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EARLY SIGNS OF POTENTIAL ADVERSE DRUG REACTIONS: ARE THEY ROUTINELY FOUND IN APPROVED DRUG LABELING TO SUPPORT SAFE SELF-CARE?

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ABSTRACT

INTRODUCTION: Serious adverse reactions (ADRs) are associated with many drug products. As a corollary to the medical tenet first do no harm, the prevailing medical advice is for the patient or consumer to discontinue use of the medicine at the early signs or symptoms of a serious ADR. Most patient and consumers self-treat with medicines outside the physician's supervision or, in the case of nonprescription medicines, as part of their independent self-care. Hence, the question: is drug labeling for use by patients, consumers and practitioners adequately labeled with the symptoms associated with emergent serious ADRs? A case assessment study of the current labeling of commonly used prescription and nonprescription medicines was undertaken to answer this question.

METHODS: FDA approved labeling was obtained from the NIH resource labeling library DailyMed for prescription medicines, and from currently marketed carton labeling of nonprescription medicines. Listings of early signs and symptoms of serious conditions associated with the selected medicines were obtained from the Mayo Clinic Foundation online library. Serious diseases/conditions examined included drug-induced cataract, acetaminophen-induced liver injury, ibuprofen-induced drug allergy, prednisone-induced cataract, and vancomycin-induced nephrotoxicity. Matching of warnings in the Adverse Reaction, Precaution, and Patient Counseling or Patient Information sections of approved labels with the Mayo listings of emergent symptoms was done to determine deficiencies in the drug labeling for serious ADRs.

OBSERVATIONS: None of the selected examples of FDA approved labeling provided a full listing of the early-signs/symptoms of ADRs associated respectively with the selected medicines.

CONCLUSION: This case assessment study focused on four widely used Rx and OTC medicines, finding deficiencies in the presentation of approved patient and consumer information about early signs and symptoms of selected serious drug-induced adverse reactions, including cataract, drug allergy, nephrotoxicity, and liver disease.

Key words: Opinion Survey, Mobile Health Apps, Clinician Opinion, Medical Technology Utilization, Diabetes Self-Care.

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INTRODUCTION

Practice of medical care dictates that in the event of an emerging adverse drug reaction (ADR) the patient or consumer should immediately discontinue use of the medicine and, in cases of potentially serious ADRs, seek medical help right away. This current practice is an extension of the medical adage, first do no harm. These principals raise the question: are patients and consumers supported by sufficient information in approved drug labeling so that they would be prompted to discontinue a medicine when early symptoms of a potentially serious ADR appear?

The answer to this question is complicated by a number of factors, including: whether early signs and symptoms are actually in drug information targeted to patients and consumers; the self-awareness of the patient or consumer to an emergent ADR; potential confusion of early signs and symptoms of a serious ADR with other common non-serious conditions; whether that information is used by health practitioners when counseling patients about first-time and subsequent uses of the medicines; whether patients and consumers access and act on that information; health literacy of patients and consumers.

Hence, this is a complex question to answer, and one that has had detailed discussion among team members in medication therapy management services, managed by the first author, at the University of California San Francisco. It is essential to consider this issue in order to optimize the likelihood that a patient or consumer will adequately self-care when taking medicines, and receive early institutional treatment when needed.

For both patients and consumers, medications are mainly taken in self-care settings without supervision of healthcare professionals. As a result, approved drug labeling represents a critical safe-guard that helps ensure that the individual not only takes the right medicine for the right reason, at the right time and at the right dosage, but also discontinues the medicine as needed at the right time. This commentary focuses on the first factor mentioned above: does approved drug labeling contain early signs and symptoms of potentially serious ADRs?

For the patient and consumer, the drug information that is needed to respond to an emerging ADR is contained in government-approved labeling. For patients in the U.S., patient-oriented Rx drug information is found in Section 17 of the Full Prescribing Information (FPI), Patient Information Sheets, and Medication Guides. This information is supplemented by Retail Drug Monographs provided by pharmacies at the point of dispensing. For consumers using nonprescription medicines, it is the OTC Drug Facts Label (ODFL) that provides what is considered by the Food and Drug Administration (FDA) to be the essential information needed for safe and effective use of OTC medicines. However, whether it is a patient or consumer using a medicine, it is likely they are medicating in a self-care setting, where a physician is likely not available at the time of the emergence of a drug-induced adverse event. Hence, drug labeling is potentially the most accessible first line of defense in self-care of serious drug-induced side effects.

On this background we undertook a case study of two leading prescription and two leading nonprescription drug products which are marketed in the U.S. and associated causally with known ADRs, in order to assess the completeness of drug labeling in listing early signs and symptoms to serious diseases/conditions.

