Electronic Pharmacopoeia: A Missed Opportunity for Safe Opioid Prescribing Information?

Jeff Lapoint • Jeanmarie Perrone • Lewis S. Nelson

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Abstract Errors in prescribing of dangerous medications, such as extended release or long acting (ER/LA) opioid formulations, remain an important cause of patient harm. Prescribing errors often relate to the failure to note warnings regarding contraindications and drug interactions. Many prescribers utilize electronic pharmacopoeia (EP) to improve medication ordering. The purpose of this study is to assess the ability of commonly used apps to provide accurate safety information about the boxed warning for ER/LA opioids. We evaluated a convenience sample of six popular EP apps available for the iPhone and an online reference for the presence of relevant safety warnings. We accessed the dosing information for each of six ER/LA medications and assessed for the presence of an easily identifiable indication that a boxed warning was present, even if the warning itself was not provided. The prominence of precautionary drug information presented to the user was assessed for each app. Provided information was classified based on the presence of the warning in the ordering pathway, located separately but within the prescribers view, or available in a separate screen of the drug information but non-highlighted.

Each program provided a consistent level of warning information for each of the six ER/LA medications. Only 2/7 programs placed a warning in line with dosing information (level 1); 3/7 programs offered level 2 warning and 1/7 offered level 3 warning. One program made no mention of a boxed warning. Most EP apps isolate important safety warnings, and this represents a missed opportunity to improve prescribing practices.

Keywords Opioids • Medication safety • Prescribing • Pharmacopoeia • Boxed warning

“Be careful about reading health books. You may die of a misprint.”

- *Mark Twain* (1835–1910)

Morbidity and mortality resulting from prescription opioid use has reached epidemic proportions in the United States [1, 2]. Although diversion from appropriate use is the primary contributor, errors in therapeutic prescribing remain a consequential cause of unintentional opioid overdose, patient morbidity and mortality, and medicolegal liability [3]. Prescribing errors occur for many reasons, but many relate to the intricacies of using newly marketed opioids, including reformulations of existing medications and the need for attentiveness to contraindications and drug interactions [3, 4].

To aid in the prevention of prescribing errors, many physicians and health systems rely on the use of computerized prescription order entry programs (CPOE) that provide decision support [5]. While these programs are able to identify many aberrant orders and reduce medication errors, there are certain limitations that are shared with the legacy systems of handwritten orders. One major limitation is that an ill-conceived but correctly ordered medication (e.g., an order inappropriate for a given patient) will often pass all of the quality and interaction checking steps. This step of initiation of a drug order requires educated decision-making and is not

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J. Lapoint

Department of Emergency Medicine, Southern California
Permanente Medical Group, 4647 Zion Ave., San Diego,
CA 92122, USA

J. Perrone

Department of Emergency Medicine, Division of Medical
Toxicology, Perelman School of Medicine at the University of
Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19107, USA

L. S. Nelson (✉)

Department of Emergency Medicine, Director, Fellowship in
Medical Toxicology, New York University School of Medicine,
455 First Avenue, Room 123, New York, NY 10016, USA
e-mail: lewis.nelson@nyumc.org

yet readily checked by most CPOE systems. For this reason, prescribers rely on guidebooks, and increasingly electronic pharmacopoeia [6, 7], often utilized as prescribing aids in the format of a smart phone application (app). The popular reference app Epocrates claims use in some form by over 50 % of US physicians [8]. While these mobile applications allow physicians to carry a wealth of information in a convenient, rapidly accessible, and updatable package, design constraints such as screen size and user interface layout may result in separation and compartmentalization of important prescribing information and relevant warnings. Because errors in prescribing are the largest contributor to adverse medication events [3], pharmacopoeia, to be clinically valuable, should simultaneously meet the need to instantly access accurate dosing data as well as present the prescriber with warnings that support safe prescribing practices without compromising the overall accessibility of the application's user interface [9].

Opioids are high-risk medications, and errors related to their inappropriate use, particularly long-acting or extended release (LA/ER) formulations, are potentially serious. This class of medications is indicated for patients with chronic pain who are tolerant to opioids, which carry boxed warnings in their product labeling about their dangers in non-tolerant individuals. Although clinicians with specialized training or who routinely prescribe ER/LA opioids to their patients may be familiar with these boxed contraindications, those less accustomed to the use of this class of medications may not be aware [10]. Physicians prescribing what they incorrectly believed were appropriate formulations and doses of LA/ER opioids leading to significant patient morbidity, and death were highlighted as important root causes of opioid related deaths [11].

On this basis of several cases, we sought to evaluate whether existing warnings and safety data about opioid formulations were prominently displayed to prescribers when referencing prescribing information in electronic pharmacopoeia. An example case that was considered as the searches were done is included here:

A 27-year-old, non-opioid tolerant woman undergoes orthopedic hardware removal and returns to the ED the following day due to significant pain in the affected limb. Her only medication at the time was oxycodone/acetaminophen. After attaining pain relief by titration with intravenous morphine to a total dose of 30 mg over 2 h, the physician consults with a colleague who recommends the use of a long-acting version of oxycodone so that the patient would not need to return to the ED. The physician prescribes a 60-mg extended release oxycodone tablet twice daily following review of the drug in a smartphone app and discharges the patient. The patient is found dead in her bed at home 36 h later; the medical examiner rules the death an accident, a therapeutic complication due to oxycodone toxicity.

