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Reducing Medication Errors Through Naming, Labeling, and Packaging

Adrienne Berman[1,2]

Errors due to look-alike or sound-alike medication names are common in the United States, and are responsible for thousands of deaths and millions of dollars in cost each year. Up to 25% of all medication errors are attributed to name confusion, and 33% to packaging and/or labeling confusion. Thousands of medication name pairs have been confused based on similar appearances or sounds when written or spoken, or have been identified as having the potential for confusion. Systems and recommendations have been developed that may reduce the occurrence of such errors.

KEY WORDS: medication errors; look-alike names; sound-alike names; packaging; labeling.

INTRODUCTION

Problems related to medications are common in the United States, and are responsible for significant morbidity, mortality, and cost. True incidences are unknown and difficult to obtain for many reasons, ranging from poor reporting, differences in definitions of what constitutes a medication error, lack of awareness of reporting techniques, lack of time, fear of litigation, inability to determine causality, reluctance to admit error, and cost. Estimates for all types of medication errors (including such variants as missed dose, wrong dosage, wrong medication, wrong time, wrong route, etc.) in the United States range from 1.5 to 35% of all doses given to hospitalized patients (depending upon the definition, methodology, location, and depth of investigation), and have been noted to occur in 2.9[(1)] to 3.9[(2)] to 6.5%[(3)] of all hospital admissions. Over half of these errors were thought to be preventable.[(1,2)] Medication errors are felt to account for almost 20% of all medical errors in several studies,[(1,2,4)] and were the most common type of iatrogenic adverse event in all but the youngest age group studied.[(4)]

[1]Health Policy and Administration, School of Public Health, University of Illinois at Chicago, Chicago, Illinois.
[2]To whom correspondence should be addressed at Department of Ophthalmology, University of Illinois at Chicago, Chicago, Illinois 60612; e-mail: aberman@uic.edu.

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Total costs associated with medical errors (healthcare costs, lost productivity, disability, lost household income) in the United States may be as high as $50 billion a year, of which half is attributable to direct healthcare costs.[5] Studies at academic medical centers found from $2.8 million[6] to almost $15 million[7] a year in costs associated with medication-related errors at those medical centers alone. Extrapolation of the lower figure nationwide results in over $2 billion a year in hospital costs associated with just preventable adverse drug events affecting inpatients.[5] Mortality estimates from medications vary widely, ranging up to 106,000 in 1994.[8] Meanwhile, actual reported mortality figures for adverse drug reactions were 6894 in 1995 per the Food and Drug Administration's (FDA) postmarketing surveillance system,[9] and 7391 in 1993 per death certificate data.[10]

SOURCES OF MEDICATION ERROR

The medication process can be broken down into prescribing, transcribing/documenting, dispensing, administering and monitoring, and medication errors can occur at any of these steps. The United States Pharmacopeia (USP) Medication Errors Reporting Program (MER) received 1106 voluntary medication error reports between July 1, 1998, and November 30, 1999. Twenty-four percent (267/1106) were potential errors, and 76% (839/1106) were actual errors. Seventy-six percent (842/1106) of the reports specified where in the medication process the error occurred. The majority occurred during dispensing (53%), and administration (25%), followed by prescribing (15%).[11] Meanwhile, a prospective study of inpatients that relied on daily chart reviews to detect errors found 49% of serious errors occurred during prescribing, 26% during administration, 14% during dispensing, and 11% during transcription.[3]

STEPS INVOLVED IN MEDICATION USE

1) Prescribing
   a) Assessing the need for and selecting the correct drug
   b) Individualizing the therapeutic regimen
   c) Designating the desired therapeutic response
2) Documenting or Transcribing
3) Dispensing
   a) Reviewing the order
   b) Processing the order
   c) Compounding and preparing the drug
   d) Dispensing the drug in a timely manner
4) Administering
   a) Administering the right medication to the right patient
   b) Administering medication when indicated
   c) Informing the patient about the medication
   d) Including the patient in administration

5) Monitoring
   a) Monitoring and documenting patient's response
   b) Identifying and reporting adverse drug events
   c) Reevaluating drug selection, regimen, frequency, and duration
6) Systems and Management Control
   a) Collaborating and communicating amongst caregivers
   b) Reviewing and managing patient's complete therapeutic drug regimen

Adapted from Ref. (5)

Some of the more common sources of medication errors are confusion between sound-alike medication names or look-alike medication names, and confusion due to similar appearances for medication packages, or similar labels for different medications. Name confusion has been attributed to cause from 12 to 25%[12–14] of medication errors in the United States, while packaging or labeling problems were involved in 33% of errors reported to the MER in 1996–1997.[15]

DEVELOPMENT OF MEDICATION NAMES

Currently, over 15,000 drug names are in use in the United States.[16] Medications have multiple names assigned by different organizations for different reasons. The chemical name, generated by the International Union of Pure and Applied Chemistry, identifies molecular structure and configuration, is usually lengthy and complicated, and is therefore rarely used clinically. The nonproprietary, generic, or established name is aimed at healthcare providers, and is assigned by the United States Adopted Name Council (USAN) using a series of guidelines to ensure uniformity and safety. This includes following a list of name stems that are incorporated into the generic name to give some indication of the chemical and/or therapeutic characteristics of the drug.[17] The official title of a medication is determined by the USP Nomenclature Committee, and is the USP monograph title for the substance. For most medications, the official title is the same as the nonproprietary name, but may also include the dosage, formulation, and route of administration. The proprietary, brand, or trademark name is determined by the pharmaceutical firm with the hopes that it will promote brand loyalty, (e.g. CLARITIN and CLARITIN-D),[3] facilitate recognition, and since there is now direct marketing of prescription drugs to the public, imply the drug's effects to the lay person (i.e. VIAGRA evokes images of vigor as well as Niagara Falls—useful images for a drug indicated for male impotence.) If the brand name is to be trademarked, the US Patent and Trade Office examines similarity between new and existing trademarks in terms of printed appearance since its goal is to prevent new trademark names from infringing on existing trademarks. The FDA's Office of Post-Marketing Drug Risk Assessment reviews proprietary names, including how they appear when handwritten, and regulates drug labeling that uses the generic, proprietary, or trademarked name.[18] Internationally, the World Health Organization (WHO) coordinates with individual nation's naming and nomenclature