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METHODS

A review of selected Rx and OTC medicines was undertaken to assess whether current approved drug labeling lacks one or more generally-recognized early signs and symptoms of potentially serious ADRs. Approved drug labeling was defined as the FDA Full Prescribing Information for prescription medicines, and FDA approved OTC Drug Facts Label (ODFL) for nonprescription medicines.

In 2006, FDA published a rule changing the format of the package insert, or Full Prescribing Information (FPI)[1]. This included adding, among other things: a table of contents; a summary of essential information; as well as a special Section 17 entitled Patient Counseling which directs practitioners to share specific drug information with patients. For this article, we arbitrarily define the pre-rule FPI and post-rule FPI, noting here that FDA has yet to complete the process of changing all pre-rule FPIs to the post-rule content and format (see Discussion).

FDA approved labeling was accessed for prescription drugs through the National Institutes of Health (NIH) DailyMed website. According to NIH, DailyMed is the official provider of FDA label information (package inserts), and provides standard, comprehensive, up-to-date labeling found in medication package inserts. FDA approved labeling for non-prescription medicines was taken from labels in current U.S. distribution. Recommendations in the approved drug labels concerning ADRs of interest were compared to the Mayo Clinic disease information for determining the extent to which approved labeling contained early signs and symptoms of the potential serious ADR.

Serious ADRs were arbitrarily chosen as: cataract, liver injury, Stevens Johnson Syndrome and drug induced nephrotoxicity. Early signs and symptoms of these conditions were found in on-line resources of the Mayo Clinic Foundation (Table 1).

The criteria for selecting medicines for this study were: widely used by the U.S. public; known association of the active drug ingredient with one of the chosen diseases; and inclusion of the disease as an adverse drug reaction in the FDA approved label. The selected medicines/ADR combinations were: Acetaminophen with liver injury, Ibuprofen with drug allergy - specifically Stevens Johnson Syndrome, Prednisone with cataract and Vancomycin with nephrotoxicity.

OBSERVATIONS

Based on a comparison of the diagnostic information from the Mayo Clinic Foundation (Table 1) and all relevant excerpts from the FPI and ODFL drug information (Table 2), none of the selected case examples provided a full listing of early signs/symptoms.

The Acetaminophen ODL provides no early signs of drug-induced liver disease, such as nausea, vomiting, excessive sweating, severe abdominal pain, loss of appetite and yellowing of the skin.

The Ibuprofen ODFL lacks certain key elements of early drug allergy recognition, specifically including in relation to Steven's Johnson Syndrome: mouth sores, specific explanation of the phrase 'facial swelling', and the fact that drug allergy can manifest within hours to days post exposure, and even if the drug was used safely before[2].

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Table 1: Selected Excerpts from the Mayo Clinic On-line Compilation of Patient Health and Care Information

Disease/Condition	Early Signs and Symptoms^	When to Seek Medical Help Statements
Cataract[6]	• Clouded, blurred or dim vision • Increasing difficulty with vision at night • Sensitivity to light and glare • Seeing 'halos' around lights • Frequent changes in eyeglass or contact lens prescription • Fading or yellowing of colors • Double vision in a single eye	Make an appointment for an eye exam if you notice any changes in your vision. If you develop sudden vision changes, such as double vision or blurriness, see your doctor right away.
Liver Disease[7]	Signs and symptoms of liver disease include: • Skin and eyes that appear yellowish (jaundice) • Abdominal pain and swelling • Swelling in the legs and ankles • Itchy skin • Dark urine color • Pale stool color, or bloody or tar-colored stool • Chronic fatigue • Nausea or vomiting • Loss of appetite • Tendency to bruise easily	Make an appointment with your doctor if you have any persistent signs or symptoms that worry you. Seek immediate medical attention if you have abdominal pain that is so severe that you can't stay still.
Drug Allergy: Stevens Johnson Syndrome[8]	Stevens Johnson Syndrome symptoms include: • Facial swelling • Tongue swelling • Hives • Skin pain • A red or purple skin rash that spreads within hours to days • Blisters on your skin and the mucous membranes of your mouth, nose, eyes and genitals • Shedding of your skin If you have Stevens-Johnson syndrome, several days before the rash develops you may experience: • Fever • Sore mouth and throat • Fatigue • Cough • Burning eyes	Stevens-Johnson syndrome requires immediate medical attention. Seek emergency medical care if you experience any of the following signs or symptoms: • Unexplained widespread skin pain • Facial swelling • Blisters on your skin and mucous membranes • Hives • Tongue swelling • A red or purplish skin rash that spreads • Shedding of your skin
Drug-induced Nephrotoxicity[9]	Signs and symptoms of acute kidney failure may include: • Decreased urine output, although occasionally urine output remains normal • Fluid retention, causing swelling in your legs, ankles or feet • Drowsiness • Shortness of breath • Fatigue • Confusion • Nausea • Seizures or coma in severe cases • Chest pain or pressure	No statements provided.

