A human factors engineering approach to a universal labeling system for communicating the risks of hazardous drugs

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Abstract

Federal law defines hazardous chemicals as any chemical that poses a physical or health hazard. A burgeoning segment of the modern arsenal of medications pose a similar risk. Cytotoxic and genotoxic medications are commonly cited examples of what this author classifies as hazardous drugs. However, due to the ambiguity or outright absence of textual warning labels on these medications, individuals who suffer incidental exposure in preparation, handling, administration and disposal of the drug-may be compromising their health and safety. The risk posed by hazardous drugs is not limited to those within the healthcare community either, due to the large number of individuals who handle hazardous drugs during the process of manufacturing, transport, administration, and disposal. The author proposes a simple, clear label by which all individuals who come in contact with hazardous drugs – regardless of background – can readily distinguish between hazardous and non-hazardous drugs. The implementation of the labeling system proposed herein has the potential to increase awareness of handling risks for hazardous drugs, thereby improving health, safety, and the environment.

Keywords: hazardous drugs, labeling, risk, safety, environment, risk communication

Key points

- Hazardous drugs are an increasingly large part of medical practice and pose a risk to over 8 million healthcare workers and even more individuals outside the medical community.
- Current warning labels for hazardous drugs can be ambiguous, difficult to read, or absent altogether from exterior packaging, posing a threat to the safety of hazardous drug handlers.
- A universal, high-visibility labeling system can make handling hazardous drugs safer for all individuals, regardless of medical knowledge.

Introduction

The genesis of the term 'hazardous drug' can be traced back to the definition proposed by the American Society of Health-System Pharmacists (ASHP) Technical Assistance Bulletin on Handling Cytotoxic Drugs in Hospitals issued in 1985[1]. Since then, the definition has evolved as drugs that pose a threat to human health and safety have become a burgeoning segment of the modern arsenal of medicines.

Early definitions were confined to antineoplastic drugs, which were later expanded to include other, non-antineoplastic cytotoxic medications. In deference to the initial Technical Assistance Bulletin, the ASHP continued to refer to 'cytotoxic drugs and hazardous drugs', differentiating the two categories even though the term 'hazardous drug', with few exceptions, encompassed cytotoxic agents as well[2]. Similarly, in 1986 the OSHA (Occupational Safety and Health Administration) guidelines focused on cancer chemotherapy drug safety, and expanded in 1995 to include "additional agents with toxicity profiles of concern.[3]" Thereafter, a National Institute for Occupational Safety and Health (NIOSH) work group published an alert in 2004[4], further expanding the ASHP definition of a hazardous drug. In the subsequent years the definition underwent further evolution; Table 1 includes a comparison of the definitions proposed by ASHP in 1990 and NIOSH in 2016.

In 2009, NIOSH estimated that "in the United States, an estimated 8 million health care workers [BLS 2007] are potentially exposed to hazardous drugs or drug waste at their work-sites."[5] Clearly, the estimate does not include the vast plethora of individuals who come in contact with hazardous drugs in the transportation and handling of drugs. As the sphere of influence of hazardous drugs continues to expand, so does the community of individuals who interact with and handle these drugs. While the Hazard Communication Standard mandates that hazardous drugs come with warnings that indicate the safety hazard they pose (29 CFR 1910.1200(f))[6], these warnings are often ambiguous, difficult to read, or are absent from package labels altogether, instead included within the pages of documentation that are included with the packaging. While these warnings may seem to be mere formalities, for healthcare professionals and other individuals who handle hazardous drugs, ambiguous or absent warning labels can result in dangerous handling errors with the potential for serious bodily harm.

The literature has no shortage of recommended safety procedures[7,8] for handling various hazardous drugs. Despite the abundance of hazardous drug-specific procedures, they are all to no avail if, in practice, handlers cannot easily and accurately identify hazardous drugs in the first place.

Definition of a hazardous drug

There has been a lack of coherence in the use of the term 'hazardous drug' in literature. NIOSH's "List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016", by its very title, differentiates between antineoplastic drugs and hazardous drugs. However, some antineoplastic drugs, not all, can be hazardous to human health and safety. Interferon alfa 2a/2b and alemtuzumab are typical examples.[9]

Federal law, however, has been consistent in its definition of a hazardous chemical as 'any chemical which is classified as a physical hazard or a health hazard'[6]. Considering that drugs, by definition, are classes of chemicals that come in contact with the body, it is only reasonable to apply the definition of a hazardous chemical to medications in order to avoid ambiguity.

