AHRQ Grant Final Progress Report

Optimizing OTC labels for older adults: Empirical evaluation of labels designed to provide older users the information they need to minimize adverse drug events

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Inclusive Dates of Project: 07/06/2018- 04/30/2024

Federal Program Officer: Farzana Samad

Acknowledgement of Agency Support: This project was supported by grant number R01HS025386 from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services (HHS). The authors are solely responsible for this report's contents, findings, and conclusions. The views expressed do not necessarily represent the views of AHRQ or of HHS.

Grant Award Number: R01HS025386

Abstract

Purpose: To investigate whether a novel front-of-pack (FOP) warning label on over-the-counter (OTC) drugs would allow older consumers (65+) to make more appropriate medication choices, thereby reducing their likelihood of a preventable adverse drug event (ADE).

Scope: The Drug Facts Label (DFL) contained on most OTCs sold in the US has been criticized. Here, we attempt to extend the benefit of FOP labeling that has been shown for nutritional labels to OTC via the use of a novel FOP for OTCs.

Methods: FOP content was informed by a national survey of pharmacists. Performance (visual attention and ability to improve decision making) of the novel FOP was evaluated in a series of experiments employing methods adopted from the field of visual cognition.

Results: Survey results indicated that drug-drug and drug-diagnosis warnings were critical to ADE prevention; as such, this information was placed in the FOP. Our results confirm that many OTCs pose potential preventable ADE risks for older adults, that participants were unaware of which active ingredients should be avoided, that the current DFL was ineffective, and that familiarity with a medication increased likelihood of erroneously saying the medication was appropriate. Experimental results show that FOP warning labels produced more attention to critical warnings, more efficient and accurate OTC decisions when given a scenario, and increased cautious decision making when evaluating whether an OTC was safe for one's own consumption, suggesting that these labels may reduce the likelihood of preventable ADEs.

Key Words: adverse drug event, OTC labeling, medication error, engineered safety, self-medication

Purpose

We adapted a front-of-pack (FOP) labeling strategy that has been demonstrated as effective for food labels for use with over-the-counter (OTC) medications and sought to determine empirically whether such a technique is effective for older adults, an at-risk population identified to be a priority at AHRQ. Information deemed most critical to mitigating the likelihood of a preventable adverse drug event (ADE) was informed by a national survey of pharmacists, and that knowledge was used to create FOP warning labels for OTC medications. Efficacy of the developed label strategies was tested using a series of six experiments that applied methods from basic research on visual cognition (change detection, a speeded decision task, a cross-product comparison task, and eye tracking) to directly measure whether information in the FOP label received more attention than the traditional Drugs Facts Label (DFL) and whether the FOP label allowed older adults to make more appropriate medical selection decisions.

Scope

Background: Over-the-counter (OTC) medicines provide many benefits, including increased access, independence, flexibility, and affordability. As a result, many people use OTCs to treat a variety of conditions. Despite their advantages, OTCs carry significant risks. Among the risks are preventable adverse drug events (ADEs) (1). Based on a meta-analysis of studies, it has been estimated that 106,000 US deaths per year are likely attributable to a preventable ADE (2); a Canadian study estimates the cost of emergency and hospital care associated with ADEs, more than half of which are thought to be preventable, at $35,700,000 (USD) annually (3). Although it is difficult to precisely quantify the relationship of OTCs to ADEs, studies suggest that OTCs are culpable (4, 5). A study in France found that 6% of ADE presentations to emergency departments were due to OTCs, and about 1% of patients who reported taking OTCs within the past 2 weeks presented due to OTC-related ADEs (4). Among those who experienced preventable ADEs that resulted from self-administration, between a third (4) and a half (5) were attributable to OTCs, not to prescription medications. Though this data, collected in Europe, suggests that ADE rates associated with OTCs are a concern, it likely underestimates the rate for the US healthcare system, where OTC use is more common, and most certainly underestimates the prevalence in older adults.

Older adults are at a higher risk of ADEs than younger people (6-13). Although many factors (e.g., changes in pharmacokinetics, pharmacodynamics, perception, cognition and motor skills; increased prevalence of poor health literacy; and inappropriate prescribing and monitoring practices (14-16)) are associated with this increased risk, a major cause is that older adults use more medications, including OTCs. Ninety-six percent of people 65+ report using OTCs (17), and they consume 30% of the OTCs sold in the US despite comprising only 13% of the population (18). Also, 25% of older adults take a combination of 10 or more OTC and prescription medications daily (19), a troubling number given that the likelihood of an ADE is 10% when taking a single medication per day but jumps to 75% for people who consume five or more medications concurrently (6, 20). Finally, rates of polypharmacy (14) and preventable ADE (21) have been reported to have doubled in the past 20 years. In short, the problem of ADEs, particularly pronounced in older adults, is increasing, making this at-risk population an ideal target for intervention.

