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Exploring the Potential for Using Drug Indications to Prevent Look-Alike and Sound-Alike Drug Errors

Exploring the Potential for Using Drug Indications to Prevent Look-Alike and Sound-Alike Drug Errors.

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Abstract

Background. Look-alike, sound-alike (LASA) drug names are a cause of medication errors with resulting patient harm and healthcare costs. This study assessed to which extent the use of the generic drug name, therapeutic class, health problem, and the U.S. Food and Drug Administration (FDA)-approved indications might be used to differentiate LASA drug pairs.

Research design and methods. We collected information about LASA drug pairs reported by the FDA to have look-alike sound-alike similarities. To assess potential for differentiating LASA drug pairs, we compared the following drug characteristics: generic name, therapeutic class, health problem, and FDA-approved indication.

Results. For the 33 FDA reported LASA drug pairs we identified a total of 432 FDA-approved indications. Using the generic name, therapeutic class, health problem and drug indication we were able to differentiate 8 (24.2%), 24 (72.7%), 25 (75.8%) and 26 (78.8%), respectively of the 33 LASA drug pairs. Using the generic name, therapeutic class, and health problem we were able to distinguish 31 (7.2%), 212 (49.1%), and 269 (62.3%), respectively of the 432 FDA-approved indications for the LASA drug pairs.

Conclusions. Including the FDA-approved indication in the drug prescription may be used to differentiate LASA drug pairs and thus, prevent wrong drug medication errors.

Key words: Drug safety; Drug errors; Look-Like Drugs, Sound-Like Drugs, FDA, Medication indications

Introduction

Medication errors occur at all stages in medication use including ordering, transcribing, dispensing, and administration.[1-3] A look-alike, sound-alike (LASA) error is the erroneous prescription, dispensing or delivery of a drug because the name of the drug is similar in appearance to or sounds like another drug.[4,5]

In 1973, Benjamin Teplitsky published the first list of look-alike or sound-alike drug (LASA) names.[6] The FDA has published lists of LASA generic and brand names[7,8] and newly FDA-identified LASA errors are subject to safety communications.[9,10] Since 2008, the Institute for Safe Medication Practices has also regularly published a list of LASA drug name pairs.[11] The United States (US) Pharmacopeia has identified 1,470 drugs involved in LASA errors.[12]

Systematic quantitative estimates of LASA incidents are lacking. LASA errors are often identified through spontaneous reporting, retrospective chart review, and computer triggers. [13] Prior research assessed LASA errors in a specific therapeutic area,[14,15] patient population [16-19] or healthcare setting.[16,20-23]

LASA errors are reported cause of medication errors threatening patient safety.[24-27] Errors due to LASA drugs may cause patients' harm and death.[16,19,28] It has been estimated that 1.4% of LASA drug errors result in adverse and harmful patient outcomes.[12] Additionally, LASA errors may also result in substantial healthcare costs.[27]

To our knowledge, no studies have assessed the potential to reduce LASA errors by using the U.S. Food and Drug Administration (FDA) approved drug indication to differentiate LASA drug pairs. Thus, the aim of this study was to assess to which extent the use of the generic drug name, therapeutic class, health problem, and FDA-approved indications may help differentiating LASA drug pairs.

Methods

We collected information about LASA drug pairs reported by the FDA to have look-alike sound-alike similarities available at the FDA Office of Generic Drugs Name Project [7] the Drug Products Associated with Medication Errors website [8] and two FDA safety communications.[9,10] The Anatomical Therapeutic Chemical (ATC) classification system therapeutic class for LASA drugs were extracted from the WHO Collaborating Centre for Drug Statistics Methodology.[29]

A complete list of indications for each drug was extracted from the latest available version of the FDA approved labels. The FDA label information was collected from the Labels@FDA and Drugs@FDA online databases.[30,31] The database Dailymed was searched as needed for labels not available at the FDA websites or for labels of drugs discontinued from the US market.[32] The indication information was extracted from the indications and usage section of the FDA label. This section provides a concise statement about the use of the drug for "the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition."[33] The indications and usage section may also include major limitations of use (e.g., use in particular subsets of the population, line of therapy status).