Table 1. A comparison of the three main sets of criteria used in the classification of hazardous drugs over the past two decades (1990 to present).

ASHP[a] Technical Assistance Bulletin (1990)	Hazard Communication Standard, 29 CFR 1910.1200 (2012)	NIOSH[b] List of Hazardous Drugs (2016)
• Carcinogenicity in animal models, in the patient population, or both as reported by the International Agency for Research on Cancer • Teratogenicity in animal studies or in treated patients • Fertility impairment in animal studies or in treated patients • Evidence of serious organ or other toxicity at low doses in animal models or treated patients • Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems)	• Acute toxicity (any route of exposure) • Skin corrosion or irritation • Serious eye damage or eye irritation • Respiratory or skin sensitization • Germ cell mutagenicity • Carcinogenicity • Reproductive toxicity • Specific target organ toxicity (single or repeated exposure) • Aspiration hazard • Physical hazard	• Carcinogenicity • Teratogenicity or other developmental toxicity • Reproductive toxicity • Organ toxicity at low doses • Genotoxicity • Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria

[a] American Society of Health-System Pharmacists
[b] National Institute for Occupational Safety and Health

This author defines a hazardous drug as any medication which falls under the Hazard Communication Standard's definition of a hazardous chemical. This is inclusive of any medication which poses a 'physical hazard or a health hazard'.

As of 2016, NIOSH recognizes over 200 medications as hazardous[9]; this number is expected to increase as more hazardous drugs come to market and as increased use of these drugs results in hereto unrecognized handling risks manifesting themselves.

Review of current labeling practice

Under the Hazard Communication Standard, all hazardous substances are required to be "labeled, tagged, or marked"[6] with an indication of the handling risks they pose. However, this labeling can be ambiguous in how it expresses the danger these drugs pose. Some hazardous drugs may not bear any indicators of handling risk on the exterior labeling whatsoever, instead bearing warnings only within the small print of package inserts. Many of these inserts can easily exceed 20 pages in length, and those for hazardous drugs often include hazard statements only after several pages of fine print, making it difficult or neigh impossible for hazardous drug handlers to readily identify if a drug is hazardous or not.

For those hazardous drugs that do in fact have exterior labeling, it is often difficult to distinguish the warning text from the rest of the label text due to the similar font, color, and formatting that is employed. In time-sensitive situations, taking the time to parse through the information on the label of every single medication handled is not practical. Although pharmacies and other medical institutions maintain lists of hazardous drugs[9] for this reason, the subtle changes in the terminology and risks associated with hazardous drugs over the years (e.g. the term 'antineoplastic' can no longer be used interchangeably with 'cytotoxic') as well as the constantly evolving formulations of drugs means that the manufacturer-supplied label is a significantly more reliable source of accurate information.

The current labeling system additionally fails to effectively communicate the amount of danger posed by hazardous drugs. At best, the difficulty in locating warning text can imply to handlers (especially patients and their families) that the handling risk is not grievous enough to warrant a high-visibility warning akin to those on other hazardous consumer products (e.g. tobacco products). At worst, the obscurity of warnings can mislead handlers into believing that a drug is not hazardous, and that there are no specialized safety procedures that need to be followed.

Recent literature has shown that hazardous drug handlers – especially those outside the pharmacy – often do not fully realize the risks that hazardous drugs pose, often presuming that standard safety procedure will be sufficient. Such oversights can be extremely dangerous to human health – common antineoplastic drugs such as cyclophosphamide are so toxic that even the bottle in which the pills are packaged requires specialized impervious gloves to handle[10,11,12,13]. Vincristine and doxorubicin are potent enough for the trace quantities that remain in the aerosolized urine of patients taking it to possibly cause a reaction in individuals caring for them[10].

Drugs such as cyclophosphamide and vincristine are just two examples of the over 200 hazardous drugs that are currently recognize by NIOSH. According to the CDC and NIOSH, in 2016 at least 8 million healthcare professionals are exposed to hazardous drugs in their workplaces[14], an increase from the 5 million employees that the US Department of Commerce expected to be exposed in 1999[8]. These statistics do not include exposed individuals outside of the medical profession: for instance, drug manufacturer employees, transport personnel, patients and their family/caretakers, etc. It is this pool of individuals, those outside the medical community, who face the most danger from hazardous drugs. Not only are there more individuals in this group, but they are at a greater risk due to their lack of medical training. Words such as 'cytotoxic' and 'teratogenic' may not convey danger to them. In the case of patients and their families, who often trust healthcare professionals implicitly, it can be easy to neglect to read the fine print in favor of trusting that the medications that are supposed to cure them is safe to handle.

