Caveat emptor: Erroneous safety information about opioids in online drug-information compendia

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ABSTRACT

Background: Healthcare professionals and consumers refer to online drug-information compendia (eg, Epocrates and WebMD) to learn about prescription medications, including opioid analgesics. With the significant risks associated with opioids, including abuse, misuse, and addiction, any of which can result in life-threatening overdose, it is important for those seeking information from online compendia to have access to current, accurate, and complete drug information to help support clinical treatment decisions. Although compendia are informative, readily available, and user friendly, studies have shown that they may contain errors.

Objective: To review and identify misinformation in drug summaries of online drug-information compendia for selected opioid analgesic products and submit content corrections to the respective editors.

Methods: Between 2011 and 2013, drug summaries for Purdue's prescription opioid analgesic products from seven leading online drug-information compendia were systematically reviewed, and the requests for corrections were retrospectively categorized and classified. At least 2 months following requests, the same compendia were then reexamined to assess the degree of error resolution.

Results: A total of 859 errors were identified, with the greatest percentage in Safety and Patient Education categories. Across the seven compendia, the complete or partial resolution of errors was 34 percent; therefore, nearly two thirds of the identified errors remain.

Conclusion: The results of this analysis, consistent with past studies, demonstrate that online drug-information compendia may contain inaccurate information. Healthcare professionals and consumers must be informed of potential misinformation so they may consider using multiple resources to obtain accurate and current drug information, thereby helping to ensure safer use of prescription medications, such as opioids.
use prescription opioid analgesics only as instructed by their healthcare professional (HCP). This recommendation presumes that prescribers are relying upon current, accurate, and complete information to make clinical decisions about which drug products to prescribe and how to counsel patients and caregivers.

Among the sources of drug information upon which HCPs and consumers rely are online drug-information compendia (ODIC), due to accessibility, ease of searching, and the presumption that they provide reliable information about specific drug products. ODIC are available as Web sites or, increasingly, as applications (apps), due to the shift toward greater use of handheld devices. As of 2015, it has been estimated that 500 million smartphone users worldwide are using a healthcare app, and by 2018, nearly one half of over 3.4 billion handheld-device users will have downloaded a healthcare app. Recent surveys among HCPs, including physicians and pharmacists, reported that over 45 percent use a smartphone to access drug information. Importantly, 33 percent of nearly 3,000 physicians surveyed reported making prescribing decisions based on information obtained by smartphone. There has been a commensurate increase in consumers accessing prescription drug information online (23 percent in 2011 vs 35 percent in 2013). ODIC Web sites may be comprehensive, while their associated apps’ content may be abbreviated (eg, Micromedex Drug Information) or comprehensive (eg, Lexi-Drugs), both of which can serve as a valuable resource to support decision making by HCPs and consumers. However, previous studies have identified errors of omission, factual errors, incomplete content, and minimization of drug safety information within various drug-information resources, including textbooks, Web sites, and apps. As ODIC are not regulated by the federal Food and Drug Administration (FDA), potential risks related to patient safety, as well as user liability and medicolegal consequences, should be considered by those who rely solely on ODIC for drug information.

While a number of initiatives have been introduced in an attempt to minimize the risks associated with opioid analgesics, the details of which are beyond the scope of this article, safe opioid analgesic prescribing requires HCPs to have access to the most current information to assist in weighing potential benefits against known risks. In an effort to ensure consistent product information and enhance the safe and appropriate use of extended-release and long-acting (ER/LA) opioid analgesics, the FDA required each ER/LA opioid analgesic’s Full Prescribing Information (FPI) be updated with safety-related changes in April 2014. A safety-related update to any product’s FPI that is mandated by FDA should signal editors and content providers for ODIC to revise their drug information. Given that this entire subclass of opioids underwent simultaneous safety updates because of concerns about adverse consequences of use, misuse, and abuse, it is reasonable to expect ODIC to be motivated to incorporate the changes in a timely manner.

The Purdue Pharma L.P. (Purdue) Medical Services (medical information) Department, which is responsible for providing complete and unbiased product-specific drug information, recognized the need for a routine review of drug summaries for its products within select ODIC. A standardized process was implemented in accordance with the FDA draft Guidance for Industry-Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices. The intent of the process was to identify misinformation and inform third parties (ie, parties other than FDA and a drug sponsor) of errors in third-party publications concerning a sponsor’s prescription drug products.

