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Comparison of Tertiary Drug Information Resources With the CDC Guideline for Oxycodone Dosing: Are Patients at Risk?

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Research Report

Comparison of Tertiary Drug Information Resources With the CDC Guideline for Oxycodone Dosing: Are Patients at Risk?

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Abstract

Background: Inappropriate prescribing of opioids is thought to play a central role in the ongoing opioid health crisis. Tertiary information resources are commonly used by clinicians for obtaining opioid dosing information. To assist health care providers in pain management, the Centers for Disease Control and Prevention (CDC) developed a guideline for prescribing opioids. **Objective:** To identify discrepancies for dosing information on oxycodone between commonly used tertiary drug information resources and the CDC Guideline. **Methods:** Searches of the tertiary drug information resources were conducted in the following order: Facts and Comparisons, Lexicomp, Medscape, and Micromedex. The term "oxycodone" was entered in the search box in the tertiary resources' applications. Drug information items retrieved were organized in tabular format. In the Google Chrome version 106.0.5249.119 search box, the term "CDC guideline for opioid dosing" was entered to retrieve current information on the CDC Guideline. **Results:** Searches produced drug information on oxycodone for available formulations, dosing regimens, recommended dosing, and maximum daily dose (MDD). Searches revealed discrepancies in dosing recommendations for oxycodone among tertiary drug resources and between tertiary drug resources and the CDC Guideline. **Conclusions:** When considering maximum daily dosing information for oxycodone from the selected tertiary drug information resources, the potential exists for patients to be at risk of addiction, overdose, and perhaps death. Improving the way opioids are prescribed through the CDC Clinical Practice Guideline can ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse or overdose from inappropriate dosing information.

Keywords

opioids, oxycodone, Centers for Disease Control and Prevention (CDC), tertiary drug information, CDC guideline, substance abuse

Background

In the United States, misuse and abuse of prescription opioids poses a serious health threat as rates of addiction, overdoses, and deaths continue unabated.[1] Evidence suggests that the current opioid crisis began in the mid-1990s, when the powerful agent OxyContin, the brand-name drug for oxycodone controlled-release, was approved by the Food and Drug Administration (FDA) and promoted by the pharmaceutical company Purdue Pharma.[2] This precipitated the initial surge of overdoses and deaths linked to the use of legal prescription opioids.[3] Currently, inappropriate and excessive prescribing of opioids by health care providers is thought to play a central role in the ongoing health crisis.[4]

For clinicians seeking drug information, 3 types of information sources exist in the biomedical literature: primary, secondary, and tertiary resources.[5] Tertiary sources offer a summary or restatement of facts and research from both primary and secondary sources and often are available via online access as electronically searchable online applications.[5]

Tertiary drug information resources play a prominent role in everyday clinical practice. Clinicians routinely rely on tertiary drug information resources to affirm knowledge

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or proactively verify the safety and efficacy of medications. Tertiary resources are commonly used by health care providers to locate information on drug dosing, drug interactions, and available commercial products.[6]

It has been reported that primary care providers may lack sufficient training in the prescribing of opioids.[7] To assist health care providers in pain management, the Centers for Disease Control and Prevention (CDC) developed and published a guideline for prescribing opioids for pain management.[8] The CDC Guideline provides recommendations for the prescribing of opioid pain medication for patients 18 years and older in primary care settings.

The objective of this study was to identify discrepancies between the dosing information from commonly used tertiary drug information resources and the CDC Guideline for oxycodone. If such discrepancy exists, this suggests that patients may be at risk from inappropriate dosing of oxycodone.

Tertiary Resource Selection

To determine tertiary resource inclusion in the analysis, our focus was to assess the comprehensive databases that are most commonly used in a clinical decision support role by health care professionals. Drug information resources commonly used by pharmacists were identified from the medical literature and include Facts and Comparisons, Lexicomp, Micromedex, and Medscape.[9,10]

Sample Selection—Oxycodone

The narcotic analgesic oxycodone was targeted in this investigation due to reports in the medical literature of the highest abuse potential for immediate-release (IR) oral formulations of the drug.[11] In addition, oxycodone has been reported to be one of the most common drugs involved in prescription opioid overdose deaths.[12] Furthermore, oxycodone has demonstrated high abuse liability on the basis of its high "likability" or pleasurable subjective effects and relative lack of negative subjective effects.[13]

Methods

Oxycodone Dosage Forms/Search Terms

For the study, the term "oxycodone" was used for database searches. In addition, the dosage forms of oxycodone were identified by 2 drug references and served as search terms for the tertiary drug resources.[14,15] Dosage forms include oral solution (liquid), concentrated oral solution, tablet, capsule, extended-release (ER)/long-acting tablet (OxyContin), and as an ER capsule (Xtampza ER) to be taken by mouth.

