FOR IMMEDIATE RELEASE

Contact Information
Email: info@painmed.org
Attn: Director of Communications
American Academy of Pain Medicine
Phone: 847-375-4731

A Position Statement from the American Academy of Pain Medicine

American Academy of Pain Medicine Comments on Rescheduling Hydrocodone: Patient and Public Health Considerations

Background

The Drug Enforcement Administration (DEA) has called for a review of scientific and pharmacological evidence regarding hydrocodone, when combined with other products or as an antitussive, in preparation for deciding whether to move these products from Schedule III to Schedule II under the Controlled Substances Act (CSA). The Academy submits these comments by public docket to the FDA Drug Safety and Risk Management Advisory Committee, tasked with reviewing the data and making a scheduling recommendation.

The Academy organized its review of the issues into the following categories based on known evidence related to hydrocodone-combination products:

- Prevalence and patterns of hydrocodone prescribing, nonmedical use, and mortality data
- The possible risks and benefits of rescheduling when considering patients with legitimate medical need
- The possible risks and benefits of rescheduling when considering populations that divert, misuse, use nonmedically, or overdose on medically prescribed opioids
- Recommendations to preserve appropriate medical access while reducing inappropriate use and associated morbidity and mortality

Introduction

A change to hydrocodone scheduling is likely to have a variety of far-reaching impacts on public and patient health because of the medication's widespread use. Hydrocodone in combination with acetaminophen is the most prescribed medication in the United States,[1] the country that consumes 99% of the world's supply.[2] The Centers for Disease Control and Prevention (CDC) reports that enough hydrocodone is prescribed for every U.S. adult to receive 5 mg every 4 hours for a

month.[3] Although staggering when presented at face value, such statistics quoted out of context tell us little about prescribing practices or patient needs. The true epidemiological question is one of exposure: Is hydrocodone too easy to obtain?

Schedule II controlled substances face tighter manufacturing and distribution rules along with stricter prescribing regulations that include a new written prescription with each refill, no call-in refills, and limits on mid-level practitioner prescribers.[4]

Some potential consequences of a schedule change include:

- More frequent patient visits
- Greater penalties for improper prescribing
- Additional paperwork for pharmacists and perhaps physicians
- Requirement to secure pills
- Higher costs for insurance companies and Medicare
- Reduced patient access to medication
- Perhaps less nonmedical use, fewer overdose deaths, and related cost savings

As a result of the more stringent regulations, prescribing would almost certainly decrease. That may be beneficial or detrimental, depending on the affected population.

Medical populations: Who is receiving hydrocodone via prescription?

Non-specialists frequently prescribe hydrocodone combinations for acute, trauma-related, and post-surgical pain, including dental procedures. Thus, scheduling decisions will have an impact reaching far beyond the specialty of pain medicine. However, hydrocodone-combination products are also widely prescribed in chronic pain settings, either alone, in combination with other opioids, or in combination with non-opioid adjuvants.

For example:

- For conditions with characteristics of intermittent pain (e.g., pain arising from endometriosis, interstitial cystitis, or sickle cell disease)
- For continuous chronic pain when long-acting opioids are not available, indicated, or advisable
- For breakthrough pain or sudden flares that occur against a background of chronic pain.

Nonmedical populations at risk for harm

Widespread prescribing of hydrocodone products contributes to quantities available for diversion, unintentional misuse, recreational abuse, and other harms up to and including addiction and overdose death. Certain evidence suggests this is exacerbated by cases in which a patient is expected to experience acute pain only for a day or two yet receives from a 10-to-30-day supply of hydrocodone. In Utah, 586 patients were surveyed two to four weeks after undergoing

procedures performed by the University of Utah urology faculty.[5] Of the 47% of patients who participated:

- Most received hydrocodone (63%)
- Only 12% requested refills
- 67% had leftover medication
- 92% received no disposal instructions
- 91% kept the extra medication at home

Leftover pills remain in the medicine cabinet where they can find their way into the hands of people with no legitimate medical need, including young people. The National Survey on Drug Use and Health suggests that more than two-thirds of past-year nonmedical users got opioids from family and friends as follows: [6]

- 54.2% obtained it free from a friend/relative
- 12.2% bought it from a friend/relative
- 4.4% took it from a friend/relative

With greater availability comes the public misperception that hydrocodone-combination products are safe. The DEA has called hydrocodone abuse the "white collar" addiction because even medical professionals sometimes underestimate the risks associated with prescribing it. A summary of national statistics shows:[7]

- Hydrocodone is second only to oxycodone in submissions of evidence to federal, state and local forensic labs
- 2.7% of 8th graders, 7.7% of 10th graders, and 8.0% of 12th graders are past-year nonmedical users of Vicodin®
- 9.3% of the U.S. population (23.5 million people age 12 and older) have used hydrocodone nonmedically

The most recent national reports do show an encouraging drop in nonmedical use of opioids among young people, including hydrocodone products. A 14% decline (from 2 million to 1.7 million) in the number of young people, ages 18 to 25, who used opioids nonmedically in the past month drove an overall 12% drop in Americans abusing prescription drugs.[6] According to the Partnership Attitude Tracking Study, teens are beginning to show more disapproval of peers who abuse prescription drugs, and nonmedical use among girls is dropping.[8] This good news must always be balanced by the realization that nonmedical use among young people remains unacceptably high.

