medications cost $9.13 per dose, and ibuprofen for injection (Caldolor), which is indicated for pain management after major orthopedic surgery.

**Conclusion**

IVA represents a major new approach to acute pain management in the perioperative setting. Although it is modestly more expensive than its NSAID competitors, the lack of cardiovascular and hemorrhagic complications makes its use very attractive. It may also be of value in reducing PO opiate requirements in patients who are especially susceptible to respiratory complications from opiates, for example, patients with obstructive sleep apnea or patients with increased intracranial pressure.

**References**


**Coming Soon:**

- Three Therapies for the Scrap Heap
- Update on the Washington State Pain Care Law
- Update on Risk of Pediatric Dosing Errors with IV Acetaminophen
One REMS for All: FDA Class-Wide Risk Evaluation and Mitigation Strategy Goes Into Effect for Transmucosal Immediate-Release Fentanyl

A new class-wide Risk Evaluation and Mitigation Strategy (REMS) plan goes into effect this month (March 2012) for transmucosal immediate-release fentanyl (TIRF) formulations.1

The new class-wide REMS replaces the individual plans developed by various manufacturers of these formulations and eliminates the glaring inconsistencies between some of them, and the need for prescribers and pharmacies to enroll in multiple programs.

As of the deadline for this newsletter, it was unclear whether the new REMS would be more like the most restrictive individual REMS plan, which required patients to use only enrolled pharmacies, or more like the less restrictive ones.

The shared system strategy, called the TIRF REMS Access Program, will be used by all sponsors of TIRF products. The TIRF REMS Access Program is the first FDA-approved class-wide REMS for drugs in the opioid class. The FDA continues to work on another shared REMS for the class of long-acting and extended-release opioids.

The current list of TIRF medicines includes Abstral (fentanyl) sublingual tablet, Actiq (fentanyl citrate) oral transmucosal lozenge and its generic equivalents, Fentora (fentanyl citrate) buccal tablet, Lazanda (fentanyl) nasal spray, and Onsolis (fentanyl) buccal film.

“This TIRF REMS will ensure safe use and access to these drugs for patients who need them,” said Janet Woodcock, MD, director of the FDA’s Center for Drug Evaluation and Research. “We have worked with the sponsors of both the innovator and generic drugs to develop this single, shared system that will streamline the process and decrease the burden of the REMS on the health care system.”1

Origin of REMS

A REMS is a risk management plan that uses strategies beyond approved labeling to manage serious risks associated with a drug. Under the Food and Drug Administration Amendments Act of 2007, the FDA has the authority to require a manufacturer to develop a REMS when the FDA finds a REMS is necessary to ensure that the benefits of a drug outweigh its risks.

Actiq and Fentora have been extensively prescribed off label for chronic pain, with numerous reports of overdose morbidity and mortality.

Effect on Patient Access

The new shared REMS for TIRF could lead to a massive reduction in the number of prescriptions for these drugs, because the majority of prescriptions are thought to be off-label uses of at least 2 of these formulations for noncancer pain.

However, the FDA said in a list of frequently asked questions and answers about the new shared REMS that it is not expected to affect patient access to TIRF medicines compared with the individual REMS.

“Having a single shared REMS for all of the TIRF medicines will make it easier for prescribers and pharmacies to participate in the TIRF REMS Access program, which we expect to improve patient access. Sponsors will also be required to evaluate the impact of the REMS on patient access to their TIRF medicines as part of required periodic assessments of the REMS, and FDA will review these assessments.”2

To enroll, prescribers must review the Education Program, successfully complete the Knowledge Assessment, and complete an enrollment form.

In outpatient settings, all health care providers must complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient before writing the patient’s first TIRF prescription. Health care providers must also provide patients with a copy of the Medication Guide during counseling about the proper use of their TIRF medicine.

Off-Label Use

Although this class is approved for use to treat breakthrough pain in adult cancer patients who already take opioids around the clock, at least 2 brands, Actiq and Fentora, have been extensively prescribed off label for chronic nonmalignant pain, with numerous reports of overdose morbidity and mortality. Both drugs also have been implicated in episodes of diversion and abuse.

The FDA approved the new shared REMS for the TIRF products on December 28, 2011, to go into effect in March 2012. This new shared system will replace the individual REMS and allow prescribers and pharmacies to enroll in just 1 system.

Actiq and Fentora have been implicated in episodes of diversion and abuse.