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Table 2: Selected Current Label Information Pertaining to Selected Adverse Drug Reactions
[ODFL, OTC Drug Facts Label; FPI, Rx Full Prescribing Information]

Drug (Type of Label)	Information for Patients
Acetaminophen[10] (ODFL)	**Liver warning:** This product contains Acetaminophen. The maximum daily dose of this product is 6 caplets (3,000mg) in 24 hours. Severe liver damage may occur if you take: • more than 4,000mg in 24 hours • with other drugs containing Acetaminophen • 3 or more alcoholic drinks every day while using this product **Stop use and ask a doctor if** • pain gets worse or lasts more than 10 days • fever gets worse or lasts more than 3 days • new symptoms occur • redness or swelling is present These could be signs of a serious condition.
Ibuprofen[11] (ODFL)	**Allergy alert:** Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: • hives • facial swelling • asthma (wheezing) • shock • skin reddening • rash • blisters If an allergic reaction occurs, stop use and seek medical help right away.
Prednisone[12] (FPI)	**Information for Practitioners includes:** **Adverse Drug Reactions** ^ *Ophthalmic:* posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos. **Information for Patients** + Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay. ^ Note there is no Section 17 Patient Counseling for Prednisone products. + 'Information for Patients' is the last section under the major heading, 'Precautions'.
Vancomycin[13] (FPI)	**Information for Practitioners includes:** **Warnings and Precautions** 5.3 Nephrotoxicity: Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) has occurred following oral VANCOCIN therapy in randomized controlled clinical studies, and can occur either during or after completion of therapy. The risk of nephrotoxicity is increased in patients >65 years of age. **Adverse Reactions** Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) occurred in 5% of subjects treated with VANCOCIN. Nephrotoxicity following VANCOCIN typically first occurred within one week after completion of treatment (median day of onset was Day 16). Nephrotoxicity following VANCOCIN occurred in 6% of subjects >65 years of age and 3% of subjects ≤65 years of age **17. Patient Counseling Information**: Patients should be counseled that antibacterial drugs including VANCOCIN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When VANCOCIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by VANCOCIN or other antibacterial drugs in the future.

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Unique among the four case examples, Prednisone has patient information in the pre-rule FPI format. As a result, this information is not in Section 17 of the post-rule FPI format, but rather under the heading, Precautions. Nonetheless, there is no specific FDA approved patient counseling information on early signs and symptoms of cataract due to Prednisone, such as: clouded, blurred or dim vision; difficulty with night vision; light sensitivity, image distortion (halos), fading colors, and other early signs.

The Vancomycin FPI complies with the post-rule FDA regulations format (i.e., 17 sections with the last one pertaining to patient counseling). However, there is no information about early signs/symptoms of nephrotoxicity in the Patient Counseling section, despite specific advice to practitioners on vancomycin-induced nephrotoxicity.

DISCUSSION

This case study shows that leading Rx and OTC drug active ingredients lack key early warning information for patients and consumers to use in the event of the emergence of a potentially serious ADR.

OTC Acetaminophen labeling provides warnings about liver disease in several ODFL sections, but lacks specific early signs of emergent drug-induced liver disease. The Acetaminophen ODFL also provides a catch-all recommendation on a carton panel that is separate from the liver warning. This catch-all advises consumers to seek medical help for *any* new symptoms. However, this catch-all recommendation is non-specific and without context, and there is no information available to suggest that non-specific catch-all recommendations on labels are actually useful to consumers.

Ibuprofen has been the subject of a published study on the adequacy of the drug allergy alert (including Stevens Johnson Syndrome), in which the current label was shown to be inadequate[2]. In that study, the first author with a team at the University of California San Francisco applied elements of the FDA guidelines on label comprehension studies, which are often used to support Rx-to-OTC switch approvals, and demonstrated a relatively inexpensive way to obtain information quickly to address improvement to drug warnings[3]. The results showed that a large majority of consumers preferred a revised OTC Ibuprofen allergy alert with a more expansive list of information on emergent drug allergy signs, symptoms and timing versus the current less informative label.