The overall goal of this effort is to ensure HCPs, especially, and consumers (including patients and caregivers) have complete, accurate, and current information upon which to base decisions. The approach described in this article to achieving the goal included review of drug information for select Purdue opioid analgesics in well-known ODIC, identification and categorization of errors, submission of content-correction requests, and tracking fulfillment of those requests.

**METHODS**

ODIC were identified by a combination of statistics on mobile app usage by HCPs, a literature search on the use and evaluation of electronic drug-information resources, and familiarity of resources to pharmacists within Purdue Medical Services. For the purpose of this project, a compendium was considered to be a comprehensive, indexed listing of FDA-approved drugs and biologicals containing a summary of pharmacologic characteristics, as well
as information on recommended uses and dosing.30 Only ODIC containing drug summaries specific to Purdue’s opioid products were examined. The ODIC reviewed contained information in one of two forms: by drug product (eg, OxyContin [oxycodone hydrochloride] extended-release tablets) or by drug substance (eg, oxycodone hydrochloride).31 For summaries by drug substance, only content identifiable as relating to one of Purdue’s opioid analgesics (eg, oxycodone hydrochloride, extended-release) was evaluated. If ODIC met these criteria, the comprehensive online version (ie, Web site or database) was then reviewed using a standardized process.

**Brief overview of the drug summary review and content-correction submissions**

Purdue pharmacists with expertise in drug information independently compared material referencing the FPI within the ODIC to the respective product FPI. While all material referencing the FPI was evaluated, the reviewer(s) paid particular attention to safety information, such as warnings, precautions, adverse reactions, and drug interactions, as the products of interest are all opioid analgesics. Misinformation that could lead to deviations in appropriate clinical care or impact treatment decisions was also evaluated. Other than that, off-label information, where present, was not reviewed as part of this project. When available, patient education material was compared to Section 17 (Patient Counseling Information) of the product’s FPI, Instructions for Use, and the Medication Guide.32

Following review of drug summaries within a compendium, Purdue proposed corrections to the ODIC that were factual, nonpromotional, and supported by the FPI. A standardized tabular format was developed to ensure uniformity and clarity in communicating identified misinformation and content-correction requests to compendia editors. For each compendium, the table containing the misinformation was cross checked by another pharmacist. It then underwent review by Medical Services’ senior product managers, a pain physician with clinical and regulatory expertise in opioid analgesics, and an in-house drug-regulatory attorney. The submissions containing requests for corrections were e-mailed to either the editor or the content provider for the ODIC. Complete details of this standardized compendia review process have been outlined in a previous publication.26

**Evaluation of the errors and the implementation of requested corrections by ODIC**

The tables submitted to ODIC were retrospectively evaluated by the same pharmacists to categorize and classify the types of identified misinformation. Errors were categorized according to a relevant topic based on the FPI or a general descriptive theme. For instance, “Safety” was used as a broad category that encompassed the following FPI sections: Boxed Warning; Contraindications; Warnings and Precautions; Adverse Reactions; Drug Interactions; Compatibility; and Overdosage. The broad category “Abuse Potential” included these subcategories: Misuse, Abuse, and Addiction; Tolerance/Physical Dependence; Controlled Substance Schedule; Addiction versus Physical Dependence; Withdrawal Syndrome; and Risk Evaluation and Mitigation Strategy.

Errors within each subcategory were then classified as:

- **Omitted**: Information from a section or subsection of the FPI was entirely missing.
- **Incomplete**: Some information from relevant FPI section was provided, but it was not materially complete.
- **Inaccurate**: Information provided was inconsistent with the FPI.
- **Other**: Misinformation that cannot be classified per the categories above.

Misinformation within each request was analyzed by groupings and categories and then totaled for errors. Examples of how this analytical process was applied include:

- **Example 1**: If a drug summary had specific adverse events (AEs) missing (incomplete), that was scored as one “Safety” error, regardless of the number of missing AEs. However, if any incidences of AEs were also incorrect (inaccurate), that was scored as another “Safety” error. For example, a drug summary that did not list seven AEs and also listed incorrect incidences for five AEs would be scored as containing two “Safety” errors: one AE, incomplete and one AE, inaccurate.
• Example 2: If a specific warning or precaution was either missing (omitted), lacked relevant information (incomplete), or was inconsistent with the FPI (inaccurate), this was scored as one “Safety” error.

