INVESTIGATING THE EFFICACY OF AN INTERACTIVE WARNING FOR USE IN PRESCRIPTION LABELING STRATEGIES

By

Ji Yon Lee

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Packaging- Master of Science

2013

ABSTRACT

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The format and the placement of prescription warning label vary. Patients' attentive behaviors for the warning labels are also varied. Some studies suggest that 'interactive warning labels,' those placed in such a way that they require physical manipulation to accomplish a necessary task (e.g. opening), result in greater rates of attention and information recall.

Research presented herein investigated the noticeability of prescription warning labels (PWLs) with varied placement. Specifically, we tested a vertical, horizontal or interactive placement of the warning using eye-tracking followed by a recall and recognition test. Each subject was handed three vials, each with a different warning placement, in sequence.

There was evidence that the placement significantly impacted the probability that patients viewed warnings ($P=0.0011$) and the amount of time that they spent viewing the information ($P<0.0001$). Also, the result suggested that people were significantly more likely to view the interactive format than the vertical ($p=0.0153$). Participants that viewed the warnings spent significantly more time viewing the information presented in interactive format than for either those in the horizontal ($P<0.0001$) or vertical ($P<0.0001$). Subjects were also better at recalling informational content that was in an interactive format as compared to the horizontal ($P= 0.0009$) or vertical placements ($P<0.0001$).

ACKNOWLEDGEMENTS

I would like to express my greatest gratitude to my advisor Dr. Laura Bix for her all support and guidance. She always takes care of and encourages me to conduct this research and help me to go further. I have been able to do my research with all passion and joy thanks to her. Furthermore, I have been able to grow further in terms of my academic achievement.

I would also like to thank my academic committee members, Dr. Diana Twede and Dr. Kami Silk for their care and help for this research.

I am really thankful to MaryKay Smith from MSU Learning and Assessment Center for helping me out to recruit the participants and conducting the experiment at Fee Hall. With her and Learning Assessment Center's help, I could finish conducting my experiment completely. Also, I am really thankful to Sandra Campbell from Olin Health Care for her help to supply all labels and bags used for the experiment. Thanks to her, the initial stage of the experiment went smooth.

I would like to thank my fellows, HUB team (Human Factor, Universal Design and Bio Mechanics). Due to their willingness to help me out and share their ideas for this research, I could have completed my research. Not only that, but they were always there for me to cheer me up.

I also would like to thank all my friends in the School of Packaging for their supports and their friendship. I could survive from adapting in U.S.A because of them. Needless to say, I am

especially thankful to Korean fellows from the School of Packaging for their care, support and love. I could extend my insight as well as my knowledge thanks to them.

I am particularly grateful for the assistance given by Statistician, Moslem Ladoni. Without his kind explanation of the statistical analysis and quick solution, I could not have completed the statistical analysis.

I would like to offer my thanks to Hyunjung Oh and Hayati Samsudin for their assistance to recruit participants and their encouragement to keep conducting my research. Also, I would like to extend my thanks to all people who participated in this research.

Special thanks should be given to my friends here and in Korea. They always support and encourage me in caring about me regardless of how they are far from me and how they are busy.

I wish to thank my family, my father, Myung Hoon Lee, my mother, Jung Ae Lee and my little sister, Soo Yon Lee. Also, I am grateful to my grandparents as well as my relatives. Their unconditional love and support toward me make my day and are the reason for why I live. With their self-sacrifice for me, I could have a chance to study here and obtain all the valueless knowledge. I know I could have not been with my family especially when they went through the difficulties, but I promise that I will pay back all my sincere love to them and will make my family happy.

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Chapter 1. Introduction

Risk is pervasive in life. According to Dingus et al. (1993), people often are in hazardous situations, which can be minimized by using safety tools. Warnings are one of the tools that help reduce or eliminate risk. The use of warnings helps to ensure proper and correct use of products.

Warnings are particularly important for products that have small margins for error and significant consequences associated with improper or inappropriate use, such as medicines. The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) defines a "medication error" as,

> Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use (NCCMERP).

A warning label is a safety tool that can be used to mitigate the likelihood of medication errors. However, to be effective, the information that they contain must be processed. Although many models of information processing exist, herein we leverage a serialized model of processing that is commonly used that indicates for information to be effective, five stages must occur: the patient must be (1) exposed to the information (2) notice the information (3) encode the information (4) comprehend the information and, finally, (5) the information must move the patient to compliance. Given the critical nature affiliated with the proper use of prescription drugs, the small margins of error associated with many and the potentially severe consequences of inappropriate use, we focus our investigation on the efficacy of varied placements of a prescription warning label (PWL).

Chapter 2. Warning Labels and Consumer Behavior

Warnings

In general, the purpose of a warning is to reduce any risk by informing consumers about it. Weinstein et al. (1978) suggest that warnings should include safety-related features indicating how consumers can avoid dangerous situations. Young and Wogalter (1990) define warnings as a means of preventing people and machines from being harmed during interactions that consist of possible hazards (Young & Wogalter, 1990).

Warnings can take many forms, such as an audible alarm system, or a chemical added to an odorless gas to inform people of gas leaks. Likewise, warning definitions vary by research team. De Greene (1970) states that different sectors of society have their own definition for warnings, indicating that in some sectors, 'warning' is synonymous with 'alerting'. According to Murrell (1969), a warning confers that an immediate action is needed to avoid disaster.

A subset of warnings related research addresses the function of warnings on goods, (Lehto & Miller, 1986), and it has been suggested that studies investigating the efficacy of product warnings have increased over the years (Wogalter, Brelsford, Desaulniers, & Laughery, 1991).

Herein, we focus our discussion of visible warnings present in labels with emphasis on packaged goods, particularly medications.

Perceived hazardousness of warning labels and familiarity with label:

Research has suggested that if people believe that a product is perceived as more

hazardous, they are willing to read the warning labels (Wogalter, et al., 1991). In other words, in cases of perceived hazards (i.e. serious threats that may result in injury), people exhibit enhanced willingness to find, read and comply with presented warnings (Wogalter, Brelsford et al. 1991).

Other researchers have studied the relationship between product familiarity and warning efficacy: as warning familiarity increases, some researchers suggest that compliance with warning information decreases (Martin & Wogalter, 1989; Otsubo, 1988; Rogers, 1987). In other words, that familiarity with warnings is inversely related to the willingness to read and search for the information (Godfrey et al. 1983; Wogalter, Brelsford et al. 1991).

Godfrey and Laughery (1984) addressed the issue of product familiarity on the behaviors associated with warning information. The team's product of study was tampons. Researchers noted that, despite the awareness of most women regarding the relationship between the use of tampons and toxic shock syndrome (TSS), they did not consider the consequence seriously because they were accustomed to the product. As a result, authors suggested a familiarity effect; that their familiarity with the product reduced reading rates of the warning label informing of TSS (Godfrey & Laughery, 1984). Concurrent with this finding, Wogalter et al. (1991) reported that if consumers are aware that products are familiar or safe, they are not willing to read warnings; the work of others supports this; as the consumers become familiar with products, their perceived likelihood of hazards decreases (Wogalter, et al., 1991; Wright, Creighton, & Threlfall, 1982).

One study specifically addressed the probability of noticing warnings related to familiarity and hazardousness (Godfrey, Allender, Laughery, & Smith, 1983). Contrary to the

work of others, Wright team found that the familiarity decreased and perceiving hazardousness increased, this does not lead consumers to read products' information (Wright, et al., 1982).

Placement of warning:

Connor et al. (2007) reported that consumers rarely rotated bottles to observe auxiliary warning labels placed on the bottom of the bottle or back of the main label (Connor et al., 2007). This led researchers to conclude that the location of label impacts the likelihood that consumers will easily find the information, a critical first step in information processing.

Wogalter et al. (1986) argued that the location of warning text of a hazardous product should be located close to products in anticipation of consumer expectations regarding warning placement. Further, the team suggests that improper location has the potential to result in leading to inappropriate product use because people may not see the warning. They reported that warning messages that are placed before the instructions catalyze better warning compliance than those placed at the end of the instructions (Wogalter, Desaulniers, & Brelsford, 1986).

Physical Interactions with the warning label:

A limited number of studies examine the effect of interactive warnings on warning efficacy. Interactive warnings require the user to physically manipulate the information in order to accomplish a necessary task (e.g. opening of the package). Most of the research that examines interactive warnings concludes that warning labels that require physical interaction increase the likelihood of attracting the consumer's attraction, are more readily recalled, and garner higher rates of compliance as compared with traditional warning labels (Duffy, Kalsher, & Wogalter, 1995; Gill, Barbera, & Precht, 1987; Hunn & A Dingus, 1992). Other researchers have suggested

that consumers rank this type of approach as preferable to traditional warnings (Wogalter, Magurno, Scott, & Dietrich, 1996).

However, research that investigates these types of labels is mixed in reports of behavioral compliance. Unlike the research noted above, Gill et al. (1997) observed no difference when comparing traditional warning labels and interactive warnings related to compliance to warning message.

Age:

Conclusions regarding the effect of age on behaviors associated with warnings are also mixed. According to Desaulniers (1991), older participants (40 and older) have higher compliance likelihoods of warning information than younger people.

Other researchers assert that older participants (defined as 55 and above) had poorer comprehensibility (Easterby & Hakiel, 1981). This is supported by another study that suggested medication is distinctly problematic for the elderly consumer when it comes to the correct comprehension of the information (Wolf et al., 2006). This is likely because as people age, their perceptual and cognitive functions are impaired (Hancock, 1999; Park et al. 1999). This issue is of increasing importance, particularly with regard to medical products, due to the rapidly aging population and their increased caplta consumption of healthcare products compared with younger consumers (Michael S Wolf, Davis, Tilson, Bass, & Parker, 2006).

The effect of label contents and design on behavior

Research has also been conducted that investigates how the content and formatting of the warning label itself plays a role in how effective it is at delivering information.

Label Contents

Explicit message contents and warning labels:

According to Wogalter et al. (1991), failure to convey warning information occurs for three reasons; failing to notice the information, not understanding the information or completely ignoring the warning label. This team suggested that explicit information presented in unequivocal terms results in better rates of comprehension.

Laughery and Stanush (1989) echoed these sentiments, indicating that consumers will afford products more serious consideration when explicit warning labels are present. They go on to say that explicit warning labels help consumers to comprehend hazards as well as appropriate safety precautions (Laughery & Stanush, 1989). A study found that patients with low literacy who are deficient in vocabulary and reading ability may guess whole contents as what they understood through the words they are able to comprehend (M.S. Wolf, Davis, Tilson, Bass III, & Parker, 2006). As such, the research team recommended, clear message contents should be required for warnings (M.S. Wolf, et al., 2006).

Presence of Symbols in warning labels:

Early work conducted by Kalsher and Racicot (1992), suggested that the presence of symbols in warnings did not impact on consumers' compliance with label information. This was contrary to work conducted by Jaynes and Boles (1990) which suggested greater compliance rates when warning information included pictorials compared to those without symbols (Jaynes

& Boles, 1990). Despite their study findings, Kalsher and Racicot (1992) articulated the importance of the presence of symbol could not be ignored because they function to enhance understanding for those with reading difficulties and for children (Kalsher & Racicot, 1992).

Subsequent studies conducted by Kalsher (1994) support the diminished rates of compliance published by Jaynes and Boles (1990). Kalsher's later study suggested that labels without pictorials were less likely to be read, noticed and preferred compared those with symbols (Kalsher, Pucci, Wogalter, & Racicot, 1994). As mentioned previously, information processing theory (Dejoy, 1991) postulates that the nature of processing to be serialized, that is exposure, noticing, encoding and comprehension are requisite to compliance.

Label Formatting

Color Effect:

Sundar (2009) reported that, when presented in a vertical orientation, the color of prescription warning labels (PWLs- small, colorful stickers applied at the pharmacy) did not significantly affect the attentive behaviors of consumers. This result was supported by Wogalter et al. (1996) who found that a supplemental label on different color cap did not significantly change the consumer's attentive behavior to read carefully the instructions.

Chapter3. Pharmaceutical Vials And Labels

Pharmaceutical vials

US pharmaceutical vials are comprised of a cap and body and incorporate several different types of labels. Vials are generally manufactured in amber or green (rarely blue) polypropylene in order to provide protection against certain portions of the UV spectrum which can be damaging to specific drug products. Vial volume varies, and is reported in drams (dr) which is the unit of either mass and commonly used vial sizes in the U.S. include: 6DR (18ML), 8DR (25ML), 13DR (45ML), 16DR (50ML), 20DR (65ML), 30DR (100ML), 40DR (130ML), and 60DR (200ML).

Labels on Pharmaceutical Vials

The Federal Food, Drug and Cosmetic Act, which applies to the manufacturer's package and labeling, is the genesis of most of the authority granted to agencies regarding labeling. The Act defines labeling as, "all labels and other printed, or graphic matter (1) upon any article or any of its containers or wrappers or (2) accompanying such article ." 21 USC§321(m). As such, the term "label," as defined by the Act, is a subset of a product's labeling. "Label" is defined as

> "means of written, printed, or graphic matter upon the immediate container of any article, and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such, word, statement, or other information also appears on the outside container or wrapper, if there be, the retail package, of such article, or is easily legible through the outside container or wrapper." 21 USC§321(k)

Regulations, under the authority of the Act, mandate the content and formatting of the information that manufacturers need to provide with their products. This information, however, focuses on information intended for healthcare providers (e.g. physicians, pharmacists, nurses), who serve as "learned intermediaries" regarding the safe and effective use of the product.

In the US, it is common practice for drugs to be removed from the manufacturer's package at the pharmacy, where they are counted into pharmaceutical vials as prescribed by a physician. At this point, new labeling is provided to patients in the form of: labels applied directly to the dispensed unit, patient package inserts (PPI) and consumer medication information (CMI). Medication guides, required for all new prescriptions and designated refills that have significant public health concerns, and PPIs, required for oral contraceptives and medications containing estrogen, are prepared by the drug manufacturer and reviewed by the FDA. The CMI is generally written by pharmacy personnel or provided to them as an outside service, and not reviewed by the Federal authority.

Herein, we limit our discussion to labels applied directly to the vial and requirements for these labels as dictated by the State of Michigan.

Definition of label

Consistent with the definition presented by the Federal government, section 333.17705 of Michigan's Public Health Code (Act 368, 1978) defines the label as,

> "a display of written, printed, or graphic matter on the immediate container of a drug or device, but does not include package liners. A requirement made by or under authority of this part that a word, statement, or other information appear on the label is not complied with unless the word, statement, or other information appears on the outside container or wrapper of the retail package of the drug or

device as displayed for sale or is easily legible through an outside container or wrapper (*Definitions; L*, 2009).