Instead of a textual label, a vivid pictorial indicator that can unambiguously and efficiently communicate danger for hazardous drugs would have the capacity to drastically improve the safety of medication handling for all individuals. It would assist pharmacists and other healthcare personnel in the rapid identification of hazardous drugs amongst non-hazardous ones during the time-sensitive conditions of the workplace, and indicate that specialized safety procedures would need to be referenced. For patients and family members, a universally understandable pictorial label would allow for an unambiguous indicator of danger, encouraging them to ask a healthcare professional about handling their medications or to read oft-overlooked patient education packets included with their prescription. For individuals without medical training, a pictorial diagram circumvents confusing jargon and ensures that they can exercise the 'right to understand'[15] that the Hazard Communication Standard and Globally Harmonized System of Classification and Labeling of Chemicals (GHS) laid the foundation for. A clear pictorial indicator can overcome linguistic, cultural, and knowledge-based barriers, and can ensure that all individuals can safely interact with these medications.

Proposed labels

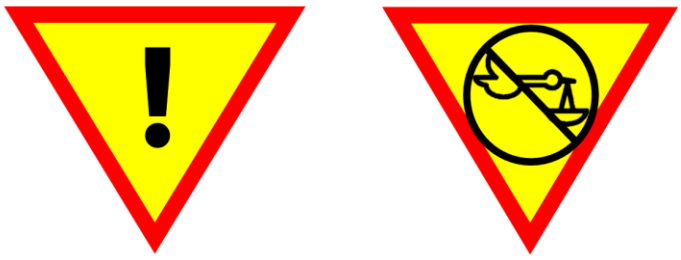

Figure 1. The hazardous drug warning labels proposed by the author, featuring high-contrast colors and clear pictograms. The general label (left) indicates that a hazardous drug poses a risk to all individuals (e.g. due to carcinogenicity, genotoxicity, cytotoxicity, etc.). The pregnancy/developmental risk label (right) indicates that a drug poses a risk to pregnant women or developing fetuses only.

Two separate labels are proposed – one which indicates that a drug is hazardous to all individuals (i.e. due to carcinogenic, genotoxic, cytotoxic, or other toxic effects) and one which indicates that a drug is hazardous to only pregnant women and/or fetuses. Both labels in the shape of an inverted triangle, featuring a vibrant yellow background and red trim along with a simple pictogram in the center. The general label features the standard exclamation mark as an indicator of risk, while the reproductive risk label features a stork carrying an infant (a common symbol associated with pregnancy and infants) overlaid with the prohibition symbol of a circle and backslash (Figure 1).

The proposed labels are designed to be high visibility pictograms to be added to the exterior labeling of any medication that meets the definition of 'hazardous drug'. It is recommended by the author that the labels be placed in the whitespace of the medication packaging on both the drug container and on any additional packaging such as boxes, etc. that the drug is transported in, and that they be sized in such a manner as to cover, at minimum, 10% of the surface area of any face on which it is placed in order to increase visibility.

Rationale

The recommended labels provide clear, visual indicators as to whether a drug is hazardous to a particular individual, and are designed in such a manner as to be easily visible and comprehensible even when resized. When compared to the labels recommended by Hazard Communication Standard[16], it is apparent that the vivid coloring and shape of the proposed label is more readily distinguished from the rest of the exterior markings, due to its application in a manner that provides high contrast and highlights the pictogram[17].

Although their simplicity means that they do not convey the specifics of the hazard a drug poses like the Hazard Communication Standard pictograms do, these labels are able to convey the most essential information – i.e. the hazardous nature of the drug, and the population to whom the drug is hazardous – in the crucial few moments when an individual first looks at the drug's packaging. In doing so, these labels succeed in alerting handlers to the presence of danger, and by engaging their attention, can encourage them to take the time to re-examine the label and to reference appropriate safety procedures before proceeding.

The simplicity of these labels also saves handlers the valuable time required to parse through the large amount of information contained in package inserts in search of warnings, instead removing any ambiguity as to whether a drug is hazardous or not. The fact that it is a purely visual label, containing no text whatsoever, removes the language barrier imposed by warning text and makes it much more visible against the small print present on the rest of the packaging[18]. Its unambiguous statement of danger has potential to prevent dangerous lapses in safety procedure or other errors caused by miscomprehension of warning text in the package insert[19].