Access of Tertiary Sources

The tertiary sources selected for this report were accessible at our academic institution. Institutional members are able to subscribe for access to Facts and Comparisons,[16] Lexicomp,[17] and Micromedex.[18] These resources are licensed for use by current students, faculty, and staff with university credentials. For users to access the drug information services offered by Medscape, content is available free of charge. Users register for a free account by visiting Medscape.com and submitting the completed registration materials.[19]

Data Collection and Keyword Searches

Searches of the tertiary drug information resources were conducted in the following order: Facts and Comparisons, Lexicomp, Medscape, and Micromedex. The process for obtaining dosing information for oxycodone primarily involved keyword searches.

A search box graphical element was present in the tertiary sources' applications. It served as the field for a query input or search term from the user to search and retrieve drug-related information from the database. For the drug information retrieval, a search box appeared as a single-line text box accompanied by a search button that initiates the search command. The 4 tertiary sources were presented in similar styles and formats, with modest stylistic and functional differences.

Facts and Comparisons

From the opening screen, the generic drug name "oxycodone" was entered in the search box, the search button was selected, and the system's search logic mapped the search term to an available monograph page, which was subsequently displayed. After performing the search, the results were presented from all available content sets that have a match to the search performed. To view the monograph for oxycodone within the content set, the hyperlinked drug name displayed was selected.

Lexicomp

Searches were initiated from the home page. The key word "oxycodone" was entered in the search box and the search icon clicked on. To assist with searching, a possible keyword list appeared after at least 2 characters were entered. When the term "oxycodone" was selected, the system automatically performed a search and displayed the results. To view the monograph on oxycodone within the content set, the hyperlinked drug name displayed was selected.

Medscape

The process for document retrieval involved entering the search term "oxycodone" in the text box, then clicking the "Perform Search" button. As described on Medscape's browser page, the Medscape search engine will default to a Freetext search, and Medscape's search engine interprets the search and determines how best to query its databases. The Medscape search engine searches through the listings in the database(s) to find the documents that closely match the request. Over 7100 monographs are provided for prescription and over-the-counter drugs, as well as for corresponding brand-name drugs, herbals, and supplements. The search term "oxycodone" brings up the dosing information.

Micromedex

At the IBM Micromedex home page, the user is presented with a keyword search box where the term "oxycodone" was entered. The next step reveals the term "Dosing oxycodone" where when confirmed, the Dosing/Administration drug monograph for oxycodone is presented. The "Search Micromedex" search box is available on every page in Micromedex Solutions, the proprietary name for the drug information resource.

Data Organization

Information items retrieved by the searches were organized in tabular format. Sections were created for each individual drug search. Each section was further populated by the corresponding drug name, available formulations, and initial dosage in each tertiary source in the following order: Facts and Comparisons, Lexicomp, Medscape, and Micromedex. Maximum dosage for each tertiary source is indicated along with relevant information. If any conversion factors or titrations were listed for the medications, that information was noted within the table in either the "Initial" or "Maximum" dosage section.

CDC Information on Oxycodone

Internet searches were conducted with the search engine Google Chrome on Windows, version 106.0.5249.119. In the search box, the term "CDC guideline for opioid dosing" was entered to retrieve the most recent information on the CDC Guideline.

For uniformity in reporting, the oxycodone dosages identified in the project were converted to morphine milligram equivalents (MMEs). An MME is defined as "the equivalent amount of milligrams of morphine that an opioid dose is equal to when prescribed."[20] Calculating MME accounts for differences in opioid drug type and strength. MMEs were calculated using the medical reference, MDCalc.[21]

When considering the dosing ranges, the maximum daily dose (MDD) was specifically noted.[22] MDD is defined as "the highest amount of allowable drug or medicine for a patient with consistent safety."