As such, labels applied at the pharmacy to drug vials are generally represented by one of two types: a large white pharmacy label and small, colorful, auxiliary labels referred to as Prescription Warning Labels (PWLs), or auxiliary labels.

White Pharmacy Label and Regulations

According to the Michigan Legislative Council, labels of prescription medication shall be attached by a qualified pharmacist. Also, the label must include following;

- "the name and address of the location from which the prescription drug is dispensed
- the patient's name and record number
- the date the prescription drug was dispensed
- the prescriber's name or, if dispensed under the prescriber's delegatory authority, shall list the name of the delegate,
- the directions for use,
- the name and strength of the prescription drug
- the quantity dispensed
- the expiration date of the prescription drug or the statement required under section 17756" (*Drug control license*).

Under the regulation of section 17756, (1) the name of the medication shall be on a prescription administered by a pharmacist unless the prescription is addressed by the designator, "do not label." In addition, the contents of prescription shall have "Discard this medication 1 year after the date it is dispensed" unless the expiration date of the medication is under "applicable state or federal law or rules or regulations or other state or federal standards." In this case, the label shall be detailed with the expiration date. (2) The name of medication shall be contained on the label of a prescription. The label shall have the name and the information

relating to the medication, or it is obliged to have the date when the medication will expire on the prescription provided by a pharmacist (*Label on prescription; contents*, 2009).

The Prescription Drug Warning Label (PWL) and Regulations

Aside from the large white labeling containing the required information, US pharmacies frequently also employ small, colorful auxiliary stickers, or the PWLs to vials. These labels are not standardized or regulated and have varied offerings, relying on the PWL manufacturer's own format (Ault, 2007). Yet, they are noted to highlight critical information for "the safe administration of prescription medications" (M.S. Wolf, et al., 2006). Example warnings include: "Do not take this drug if you become pregnant", "Refrigerate", "Warning: Do not take this medication while driving." As seen in Figure 1, the terms and the colors used on labels are different from each other. In addition, there is no standardized, consistent use of symbols.

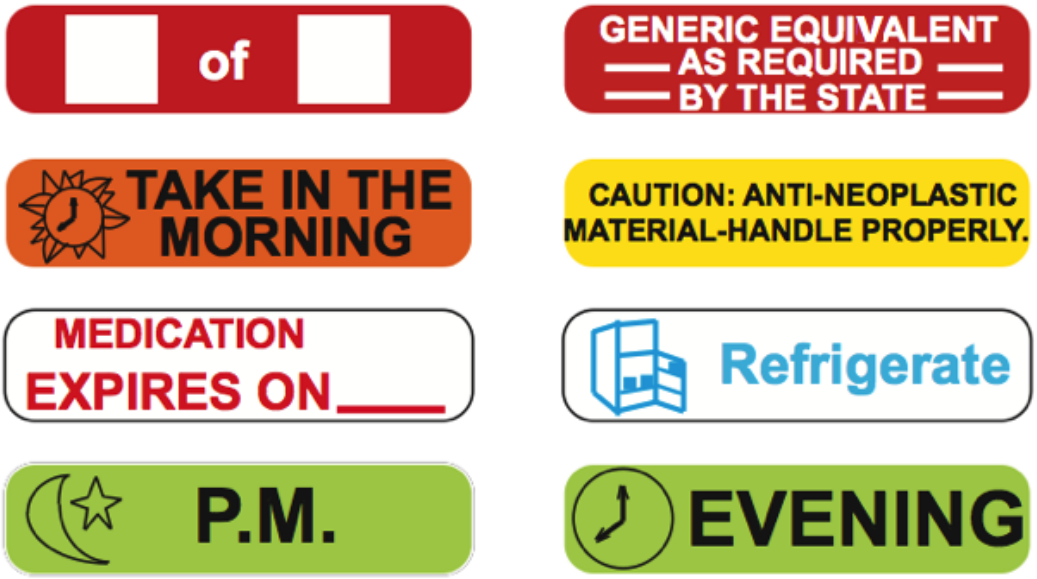


Figure 1. Examples of Prescription Drug Warning Labels
(Adapted from: http://www.pharmex.com/PharmacyWarningLabels/WarningLabels/wlspa.asp)
"For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this thesis."

Chapter 4. Interactivity

The term "interactivity" (as it relates to warning information) was defined in 1992 as a "physical interaction between consumers and products or warning labels" (A.Dingus, 1992). Duffy et al. (1995) brought increasing specificity by defining an "interactive label" as one that "requires manipulation by users before or during use of a product." This is consistent with the definition reported by Rousseau et al. (1998), who defined the interactive warning as one which requires "the product user to physically manipulate the warning when using the product" to accomplish a particular goal or task.

Some researchers have suggested the noticeability of these labels to be their most important attribute, as it is noticeability which increases the probability of reading and, presumably, warning compliance (Duffy, et al., 1995). As such, Dingus (1992) suggested that compliance with warnings would be enhanced by the use of interactive formats (A.Dingus, 1992).

Examples and previous studies of interactive format

Interactive warnings have been used in varied environments and take on numerous forms.

Lockout tags:

Perhaps the best-known example of an interactive warning is a lock-out tag. During an activated lockout, employees who wish to operate a machine must remove a tag prior to unlocking a power source. In other words, when lockout tags are placed, switches that control critical processes are labeled in such a way that tags must be removed prior to reactivation of

power. Studies have indicated that this is an effective means or warning because work is harmonized with warning labels (Lehto & Miller, 1988).

Billboard configurations (Dingus & Hunn, 1992):

Dingus et al. designed an auxiliary label for spray bottles using recommendations from *ANSI Z535, Safety Signs and Colors*. During the course of their study, they used two interactive warning labels; a one-time interactive warning, and a continuously interactive trigger-blocking warning. The one-time warning configuration attached onto the nozzle and was removed prior to use, whereas in the continuous format, a "block that consisted of a spring-like acrylic plastic flap that covered the trigger of the product" had to be moved out of the way each time the product was used (Hunn & A Dingus, 1992). Results indicated that the continuous interactivity format generated higher rates of compliance that use of glove under the situation that the subjects were provided it or not than the one-time use format.

Gill et al. tested the warning efficacy of messages intended to warn against the use of unsafe extended power cords with a heater. Three formats of warning label were used for this experiment; (1) a traditional design, (2) a "ski pass design" which was described as "a tag with red color coding pictographs, and written warnings affixed near the male end of the heater's electric cord", and (3) an interactive design. The authors described the interactive format as "a ski pass" warning label design affixed to a flexible, curved piece of plastic that was attached to the male end of the cord such that it had to be bent back in order to connect the cord to a power

source". It was reported that half of the participants recalled the interactive format, five out of 20 recalled the traditional format and six out of 20 the ski pass (Gill, et al., 1987).

Warning Label of File Cabinet Drawer (Frantz & Rhoades, 1993):

Frantz and Rhoades developed an interactive warning for file cabinet drawers and compared it to a more traditional label to investigate warning efficacy; four conditions were created: (1) a conventional warning printed on the file cabinet's shipping container (condition 1), (2) a warning attached to the bottom of the top file drawer (condition 2), (3) an interactive warning, which held drawers shut by covering both the top and bottom portions of the drawer , and (4) another interactive warning where a paperboard bridge was attached across from the right to the left of the top drawer. The last two warnings could be considered as interactive warning format based on the fact that a physical interaction was required in order to perform desired tasks (opening the drawer).

Participants were led to believe that they were participating in a study that involved organizing furniture and supplies in an office environment. All objects were packed to prevent biased attention to the file cabinet. Each subject was randomly given two file cabinets, and then they were asked to unpack the furniture and supplies, and place the files in either the top or the bottom of the cabinet. Reported results indicated that 93% of participants noticed the warnings under condition 3 and 4 (the interactive formats), and among them, 67% of participants even read the two warning labels whereas 0% of subjects under condition 1 and 33% subjects under condition 2 only noticed the labels.

Tag Label, Wings Label and Box Label (Barlow & Wogalter, 1991):

Barlow and Wogalter tested six different experimental labels versus a control label on a fictional glue product. Tested experimental conditions of labeling included: (1) a wing label, (2) a tag label, (3) a cap label, (4) a box label, (5) a disc label and (6) a wrap-around label. These experimental labels were developed to have enough space to contain more text than the traditional labels. The warning message was:

> **"WARNING: Eye and skin irritant. Avoid contact with skin and eye In case of contact, flush with water. Avoid prolonged breathing of vapors. Use with adequate ventilation. KEEP OUT OF REACH OF CHILDREN"** (Barlow & Wogalter, 1991).

Among these labels, three could be defined as interactive formats: the tag label, the wings label and the box label. Specifically,

1) The tag label was comprised of a tag containing warning information that was placed between the cap and the body of bottle. As a result, people needed to remove it before they could use the product.

2) The wing label formed a wings-like box around the body of the product such that it became hard to open the cap without removing the label.

3) The box label consisted of a box affixed to the body of the product. Although its addition did not add sufficient space to replace all text present on the package itself, it was sufficiently large to inconvenience people during the opening process as a result of limited gripping space.

The other labels tested by this group were more traditional, lacking the interactive format that is the central focus of research presented herein. For example, the disk label was comprised of a thin disk-shaped box on the product at the bottom of the body, allowed enough space for

people to hold the bottle to turn the cap, and, as such, people may not interact with the label. Participants of two age groups (younger and older) were given the bottles, and asked to rate designs using a 6-point scale. Two of the three interactive warnings were rated as an effective label to be noticed or read by participants. The results suggested that younger participants found the tag label to be the most effective with regard to the warning noticeability and the likelihood of reading warning. For the older population, the tag label was also rated the most effective regarding noticeability and the winged label was highly rated on the likelihood of reading.

Fin Label (Wogalter, et al., 1996) :

Wogalter et al. (1996) investigated the efficacy of employing an interactive strategy with an over-the counter medication (OTC). A label containing the most important warning information (excerpted from the traditional bottle label) was used to test this strategy.

Five square OTC bottles employed different label strategies during this study. All bottles had traditional labels on all four sides of the bottle except for one of two control bottles; it had only the front label. Another control bottle had the four main labels on each side of the bottle but it did not have the supplemental label (the interactive format) on the cap. The three experimental bottles had not only all main labels but also the supplemental, interactive label. Additionally, each of the experimental bottles had caps of different colors. The main label contained information identical to that of the commercially available OTC.

All the participants in this study consisted of older consumers, and three steps were employed during testing. In step one participants were asked to determine "how to use this medication and who should take this or not" and given a conventional bottle. This portion of the

testing was intended to familiarize participants. After the initial step was completed, one of the five bottles was randomly assigned to participants, and they were asked to complete a questionnaire relating to information from the label after the experimenter had removed the bottle (authors referred to this as a knowledge test). During the final step of testing, participants were given all five bottles and asked to rank the bottles, by preference, from the least preferred to the most preferred.

There was no evidence of significant difference among the experimental bottle with regard to the knowledge test. However, the result of the knowledge test showed that participants had the greater score of the test relating to the bottle with the supplemental label. Ranking data suggested older consumers preferred bottles with supplemental labels. (Wogalter, et al., 1996).

Research on behavior

Gill, et al. (1987) indicate, "If a warning label is to be effective in mediating safe user behavior, then it must attract the users' attention and induce them to read its contents." Their team reported that participants paid more attention to an interactive format, based on the fact that 50 percent of the participants recalled the interactive format; 30 percent on the ski pass label and 25 percent on the traditional format (See the example of "Billboard Configuration"). The researchers emphasized the importance of attention and concluded that attention could be enhanced through the use of interactive labeling formats (A.Dingus, 1992).

Studies related to the impact of interactive warnings on information compliance are controverted. Gill et al.'s work (1987) suggested no evidence of difference in behavioral

compliance based on warning format as measured by questionnaire. Similarly, Hunn and Dingus (1992) did not find an effect of warning type on compliance of warning.

At the same time, other researchers report interactive formats to be an effective in achieving compliance. Frantz and Rhoades (1993) reported (See *Warning Label of File Cabinet Drawer*) a significant effect on behavioral compliance when the warning label impeded task performance (drawer opening).

Duffy et al. examined warning effectiveness for four treatments: no label (no label on an extension cord), tag (the traditional warning label format on the extension cord), interactive with color-absent (the warning label attached to the extension cord on the outlet cover on a female connector without color), and an interactive with color-present (they employed warning labels attached to a power strip on the outlet cover of a female connection with color). The participants were under either "low task load condition" or "increased task load condition." During low task loads, they were asked to plug a television, videocassette recorder, and videotape rewinder into a power strip with the warning, "Warning. Electric Shock and Fire. Do not plug more than two items into this cord". In the increased task load condition, the participants were asked to complete the same task while they were listening to an audiotape lecture. After the task, each group completed a questionnaire relating to the degree of hazardousness of the product, the likelihood of being injured by the product and their degree of familiarity of the product. Both of the interactive formats (with and without color) resulted in higher rates regarding noticeability, recall of content and behavioral compliance to warning labels than that of tag label and no-label control conditions (Duffy et al., 1995).

Interactive Format on Pharmaceuticals

There is very limited literature regarding the use of interactive warning labels on pharmaceuticals. As previously reviewed, Wogalter et al. (1996) investigated varied types of warnings with an OTC drug product. Although their study did not focus on the effect of interactive warning on noticeability, recognition and recall, consumers reported a preference for the bottle with an interactive label (See the detailed in the example of *Fin Label*). Also, they conjectured that the reason why the elderly people preferred the supplemental warning label was that the font size enabled easy reading (Wogalter, et al., 1996).

Chapter 5. Objectives and Hypothesis

We hypothesized that an interactive format would assist consumers in noticing and recalling the critical information present on PWLs. To test this hypothesis we employed an eye tracking methodology and tests of recall and recognition to accomplish the following objectives:

1) To test the impact of an interactive warning system for medical vials on the attentive behaviors of older (50+) and younger patients (18-29).

2) To test the impact of an interactive warning on the ability of patients to recall the warning information in older (50+) and younger patients (18-29).

Chapter 6. Materials and Methods

Materials

Near Point Visual Acuity card:

Participants were given a Dow Corning Opthalmics' visual acuity card, capable of measuring near point visual acuity from 20/20 to 20/120. They were asked to hold this card at approximately 16 inches from their eyes and read aloud the lowest line on the card that they were able. The lowest that they could accurately read was recorded as their near-point visual acuity.

REALM-R Card:

REALM-R testing, Rapid Estimate of Adult Literacy in Medicine- Revised, a shortened version of REALM (Bass III, Wilson, & Griffith, 2003), was conducted with all participants. This method quickly identifies participants likely to have health literacy problems, by rapidly evaluating their ability to read words that patients need to understand in order to follow a physician's directions or understand typical medical terminology (Bass III, et al., 2003).