Recent statistics on total and single-drug opioid deaths as reported by the CDC can be viewed in the Table.[9] Statistics on hydrocodone mortality are sometimes difficult to interpret because official reports often combine opioid categories. Thus, the 31 deaths associated with hydrocodone in 2009 as reported by the American Association of Poison Control Centers (AAPCC) are almost certainly underestimated.[7] (In addition, AAPCC reported 27,753 total exposures and 12,559

single exposures related to hydrocodone). In Florida, 910 deaths associated with hydrocodone were reported between 2003 and 2007.[10] However, inadequate medical-examiner reporting may also be a problem, as discussed under the Recommendations section.

Potential benefits of a schedule change

A change to Schedule II might cause some physicians and other providers to rethink their current prescribing practices. The quantity and duration of prescriptions may drop as providers limit prescribing for pain conditions that warrant the use of an opioid. If patients formerly treated with short-acting hydrocodone products are switched to long-acting opioids, the patients may benefit from stricter monitoring guidelines that accompany therapy with long-acting agents. If exposures drop as a result of the new schedule, fewer people vulnerable to the disease of addiction may come into contact the substance via legitimate prescription. Fewer hydrocodone pills may be left over to cause harm in the form of illicit use or accidental overdose.

Risks of a schedule change

On the other hand, current patients with legitimate medical need may have problems obtaining their medication, particularly if they live in rural or other underserved areas. Their costs may increase through more co-pays, more clinic visits, and higher price of a Schedule II medication. Phone refills would be discontinued. Even under FDA rules that allow three consecutive 30-day Schedule II prescriptions to be written, clinic visits are likely to increase with the stricter medical monitoring accorded Schedule II opioids. Costs to private and government payers, including Medicare, may also increase. Some physicians, particularly in primary care, would decrease prescribing rather than face increased regulatory scrutiny that accompanies Schedule II controlled substances. This could have grave consequences in pain left untreated.

Further consequences could occur if less regulated medications are substituted for hydrocodone. Such possible "balloon effect" medications all have risks and side-effect profiles and may not represent the safest, most effective medication choice.
Possibilities and their accompanying risks include:

- Codeine (lack of efficacy, overdose)
- Tramadol (seizures, serotonin syndrome)
- Non-steroidal anti-inflammatory drugs (Bleeding, renovascular effects, gastrointestinal effects, myocardial infarction)[11]
- Benzodiazepines (nonmedical use, addiction, overdose)[12]
- Other (including methadone)

If patients formerly treated with short-acting hydrocodone products are switched to long-acting opioids, some harms may increase. In a review of malpractice claims filed against anesthesiologists for medication mismanagement, the majority of deaths associated with opioids involved long-acting formulations.[13] Consider also if patients typically prescribed hydrocodone were instead prescribed methadone, another Schedule II opioid, because it is less expensive.

Methadone was found in one-third of opioid-related deaths in 13 states, and accounted for 39.8 percent of single-drug opioid deaths despite average distribution rates of only 2 percent of total opioid prescriptions nationally.[9]

Risks if schedule remains unchanged

If hydrocodone-combination products remain Schedule III medications, we should assume they would continue to be highly prescribed and widely available. Their availability to treat pain must be balanced by an understanding of their risks, including:

- Liver toxicity with high-dose acetaminophen[14]
- Continuing or worsening problems with:
  -Nonmedical use
  -Addiction
  -Diversion
  -Overdose

The Academy's position

The Academy neither supports nor opposes rescheduling but takes the position that action is needed whether the schedule changes or remains the same.

Primary risks arise from:

- Failing to treat pain
- Failing to stop incautious prescribing
- Failing to educate physicians
- Failing to educate patients and the public

The Academy affirms that there is no medical reason to assert that hydrocodone-combination products are safer than Schedule II opioids. Hydrocodone combinations are similar to Schedule II opioids biologically, physiologically, and pharmacologically.