Results

Searches of the tertiary drug information resources produced drug information on oxycodone for available formulations, dosing regimens and recommended dosing, and MDD, expressed in milligrams (mg) and MME. The searches reveal discrepancies in dosing recommendations for oxycodone among tertiary drug resources and between tertiary drug resources and the CDC Guideline (Table 1.)

The CDC Guideline does not provide specific dosing parameters for the individual opioid medications but offers general recommendations for safe dosing.[8]

Per the CDC Guideline, dosing recommendations are summarized as follows:

1. Start with the lowest effect dose of IR opioid medications prior to ER when treating chronic pain and slowly increase the dose.
2. Use caution when exceeding 50 MME per day as these doses have demonstrated a minimal improvement in pain intensity with higher risks of use associated.
3. 50 MME per day is 33 mg of oxycodone (~2 tablets of oxycodone sustained-release 15 mg)
4. 5-10 MME per dose (~5 mg) or 20-30 MME/day (~15-20 mg/day) is a recommended maximum dosage for opioid-naive patients.
5. 2016 Guideline recommends to limit acute treatment with 7 or less days of opioid therapy[23]; no recommendation on time frame with the 2022 Guideline.

For comparison purposes, 50 MME was used as a baseline to distinguish oxycodone dosing levels between the CDC Guideline and the tertiary drug resources. The tertiary resources present oxycodone dosing recommendations as a range (ie, lowest initial dose to highest recommended dose) and dosing frequency and schedule per 24-hour period.

For IR dosing of oxycodone, Lexicomp dosing information was compatible with the 50 MME CDC Guideline for initial dosing. However, for Facts and Comparisons, the oxycodone dosing information exceeded the CDC Guideline by 180% for initial dosing of the upper dosage limit of the dosage range. For Medscape and Micromedex, the oxycodone dosing information exceeded the CDC Guideline by 270% for initial dosing of the upper dosage limit of the dosage range.

For oxycodone ER oral capsule and tablet formulations, dosing information was compatible with the CDC Guideline for initial dosing for all 4 tertiary drug resources. However,

Table 1. Comparison of Dosing Recommendations for Various Oxycodone Formulations.

Oxycodone				
	IR formulation	ER capsules[a]	ER tablet[a]	Oxycodone/APAP
Facts and comparisons				
Initial acute pain	5 mg q4-6h (30-45 MME/day) or 5-10 mg q4-6h[b] (30-90 MME/day)	—	—	5 mg (moderate pain) or 10-20 mg (severe pain) q4-6h[b] (30-180 MME/day) or 2.5-10 mg q4-6h[b] (15-90 MME/day)
Initial chronic pain	2.5-10 mg q4-6h[b] (15-90 MME/day)	Dose conversions recommended	Dose conversions recommended	
Maximum	—	288 mg/day[b] (432 MME/day)	—	4 g per day of APAP[c]
Lexicomp				
Initial acute pain	5 mg q4-6h (30-45 MME/day) or 5-10mg q4-6h[b] (30-90 MME/day)	—	—	5 mg (moderate pain) or 10-20 mg (severe pain) q4-6 h[b] (30-180 MME/day) Or 2.5-10 mg q4-6h[b] (15-90 MME/day)
Initial chronic pain	2.5-10 mg q4-6h[b] (15-90 MME/day)	Dose conversions recommended	Dose conversions recommended	—
Maximum	—	288 mg/day[b] (432 MME/day)	—	4 g per day of APAP[c]
Medscape				
Opioid naïve acute pain	5-15 mg q4-6h[b] (30-135 MME/day)	—	—	2.5 mg 1-2 tablets q6h (15-30 MME/day) or 5-10 mg 1 tablet q6h[b] (30-60 MME/day)
Opioid-tolerant acute pain	10-30 mg q4-6h[b] (60-270 MME/day)	—	—	
Initial chronic pain	—	9 mg q12h (27 MME/day)	10 mg q12h (30 MME/day)	
Maximum	—	—	—	4 g per day of APAP[c]
Micromedex				
Initial acute pain	5-15 mg q4-6h[b] (30-135 MME/day)	—	—	2.5-10mg q6h (15-60 MME/day)
Initial chronic pain	—	9 mg q12h (27 MME/day)	10 mg q12h (30 MME/day)	
Maximum	—	288 mg/day[b] (432 MME/day)	—	4g/day of APAP[c] and 60mg/day for oxycodone component (90 MME/day)