During testing, participants were asked to read 11 words: Fat, Flu, Pill, Allergic, Jaundice, Anemia, Fatigue, Directed, Colitis, Constipation and Osteoporosis. Participants were handed a card that listed the eleven words, and asked to read each word aloud. Further, they were instructed, "Please do the best you can to read each word; say 'blank' if you come to a word you do not know." The first three words served as an acclimation period, and, therefore, were not counted as part of the score. When a subject mispronounced or passed a word (by saying "blank"), it was not tallied. When the total score was less than 6, the participant's data was recorded as at risk for poor health literacy (*REALM-R*)

Vials:

During testing, participants were handed (in sequence) three 16 dram vials. Vials were outfitted with a push-turn closure system (vial; Owens-Illinois, IL, Cap) and each of the three had a prescription warning label (PWL). PWLs were positioned on the vial so that there were three different treatments with regard to placement (see Table 1).

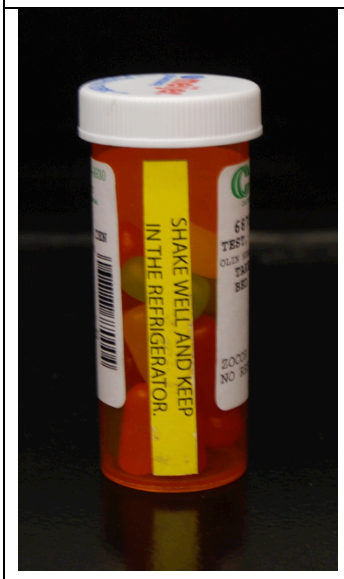
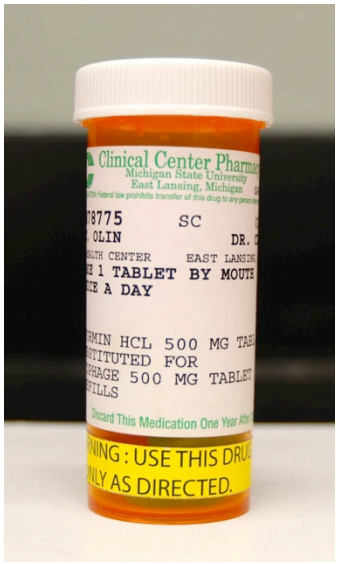
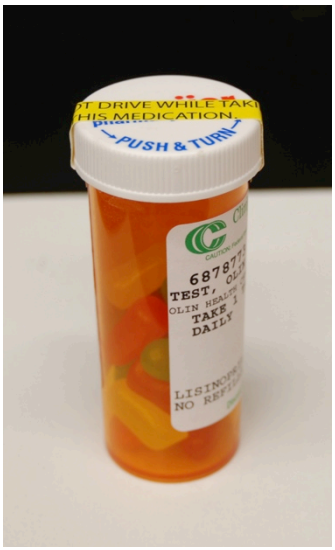
A. Vertical Orientation	B. Horizontal Orientation	C. Interactive Format
		

Figure 2. Vials with three treatments of PWL

Prescription Warning Labels:

The all yellow PWLs had the dimension 7 cm x 1 cm and were attached in one of three ways (see Table 1):

1. A vertical orientation (to the side of the large, white pharmacy label) (see Figrue 2-A)
2. A horizontal orientation (at the bottom of the large, white pharmacy label) (see Figrue 2-B)

3. An “interactive format,” where the PWL must be broken in order to open the cap of the vial (see Figrue 2-C).

Texts of Warning Labels:

Warning label text was selected after a series of messages typically used on PWLs were evaluated using a Flesch Reading Ease test imbedded within Microsoft® Word 2010. The Flesch Reading Ease test provides a measure of comprehension difficulty for adults. The test returns responses which range from 0 to 100, with higher scores indicative of easier text (Flesch, 1948). According to Flesch (1948), the range of 60 to 70 is correlated with “adequate literacy levels.” Three messages were chosen because they are commonly used on medications, and tested to be within the range of 60-70, returning an identical Flesch score of 66.7. (See Figure 2 and Appendix 4)

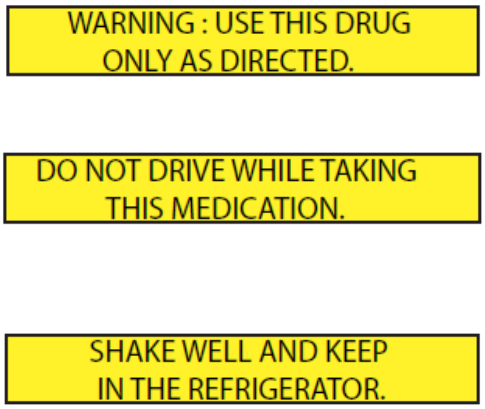


Figure 3. The figure of the labels

ASL mobile Eye Tracker:

Eye tracking was conducted using an Applied Science Laboratories (ASL; Boston, MA) Mobile Eye Tracking system. The system tracks eye movement using a dark pupil technique. One of the benefits of using this mobile eye tracker is to overcome limitations that an immobile

Eye Tracker must use in the laboratory; the participants can move with fewer limitations as compared to tethered systems.

Supplemental Tools for the Eye Tracking Test:

Pretesting of the Mobile Eye revealed that tracking subjects who were completely unfettered frequently gazed downward; these extreme rotations of the eye resulted in an occlusion of the beam as the result of the interference of the iris and/or lashes. Thus, an experimental fixturing was created and employed throughout all testing to ensure a consistent "opening zone," enabling reliable, accurate tracking throughout the entirety of the opening task.

Figure 3 depicts the calibration plane created to enhance accuracy of calibration prior to testing, and Figure 4 the "arm rest fixture" that was used during testing. To create this fixture, we placed a cellular foam topped with corrugated (17" x 8" x 5") on the desk in front of test participants, and asked people to perform the opening task with their hands resting on top of it. This accomplished two things: opening occurred very close to the calibrated plane (improving accuracy) and it discouraged extreme rotation of the eye, which occluded with tracking.

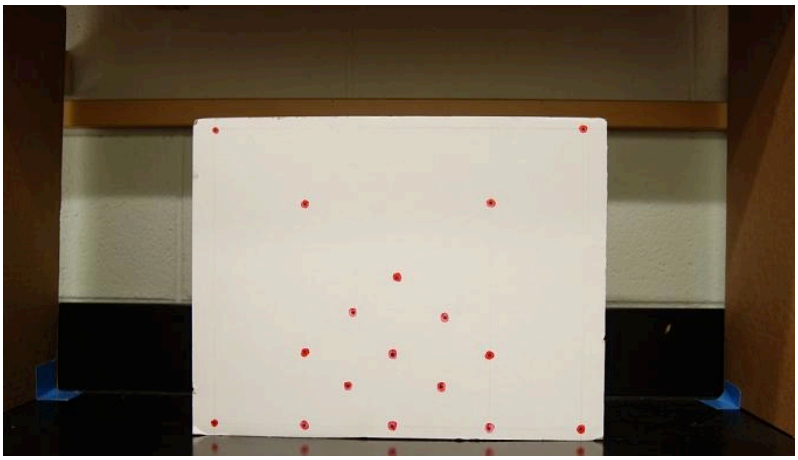


Figure 4. A calibration system

Figure 5. "Arm Rest" fixture

Methodology

Testing was conducted in accordance with procedures approved in accordance with IRB 11-1207.

Participants

Sixty-five subjects comprised of two age groups, "older" (50+) and younger (18-29), were recruited using approved advertisements (See Appendix 2) sent via email or posted on several boards in and around the campus of Michigan State University.

A total of 96 subjects were recruited for this experiment, data from 65 of which were used for the analysis. A total of 31 subjects were not included in the final analysis; 28 were excluded because the angle of view occluded tracking for significant portions of the testing. Three were excluded because difficulties with the computer files prevented data from being accurate.

Blocked Counter Balancing Design:

In order to avoid potential confounds, a counterbalanced block design was employed (See Figure 5 and 6). Possible combinations of three message/texts with three levels of placement are 9. However, to control for potential effects of run order a total of 36 subjects (9 × 4 × 1) were needed to complete one block. For example, if the text 'WARING: Use this drug only as directed' was placed vertically (see Table 1) on the vial, both the message and the location could not be used again for the next run order so that there are 4 possible combinations for the second run order. As a result, 36 subjects were needed for each age group to satisfy the Blocked Counter Balanced design (See Figure 5, 6 and Appendix 5).

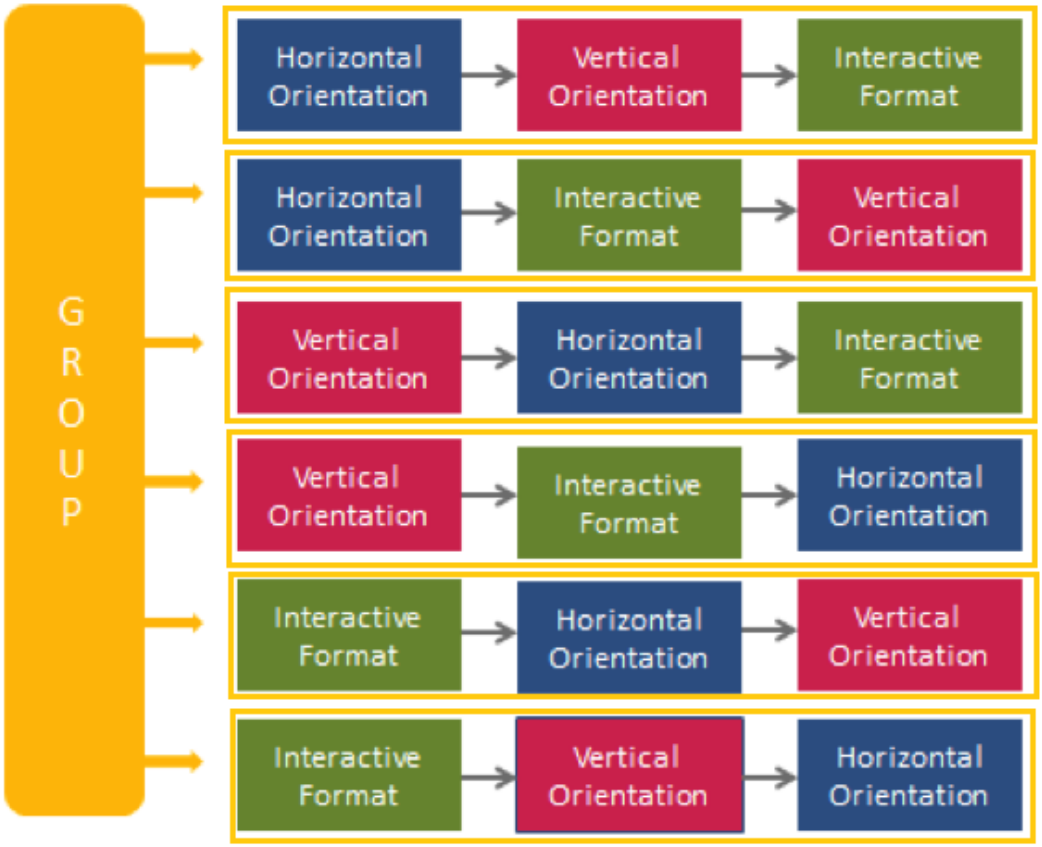


Figure 6. Counter Balanced Design Adapted from: http://www.experiment-resources.com/counterbalanced-measures-design.html **(**Each color on the blocks in this figure refers to different message contents)

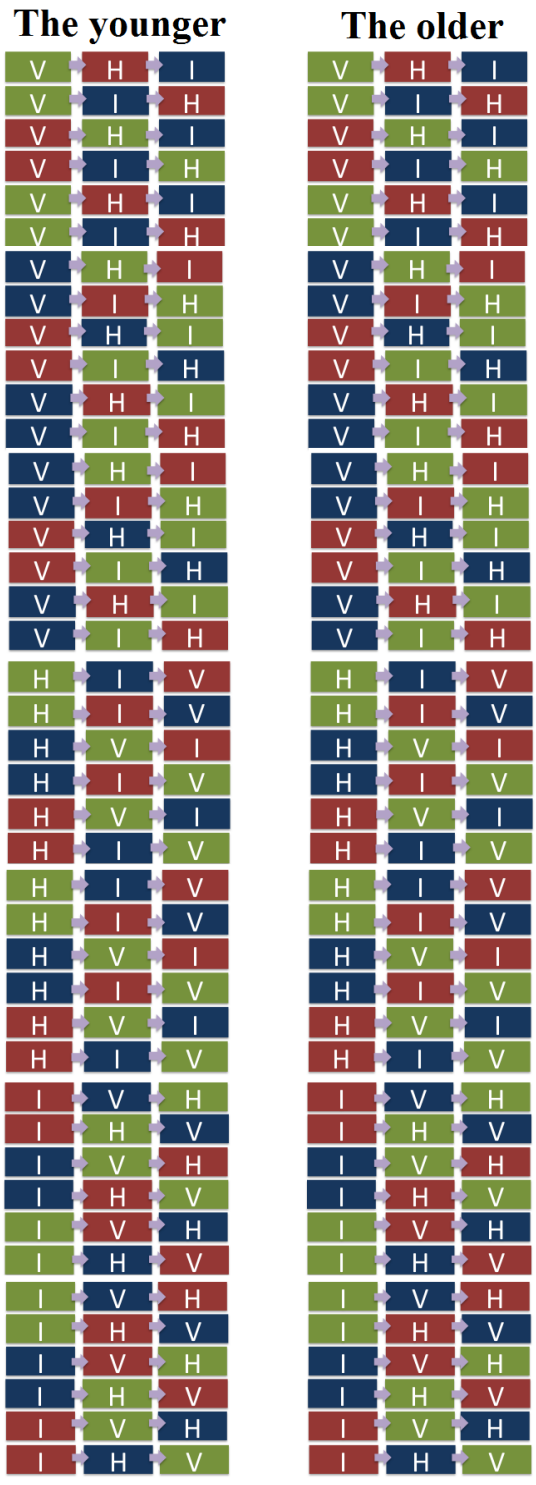


Figure 7. The counter balanced design for both populations (The character 'V', 'H' and 'I' indicate vertical placement, horizontal placement and Interactive format, respectively)

The order of the rows within the blocks (what a given subject would see) was randomized prior to testing and pre printed for each of the two blocks (younger and older).

The color code in Figure 6 indicates that different texts of warning message. The green, red and blue color refer to 'Do not drive while taking this medication', Warning: Use this drug only as directed' and 'Shake well and keep in the refrigerator', respectively.

Consent Form, Health Literacy and Visual Acuity Testing

Participants began with a written and oral consent process (See Appendix 1, and 2). Immediately following the informed consent process, each subject's health literacy and visual acuity was tested and recorded as previously described.