• Example 3: Misinformation that could not be classified as omitted, incomplete, or inaccurate was also scored as an error (other). Examples include lack of distinction among drug products with the same active ingredient (e.g., immediate-release vs extended-release formulations or intravenous vs oral dosage forms), referencing an outdated FPI, and lack of identifying off-label information as such.

After at least 2 months following the submission of a request for correction, drug summaries within each compendium were reexamined to determine whether content-correction requests had been implemented by the ODIC. Re-examination was performed by comparing the standardized table for each submission to the compendium’s current drug summary. Any disagreements among the Purdue pharmacists relating to the degree of fulfillment of content-correction requests were resolved by consensus.

The degree of correction was assessed and classified using the following terms:

• Resolved: Complete correction of the identified content.

• Partially Resolved: Content correction was made in part, but error still remains.

• Unresolved: Content correction was not made.

RESULTS

Ten ODIC were identified, of which seven met the inclusion criteria. The initial evaluation of each compendium occurred between the fourth quarter of 2011 and the end of the third quarter of 2013. The ODIC evaluated were: Epocrates; Facts & Comparisons: A to Z Drug Facts; Gold Standard: Clinical Pharmacology; MedlinePlus; Medscape Reference; UpToDate; and WebMD. Of these compendia, five contained summaries based on drug substances and two had summaries by drug product. Five compendia were aimed at HCPs, whereas two targeted consumers. Depending on when the review was conducted, up to eight opioid analgesics were included in the evaluation of a compendium (three ER/LA, three immediate release, and two injectable). The number of products reviewed depended on (1) which products a compendium chose to include and (2) whether an included product was commercially available at the time of review (i.e., a product no longer available from the manufacturer but included in a drug summary was not reviewed).

Identified misinformation

Across the seven ODIC reviewed, 859 errors were identified and categorized as shown in Table 1. Categories containing ≥10 percent of the identified errors included Safety (30 percent) and Patient Education (15 percent). Twenty percent of errors were classified as omitted, 29 percent as incomplete, and 20 percent as inaccurate. The remaining 31 percent were classified as other.

Examples of misinformation relating to Butrans (buprenorphine) Transdermal System CIII; Dilaudid (hydromorphone hydrochloride) Tablets, Oral Liquid, and Injection CII; Dilaudid-HP Injection (hydromorphone hydrochloride) CII; MS Contin (morphine sulfate extended-release tablets) CII; and OxyContin (oxycodone hydrochloride) extended-release tablets CII are presented in Table 2.

Implementation of corrections

The resolution status (i.e., Resolved, Partially Resolved, and Unresolved) of the total errors is shown in Table 3. Only 28 percent of the identified errors were resolved (Figure 1).

Remaining errors

Across the seven ODIC reviewed, 568 errors remain unresolved. These were classified as omitted (19.9 percent), incomplete (27.8 percent), inaccurate (18.3 percent), and other (34.0 percent). Categories containing ≥10 percent of unresolved errors included Safety (28 percent), Patient Education (16 percent), Abuse Potential (11 percent), and Technical Information (10 percent) as shown in Figure 1.

DISCUSSION

The standardized process designed and implemented to identify misinformation about drug
### Table 1. Summary of errors across compendia