The health problem information was extracted from the FDA-labeled indication. The health problem was defined as the disease, condition, manifestation or symptom described in the indications and usage section of the label. The general concept of the health problem as defined in the FDA-approved label was used for the analysis. We also examined the most detailed concept of the health problem contained in the FDA-approved label. For example, cyclosporine is indicated for "the treatment of patients with severe active, rheumatoid arthritis where the disease has not adequately responded to methotrexate." In this case, we considered "arthritis" to be the general health problem, and "treatment of patients with severe active, rheumatoid arthritis" the most detailed health problem concept.

Table 1 provides an example of a LASA drug pair (i.e., daunorubicin citrate liposomal and doxorubicin liposomal) and illustrates how a side-by-side comparison of the drug characteristics may help differentiating two LASA drugs that have similar generic names.

Dunorubicin and doxorubicin cannot be differentiated using their therapeutic class or the general health problem. The detailed health problem may help in part to differentiate these two subtly different drugs and indications because while “AIDS-related Kaposi’s sarcoma” is a parent concept of “Advanced HIV-associated Kaposi's sarcoma” the FDA-approved indication differs in terms of the line of therapy and specifies that daunorubicin is the first line therapy for patients with advanced HIV-associated Kaposi's sarcoma.

Table 1. Example of Differences in the Characteristics of a Look-Alike/Sound-Alike Drug Pair

Generic name	**daunorubicin citrate liposomal**	**doxorubicin liposomal**
Therapeutic subgroup	Antineoplastic Agents	Antineoplastic Agents
General health problem	Kaposi’s sarcoma	Kaposi’s sarcoma
Detailed health problem	Advanced HIV-associated Kaposi's sarcoma	AIDS-related Kaposi’s sarcoma
Indication	First line cytotoxic therapy for advanced HIV-associated Kaposi's sarcoma. Not recommended in patients with less than advanced HIV-related Kaposi's sarcoma.	Treatment of AIDS-related Kaposi’s sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy.

We collected the indications for all routes, dosage forms, and strengths approved for the each drug to account for possible changes in indications depending on those drug characteristics. To assess differences among LASA drug pairs, we compared each of the following drug characteristics: generic name, therapeutic class, health problem, and FDA-approved indication. We also assessed differences among LASA drug pairs including all of the above characteristics as a bundle.

We assessed differences in the FDA-approved indications for each LASA drug pair to account for drugs that have multiple indications with different health problems or therapeutic class. We also assessed if the indications of each LASA drug pair were the same or different.

Data were descriptively assessed following a structured and standardized approach. A standardized data abstraction form, using a spreadsheet template in MS Excel, and a checklist were developed and utilized by the authors to assess differences in LASA drug pairs. The data abstraction form included the generic name, general and detailed health problems, and indications described in the FDA-approved drug label and the therapeutic subclass from the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification

System.[29] The data abstraction form also included characteristics of assessed drugs. Two authors abstracted information from the FDA approved-label independently. The results from the data abstraction were compared after completing the review of the labels. Discrepancies between authors were resolved by a third author retrieving the information from the drug label. Descriptive analyses were performed using MS Excel 2013.

Results

As of July 30, 2016, we collected information for 33 LASA drug pairs reported by the FDA. LASA drug pairs included 21 (31.8%) brand names and 45 (68.2%) generic names (Table 2). The LASA drug names included a total of 60 different active ingredients. An active ingredient may be included in more than one LASA drug pair; 6 single active ingredients (i.e., hydralazine, hydromorphone, hydroxyzine, methyltestosterone, tolbutamide, and topiramate) were each included in 2 LASA pairs. The therapeutic classes with the highest number of LASA drugs included nervous system (16 drugs, representing 24.2% of all LASA drugs), alimentary tract and metabolism (14, 21.2%), antineoplastic and immunomodulating agents (10, 15.2%), and cardiovascular system (9, 13.6%). There were 4 drugs (i.e., medroxyprogesterone acetate, methylprednisolone acetate, prednisolone, and prednisone) with codes in 3 or more ATC anatomic classes.

LASA drug pairs included a total of 432 FDA-approved indications with a median of 2 indications per drug (range 1-77) (Table 3). Of the total 432 FDA-approved indications, 152 (35.2%) were the same indication for both drugs in the pair and 280 (64.8%) were different. There were 20 drugs (30.3% of all LASA drugs) with only 1 approved indication.

Two LASA drugs (acetohexamide and sulfisoxazole) were discontinued from the U.S. market as of July 31, 2016. In addition, there were changes in 2 brand names to differentiate LASA drugs -Levoxine changed to Levoxyl in 1994, and Omacor changed to Lovaza in 2007.