In response, the Consumer Healthcare Products Association (CHPA) and the Gerontological Society of America (GSA) assembled a panel of experts with the goal of identifying critical gaps in the "relatively neglected area of OTC use among older adults in order to promote safe and effective use of the same." (22) Among the key research priorities identified in the report was the development of "optimized and standardized labeling of OTC medications so information is presented in a format that is easily accessible to the aging population." (23)

The call for this type of work is not limited to the GSA/CHPA efforts; a systematic review of studies investigating OTC labeling suggests the need for research ensuring that consumers can "effectively find and understand information to facilitate safe and effective self-management." (24)

Labeling strategies that enable consumers to easily identify products/situations associated with increased potential for ADEs are of particular importance for OTCs; the prescribing physician and the dispensing pharmacist act as "learned intermediaries" for prescription drugs, but this is not the case for OTCs (25). Although consumers can seek information from other sources when selecting OTCs, research suggests that, in a majority of cases, the label is the sole source of information used (26-31).

Given the risks associated with improper OTC use, the critical importance of labeling for these products and the elevated, and increasing, risk for preventable ADEs among older consumers, research examining label strategies that more effectively communicate information important in averting potential preventable ADEs is needed (23).

Current Approach: To answer this call to action, we performed a series of experiments focused on improving attention to critical information on OTC labels by implementing a front-of-pack (FOP) warning label. Our emphasis on attention stems from work showing that failing to attend to critical information on OTC labels may be endemic and problematic (32-34). For instance, survey respondents indicated that they used symptom relief (78%), brand name (54%), and price (47%) when making OTC purchasing decisions, but no respondents mentioned use of information about the active ingredient or disease or drug contraindications (32), perhaps because many people falsely believe OTC medications carry little risk (10, 35, 36). This failure suggests that a label that drives attention toward information critical for the reduction of preventable ADEs would be beneficial. Even so, most of the research on OTC labeling has focused on late stages of processing (comprehension) without considering how label designs impact early stages of processing (attention). For instance, many studies investigating OTC label comprehension and usage explicitly direct participants to attend to specific label information (37-39). This explicit direction limits the ability to assess how various designs/layouts attract attention to critical information. To address this shortcoming, our experiments directly measured how varied label designs influence both early (attention) and late (comprehension) stages of information processing.

We focused on creating an FOP warning label for OTCs, because we saw parallels between drug and nutrition labeling. In 2002, the US FDA began requiring a "Drug Facts Label (DFL)" for most OTC medicines sold in the US. The DFL mimicked the Nutrition Facts Panel (NFP), comprehensive nutrition labeling required on most packaged foods since the early 1990s. As the required nutrition labeling matured, it became widely criticized (40-45). Critiques suggested that people often failed to access information in the NFP and may even actively ignore it (42). As a result, policymakers and researchers recently have focused on ways to optimize nutrition labeling. An approach that has gained significant global traction is the use of FOP labeling. FOPs prioritize nutrition information commonly associated with disease states (i.e., fat, saturated fat, sugar, and sodium) by placing truncated nutrition information on the front of the package. It has been indicated that the FOPs' simplified formats and prominent positioning garners attention readily (46-49), enhances cross-product comparisons through improved understanding (50-54), and positively influences dietary choices (55-57). Our research (40-42), with others (see Hawley for a review (58)), provides strong evidence of the efficacy of FOP labels for food products.

We leveraged this work in nutritional labeling to evaluate whether prioritizing information critical for avoiding preventable ADEs by placing it in an FOP may provide similar benefits for OTC labeling. This approach requires knowledge about which information should be prioritized for placement in the FOP. To address this, we conducted a national survey of pharmacists to determine the OTC information most critical for avoiding preventable ADEs in older populations.

A second method of prioritizing information that may be beneficial is to present critical information using text that has been highlighted. Based on evidence suggesting that highlighting the active ingredient acetaminophen has the potential to reduce preventable ADEs, there has been a regulatory change mandating that the active ingredient acetaminophen must be highlighted (59-60). However, the approach falls short of a full FOP label. Here, *we tested labels that prioritize critical information in two ways – by placing it within an FOP and by highlighting it.* Our systematic analysis of these two factors provides objective data about each approach's ability to increase attention to, and comprehension of, label information critical to reducing preventable ADEs.