When the CSA was enacted, hydrocodone was used mainly as a cough suppressant. It has been available commercially since the 1980s in combination with acetaminophen or other non-opioid analgesics. The dosage limit for these combination products was set at 15 mg.[15] The low dose per unit together with its wide use for short-term pain probably contributed to its status as a less regulated opioid.

However, the Academy stops short of arguing to reclassify hydrocodone-combination products as being necessary to properly recognizing their side-effect profile and abuse potential. Consider, for example, how hydrocodone's prominence in measures of adverse outcomes compares with its high prescribing volume. In 2004, John Coleman, Ph.D., president of the Prescription Drug Research Center in Fairfax, Virginia, performed an analysis using data from the Automation of Reports and Consolidated Orders System and the Drug Abuse Warning System. Coleman found that the quantity of hydrocodone prescriptions equaled the total of all Schedule II opioids combined, yet hydrocodone ranked only No. 10 in health consequences, when emergency-department mentions are compared with prescriptions filled [John Coleman, Ph.D., written

communication, October 9, 2012]. Coleman characterized this finding as a "relatively modest misuse profile."

Furthermore, evidence is lacking that rescheduling would reduce nonmedical use and mortality. Note that oxycodone is more commonly abused despite being less frequently prescribed than hydrocodone[7] and is also more liked by recreational drug users than hydrocodone when both drugs are administered intravenously.[16] Thus stricter scheduling did not reduce demand for oxycodone among nonmedical users. If rescheduling takes place, increased costs, reduced access, and risks associated with alternative medications could bring significant unintended consequences to patients. Inadvertently redirecting prescribers and patients to methadone as an alternative is only one such example. Another would be if physicians refused to prescribe opioids at all, even though they are indicated, due to more stringent regulations.

It is the Academy's view that leaving the scheduling as is also carries risk. The risk arises principally as the result of:

- Inadequate physician education on safe use
- Misperception on the part of the public, patients, and healthcare providers that hydrocodone is 'safe" because it is widely available
- Excessive quantities available for nonmedical use and diversion due to prescribing in excess of need for acute, trauma-related, and post-surgical pain (i.e., automatic 30-day supply)

The following section details the Academy's call to action in improving safety outcomes related to hydrocodone combinations.

Recommendations

The ultimate goal for physicians is patient and public health. Gaps in physician education must be addressed regardless of whether the schedule changes.

Physician education for Schedule II or III should:

- Address knowledge gaps in acute, subacute, and chronic pain
- Start in medical school and continue through the life of the practice
- Emphasize safety
- Encourage comprehensive, multidisciplinary care

Physician education should emphasize the following steps:

- Careful assessment and formation of a differential diagnosis
- Psychological assessment including risk of addictive disorders
- Informed consent
- Treatment agreement
- Appropriate trial of opioid therapy +/- adjunctive medications
- Cautious prescribing of co-medications (e.g., benzodiazepines, antidepressants) for chronic pain

- Assessment and reassessment of pain, level of function, adverse effects, and medication regimen adherence
- Reduce risk based on results of ongoing monitoring
- Thorough documentation in the medical records

If hydrocodone combinations change to Schedule II

It is important that a schedule change not bring about a new failure by the medical community to assess for and treat pain adequately. This is one of the primary dangers of new stricter regulations. Clinicians should perform the usual assessments they would for any Schedule II medication. Currently, many hydrocodone-combination products are prescribed by mid-level providers. Therefore, everyone who prescribes must understand the new rules and how their practices would change as a result.

If the schedule change takes place, governmental and other bodies must perform follow-up studies to assess the effect. This should be done for a variety of patient and non-patient populations.

At a minimum, data should be collected and analyzed on:

- Patient safety
- Patient outcomes
- Patient access to appropriate pain medication
  -Post-surgical
  -Trauma
  -Other acute
  -Chronic
- Public health
- Nonmedical use and related harms

We also need clearer data on how opioids contributed to deaths. Updated toxicological categories are needed to code and classify which specific opioids are responsible for deaths as reported in vital statistics databases.

Essential data to be collected include:[17]

- Whether a specific opioid:
  -Caused death
  -Contributed to death
  -Was present
- Whether an opioid was found:
  -Alone
  -Combined with prescription drugs
  -Combined with alcohol
  -Combined with illegal drugs

If hydrocodone combinations remain in Schedule III

Physicians and other providers should be encouraged to take Schedule III prescribing seriously with a new emphasis on cautious prescribing and adequate follow-up.

Providers should:

- Perform risk stratification for potential nonmedical use or addiction, a step that is frequently overlooked in Schedule III prescribing.
- Educate patients about liver toxicity risks
- Prescribe only the necessary quantity to prevent leftover medication
- Monitor and document appropriately

The American Academy of Pain Medicine seeks to optimize the health of patients in pain and to eliminate pain as a major public health problem by advancing the practice and specialty of pain medicine through education, training, advocacy, and research. Founded in 1983, the Academy has approximately 2,400 physician members from a variety of disciplines, including anesthesiology, internal medicine, neurology, orthopedic surgery, physiatry, family practice, and psychiatry.