Using the generic name, therapeutic class, general health problem and drug indication we were able to differentiate 8 (24.2%), 24 (72.7%), 25 (75.8%) and 26 (78.8%), respectively of the 33 LASA drug pairs.

Table 2. United States Food and Drug Administration-Reported Look-Alike/Sound-Alike Drug Pairs that can be Differentiate Using Selected Drug Characteristics

Look-Alike/Sound-Alike Drug Pairs		Drug Characteristics Used to Differentiate Look-Alike/Sound-Alike Drug Pairs					
		Generic Name	Therapeutic Subgroup	General Health Problem	Detailed Health Problem	Indication	Total Differentiating Attributes
acetazolamide	acetohexamide	No	Yes	Yes	Yes	Yes	4
Amaryl* (glimepiride)	Reminyl* (galantamine hydrobromide)	Yes`	Yes	Yes	Yes	Yes	5
Amicar* (aminocaproic acid)	Omacor* (omega-3 acid ethyl esters)	Yes	Yes	Yes	Yes	Yes	5
bupropion	buspirone	No	Yes	Yes	Yes	Yes	4
chlorpromazine	chlorpropamide	No	Yes	Yes	Yes	Yes	4
clomiphene	clomipramine	No	Yes	Yes	Yes	Yes	4
cycloserine	cyclosporine	No	Yes	Yes	Yes	Yes	4
daunorubicin	doxorubicin	No	No	No	No	No	0
dimenhydrinate	diphenhydramine	No	Yes	Yes	Yes	Yes	4
dobutamine	dopamine	No	No	Yes	Yes	Yes	3
Durezol* (difluprednate)	Durasal* (salicylic acid)	Yes	Yes	Yes	Yes	Yes	5
Flomax* (tamsulosin hydrochloride)	Volmax* (albuterol sulfate)	Yes	Yes	Yes	Yes	Yes	5
glipizide	glyburide	No	No	No	No	No	0
hydralazine	hydromorphone	No	Yes	Yes	Yes	Yes	4
hydralazine	hydroxyzine	No	Yes	Yes	Yes	Yes	4
hydromorphone	hydroxyzine	No	Yes	Yes	Yes	Yes	4
Kaletra* (lopinavir; ritonavir)	Keppra* (levetiracetam)	Yes	Yes	Yes	Yes	Yes	5
Lanoxin* (digoxin)	Levoxine* (levothyroxine sodium)	Yes	Yes	Yes	Yes	Yes	5

*Brand name

Look-Alike/Sound-Alike Drug Pairs		Drug Characteristics Used to Differentiate Look-Alike/Sound-Alike Drug Pairs					
		Generic Name	**Therapeutic Subgroup**	**General Health Problem**	**Detailed Health Problem**	**Indication**	**Total Differentiating Attributes**
Maalox Total Relief* (aluminum hydroxide; magnesium hydroxide; simethicone)	Maalox liquid products* (bismuth subsalicylate)	Yes	No	Yes	Yes	Yes	4
medroxyprogesterone	methyltestosterone	No	No	Yes	Yes	Yes	3
methadone	Metadate* (methylphenidate hydrochloride)	No	Yes	Yes	Yes	Yes	4
methylprednisolone acetate	methyltestosterone	No	Yes	Yes	Yes	Yes	4
mitoxantrone	methotrexate	No	No	No	Yes	Yes	2
nicardipine hydrochloride	nifedipine	No	Yes	Yes	Yes	Yes	4
prednisolone	prednisone	No	No	No	No	No	0
risperidone	ropinirole	No	Yes	Yes	Yes	Yes	4
sulfadiazine	sulfisoxazole	No	No	No	No	No	0
Taxol* (paclitaxel)	Taxotere* (docetaxel)	No	No	No	No	No	0
tolazamide	tolbutamide	No	No	No	No	No	0
tolbutamide	topiramate	No	Yes	Yes	Yes	Yes	4
Topamax* (topiramate)	Toprol-Xl* (metoprolol succinate)	Yes	Yes	Yes	Yes	Yes	5
vinblastine	vincristine	No	No	No	No	No	0
Zantac* (ranitidine hydrochloride)	Zyrtec* (cetirizine hydrochloride)	No	Yes	Yes	Yes	Yes	4

*Brand name. Note: “Yes” identifies a dug characteristic that differentiates the LASA drug pair. “No” identifies a drug characteristic that does not differentiate the LASA drug pair.

