Safety profile of the analgesic Trezix, containing the mild opioid dihydrocodeine

A whitepaper

Wraser Pharmaceuticals

Sharp rises in opioid abuse and overdose rates in the United States over the past two decades have prompted much-needed review of prescription rates and ease of access to controlled substances. Combatting these alarming trends requires assessing which opioids are more addictive and habit-forming than others, and setting standards and guidelines for prescribing that accurately reflect the relative risk of a drug.

Trezix (NDC drug name 66992-0340), an oral analgesic used to manage moderate to moderately severe pain, has a lower morphine milligram equivalent (MME) dose than stronger opioids such as morphine, hydrocodone, and fentanyl.[1] It is formulated as a short-acting opioid, which has a lower risk of addiction or overdose than long-acting opioids.[2]

In this report we present an overview of the safety and usage data for Trezix and similar low-dose dihydrocodeine combinations. It is our carefully-considered opinion that Trezix should not be regulated as strictly or in the same classification as opioids of morphine-equivalent or higher strength.

Pharmacology of Trezix

Each Trezix capsule contains a combination of 16mg dihydrocodeine, 320.5mg acetaminophen, and 30mg caffeine.

Dihydrocodeine is a partially-synthetic opioid analgesic and antitussive. It is synthesized by hydrogenating codeine, converting the double bond between carbons 7 and 8 in the main molecule into a single bond and adding a hydrogen atom to the two carbons.[3] In the body, it is metabolized into dihydromorphine, which is an agonist for opioid receptors on neurons in the central and peripheral nervous system.[4]

Acetaminophen (paracetamol) is an analgesic used to treat mild pain and fever. It is frequently used in combination with opioids for the treatment of more severe pain from cancer, surgery, and chronic conditions. Long-term use of acetaminophen does not result in addiction or dependency.[5] Adults can take 3-4g per day safely, and it is widely available over-the-counter in 500mg doses.[6]

Caffeine is a mild stimulant that affects the central nervous system. Combination with other pain relievers and other drug types can enhance their efficacy.[5] It is the world's most widely-used

psychostimulant, capable of creating a mild form of tolerance and physical dependency with minor withdrawal symptoms.[7] Caffeine is classified by the FDA as GRAS (generally recognized as safe).

Regulation of Trezix

Drug Enforcement Administration (DEA) classification lists Trezix as a Schedule CIII substance. Schedule III drugs are defined as "drugs with a moderate to low potential for physical and psychological dependence."[8] All products containing dihydrocodeine, including Trezix, are available by prescription only in the United States. However, combination drugs containing low doses of dihydrocodeine in fixed combination with other analgesics like acetaminophen (paracetamol), salicylic acid (aspirin), ibuprofen, and caffeine can be attained over-the-counter in some countries like the United Kingdom, Japan, and South Africa.[9,10]

Opioid strength of dihydrocodeine in relation to morphine

The MME conversion factor of dihydrocodeine is 0.25, meaning it is one-quarter the strength of morphine by weight. This is slightly stronger than codeine, at 0.15, and tramadol, at 0.10. However, the vast majority of other opioid analgesics are many times stronger than dihydrocodeine based on MME value (see Table 1).

For example, a 16mg dose of dihydrocodeine is equivalent to a 30mg dose of codeine, a 5mg dose of hydrocodone, and a 1.6mg dose of oxycodone.

Dihydrocodeine is considered a "weak" opioid and is often used in first-line management of surgical or cancer-related pain before stronger medications like morphine or oxycodone are given.[11] Because of its favorable safety profile and low habit-forming properties, dihydrocodeine is sometimes also prescribed for the treatment of addiction to stronger opioids like heroin.

