

Interpretations of a Teratogen Warning Symbol

KATHERINE LYON DANIEL,^{1*} KAREN DENARD GOLDMAN,² SUE LACHENMAYR,³
J. DAVID ERICKSON,¹ AND CYNTHIA MOORE¹

¹*Birth Defects and Pediatric Genetics Branch, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia 30341*

²*Health Education and Promotion Program, Health Services Department, Lehman College, City University of New York, New York, New York 10012*

³*New Jersey Department of Health and Senior Services, Lebanon, New Jersey 08833*

ABSTRACT

Background: Warning symbols are used on teratogenic medications to communicate the message that women should (1) not take that medication if they may already be pregnant, and (2) not get pregnant while taking that medication. Communications research indicates that people interpret symbols or pictures in different ways. Other studies have shown that patients do not always receive education materials that are part of prescription protocol. Researchers at the Centers for Disease Control and Prevention (CDC) tested the interpretation of the teratogen warning symbol and its ability to convey the correct information without accompanying education.

Methods: A teratogen warning symbol currently printed on some medication packaging uses graphics and text warning the user not to get pregnant. Researchers interviewed women of childbearing age about their interpretation of the warning symbol and its meaning. Ninety-seven women were interviewed in a variety of locations, including public health clinics, literacy and job training offices, health clubs, and malls.

Results: Only 21% of women interpreted correctly without prompting that they should either not take the medication if they are pregnant or not get pregnant while taking the medication. Twenty-seven percent of women first thought the symbol meant the package contained birth control medication, and 24% said it simply indicated the package contained drugs or medicine. An additional 7% said they did not know what the symbol was supposed to mean; 39% of respondents offered circumstances in which prescription medications might be shared.

Conclusions: Misinterpretation of warning symbols can result in serious consequences. This research should serve as an urgent call for mandating education for all patients receiving drugs with teratogenic properties, and careful pretesting and modification of warning symbols before they are used on medications with teratogenic effects.

Teratology 64:148–153, 2001.

Published 2001 Wiley-Liss, Inc.†

INTRODUCTION

Since 1988, a warning symbol has been used to inform prospective patients and consumers that a medication is a teratogen—a substance known to cause birth defects (Fig. 1). The symbol depicts the silhouette of a pregnant woman covered by the international symbol for “No” (a red circle with a slash across it). The phrases “Avoid Pregnancy,” “Do NOT Get Pregnant,” or a combination of both messages are superimposed on the circle and/or slash, or appear above and below the symbol itself. This symbol has appeared on prescription drug labeling, medication packaging, and educational materials and has been published on the Internet in private industry and federal government web pages. The warning symbol has been used for the widely used acne medication isotretinoin (Accutane®). Accutane has been advocated to treat both serious and mild acne, and approximately 2,000 pregnancies have occurred in women taking Accutane (Cunliffe et al., '97; Dermatologic and Ophthalmic Drugs Advisory Committee, '00a). The warning symbol is now being used for the drug thalidomide (Thalomid®), which was approved for the first time in the United States in 1998 (Lary et al., '99). Thalidomide was responsible for severe disabling birth defects in an estimated 10,000 children during the 1950s and 1960s before it was taken off the market. However, applications for thalidomide's anti-angiogenic and immunomodulatory properties are increasing, and it is likely to be prescribed more frequently (Lary et al., '99). Among women, the total number of physician visits for acne that resulted in Accutane prescriptions has grown from an estimated 150,000 in 1989 to 406,000 in 1997 (Stern, '00).

The teratogen warning symbol was used as part of the Accutane Pregnancy Prevention Program developed by the manufacturer in 1988. The following year,

*Correspondence to: Katherine Lyon Daniel, Birth Defects and Pediatric Genetics Branch, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Hwy, F-45, Atlanta GA 30341.
E-mail: kdl8@cdc.gov

Received 6 November 2000; Accepted 7 May 2001



Fig. 1. Teratogen warning symbol used in conjunction with the questionnaire to determine women's interpretation of this symbol.

in 1989, Accutane packaging was changed from loose pills in a bottle to a blister pack, and the symbol was placed behind every capsule (Mitchell, '95). The symbol has been used as one component of educational programs on the appropriate and inappropriate uses of medications. These programs are either voluntary or mandatory. When used as part of these materials, the symbol is intended as a visual aid to remind patients of the danger of therapeutic agents they should have learned about in an initial counseling or education session on the medication and contraceptive issues. For some of these teratogenic drugs, prescription has become more acceptable over time for a wider range of conditions and severities (Cunliffe, '97). Patients do not always receive sufficient information, and some may not receive any counseling at all (MMWR, '00).