<table>
<thead>
<tr>
<th>Categories of errors</th>
<th>Subcategories of errors</th>
<th>Number of errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications and usage</td>
<td>Indications and usage; limitations of use</td>
<td>28</td>
</tr>
<tr>
<td>Dosage and administration</td>
<td>General dosing considerations; opioid-naive dosing; dosing frequency; conversion; titration; cessation; administration/application</td>
<td>64</td>
</tr>
<tr>
<td>Safety</td>
<td>Boxed warning; contraindications; warnings and precautions; adverse reactions; drug-drug interaction; compatibility; overdosage</td>
<td>255</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Mechanism of action; pharmacokinetics</td>
<td>63</td>
</tr>
<tr>
<td>Technical information</td>
<td>Listing discontinued products/strengths; misuse of trademarked name; reference to other brand/manufacturer/distributor/generic; dosage strength; storage; disposal; ingredient/formulation; Purdue product omitted from monograph; lack distinction</td>
<td>79</td>
</tr>
<tr>
<td>Abuse potential</td>
<td>Controlled substance: misuse, abuse, addiction; tolerance/physical dependence; controlled substance schedule; addiction versus physical dependence; withdrawal syndrome; risk evaluation mitigation strategy</td>
<td>78</td>
</tr>
<tr>
<td>Reference support</td>
<td>Missing references to support statements; incorrect reference used; referencing outdated FPI</td>
<td>50</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Improper description of formulation; product images</td>
<td>18</td>
</tr>
<tr>
<td>Off-label information</td>
<td>Missing acknowledgment/clarification when information is off-label</td>
<td>30</td>
</tr>
<tr>
<td>Special patient populations</td>
<td>Safety and dosing/administration related to renal, hepatic, geriatric, pregnancy, labor and delivery, lactation, neonatal withdrawal syndrome</td>
<td>63</td>
</tr>
<tr>
<td>Patient education</td>
<td></td>
<td>131</td>
</tr>
<tr>
<td>Total number of errors</td>
<td></td>
<td>859</td>
</tr>
</tbody>
</table>

### Table 2. Examples of misinformation

<table>
<thead>
<tr>
<th>Error classification</th>
<th>Category and subcategory of error</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omitted</td>
<td>Safety, Drug-Drug Interaction</td>
<td>The drug-interaction information for OxyContin and drugs affecting the Cytochrome P450 isoenzyme system was omitted</td>
</tr>
<tr>
<td></td>
<td>Safety, Boxed Warning</td>
<td>Boxed Warning for Dilaudid Oral Liquid and Tablets is missing</td>
</tr>
<tr>
<td></td>
<td>Dosing and Administration, Dosing Frequency</td>
<td>The dosing frequency for MS Contin is missing</td>
</tr>
<tr>
<td></td>
<td>Safety, Warnings and Precautions</td>
<td>The warning related to the use of OxyContin in elderly, cachectic, and debilitated patients was incomplete, as the recommendation to closely monitor such patients was missing</td>
</tr>
<tr>
<td></td>
<td>Dosing and Administration, Administration/Application</td>
<td>Add “side of chest” as an application site for Butrans, as only three of four recommended sites are listed</td>
</tr>
<tr>
<td></td>
<td>Special Patient Populations, Hepatic</td>
<td>Warning on hepatotoxicity is present for Butrans, however, monitoring parameters are missing</td>
</tr>
<tr>
<td>Inaccurate</td>
<td>Safety, Contraindications</td>
<td>Opioid nontolerance applies to Dilaudid-HP only as Dilaudid Injection can be administered in opioid-naive patients</td>
</tr>
<tr>
<td></td>
<td>Pharmacology, Pharmacokinetics</td>
<td>Delete reference to “active prodrug” as oxycodone is not a prodrug</td>
</tr>
<tr>
<td></td>
<td>Safety, Drug-Drug Interaction</td>
<td>CYP3A4 inducers (not inhibitors) may lead to decreased oxycodone efficacy or withdrawal in opioid-dependent patients</td>
</tr>
</tbody>
</table>
products presented in ODIC yielded 859 errors, compared to information in the product FPIs among seven popular ODIC. Only 34 percent were corrected in response to a table that: (1) restated the error, (2) provided the relevant language from the FPI documenting that it was an error and not merely a difference of opinion, and (3) suggested corrective language. While this indicates some willingness on the part of content providers/editors of ODIC, the remaining misinformation about opioid analgesics is very concerning, as these resources are increasingly employed during clinical decision making. HCPs who prescribe, dispense, or administer opioid analgesics should be cautious about relying solely upon these unregulated drug information tools.

The federal government's official repository of current versions of all FDA-approved FPIs is the National Library of Medicine's DailyMed, which makes FPIs available by both proprietary product names and drug substances.33 Drugs@FDA is another useful resource, containing more information about a product than its FPI, such as approval history.34 Further, most pharmaceutical companies have current versions of their products’ FPIs online and many also have a medical information department staffed with specially trained HCPs who can provide nonpromotional and balanced drug information upon request.