***Calibration Procedure*:**

Participants were seated on a chair of adjustable height in front of the area previously described. At this point, each subject was asked to wear the eye tracking system, comprised of a pair of glasses outfitted with the necessary optics, on his/hers head. Participants were calibrated to the visual plane (see Figure 3). To do this, the participants were asked to look at several different points on the corrugated board, and to move their head slightly to the right. This process was repeated for two to three more dots. At this point, they were asked to rotate their head so that they were looking at the board directly, and asked to direct their gaze to random dots throughout the plane to verify that the calibration procedure had succeeded.

Eye Tracker Test

After going through calibration procedure, the subject was instructed:

> "I will give you three packages which contain three vials. When you get these packages, I would like you to open the package and then take out the vial and open the vial as you usually would. Imagine that this medication is new to you, and you just obtained this medication from a pharmacy."

Their eye movements were recorded as they were handed the three packages (one at a time) until they finished by successfully opening the third vial.

Possible dependent variables for the eye tracking data included:

- Noticed yes/no (binary variable)
- Time to first hit (continuous variable)
- Time in zone (continuous variable)

Recall and Recognition Test

After testing with the eye tracker, participants were handed a clean sheet of paper and asked to write down everything about the warning labels they could recall about the prescriptions that they had just opened (a test of free recall). Following this, they were handed a diagram (see Figure 6) and asked to the circle the three labels that they had just viewed (a test of recognition).

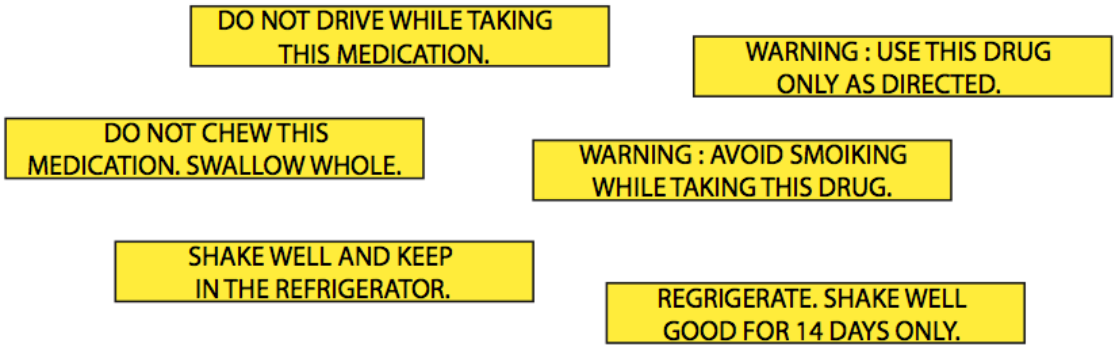


Figure 8. The Diagram of Recognition Test

Chapter 7. Results and Discussion

Participants

Data from 65 subjects (aged 18-86), 42 females and 23 males, were included in the final analysis. Thirty-four of the subjects comprised the 50 and older age group (ave 59.12 SD ±8.22) and 31 subjects were in the younger group (ave 23.68 ± 3.31 years). Frequency counts by age and gender are depicted in Table 2 and Figure 8.

Table 1. The number of subjects by gender and age group

	The younger 18-29	**The older 50+**	**Total**
Female	21 (participants)	21 (participants)	42 (participants)
Male	10 (participants)	13 (participants)	23 (participants)
The total number of population	31 (participants)	34 (participants)	**65** (participants)

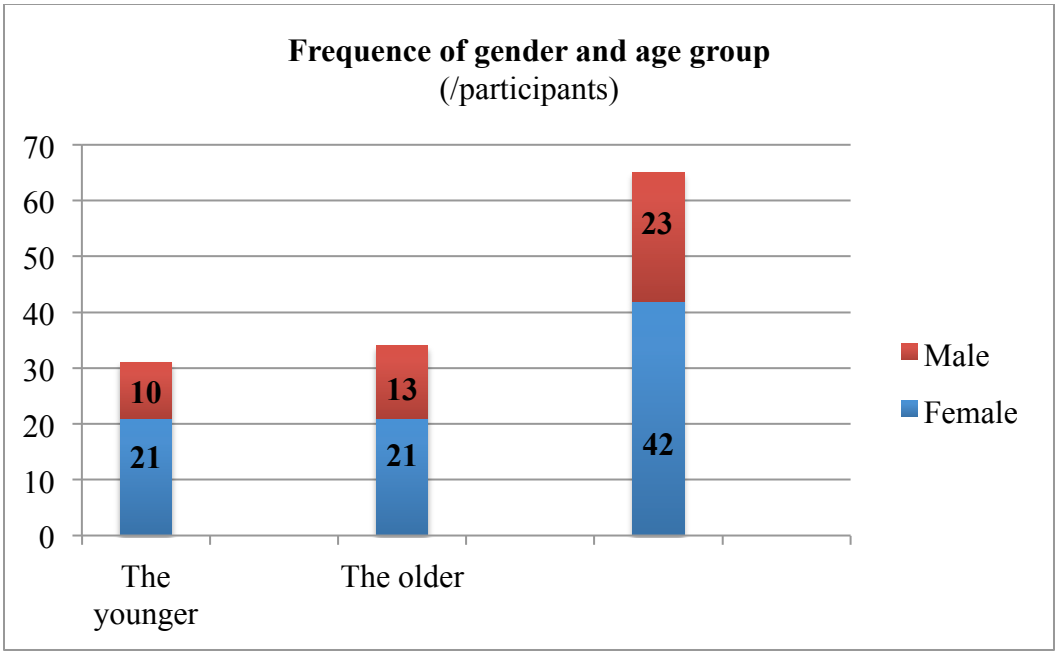


Figure 9. Gender and Age

As expected, the average medication consumption per a day of the younger population was reported to be less (0.39±0.61) than the older population (3.088±2.36) (see Table 3 and Figure 9). 67% of the population aged 18-29 reported that they took no daily meddications while 21/34 (61.7%) of the population over the age of 50 indicated that they took at least 2 medications per a day.

None of the subjects tested were reported as at risk for poor health literacy based on the REALM-R results.

Table 2. Frequency of participants according to presciption medication consumption status		
The number of distinct presciption medications consumed per day	Younger age group, 18-29 years of age (Participants)	Older age group, 50 years and older (Participants)
0	21	4
1	8	4
2	2	10
3	0	3
4	0	5
5	0	3
6	0	2
7	0	1
8	0	1
9	0	0
10	0	1
Total	**31 participants**	**34 participants**

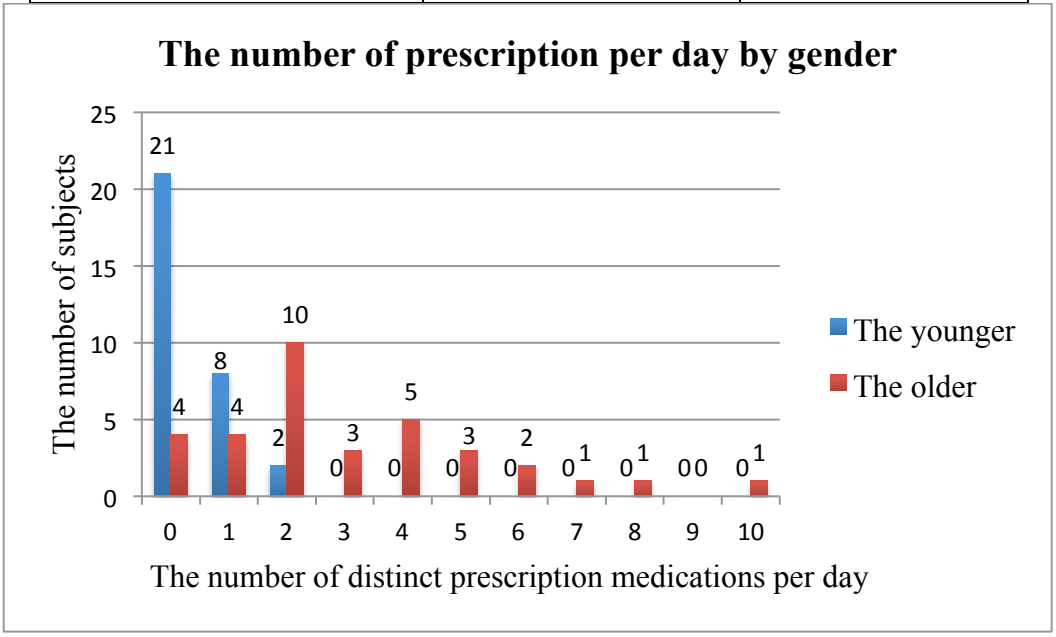


Figure 10. Medication Consumption

Table 4 and Figures 10 represent the frequencies of the near point visual acuity test.

Table 3. The percentage values and the frequencies of visual acuity by age group

Visual acuity	The younger, 18-29 years of age (Participants)		The older 50 years and older (Participants)	
20/20	48.3%	15	29.4%	10
20/30	38.7%	12	44.1%	15
20/40	6.4%	2	11.7%	4
20/50	6.4%	2	8.8%	3
20/60	0%	0	2.9%	1
20/70	0%	0	0%	0
20/80	0%	0	2.9%	1

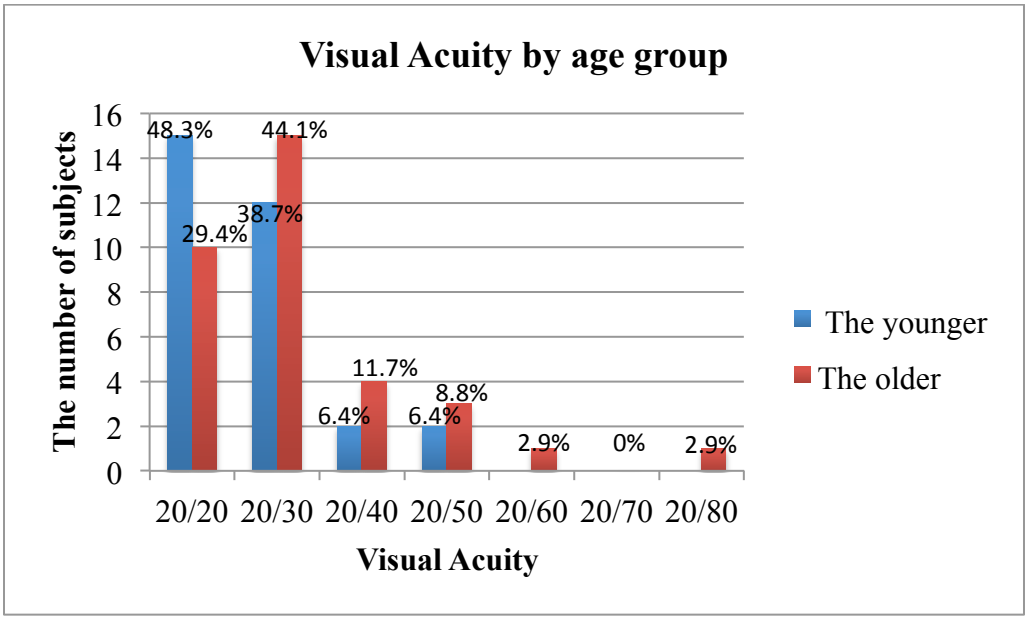


Figure 11. Participant Frequency by Visual Acuity

Eye Tracking

Three zones (horizontal (Table lA), vertical (Table 1B), and interactive format (Table 1C) were analyzed using the following;

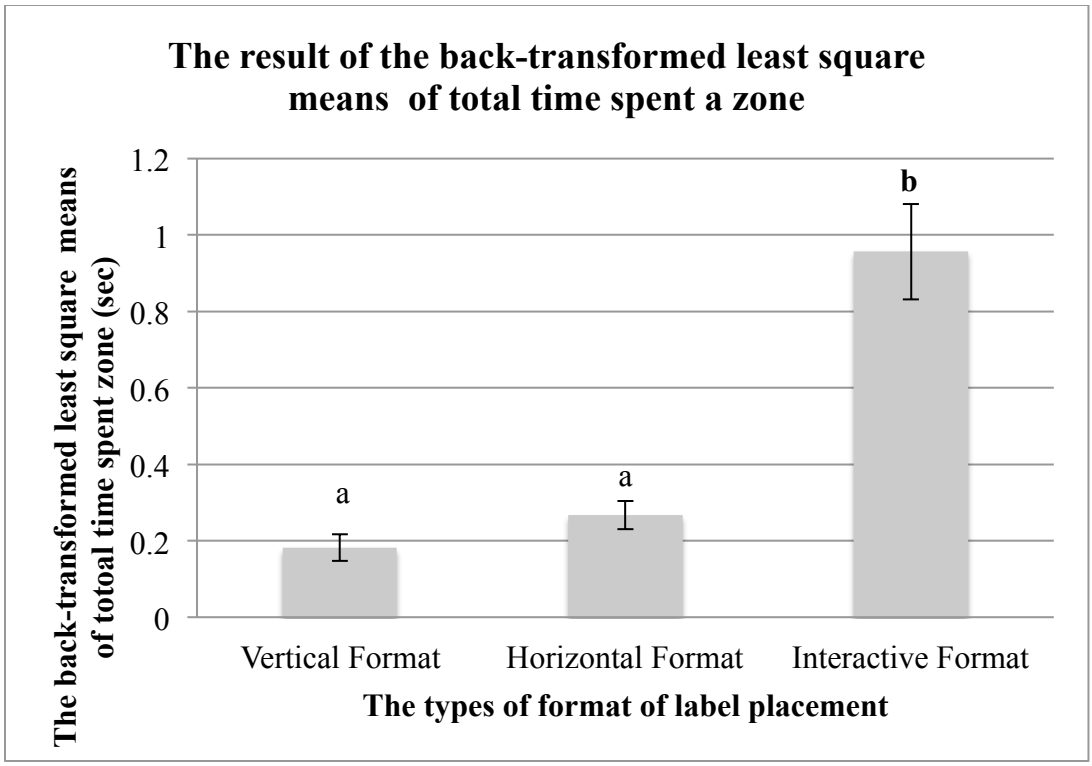
- The total time the subjects spent on a PWL based on the placement (continuous variable)
- The time before the subjects saw a zone, also called time to first hit (continuous variable)
- The probability of noticing a zone (yes/no; a binary attribute)

The total time spent on a PWL, based on placement

To investigate the efficacy of the placement of the PWL, the continuous variable of the sum of the total time devoted to the warning was used. Gazetracker software was used to analyze the dependent variable, total time spent in a given placement (horizontal, vertical or interactive) by summing all the time a given subject spent on the PWL.