The case study of the Prednisone FPI, which provides no early signs/symptoms of cataract, provides an example of the many drugs which do not have updated FDA patient counseling information (i.e., FPIs in the post-rule format with a Section 17 on Patient Counseling). Prednisone was introduced in 1955 by Schering, under the brand names Meticorten. As a generic, it has been used for more than 30 years in the U.S[4]. The FDA revision of the PFI implemented as a final rule was in 2006[5]. However, FDA has used a risk management perspective as its approach to implementation of many mediation policy decisions. As applied to improving FPIs, FDA's approach has focused on ensuring all new drugs approved after the regulatory compliance date have the newer post-rule FPI format, while allowing already approved older drugs to be updated retrospectively as needed. As a result, patient counseling information is sparse for Prednisone in the currently used pre-rule FPI. The potential significance is that the post-rule FPI Section 17 entitled 'Patient Counseling' is

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written in the grammatical imperative [i.e., 'The patient shall be informed….(insert warning, side effect etc.)...]'.Thus, the post-rule FPI Patient Counseling section places a burden on the health practitioner to choose to fulfill FDA's directive or not. If the health practitioner chooses not to counsel as FDA recommends, then the implication is that she/he should have a solid rationale not to do so. Hence, the currently used Prednisone pre-rule FPI is deficient in both early signs and symptoms of drug-induced cataract as well as the current U.S. approach to attempt to facilitate active patient counseling on Rx medicines.

The case study of Vancomycin raises several important issues. First, the information in the FPI addresses the link of Vancomycin to nephrotoxicity, but makes no mention in Section 17 Patient Counseling of early signs and symptoms, thereby creating a gap in self-care information during prescription drug therapy. Second, the Vancomycin FPI provides information to practitioners but not patients about 'patient-related risk factors' including: age older than 60 years, underlying renal insufficiency, intravascular volume depletion, diabetes, and heart failure, among others. Practitioners are also apprised that nephrotoxicity 'can occur either during or after completion of therapy' with Vancomycin. An added point is that Vancomycin-induced nephrotoxicity is rare, being more likely to affect patients who are on a high dose, are older, or may have altered gut absorption. These issues raise a core question about what information patients should receive about emergent symptoms of drug-induced toxicity. Knowing the early signs/symptoms of an ADR, whether or not you as the patient are in a higher risk group at increased risk for this rare ADR, and that the ADR may occur either during or after completion of therapy is a logical association of facts for presentation in the FPI Section 17 of Vancomycin for use by practitioners in counseling patients.

We conclude that the potential revisions to current labels of the selected medicines assessed in this case study would be important to patients and consumers. If these revisions were also incorporated into Patient Counseling sections of FPIs, practitioners would be alerted as to the importance of counseling on early signs and symptoms of emergent ADRs.

Potential Limitations: This report is a case study assessment of four U.S. medicines in relation to a specific study question. As such the results apply to the four medicines and possibly to other drugs in their respective classes, since FDA often uses a class labeling approach. The extent to which the findings of these case studies relate to a broader selection of drugs requires further study. However, given that the four selected medicines are widely used in the US, and worldwide, it is reasonable to project that early signs and symptoms that are lacking from their labeling could affect many patients and consumers.

It is possible that some health practitioners will not agree with the early signs and symptoms defined by the information sources in this study. However, Mayo Clinic Foundation has a peer review process for all information posted to its website, and is widely regarded as a leading health institution in the U.S.

Finally, this study was not designed to address whether the appearance of early signs and symptoms on a drug label will actually have an impact of better outcomes, e.g. in recovery from serious ADRs. However, the general medical and regulatory consensus is that when a patient or consumer has a

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serious adverse reaction, it is medically prudent and necessary to remove the offending agent by discontinuation of therapy. There are many examples in FDA drug labeling that support this view, as evidenced for example by the standard phrase in ODFL labeling advising consumers who may be experiencing a drug-induced side effect to 'stop use and seek medical attention right away'.

CONCLUSION

Patient and consumer awareness of early signs and symptoms of drug-induced adverse reactions is generally considered to be important, as a matter of common medical sense. The earlier an emergent potential ADR is recognized, the earlier a patient or consumer may engage in in self-care by seeking medical help.

This case assessment study focused on four widely used Rx and OTC medicines, finding deficiencies in the presentation of approved patient and consumer information about early signs and symptoms of selected serious drug-induced adverse reactions, including cataract, drug allergy, nephrotoxicity, and liver disease.

Government agencies should consider encouraging sponsors responsible for drug development and regulatory lifecycle management of marketed drug products to more specifically address early signs and symptoms of emergent drug side effects in approved drug labeling. As needed, FDA should also encourage use of label comprehension studies to evaluate consumer preferences in the presentation and content of this type of information on both Rx and OTC drug products.

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