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Special considerations for proprietary name review: focus on products that may be prescribed “as directed”

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Abstract

Background—Look-alike and sound-alike (LASA) drug name similarity is often cited as a major factor contributing to wrong drug errors. When present on a prescription, differing product characteristics or directions for use may help healthcare professionals differentiate between two LASA drug names. However, evidence suggests that 1–5% of prescriptions include only the signa “use as directed” rather than explicit directions for use.

Methods—Using nationally projected U.S. outpatient physician survey data, we analyzed drug classes and their associated signa to identify products commonly prescribed with the signa “as directed”.

Results—The following categories of products are commonly associated with the signa “as directed”: 1) inhalers; 2) oral contraceptives; 3) one time treatments, such as those for lice or scabies; 4) pre-packaged items with specific directions for use on the package; 5) migraine medications; 6) erectile dysfunction medications; 7) bowel evacuation/colonoscopy preparations; 8) topical medications; 9) medications with regimens that may change frequently (e.g., warfarin, insulin); 10) otic products; 11) transdermal products; 12) products administered vaginally; 13) products administered rectally; and 14) products that may be titrated upon initiation.

Conclusions—Prescriptions for these products with the signa “as directed” may not include product characteristics or other directions for use. The potential for products to be prescribed with the signa “as directed” should be taken into consideration when evaluating the safety of proposed proprietary names. Sponsors and the FDA can utilize the results of our research to aid in the selection and review of proposed proprietary names, respectively.

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Keywords

proprietary name review; drug name confusion; medication error; signa; directions for use; wrong drug

BACKGROUND

Wrong drug errors are among the most common types of errors associated with the prescribing and dispensing phases of the medication use system.¹ According to one study's analysis of pharmacist liability claims, wrong drug claims accounted for 43.8% of the total closed claims from 2002–2011. The study cites failure to separate or otherwise distinguish among sound-alike drugs as the most common explanation for wrong drug dispensing errors.² While computerized prescriber order entry (CPOE) can eliminate some look-alike sound-alike (LASA) wrong drug errors related to verbal orders and illegible handwriting, CPOE may also contribute to wrong drug errors. Truncated names and dropdown menu adjacency errors can both contribute to CPOE-related wrong drug errors.^{3,4}

Among all wrong drug errors reported to Pennsylvania's mandatory Patient Safety Reporting Program, 34% have been attributed to drug name confusion.⁵ LASA drug name similarity has been cited as contributing to upwards of 25% of reported medication errors in the US.⁶ Drug name mix-ups can occur between two proprietary names, two nonproprietary names, or one proprietary and one nonproprietary name. This article defines the term *proprietary name* as the name owned by a company for describing its brand of a particular product; the proprietary name is sometimes referred to as the brand name or the trademark. The *nonproprietary name* is in the public domain and is sometimes referred to as the generic or established name. A 2008 review of over 26,000 errors reported to MEDMARX and the USP-ISMP Medication Errors Reporting Program identified 1,470 unique drugs implicated in medication errors due to drug names that may have looked and/or sounded alike. Of the reported names, 57% were proprietary names.⁷

As part of the Prescription Drug User Fee Act IV performance goals fiscal years 2008 through 2012, the U.S. Food and Drug Administration (FDA) committed to implementing various measures to help reduce medication errors related to LASA proprietary names.⁸ When evaluating the safety of a proposed proprietary name, FDA considers many potential sources for error, including phonetic (sound-alike), spelling, and orthographic (look-alike) similarities, as well as the role of product characteristics. Although differences in product characteristics often cannot mitigate the risk of a medication error for highly similar names (combined Phonetic Orthographic Computer Analysis [POCA]ⁱ score 70%). FDA reviews the strength and dose to determine whether sufficient differences exist to mitigate name confusion for moderately similar name pairs (combined POCA score 55% to 69%),⁹ different strengths and doses for products whose names are moderately similar may decrease

ⁱPOCA is a system designed by FDA. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonetic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

the risk of confusion. Conversely, moderately similar name pairs may have a higher potential for confusion if the products 1) have overlapping or similar strengths or doses, or 2) are available as a single strength where the strength may be omitted. The ability of other product characteristics (e.g., route, frequency) to mitigate name confusion may be limited when the strength and/or dose overlaps. These product characteristics are often elements included on a prescription or medication order and may help healthcare professionals differentiate between two drug names that look or sound similar.

