



Review

Gender difference in prescription opioid abuse: A focus on oxycodone and hydrocodone



Manuela Graziani^{a,b,*}, Robert Nisticò^c

^a Department of Physiology and Pharmacology "Vittorio Erspamer", Sapienza University of Rome, Rome, Italy

^b Drug Addiction and Clinical Pharmacology Unit, University Hospital Umberto I, Sapienza University of Rome, Rome, Italy

^c Department of Biology, University of Rome 'Tor Vergata', Rome, Italy

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ABSTRACT

Several data gathered in the last decade indicate an increase of abuse of prescription opioid drugs oxycodone (OXY) and hydrocodone (HYDRO) in women. However, to date there are no conclusive evidences investigating the gender-dependent abuse liability of prescription opioids. This study aims to supply a specific focus on women's data through a selective summary of the literature analyzing gender differences in the pharmacokinetic and pharmacodynamic dimension of OXY and HYDRO. Findings from this study suggest that the majority of OXY and HYDRO pharmacokinetic and pharmacodynamic effects do not differ according to gender, though confirming a significant difference in the incidence of adverse effects as demonstrated by the increased gastrointestinal adverse reactions in female subjects. Although the majority of recent clinical studies include an equal number of female and male subjects, the main outcome parameters do not relate specifically to gender differences. Due to the gender influence in activity of CYP3A4 and its crucial role in metabolism of both OXY than HYDRO, we suggest that assessing pharmacokinetic and pharmacodynamic interactions in clinical studies may be useful to clarify the effect of the higher CYP3A4 activity in female in relation to CYP2D6 genotype. Overall, considering the paucity of data regarding gender differences in European Union, this work highlights that impact of new abuse deterrent formulations should be assessed with a special focus on data concerning female subjects.

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1. Introduction and epidemiological data

Non-medical use of prescription drugs (NMUPD) such as opioids, central nervous system depressants and stimulants is actually

on the rise [1]. According to a Monitoring the Future study, among young people, prescription drugs are the second-most abused category of drugs, after marijuana [2]. Drug misuse can lead to abuse and dependence, as corresponding to the definition of abuse/dependence listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [3].

* Corresponding author at: Department of Physiology and Pharmacology "Vittorio Erspamer", Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy.
E-mail address: manuela.graziani@uniroma1.it (M. Graziani).

It has been estimated that in 2013 in United States of America (USA) there were approximately 2 million persons aged 12 or older who used prescription drugs for the first time within the past year, which averages to about 5.500 initiates per day [4]. In 2013 the average age of first non-medical use for pain relievers was 21.7 years [4]. The most prevalent category of misused prescription drugs among youths in 2013 was pain relievers. Results from the 2014 USA National Survey on Drug Use and Health [5] indicate that 4.3 million people aged 12 or older (1.6% of the population) were current non-medical users of pain relievers.

Moreover within a five-year period (2004–2008), the number of emergency department access linked to the non-medical use of prescription pain relievers has more than doubled, rising from 144.644 to 305.885 visits per year [1]; rates of deaths related to overdose of prescription drugs increased rapidly during 1999–2006 [6] and the increase is mainly associated to deaths involving prescription opioid analgesics.

Recent data from Poison Center on the trend in abuse, misuse and use with suicidal intent of prescription opioids [7] revealed a female percentage on calls of 55.7% among adults 20–59 years of age and of 59.1% among older subjects (60+ years). Furthermore the number who received treatment for non-medical use of prescription pain relievers increased from 2002 (360.000 subjects) to 2013 (746.000 subjects) [4].

The most common opioids prescribed for pain treatment are immediate-release oxycodone (OXY), hydrocodone (HYDRO), morphine and codeine, and sustained-release oxycodone, methadone, transdermal fentanyl and morphine [8] while the three prescription opioid pain relievers most frequently involved in hospital emergencies department visits from 2004 to 2008 were oxycodone, methadone and, to a lesser extent morphine, fentanyl and hydro-morphone [1]. Studies on trends in non-medical prescription opioid use (NMPOU) such as HYDRO, OXY, codeine and morphine show that in USA NMPOU is most prevalent among individuals from 18 to 25 years of age [9,10]. Data on a sample of 3520 patients entering drug treatment programs with prescription opioid as primary drug showed that OXY and HYDRO were the most abused drugs [11].