Table 4. The back-transformed least square means and standard errors of the total time spent on the PWL by label placement

Placement	Vertical Format	Horizontal Format	Interactive Format
Mean values (seconds)	0.18 ± 0.035^{a}	0.27 ± 0.037^{a}	$\mathbf{0.96} \pm 0.13^{\mathbf{b}}$



*Different letters suggest statistical significance at α=0.05

Figure 12. The back-transformed least square means of the total time spent by PWL placement

Based on box plot and stem-leaf plots, data suggested a failure to meet normality assumptions and, as such, data were log transformed prior to analysis.

The response variable, the total time spent on a zone, was modeled as a Gaussian variable. The model was fitted using a generalized linear mixed model with SAS (Version 9.2, SAS institute Inc., Cary, NC). The placement of the warning labels was modeled as a fixed effect.

The effect of health literacy, number of prescription drugs per day, and age were included in the model at the beginning stage of analysis, but all of them were dropped because those effects did not show any significance to fit in the model based on Type 3 test p-value ($p>0.05$). Table 6 presents the results of the analysis.

Table 5. Results of the Type 3 Tests on the Total Time Spent in a Zone				
Effect	**Num of DF**	**Den of DF**	**F Value**	**Pr > F**
Age group	1	60	1.36	0.2486
Gender	1	60	0.20	0.6552
Age group*Gender	1	60	0.06	0.8084
Placement of the PWL	**2**	**122**	**13.47**	**<.0001***
Age group * Placement of the PWL	2	122	1.38	0.2565
Gender* Placement of the PWL	2	122	0.03	0.9661
Age Group*Gender* Placement of the PWL	2	122	1.08	0.3431
Visual Acuity	1	122	3.63	0.0590
***Bolded effects suggest significance at α=0.05.**				

The results of Type 3 test suggested evidence of significant differences in the placement of warning label on the time spent in the warning zone (See Table 6). Post hoc pair wise comparisons were conducted using Fishers LSD (see Table 5 and Figure 11).

Table 6. Pairwise Comparisons of log transformed data on time spent a zone							
Effect	**PWL Placement**		**Estimate**	**Standard Error**	**DF**	**t value**	**Pr > |t|**
	1	**2**					
Placement	Vertical	Horizontal	-0.16	0.16	122	-0.97	0.3339
	Vertical	**Interactive**	**-0.70**	**0.16**	**122**	**-4.32**	**<.0001***
	Horizontal	**Interactive**	**-0.54**	**0.13**	**122**	**-4.27**	**<.0001***
***Bolded effects suggest significance at α=0.05**							

Pairwise comparisons yielded no evidence of significant differences on the total time spent on the vertical placement when it was compared with the time spent on the horizontal

placement. However, analyses suggested statistically significant differences in the total time spent when the horizontal and interactive placements were compared (P<0.0001), and when the total time spent on the vertical and interactive formats were compared (P<0.0001) (see Table 5 and Figure 11). This suggests that subjects spent more time on the PWL when it was placed in an interactive position compared with the time that was spent on either of the other placements.

The total time spent before a PWL was visually hit for the first time

The continuous variable representing the time that participants spent prior to their first visual "hit" to the PWL by placement was also used as a dependent variable for analysis. As with total time in zone, this variable was not normally distributed, so the response variables were transformed to log scale and the model was fitted using a mixed model with SAS.

Table 7. The back-transformed least square means of the total time before a zone hits at the first time

Placement	Vertical Format	Horizontal Format	Interactive Format
Mean values (seconds)	6.24 ± 1.12^{a}	4.43 ± 0.72^{a}	4.55 ± 0.63^{a}

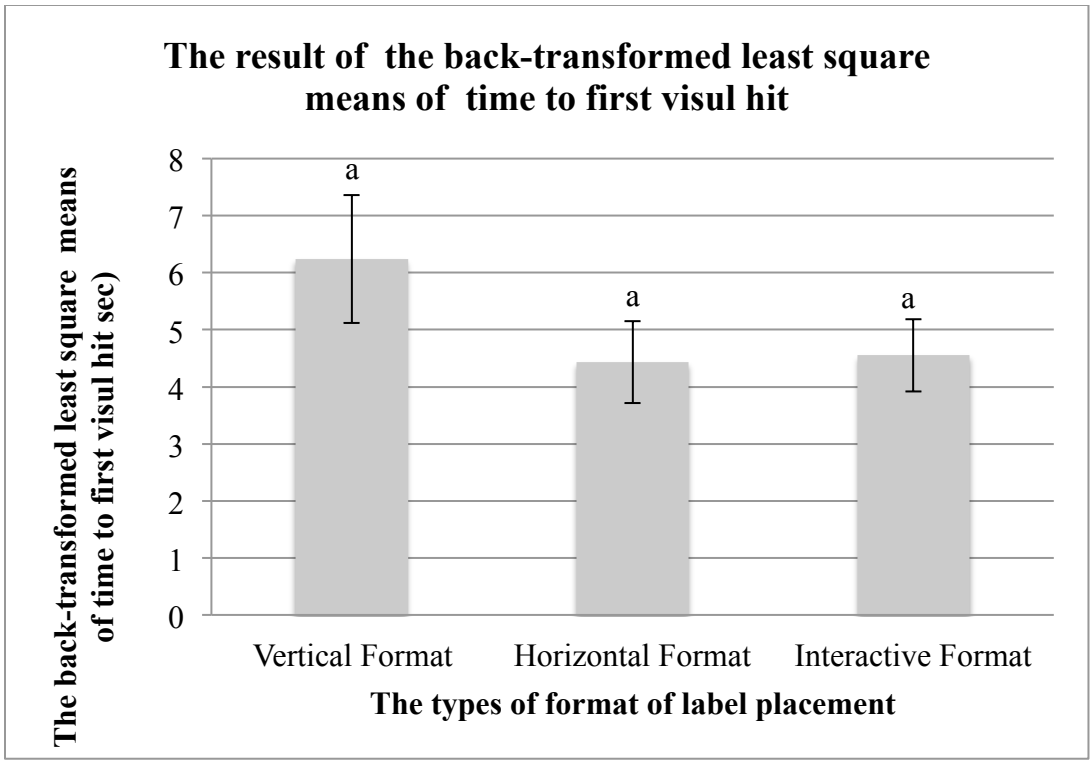


Figure 13. The back-transformed least square means of the time spent before the first hit to a zone

The effect of health literacy and the number of prescription drugs per day were included in the model at the beginning stage of analysis, but were dropped because these variable did not improve the model fit based on Type 3 test p-value ($p>0.05$).

Table 8. Type 3 tests of fixed effects for the time to first hit				
Effect	**Num of DF**	**Den of DF**	**F Value**	**Pr > F**
Age Group	1	58	1.14	0.2895
Gender	1	58	0.17	0.6858
Population*Age Group	1	58	0.57	0.4519
PWL Placement	2	65	0.37	0.6905
Age Group * PWLPlacement	2	65	1.29	0.2833
Age Group * PWL Placement	2	65	0.15	0.8577
Age Group *Gender* PWL Placement	2	65	1.28	0.2855

There is not enough evidence for a significant effect of any of the factors on time to first hit (See Table 8 and Figure 12); this was the case for both the model presented in Table 9 and in a simplified model which included: age group, gender and placement.

The probability of noticing a PWL:

Data were also analyzed based on the probability of being hit (a binary response variable; hit yes/no). When the eye tracker registered any time in one of the three PWL placement zones (horizontal, vertical or interactive), data was coded as a yes. As such, three categorical variables were included in the analysis; the three placements of PWLs (the vertical orientation, the

horizontal orientation and the interactive format). Table 11 indicates the frequency (and percentage of participants) that visually hit each of these four zones of consideration.

Table 9. The probability from back-transformed least square means of noticing a zone			
Placement	**Vertical Format**	**Horizontal Format**	**Interactive Format**
Probability	0.60 ± 0.069^{a}	0.78 ± 0.055^{b}	0.90 ± 0.038^{b}

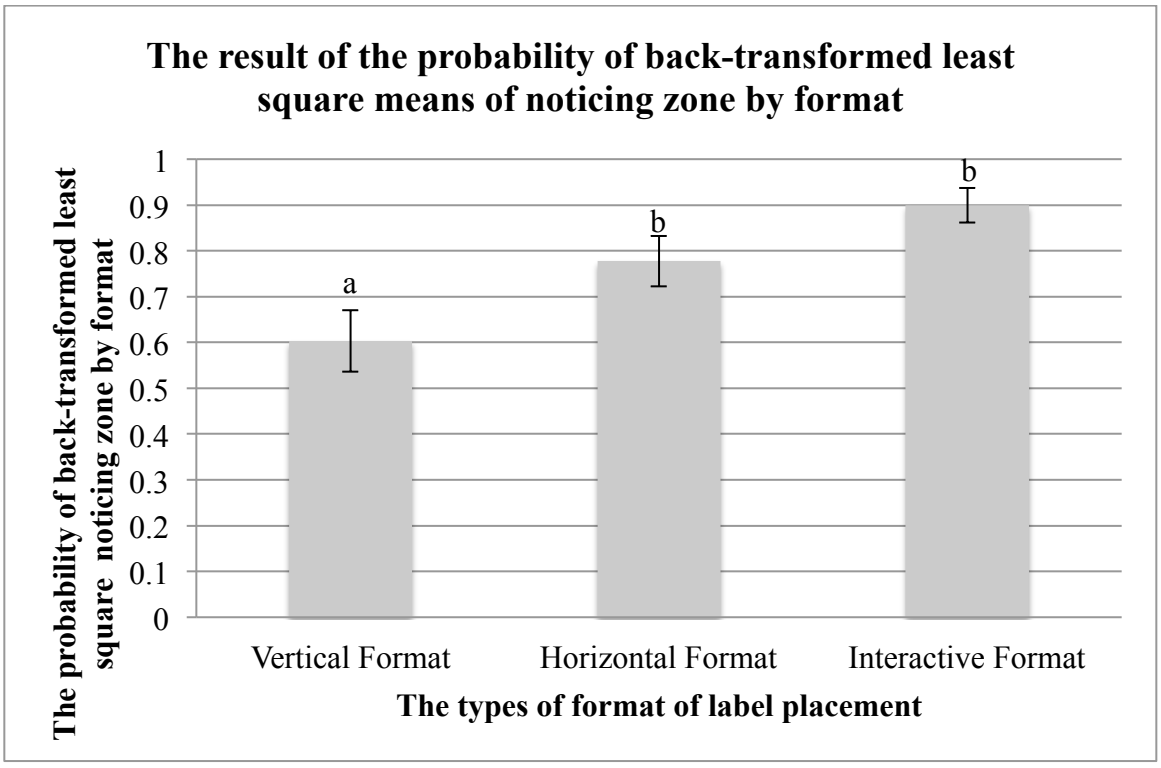


Figure 14. The probability of back-transformed least square means of noticing a zone

Table 10. Frequency and percentage of noticeability binary variable					
		PWL			White Pharmacy Label
		Vertical format	Horizontal Format	Interactive Format	
Noticed the zone	Frequency (participants)	39	50	58	65
	Percent (%)	60.00	76.92	89.23	100

Table 11 indicates that all 65 participants (100%) visually attended the large, white prescription label affixed to the front of the vial, while 89.23% (58/65) of participants attended the interactive and 76.92% (50/65) horizontal placements, in contrast to 39% (39/65) who viewed the vertical placement, a placement very frequently employed by US pharmacies for these labels.

To test for significant effects, the response variable, the probability of noticing a zone, was modeled as a binary response. The model was fitted using a mixed model with SAS. The formats of warning label were modeled as the fixed effects.

Of the tested effects only placement suggested evidence of significance based on a Type 3 test p-value ($p>0.05$). Thus, the final model included only the placement effect as a fixed variable and the random variable subject, as well as the interaction terms among subject, age group and gender (See Table 12).

Post- hoc pairwise comparisons were conducted using Fisher's LSD (see Table 10 and Figure 13).

Table 11. The result of Type 3 test of fixed effect for the probability of noticing a zone				
Effect	Number of Df	Den Df	F-value	Pr> F
Population	1	61	0.44	0.5094
Gender	1	61	0.11	0.7468
Population*Gender	1	61	0.21	0.6475
PWL Placement	**2**	**128**	**7.14**	**0.0011***
***Bolded information suggests evidence of statistical significance at α=0.05.**				

Comparisons of the vertical placement and the horizontal placement suggested significant differences in the probability of being visually hit (P=0.0376). The comparison of the vertical placement and the interactive placement, also suggested evidence of significant differences (P=0.0003). However, when the horizontal and interactive were compared, no evidence of difference was apparent at α=0.05 (P=0.0647).

Recall Test

Upon completion of the eye-tracking portion of the test, test participants were asked to freely recall all that they could of the vials that they viewed during eye tracking. Responses relating to PWLs were categorized using two factors; the location of PWL and the informational contents of PWL; each category was recorded in a binary fashion (mentioned; yes/no). We then collapsed the two categories into a third we termed, 'general recall' (recalled something specific to the warning label; yes/no). This general category was encoded as a 'recalled' when they recalled at least one of the two (informational content or warning placement). Other factors that were freely recalled, including: vial color, cap, the informational contents of the large, white pharmacy label, etc were not included as part of the analysis.

All the values here are the binary value, which was coded as 1 or 2. It was coded as 2 (binary value) when the subjects did not recall the label; 1 was coded (binary value) when the subjects did recall something about the warning label. As such, values approaching two suggest that a large portion of the population did not mention either the placement or the message relating to that placement.

Recall Contents

The response variable was coded as 'information recalled' when a subject mentioned phrases relating to the warning information. As mentioned in Materials and Method chapter, each of the three PWLs provided to a subject had a unique message and placement. As a result, if the subject wrote phrases related to the warning information content, the placement of label could be identified specific to that participant. Table 13 shows the example of the phrases.

Table 12. Criteria of encoding data for recalling informational content (see Figure 2)

Warning	Elements
Text 1	Do not drive/ taking this medication
Text 2	Warning/ Use as directed
Text 3	Shake/ Refrigerator

If the subject wrote some phrase containing both 'do not drive' and 'taking this medication', the subject was referred to recall the text 1 of warning message which is 'Do not drive while taking this medication'. Likewise, if the answer of this test contained the phrase 'warning' and 'use as directed', then they were regarded as recalling the text 2 ' Warning: Use this drug only as directed'. For the text 3, the original message was 'Shake well and keep in the refrigerator' and the subject wrote 'shake' and 'refrigerator', then considered as recalling text 3.

The response variable for recall testing was modeled as a binary variable (recalled; yes/no). The model was fitted using a generalized linear mixed model. The distributional assumption did not suggest normality, so logit of Link Function was used.