Finally, we note that most studies evaluating the content and formatting of OTC labeling utilize surveys and questionnaires (10, 61); guided interviews (37, 62-64); and focus groups (62, 65), but there has been little attempt to evaluate the validity of these self-report measures in the OTC literature. That said, there is a body of research that suggests that self-report measures may be problematic, particularly when people introspect about visual information that they are likely to notice (66) or that is the basis for their decision making (67, 68). Only recently have researchers begun to use objective measures to evaluate OTC labels (see Tong for a thorough review (24)), but many of these suffer from the failure to assess attention, discussed previously.

Our review of the literature suggested that objectively measuring how labeling influences consumer behavior was a significant gap. *Research presented here adopted methods from the field of visual cognition (eye tracking, change detection, search, and speeded comparisons) to empirically assess the efficacy of an FOP strategy for OTC labels used by older adults, providing empirical/objective measures of older consumers cognitive processing and use of label content.* Across six studies, we performed research with the goals of providing the following knowledge:

- The label content that experts believe should be prioritized to reduce preventable ADEs in older adults.
- The impact that prioritizing this information using an FOP label and/or highlighting had on attention to and comprehension of information critical to preventable ADE reduction in older adults.
- The efficacy of an optimized OTC label for improving older adults' selection of appropriate OTCs.
- How any identified benefits of an optimized OTC label utilizing mock products generalized to more complex and familiar commercially available OTCs.

Methods

Given our goal of creating an effective front of pack warning label for OTC medications, we began our investigation with a national survey of pharmacists (n=318) to assess expert opinion related to which information would be most critical to prioritize in front of pack warning if the goal were reducing preventable ADEs in older populations. Detailed methods of our approach are available in the publication of that study (69); in brief, pharmacists were asked to rank order which aspects of the legally required DFL for OTC medications were most critical for older consumers to notice in order to avoid preventable ADEs. This allowed us to determine whether there was expert consensus about the aspects that would be most important to include in an OTC front-of-pack warning label.

Using the information from the survey, we developed a novel warning label that pulled the subset of most critical information onto a front of pack warning label. In brief, the information in this critical subset were the warnings concerning drug/drug and drug-diagnosis warnings. We then evaluate the ability of this FOP to increase attention to, and facilitate appropriate selection of, OTC medications among older adults.

Experiment 6 used commercially available OTC brands, but packages for Experiments 1-5 consisted of single-ingredient, mock brands of OTC drugs to eliminate the possibility that prior brand knowledge influenced participants' behavior. Each mock brand was based on an existing OTC medication, and the corresponding DFLs were based on the commercially available base to ensure that they were plausible and accurate. All packaging graphics were created so that they were adherent to requirements set forth in the Code of Federal Regulations (CFR) Title 21CFR §201.66.

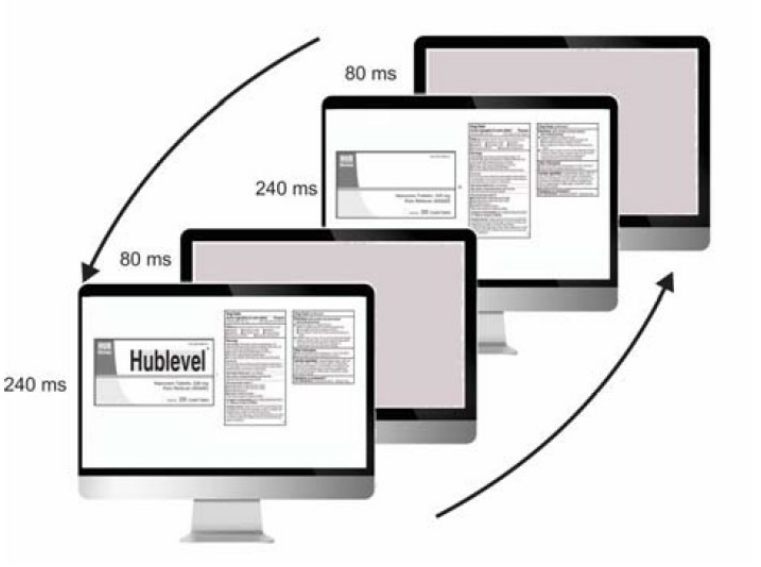

Figure 1. An example of the change detection method used in Experiment 1. In this example the mock brand name is appearing and disappearing across alternations. In critical trials the active ingredient or one of the warnings would appear and disappear.