In Europe recent general population surveys on the use and abuse of prescription medication have highlighted that data on the dimension of the problem in the European Union (EU) are very limited [12,13]; the NMUPD, except for opioid substitution drugs, has not been regarded as a major problem [14]. Moreover only some countries in Europe monitor the prevalence and patterns of NMUPD [15]. However, data on the NMPOU have been reported in Europe [16].

Factors contributing to the differences between the global regions in misuse of prescription opioids (PO) is actually object of discussion [17–19]: discrepancies in health-care organization and pharmacovigilance systems, medical-professional culture as well as in pharmaceutical orientation may be evoked to explain the observed differences in PO abuse across North America and European Union countries.

1.1. Gender prevalence

The growing use of both legal and illegal drug misuse and abuse by women requires an appropriate focus [20–22]. Data from the 2012 US National Survey on Drug Use and Health [23] show that the rate of current illicit drug use among persons aged 12 or older was higher for males than females (11.6 vs 6.9%), while importantly the rate of non-medical users of psychotropic drugs was quite the same (2.8 vs 2.4%). Conversely, data indicate that women were more likely than men to report use of any PO (29.8% females vs 21.1% males) and abuse of any PO (15.4% females vs 11.1% males) [24]. Moreover white women are more likely to abuse prescription pain relievers than women of any other ethnicity [10].

In Europe and the Mediterranean region, very recent data reflect the gender dimension of NMUPD [12]: in those countries reporting on the use of prescription drugs in lifetime, it is immediately apparent that female use surpasses that of males, women being a high risk group for NMUPD. Accordingly, in some European countries the number of overdoses (including deliberate overdose) is higher in females [12]. Due to the gap between data collection strategies from the different European countries (distinction or no distinction between analgesics and sedatives, information available only for a period of lifetime, poor accuracy in reports to detect rate differences between gender, presence or absence of prescription registration), it is actually difficult to identify conclusive data on the epidemiological gender dimension of NMPOU in Europe and the Mediterranean region [12]. Gender differences in NMPOU have been studied with regard to risk factors [8]. A longitudinal study performed on patients (N=610, 55% females) who used prescribed opioids for chronic non-cancer pain showed that women obtained a higher score than men on the Prescription Drug Use Questionnaires, suggesting that women are at greater risk to misuse opioids. Opioid abusing women with chronic pain reported more psychiatric comorbidity than men [25], being NMPOU in female subjects closely related to psychological distress and stressful life experiences [26]. Some differences between genders were also found in characteristics of abuse history: interestingly, the known telescoping effect (faster progression from initiation to development of drug dependence) among women [27] has been referred also to prescription opioids [28].

Notably, both pharmacological and non-pharmacological factors are involved in the acquisition and maintenance of drug abuse and dependence. To date, gender differences in pharmacological response to substance of abuse are scarcely investigated and only few clinical studies on opioid pain relievers' drug abuse include gender as a variable. Increasing knowledge of pharmacological aspects (both pharmacokinetics and pharmacodynamics) of opioid drugs with relevance to female and male differences may give an essential contribution for a better understanding of factors that influence opioid pain relievers abuse among women.

2. Aim of the study

This study aims to supply a specific focus on women data through a selective summary of the literature analyzing gender differences in pharmacokinetics and pharmacodynamics of the most abused prescription opioid drugs oxycodone and hydrocodone.

3. Method

We reviewed the literature and searched for published articles and their citations related to women and to gender differences in opioids pharmacokinetics and pharmacodynamics. The MEDLINE database was examined from 1995 to 2015, using PubMed. The review also considers publications and other documents from federal offices, government agencies, and professional societies.

Main key words used were: prescription drugs; oxycodone; hydrocodone; opioids; pharmacology; pharmacokinetics; pharmacodynamics; gender/gender difference; individually and variously paired.

4. Oxycodone

OXY is a semisynthetic μ -opioid receptor agonist, structurally and pharmacologically similar to morphine. Data from a very recent Cochrane review [29] assessing OXY efficacy and tolerability as pain reliever for patients with cancer pain provide evidence that OXY (and also morphine) can be used as first line

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