Pharmacological Research 91 (2015) 99–103

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited Review

# Hydrocodone extended-release: Pharmacodynamics, pharmacokinetics and behavioral pharmacology of a controversy

Harry J. Gould III[a,b,d,e,f], Dennis Paul[a,b,c,d,e,f,*]

[a] Department of Neurology, LSU Health Sciences Center, New Orleans, LA 70112, United States
[b] Department of Anesthesiology, LSU Health Sciences Center, New Orleans, LA 70112, United States
[c] Department of Pharmacology and Experimental Therapeutics, LSU Health Sciences Center, New Orleans, LA 70112, United States
[d] Neuroscience Center of Excellence, LSU Health Sciences Center, New Orleans, LA 70112, United States
[e] Center of Excellence for Oral and Craniofacial Biology, LSU Health Sciences Center, New Orleans, LA 70112, United States
[f] Alcohol and Drug Abuse Center of Excellence, LSU Health Sciences Center, New Orleans, LA 70112, United States

ARTICLE INFO

*Article history:*
Received 10 September 2014
Received in revised form
24 September 2014
Accepted 24 September 2014
Available online 6 October 2014

*Keywords:*
Hydrocodone
Abuse liability
Abuse deterrents
Opioid analgesics
Acetaminophen
Pain
Pain management
Risk mitigation

ABSTRACT

Recently, the U.S. Food and Drug Administration (FDA) approved Zohydro®, an extended release formulation of the opioid analgesic hydrocodone that contains no acetaminophen. This approval was against the recommendation of the FDA's Expert Panel. Subsequently, both chronic pain advocates and anti-drug abuse advocates have steadfastly expressed their support of, or astonishment at this decision. Here, we review the pharmacokinetics, pharmacodynamics, safety and abuse liability of this hydrocodone formulation and how it relates to the Expert Panel's opinion and the FDA decision. We discuss the important issues, risk mitigation, potential use of abuse deterrents, and how the different viewpoints of the Expert Panel and FDA decision makers resulted in the approval and subsequent controversy.



**Contents**



Albert Schweitzer eloquently expressed both the problem and the challenge that faces society and healthcare providers who manage pain when he said, "Pain is a more terrible lord of mankind than even death". Opioid analgesics have been used successfully for decades in clinical practice for managing moderate to severe pain and are considered to be the most effective tool in our therapeutic armamentarium for this purpose. That opioid medications have significant beneficial effects is readily accepted, and their use in the treatment of acute pain and for pain associated with terminal disease is common in spite of the well-publicized detrimental effects related to their potential for misuse, abuse and addiction. Their use, however, continues to be fraught with controversy. Which formulations, if any, should be used, and how much is reasonable? Despite uncertainty, the search for newer and better medications and formulations continues with the hope that we will be able to provide relief with fewer adverse effects for a larger percentage of

* Corresponding author at: Department of Pharmacology and Experimental Therapeutics, LSU Health Sciences Center, 1901 Perdido Street, New Orleans, LA 70112, United States. Tel.: +1 504 568 4740; fax: +1 504 568 2361.
*E-mail address:* dpaul@lsuhsc.edu (D. Paul).

http://dx.doi.org/10.1016/j.phrs.2014.09.006
1043-6618/

the ever-increasing number of under-treated patients with chronic pain.

In early 2014, the FDA approved a 12-h extended-release formulation of hydrocodone (Zohydro ER®) against the recommendation of its advisory panel [1,2]. It also occurred at a time that several regulatory bodies have called for a reduction in opioid prescriptions [3,4]. This action has fueled the controversy over the prudent use of opioid analgesics for the treatment of chronic pain of non-malignant origin.

## Rationale for seeking additional therapeutic options for analgesia

When opioid medications are used by well-trained practitioners in the proper settings, they can provide benefit for the management of acute pain and chronic pain associated with terminal disease. This realization has led to the consideration and gradual, albeit partial, acceptance of the use of opioids for managing chronic pain of non-malignant origin. In the early 1990s, opioids were viewed by many to have few adverse effects and low abuse potential when used in the appropriate patients [5,6], and thus were deemed to be reasonable options in the therapeutic arsenal for managing chronic non-malignant pain [7]. Unfortunately, the knowledge base upon which general practitioners could assess need, the evidence-base to support drug selection, and the tools for monitoring responses to opioids for chronic use were limited [8]. In the hands of practitioners with the insufficient training in pain assessment, there was a dramatic increase in the utilization of opioid medications, and limited vigilance in monitoring for misuse, abuse, diversion and addiction, that led to the over-prescribing of opioid medications. Opioids generally became more readily available which resulted in increased inappropriate use of prescription drugs by individuals who experiment with chemical modification of their internal environment to achieve relief from suffering related to psychological, emotional and spiritual generators of pain.