Maximum dosing recommendations provided by the various drug information references were found to display the most discrepancies when compared with the CDC recommendations for maximum morphine milliequivalents per day (MME/day). The combination product of oxycodone/APAP, however, was found to have initial dosing recommendations exceeding the maximum MME/day cutoff; this potential diversion was found to occur only with the Facts and Comparisons and Lexicomp references. Initial dosing recommendations for the IR formulations of oxycodone, per the Medscape and Micromedex references, were found to potentially exceed the maximum MME/day recommendations while other drug references cited dosing within the CDC limits.

Abbreviations: APAP, acetaminophen; ER, extended-release; IR, immediate-release; H, hour; MME/day, morphine milligram equivalents per day.

[a]Recommended for opioid tolerant patients only.

[b]Dosing regimen potentially exceeding CDC recommended max of 50 MME/day. IR formulation: 270% above max at highest dosing recommendation (Medscape and Micromedex recommendations only). ER capsule max: 864% above max at highest dosing recommendation. Combination oxycodone/APAP: 360% above max at highest dosing recommendation (Lexicomp and Facts & Comparisons recommendations only).

[c]Based on APAP component of combination product.

the maximum daily dosage for oxycodone exceeded the CDC Guideline for Facts and Comparisons, Lexicomp, and Micromedex by 864%. This information was not provided by Medscape.

Oxycodone/Acetaminophen

The tertiary resources provided information on combination dosing of oxycodone with acetaminophen (APAP) as an adjunct analgesic drug for IR formulation. The oxycodone and ibuprofen combination product as well as the oxycodone and acetaminophen (APAP) ER product have been discontinued in the United States.[24,25]

Oxycodone and acetaminophen (APAP) IR is available as a tablet and oral solution. Facts and Comparisons and Lexicomp made a distinction between dosing for moderate pain and severe pain, with higher dosing recommendations for severe pain. According to these tertiary resources, for severe pain, the combination dosing recommendation for the oxycodone component exceeded the CDC Guideline by 360%. For Medscape and Micromedex, the dosing recommendations for the oxycodone component of the oxycodone/APAP combination exceeded the CDC Guideline for the high end of the dosing range by 180% above maximum.

Justification for Safety Concerns

This study revealed that for the selected tertiary drug resources, when considering the dosing intervals and maximum daily dosages at which oxycodone may be administered, the potential exists for patients to be at higher risk of overdose, addiction, and perhaps even death.

According to the former principal deputy director of the of the Centers for Disease Control and Prevention Dr. Anne Schuchat,

> the amount of opioids prescribed in the U.S. is still too high, with too many opioid prescriptions for too many days at too high a dosage. Healthcare providers have an important role in offering safer and more effective pain management while reducing risks of opioid addiction and overdose.[26]

The 2022 CDC Clinical Practice Guideline provides recommendations for clinicians prescribing opioids for pain care.[8] The 2022 CDC Guideline provides an update of the 2016 CDC Opioid Prescribing Guideline[23] to provide evidence-based recommendations for prescribing opioid pain medication for acute, subacute, and chronic pain for outpatients aged ≥ 18 years. (Excluded is pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care.)

According to the recent CDC Guideline, "the lowest starting dose for opioid-naïve patients is often equivalent to a single dose of approximately 5–10 MME or a daily dosage of 20–30 MME/day." As described in the tertiary resources, the initial dosing recommendations for IR formulations of oxycodone exceed the CDC Guideline recommendation.

Regarding higher dosing of opioids, according to the recent CDC Guideline,

> many patients do not experience benefit in pain or function from increasing opioid dosages to ≥50 MME/day but are exposed to progressive increases in risk as dosage increases. . . additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits for pain and function relative to risks to patients as dosage increases further.

In addition, the CDC Guideline asserts,

> benefits of high-dose opioids for pain are not well established. Few trials evaluated opioid dosages of ≥90 MME/day. Opioid dosages of 50–90 MME/day were associated with a minimally greater (below the threshold for small) improvement in mean pain intensity compared with dosages of <50 MME/day.