In addition, medications may be taken or prescribed contrary to indications, and warnings about teratogenic potential of medications are unheeded by some patients (Mitchell, '95). For example, studies of isotretinoin use to assess prevention program effectiveness have indicated that patient compliance with pregnancy prevention measures during the course of treatment ranged from 32% to 38% (Pastusak et al., '94). Of women whose pregnancies were reported to the manufacturer, only 51% resulted from contraceptive failure (Dermatologic and Ophthalmic Drugs Advisory Committee, '00b). One survey of 14 women who became pregnant while using isotretinoin found that none of the women had been exposed to all elements of the multifaceted education program designed by the drug manufacturer to reduce the likelihood of pregnancy during medication use (MMWR, '00). This exhorts us to ensure the effectiveness of the warning symbol in conveying a serious prevention message where other forms of education may be lacking. The best way to understand this is to pretest the symbol in a sample of the intended target audience that has not been exposed to previous education materials (Lippin and Fingeret, '91; Theis, '95).

Some teratogens are so potent that just one dose taken in early pregnancy can cause severely disabling or fatal birth defects. For these medications, there may be "no safe dose, no safe duration of fetal exposure, no safe period of exposure during pregnancy" (Dai, '92). Research on physician-patient interaction by Lipkin ('96) demonstrated that physicians often used overly technical explanations and that, even under ideal conditions, patients retained only 75% of what they heard. When patients receive incomplete or inadequate counseling, or are not able to read or understand the information presented to them, labeling and warning symbols on medication packaging take on a larger educational burden. To be fully effective in helping to prevent birth defects, a teratogen warning symbol should effectively convey two related messages: that nonpregnant women who are taking the accompanying medication should not become pregnant, and that pregnant women (or women who might be pregnant) should not take the medication. The research question of this study was: How do women interpret the teratogen warning symbol outside of the context of a patient education program?

METHOD

A questionnaire instrument was developed to determine women's interpretation of the teratogen warning symbol, and the instrument was pretested with 24 women in well-baby, Special Supplemental Nutritional Program for Women, Infants, and Children (WIC), and family planning clinics within the New York metropolitan area and surrounding suburbs. After refinement of the instrument, 97 ethnographic interviews were conducted with women of childbearing age in 10 locations: a well-baby clinic, a family planning clinic, an HIV/AIDS treatment clinic, a health club, a prenatal-care clinic, a WIC clinic, a literacy program office, a home health aide training program office, an HIV/AIDS peer training seminar location, and a shopping mall. The questions were open-ended in format, allowing participants to contribute information in their own words. Although the questions on the instrument were standardized, the ordering of follow-up questions and prompts sometimes varied depending on the participant's responses. This was designed to achieve standardized data collection while still allowing the interviewer to pursue unanticipated responses (Patton, '87). Locations were chosen to include participants of varied race, ethnicity, age, and education (Table 1), and to make sure that participants included some women with lower literacy skills and others with limited English proficiency. Two interviewers were trained and checked for consistency, and interviews were conducted in the language of the participant's choice. Interviews in Spanish were conducted with a bilingual interviewer. Interviewers recorded the answers on a form for later analysis; most interviews were also tape-recorded. A limited number of interviews were conducted at each setting.