According to a press release from the FDA, the goals of the TIRF REMS Access Program are to ensure patient access to important medications and mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

- Prescribing and dispensing TIRF medicines only to appropriate patients, including use only in opioid-tolerant patients;
• Preventing inappropriate conversion between fentanyl products;
• Preventing accidental exposure to children and others for whom TIRF medicines were not prescribed; and
• Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Enrollment Automatically Transfers

Prescribers and pharmacies already enrolled in an individual REMS program for at least 1 TIRF medicine will automatically be transitioned to the shared TIRF REMS Access Program, according to the FDA.

Prescribers and their patients who use TIRF medicines only in an inpatient setting, such as hospitals, hospices, or long-term care facilities, will not be required to enroll in the TIRF REMS Access Program.

However, long-term care and hospice patients who obtain their medications from outpatient pharmacies will have to remain enrolled in the TIRF REMS Access Program.

FDA Investigating Reports of Anticoagulant Dabigatran Etxilate (Pradaxa)

The FDA is evaluating postmarketing reports of serious bleeding events in patients taking dabigatran etexilate mesylate (Pradaxa, Boehringer Ingelheim).1

Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies, and interventional pain management practitioners must continually be aware of new drugs approved as anticoagulants.

The drug has no antidote or reversal agent and has a relatively rapid onset, with full anticoagulation effect achieved 1 to 2 hours after the initial dose.

Pradaxa is an anticoagulant medication used to reduce the risk of stroke in patients with nonvalvular atrial fibrillation (AF), the most common type of heart rhythm abnormality. From approval in October 2010 through August 2011, a total of approximately 1.1 million Pradaxa prescriptions were dispensed, and approximately 371,000 patients received Pradaxa prescriptions from US outpatient retail pharmacies.2

The Pradaxa drug label contains a warning about significant and sometimes fatal bleeds. In a large clinical trial (18,000 patients) comparing Pradaxa and warfarin, major bleeding events occurred at similar rates with the 2 drugs.

The FDA is working to determine whether bleeding in patients taking Pradaxa is occurring more commonly than would be expected on the basis of observations in the large clinical trial that supported the approval of Pradaxa.

At the pain management program of at least 1 large major academic medical center, patients are now being asked to stop taking dabigatran 7 days before any elective epidural pain procedures, and not restart it until at least 24 hours after epidural catheter placement or neuraxial injection, and at least 48 hours after major surgery.

The reason for the caution is that the drug has no antidote or reversal agent and has a relatively rapid onset, with full anticoagulation effect achieved in 1 to 2 hours after the initial dose. No ongoing laboratory monitoring can effectively establish the level of anticoagulant effect. Thrombin time (TT) provides a sensitive measure of circulating dabigatran. If the TT is normal, no dabigatran effect should be present; the degree of TT abnormality does not effectively measure the risk of hemorrhage. Only a normal TT is therefore valuable.

Dabigatran etexilate was approved just over a year ago by the FDA to reduce the risk of ischemic stroke or systemic embolism in AF patients. The drug is metabolized to dabigatran, a direct thrombin inhibitor. It is indicated for patients with difficulty in maintaining stable states of therapeutic anticoagulation with warfarin, or with limited access to warfarin management.

Re-Enrollment Every 2 Years

Prescribers will be required to re-enroll in the TIRF REMS program every 2 years from the date of enrollment into the TIRF class REMS or from the date of enrollment into the individual REMS, whichever was earlier.

More Information to Be Online by This Month

Additional information about the enrollment process can be found on the TIRF REMS Access Program website: www.TIRFREMSAccess.com, which was expected to be available by this month’s go-live.

References


The drug undergoes renal excretion with a half-life of 12 to 17 hours, dependent on baseline renal function. In patients with CrCl greater than 30 mL/min, the dose is 150 mg twice daily; for patients with CrCl of 15 to 30 mL/min, the dose is 75 mg twice daily; it should not be used in patients with stage V chronic kidney disease with a CrCl less than 15 mL/min.

At the Mayo Clinic, the Pharmaceutical Formulary Committee has recommended that for procedures with a risk of hemorrhage, in patients with a CrCl of more than 50 mL/min, the drug should be discontinued 5 days before the procedure. For patients with a CrCl of less than 49 mL/min, dabigatran should be discontinued for 7 days. For elective procedures with a high risk of hemorrhage, a preoperative thrombin time could be considered.

References

Suggested Readings


Prevalence of Opioid Use Addiction Unchanged by New DSM Criteria, One Study Finds
Sonia Elabd, MA

The proposed wording for the upcoming 5th edition of the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), expected in May of 2013, includes several revisions regarding opioid use and dependence compared to the current (4th) edition, known as DSM-IV—and the switch to using an Arabic numeral rather than Roman in the abbreviation is just the beginning.