Table 3. Indications of the Food and Drug Administration-Reported Look-Alike/Sound-Alike Drug Pairs that are Possible to Differentiate Using Selected Drug Characteristics

Look-Alike/Sound-Alike Drug Pairs	# of FDA Approved Indications	Drug Characteristics Used to Differentiate Look-Alike/Sound-Alike Drug Pairs Indications				
		Generic Name	Therapeutic Subgroup	General Health Problem	Detailed Health Problem	Indication
acetazolamide	4	0	4	4	4	4
acetohexamide	1	0	1	1	1	1
Amicar* (aminocaproic acid)	1	1	1	1	1	1
Omacor* (omega-3 acid ethyl esters)	1	1	1	1	1	1
bupropion	3	0	3	3	3	3
buspirone	2	0	2	2	2	2
chlorpromazine	10	0	10	10	10	10
chlorpropamide	1	0	1	1	1	1
clomiphene	1	0	1	1	1	1
clomipramine	1	0	1	1	1	1
cycloserine	3	0	3	3	3	3
cyclosporine	6	0	6	6	6	6
daunorubicin	3	0	0	0	0	1
doxorubicin	18	0	0	15	15	16
dimenhydrinate	2	0	2	2	2	2
diphenhydramine	2	0	2	2	2	2
dobutamine	1	0	0	1	1	1
dopamine	3	0	0	3	3	3
Durezol* (difluprednate)	2	2	2	2	2	2
Durasal* (salicylic acid)	1	1	1	1	1	1
Flomax* (tamsulosin hydrochloride)	1	1	1	1	1	1

	# of FDA Approved Indications	Drug Characteristics Used to Differentiate Look-Alike/Sound-Alike Drug Pairs Indications				
		Generic Name	Therapeutic Subgroup	General Health Problem	Detailed Health Problem	Indication
Volmax* (albuterol sulfate)	1	1	1	1	1	1
glipizide	1	0	0	0	0	0
glyburide	1	0	0	0	0	0
hydralazine	2	0	2	2	2	2
hydromorphone	2	0	2	2	2	2
hydralazine	2	0	2	2	2	2
hydroxyzine	14	0	14	14	14	14
hydromorphone	1	0	1	1	1	1
hydroxyzine	14	0	14	14	14	14
Kaletra* (lopinavir; ritonavir)	1	1	1	1	1	1
Keppra* (levetiracetam)	3	3	3	3	3	3
Lanoxin* (digoxin)	2	2	2	2	2	2
Levoxine* (levothyroxine sodium)	3	3	3	3	3	3
Maalox Total Relief* (aluminum hydroxide; magnesium hydroxide; simethicone)	2	2	0	2	2	2
Maalox liquid products* (bismuth subsalicylate)	2	2	0	2	2	2
medroxyprogesterone	6	0	0	6	6	6
methyltestosterone	2	0	0	2	2	2
methadone	2	0	2	2	2	2
Metadate* (methylphenidate hydrochloride)	2	0	2	2	2	2
methylprednisolone acetate	59	0	59	59	59	59
methyltestosterone	2	0	2	2	2	2
mitoxantrone	3	0	0	2	3	3
methotrexate	12	0	0	10	12	12
nicardipine hydrochloride	1	0	1	1	1	1

Look-Alike/Sound-Alike Drug Pairs	# of FDA Approved Indications	Drug Characteristics Used to Differentiate Look-Alike/Sound-Alike Drug Pairs Indications				
		Generic Name	Therapeutic Subgroup	General Health Problem	Detailed Health Problem	Indication
nifedipine	2	0	2	2	2	2
prednisolone	59	0	0	1	1	1
prednisone	77	0	0	15	18	18
Amaryl* (glimepiride)	1	1	1	1	1	1
Reminyl* (galantamine hydrobromide)	1	1	1	1	1	1
risperidone	3	0	3	3	3	3
ropinirole	3	0	3	3	3	3
sulfadiazine	12	0	0	1	1	1
sulfisoxazole	10	0	0	0	0	0
Taxol* (paclitaxel)	5	0	0	2	4	4
Taxotere* (docetaxel)	6	0	0	4	5	5
tolazamide	1	0	0	0	0	0
tolbutamide	1	0	0	0	0	0
tolbutamide	1	0	1	1	1	1
topiramate	5	0	5	5	5	5
Topamax* (topiramate)	5	5	5	5	5	5
Toprol-Xl* (metoprolol succinate)	4	4	4	4	4	4
vinblastine	11	0	0	9	9	9
vincristine	7	0	0	5	5	5
Zantac* (ranitidine hydrochloride)	8	0	8	8	8	8
Zyrtec* (cetirizine hydrochloride)	3	0	3	3	3	3