TABLE 1. First response to question "what is this?" by demographics of respondent, percent (n)

| Description categories | Birth control % (n) | Drugs/medicine % (n) | Don't take if pregnant ^a % (n) | Hormones/vitamins for women % (n) | I don't know % (n) | Don't get pregnant ^a % (n) | Other % (n) | Total % (n) |
|------------------------------|---------------------|----------------------|---|-----------------------------------|--------------------|---------------------------------------|-------------|-------------|
| Teen | 13 (1) | 63 (5) | 13 (1) | 13 (1) | — | — | — | 8 (8) |
| 20–40 | 33 (18) | 18 (10) | 20 (11) | 7 (4) | 6 (3) | 2 (1) | 14 (8) | 57 (55) |
| 40+ | 24 (8) | 27 (9) | 18 (6) | 9 (3) | 12 (4) | — | 12 (4) | 35 (34) |
| Black | 24 (8) | 18 (6) | 21 (7) | 12 (4) | 12 (4) | 3 (1) | 10 (3) | 34 (33) |
| White | 33 (11) | 18 (6) | 24 (8) | 9 (3) | 6 (2) | — | 10 (3) | 34 (33) |
| Hispanic | 21 (5) | 42 (10) | 13 (3) | 4 (1) | 4 (1) | — | 20 (4) | 25 (24) |
| Asian | 25 (1) | 50 (2) | — | — | — | — | 25 (1) | 4 (4) |
| Other | 66 (2) | — | — | — | — | — | 33 (1) | 3 (3) |
| Elem./some HS | 29 (6) | 36 (8) | 10 (2) | 5 (1) | 10 (2) | — | 14 (3) | 23 (22) |
| HS grad/Voc/Some coll. | 27 (13) | 29 (14) | 13 (6) | 15 (7) | 6 (3) | 2 (1) | 8 (4) | 49 (48) |
| Coll. grad/Grad school | 30 (8) | 7 (2) | 37 (10) | — | 7 (2) | — | 19 (5) | 28 (27) |
| Well-baby/fam. planning | 42 (10) | 13 (3) | 8 (2) | 13 (3) | 13 (3) | — | 13 (3) | 25 (24) |
| HIV | 24 (7) | 35 (10) | 10 (3) | 10 (3) | 7 (2) | 3 (1) | 10 (3) | 30 (29) |
| Low literacy | 33 (4) | 8 (1) | 17 (2) | 8 (1) | 17 (2) | — | 17 (2) | 12 (12) |
| Health club | 28 (5) | 6 (1) | 50 (9) | — | — | — | 17 (2) | 18 (17) |
| Mall | 7 (1) | 64 (9) | 14 (2) | 7 (1) | — | — | 7 (1) | 14 (14) |
| Had child | 28 (14) | 34 (17) | 12 (6) | 6 (3) | 8 (4) | — | 12 (6) | 52 (50) |
| Not had child | 27 (11) | 15 (6) | 24 (10) | 10 (4) | 7 (3) | 2 (1) | 15 (6) | 42 (41) |
| Total responses ^b | 28 (27) | 25 (24) | 19 (18) | 8 (8) | 7 (7) | 1 (1) | 12 (12) | 100 (97) |

^aCorrect answer.

^bTotals do not always equal 100 because of rounding, and/or missing data.

PROCEDURE

First, participants were shown a computer-generated picture of a medication blister pack with the warning symbol as it appears on a medication package and were asked what they thought it was. This initial view of the symbol was the actual size used on packages of teratogenic drugs (approximately one square inch).

Second, participants were shown slightly enlarged versions of the symbol printed in color on a page, with the accompanying text ("Do NOT Get Pregnant"). The interviewer explained that the symbol would be printed on a package of medication. Interviewers recorded initial responses on conversation guideline sheets without comment and probed for other interpretations. In the event that participants still gave interpretations that did not include the intended message/s, the interviewer followed up with a little more information, for example, "and if I told you this wasn't birth control, what else might this symbol mean?"

Third, the interviewer explained the concept of teratogens, revealed the intended message of the symbol to participants, and asked for their reaction to that information. A full page-sized symbol without the accompanying text was shown to women to facilitate discussion of the symbol itself (apart from the text). Women were asked how they thought the symbol might be improved to more clearly communicate the intended message. Several potential alternative phrases developed using information from the pretest were provided to choose from if participants did not have a suggestion. Questions at the close of the interview included participant demographics and, in later interviews, views on medication sharing were added.