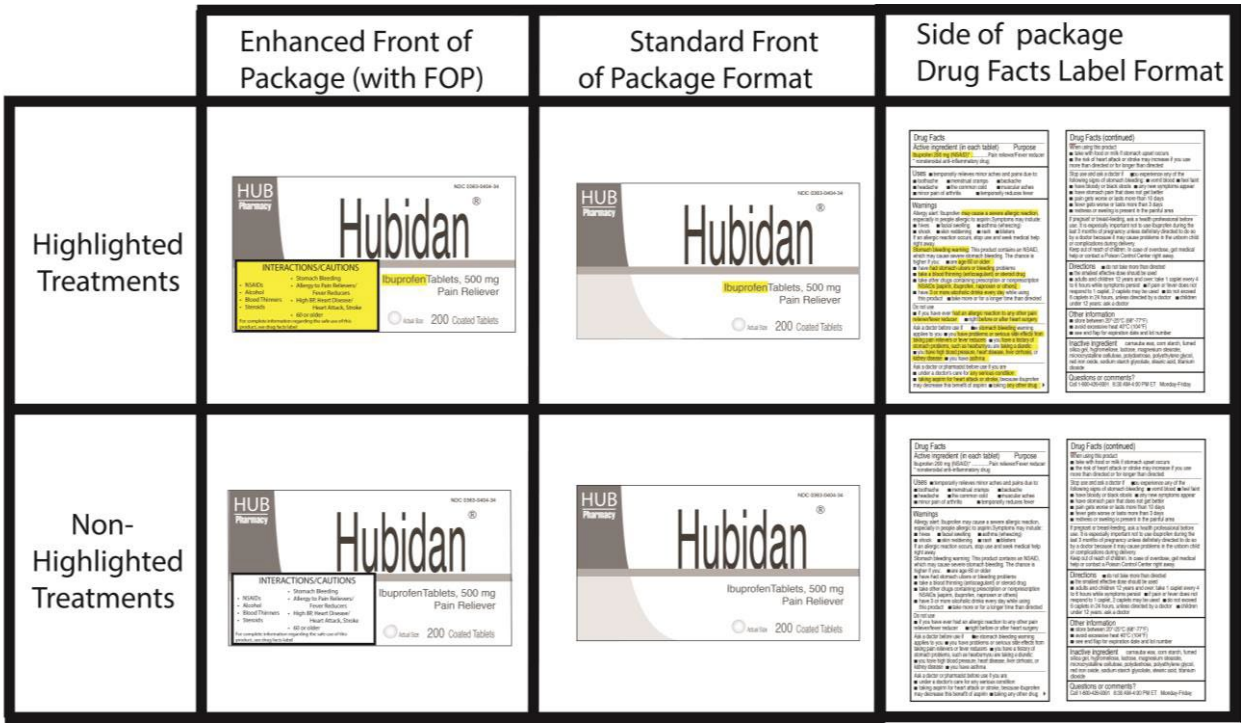

Figure 2. Examples of the four label treatments. Each type of package front will appear alongside the Drug Facts Label in its row. The highlighting treatment will involve highlighting the active ingredient and all drug-drug and drug-diagnosis warnings in both the front label (when present) and the DFL.

Experiment 1 utilized a change detection task (70) to investigate how information formatting influenced attention to critical information (active ingredient and drug-drug/drug-diagnosis warnings). During test trials (see Figure 1), an image and a slightly altered image continually alternated on a computer screen, separated by a brief blank screen, until the participant found the change. This type of change detection requires attention to the change, and the blank screens interrupt motion transients that would draw attention to changes (70). Thus, the time required to detect the change is used as a proxy of the time when attention is first deployed to the location of the change (71, 72). In addition, participants searched for any changes rather than prespecified target objects, allowing the evaluation of attentional prioritization of critical label information (warnings/active ingredients) without informing participants that this information was important to our study or that we were tracking attentional deployment. As a result, the method provided an objective evaluation of different label techniques' ability to attract attention to critical information among people who did not have the goal of seeking the information of interest, providing a good measure of the label format's influence on the bottom-up attentional system.

Additional details of the method can be found in the publication of this experiment (73); in brief, we created four label designs for each of our mock brands. These four labels included the current standard label, a standard label in which critical information was highlighted, a modified label that included our novel FOP warning label, and label that included both this novel warning label and highlighting (see Figure 2). During the experiment, flattened depictions of each type of label were shown so that the front of the package and the DFL were visible simultaneously without having to rotate to a different face of the package. We compared the time to detect changes to critical information across label types to empirically evaluate how highlighting and the inclusion of an FOP label increased attention to this critical information.