Table 13. The probability value from back-transformed least square and standard error of recalling content

Placement	Vertical Format	Horizontal Format	Interactive Format
Probability	0.15 ± 0.052^{a}	0.24 ± 0.0575^{a}	$0.47 \pm 0.071^{\mathrm{b}}$

Table 14. The averages and the standard deviation of recalling content (A value of "2" was indicated for failure to recall label information, while a "1" was recorded for those that did recall something about the information)

Placement	Vertical Format	Horizontal Format	Interactive Format
Average	1.82 ± 0.39^{a}	1.75 ± 0.43^{a}	$1.52 \pm 0.50^{\mathrm{b}}$

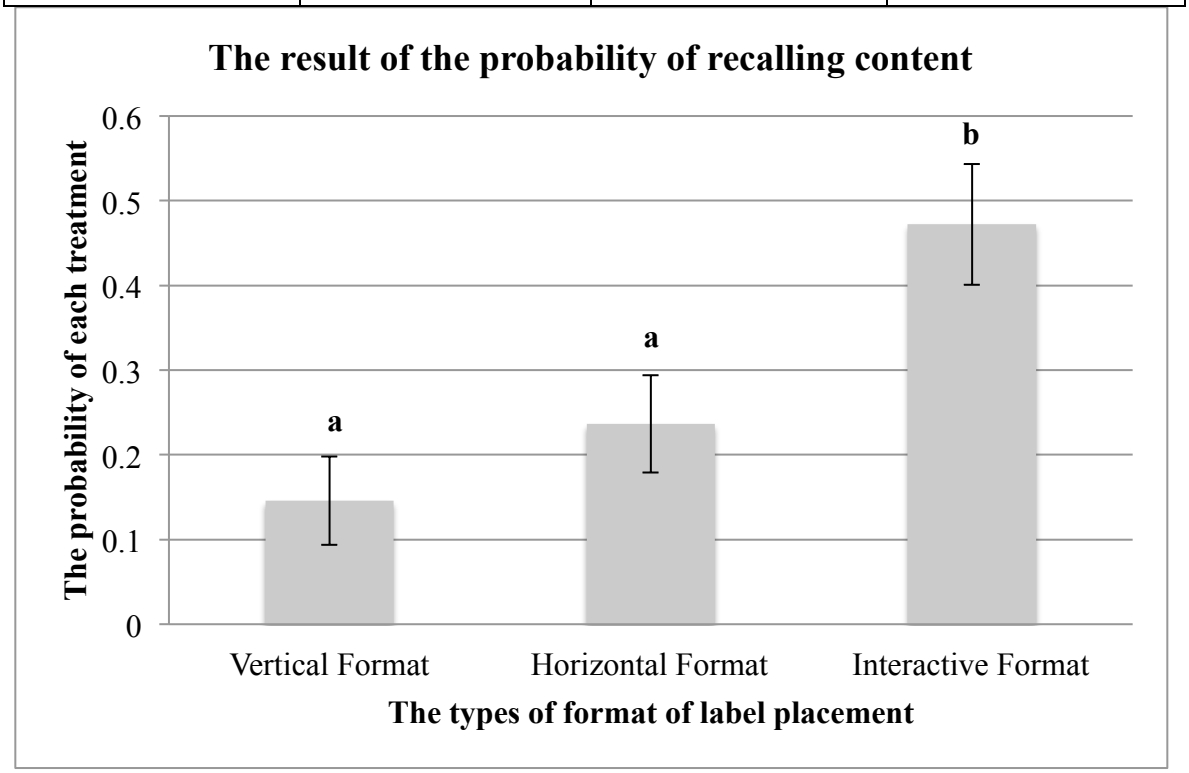


Figure 15. the probability from back-transformed least square for recalling informational content

All effects were included in the model at the beginning stage of this analysis, but none of them suggested significant differences at p-value (<0.05) except for the effect of placement, so these were removed in the model for the further analysis (See table 16).

Table 15. The result of Type 3 text for recalling content

Effect	Number of Df	Den Df	F-value	P-value
Age Group	1	61	0.30	0.5870
Gender	1	61	0.99	0.3243
Age Group*Gender	1	1	0.51	0.4773
PWL Placement	**2**	**122**	**0.0021**	**0.0021**
Age Group* PWL Placement	2	122	0.03	0.9740

***Bolded effects suggest significance at α=0.05.**

As indicated in table 16, only PWL placement provided evidence as affecting recall of informational content (p=0.0021) whereby, interactive placement of the warning performed significantly better than either the horizontal or vertical placements.

Pairwise comparisons were conducted using Fisher's LSD (see Table 14, Table 15 and Figure 14). The statistical analysis suggested that the subjects more frequently recalled information appearing in the interactive placements than that appearing in vertical placements (p<0.0001). Likewise, subjects were more likely to recall information in the interactive placement than horizontal placements (P=0.0009). No evidence for statistical significance was evident when the horizontal placement and the vertical placement were compared (See Table 14, 15 and Figure 14).

Recall Placement

In addition to whether or not people recalled the informational content of warnings placed differently, we also coded for whether or not participants mentioned a specific warning placement (vertical, horizontal or "over the cap" (i.e. interactive)). When the subjects mentioned the location of label, the response variable of the recall placement was coded as 'recalled the location of the warning'. See Table 17 for example statements.

Table 16. Criteria of encoding data for recalling placement

Elements	Example
Vertical Format	The yellow sticker on the side..
Horizontal Format	The label was at the bottom of bottle..
Interactive Format	The label on the cap..

As with the other recall category (informational content), this response variable was modeled as a binary variable. The model was fitted using a generalized linear mixed model. The distributional assumption did not show it has normality, so logit of Link Function was used.

All effects were included in the model at the beginning stage of this analysis, but none of them showed significant difference by p-value (<0.05), so only the placement effect was used as a fixed effect while the interaction term of subject, age group and gender were used as random effects (See Table 18).

Table 17. The result of Type 3 test for recalling placement

Effect	Number of Df	Den Df	F-value	P-value
Age Group	1	63	3.11	0.0825
PWL Placement	2	126	2.39	0.0956
Age Group*PWL Placement	2	126	0.00	0.9965

Pairwise comparisons were conducted using Fisher's LSD (Table 19, 20 and Figure 15). This indicates that the estimated least square mean and standard error of the result of recall placement. There was not evidence that response rates of recalling warning placement are significantly different from each others.

Table 18. The probability from back-transformed least square of recalling placement

Placement	Vertical Format	Horizontal Format	Interactive Format
Probability	0.046 ± 0.027^{a}	0.046 ± 0.072^{a}	0.14 ± 0.050^{a}

Table 19. **The average and the standard deviation of recalling placement** (A value of "2" was indicated for failure to recall label placement while a "1" was recorded for those that did recall something about the placement)

Placement	Vertical Format	Horizontal Format	Interactive Format
Average	1.91 ± 0.29^{a}	1.93 ± 0.24^{a}	1.83 ± 0.38^{a}

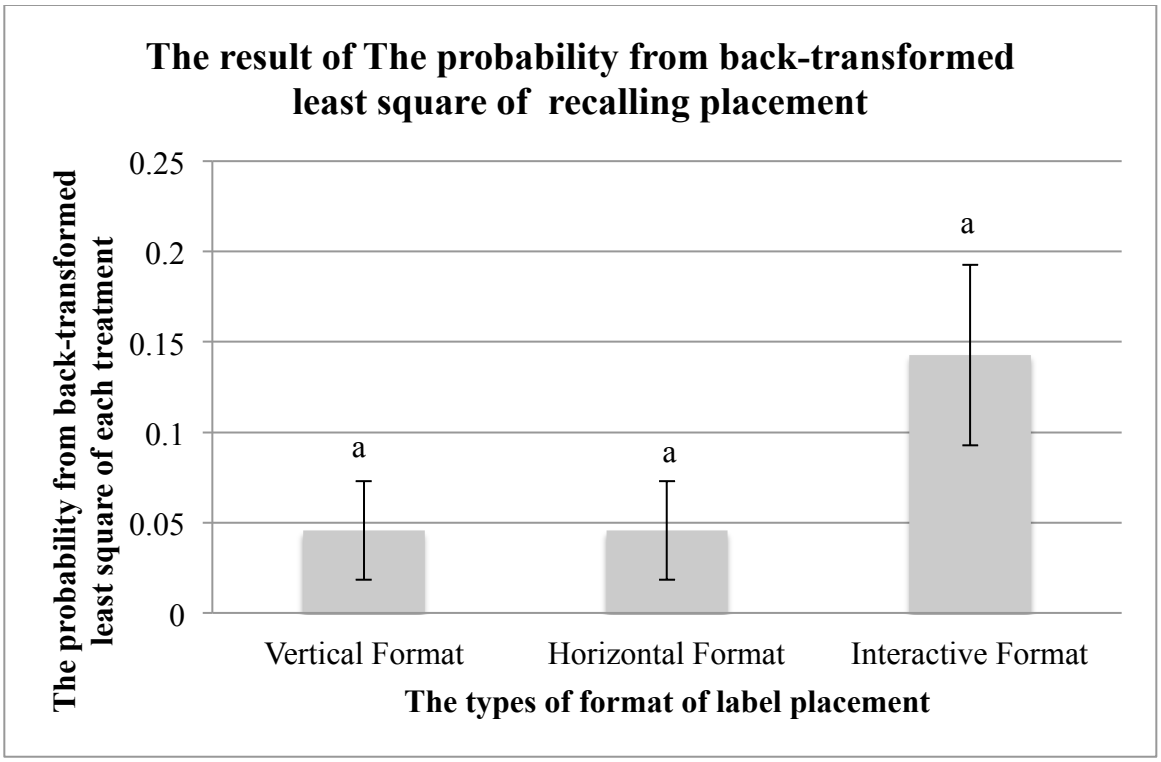


Figure 16. T**he probability from back-transformed least square of each treatment of recalling placement**

The any of recall evaluation

Recall rates were also assessed by integrating the two pieces of information (recall of message content OR recall of warning placement) into a single category, "recalled something about the warning." As with the first two, the dependent variable was modeled in a binary fashion. The model was fitted using a generalized linear mixed model. The logit function was used to have normal distribution of the data set.

All effects were included in the model at the beginning stage of this analysis, but none of them showed significant difference by p-value (<0.05), so the final model used warning

placement as a fixed effect while the interaction term of subject, population and gender were used as random effects (See table 21).

Table 20. The result of Type 3 text of any recall evaluation				
Effect	**Number of Df**	**Den Df**	**F-value**	**P-value**
Age Group	1	61	0.48	0.4923
Gender	1	61	0.40	0.5270
Age Group*Gender	1	1	0.02	0.8843
PWL Placement	**2**	**122**	**9.88**	**0.0001**
Age Group * PWL Placement	2	2	0.18	0.8330
Gender*PWL Placement	2	122	1.31	0.2732
Age Group *Gender*PWL Placement	2	2	1.34	0.2646

Pairwise comparisons were conducted using Fisher's LSD. As seen in Table 22 and Figure 16, in general, the subjects recalled the interactive format more than the vertical ($p<0.0001$) or the horizontal ($p=0.0009$). However, comparison of recall rates for the vertical and the horizontal placements provided no evidence of statistical difference on the likelihood of recalling information (content or placement) about the warning (See table 22 and figure 15).

Table 21. The probability from back-transformed least square of any recall evaluation			
Placement	**Vertical Format**	**Horizontal Format**	**Interactive Format**
Probability	0.20 ± 0.060^{a}	0.29 ± 0.30^{a}	0.62 ± 0.068^{b}

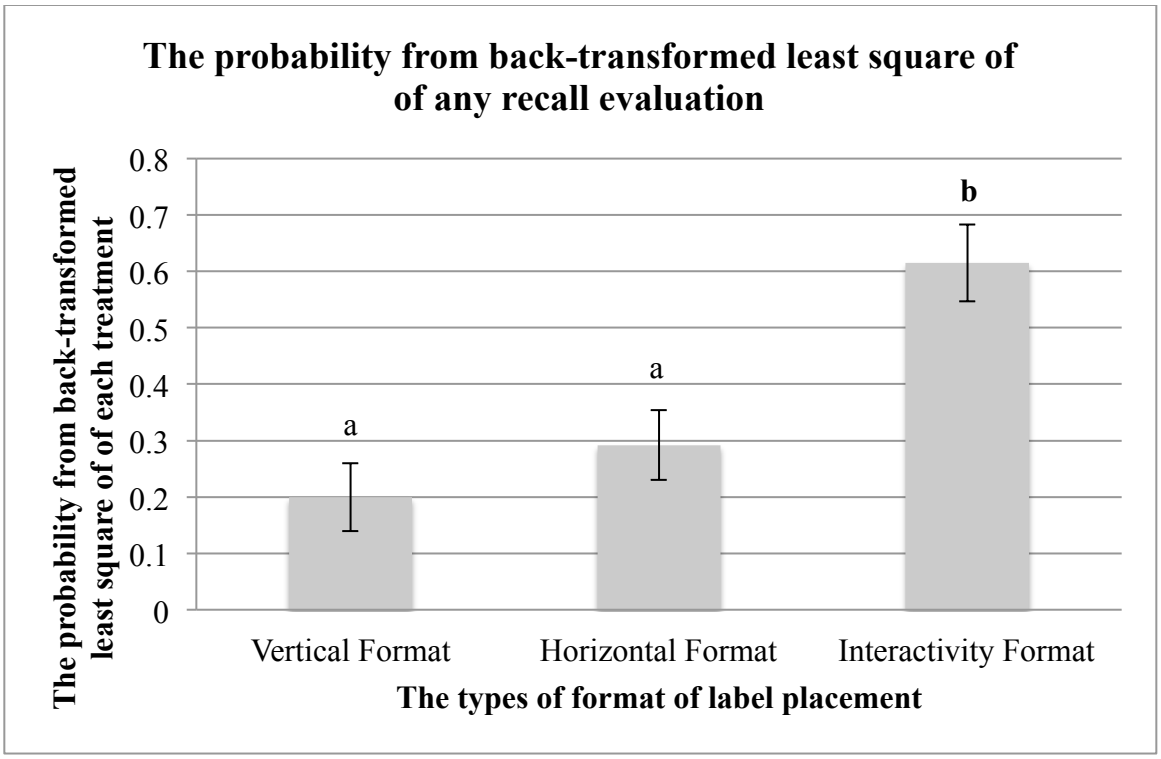


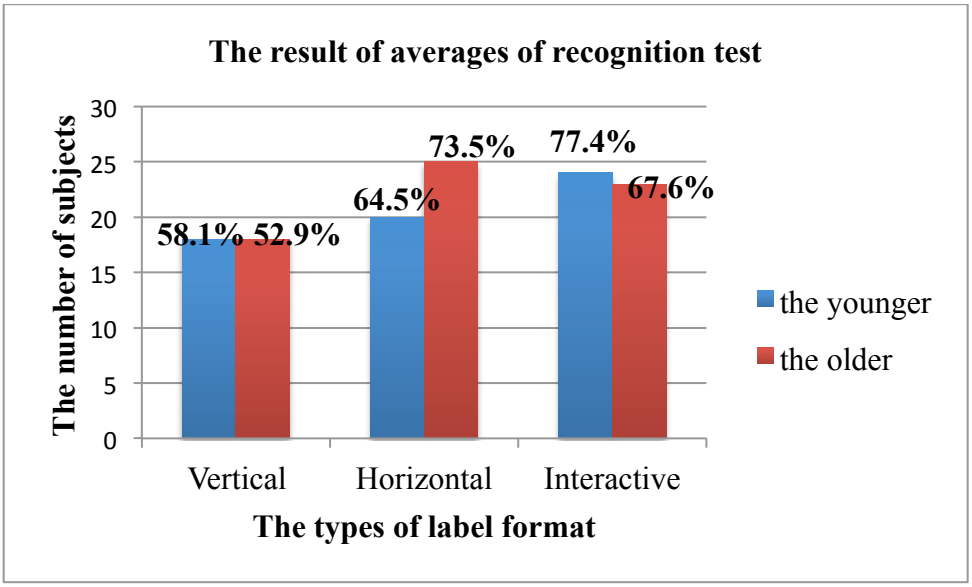
Figure 17. T**he probability from back-transformed least square of any recall evaluation**

Recognition Test

During the recognition test, participants were asked to circle the three warnings that they had been presented from a set of six (See Figure 7). Correct response rates for the recognition test are provided in Table 23 and Figure 17.