ANALYSIS

The responses were recorded and coded, then analyzed inductively across cases using qualitative analysis techniques described by Miles and Huberman ('94). These include (1) grouping or condensing data, (2) creating a display of indices in matrix form, (3) partitioning or dividing the data points in logical ways, and (4) verifying the data clusters so that variables of interest can be labeled and distinctions between them can be further examined. The partitioning and clustering activities allow for the observation of patterns or themes that are reported in results below. For some variables, the data were analyzed and reported quantitatively using percentages of respondents.

RESULTS

Ninety-seven women participated in the interview. Eight percent of the respondents were teens aged 18 or 19 years, 56% were aged 20–40 years, and 35% were older than 40 years (Table 1). Thirty-three percent of the women identified themselves as black, 33% as white, 25% as Hispanic, 4% as Asian, and 3% as other. About 23% of the sample had less than a high school degree; 49% had a high school degree, GED, vocational school degree, or some college classes; and 28% had a college degree or beyond. Fifty percent of the respondents reported that they had had a child, 41% reported they had not, and 9% declined to answer.

The order of presentation of the materials did not systematically affect the interpretation in the pretest. Eight unique conceptual themes or response categories were clustered into categories (Table 2). The themes are presented in order of the most common first impressions:

TABLE 2. Response summaries of teratogen warning symbol interpretations

| Description or theme | First interpretation: "what is this?" | Second interpretation: "what does this symbol mean?" | Third interpretation: "what else might it mean?" | Total responses | Total ^b % |
|--|---------------------------------------|--|--|-----------------|----------------------|
| Birth control | 27 | 40 | 9 | 76 | 29 |
| Drugs/medicine | 24 | 1 | 1 | 26 | 10 |
| <i>Don't take if pregnant</i> ^a | 18 | 20 | 15 | 49 | 19 |
| Hormones/vitamins | 8 | 1 | 2 | 11 | 4 |
| Don't know | 7 | 2 | 7 | 16 | 6 |
| <i>Do not get pregnant</i> ^a | 1 | 17 | 2 | 25 | 9 |
| Danger | 5 | 2 | 5 | 12 | 5 |
| Abortion pill | 1 | 2 | 12 | 15 | 6 |
| Harmful to fetus | 1 | 1 | 4 | 6 | 2 |
| For HIV/AIDS | 1 | 0 | 7 | 8 | 3 |
| Bad to get pregnant | 0 | 5 | 5 | 10 | 4 |
| Other | 4 | 4 | 3 | 10 | 4 |
| Total responses | 97 | 95 | 72 | 264 | 100 |

^a“Correct” responses.

^bTotal does not equal 100 because of rounding.

Theme 1—“Birth Control”: Twenty-eight percent of the women interviewed reported their first interpretation was that the symbol indicated the medication was birth control or was used for emergency contraception. A total of 78% of women reported this interpretation at some point in the interview.

Theme 2—“Drugs or medicine”: Twenty-five percent of respondents initially interpreted the symbol solely to indicate that the package contained drugs or medicine, without an associated warning.

Theme 3—“If Pregnant, Don't Take This Medication” (correct message): Nineteen percent of respondents reported as their first interpretation that women who were already pregnant should not take the medication. Fifty-one percent reported this interpretation at some point in the interview.

Theme 4—“Hormones or Vitamins”: Eight percent of women first thought the symbol meant the package contained hormones or vitamins; a total of 11% of women interpreted this throughout the interview.

Theme 5—“I Don't Know”: Seven percent of women were unable to interpret what the symbol might mean. An additional 9% did not offer any additional interpretations after their initial thoughts.

Theme 6—“If Taking This Medication, Don't Get Pregnant” (correct message): One percent of women reported first that the symbol warned nonpregnant women they should not get pregnant while taking the medication; 26% reported this at any time during the interview.

Theme 7—“Danger for Pregnant Women”: In a related interpretation to Theme 2, 12% of the respondents said they thought it meant the pills were “dangerous” for pregnant women, but without further explanation.

Theme 8—“Abortion Pill”: A total of 16% said they thought the symbol meant that the pill could or

might induce an abortion; only one person gave this as the first interpretation.

Theme 9—“Other Responses”: Five women gave various other responses first, including that the drug was for HIV/AIDS treatment, or that the symbol indicated that pregnancy is “bad.” About 25% of women gave answers in this category at some point in the interview.