The literature also indicates that the proposed warning labels are of the ideal design to capture attention, both on a conscious and unconscious level. According to Wogalter and Vigilante[20], discernibility of a warning is 'closely tied to brightness and color contrast' – in particular, the color combinations of black and saturated yellow or white and saturated red are

recommended for maximal contrast[21]. Both contrasting color pairs are present in the proposed labels – the black pictograms at the center of each label are surrounded by saturated yellow fill to provide highlighting[22], while the edge of the labels is a saturated red that interfaces with the whitespace of the surrounding area.

The sharply defined inverted triangle shape of the recommended labels is also one that the literature supports as being attention capturing. Larson et. al. noted in a 2009 study that a "simple V-shape [angle] is capable of activating neural networks instantiating detection of threat and negative affect", specifically the neural networks associated with the fight-or-flight response in the amygdala[23]. Later studies[24] elaborated on this finding, noting that a downward-pointing V-shape, like that present in an inverted triangle, allowed for the concept of a threat/danger to be transmitted rapidly[25], even with minimal exposure to the shape, and that the shape may engage attention for longer than similar figures. It is possible that the inverted triangle shape resembles the facial shape of primitive humans' ancient predators, thereby making it an ideal figure for use in a label intended to capture attention and convey a sense of danger.

Thus, the proposed label utilizes the ideal shapes, colors, and contrast to take advantage of a number of subconscious processes developed through millennia of evolution to nonverbally capture and retain the attention of the handlers of hazardous drugs. The fact that it does so in a universally understandable manner that can be displayed even on the smallest of ampule label makes it ideal as a cost-effective means of improving the safety of all individuals who handle hazardous drugs.

Discussion

The two greatest obstacles that might impact the use of the proposed warning labels are the financial burden and the possibility of alert fatigue. With regards to implementation, drugs can be easily identified as requiring the label when reviewed by the FDA or other regulatory agency for approval. The simple design and small size of the label also allow integration into existing manufacturer packaging with relative ease, and the warning label's role in referring handlers to the appropriate safety procedures (which are already included with the package insert) means that it is associated with a smaller materials cost than alternative methods, such as pull-out labels (which require the use of extra material for each package), might otherwise incur. The recommendation that the warning label occupy a minimum percentage of surface area on any face that it appears has the benefit of increasing the label's visibility on smaller containers (e.g. ampules) without requiring an increase in container size, another factor which reduces the financial burden on the manufacturer.

The application of these labels only on drugs that are identified as hazardous by a regulatory agency such as the FDA also facilitates the limitation of alert fatigue. Given the unique visual nature of the warning labels, in contrast to standard textual warnings that appear on medications, and the fact that the labels will only be present on medications that actively require safety measures on the part of the handler, individuals are unlikely to become habituated to them.

The lack of any apparent downsides with regards to alert fatigue or financial burden render the design of the proposed warning labels a practical alternative to the current text-based

warning system currently used by the pharmaceutical industry. Considering the potential benefits of the new label – increased visibility and comprehension speed, and the possibility of a more universally understandable label, among others – the proposed label may very well be a better alternative to the current warning system.

Conclusion

As hazardous drugs become an increasingly large part of medical practice and pose an increasing health risk to those who come in contact with the drug, prudence and safety militates in favour of an appropriate warning system to ensure the safety of all individuals. This includes individuals who may not necessarily have medical expertise, such as patients, their families and/or caregivers, transport personnel for hazardous drugs, etc. In order to ensure that all these individuals, regardless of their medical knowledge, are aware of the dangers that hazardous drugs pose, it is necessary for a hazardous drug warning label to be universally comprehensible, highly visible against the rest of the drug's packaging, and attention-capturing.

The two warning labels proposed by this author – one for general risk and one for pregnancy/developmental risk - meet all three of those criteria, and have the additional benefit of having no apparent downsides with regards to alert fatigue or excessive implementation costs. The proposed labels also are designed in a manner that integrates design principles shown in the literature to be associated with increased attention capture and maintenance, thereby making them more effective warnings than the current system.

If implemented, these warning labels have the potential to increase awareness of handling risks for hazardous drugs, and thereby improve the safety of hazardous drugs for all individuals.

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