With the recall test, values of this recognition test were coded as binary value, correctly identified as present or correctly rejected as not present. One indicates a correct response; two represents an incorrect response.

Table 22. The result of averages of recognition test (Correct response)				
Placement	**The younger**		**The older**	
	Percent (%)	**Frequency (participants)**	**Percentage**	**Frequency (participants)**
Vertical	58.1	18	52.9	18
Horizontal	64.5	20	67.6	25
Interactive	77.4	24	73.5	23



***The percentages indicate the ratio of being recognized by each age group**

Figure 18. Recognition Test

The response variable was modeled as a binary variable. The model was fitted using a generalized linear mixed model. The data set were not normally distributed, so the dependent variables were log transformed.

Table 23. The result of The probability from back-transformed least square of recognition test			
Placement	**Vertical Format**	**Horizontal Format**	**Interactive Format**
Probability	0.51 ± 0.067^{a}	0.75 ± 0.067^{b}	0.73 ± 0.058^{b}

Table 24. The result of the average of recognition test (A value of "2" was indicated for failure to recall label information or placement, while a "1" was recorded for those that did recall something about the information or the placement)			
Placement	**Vertical Format**	**Horizontal Format**	**Interactive Format**
Averages	1.77 ± 0.58^{a}	1.58 ± 0.60^{b}	1.51 ± 0.59^{b}

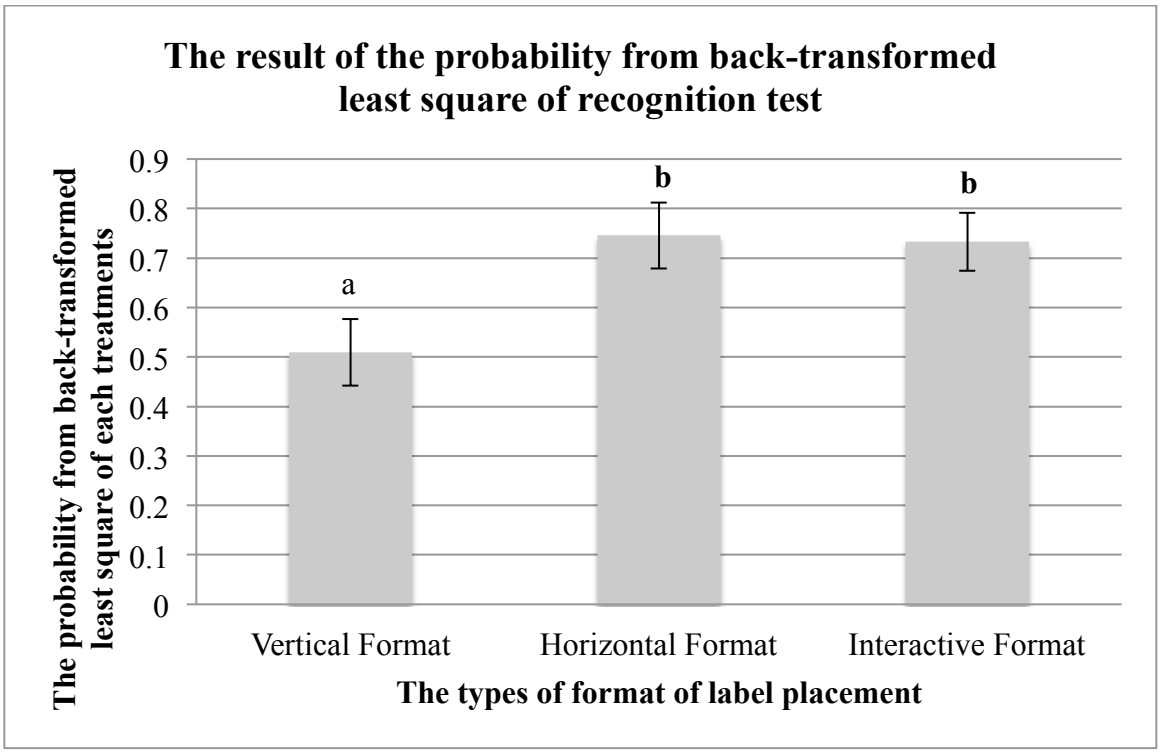


Figure 19 The probability from back-transformed least square of each treatment of Recognition Test

The effect of health literacy, number of prescription drugs per day, and age were included in the model at the beginning stage of analysis, but all of them were dropped because the effects did not show any significance to fit in the model based on Type 3 test p-value ($p>0.05$).

Table 25. The result of Type 3 test on recognition test

Effect	Number of Df	Den of Df	F-value	Pr>F
Age Group	1	0	0.23	.
Gender	1	0	0.00	.
Age group* Gender	1	0	3.60	.
PWL Placement	**2**	**122**	**4.17**	**0.0178**
Age Group* PWL Placement	2	122	0.78	0.4619
Gender*PWL Placement	2	122	0.91	0.4039
Age Group *Gender* PWL Placement	2	122	0.62	0.5381

Of all tested variables, only PWL placement suggested a significant effect on rates of correctly recognizing warning information. As such, only the placement effects were included in the model (See Table 26).

Pairwise comparisons conducted using Fisher's LSD are presented in Table 24, Table 25 and Figure 18. The statistical analysis suggests that participants correctly recognized information that appeared in the horizontal placement more often than the information appearing in a vertical

placement (p=0.0189). Further, participants recognized the warnings appearing in an interactive placement more frequently than those in vertical placements (P=0.0153). However, there was not enough evidence that rates of correctly identifying the information was influenced by whether it appeared in the horizontal or interactive placements (See Table 24, Table 25 and Figure 18).

Chapter 8. Conclusions, Limitations and Future Research

Discussion

Evidence presented herein suggests that interactive placement of PWLs (specifically, across the cap) is an effective way to garner the attention of both younger and older adults. The probability that a subject would look at the warning ($P=0.0011$) and the time subjects spent attending warning information ($P<0.0001$) were both significantly influenced by the placement of the warning label. Finer comparisons suggested that the probability of noticing the warning was significantly enhanced when it was displayed in an interactive ($P=0.0003$) or a horizontal ($P=0.0376$) as compared to vertical ($\alpha=0.05$). There were not enough evidence on the significant difference between an interactive and a horizontal placement ($P=0.0647$). Once people did look at the warning, they spent a significantly longer amount of time viewing the interactive format as compared with either the vertical ($P<0.0001$) or the horizontal ($P<0.0001$). There was no evidence that placing the warning in different orientations significantly affected the time it took to first notice it ($\alpha=0.05$). Not only did the subjects spend more time viewing the information that appeared in an interactive placement, data supported the idea that subjects were better at recalling the informational content that was presented in an interactive placement as compared with the horizontal ($P=0.0009$) or vertical ($p<0.0001$). Specifically, what they mostly remembered was the contents, not the location itself.

Data also suggested improved rates of recognition of information that appeared in an interactive format as compared with vertical placements ($P=0.0153$).

All in all, herein, the interactive format of warning labels is strongly suggested based on

the fact that the subjects recalled the label contents when it is presented in an interactive format more than when it presented in a horizontal and a vertical format although there is not enough evidence that the recognition ratio of the horizontal format and the interactive format is significantly different. Also, in terms of economic aspects, there would not be any cost on having the interactive format on prescription medication because only difference between the interactive format and the others is the placement.

Limitations

In order to enhance the accuracy and consistency of the tracking, we devised an experimental fixture (see Figure 4) and asked people to open the vials that they were handed as their hands or arms rest on said fixture. As such, we created a system which prevented subjects from dropping their hands to their laps (creating a steep angle of view which would like occlude tracking). Although this set up undoubtedly alters completely unfettered behaviors and may affect results, work presented here represents one of the first studies to directly measure the attentive behaviors that people employ as they interact with prescription labeling. A large portion of existing studies that examine investigate pharmaceutical labeling strategies rely on self reports, Likert scales and other methods that are largely qualitative in nature (Gryfe-Becker, Segal, & Einarson, 1989; Wogalter et al.,1996; M.S. Wolf, et al., 2006) . To enhance realism, the amount of time that was afforded for opening was not truncated or mandated in anyway and consumers were not informed of the study purpose (to study warnings), but instead triggered with a scenario and asked to perform a task.

It is also possible that this scenario, “I will give you three packages which contain three vials. When you get these packages, I would like you to open the package and then take

out the vial and open the vial as you usually would. Imagine that this medication is new to you, and you just obtained this medication from a pharmacy."

Although we carefully drafted and considered this language for use in the study so as to not bias participants toward the warning messages, it is quite possible that they considered this a study of opening and actually were biased against regarding the warning information.

There was a slight confound with placement and label size. While the horizontal and vertical label placements enabled the full label to be displayed, limited space on the cap area shortened the area of the look zone for this format. However, this condition creates a conservative estimate with regard to our hypothesis, and the vast majority of results suggested a evidence of significance in spite of it.

The study herein only investigated certain aspects of the interactive warning. Further research is needed to determine how robust messages that are applied to the closure system are prior to being implemented on a wide spread basis.

Future Study

Because the study presented herein provides evidence of efficacy of an interactive placement regarding attention and recall of message contents, a label optimization study is recommended to refine the labels for commercial use. Further, for this study, label design was limited to existing PWL formatting. A more wholistic approach (i.e. a more comprehensive approach to both the label design and information processing) to the design and evaluation of labeling for pharmaceuticals is recommended.

An investigation of symbols and warning messages is recommended. There are no

regulations on symbols although some guidelines to make symbols are suggested by American National Standards Institute (ANSI). However, some symbols lead patients to misunderstand warning messages. Likewise, warning messages vary in delivering the same information content (e.g. 'Take in the morning' and 'A.M.'). Previous research has suggested that many of the symbols currently applied to PWLs result in confusion, particularly among those with low literacy (Wogalter, Brelsford et al. 1991). Thus, further research, not just of PWLs, but of prescription drug labeling and the information processing model is needed to objectively assess how designs can best convey necessary information to patients that require it.

APPENDICES

APPENDIX 1: CONSENT FORM

Michigan State University

School of Packaging

INSTRUCTIONS AND RESEARCH CONSENT FORM – Prescription vial use experiment

You are being asked to participate in a research study. Participation is voluntary, you may choose not to participate at all, or you may refuse to participate in certain procedures or answer certain questions or discontinue your participation at any time without consequence (e.g. will not affect your grade or evaluation, and you will still receive the participant incentive). This study will take no longer than 1 hour of your time.

To participate in this study you MUST:

- Be 18-29 years of age
- Not be legally blind
- Not wear hard contact lenses
- Administer your own medications
- Be willing and able to travel to the School of Packaging, where the study will take place

As part of this research, we will record your gender, ethnicity, educational background, age and the number and types of prescription and OTC medications that you take each day. We will also ask you to read several words aloud as a measure of your ability to read labels. We will ask you to read a series of numbers made of colored dots; this will test your ability to see color. We will also ask you to read the smallest line of a card consisting of a series of lines of text as a measure of your visual acuity (20/20, 20/30, etc.). We will also track the movements of your eye as you open a series of three packages.

Although there is not physical risk to you as a result of your participation in this study, we will ask questions about the amounts and types of medications that you use each day. We will also ask you to read aloud a series of words. It is possible that some of this information may be embarrassing to you. In the event that you are uncomfortable

with any of the tasks, you may elect to skip a portion of the study, or discontinue altogether. This study does not guarantee any beneficial results to you. The study however does carry a potential benefit to society. Using the data generated in this study, it is our hope that we can design labels that are easier for people to use.

You are free to discontinue your participation in the study at any time without penalty.

You are aware that if you choose to discontinue your participation you will still receive the $30 cash incentive.

All information will be tied to a subject number; you will not be identified by name and your confidentiality will be maintained to the maximum extent of the law. Information retrieved during this entire study will be protected on a password protected computer or in a locked file cabinet on the campus of Michigan State University for a minimum of three years after the close of the project. Only the appointed researchers and the Institutional Review Board will have access to the research data. Within these restrictions, results of the study will be made available to you at your request.

Setup and Calibration:

We will be using eye tracking during this study. The eye tracker is a very sensitive eye movement monitor, which can tell us exactly where your eyes are looking while you are viewing a package. A beam of light that cannot be detected by the human eye will be shone into your eye. The instrument tracks the movement of your eye by tracking the movement of the beam.

You will wear a light camera on your head. Once the camera and head gear is adjusted, we will prepare the eye movement equipment. You will be asked to sit at a desk. For a period of about 5 minutes you will be asked to sit as still as possible, and move nothing but your eyes. While holding your head and body as still as possible, you will be asked to look at certain locations in space so that the researcher can calibrate your eye's position.

Eye Tracking Test:

Once you have been calibrated to the equipment, you will be handed a series of three bags, one at a time, and asked to use the contents. Please handle the vials as you usually would if you were viewing a new medication. At the end of this test you will be asked to answer a short questionnaire based on the vials that you just viewed.

If you have any questions at any time please ask.

Contact information:

If you have concerns or questions about this study, such as scientific issues, how to do any part of it, or to report an injury, please contact the researcher, please contact the researcher Laura Bix 517-355-4556; 153 Packaging Building East Lansing MI 48824 bixlaura@msu.edu.

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 207 Olds Hall, MSU, East Lansing, MI 48824.

Full disclosure:

Dr. Laura Bix has received funding from prescription drug companies for previous research. They are not affiliated with the current study. Additionally, she has served as an expert witness (plaintiff) in trials that involve the labeling of prescription drug products. Those trials involved manufacturer's labels, where this study involves those applied at pharmacy.