*Brand name

In addition, using the most detailed health problem alone, defined in the FDA-approved drug label, we were able to differentiate the same number of LASA drug pairs as using the drug indication (26; 78.8%). Using all of the assessed drug characteristics (i.e., generic name, therapeutic class, general and detailed health problem, and indication) as a bundle we managed to differentiate the same number of LASA drug pairs and FDA-approved indications as using the FDA-approved indication alone.

Likewise, using the generic name, therapeutic class and general health problem we differentiated 31 (7.2%), 212 (49.1%), and 269 (62.3%), respectively of the 432 FDA-approved indications for the 33 LASA drug pairs assessed in this study. Using only the most detailed health problem we differentiated the same number of LASA drug pair indications that were identified using the FDA-approved indication with the exception of 2 indications in the LASA pair daunorubicin/ doxorubicin that differ in FDA-recommended line of therapy.

The FDA may approve the same indication for several drugs. There were 7 (21.2%) LASA drug pairs (daunorubicin/doxorubicin, glipizide/ glyburide, prednisolone/prednisone, sulfadiazine/sulfisoxazole, Taxol/Taxotere, tolazamide/ tolbutamide, and vinblastine/ vincristine) that had a total of 152 (35.2%) FDA-approved indications that we could not differentiate using the drug characteristics assessed in this study (i.e. generic name, therapeutic class, general and detailed health problem, and indication).

Discussion

The indication, or purpose of a drug, is an essential component of the information needed for appropriate drug selection, prescribing, and utilization. The drug indication is the link between the patient's health problem and a specific drug being prescribed to a patient. This study provides evidence that including the FDA-approved drug indication in the prescription may be used to differentiate two-thirds of the LASA drugs pairs and thus, it has the potential to identify and prevent LASA errors and harm.

LASA drug errors are a cause of medication errors in the US and may result in significant patients' harm and health care costs. Evaluating the true incidence of LASA errors and its related

outcomes remains a challenge due to poor reporting, differences in definitions of medication errors, fear of litigation, inability to determine causality, and cost.

Several strategies have been proposed to reduce LASA medication errors including the use of Tall Man lettering,[22,34] computerized provider order medication entry with (or without) electronic prescription transmission, medication reconciliation processes, barcode systems, and package changes.[1,35,36] Additional proposed measures include enhancing labeling for injectable medications that have similar appearing packaging, including security symbols, putting special labels on packaging of high-risk drugs, and revising processes for selecting, maintaining and updating the list of LASA drugs.[26]

The FDA has published guidance intended to assist the industry in the selection of drug names for new medications as well as in the submission of safety aspects related with a proposed proprietary name to reduce medication errors.[37] Better pre-approval testing of drug names to reduce the number of confusing LASA drug pairs has also been proposed.[38] Proactive assessment of potential medication errors includes evaluation of potential look-alike packaging problems in addition to the drug names.[25] Harmonization of standards in international regulatory legislation has been also suggested.[39] The Joint Commission National Patient Safety Goals (NPSG) for 2005 required accredited organizations to identify and, at a minimum, annually review the list of LASA drugs and to proactively implement safety strategies to help prevent LASA drug related errors.[40] In 2010, the LASA NPSG was included as one of the Joint Commission Medication Management standards. [41]

In clinical practice, including the FDA-approved indication in the prescription might serve as a distinguishing feature to highlight and alert members of the health care team of a discrepancy between what would otherwise appear to be similar LASA drug pairs and thus, potentially prevent LASA drug errors. Other information, beyond the indication, adds little to the ability to differentiate drug LASA pairs. In cases where the LASA pair involves a brand name, the generic name may be used to differentiate the drugs. It is for this reason that many have urged use of the generic drug names rather than brand names for enhanced safety to avoid LASA errors[42] -there are fewer generic names than brand names and generic names usually refer to

the chemical class. In addition, generic prescribing reduces the amount of information included in the prescription label improving clarity of the prescription.