[3]It is standard practice in the pharmaceutical industry to use all capital letters to designate proprietary, brand, or trade names instead of using TM or®.

committees (such as the FDA and USAN) to recommend a single worldwide name (the International Nonproprietary Name, or INN) for every active pharmaceutical. As of 2000, over 7000 INNs had been established.[19] Kenagy and Stein provide more detailed information on the intricacies of the current processes for naming medications.[20]

MEDICATION NAMES AND MEDICATION ERRORS

Since confusion between look-alike and sound-alike medication names is so common, the USP maintains an extensive list of confused, or potentially confusable pairs. The most recent update of their Look-Alike Sound-Alike Drug Names List[21] includes over 1500 pairs of medications (more than 750 unique names) that have been reported as having been confused to the USP MER. The American Drug Index,[22] a standard pharmacy reference, has a list of over 1200 pairs of look-alike and/or sound-alike medication names in its 2002 edition, many of which are not found in the USP list. A metacompilation of published lists of confused name pairs currently totals over 1400 individual names, or close to 3000 pairs.[23] In addition, the Institute for Safe Medical Practices (ISMP) (www.ismp.org) publishes an electronic newsletter every 2 weeks that rapidly disseminates newly discovered look-alike/sound-alike pairs. Recently reported new confusions include FEMHRT (hormone-replacement therapy for postmenopausal women) instead of FEMARA (used for breast cancer that progresses on anti-estrogen therapy), and DIPRIVAN (propofol, an injectable anesthetic induction agent) instead of DITROPAN (an oral antispasmodic for the bladder).[24]

It has been proposed that generic medication names or INNs be used to reduce the chance of errors due to sound-alike, look-alike proprietary names as well as to avoid duplicate prescriptions due to multiple proprietary names for the same active drug. There are multiple case reports in the literature of patients being admitted to the hospital for side effects resulting from overdoses caused by taking two or more prescriptions with the same active ingredient but different brand names.[25] However, the opposite has also been proposed—that trade names be used due to similar-sounding generic names, particularly in certain drug classes. For example, the majority of the cephalosporin antibiotics have generic names that look and sound very similar, but often have very different proprietary names.[26]

One solution is for healthcare workers to use the generic as well as the trade name on prescriptions and medication orders, whether inpatient or outpatient, particularly when a drug is known to have the potential for name confusion. While it will result in longer prescriptions, as well as the time required to write the prescriptions, it will reduce the chance for medication errors due to misinterpretation of either of the names since the second name is present as an internal control. An additional benefit of including the generic name on all prescriptions is that healthcare providers may realize a patient is taking duplicate prescriptions containing the same medication. Given the proliferation of medications with the same active ingredient, but many different trade names, and the propensity for patients to see more than one physician and to obtain medications from more than one

pharmacy, patients may be taking multiple doses of the same medication under different names.

Many drugs are found in multiple forms and often have different names, dosages, or indications. Over-the-counter products frequently use brand-name extension, where a successful brand name is used on a new product that may not contain the same active ingredients as the original product. This can lead to significant problems for patients with medication sensitivities or contraindications who were able to take the original product without trouble. CHLOR-TRIMETON contains chlorpheniramine maleate (an antihistamine safe in cardiac disease or hypertension), while CHLOR-TRIMETON NONDROWSY contains pseudoephedrine (a decongestant contraindicated for patients with cardiac disease or hypertension.)[27] Acetaminophen (TYLENOL) is found in everything from pain pills and headache remedies to cold and cough medicines, and the fact that there is acetaminophen in the product is usually not clearly labeled. Since many patients self-medicate with multiple over-the-counter medications when they don't feel well, there is risk of acetaminophen overdose, particularly for children and patients with compromised liver functions.[28]

Prescription medications also have multiple trademarked names for the same active ingredient. In the United States, verapamil (used for high blood pressure as well as assorted heart conditions) can be found in a total of 42 preparations under the brand names CALAN, CALAN SR, COVERA-HS, ISOPTIN, ISOPTIN SR, TARKA, VERELAN, and VERELAN PM, as well as under the generic names verapamil and verapamil ER from six more manufacturers.[29] Meanwhile in Germany, verapamil was marketed as AZUPAMIL, DURASPOTIN, FALICARD, ISOPTIN, JENAPAMIL, VERA, VERABETA, VERAGAMMA, VERAHEXAL, VERALICK, VERAMEX, VERANORM SS, verapamil, VERASAL, and VEROPTIN-STADA in 2001.[25]

In addition, different brand names can be used for the same medication when it has different indications. Examples include bupropion for depression (WELLBUTRIN) and smoking cessation (ZYBAN), finasteride for benign prostatic hypertrophy (PROSCAR) and male pattern baldness (PROPECIA), and fluoxetine for depression, bulimia, and obsessive-compulsive disorder (PROZAC) and premenstrual dysphoric disorder (SARAFEM). Reasons for this include marketing issues, patent extension under a new trademark, third-party reimbursement (i.e. bupropion may be covered as WELLBUTRIN for depression, but not as ZYBAN for smoking cessation), stigmas associated with one of the names (i.e. women taking fluoxetine for premenstrual syndrome do not want a prescription for PROZAC), or completely different doses and indications (i.e. PROPECIA 1 mg for baldness, PROSCAR 5 mg for prostatic hypertrophy.)[30]