Evidence suggests that product characteristics and directions for use are omitted on some prescriptions and replaced with the signa “as directed,” a practice that can contribute to wrong drug errors. The first study ever published that examined inadequately written prescriptions found that 4% of outpatient prescriptions were written “as directed.”¹⁰ Results of a recent survey suggest that this rate has remained unchanged over time, with the majority of respondents indicating that 1–5% of prescriptions contain the signa “use as directed.”¹¹ The Institute for Safe Medication Practices (ISMP) has published reports of drug mix-ups that have been attributed, at least in part, to medications being prescribed with the signa “use as directed.” Prior to the product being discontinued, prescriptions for the colonoscopy preparation drug Visicol written “take as directed” were inaccurately dispensed with the opioid Vicodin. Two of the errors resulted in severe harm after the patients took over a dozen Vicodin tablets in preparation for their colonoscopies. In another case, a verbal order for “Clindesse use as directed” was inaccurately transcribed and dispensed as Clindets pledgets, rather than the intended vaginal gel.^{11–13}

When directions for use are omitted and replaced with “use as directed” on a prescription or medication order, differences in product characteristics may no longer play a role in mitigating the risk of a wrong drug medication error. Consequently, this paper sought to identify prescription products commonly prescribed with the signa “as directed” to aid sponsors and the FDA in the selection and review of proposed proprietary names, respectively.

METHODS

This article does not contain any studies with human or animal subjects performed by any of the authors.

We utilized the Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel™ database in an effort to identify prescription products prescribed with the signa “as directed.” Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel™ is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physician practices representing 30 specialties across the U.S. that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit, and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. All drugs reported on the survey

are classified according to the uniform system of classification (USC) system. Developed by IMS Health, the USC is widely accepted in North America as the standard for pharmaceutical product classification. Most drugs within the same USC class share common indications, chemical ingredients, or similar pharmacological or physiological reactions.¹⁴

For each drug reported on the survey, the associated directions for use (signa) are also collected. The most common physician intended directions for use (signa) are compiled for each drug occurrence. The term “drug occurrences” refers to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. In this article, “as directed” encompasses all variations of the signa, including “use as directed,” “take as directed,” “ut dictum,” “ut dict,” and abbreviations for such signa (e.g., UD, UAD, TUD).

We queried the Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel™ database for the cumulative time period from 01/2013 through 12/2015 by USC drug class. We excluded the following from our analysis:

1. USC classes with less than 100,000 occurrences; this value was considered a very small sample size with correspondingly large confidence intervals,
2. USC drug classes that had no occurrences associated with the signa “as directed,” and
3. USC classes which contained solely non-prescription products, including homeopathic products, non-drug preparations, and saline laxatives. Classes that included products available as both prescription and non-prescription (e.g., permethrin, omeprazole, fluticasone propionate) were included in the analysis.

The resultant USC classes each contained one or more prescription product associated with the signa “as directed.” We further analyzed each remaining USC class to determine the percentage of products associated with the signa “as directed” within each class. For example, the USC class of otic anti-infectives with glucocorticosteroids contained six products, five of which were associated with the signa “as directed,” corresponding to 83.33%. We focused the remainder of our analysis on USC classes where 75% of the reported products within the class were associated with the signa “as directed.” Sixteen of these USC classes contained less than 3 reported products within the class. Within these sixteen classes, the products associated with the signa “as directed” were analyzed at the product-level. For the remaining USC classes with three or more reported products within the class, we concluded that use of the signa “as directed” may be a class effect, meaning that any product within the class can potentially be prescribed with the signa “as directed.”

The USC class to which a new drug or therapeutic biologic will ultimately be assigned is generally unknown during the evaluation of the proposed proprietary name. In some cases a product may be assigned a temporary USC or a new USC may need to be created after the product is approved by the FDA.¹⁴ Therefore, to improve the utility of the study results, we restructured the resultant USC classes and products associated with the signa “as directed” into broader categories based on: commonalities with previously published categories (as described further below); therapeutic class; and route of administration.

We performed a cross walk by mapping the results of the present analysis to the corresponding results of a 2016 ISMP survey of pharmacists.¹¹ For example, the USC class of estrogen and progestin oral contraceptives from the present analysis was mapped to oral contraceptives and the USC class of pre-xray evacuation products was mapped to bowel evacuation/colonoscopy preparations.

Several USC classes identified in the present analysis were unable to be mapped to the ISMP survey results. These classes were further analyzed to identify commonalities based on route of administration and therapeutic class.