The patient's health problems currently can be found in the electronic health record (EHR), [43] although pharmacists often do not have direct access to the patient's EHR. Linking each drug to a specific health problem for which the drug is being prescribed may be used to differentiate LASA drug pairs. Including the health problem in the prescription would represent a step towards providing better information for clinicians, patients and caregivers. The FDA-approved indication provides even further refinement with its more detailed information that could potentially differentiate more subtly different LASA drug pairs. The FDA-approved indication for example states if the drug is for treatment, prevention or palliation. The FDA-approved indication may also contain information regarding limitations of use related to patients' demographic characteristics, disease stage, and line of therapy that is often not included in the patient's problem list [44] that could serve as a more specific flag for a potential misuse or LASA errors.

There were several LASA drug pairs that have the same FDA-approved indication and thus, could not be differentiated in clinical practice using the drug characteristics assessed in this study. Other drug characteristics such as warnings and precautions, contraindications, population subgroups, route of administration, dosage form, strength, and dose recommendation and frequency might also be useful to differentiate LASA drug pairs that have the same indication. In some cases, the drugs may be therapeutically interchangeable, suggesting an erroneous substitution would not have serious consequences as opposed to other LASA pairs with completely different indications.

There is growing consensus that including the indication in the prescription is desirable and feasible given emerging capabilities of electronic prescribing.[45] We have shown here one safety benefit that is both potentially powerful but also imperfect, since it could help differentiate most, but not all LASA. Some EHR and electronic prescribing systems are already capable of linking the drug with the health problem list, the indication and other drug characteristics but engineering the workflow to make this easier and accurate remains a current work in progress.[46] The use of the detailed health problem and the FDA-approved indication may be

too complex to differentiate LASA drug pairs without the use of electronic decision support systems. Health systems without fully integrated electronic decision support systems could still benefit from the use of the generic name, the therapeutic class and the general health problem to differentiate drug LASA pairs. For these clearly differentiated pairs inclusion of the indication would help pharmacists, other clinicians and patients more easily recognize and intercept LASA prescribing, dispensing and administration errors.

The increasing use of electronic prescribing may reduce LASA drug errors, but might also potentially contribute to LASA drug errors due to picklist errors (juxtaposition picking errors from drug dropdown lists). The use of the indication may also potentially reduce this type of LASA errors.

This study examined LASA drug pairs identified by the FDA and did not include indications not approved by the FDA (i.e. off-label indications). We elected to confine the scope of our study to approved labeled indications because we felt this would be a conservative approach for obtaining a valid set of established indications to cross reference with prescription indications. There is no inherent reason such a system could not be used for both labeled and off-labeled indications.[45] An important question for the present study is how this might impact on our conclusion that FDA approved indications could help flag LASA medication errors. We believe there is no fundamental reason given drugs general pharmacologic properties (e.g. antibiotics are generally not used off- label for hypertension) although we cannot exclude the possibility that in rare cases a broadened medication list could permit a lowered bar that could as a result, overlook a LASA drug pair. We could also envision a related positive byproduct that would potentially flag off-label uses, although we would want to be cautious about added alert/fatigue burden on prescribers.

Concerns regarding the additional prescriber's time and effort needed to specify the indication in the prescription and patient's privacy have not been assessed in this study. However there is growing capability to automate such linkages and thereby facilitate incorporating the indication into the drug prescription and prescribing workflow. The Health Insurance Portability and Accountability Act of 1996 and other current patient confidentiality and privacy regulations do not preclude against the inclusion of the indication in the prescription. However, a patient can

request not to include the indication in the prescription. More research is needed to empirically determine to which extent including the indication and other drug characteristics in the prescription prevent LASA drug errors in clinical practice.

Conclusions

Using the drug indication we were able to differentiate over three-fourths of assessed FDA identified LASA drug pairs. Including the FDA-approved indication in the drug prescription helps to differentiate LASA drug pairs and thus, may improve medication safety.