Methods

Based on available download and usage data [12], we choose six popular medication reference apps available for the iPhone and an online reference commonly used at our institution to evaluate for the presence of relevant drug warnings. Warning types were categorized using investigator-defined classification as follows: category 1—warnings are in line with dosing information, category 2—warnings are advertised but listed separately from dosing information, category 3—warnings are listed but are not advertised and listed in a separate section from dosing information, and category 4—no boxed warnings are present. Some contraindications or warnings may be present but are not advertised and are located in a separate section. The most recent version of each program was utilized (version noted in Table 1). Two investigators reviewed each program independently. We assessed for the presence of an easily identifiable (i.e., prominent) indication that a boxed warning was present, even if the warning itself was not provided verbatim. Using the aforementioned case as a template, we attempted to order each opioid formulation (Table 1). The prominence of precautionary drug information presented to the user was assessed for each app. Provided information was classified based on the presence of the warning in the ordering pathway, located separately but within the prescribers view, or available in a separate screen of the drug information, but non-highlighted. Following the independent classification, any disagreement among the investigators was arbitrated by the third investigator.

Results

Seven programs were evaluated for the presence of warning information in the dosing information of seven drugs by the two investigators. Agreement on classification was perfect, and there was no need for arbitration. Only 2/7 programs used made warning placement in line with dosing information, and 4/7 programs offered warning but placed them in separate sections from the dosing information. One program made no mention of boxed warning for any of the medications queried (Table 1).

Discussion

Drug reference apps are designed for ease of use in clinical settings. However, the isolation of important safety warnings for the sake of usability may increase the likelihood that a potentially dangerous prescription is provided to the patient. Furthermore, there was variability in the warnings offered. We found that most applications do not place warnings ahead of and on the same screen as prescribing information, a situation

Table 1 Status of the warnings presented by the electronic pharmacopoeia when attempting to reference a specific medication

Medication (brand example)	Pepid	Skyscape	Medscape	Epocrates	Micromedex	Tarascon	Up to date
Oxycodone CR (Oxycontin)	4	3	2	2	2	1	1
Fentanyl transdermal (Duragesic)	4	3	2	2	2	1	1
Morphine CR (MS Contin)	4	3	2	2	2	1	1
Methadone	4	3	2	2	2	1	1
Tapentadol (Nucynta)	4	3	2	2	2	1	1
Xymorphone ER (Opana)	4	3	2	2	2	1	1

Category 1—warnings are in line with dosing information. Category 2—warnings are advertised but listed separately from dosing information. Category 3—warnings are listed but are not advertised and listed in a separate section from dosing information. Category 4—no boxed warnings are present. Some contraindications or warnings may be present but are not advertised and are located in a separate section

CR controlled release, ER extended release, IR immediate release

[Program versions: Pepid EM Platinum Suite v 3.4; Skyscape Rx Drugs v 1.8.42; Medscape from WebMD v 4.3; Epocrates v 13.7; Micromedex Drug Information v 1.49; Tarascon Pharmacopoeia v 2.7.1_283; Uptodate, accessed July 12, 2013]

that may allow the prescriber to easily overlook such important material [13].

To the busy clinician with limited time and resources to devote to any individual task, prescribers rely on the convenience offered by electronic pharmacopoeia [14]. This media provides the opportunity to deliver timely, current, and accurate information at the time they are needed. Although printed pharmacopoeia do not always offer this type of warning, the expectation of clinical decision support from electronic versions may provide a false sense of safety by the absence of a warning.

It is well described that prescribers using electronic order entry systems often ignore relevant warnings [15], regardless of their importance. Drug safety alerts are overridden by clinicians in 49 % to 96 % of cases [13] and allergy alerts in 77 % [15]. Alert fatigue is a growing concern for CPOE, but the performance of warnings in electronic prescribing pharmacopoeia has not been studied. Since the context of these warning are different (e.g., looking for drug info in the pharmacopoeia vs ordering an already identified medication in the CPOE), the effectiveness of such warnings may be distinct. Regardless, it seems logical to provide significant safety information to prescribers and to highlight the most consequential warning. Boxed warnings, as with the prescription opioids, should require acknowledgement by the user.

We chose the ER/LA opioids because they are associated with therapeutic complications [16], have complicated dosing instructions, and carry a class-wide boxed warning. Interestingly, no mention was made in any of the programs about the recently introduced risk evaluation and mitigation strategies (REMS) for transdermal fentanyl [17].

The study is limited by having only two reviewers evaluate each program. However, the evaluation was objective involving the presence and position of prescribing warnings, and the reviewers were in agreement regarding the warning classification on all of the drug queries. Mobile applications are

updated frequently making our data applicable only to the versions sampled. However, during the drafting of this manuscript, several applications had no changes to the presence of dosing warning or how they were presented. Mobile applications were chosen based on popularity in the Apple iTunes App Store. In this sample, applications available for download at sites other than the iTunes App Store were not evaluated. While not every available mobile prescribing application was evaluated, our sample includes popular programs used by prescribers as drug reference guides. As the App Store is available worldwide, our results should be generalizable to areas outside the US although we did not directly assess this issue. We did not evaluate any printed reference source since the goal of the study was to evaluate the safety aspects of electronic pharmacopoeia.

In summary, the finding that multiple programs fail to prominently display drug safety information may be an impediment to safe prescribing of these potentially dangerous opioid medications and may represent a missed opportunity to improve prescribing practices.

Conflict of interest The authors have no financial conflicts of interest to report.

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