RESULTS

The results in Table 1 show the twenty USC classes that contain drugs that are likely to be prescribed “as directed.” This table also lists examples of products associated with the signa “as directed” for each of the twenty classes; the list of example products is not exhaustive. Table 2 contains sixteen USC classes for which the likelihood of being prescribed with the signa “as directed” was unable to be determined for the class because there were less than three reported products within the class. All of the products associated with the signa “as directed” for each of the sixteen classes is included in Table 2. The list of products is all inclusive.

General classifications of products that were identified in both the present analysis as well as the ISMP survey include: 1) inhalers; 2) oral contraceptives; 3) one time treatments, such as those for lice or scabies; 4) pre-packaged items with specific directions for use on the package (e.g., methylprednisolone, azithromycin, methotrexate, varenicline, prenatal multivitamins); 5) migraine medications; 6) erectile dysfunction medications; 7) bowel evacuation/colonoscopy preparations; 8) topical medications (e.g., antifungals); and 9) medications with regimens that may change frequently (e.g., warfarin, insulin).

The current study revealed that several classes and products associated with the signa “as directed” are administered by routes of administration other than orally. Aside from the categories mentioned above (e.g., inhalers, topical medications), products administered by the following routes of administration may be prescribed “as directed”: otic, transdermal (e.g., contraceptives, testosterone, and non-narcotic pain relievers), vaginal (e.g., contraceptives, antifungals) and rectal (e.g., antihemorrhoidal agents).

DISCUSSION

Physician-reported rationale for writing “take as directed” on prescriptions supports the results of the cross walk. A viewpoint survey conducted by Cirm indicated that physicians defend the use of “take as directed” when oral contraceptives are ordered and when the prescriber may need to make frequent changes to a regimen. Anticoagulants, such as warfarin, were the therapy most cited as requiring frequent regimen modifications necessitating use of the signa “take as directed.”¹⁵

While vaginal products were not specifically identified in the ISMP survey results, reports of drug name mix-ups involving vaginal products support this finding.^{11–13}

The ISMP survey results indicate that several injectable products are prescribed with the signa “use as directed.” Fertility injections, injectables to be administered at a clinic, hemophilia injections, and the as needed emergency medication, epinephrine, were among the injectable products identified.¹¹ However, our analysis only identified a limited number of injectable products. Aside from insulin, human glucagon-like peptide-1 (GLP-1) analogs and the antineoplastic enzyme receptor agent, bortezomib were the only two injectable products identified that are not available in other dosage forms. The findings that indicate that GLP-1 analogs are associated with the signa “as directed” may be explained by the fact that patients may be titrated up to the maximum dose if optimal glycemic response is not achieved with the starting dose. However, injectables such as bortezomib that require reconstitution or intravenous administration are not likely to be prescribed and dispensed to outpatients, unless the product is to be administered at a clinic.

The results of the present analysis also indicate that products which may be titrated upon initiation (e.g., antidepressants, GLP-1 analogs, metformin) are associated with the signa “as directed.” However, the use of this signa would not be expected for patients stabilized on a maintenance dose. We were not able to rationalize why oral anti-infectives not pre-packaged with specific directions for use on the package (e.g., combination sulfamethoxazole-trimethoprim, antibiotics for trichomoniasis, aminopenicillins) or antineoplastic agents may be prescribed “as directed.” Oral anti-infectives may require weight-based dosing and may have a wide range of acceptable doses based on the indication, which is why this finding is unexpected. These findings may illustrate limitations of the data source.

The results of this study suggest that certain prescription products may have a higher likelihood of being prescribed with the signa “as directed.” Prescriptions and medication orders for these products may not include product characteristics such as the strength, route, dosage, and frequency to help healthcare professionals differentiate between two LASA drug names and mitigate the risk of wrong drug errors. Therefore, the likelihood of a product being prescribed with the signa “as directed” should be taken into consideration when Sponsors and the FDA select and review proposed proprietary names, respectively.

Limitations

Our study is not without limitations. The data was based on survey responses: we note that a reported “drug occurrence” does not necessarily result in the generation of a prescription or medication order. A drug occurrence can result from a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order, a prescription written, or a combination of these. This limitation may help to explain why products such as the antineoplastic enzyme receptor, bortezomib, appeared in our results. Nevertheless, this study should serve as a starting point from which future research can be conducted using actual utilization data.

We note that the aim of the study was not to identify all products prescribed “as directed” at the product-level. We sought to identify products that may be commonly prescribed using the signa “as directed” and categorize these products into broad categories based on: commonalities with previously published categories; route of administration; and therapeutic class. As a consequence, individual products with a propensity for being prescribed “as

directed,” such as epinephrine, may not have been captured in the study results. For example, despite 12% of epinephrine occurrences being associated with the signa “as directed” (Syneos Health Research & Insights, data not shown), the USC class to which epinephrine belongs (Cardiac Therapy, Other) was excluded from the analysis because < 75% (60%, n = 6 out of 10) of the reported products within the class were associated with the signa.

