What is the addiction risk associated with tramadol?

EVIDENCE-BASED ANSWER

Tramadol (Ultram, generic and with acetaminophen in Ultracet) carries a risk of substance abuse (strength of recommendation [SOR]: **B**, based on case report surveillance programs). While it appears that tramadol's risk of substance abuse is low (SOR: **B**, based on case report surveillance programs), tramadol is associated with a withdrawal syndrome usually typical of opioid withdrawal (SOR: **B**, based on case report surveillance programs, and a prospective descriptive study).

EVIDENCE SUMMARY

Tramadol is a novel, central-acting synthetic opioid with weak mu-opioid activity, and is approved for treatment of moderate to moderately severe pain in adults. Anecdotally, some clinicians have assumed this popular analgesic's nonscheduled status under the Controlled Substance Act (CSA) means tramadol has no substance abuse potential. (The term "abuse" herein denotes substance abuse or dependence.)

Evidence of tramadol abuse in the US comes primarily from federally operated programs collecting adverse drug event (ADE) data. The MedWatch program of the Food and Drug Administration (FDA) provides a central depository for receiving and compiling postmarketing voluntary case reports. While passive reporting systems can significantly underestimate serious ADE numbers, these reports are often the first evidence of an ADE after a new drug's release into the market.[1] MedWatch has received 766 case reports of abuse associated with tramadol, as well as 482 cases of withdrawal associated with tramadol from the drug's initial US marketing in 1995 through September 2004.[2,3]

The Drug Abuse Warning Network (DAWN) is a federally operated, national surveillance system that monitors trends in drug-related emergency department visits. Over the period from 1995 to 2002, DAWN reported drug-related emergency department visits mentioning tramadol in more than 12,000 cases. Tramadol case numbers significantly increased 165% during this time. For perspective, during the same period, DAWN found nalbuphine (Nubain, also not CSA scheduled) in 118 cases, propoxyphene drug combinations (CSA Class IV) in more than 45,000 cases, codeine drug combinations (CSA Classes III & V) in about 50,000 cases, and hydrocodone drug combinations (CSA Class III) in around 128,000 cases.[4]

Using data from observational postmarketing studies, investigators have extrapolated a tramadol abuse rate for the general tramadol-exposed population.[5,6] Ortho-McNeil, Ultram's manufacturer, funded a surveillance program that compiled tramadol abuse and withdrawal case reports from 2 sources: (1) periodic surveys for tramadol abuse case reports from a group of 255 substance abuse experts studying and caring for addiction communities, and (2) voluntary ADE case reports from health care professionals and consumers received by Ortho-McNeil. Over 3 years of surveillance, the program received 454 case reports classified as tramadol abuse. Over 5 years of surveillance, 422 cases of substance withdrawal, with primarily opioid withdrawal symptoms, were reported. There are significant threats to the validity and generalizability of the investigators' estimated abuse rate of 1 to 3 cases per 100,000 tramadol-exposed patients. The abuse cases were collected in nonrepresentative samples of the tramadol-exposed population. Tramadol exposure is likely suppressed in addiction communities with access to preferred, more potent or euphoriant opioids than tramadol. Voluntary case reports of tramadol abuse significantly underestimate the actual number of abuse cases in the tramadol-exposed population. In addition, the low survey return rate (49%) further decreases the accuracy of any estimation of tramadol abuse rates.

Prospective studies among patients with known abuse, or at high risk of abuse, reported a tramadol abuse rate, as well as subjective experiences of tramadol withdrawal. A 3-year post-mar-

keting cohort study measured tramadol's nonmedical misuse rates using urine drug testing for tramadol among 1601 participants in 4 US state monitoring programs for impaired healthcare professionals.[7] Tramadol exposure occurred in 140 (8.7%) participants. Thirty-nine (28%) were classified as extensive experimentation or abuse of tramadol. Overall, the rate of extensive experimentation or abuse was 18 cases per thousand person-years. The Hawthorne effect, where awareness of being monitored alters a subject's behavior, may threaten these measured frequency rates' generalizability. Another prospective study assessed the subjective tramadol withdrawal experience in 219 patients with a diagnosis of "Tramadol misuse" who were attending 6 drug detoxification centers in China.[8] Validated drug dependence symptom scales found that while the degree of physical dependence reported was uniformly mild, the majority of patients reported the psychic dependence symptom of tramadol craving.

The FDA's Drug Abuse Advisory Committee performed a formal review of the tramadol abuse evidence in 1998, including the data from Ortho-McNeil's surveillance studies and federal case reporting/surveillance programs. The FDA did not recommend changing tramadol's unscheduled status.[9] The FDA's considered decision to not schedule tramadol as a controlled substance implies its abuse risk to the general population is *low* in comparison to its novel analgesic benefit.