On rare occasions, drug pairs can have both generic and proprietary names that can be confused for the same medication, but that is very unusual. VALTREX (valacyclovir)/VALCYTE (valganciclovir),[31] and VIRACEPT (nelfinavir)/VIRAMUNE (nevirapine)[32] are two of the rare cases where both the generic and proprietary names could be confused for the same drug. However, these are the exceptions, and the vast majority of medications do not have proprietary and generic names that can be confused with both the proprietary and generic names of another

drug. For example, the proprietary name PAXIL has been confused with the proprietary name PLAVIX, but paroxetine, the generic name of PAXIL, is very dissimilar from clopidogrel, the generic name of PLAVIX.

The problems are not limited to confusing one brand name prescription medication with another brand name prescription medication. Generic medications, medical devices, and even blood tests have also been misread or misheard in the place of the requested medication in written prescriptions, hospital orders, verbal orders, and on medication bins and packages. A few examples include BENADRYL—benazepril (trademark nonprescription versus generic prescription), LAMISIL—LAMICEL (proprietary nonprescription medication versus proprietary prescription medical device), ARIXTRA—Anti-Xa (trademark prescription medication versus blood test), amiodarone—amrinone (two generic heart medications with opposite effects), iodine—IOPIDINE (sterilizing skin cleanser versus proprietary prescription eye drop) and PLAVIX—PAXIL (two trademarked prescription medications with very different indications).

It has also been suggested that the nomenclature for extended-release medications should be standardized. Many medications that used to be dosed multiple times a day are now given only once or twice a day due to advances in delivery systems and formulations. However, errors occur because regular forms of the medications are used where the extended-release version is intended, or vice-versa, or if an extended-release medication is dosed at an inappropriate interval. Multiple suffixes (e.g. LA, XL, XR, CC, CD, ER, SA, CR, XT, SR) are used to indicate long acting, slow-, delayed-, or extended-release medications. However, the suffix in and of itself does not necessarily indicate if the medication is given once a day or twice a day, or if it is delayed release or slow release. Some extended- or delayed-release products, such as CARBATROL (extended-release TEGRETOL),[33] or DEPAKOTE (delayed-release divalproex sodium) do not indicate their long-acting nature as part of their names, and additionally, DEPAKOTE and DEPAKOTE ER (divalproex sodium extended release) have the potential for confusion. METADATE ER and METADATE CD, both extended-release methylphenidate hydrochloride, are not interchangeable, since the CD version is given only once a day, and the ER version two to three times a day. RITALIN LA and RITALIN SR, two additional extended-release methylphenidate products, only add to the confusion.[34]

Occasionally, name confusion can result in enough medication errors and patient morbidity/mortality that the name has to be changed. As of July 1, 2000, amrinone (a positive inotropic agent) that had been frequently confused with amiodarone (an anti-arrhythmic) during emergency/code situations (where both are used to treat different cardiac conditions) had its name changed to inamrinone.[19] However, this name change is only effective in the United States, so the name amrinone continues to be used overseas. CELEBRA (an antiarthritis drug) was changed to CELEBREX in 1999 to avoid confusion with CELEXA (the antidepressant citalopram). However, this resulted in CELEBREX also becoming confused with CEREBYX (the epilepsy medication fosphenytoin sodium).[35]

A team at the University of Illinois in Chicago has been working for several years to develop and perfect a computer program that can screen medication names based on spelling (orthographic) and sound (phonological) similarities. Since there

are over 15,000 existing medications in the United States, evaluating a single new drug name requires over 15,000 comparisons, and retroactively screening all existing names requires over 112 million comparisons.[16] Most recently, they have been able to achieve a sensitivity of 93.7%, specificity of 95.9%, and accuracy of 94.8% for detecting confusing name pairs with their program.[23] In June of 1999, the USAN contracted with the University of Illinois to screen proposed drug names for potential look-alike/sound-alike problems. However, existing nonproprietary (generic) names will not be screened retroactively.[35] The FDA has instituted a risk analysis system for the review and evaluation of proposed proprietary drug names, and rejects approximately one-third of all proposed names because of their potential for confusion.[36]

Proposals to reduce look-alike confusion in the pharmacy and on the hospital floors involve increasing awareness of the similarities between drug pairs, as well as emphasizing the differences between drugs with similar names. One of the more common methods to do this involves emphasizing the syllables that the confused pairs differ in. This is most commonly done with color, bold-faced type (hydr**oxy**zine and hydr**ala**zine), or "tall-man" letters (hydroCHLOROthiazide and hydroFLUMEthiazide). The FDA has a list of 33 frequently confused names that it has recommended "tall-man" letters for.[37] The following list contains suggestions from the ISMP and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to reduce look-alike/sound-alike confusion.[30,36]

SUGGESTED STRATEGIES TO REDUCE LOOK-ALIKE/SOUND-ALIKE ERRORS

1. Do not store known problem medications alphabetically by name. Store them out of order, or in an alternate location. Affix "name alert" stickers to areas where known look-alike/sound-alike products are stored.
2. Change the appearance of look-alike names on pharmacy and nursing unit bins and shelves, computer screens, medication administration records, and pharmacy product labels. Emphasize the parts of the names that are different by highlighting, coloring, boldfacing, or using "tall man" letters (e.g. hydrALAzine, hydrOXYzine.)
3. Install "flags" on all computer systems (pharmacy, order-entry, electronic medical record) as well as on automated medication cabinets for the most seriously confused pairs so that an alert is generated by entering either half of a pair. If possible, make the alert visual and auditory.
4. Require both the brand and generic name on all orders for known look-alike/sound-alike medications. In addition, consider requiring both the brand and the generic name for all orders. This allows for internal error checking since it is unlikely that both the generic as well as the brand name would have a look-alike or sound-alike, as well as allowing for the opportunity to detect duplicate or redundant prescriptions.
5. Prescriptions should clearly specify the medication strength, dosage, route of administration, and frequency, even for drugs with only one available dose or one accepted route of administration.