CONCLUSION

For moderately similar name pairs, when differences exist between the product characteristics or directions of use and these are noted on a prescription or medication order, it may decrease the risk of name confusion. In instances where the products have overlapping or similar strengths or doses, or are available as a single strength where the strength may be omitted, moderately similar name pairs may have a higher potential for confusion. In these instances, other product characteristics may play a limited role in helping to mitigate the risk of wrong drug medication errors. However, it is likely that products within the categories identified in this paper may be prescribed with the signa “as directed” therefore; differences in product characteristics may no longer play a role in mitigating the risk of a wrong drug medication error.

Sponsors and the FDA can utilize the categories of products commonly associated with the signa “as directed” identified in this paper to aid in the selection and review of proposed proprietary names, respectively. Specifically, Sponsors and the FDA should consider utilizing the signa “as directed” when conducting name simulation studies for products within the categories identified in this paper. Additionally, differences in product characteristics may not be an appropriate failure mode prevention if the signa “as directed” may be used.

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Table 1

Classes likely to be prescribed with the signa “as directed” with example products

USC Class	Products associated with the signa “as directed”
Allylamines	Naftifine hydrochloride Terbinafine hydrochloride
Aminopenicillins	Ampicillin Amoxicillin trihydrate
Anthelmintics	Albendazole Ivermectin
Antihemorrhoidal corticosteroids	Hydrocortisone (rectal) Pramoxine and hydrocortisone
Combination bronchodilators	Fluticasone furoate and vilanterol Salmeterol and fluticasone
Disease-modifying antirheumatic drugs	Apremilast Methotrexate
Estrogen and progestin oral contraceptives	Estrogen valerate and dienogest Drospirenone, ethinyl estradiol, and levomefolate calcium
Fast acting analog human insulin	Insulin aspart Insulin glulisine
Helicobacter pylori agents	Omeprazole/clarithromycin/amoxicillin Metronidazole, bismuth subsalicylate, and tetracycline
Human glucagon-like peptide-1 (GLP-1) analogs	Dulaglutide Exenatide
Oral corticoids-plain	Methylprednisolone Prednisone
Other contraceptives (non-oral)	Ethinyl estradiol and etonogestrel (vaginal ring) Ethinyl estradiol and norelgestromin (transdermal)
Otic anti-infectives with glucocorticosteroids	Acetic acid, propylene glycol diacetate, and hydrocortisone Fluocinolone
Pre-xray evacuation	Bisacodyl and polyethylene glycol with electrolytes Potassium phosphate and sodium phosphate
Scabicides and pediculocides	Benzyl alcohol Permethrin
Selective serotonin reuptake inhibitor antidepressants	Fluoxetine hydrochloride

USC Class	Products associated with the signa “as directed”
	Fluvoxamine
Serotonin 5-HT-1 receptor agonists	Naratriptan hydrochloride Sumatriptan
Sexual function disorder	Prostaglandin e Sildenafil citrate
Smoking deterrents	Nicotine polacrilex Varenicline tartrate
Vaginal imidazoles	Butoconazole nitrate Tioconazole

Table 2

Products associated with the signa “as directed” and their corresponding class

Products associated with the signa “as directed”	USC Class
Metronidazole Tinidazole	Antibiotics for trichomoniasis
Abiraterone acetate Bortezomib	Antineoplastic enzyme receptor
Metformin hydrochloride	Biguanide (alone)
Insulin regular and insulin NPH	Combination human insulins
Sulfamethoxazole/trimethoprim	Combination sulfamethoxazole-trimethoprim
Azithromycin	Extended spectrum macrolide
Lenalidomide	Glutarimide derivative
Lactulose Polyethylene glycol 3350	Hyperosmolar laxatives
Insulin detemir Insulin glargine	Long acting analog human insulin
Prenatal vitamins	Prenatal multivitamins
Vilazodone hydrochloride Vortioxetine	Selective serotonin reuptake inhibitors/5-HT receptor partial agonists
Diclofenac epolamine Lidocaine	Synthetic non-narcotic patches
Testosterone	Transdermal androgens
Clindamycin phosphate Metronidazole	Vaginal antibacterial
Terconazole	Vaginal triazoles
Warfarin sodium	Vitamin K antagonist