Some potential limitations of this project’s approach should be considered when interpreting the results herein. All the products included in the review of compendia are opioid analgesics, which contain controlled substances; therefore, these results may not be generalizable to other drug classes. It is unknown if ODIC update certain drug classes more frequently than others, which could result in differing numbers of errors for nonopioid drugs.

Inconsistencies between information in a compendium and a product’s FPI were identified by pharmacists knowledgeable of the product’s FPI.

<table>
<thead>
<tr>
<th>Error classification</th>
<th>Fulfillment of content-correction requests</th>
<th>Number of errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omitted</td>
<td>Resolved</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Partially Resolved</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Unresolved</td>
<td>113</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Resolved</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Partially Resolved</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Unresolved</td>
<td>158</td>
</tr>
<tr>
<td>Inaccurate</td>
<td>Resolved</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Partially Resolved</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Unresolved</td>
<td>104</td>
</tr>
<tr>
<td>Other*</td>
<td>Resolved</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Partially Resolved</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Unresolved</td>
<td>193</td>
</tr>
</tbody>
</table>

*Errors that were not classified as inaccurate, incomplete, or omitted. Examples include: errors in areas such as off-label information, reference support, and miscellaneous.
content, instead of using a document-compare feature in a word-processing program. This may have introduced selection bias, as well as human error. To mitigate these, all drug summaries on a particular product were reviewed by the same pharmacist(s) and any discrepancies were resolved by consensus. During each compendium review, pharmacists were mindful of the detail and specificity of the drug summaries, the compendium's intended audience (HCPs vs consumers), and that third-party drug summaries are not expected to be an exact duplication of a product’s FPI. Following the pharmacists’ review, each table was reviewed by a pain physician with years of experience in the clinical management of opioid-analgesic therapy to ensure the misinformation identified, and proposed content-correction requests were material and clinically relevant.

The overall number of errors could have been impacted by specific factors. First, drug summaries were of varying quality and level of detail; therefore, ODIC with more comprehensive drug summaries may have been associated with a greater number of errors. Conversely, ODIC with briefer summaries could omit more safety information. Additionally, with a focus on safety and abuse potential, certain categories may have yielded a greater percentage of errors as a result of this somewhat targeted approach. Further, some product entries in ODIC appeared to have referenced outdated product FPIs, contributing to a number of errors. By utilizing and maintaining consistency with the most current version of the FPI, errors related to on-label information in ODIC could be reduced. Last, the scoring method may have impacted the total number of errors as it was not validated; however, it was consistently used across the seven compendia.

It cannot be confirmed with certainty that updates made to ODIC drug summaries were a direct result of Purdue’s submissions; however, it is likely given the association between the timing of submissions and implementation of some specific changes. Factors that may have influenced the errata rate include the time required by a compendium to update content, editorial policies about correction requests from pharmaceutical companies despite supporting FPI evidence, and space or format limitations of the ODIC.

The intent of this analysis was to evaluate ODIC as a source of drug information. Given the varying degree of clinical detail contained in the drug summaries reviewed across the ODIC and access differences across potential target audiences (ie, HCPs vs consumers), meaningful and representative compendium-to-compendium comparisons of identified misinformation cannot be made. Therefore, the identified errors across the seven ODIC are presented in totality rather than individually. HCPs, especially, and consumers should be cognizant that ODIC, in general, may not be accurate, up-to-date, or complete; therefore, utilization of more than one drug-information reference should be considered.

CONCLUSION

ODIC can be valuable to HCPs and consumers as they are readily available resources for user-friendly information on drug products, including opioid analgesics. Given the growing reliance upon drug summaries provided by ODIC and heightened safety concerns about opioids, it is essential that the information is correct, complete, and up-to-date. The use of inaccurate drug information may result in preventable patient harm, such as life-threatening overdose with opioids, as well as medicolegal consequences for HCPs, for healthcare institutions and systems, and for compendia themselves. Therefore, HCPs and consumers seeking reliable on-label drug product information should consult multiple sources, including a product’s FPI, which has been reviewed in detail and approved by the FDA.

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