Combination Themes 2 and 3—“Complete understanding” (both correct messages): Nine women (11%) reported both of the “correct” desired messages during the course of the interview. Only 20% of participants were able to identify either one of the “correct” messages first, without probing.

Sixty-one women were asked whether there was a situation in which it was okay to share medications: 39% said it was never okay, 21% said for nonprescription medications only (e.g., for headaches or pain relief), and 39% gave circumstances in which sharing prescription medication was acceptable. Reasons for sharing included: it is common practice (everyone does it), cost of medication, share with friends and family, to help others, the same medication for which person has a prescription, and illegal/irresponsible use (addiction/to get high/to calm nerves).

DISCUSSION

A large proportion of the women in this study did not understand the intent of the warning symbol when they saw the symbol without counseling or education. By itself, this symbol does not appear to communicate the risk for birth defects. Twenty-eight percent of women interpreted the message with a meaning opposite of its intent: they initially thought this symbol meant the medication prevented pregnancy. This demonstrates a serious weakness of this symbol and its use in helping to prevent teratogenic exposure. In fact, this incorrect interpretation may increase teratogenic risk

because women who have not received counseling may be less likely to use other birth control methods while using this medication.

All participants confirmed that once they had been told what the message was supposed to convey, they could easily see and understand the correct warning message(s). This demonstrates the difference between "recognition" of a message and initial "interpretation" of a message and underscores the importance of initial education and counseling. The study also showed that many women experienced difficulty seeing beyond their initial interpretation. Once some participants had reached a conclusion they repeatedly stated that the medication must be birth control, even when the interviewer suggested otherwise. This tendency is consistent with the interpretation of risk information (Arnon and Kreitler, '84; Hogarth, '87), especially when the patient has no reason to question her initial interpretation. This also underscores the importance of providing complete education for all patients, including testing the patients' understanding of risks and counseling patients not to share medications with others.

The nature of the weaknesses of the symbol were that some women reported they did not understand the meaning of the international symbol for "NO," (the red circle with a slash through it), some read the words as "TO not get pregnant" instead of "DO not get pregnant," and a few said they had not read beyond their initial interpretation because it was a directive statement and/or negative in tone. Once the intent of the message was explained, many participants reported they wanted more information about why they should heed the warning. A few expressed resentment at being directed to take action without being given a reason. When asked for improvements, a number of participants suggested that warning messages that explained the outcome would be most effective for them (examples include "Causes Birth Defects" or "Will Cause Birth Defects").

This study has several limitations. First, participants were recruited from a convenience sample and may not be typical of patients who could be prescribed these medications. The results should be interpreted to apply to a high-risk group of lower socioeconomic status and limited literacy skills (although one-half of the sample reported some education beyond high school, and one quarter had a college degree). Second, as discussed earlier, the symbol was shown to women completely outside of a patient education context—they had not received any information previously about birth defects, teratogens, or other related issues. Therefore, these results may or may not apply to women who receive brief or limited educational counseling along with their prescription. The conditions under which these findings do apply include: instances where no education is provided, when medication is shared with others, when medication samples are obtained from health-care providers or friends, or when the medication is obtained in other countries where pregnancy prevention programs accompanying terato-

genic drugs are less common or nonexistent. Of particular concern in this country are patients who have low literacy skills, limited intellectual capacity, or limitations in the language of the warning text. Their reliance on visual cues underscores the importance of universally understood symbols. Research results by Lippin and Fingeret ('91) demonstrated that pictograms often needed to be explained before low literacy patients understood their meaning. Presenting the symbol out of context may contribute to some of the vague response themes such as "Drugs or Medicine" and "Hormones or Vitamins." The response "Danger for Pregnant Women" might indicate at least a partial understanding of the risk. Repeat treatment/use is another important issue because patients may not receive the same counseling as they did during the initial visit and course of treatment, and may forget the contraindications.