Trends in low-dose dihydrocodeine use

Contrary to the rise in use of morphine-equivalent-strength and higher-than-morphine-strength opioid analgesics, the rate of lower-than-morphine-strength opioid analgesics among adults over the age of twenty has been steadily declining in the United States since 1999.[12]

In European countries, dihydrocodeine is preferably prescribed over codeine, hydrocodone, or morphine for pain relief. Doctors in the United States prescribe hydrocodone, a stronger opioid, much more frequently than other countries, so dihydrocodeine prescription rates are lower here.[13]

There has been no rise in opioid prescribing rates in the United States equivalent to the rise in opioid use. Overall, prescribing rates of opioids in general has declined from 2012 to 2017.[14] Prescriptions for dihydrocodeine specifically decreased by 98.7% between 2009 and 2014, and in 2014 accounted for less than 0.1% of all opioid prescriptions dispensed. The total mass of legally-dispensed dihydrocodeine likewise decreased by 68.6% from 2009 to 2013.[15]

Overdose and abuse rates of dihydrocodeine compared to other opioids

Epidemiological information regarding prescription, addiction, and overdose rates of dihydrocodeine is limited, in large part because it typically is lumped into the broader opioid category and details on specific drugs are often not included in incident reports or death certificates.[16]

When broken down into more specific classifications, dihydrocodeine falls into categories with lower potentials for misuse, addiction, and harmful effects than other types of opioids typically of concern. For instance, the likelihood of continued use after 1 and 3 years from prescribing date for Schedule III-IV opioids is 5.0% and 2.2%, respectively, compared to 27.3% and 20.5% for long-acting opioids, 13.7% and 6.8% for tramadol, and 8.9% and 5.3% for short-acting Schedule II opioids (see Table 2).[17]

The rate of drug overdose deaths caused by synthetic opioids (other than methadone) has risen much more rapidly over the past few years than overdose deaths caused by natural or semisynthetic opioids. From 1999 to 2017, the rate of overdose deaths from synthetic opioids (such as fentanyl and tramadol) rose 2,900%, whereas overdose deaths from natural or semisynthetic opioids (such as morphine, oxycodone, and dihydrocodeine) rose only 340%. From 2016 to 2017 alone, overdose deaths from synthetic opioids spiked by 45%, while overdose deaths from natural or semisynthetic opioids stagnated.[18]

In the year 2014, approximately 31,270 drug overdose deaths involved opioids. Of these, 17.3% involved oxycodone, 13.4% involved fentanyl, 12.9% involved morphine, and 10.5% involved hydrocodone. Deaths involving codeine and dihydrocodeine have been insignificant enough to not be included in most reports from the United States.[19] A report from the United Kingdom found a total of 584 fatalities in which dihydrocodeine was detected in the body between the years 1997 and 2007; the vast majority of these (96.1%) involved at least one other type of drug.[20]

Many overdose deaths in the United States also involve a mix of opioids and other drugs. Opioids mixed with alcohol can be particularly lethal, with alcohol consumption contributing to about 15% of all drug overdose deaths in 2014. Of the deaths that involved both drugs and alcohol, 17.2% involved hydrocodone, 16.7% involved oxycodone, 13.0% involved morphine,

and 12.2% involved fentanyl. No deaths were reported resulting from a mix of alcohol and codeine or dihydrocodeine.[14,19]

Typical prescribed dosing of Trezix has a low risk of habit-formation

The standard recommended usage of Trezix for adults is to take 2 capsules every 4 hours as needed, but typically limited to no more than 10 capsules per 24-hour day.[5] One capsule of Trezix contains 16mg dihydrocodeine, or 4 MME. A patient taking Trezix as prescribed, therefore, will not be taking more than 40 MME per day, and a typical use of 6 capsules over a 24-hour period is equivalent to 24 MME.