6. Write the purpose of the medication on the prescription since many look-alike/sound-alike medications are used for different purposes.
7. Develop a specific policy for taking verbal or phone orders. For example, clearly repeat back the medication, dose, route, frequency, and indication, and request or provide correct spelling. Accept verbal or phone orders only when truly necessary.
8. Provide the generic and the brand name on all medication labels.
9. Employ at least two independent checks during the dispensing process. (e.g. one person interprets and enters the prescription or order, a second person compares the original order to the dispensed label.)
10. Provide patients with written information about their medications, including the brand and generic names. Do not dispense medications that the patient doesn't recognize without double-checking.
11. Develop and follow criteria for drugs that will be stocked within an institution (i.e. what is on the formulary.) Consider the potential for confusion with look-alikes or sound-alikes when adding new medications to the formulary. Let nurses, pharmacists, technicians, physicians, and unit secretaries view written samples of the name, and have them pronounce it to see if it looks or sounds like another product.

PACKAGING AND LABELING

Labeling and packaging of medications has also contributed to medication errors. During a 1-year period (June 1996–May 1997), the USP found that 33% of the reports to its voluntary MER database cited labeling or packaging as having contributed to a medication error, including almost 30% of the fatalities reported. Specific concerns cited in those reports included:

1. Lack of prominent placement of drug name and strength
2. Small size and poor readability of printed information
3. Insufficient prominence given to route of administration (e.g., nasal vs. injection, intravenous vs. intramuscular)
4. Poorly designed or cluttered labels
5. Lack of differentiation between drug products that have similar names
6. Similar-appearing labels or packages of different products
7. Poor use or absence of color to differentiate products
8. Prominence of company logos versus information that identifies the product
9. Inadequate warnings about proper drug use

From Ref. (15)

Serious efforts to uniquely label medications began in 1965, when Eli Lilly introduced the Identicode System, where the Lilly logo and an alphanumeric code were imprinted on every solid dosage form. At that time, it was found that it only took 15 seconds to achieve 99% accuracy in identifying a medication with this system in place.[38] In 1993, the FDA mandated that all nonprescription and prescription solid dose forms be imprinted in this fashion. However, it appears that the system does not

work that well any more. A recent study found that healthcare providers could only identify from 35% (nurses and medical students) to 55% (pharmacists and poison center specialists) of the manufacturers in a sample of solid-dosage medications. No effort was made to even try to identify the medication itself or the dose.[39] The recent proliferation of manufacturers, medications, formulations, and doses appears to be a major part of the problem. One of the keys to the current Identicode system is being able to identify the manufacturer's logo on the pill or capsule, and if the logo cannot be clearly recognized, the medication cannot be identified easily.

Currently, medications in the United States listed under Section 510 of the Federal Food, Drug, and Cosmetic Act have a 3-part, 10-digit NDC (National Drug Code) identifier that identifies the vendor/labeler, product (specific strength, dosage form, and formulation for a particular firm) and package size. This code appears on the medication packaging, but does not appear on the medications themselves. The FDA has just proposed a regulation mandating bar codes containing a minimum of the information in the NDC on all prescription medications and vaccines, as well as some over-the-counter medications (such as ones that are commonly used in hospitals.) Hospitals would place a bar-coded wristband on all patients at admission, and all medications would be bar-coded. Before any medication (including IVs and blood products) would be administered to the patient, the patient's wristband and the medication would be scanned, and the computer would match patient, medication, dose, time, allergies, contraindications, therapeutic duplications, etc., and notify the caregiver if there was a problem. The FDA estimates that there will be a 50% reduction in medication errors over the next 20 years.[40] Recently, the North Chicago VA Hospital stated that bar codes had reduced medication errors there by 88%.[41]

Certain fields of medicine have been using standardized packaging or labeling of medications for years in an attempt to decrease medication errors. Ophthalmology is one field where standardization in packaging has made it easier for patients as well as healthcare providers to understand which medications are being used. Since many ophthalmology patients have poor vision, manufacturers have been using brightly colored bottle tops for many years to help patients identify the different eye drops. More recently, this use of color has been standardized. The American Academy of Ophthalmology, along with the FDA and pharmaceutical manufacturers, has developed a uniform color-coding scheme for topical medications where the colors were chosen taking the medication and its side effects, the disease being treated (since certain ocular diseases affect some colors more than other colors), and risk of serious complications if a switch occurred into account (Table I).[42]

It has been argued that having different medications packaged in a similar fashion can increase the risk of medication confusion (e.g. where a patient might use the wrong glaucoma drop by grabbing the wrong "orange top" without bothering to look at the label.) However, at least in ophthalmology, the error would be made within the same medication class where marketing more than any marked pharmacological difference differentiates most medications. The colored bottle tops also makes it easier for patients to realize when they are taking duplicate or similar prescriptions, since they often cannot or do not read the bottle labels.