Most notably, opioid abuse and opioid dependence—distinct from each other in the DSM-IV—may be combined in DSM-5 to become one disorder defined as “opioid use disorder.”

According to the American Psychiatric Association DSM-5 Development website (www.dsm5.org), “problems identified with DSM-IV division between abuse and dependence led to many studies of the structure of the abuse and dependence in a variety of general population and clinical settings. Given the empirical evidence, the DSM-5 Substance Use Disorders Work Group recommends combining abuse and dependence into a single disorder of graded clinical severity.”

Removing Certain Criteria

The Substance Use Disorders Work Group also proposes removing the criterion of “recurrent substance-related legal problems” because, according to extensive data analysis, the work group states, this criterion has a very low prevalence compared to other criteria, and its presence contributes very little to the diagnosis.

Although the new criteria will still include withdrawal and tolerance symptoms associated with opioids, they will not include those symptoms for individuals taking medications, including analgesics, antidepressants, anti-anxiety medications, and beta-blockers, under medical supervision, as the 4th edition did.

DSM to Switch From Roman to Arabic Numerals

Some practitioners won’t give it a second thought, but for those of us who notice such things, there is an explanation for why DSM-IV will update to DSM-5. The switch to Arabic numerals is a deliberate one.

The American Psychiatric Association anticipated that the switch from Roman numerals would need explaining, based on the Frequently Asked Questions page of its website. Here is an excerpt:

“Why is the traditional Roman numeral being dropped from DSM?”

Roman numerals have been attached to DSM since the second edition of the manual was published more than four decades ago. But in the 21st century, when technology allows immediate electronic dissemination of information worldwide, Roman numerals are especially limiting. Research advances will continue to require text revisions to DSM, and a TR designation, as was done with DSM-IV-TR, can only be appended once. After DSM-5 is published in 2013, future changes prior to the manual’s next complete revision will be signified as DSM-5.1, DSM-5.2 and so on.”
The DSM of the Near Future? Proposed New Criteria and Diagnosis Terms

A work group of the American Psychiatric Association (APA) is revising the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The following changes have been proposed in the criteria used to diagnose patients who may be abusing opioids or have other problems in the categories of dependence, addiction, abuse, craving, and others.

A great deal of information is available on the website, www.dsm5.org, including a statement about the desire to be transparent and inclusive. The website says, “Aided by technology, the development of DSM-5 has been the most open in the history of DSM. DSM-5 Work Groups have posted reports on their activities and discussions on our website. The site, which has a section where interested parties can send the APA comments, helps facilitate the exchange of information from around the world.”

Here is a condensed version of some of the proposed language—not yet finalized (timeline follows on page 12 of this issue)—that could help doctors and nurses to diagnose and treat patients who are in chronic pain. To comment directly to the APA about this guideline, go www.dsm5.org.

**Opioid Use Disorder:**

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance)
2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving or operating a machine when impaired by substance use)
3. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
4. Tolerance, (Note: Tolerance is not counted for those taking medications under medical supervision such as analgesics, antidepressants, ant-anxiety medications or beta-blockers.)
5. Withdrawal, (Note: Withdrawal is not counted for those taking medications under medical supervision such as analgesics, antidepressants, anti-anxiety medications or beta-blockers.)
6. The substance is often taken in larger amounts or over a longer period than was intended
7. There is a persistent desire or unsuccessful efforts to cut down or control substance use
8. A great deal of time is spent in activities necessary to obtain, use, or recover from its effects
9. Important social, occupational, or recreational activities are given up or reduced because of substance use
10. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
11. Craving or a strong desire or urge to use a specific substance.

With Physiological Dependence: evidence of tolerance or withdrawal (i.e., either Item 4 or 5 is present)

Without Physiological Dependence: no evidence of tolerance or withdrawal (i.e., neither Item 4 nor 5 is present)

**Source**


Adding a “Craving” Criterion

The work group has suggested adding the criterion of craving or “a strong desire or urge to use a specific substance” has been suggested because it is “a common clinical symptom, tending to be present on the severe end of the severity spectrum.”

Furthermore, the work group proposes that 2 positive criteria are necessary to diagnose an opioid use disorder. Previously, according to DSM-IV, 3 criteria were needed to make a diagnosis of opioid dependence, and only 1 criterion was necessary to diagnose opioid abuse.

“The most significant impact of the changes are in the words to describe the behaviors,” said Lynn Webster, MD, FACPMP, FASAM, an American Academy of Pain Medicine board member and founder and medical director of Lifetree Clinical Research and Pain Clinic in Salt Lake City, Utah (personal communication).