I voluntarily agree to participate in the Eye Tracking and label legibility study.

Sign: _____

Date: _____

You will be provided with a copy of your signed consent form.

APPENDIX 2: RECRUITMENT ADVERTISEMENT

Figure 20. Recruitment Advertisement

APPENDIX 3: DATA COLLECTION SHEET

DATA COLLECTION SHEET

Subject #: _____ Age: _____

Male _____ Female _____

Total # of Prescription Drugs you are currently taking (each different name counts as one):_____

Pre-Testing

Literacy Score:

Researcher hands card to participants and instructs them, “Please hold this document at convenient reading distance and read aloud. I would like you to read as many words as you can from this list. Begin with the first word in List and read aloud. When you come to a word you cannot read, do the best you can or say, 'blank' and go onto the next word." (6 or less has poor health literacy)

Fat Flu Pill Allergic Jaundice Anemia Fatigue

Directed Colitis Constipation Osteoporosis

Visual Acuity:

Researcher hands visual acuity card to participants and instructs them, “Please hold this card at approximately 16 inches from your eyes read, aloud, the lowest line on the card that you are able. This is like the eye test that you take at the doctor and will give us a sense of your visual acuity.”

20/100:	S D K H N	O C V R Z
20/150:	H C Z S V	O O R N K
20/100:	O N H D R	Z K S C V
20/80:	Z V R C K	N O H D S

20/60:	K N C S O	V H Z R D
20/50:	R V D K C	S H O N Z
20/40:	H N D C R	V S K Z O
20/30:	Z C O N S	D H R V K
20/20:	C K D Z H	R N O S V

Result: 20/_____

Recall and Recognition Test

Free-recall Test

Please write down anything that you can remember about the warnings that were present on each of the vials.

Recognition Test

Please pick out the exact 3 labels that you just viewed.

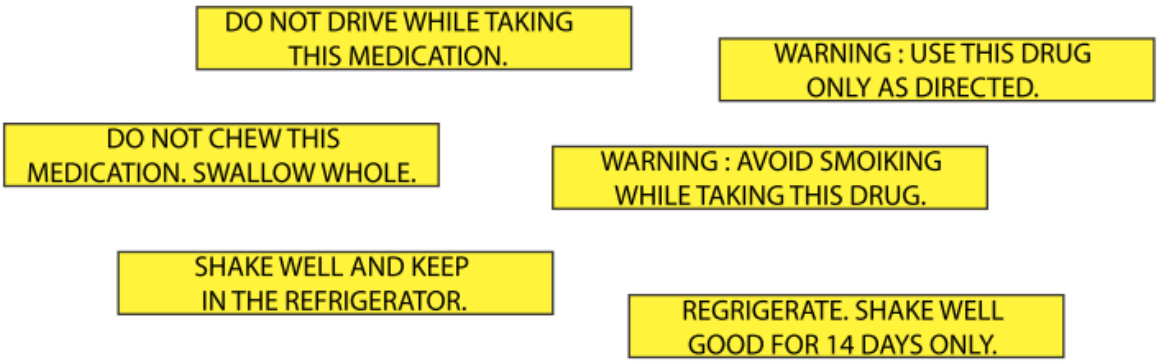


Figure 21. Recognition test figure

APPENDIX 4: READABILITY TEST

Table 26. Readability Test

	Text of warning Label	Flesch reading ease test	Flesch-Kincaid Grade Level Test
1	For external use only.	54.7	6.6
2	Take with food.	100.0	0.0
3	Medication should be taken with plenty of water.	50.6	8.1
4	Take this medication 1/2 hour before meals.	71.8	5.2
5	Do not drink milk or eat dairy products while taking this medication.	67.7	6.7
6	Do not chew this medication, swallow whole.	66.7	6.6
7	Do not take this medication if you are pregnant.	75.5	4.9
8	Do not drink alcoholic beverages when taking this medication.	19.1	12.8
9	May cause drowsiness or dizziness.	49.4	7.6
10	Keep out of reach of children.	100.0	0.5
11	Store in cool, dry place.	100.0	0.0
12	Do not take this drug if you become pregnant.	94.3	2.3
13	Harmful if swallowed. Use only as directed.	58.2	6.0
14	Chew tablets before swallowing.	33.5	9.5
15	Do not take with nitrates.	100.0	0.5
16	Shake well and keep in the refrigerator.	66.7	5.6
17	Finish all the medication unless otherwise directed by prescriber.	9.7	14.1
18	Take only at recommended doses.	32.5	9.9
19	No aspirin without MD approval. Continue low dose aspirin unless MD stops.	32.5	9.9
20	Immediately report bleeding or bruising to your doctor.	29.5	11.11
21	If you drink alcohol, discuss the safe use of alcohol while taking this this medication with your healthcare professional.	45.0	11.6
22	Do not take aspirin products without doctor approval. Continue taking low-dose aspirin to prevent heart attack/stroke unless doctor tells you to stop.	48.0	9.4
23	Rinse mouse thoroughly after each use.	73.8	4.4
24	Anti-neoplastic material-handle properly.	0.0	44.5
25	Refrigerate.	0.0	32.0
26	Caution: Do not take with alcohol or no prescribed drugs without consulting your doctor.	53.6	9.2
27	Refrigerate. Shake well. Good for 14 days only.	66.6	4.6
28	Limit the use of caffeine-containing beverages (Coffee, Tea, soft drinks). They may change the effects of this medicine.	52.0	8.2
29	Do not crush.	100.0	0.0

Table 26 (Cont'd)

30	Controlled substance. Danger unless used as directed.	46.1	7.6
31	May be refilled 2 times.	100.0	0.5
32	This drug is available in a cost saving generic. Please ask us about it.	72.8	4.8
33	Caution: This drug alone or with alcohol may impair your ability to drive.	56.9	8.9
34	The increase in cost of your prescription is due to a price increase by the manufacturer.	63.6	8.3
35	This prescription refilled on.	54.7	6.6
36	For rectal use only.	75.8	3.6
37	This item was specially ordered for you. Please contact us a day ahead to reorder.	69.5	5.4
38	Caution: Dosage strength different from order. Use appropriate amount.	33.0	9.7
39	For oral use only.	75.8	3.6
40	Please contact your physician before ordering refills.	30.5	10.7
41	This patient requested that a safety cap not be used on this prescription.	63.4	7.6
42	Do not use after Date.	100.0	0.5
43	According to law this prescription cannot be refilled nor copy given.	49.5	9.0
44	You should avoid prolonged or excessive exposure to direct and/or artificial sunlight while taking this medication.	30.3	13.2
45	If may be advisable to drink a full glass of orange juice or eat a banana daily while taking this medication.	56.6	10.5
46	Take medication on an empty stomach. 1 hour before or 2 to 3 hours after a meal unless otherwise directed by your doctor.	62.7	7.3
47	Note: Dosage strength.	90.9	1.3
48	Shake well before using.	75.8	3.6
49	Do not use after.	97.0	0.7
50	This prescription cannot be refilled.	49.4	7.6
51	For the eye.	100.0	0.0
52	Keep in refrigerator. Do not freeze.	62.7	5.2
53	Obtain medical advice. Before taking nonprescription drugs. Some may affect the action of this medication.	38.2	9.1
54	May cause discoloration of the urine or feces.	61.2	6.7
55	Important: Finish all this medication unless otherwise directed by prescriber.	2.1	15.4
56	May cause drowsiness. Alcohol may intensify this effect. Use care when operating a car or dangerous machinery.	36.8	9.5
57	Some nonprescription drugs may aggravate your condition. Read all labels carefully. If a warning appears, check with your doctor.	56.1	7.0
58	It is very important that you take or use this exactly as directed. Do not skip doses or discontinue unless directed by your doctor.	56.5	7.1

Table 26 (Cont'd)

59	This is the same medication you have been getting. Color, size or shape may appear different.	56.5	7.1
60	This prescription cannot be refilled without a written duplicate from your physician.	39.5	10.7
61	Directions changed refer to chart.	66.4	5.2
62	Generic substitution made.	0.0	17.0
63	Substituted for brand prescribed.	12.4	12.5
64	Apply patch to a clean, dry, hair-free area of the skin. Alternate the application area with each change.	70.8	5.6
65	Warning: State and federal law prohibits the transfer of this drug to any person other than the person for whom it was prescribed.	54.7	11.3
66	Thank you. We appreciate your business.	62.7	5.2
67	Supper.	36.6	8.4
68	Certain medications (Antibiotics, Anti-infective) may alter the effectiveness of birth control pills. Ask your physician or pharmacist.	56.5	7.2
69	Protect from sunlight.	62.7	5.2
70	This medication may cause constipation.		
71	Take this medication at least 2 hours before or 2 hours after magnesium or aluminum containing antacids, iron or vitamins/minerals.	24.3	15.0
72	Take with 8oz. of plain water at least 30 min. before first food/beverage/drug of the day. Don't lie down for 30 min.	85.1	5.8
73	Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.	59.1	7.3
74	Shake well and keep in the refrigerator.	66.7	5.6
75	Do not drive while taking this medication.	66.7	5.6
76	Warning: Avoid smoking while taking this drug.	66.7	5.6
77	Warning: Use this drug only as directed.	66.7	5.6

APPENDIX 5: Counter Balanced Design For one population.

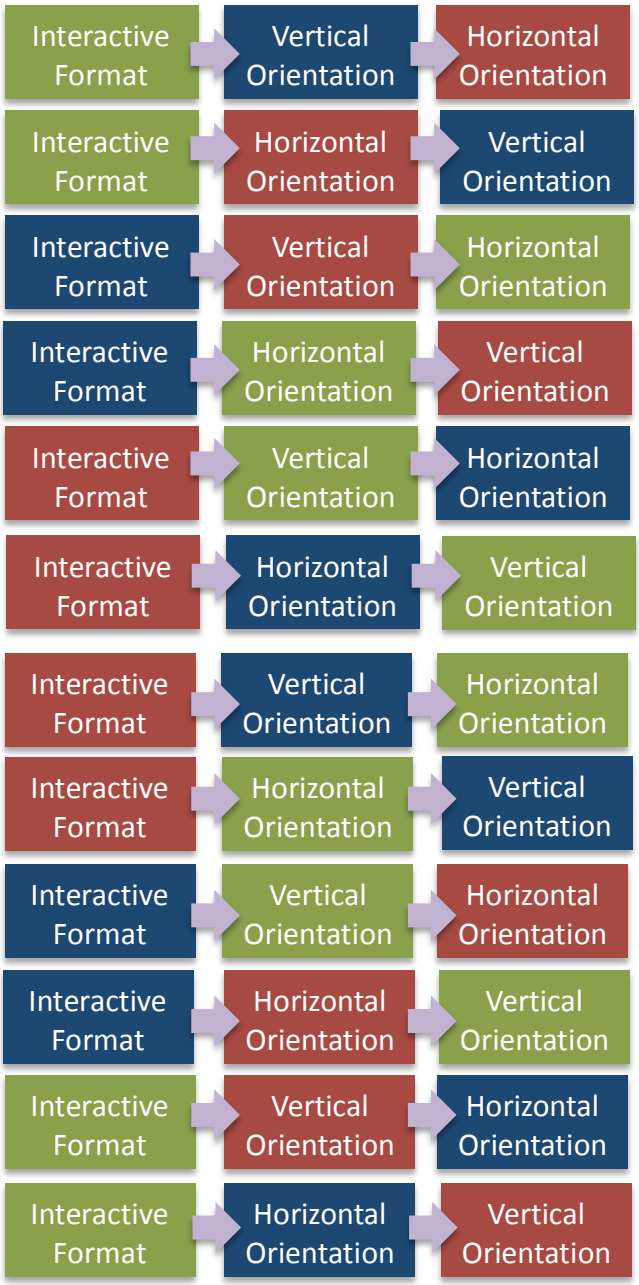
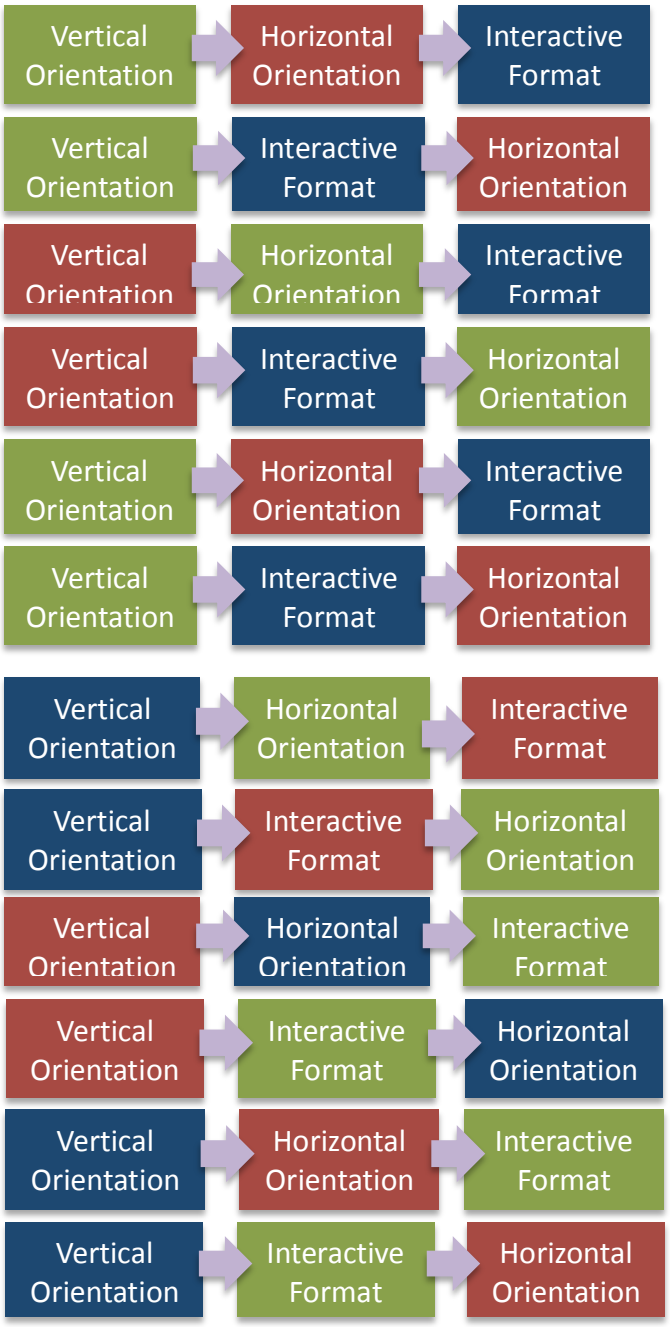


Figure 22. Counter Balanced Design For one population

Figure 22. (cont'd)



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