In a similar fashion, anesthesiologists in the United States, Canada, Australia, and New Zealand have developed a standardized color-coded label system for labels

Table I. Color Codes for Topical Ophthalmic Medications

Medication class	Color	Pantone number	Example
Anti-infectives	Tan	467	OCUFLOX, gentamicin
Steroid anti-inflammatories	Pink	197	PRED-FORTE, dexamethasone
Mydriatics and cycloplegics	Red	1797	MYDRIACYL, atropine, phenylephrine
Nonsteroidal anti-inflammatories	Gray	4	VOLTAREN
Miotics	Dark Green	348	pilocarpine, carbachol
Beta-blockers	Yellow	Yellow C	TIMOPTIC, BETAGAN
Beta-blocker combinations	Dark blue	281	COSPT
Adrenergic agonists	Purple	2583	IOPIDINE, ALPHAGAN-P
Carbonic anhydrase inhibitors	Orange	1585	TRUSOPT, AZOPT
Prostaglandin analogues	Turquoise	326	TRAVATAN, LUMIGAN

Note. Ref. (42) used with permission.

for the syringes of medications drawn up for use in the operating room (Table II).[43] This standardized system is not used by the manufacturers for the prepackaged medications, but only applies to the labels that are placed on syringes by the anesthesiologists themselves.

While pharmaceutical manufacturers have not standardized colors in other fields, there appears to be a trend towards special packaging for easily confused drugs that have particularly deadly outcomes. After numerous problems with potassium chloride for injection (where concentrated potassium chloride was mistakenly injected instead of sterile water or 0.9% sodium chloride, which often led to a fatal outcome), all vials of potassium chloride solution now have a black top to help reduce confusion and are clearly labeled "Must be diluted" before use.[44] Neuromuscular blocking agents have also been responsible for many deaths in a similar fashion when their vials were confused with sterile water or saline for injection. The FDA approved

Table II. Standardized Labels for Anesthetic Syringes in the United States

Medication class	ASTM D4774-94 Standard	Example
Induction agents	Yellow	pentothal, PROPOFOL
Sedatives and tranquilizers	Orange 151	VERSED, VALIUM
Muscle relaxants	Fluorescent red 805	succinylcholine, vecuronium, atracurium
Muscle relaxant antagonists	Fluorescent red 805 or warm red with diagonal white stripes	neostigmine, physostigmine
Narcotics	Blue 297	morphine, fentanyl, Sufenta
Narcotic antagonists	Blue 297 with diagonal white stripes	naloxone
Major tranquilizers	Salmon 156	chlorpromazine
Vasopressors	Violet 256	epinephrine, phenylephrine
Hypotensive agents	Violet 256 with diagonal white stripes	nitroprusside, labetalol
Local anesthetics	Grey 401	lidocaine, bupivicaine
Anticholinergics	Green 367	atropine, glycopyrrolate
Anti-emetics	Salmon 156	droperidol, REGLAN

Note. Adapted from Ref. (43).

special packaging and labeling, and the changes were expected to become official in August of 2003. However, concerns over the color selected for the packaging have delayed implementation. Per the original plan, all neuromuscular blockers were to be packaged in vials with a closure that was entirely "Anesthesia Red" (Pantone Red 811), with "Warning Paralyzing Agent" or "Paralyzing Agent" on both the vial cap as well as the vial overseal, and ampoules were to have "Anesthesia Red" bands on their necks.[45]

Occasionally, company names, logos, or color schemes are more prominent on packages than is the drug information. Recently, there was confusion with Bausch and Lomb's generic versions of two popular ophthalmic ointments that had identical packages and coloring schemes, and very similar names, differing in only the third ingredient (neomycin/polymyxin B sulfates/bacitracin zinc versus neomycin/polymyxin B sulfates/dexamethasone). The coloring of the box and the company name were much more noticeable than the different third ingredient. Bausch and Lomb, after urging from the FDA, has agreed to repackage the second medication with pink labeling to conform to the color-code recommendations of the American Academy of Ophthalmology.[46]

Poor design can also lead to medication errors. Confusion between several types of prefilled syringes of lidocaine hydrochloride led to a series of serious errors. Lidocaine hydrochloride is commonly used to control cardiac arrhythmias, and is administered via a loading dose followed by a continuous intravenous infusion. Prefilled syringes containing 100 mg of lidocaine (the most common loading dose) as well as prefilled syringes containing 1 or 2 g of lidocaine (to make the infusion by injection into a bag of 5% dextrose) were frequently confused due to similarities in appearance and design, and on multiple occasions patients were given the concentrate instead of the load. Eventually, the syringes were withdrawn from the market in 1993.[26]

Bulk packages that contain multiple doses have also been the source of medication errors and fatalities. A 31-g bulk package of TIMENTIN was accidentally administered several times to one patient instead of the prescribed 3.1 g dose. The patient eventually died from acute renal failure and congestive heart failure. Both nurses involved stated that they confused the 31-g- and 3.1-g packages, which looked very similar, as well as misreading "31 g" as "3.1 g."[24]

The way a concentration, dosage, or strength is indicated on a medication package can also lead to errors. There have been multiple error reports in regards to intravenous gentamicin where the prominence of the concentration on the label (40 mg/mL) led to the injection of the entire package (20 mL, or 800 mg total) instead of the correct 40 mg dose since the concentration was more visible than the total volume and total dose. One proposed solution to this is to list package or vial contents by total dose or weight rather than by concentration.[14] However, this may then lead to problems for people with weak math skills, particularly during emergency situations where rapid action is called for.