**Challenge Lies in Educating Clinicians**

“It is far less judgmental or pejorative to use the terms opioid use disorder than opioid abuse or opioid addiction. The challenge will be to also educate clinicians what the motives are for the spectrum of opioid use disorders and tailor the therapies according to the motives. Individuals who have an opioid use disorder because of using heroin will require an entirely different treatment approach than someone overusing their prescribed

Continued on page 12
1. All of the following statements regarding IVA are true except
   A. IVA is capable of providing statistically significant and clinically relevant analgesia within a 15-minute infusion.
   B. IVA achieves $T_{\text{max}}$ 30 minutes faster than that observed with equivalent oral doses.
   C. Rapid plasma levels of acetaminophen result in rapid CNS levels and rapid therapeutic effectiveness.
   D. Direct intrathecal administration of acetaminophen has been approved by the FDA.

2. IVA does not have any approved FDA indication for patients with chronic pain.
   A. True
   B. False

3. Within the therapeutic dosage range, small amounts of NAPQI, a toxic intermediate, are produced by the cytochrome P450 CYP2E1 enzyme.
   A. True
   B. False

4. IVA is contraindicated in patients with severe hepatic impairment or severe active liver disease.
   A. True
   B. False

5. All of the following diseases are indications to use acetaminophen with caution except
   A. alcoholism
   B. chronic malnutrition
   C. severe renal impairment
   D. hyperthyroidism

6. Acetaminophen should be used only as a third-line therapy for management of musculoskeletal symptoms in patients with known cardiovascular disease or those at risk for ischemic heart disease.
   A. True
   B. False

7. Acetaminophen is pregnancy category
   A. A
   B. B
   C. C
   D. X

8. If a patient presents with a CrCl less than 30 mL/min, the dosing interval should be
   A. lengthened
   B. unchanged
   C. shortened

9. All of the following statements regarding rectal administration of acetaminophen are true except
   A. Rectally administered acetaminophen has different pharmacokinetics than oral acetaminophen.
   B. Rectally administered acetaminophen has poorer bioavailability than the oral formulation.
   C. Much larger doses of the rectal formulation are required to achieve acceptable plasma and CNS levels.
   D. Rectal administration frequently results in overdose.

10. The Remy et al meta-analysis demonstrated a morphine-sparing effect of acetaminophen but not a decrease in morphine-related adverse effects.
    A. True
    B. False
opioids to try to obtain additional relief from their pain, whether
it is a reduction in pain intensity or to seek an oasis from their
pain by becoming sedated and fogged with the medication.”

Although it would seem that patients having to meet fewer
diagnostic criteria would have increased the prevalence of peo-
ple with the condition, a study published in *Journal of Addictive
Diseases* found otherwise. Boscarino et al\(^1\) conducted inter-
views of more than 700 individuals to estimate the prevalence of
opioid use disorder. The authors drew from a random sample of
outpatients who had been seen at Pennsylvania clinics and had
been prescribed opioids for non-cancer pain 4 or more times in a
12-month period. They then compared results when using the
DSM-IV criteria with results when using the proposed DSM-5
diagnostic criteria.

According to the proposed new criteria, 34.9% of patients in
the study undergoing long-term opioid therapy met the crite-
rria for having opioid use disorder. Under DSM-IV, 35.5% of
patients met the criteria. The data also showed that “92% of
those with a DSM-5 opioid-use disorder also meet the criteria
for DSM-4 opioid dependence, and 95% of those without a
DSM-5 opioid-use disorder do not meet the criteria for DSM-4
opioid dependence.”

The authors wrote that, “This finding is surprising, given the
differences between these diagnostic criteria. The DSM-5
changes proposed were expected to have an effect, especially
because prescription opioid dependence estimates that included
these withdrawal and tolerance symptoms were thought to be
too high. As demonstrated, this was not the case.”\(^1\)

According to the researchers, the reason for this finding is that
patients who would have been excluded by certain criteria, such as
elimination of withdrawal and tolerance symptoms, under the new
classification were included with the addition of other criteria,
such as craving.

“Combining the criteria of abuse with dependence (addiction)
and eliminating tolerance and withdrawal is a practical way to
lessen the impact of misdiagnosing due to the iatrogenic effect of
opioid therapy,” Webster said (personal communication). “The
prevalence is consistent with other reports, but the motives behind
the prevalence for those with moderate and severe opioid use dis-
order are probably considerably different, not unlike the factors
that contributed to the two terms abuse and addiction (depen-
dence).”

**Reference**

tion opioid-use disorder among chronic pain patients: comparison of the