The Centers for Disease Control and Prevention (CDC) considers a daily intake of 90 MME or more to be a high opioid dose. They recommend avoiding daily doses of 90 MME or higher if possible. Caution is advised for doses of 50 MME per day or higher, as the risk of opioid abuse is twice as likely at this level than for doses of 20 MME per day or less.[21]

Chronic pain sufferers, accounting for most opioid abuse, do not turn to dihydrocodeine

The vast majority (81%) of Americans who take non-prescribed prescription drugs report doing so because of high levels of chronic pain, as do 51% of heroin users.[14] People self-medicating for chronic pain tend to turn to stronger painkillers, rather than analgesics for moderate amounts of pain like dihydrocodeine. Hydrocodone, oxycodone, and fentanyl, which can be manufactured illicitly in amateur laboratories, are the leading choices for non-prescribed prescription drug use.[15,19]

Few cases of dependency on dihydrocodeine are mentioned in case reports, and recovery has typically been rapid once proper treatment begins.[22] Overdoses of dihydrocodeine likewise have been infrequently reported, and have been successfully treated with naloxone.[23] Of all opioid-containing drug items analyzed by the DEA in 2007, just 1.24% tested positive for dihydrocodeine, compared to 39.66% for hydrocodone and 31.24% for oxycodone.[24] Reports from the DEA from later years did not include drug test statistics for dihydrocodeine.[15]

Additional safety information for Trezix

When taken properly, side effects from the use of Trezix and other low-dose dihydrocodeine-containing drugs are generally mild. They are similar to the side effect profiles of other narcotics, like constipation, mild euphoria, feelings of tranquility, dizziness, or sleepiness, which may interfere with the ability to operate a motor vehicle.[5,25] Because of its metabolic processing, Trezix should not be taken along with monoamine oxidase inhibitors (MOAIs).[5]

Summary

Trezix, with a low dose of dihydrocodeine, is a weak opioid used to manage moderate to moderately severe pain. With a low MME compared to most other opioids, it has low habit-forming properties. Cases of dihydrocodeine dependency and overdose are rare. Dihydrocodeine is preferred to other stronger opioids as a first line of pain management in many other countries in Europe and the rest of the world, and is also sometimes used to treat addictions to more hazardous opioids.

Because of its favorable safety profile, Trezix does not pose as much of a danger for misuse and other harmful effects as Schedule II and long-acting opioid drugs. This needs to be considered when reviewing and developing guidelines and regulations for opioid prescribing and monitoring. It does not make sense to govern it as strictly as those opioids that do frequently cause addiction and health damage, and it should remain easily accessible to those who would benefit from its pain relieving effects.

Tables

Drug Name	MME Conversion Factor	1mg Morphine Equivalent Dose
Codeine	0.15	6.7mg
Dihydrocodeine	0.25	4mg
Fentanyl (tablets/lozenges)	103.0	9.7μg
Fentanyl (patch)	7200.0	0.14μg
Hydrocodone	1.0	1.0mg
Methadone	3.0	0.33mg
Morphine	1.0	1.0mg
Opium	1.0	1.0mg
Oxycodone	1.5	0.67mg
Tramadol	0.1	10mg

Table 1. Milligram morphine equivalent (MME) conversion factors of selected commonly-used opioids.[21]

Prescribed Drug	Probability of continued opioid use after: 1 year	3 years
Long-acting opioid	27.3%	20.5%
Tramadol	13.7%	6.8%
Schedule II short-acting opioid (other than hydrocodone or oxycodone)	8.9%	5.3%
Hydrocodone, short-acting	5.1%	2.4%
Oxycodone, short-acting	4.7%	2.3%
Schedule III-IV opioid (such as Trezix) or nalbuphine	5.0%	2.2%

Table 1: Probabilities of continued opioid use by opioid category.[17] Long-acting opioids include morphine, oxycodone, buprenorphine, fentanyl, buprenorphine, oxymorphone, and tapentadol. Schedule II short-acting opioids include fentanyl, morphine, methadone, hydromorphone, levorphanol, meperidine, methadone, oxymorphone, and tapentadol. Schedule III-IV opioids include codeine, dihydrocodeine, butorphanol, pentazocine, and propoxyphene.

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