Expressing concentrations as a dilution ratio (e.g. epinephrine 1:1000 or 1:10,000) or as a percentage (e.g. lidocaine 1% or 2%) can also lead to errors since many medical personnel have a hard time converting these expressions into concentrations. Since many of these medications are used in emergency situations such as resuscitations or codes (e.g. lidocaine, epinephrine, calcium, magnesium sulfate, neostigmine, sodium

bicarbonate), a delay can occur when dose is ordered in milligrams, or if an order is given for one concentration when a different concentration is the only one available.[47] For example, to get a 100 mg lidocaine dose when only a 1% solution is available requires the knowledge that a 1% solution is 1 g of lidocaine in 100 mL of solution, which is the same as 1000 mg/100 mL, which is the same as 10 mg/mL, so 10 mL needs to be used to deliver the dose. Recommendations include stocking resuscitation charts with only one standard concentration of medications in accordance with what is used in the resuscitation algorithms and posting conversion charts in locations where medications with anachronistic labeling might be drawn up.

The way numbers are printed on packages or in prescriptions and orders can also lead to medication errors. Leading zeros should always be included on decimal doses, such as in "0.2," and never written as ".2" which can easily be mistaken for "2," a 10-fold difference. Conversely, trailing zeroes should never be added to whole numbers, such as "2.0" which can easily be mistaken for "20," once again a 10-fold error.[48]

Another feature to be aware of is medication names ending in "l" may have that terminal "l" misinterpreted as a leading "1" if there is not a large enough space between the "l" and the beginning digit of the dose. With a written prescription, if the supposed "1" is added to the beginning of the dose after the medication name, the dose would be increased by an order of magnitude. For a medication package, adding the terminal "l" of the name to the beginning of the dose would result in underdosing, since the package would be thought to hold ten times more than it actually does. For example, Tegretol 300 mg has been interpreted as Tegretol 1300 mg. Adequate spacing between medication names and dosages is essential to prevent these types of errors, both with handwritten orders as well as with computer screens and medication packaging.[49]

On occasion, medications are packaged in a format usually reserved for another type of medication. For unknown reasons, nonlocular medications and samples are packaged to look like eye drops. Samples of ELOCON 0.1% lotion, a topical steroid solution containing 40% isopropyl alcohol, have been frequently used as eye drops by accident, causing ocular burning, blurring, and redness. The ELOCON sample looks like an eye drop bottle, and the warning "For dermatological use only. Not for ophthalmic use" is in very small print.[32] In England, stoma deodorant was packaged almost identically to eye drops, and the patient suffered bilateral corneal acid burns due to the low pH.[50] In a similar fashion, bottles of cyanoacrylate glue (such as nail glue or Super Glue[B]) (A. Berman, personal communication), while not medications, are frequently mistaken for eye drops, with rather unpleasant results.

Even ophthalmology products are not immune to being mimicked by ophthalmology pharmaceutical manufacturers. Recently, promotional markers advertising two types of glaucoma drops from two different manufacturers were packaged to look like the eye drops being advertised, complete to the appropriately color-coded cap for each drug! (A. Berman, personal communication). Dermatological manufacturers have also packaged promotional pens and markers to look like tubes of topical medications. One patient had to go to the emergency room due to an allergic reaction to purple ink from a PROTOPIC promotion that she mistakenly applied to her skin since the promotional marker looked identical to a standard 30-g tube of the medication.[51]

CELEBREX, already notorious for the CELEXA-CEREBYX-CEREBRA name confusion, has also had packaging and labeling problems with samples. Sample packs containing three 200 mg CELEBREX capsules were labeled only "CELEBREX 200 mg" on the box as well as the blister card containing the three capsules. This led to confusion as to whether the three capsules totaled 200 mg, or each tablet contained 200 mg. Despite multiple reports of overdoses where all three capsules were taken at once, the manufacturer has not changed the labeling and packaging.[32]

The National Coordination Council for Medication Error Reporting has made a series of recommendations for medication labeling and packaging that may help to reduce the incidence of medication errors. These recommendations are based on a review of errors reported to the MER and include recommendations for manufacturers, regulators, and standard-setters. These recommendations include:

National Council Recommendations for Medication Labeling and Packaging

1. Printing on the cap and ferrule of injectables should be restricted to conveying warnings.
2. Employ failure mode and effects analysis in design of devices and in the packaging and labeling of medications and related devices.
3. Machine-readable coding (e.g., bar coding) for labeling of drug products. The National Council recognizes the importance of standardizing these codes for this use.
4. Print the drug name (brand and generic) and the strength on both sides of injectables and IV bags, containers, and overwraps. For large-volume parenterals and IV piggybacks (minibags), the name of the drug should be readable in both the upright and inverted positions.
5. Industry to support the development of continuing education programs focusing on proper preparation and administration of its products.
6. The use of innovative labeling to aid practitioners in distinguishing between products with very similar names—for example, the use of tall letters such as VinBLAStine and VinCRIStine.
7. Avoid printing company logos and company names that are larger than the type size of the drug name.
8. Collaboration among industry, regulators, standards-setters, healthcare professionals, healthcare organizations, and patients to facilitate design of packaging and labeling to help minimize errors.
9. Further development of the FDA's error prevention analysis efforts to provide consistent regulatory review of product labeling and packaging relative to the error-prone aspects of their design.
10. That the USP/FDA examine feasibility and advisability of use of tactile cues in container design and on critical drugs. Such cues may be in the design of the container or embedded in the label.
11. Expansion of the concepts of simplification to apply to:
    a) Package inserts
    b) Labeling of other pharmaceutical dosage forms.[15]

ABRREVIATIONS, VERBAL ORDERS AND LEGIBILITY

Abbreviations, both standardized as well as institution and provider-dependent, also contribute to the confusion. One study found that no single individual was able to interpret more than 50% of the Joint Commission-approved abbreviations when they were shown a list.[52] The ISMP maintains a list of abbreviations to be avoided since they have led to many medication errors,[53] as does the Joint Commission on Accreditation of Healthcare Organizations.[48] For example, AD (aura dexter, or right ear) has been confused with "as directed," OD (oculus dexter, right eye), QD (once daily), and PO (by mouth).[31] Caution with abbreviations is even required with computerized prescriber order entry, which has been found to reduce medication errors by more than 50%[54] The Greek letter mu (μ), used as a prefix for micro (as in microgram, 0.00001 g) may be incorrectly translated by some word processors as "m," as in "mg," a 1000-fold increase from μg, or will occasionally not show it at all. In addition, handwritten "μ"s may be misread as "m," or "U" as in unit. The recommended abbreviation is "mcg."[55]