CONCLUSIONS

The existing teratogen warning symbol may be an effective reminder of educational counseling if the health care provider has already conveyed that information. However, for women who have not received this education, the symbol is likely to convey a message counter to its intent and could possibly increase the likelihood that a patient would not use effective contraception while taking a prescribed teratogenic medication. Although drugs with teratogenic properties may provide significant and unique benefits, their effectiveness is coupled with the potential for harmful effects. It is thus imperative that women patients clearly understand the teratogenic risks and the need to avoid pregnancy. Recommendations include the following: (1) health-care providers who prescribe teratogenic medications should always provide complete educational counseling about birth defects and pregnancy prevention; and (2) although the warning symbols should be used to reinforce the educational counseling conducted by the referring physician, drug manufacturers and package designers should assume the responsibility to carefully test the interpretation of warning symbols outside of the context of education programs for their effectiveness in communicating the potential risks of the teratogen and modify symbols as needed. The need for a warning symbol, tested for effectiveness and clarity for both the general population and higher risk groups, is imperative to help prevent birth defects associated with teratogenic medication use.

LITERATURE CITED

- Arnon R, Kreitler S. 1984. Effects of meaning training on overcoming functional fixedness. *Curr Psychol Res Rev* Winter:11-24.
- Cunliffe WJ, van der Kerkhof PCM, Caputo R, Cavicchini S, Cooper A, Fryand OL, Gollnick H, Layton AM, Leyden JJ, Mascaro JM, Ortonne JP, Shalita A. 1997. Roaccutane treatment guidelines: results of an international survey. *Dermatology* 194:351-357.
- Dai WS, LaBraico JM, Stern RS. 1992. Epidemiology of isotretinoin exposure during pregnancy. *J Am Acad Dermatol* 26:599-606.

- Dermatologic and Ophthalmic Drugs Advisory Committee. Briefing Information, 2000a. Appendix II: overview of Accutane and pregnancy exposure, September 18–19, 2000, Rockville MD: US Department of Health and Human Services, Food and Drug Administration [<http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3639b1.htm>].
- Dermatologic and Ophthalmic Drugs Advisory Committee. Briefing Information, 2000b. Pregnancy prevention program: a risk management program to reduce pregnancies during Accutane treatment, September 18–19, 2000, Rockville MD: US Department of Health and Human Services, Food and Drug Administration [<http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3639b1.htm>].
- Hogarth R. 1987. *Judgement and choice: the psychology of decision*. 2nd ed. New York: John Wiley & Sons. p 114–119.
- Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun, JT, Curry CJ, Fernhoff PM, Grix AW, Lott IT, Richard JM, Sun SC. 1985. Retinoic acid embryopathy. *N Engl J Med* 313:837–841.
- Lary JM, Daniel KL, Erickson JD, Roberts HE, and Moore CA. 1999. The return of thalidomide: can birth defects be prevented? *Drug Safety* 3:161–169.
- Lipkin M. 1996. Physician–patient interaction in reproductive counseling. *Obstet Gynecol* 88:31S–40S.
- Lippin TM, Fingeret HA. 1991. How adults with limited literacy skills cope with reading medication labels. Durham, NC: Literacy South. p 21–23.
- Miles MB, Huberman AM. 1994. *Qualitative analysis: an expanded sourcebook*. Thousand Oaks, CA: Sage. p 1–11.
- Mitchell AA, Van Bennekom CM, Louick C. 1995. A pregnancy prevention program in women of childbearing age receiving isotretinoin. *N Engl J Med*, 333:101–106.
- Pastuzak A, Koren G, Rieder MJ. 1994. Use of the retinoid pregnancy prevention program in Canada: patterns of contraceptive use in women treated with isotretinoin and etretinate. *Reprod Toxicol* 8:63–68.
- Patton MQ. 1987. *How to use qualitative methods in evaluation*. Newbury Park, CA: Sage. p 108–143.
- Stern RS 2000. Medication and medical service utilization for acne: 1995–1998. Report to the Dermatologic and Ophthalmic Drugs Advisory Committee, September 18–19, 2000. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration.
- System for Thalidomide Education and Prescribing Safety (STEPS). 1998. [prescriber folder]. Warren, NJ: Celgene Corp.
- Theis SL, Johnson JH 1995. Strategies for teaching patients: a meta analysis. *Clin Nurse Spec* 9:100–105.