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References

1. Cohen MR. Medication Errors. 2nd ed. Washington, DC: American Pharmacists Association; 2007.
2. Barker KN, Flynn EA, Pepper GA, Bates DW, Mikeal RL. Medication errors observed in 36 health care facilities. Arch Intern Med. 2002;162:1897-1903.
3. Flynn EA, Barker KN, Carnahan BJ. National observational study of prescription dispensing accuracy and safety in 50 pharmacies. J Am Pharm Assoc. 2003;43(2):191-200.
4. Lambert BL, Lin SJ, Chang KY, Gandhi SK. Similarity as a risk factor in drug-name confusion errors: the look-alike (orthographic) and sound-alike (phonetic) model. Med Care. 1999;37:1214–1225.
5. Lambert BL, Chang KY, Lin SJ. Effect of orthographic and phonological similarity on false recognition of drug names. Soc Sci Med. 2001; 52:1843–1857.
6. Teplitsky B. Hazards of sound-alike, look-alike drug names. Calif Med. 1973;119(5):62.
7. U.S. Food and Drug Administration. Office of Generic Drugs Name Differentiation Project. Available at: https://www.fda.gov/Drugs/DrugSafety/MedicationErrors/ucm164587.htm Accessed April 4, 2017.
8. U.S. Food and Drug Administration. Drug Products Associated with Medication Errors. Available at: http://www.fda.gov/drugs/drugsafety/medicationerrors/ucm286522.htm. Page Last Updated: September 16, 2014. Accessed July 30, 2016.
9. U.S. Food and Drug Administration. Drug Name Confusion: Amicar and Omacor. FDA Patient Safety News: Show #49, March 2006. Available at: https://wayback.archive-it.org/7993/20170113073945/http://www.fda.gov/downloads/Safety/FDAPatientSafetyNews/UCM417829.pdf. Accessed April 4, 2017.
10. Ortho-McNeil Neurologics, Inc. Alert: Topamax® (topiramate) and Toprol-XL® (metoprolol succinate) Dispensing Errors. Dear Pharmacist Letter. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164876.pdf. Accessed July 30, 2016.

11. The Institute for Safe Medication Practices. FDA and ISMP Lists of Look-Alike Drug Names with Recommended Tall Man Letters. Available at: https://www.ismp.org/tools/tallmanletters.pdf. Accessed August 1, 2016
12. Hicks RW, Becker SC, Cousins DD, eds. (2008). MEDMARX data report. A report on the relationship of drug names and medication errors in response to the Institute of Medicine's call for action. Rockville, MD: Center for the Advancement of Patient Safety, US Pharmacopeia. Available at: http://www.labatecpharma.com/wp-content/uploads/2012/02/2008MEDMARX-DataReport.pdf. Accessed August 1, 2016
13. Galanter WL, Bryson ML, Falck S, et al. Indication alerts intercept drug name confusion errors during computerized entry of medication orders. PLoS One. 2014;9:e101977.
14. Kovacic L, Chambers C. Look-alike, sound-alike drugs in oncology. J Oncol Pharm Pract. 2011;17:104–18.
15. Schulmeister L. Look-alike, sound-alike oncology medications. Clin J Oncol Nurs. 2006;10(1):35-41.
16. Shaw KN, Lillis KA, Ruddy RM, Mahajan PV, Lichenstein R, Olsen CS, Chamberlain JM; Pediatric Emergency Care Applied Research Network. Reported medication events in a paediatric emergency research network: sharing to improve patient safety. Emerg Med J. 2013;30(10):815-9.
17. Bundy DG, Shore AD, Morlock LL, Miller MR. Pediatric vaccination errors: application of the "5 rights" framework to a national error reporting database. Vaccine. 2009;27(29):3890-6.
18. Basco WT Jr, Ebeling M, Hulsey TC, Simpson K. Using pharmacy data to screen for look-alike, sound-alike substitution errors in paediatric prescriptions. Acad Pediatr. 2010;10:233–7.
19. Sauberan JB, Dean LM, Fiedelak J, Abraham JA. Origins of and solutions for neonatal medication-dispensing errors. Am J Health Syst Pharm. 2010 Jan 1;67(1):49-57.
20. Varadarajan R, Barker KN, Flynn EA, Thomas RE. Comparison of two error-detection methods in a mail service pharmacy serving health facilities. J Am Pharm Assoc. 2008;48(3):371-8.
21. Friedman MM. Medication safety: look-alike/sound-alike drugs in home care. Home Healthc Nurse. 2005;23(4):243-53.
22. Zhong W, Feinstein JA, Patel NS, Dai D, Feudtner C. Tall Man lettering and potential prescription errors: a time series analysis of 42 children's hospitals in the USA over 9 years. BMJ Qual Saf. 2016;25(4):233-40.
23. Beso A, Franklin BD, Barber N. The frequency and potential causes of dispensing errors in a hospital pharmacy. Pharm World Sci, 2005. UK Study
24. Schnoor J, Rogalski C, Frontini R, Engelmann N, Heyde CE. Case report of a medication error by look-alike packaging: a classic surrogate marker of an unsafe system. Patient Saf Surg. 2015;9:12.
25. McCoy LK. Look-alike, sound-alike drugs review: include look-alike packaging as an additional safety check. Joint Comm J Qual Patient Saf 2005;31(1):47-53
26. Cohen MR. Maalox brand name extension causes; confusion near sight/sound dead hit! Omacor-Amicar; look- alike Tylenol packets. Hospital Pharm. 2006;41(1):13–6.
27. Berman A. Reducing medication errors through naming, labelling, and packaging. J Med Syst. 2004;28:9–29.
28. Tuohy N, Paparella S. Look-alike and sound-alike drugs: errors just waiting to happen. J Emerg Nurs. 2005;31:569–71.

29. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2016. Available at: http://www.whocc.no/atc_ddd_index/ Accessed June 30, 2016.
30. U.S. Food and Drug Administration. FDA Online Label Repository. Available at: http://labels.fda.gov.
31. U.S. Food and Drug Administration. Drugs@FDA. FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/
32. U.S. National Library of Medicine. DailyMed. Available at: https://dailymed.nlm.nih.gov/
33. 21CFR201.57(c)(2)1 Indications and usage.
34. Lambert BL, Schroeder SR, Galanter WL. Does Tall Man lettering prevent drug name confusion errors? Incomplete and conflicting evidence suggest need for definitive study. BMJ Qual Saf. 2016;25:4 213-217
35. Neuspiel DR, Taylor MM. Reducing the risk of harm from medication errors in children. Health Serv Insights. 2013;30(6):47-59.
36. Kondrak G, Dorr B. Automatic identification of confusable drug names. Artif Intell Med. 2006;36(1):29–42.
37. US Food and Drug Administration. Contents of a Complete Submission for the Evaluation of Proprietary Names. Guidance for Industry. Available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf. Accessed June 30, 2016.
38. Schroeder SR, Salomon MM, Galanter WL, Schiff GD, Vaida AJ, Gaunt MJ, Bryson ML, Rash C, Falck S, Lambert BL. Cognitive tests predict real-world errors: the relationship between drug name confusion rates in laboratory-based memory and perception tests and corresponding error rates in large pharmacy chains. BMJ Qual Saf. 2016 May 18. [Epub ahead of print].
39. Ciociano N, Bagnasco L. Look alike/sound alike drugs: a literature review on causes and solutions. Int J Clin Pharm. 2014;36(2):233-42.
40. 2005 Joint Commission National Patient Safety Goals: Practical Strategies and Helpful Solutions for Meeting These Goals. Goal 3: Improve the safety of using medications. Available at: http://teacherweb.com/NY/StBarnabas/Law-PublicPolicy/JCINT-2005.pdf. Accessed Aug 2, 2016
41. The Joint Commission. Look-alike/sound-alike drug list. January 5, 2011. Available at: https://www.jointcommission.org/lasa/ Accessed June 23, 2017
42. Collier J. The cases for and against prescribing generic drugs: generic prescribing benefits patients. BMJ, 1988;297:1596, 1598.
43. Slight SP, Berner ES, Galanter W, Huff S, Lambert BL, Lannon C, Lehmann CU, McCourt BJ, McNamara M, Menachemi N, Payne TH, Spooner SA, Schiff GD, Wang TY, Akincigil A, Crystal S, Fortmann SP, Bates DW. Meaningful Use of Electronic Health Records: Experiences from the Field and Future Opportunities. JMIR Med Inform. 2015;18;3(3):e30.
44. Alqahtani S, Seoane-Vazquez, Rodriguez-Monguio R, Eguale T. Priority review drugs approved by the FDA and the EMA: time for international regulatory harmonization of pharmaceuticals? Pharmacoepidemiol Drug Saf 2015;24(7):709-15.
45. Schiff G, Seoane-Vazquez E, Wright A. Incorporating indications into medication ordering: Time to enter the age of reason. NEJM. 2016;375(4):306-309.
46. Schiff GD, Hickman TT, Volk LA, Bates DW, Wright A. Computerized prescribing for safer medication ordering: still a work in progress. BMJ Qual Saf. 2016 May;25(5):315-9.