Acknowledgment: Medical writer Beth Dove, of Dove Medical Communications, LLC, provided technical assistance.

References

1. According to the IMS Institute for Healthcare Informatics. Reported by: DeNoon DJ. Most-prescribed drug list differs from list of drugs with biggest market share. WebMD Health News, April 20, 2011. Available at: http://www.webmd.com/news/20110420/the-10-most-prescribed-drugs.
2. Kuehn BM. Opioid prescriptions soar: increase in legitimate use as well as abuse. JAMA. 2007;297(3):249-51.
3. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morb Mortal Wkly Rep. 2011;60(43):1487-92.
4. Code of Federal Regulations. Title 21: Food and Drugs Controlled Substances Listed in Schedule II.1306.11 Requirement of Prescription, June 2012. Available at: http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=8a13fb1f4c0d7fdcb908504abaec4670&rgn=div5&view=text&node=21:9.0.1.1.7&idno=21#21:9.0.1.1.7.0.19.10.
5. Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of postoperative narcotics: a look at postoperative pain medication delivery, consumption and disposal in urological practice. J Urol. 2011;185(2):551-5.
6. Substance Abuse and Mental Health Services Administration, *Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-44, HHS Publication No. (SMA) 12-4713. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2012.
7. "Hydrocodone." Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section, June 2011.
8. *The Partnership Attitude Tracking Study: 2011 Parents and Teens Full Report*. Sponsored by MetLife Foundation. Released May 2, 2012.
9. Centers for Disease Control and Prevention (CDC). Vital signs: risk for overdose from methadone used for pain relief - United States, 1999-2010. MMWR Morb Mortal Wkly Rep. 2012;61:493-7.
10. Hawley C. Narcotic hydrocodone abuse on the rise. HuffPost Health Living; August 20, 2011. Available at: http://www.huffingtonpost.com/2011/08/22/narcotic-hydrocodone-abuse_n_932960.html.
11. Chou R, Qaseem A, Snow V, et al; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147(7):478-91.
12. Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. NCHS Data Brief 2009; (22):1-8.
13. Fitzgibbon DR, Rathmell JP, Michna E, Stephens LS, Posner KL, Domino KB. Malpractice claims associated with medication management for chronic pain. Anesthesiology. 2010;112(4):948-56.
14. Acetaminophen, Tylenol and others. Medicinenet.com; September 9, 2007. Available at: http://www.medicinenet.com/acetaminophen/article.htm.

15. Smith MY, Haddox JD, Di Marino ME. Correlates of nonmedical use of hydromorphone and hydrocodone: results from a national household survey. J Pain Palliat Care Pharmacother. 2007;21(3):5-17.
16. Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, Walsh SL. Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. Psychopharmacology (Berl). 2010;212(2):193-203.
17. Webster LR, Dasgupta N. Obtaining adequate data to determine causes of opioid-related overdose deaths. Pain Med 2011;12(S2):S86-S92.

Table. Drug-Related Deaths Involving Opioids by Type in 13 states: Drug Abuse Warning Network Medical Examiner System, 2009[9]

Opioid	No.	Death Rate per 100 kg MME	RR	(95% CI)
All deaths				
Buprenorphine	20	0.8	0.02	(0.01 – 0.04)
Fentanyl	364	7.7	0.28	(0.25 – 0.32)
Hydrocodone	550	14.3	0.42	(0.38 – 0.47)
Hydromorphone	74	9.1	0.27	(0.21 – 0.34)
Morphine	824	20.2	0.64	(0.58 – 0.70)
Oxycodone	1,097	8.7	0.26	(0.24 – 0.28)
Methadone	1,034	33.6	1.00	referent
Total*	**3,294**	**10.4**		
Single-drug deaths				
Buprenorphine	2	0.1	0.01	(0.00 – 0.03)
Fentanyl	99	2.1	0.26	(0.21 – 0.33)
Hydrocodone	42	1.1	0.11	(0.08 – 0.16)
Hydromorphone	4	0.5	0.05	(0.02 – 0.14)
Morphine	153	3.8	0.41	(0.34 – 0.50)
Oxycodone	150	1.2	0.12	(0.10 – 0.15)
Methadone	298	9.7	1.00	referent
Total	**748**	**2.4**		

MME = Morphine Milligram Equivalent
RR = Rate Ratio
CI = Confidence Level
*Counts for each opioid might not sum to the total shown for all deaths because some deaths involved more than one opioid.

###