RECOMMENDATIONS FROM OTHERS

Ortho-McNeil's revised 2001 product package insert for Ultram states, "Tramadol may induce psychic and physical dependence of the morphine type (mu-opioid). *Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence*" (italics in original, emphasizing 2001 addition). The risk for patients with a history of substance abuse has been observed to be higher.[10]

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CLINICAL COMMENTARY

Though it may not have high abuse potential, prescribe tramadol cautiously

Although tramadol appears to have a low potential for abuse, the literature does reveal evidence of abuse, addiction, and withdrawal, even in patients without a history of such problems. We do not know if tramadol is less addictive than other narcotics in high-risk patients. For patients at risk for dependence, tramadol is a reasonable alternative to other opioids, but abuse appears more likely in these patients. Tramadol may be most appropriate for treatment of acute painful conditions, but it can be administered chronically under a watchful eye. Providers should prescribe it cautiously, particularly in patients with a history of abuse or addiction, at least until more definitive evidence surfaces.

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What are the indications for evaluating a patient with cough for pertussis?

EVIDENCE-BASED ANSWER

Pertussis should be considered in infants with apnea or severe coughing illnesses of any duration, and in older children or adults with prolonged cough (eg, longer than 2 weeks), especially if accompanied by inspiratory whoop or household exposure to a prolonged cough illness (strength of recommendation [SOR]: **B**, based on consecutive cohort studies with poor reference standards). Coughing paroxysms, posttussive vomiting, and absence of fever, while typical of pertussis, are of little help in distinguishing it from other causes of prolonged coughing illnesses (SOR: **B**, based on consecutive cohort studies with poor reference standards).

EVIDENCE SUMMARY

Pertussis is an important cause of cough in all age groups. Ten prevalence studies of adolescents and adults seeking medical attention for a prolonged cough (defined variously as >1–4 weeks) found acute pertussis in 12% to 32%.[1]

While cough longer than 2 weeks, inspiratory whoop, posttussive vomiting, coughing paroxysms, and absence of fever are commonly associated with pertussis, relatively few studies have assessed the sensitivities and specificities of these symptoms. The **Table** summarizes results from 5 cohort series of children and adults with laboratory-confirmed pertussis. Comparison groups were variously defined by negative pertussis cultures, negative pertussis serology, or serologic confirmation of other respiratory infections. Likelihood ratios (LR) were calculated from the data presented in each paper.

The magnitude and variability of these likelihood ratios suggest that individual symptoms may be of limited help in distinguishing pertussis from other causes of prolonged cough. Combinations of symptoms may be slightly more helpful. In a study comparing 10 patients with culture-confirmed pertussis with 10 patients with serologically confirmed mycoplasma pneumonia, the combination of cough >14 days and whoop had a sensitivity of 80%, a positive LR (LR+) of 8 and a negative LR (LR–) of 0.22.[2] A cohort series of children aged <5 years with suspected pertussis compared 33 with positive cultures to 55 with negative cultures. The constellation of spasmodic cough and lymphocytosis (>10,000) had a sensitivity of 83%, a LR+ of 2.5, and a LR– of 0.25. Cough >14 days with whoop and vomiting had a sensitivity of 67%, a LR+ of 3.2, and LR– of 0.42.[3]

Infants aged <6 months with pertussis are at particular risk for atypical presentations and serious complications. In a US series of 18,500 infants with pertussis, apnea was seen in 64% of infants under 1 month and in 44% between 6 and 11 months. Forty percent of the 6- to 11-month-olds had received at least 3 doses of pertussis vaccine.[4] A British study of 126 infants aged <5 months admitted to the pediatric intensive care unit with apnea, bradycardia, or respiratory failure found that 20% had pertussis. Apnea as a predictor of pertussis had a sensitivity of 68% and a specificity of 60%.[5]

Pertussis should be considered early in the evaluation of young infants with cough. In a case-control study comparing 15 fatal cases of pertussis with 32 who survived (infants aged <6 months), the mean number of days from symptom onset to hospital admission were 5.3 (fatal) and 8.6 (survivors). Rates of apnea on admission were 40% and 52%.[6] A case series of 9 infants aged <7 weeks requiring admission to an intensive care unit for pertussis found that 8 had been sick for less than 4 days at the time of admission. All 9 presented with poor feeding and cough, and 5 had experienced apnea.[7]

RECOMMENDATIONS FROM