> Stated more directly regarding health risks, "higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven't been shown to reduce pain over the long term."[27]

Furthermore, higher dosages also carry an increased risk for addiction. In a petition by a group of health care professionals to the U.S. Food and Drug Administration, it is asserted "A person taking a relatively low dose of prescribed opioids is 15 times as likely to develop an opioid use disorder (OUD) as a person who has not been prescribed opioids. At extremely high dosages of more than 120 MME a day, that risk soars to 122 times that of a person who has not taken an opioid.[28]

Additional evidence supports the health risks of higher dosing of opioids, notably oxycodone. As described in the 2022 CDC Guideline,

> four observational studies identified in the clinical evidence reviews consistently found an association between higher doses of long-term opioids and risk for overdose or overdose death. Opioid dosages for chronic pain of 50 to <100 MME/day in observational studies have been associated with increased risks for opioid overdose by factors of 1.9–4.6 compared with dosages of 1 to <20 MME/day, and dosages of ≥100 MME/day were found to be associated with increased risks for overdose 2.0–8.9 times the risk at 1 to <20 MME/day.

Moreover, as described in the CDC Guideline,

> when opioids are prescribed for acute pain, similar associations have been found, with dosages of 50 to <100 MME/day associated with 4.73 times the risk for overdose and dosages of ≥100 MME/day associated with 6.64 times the risk, compared with dosages of 1 to <20 MME/day.

Finally, from the 2022 CDC Guideline it is stated,

> In a national sample of Veterans Health Administration patients with chronic pain who were prescribed opioids, mean prescribed daily opioid dosage among patients who died from opioid overdose was 98 MME (median: 60 MME), compared with mean prescribed daily opioid dosage of 48 MME (median: 25 MME) among patients not experiencing fatal overdose.
>
> The 2022 CDC Guideline on opioid dosing maintains greater flexibility for clinical judgment in dosing decisions yet maintains cautionary advice on safety compared to the 2016 CDC Guideline. As stated in the current CDC Guideline,
>
> The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision-making. Risks of opioid use, including risk for overdose and overdose death, increase continuously with dosage, and there is no single dosage threshold below which risks are eliminated.[29]

Tertiary sources provide concise information on a medical topic because the information has been filtered by the author or editor resulting in a concise summary of the subject.[5] For busy practitioners, often these resources are convenient and can be easy to use, as well as being familiar to most practitioners. These references often may serve as an initial place to identify information, since they can provide a relatively complete overview of information available on a specific medical topic.

As tertiary resources include a variety of types such as textbooks, review articles in journals, and clinical guidelines, the focus of this report was on tertiary resources that are available via online access as electronically searchable online applications.

Conclusions

Drug dosing information for oxycodone is readily available from medical databases such as Facts and Comparisons, Lexicomp, Medscape, and Micromedex. Limitations exist for tertiary drug resources that indirectly support the objective of this study.

A reported major drawback is the lag time associated with updating information. It is understood that medical information changes very rapidly; consequently, it is possible that information may be outdated before publication. This appears to be the case with maximum daily dosage of oxycodone the tertiary drug resources in this study and the CDC Guideline. The tertiary drug resources require that information be reviewed and summarized resulting in an inherent delay in communicating new information.

In addition, it has also been reported that information in a tertiary resource may be incomplete, due either to space limitations of the resource or incomplete literature searches by the author. In this case, the absence of information potentially could expose patients to inappropriate doses of oxycodone. Tertiary drug information resources may not include sufficient detail on precautions as the case with the CDC Guideline. Other problems may include errors in transcription, human bias, incorrect interpretation of information, or a lack of expertise by authors.[30]

Clinicians may opt to use tertiary drug information resources to determine a proper dose for a patient and minimize any potential under/overdosing. However, when considering the CDC Guideline, discrepancies exist between the tertiary drug references identified in this study on oxycodone dosing recommendations, particularly regarding maximum daily dosages. Based on dosing values for oxycodone in the tertiary drug resources, doses at the higher range and shorter frequency potentially could put a patient at risk for addiction and overdose if administered for a prolonged period of time. Improving the way opioids are prescribed through the CDC Clinical Practice Guideline can ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse or overdose from these drugs.

Author Contributions

AE: substantially contributed to conception or design; contributed to acquisition, analysis, or interpretation of data; critically revised the manuscript for important intellectual content; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MAV: substantially contributed to conception or design; contributed to acquisition, analysis, or interpretation of data; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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