Legibility of prescriptions has been a chronic problem for all healthcare workers, and incidents abound where incorrect medications have been administered or dispensed due to misinterpretations of handwritten prescriptions, blurry faxes, or indistinct carbon copies. Over 10% of medication orders were judged illegible in one study,[56] while a much older study found one-third were illegible.[57] Fifteen percent of the medication errors reported to the United States Pharmacopeia's Medication Error Reporting System are attributed to illegible handwriting leading to misinterpretation of prescriptions or medication orders.[58] The increasing use of computerized physician order entry will reduce, and hopefully eliminate, problems due to illegibility.

Verbal orders have also been notorious for contributing to medication errors. One study found over 20% of inpatient orders were given verbally.[56] The British hospital system does not allow verbal orders, and has been found to have less than half the rate of medication errors compared to the United States in one study,[59] although other differences between the hospital systems may also contribute to the findings. Suggestions include having the recipient of the verbal order read the entire order back, saying confusing numbers (such as numbers in the teens) as, for example, one-five instead of "fifteen" (which can sound like "fifty" over the phone), spelling medication names, or, more drastically, not allowing verbal orders to be taken at all except in emergencies.

SYSTEMS ANALYSIS AND MEDICATION ERRORS

Michael R. Cohen, the founder of the Institute for Safe Medical Practices, and a long-time activist for improvements in medication system safety, said it clearly, "...Healthcare has a long history of tying (sic) serious medication errors primarily to the carelessness of practitioners while overlooking other major contributing factors such as dangerous pharmaceutical packaging, nonexistent warn-

ing systems, look-alike labeling, poorly conceived drug nomenclature, and faulty design of devices . . . Unlike airline pilots and aerospace engineers . . . we in healthcare have all too often in responding to serious errors have not designed appropriate systems to prevent such errors or inhibit their translation in to fatal accidents."[60]

Accidents can result from a faulty system that induces errors or makes them more difficult to detect, leading to a chain of events that culminates in a poor outcome. The Challenger disaster is an obvious illustration of this, where multiple small problems combined to cause catastrophe, but many iatrogenic injuries are also the results of poor system designs. Similar medication packages for very different drugs, similar names for drugs with opposite effects (e.g. amiodarone and amrinone), and storing dangerous drugs on the floor are all examples. The medical field's attribution of blame at the individual level as opposed to the system level is another feature of poor system design that makes errors hard to detect, as well as making it less likely that errors will be voluntarily disclosed. One of the major tenets of "continuous quality improvement" is to "drive out fear." If healthcare workers are afraid of reporting mistakes due to punitive environments, systems will never be improved since it will be impossible to determine how they are broken. Healthcare would do well to learn from the Federal Aviation Administration, which gives pilots immunity as part of the accident investigation process.

One way of preventing certain types of errors is known as a "forcing function," which is a technique or procedure that makes it difficult or impossible for a particular type of error to occur. This is seen every day while driving, where the engineering makes it impossible (in theory) to shift from "Park" into "Drive" or "Reverse" without having the brake depressed. With medications, forcing functions could be used to keep dangerous drugs such as neuromuscular blockers and concentrated potassium chloride solutions out of floor stock, where the potential for confusion with sterile saline or water for injection is high. While this will not prevent a vial of atracurium from being accidentally mixed with the sterile water vials in the pharmacy bins (e.g. 10 mL vials of atracurium (Bedford) and sterile water (Abbott) have similar purple accents, and have been mistaken for each other)[61] the extra step involved with getting the dangerous vial from the pharmacy adds the opportunity for another "check" in the process, as well as breaking the cycle of complacency associated with grabbing a vial from the bedside bin in the ICU and flushing a line without carefully reading the label.

Confirmation bias, the natural human tendency to see what is expected rather than what is actually there, is a frequent contributor to errors involving look-alike/sound-alike medication names and confusing medication labeling and packaging. When a bottle of hydralazine is grabbed instead of hydroxyzine, or a prescription for CELEBREX is misread as CEREBYX, healthcare providers see confirming evidence more easily than contradictory evidence. When calculations for drug dosages are checked, errors such as a misplaced decimal point are less likely to be found when the original calculation is reviewed, as opposed to being redone independently. The benefits of independent checks can be easily calculated—if the chance of one person making an error is 5%, the chance of two people making

the same error independently would be 5% × 5%, or 0.25%. Given time, money, and personnel constraints in healthcare today, independent double checks should be limited to medications with the highest risk of causing problems (e.g. heparin, insulin, chemotherapy, narcotics), or when there are complicated calculations involved.