Unfortunately, there is no panacea when it comes to managing pain because patients do not respond similarly to a given medication and may fail to realize the benefits of several formulations due to adverse effects, lack of efficacy due to single nucleotide polymorphism variants [9–11], or the development of tolerance [12]. In spite of the consensus that patients with valid complaints of pain should receive treatment for their pain, there is an equally valid consensus that there is a real and urgent need to decrease the unintended and undesirable consequences that opioid diversion has on society [13,14].

Proponents of the new extended-release formulation of hydrocodone argue that there is a real and unmet need for alternate safe and effective options for the management of pain. In addition, they reason that current formulations of hydrocodone all contain an adjuvant analgesic, usually acetaminophen, which has led to a high incidence of hepatotoxicity for those who develop tolerance to the opioid effect and for those who abuse these combination drugs [15]. Opponents contend that controlled release morphine and oxycodone formulations already serve the need for a long-acting high efficacy analgesic [16]. Moreover, current pharmaceutical development strategies frequently incorporate an abuse deterrent in formulations of opioids that have been, or are expected to be abused [17,18]. This leads to three fundamental questions. First, is the risk–benefit ratio sufficient to warrant introducing an additional formulation of hydrocodone as a single drug therapy? Second, can we improve the risk–benefit ratio for chronic pain patients who have not received adequate analgesic coverage by other therapies? Third, does the chronic pain market, in which a high degree of tolerance is common and acetaminophen combinations are to be avoided, warrant another long-acting mu opioid agonist? A review of the pharmacodynamics and pharmacokinetics of hydrocodone and acetaminophen may lead to a better understanding of both sides of this controversy.

Hydrocodone produces its analgesic effect by activating mu opioid receptors (MORs). MORs are G-protein coupled receptors that inhibit cAMP production and activate G-protein mediated inwardly rectifying potassium channels (GIRKs). The analgesic effect appears to be associated with the latter signaling pathway [19]. In *in vitro* experiments, hydrocodone itself is a low efficacy agonist. It is metabolized by CYP2D6 to hydromorphone, which is responsible for most of the drug's effects [20]. Hydrocodone is also metabolized by glucuronidation to hydrocodone-3β-glucuronide and hydrocodone-6β-glucuronide. Similarly, hydromorphone is glucuronidated to hydromorphone-3β-glucuronide and hydromorphone-6β-glucuronide [20]. The 3β metabolites are analgesically inactive, but 6β metabolites of opioids may be as much as 100 times more potent at MORs than the parent compound [21,22]. As the dose of an opioid increases beyond typical starting doses, delta opioid receptors and kappa opioid receptors are activated. Like oxycodone and dihydrocodeine, hydrocodone is about 10 times more potent than its parent molecule, codeine. It is, therefore, equally potent and equally efficacious to morphine and carries the same potential for adverse effects. Hydrocodone is less polar than codeine, and thus has more rapid pharmacokinetic properties. The speed at which a drug of abuse crosses the blood–brain-barrier is correlated to its reinforcing quality [23,24] and the frequency of its abuse [17]. Hydrocodone's established potential for abuse raises significant concerns regarding the approval of yet another formulation for this medication and is the primary reason that an FDA panel recommended against approval of hydrocodone as a single drug therapy.

An unfortunate feature of opioid medications in general is that with repeated administration, tolerance may develop to the analgesic effect resulting in a need to increase dosing to maintain the desired effect in a significant percent of cases. Unfortunately, until the availability of Zohydro ER®, none of the formulations of hydrocodone provided a means to deliver medication over a sustained period of time, which is intuitively preferred for optimum management of chronic pain [25,26] (but see [7,27,28] for reviews). For these reasons, the new formulation of hydrocodone appeared attractive because there would now be an extended-release capsule with a dose option that could provide the desired, sustained, analgesic effect with fewer pills that did not contain an add-on drug to reduce safety.

In order to enhance efficacy, most formulations of codeine and its derivatives have been compounded with acetaminophen. Until recently, hydrocodone was combined with as much as 750 mg of acetaminophen, the maximum recommended dose (Maxidone®, Vicodin ES® and generic formulation). There are two reasons that these combination analgesics were considered more favorable than treating with the opioid alone. First, opioids and acetaminophen produce analgesia through entirely different mechanisms, and have entirely different adverse effect profiles. Thus, at beginning therapeutic doses, the two drugs will produce additive or synergistic analgesia without an increase in adverse effects [29]; formulations with hydrocodone alone would require a greater opioid dose to achieve the same efficacy as a hydrocodone–acetaminophen combination. Unfortunately, the add-on medications, although considered relatively safe, are not without potential problems of their own.

The new formulation of hydrocodone, because it is an extended-release capsule, offers uniform analgesic coverage for 12 h. The resulting continuous level of analgesic purportedly reduces the baseline pain to a level that returns some control of quality of life to the patients rather than re-enforcing the need to reach for the pill bottle each time that pain increases. Extended-release formulations