Tufts Health Care Institute Program on Opioid Risk Management

Meeting on Co-Ingestion of Alcohol with Prescription Opioids

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EXECUTIVE SUMMARY

Pain is the most common reason for seeking medical care. Opioids, widely accepted as being a keystone in the management of chronic pain, are the most highly prescribed medications in the United States. But enhanced access to these analgesics has led to a marked increase in the non-medical use of prescription opioids. The last decade has also seen a parallel rise in the number of Americans that abuse alcohol, or are dependent on it (to 17.6 million people > 18years old in 2001-2002, 8.46 percent of the population). Because of the potential to co-ingest alcohol with prescription opioids, package inserts for most opioid medications carry warnings against using the drugs together with alcohol. However, very few studies have addressed the nature of alcohol-opioid interactions: we know little about how often the two are consumed together, and about the dangers of chronic, concurrent use: how often does the combination lead to fatality or other significant consequences? How does use of one influence the risk of being dependent on the other? *This meeting had threefold objectives: 1) to develop an understanding of the magnitude of alcohol-opioid interaction as a public health problem; 2) to review the biology and pharmacology underlying alcohol-opioid interactions; and 3) to explore the feasibility of and commercial potential for finding solutions to the alcohol-opioid interaction problem, with a focus on developing alcohol-resistant formulations of prescription opioids in which no opioid is released upon exposure to alcohol.*

Understanding the epidemiology of alcohol and opiate abuse is critical for controlling it, and for developing innovative treatments. A number of surveys (MTF, DAWN, NESARC, NSDUH, SAMHSA, RADARS® System) track local, regional and national trends on the prevalence of alcohol use and also of non-medical use of prescription opioids; however, few have collected statistics on the effects of co-ingestion over the long term. Data from Medical Examiners show a distinct upward trend in fatalities resulting from combined use of alcohol and prescription opioids. The NESARC dataset documents that the vast majority of people with an opioid disorder also have an alcohol use disorder, and that individuals with pre-existing alcohol dependence are about 20 times more likely to develop an opioid use disorder, relative to people who are not alcohol- dependent. The RADARS System tracks calls received by poison centers in all 50 states; their statistics from 2003-2007 show that 20-29-year olds comprise the largest group abusing and misusing opioids, and significantly more individuals call into these centers having used opioids in combination with alcohol than either one alone. Similarly, the majority of adolescent and young adult past-year non-medical users of prescription opioids also report co-ingestion with alcohol; alcohol co-ingestion is more prevalent with prescription opioids than with any other scheduled medication classes, and non-medical use of opioids increases with the severity of alcohol drinking (NSDUH). In general, then, alcohol and opioid use disorders are highly co-morbid, raising many issues about how best to treat these populations.

These data collectively make a strong case for public education and training (drug education, teaching good decision-making and social skills, addiction counseling) at the community level, and in schools/colleges; and argue for focus at the legislative level to be shifted from incarceration of abusers to prevention and treatment. The fact that many abusers admit to getting their opioids from doctors, or from friends/family who have been prescribed the drugs, points to an urgent need for educating physicians that treat patients in pain management programs: very few physicians report making consistent use of urine drug monitoring, despite the recommendation of the Office of National Drug Control Policy that such screening be part of every primary care setting. And how social attitudes factor into such screening also merits study: e.g., screening for blood alcohol levels has been much more successful than testing for opiates in urine, perhaps in part because excessive drinking of alcohol is more socially acceptable, even more sanctioned, than is opioid misuse. In keeping with this, validated self-report tests (Alcohol Use Disorders Identification Test or AUDIT) are successful in uncovering alcohol abuse or dependence, while self-report of opioid abuse (SOAPP, PMQ) is not fully predictive of aberrant drug-related behaviors.

Pharmaceutical companies are developing tamper-resistant opioids targeted at preventing release of the active ingredient when administered via an unintended route, but few formulations are directed at *developing long-acting depot formulations that are also resistant to alcohol-related dose-dumping*, or specifically mitigating the effects of co-ingestion. Among other approaches, the use of naltrexone, which blocks the effects of the opiates and also reduces the reinforcing effects of alcohol, is worth exploring; so is incorporation of a prodrug, or developing a formulation in which co-ingestion promotes release of disulfiram. Important considerations in developing such "dual action" formulations include: i) how would inhibiting release of the opioid affect patients who are on therapeutic doses of the analgesics, and who accidentally take a glass of wine or a beer; ii) would the order of administration affect the outcomes, e.g., administering the opioid first followed by alcohol consumption, versus starting with a high blood level of alcohol, then taking the opioid; ii) how extensive and how severe is the problem of alcohol co-ingestion with prescription opioids, and thus how many high risk pain patients would benefit from such drugs? In other words, what is the market for such products, and would their development be commercially viable?

Academic research has been invaluable for elucidating the pharmacokinetics (how drugs get to the site of action in the brain), pharmacodynamics (how they work on the brain), and interacting pharmacogenetics (how genetic variations influence an individuals response to drugs and treatment) associated with opioids and alcohol use. The active ingredient in prescription opioids may be administered via crushing/snorting, sublingual placement, inhaling, smoking, or IV injection; it is then liberated (immediate/ extended release), metabolized (glucuronidated, demethylated, converted) and absorbed into the bloodstream: alcohol can inhibit or potentiate these processes at any level, increasing drug toxicity. For drugs to induce euphoria, neural activity must be triggered in reward/reinforcement centers of the brain: ventral tegmental area, nucleus accumbens, amygdala, and prefrontal cortex. In particular, drug reinforcement is associated with increased levels of dopamine in the nucleus accumbens and the interaction between dopamine and the brain's endogenous opioid peptides (endorphins, enkephalins, dynorphins), mediated via activation of the mu and delta opioid receptors. Ethanol induces a large release of beta endorphin, potentiating the reward response triggered by opioids. Pharmacogenetic studies have documented polymorphisms in the mu-opioid receptors and also variations in their ability to metabolize alcohol. Such alterations can alter receptor sensitivity, alter release of beta-endorphin, affect the risk of addiction, and trigger metabolic interactions in the liver; thus, treatment efficacy varies greatly for individuals with such genetic variations.

In terms of recommendations for therapy, clinicians who prescribe opioids to patients for pain treatment, or for agonist therapy of addiction, need to consider potential alcohol-opioid interactions in patients. Applying "Universal Precautions" is recommended for all patients using opioids, regardless of risk stratification: this includes collecting appropriate history and physical examination data with diagnostic formulation, psychological and substance assessment, getting informed consent and developing a treatment agreement that sets clear goals for treatment, monitoring and reassessing the goals on a regular basis, routinely doing toxicology screens, and assessing pain, compliance, side effects, mood, sleep, progress towards goals. Therapy should be adjusted/restructured as indicated, based on the reassessment. Screening tools should include use of validated scales or questionnaires. If aberrant opioid and/or alcohol use behaviors are identified, a differential diagnosis of the causes should include self medication of mood or sleep disorders, traumatic memories, pain; elective drug use for reward/euphoria; addiction to alcohol or opioids or both; diversion for profit or to share with others; dose escalation or alcohol use by patient to self-medicate opioid resistant pain due to tolerance, hyperalgesia, neuropathic pain; and genetic variability in responsiveness to specific opioids. Recovery should be supported with use of addiction or psychiatric treatment as necessary, including opioid agonist therapy

(methadone or buprenorphine). Despite these precautions, if personal or public safety cannot be secured and if all treatment variations for an individual are ineffective, clinicians should implement a rational strategy to release the patient from the treatment program.