Health care is behind many other industries in regards to systems analysis when errors occur, and systems redesign to prevent errors. Systems failures with medication errors can be broken down into broad categories:

Systems Failures Leading to Medication Errors

1) Communication deficits
   a) Misunderstanding a medication order, medication name confusion, transcription errors, errors in transitions between providers or units
2) Knowledge deficits
   a) Lack of information about the patient
      i) Allergies, contraindications, cross-reactions
   b) Lack of information about the drug
      i) Interactions, contraindications, doses, routes of administration, side effects
3) Performance deficits
   a) Rule violations (failure to follow established procedures)
   b) Faulty identity and dose checking
   c) Slips and memory lapses
   d) Calculation or preparation error
4) Systems deficits
   a) Equipment failure
   b) Monitoring failure
   c) Training failure
   d) Inadequate staffing
   e) Labeling and packaging deficits

The most common causes of medication errors appear to be human factors such as performance deficits, knowledge deficits, errors in preparation and calculation, and slips and memory lapses. In one study, over 65% of medication errors were attributed to human factors, followed by 16% due to communication problems and 16% due to naming, labeling, and packaging confusions.[62] Another study found almost 60% of medication errors were related to knowledge deficits of various sorts (30% to lack of knowledge and use of knowledge regarding the drug and drug therapy, 29.2% to lack of knowledge and use of patient characteristics and history), 17.5% related to errors in calculations or expression of rates and units, and 13.4% related to drug nomenclature (incorrect names, dosage forms, or abbreviations.)[13] A third study also found that knowledge errors (lack of drug knowledge, lack of patient knowledge or allergy information) account for almost half of the identified medication errors.[12] The Institute of Medicine has come up with an extensive list of recommendations to help decrease medication errors.

INSTITUTE OF MEDICINE PRINCIPLES TO REDUCE ERRORS IN HEALTHCARE

1) Provide Leadership
   a) Make patient safety a priority corporate objective.
   b) Make patient safety everyone's responsibility.
   c) Make clear expectations of safety oversight.
   d) Provide resources for error analysis and redesign.
   e) Develop process for dealing with unsafe practitioners.
2) Respect Human Limits in Process Design
   a) Design jobs for safety.
      i) Minimize staff distraction
      ii) Address training needs
      iii) Limit part-time workers and floats
      iv) Avoid assigned shift inversions
      v) Allow appropriate staffing levels
   b) Avoid reliance on memory.
      i) Use protocols and checklists
      ii) Drug–drug interaction checking software
      iii) Dosing cards
   c) Use constraints and forcing functions.
      i) Devices should default to safest mode in failure
      ii) Remove concentrated KCl from floor stock
      iii) Orders not filled without height, weight, allergy info
      iv) Luer locks for syringes and IV lines
   d) Avoid reliance on vigilance.
      i) Use checklists
      ii) Use automation
      iii) Limit long shifts
      iv) Rotate staff with repetitive functions
   e) Simplify key processes.
   f) Standardize work processes.
3) Promote Effective Team Functioning
   a) Train in teams those who will work in teams.
   b) Include the patient in care process and safety design
4) Anticipate the Unexpected
   a) Adopt a proactive approach: Examine processes of care for threats to safety and redesign them before accidents occur.
      i) Order entry systems that provide real-time alerts
      ii) Bar coding for positive identification and detection of misidentified patients, records, and so forth
      iii) "read back" for oral orders and instructions
      iv) Monitor vital signs, blood levels, and other labs for patients receiving hazardous drugs.
   b) Design for recovery.
      i) Have antidotes for high-risk drugs up-to-date and accessible

ii) Have procedures in place for quick response to adverse events
(1) Standardize processes across units
(2) Drill personnel to familiarize them with procedures and actions
iii) Devices should default to safest mode in failure
iv) Perform simulation training.
c) Improve access to accurate, timely information.
i) Have pharmacists available on wards and rounds.
ii) Computerized lab data alerts for abnormal values
iii) Lab reports and medication administration records at the patient's bedside.
iv) Place protocols in the patient's chart.
v) Color-code wristbands to alert of allergies.
vi) Track errors and near misses and report them
vii) Accelerate laboratory turnaround time.

5) Create a Learning Environment
a) Use simulations whenever possible.
b) Encourage reporting of errors and hazards.
c) Ensure no reprisals for reporting of errors.
d) Develop a working culture in which communication flows freely regardless of authority gradient.
e) Implement mechanisms for feedback and learning from error.

6) Medication Safety
a) Adopt a system-oriented approach to medication error reduction.
b) Implement standard processes for medication doses, dose timing, and dose scales on a given unit.
c) Standardize prescription writing and prescribing rules.
d) Limit the number of different kinds of common equipment.
i) Simplification is almost as good as standardization
e) Implement physician order entry.
f) Use pharmaceutical software.
g) Implement unit dosing.
h) Have the central pharmacy supply high-risk intravenous medications.
i) Use special procedures and written protocols for the use of high-risk medications.
j) Do not store concentrated solutions of hazardous medications on patient care units.
k) Ensure the availability of pharmaceutical decision support.
l) Include a pharmacist on rounds of patient care units.
m) Make relevant patient information available at the point of patient care.
n) Improve patients' knowledge about their treatment
i) Is this the drug my healthcare provider ordered?
ii) What are the trade and generic names?
iii) What is the drug for?
iv) What is it supposed to do?
v) How and when am I supposed to take it, and for how long?
vi) What are the likely side effects? What do I do if they occur?

vii) Is this new medication safe to take with other over-the-counter or prescription medication or with dietary supplements that I am already taking?
viii) What food, drink, activities, dietary supplements, or other medication should be avoided while taking this medication?

Adapted from Ref. (5)

CONCLUSION

Medication errors remain a significant source of morbidity and mortality, and are estimated to cost billions of dollars a year in the United States alone. The underlying systems have significant problems, including the system for error reporting, as well as systems to differentiate existing similar medication names and packages. Recommendations and guidelines exist that may help decrease all medication errors, including those from look-alike and sound-alike drugs and misleading packaging and labeling. Forcing functions, such as removing dangerous medications from floor stock, have decreased some serious medication errors due to packaging, labeling and naming confusion. Progress is being made on preventing confusing names, labels, and packages from making it to pharmacy shelves and hospital wards in the first place, and computerized order entry and patient/medication bar coding should help decrease medication errors significantly in the future.

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