In experiments 2 and 3, participants were given a series of scenarios and asked to answer questions for products with labels that varied in formatting (label designs similar to Experiment 1), thereby allowing an empirical evaluation of how well various labels allowed people to access and use critical information when that was their explicit goal. The critical information for half the scenarios required the participant to access active ingredient(s) (e.g., does this product contain ibuprofen?). In the remaining half, the critical information required participants to access a warning label, a drug-drug or drug-diagnosis warning (e.g., Can you take this drug if you are taking a daily aspirin? Is this safe for someone with hypertension?). The main experimental manipulation was the design of the information that appears on the label (see Figure 2). As with experiment 1, the labels were presented in flattened format with both the front panel and the side panel with the DFL visible.

In Experiment 2, participants made a yes (this drug would be appropriate given the scenario)/no (this drug would be inappropriate given the scenario) judgment when presented with a single drug package, allowing us to empirically evaluate the label design's impact on absolute judgements. In Experiment 3, the main difference was that the participants were presented simultaneously with two drug labels and had to select which of the two drugs would be appropriate given the scenario, allowing an investigation of the various label designs ability to support effective cross-product comparisons. In both experiments, we investigate both speed and accuracy of the decisions as a function of label designs. Additional details of the methods and results for these experiments can be found in the publication of the experiment (74).

Beginning with Experiment 4, we switched from scenarios to experiments that asked people to make judgments about whether specific OTC medications would be appropriate for the individual participant to take, given their health status. During each trial, study participants were asked to answer the question, "If you had the condition(s) this product treats, would it be appropriate for you to take?" by clicking yes/no. Experiment 4 varied the amount and type of information the participants were given

on each trial to identify what facilitates an informed decision concerning OTC appropriateness. In each trial, participants were shown one of five levels of information.
One level involved presenting only the mock brand name – a presentation that that provided no information about the safety of the medication, which was used to assess people's general bias toward saying any OTC medication was appropriate for them or not. The second level involved only the drug purpose (e.g., pain reliever), which again provided no information about the appropriateness but may have increased familiarity (e.g., I take pain relievers and many of them are safe for me). The third level presented only the active ingredient, to assess whether people were aware of active ingredients that they should avoid given their health status. The fourth level included the entire front of pack, which included the mock brand name, the purpose, and the active ingredients, to assess how simultaneously providing multiple pieces of information impacted decision making (would presenting too much information reduce its effectiveness?). The fifth level presented the entire legally required DFL. In theory, this level provides all the information needed for participants to make a correct determination, but this condition allowed an empirical evaluation of how well the DFL functioned. Each subject saw all five levels of information for each of nine medications—a total of 45 trials. The trials were presented in five mini-blocks of nine trials, such that each drug appeared at one level of information during each mini-block. Within each mini-block, there was a mix of level of information, and across the five mini-blocks, each drug appeared at each level of information.

This experiment, and all subsequent experiments, required us to evaluate whether the correct decision for each drug presented was an appropriate/inappropriate response for the given participant. To achieve this evaluation, all participants were asked to bring to the study the packaging for all prescriptions, OTCs, herbal remedies or vitamin supplements that they had taken in the previous week (both scheduled and as-needed). These were scanned with an Rx Label scanner, which populated the relevant information like drug name and dosage amounts into a database that redacted personal identifying information but linked to a subject code. After participants completed the experiment, researchers conducted a guided interview to ensure the accuracy of dosage information, etc. (e.g., many participants used the medications in ways other than prescribed or indicated on the labeling). This interview also built a health history (e.g., diagnoses), and collected data regarding participants familiarity with, and knowledge of, different active ingredients. Medication diaries and health histories were then evaluated by the project pharmacists at University of Wisconsin (under the direction of Dr. Beth Martin). The pharmacists evaluated whether or not each of the active ingredients tested were appropriate for a given participant to take based on their reported health and medication histories. When the pharmacist determined a drug to be inappropriate for a given individual, they coded the result as a potential drug-drug interaction, a potential drug-diagnosis interaction, or another problem (e.g., anticholinergic load). Pharmacists' assessments were used to code whether the participant's responses regarding appropriateness were correct or not. A combination of participant response (y/n) and pharmacist response (y/n) yielded incongruent (answers in disagreement) or congruent responses (answers in agreement). Of particular interest are incongruent trials we termed "problematic"; specifically, incongruence was when the participant believed the drug to be appropriate and the pharmacist did not. These incongruencies are the ones most likely to lead to adverse drug events.

Experiment 5 used the same participants as Experiment 4 and again asked them to evaluate whether a given drug was appropriate for them to take, while their eye movements were tracked. However, in this case they were presented with a computer-generated 3D rendering of the package. At the beginning of each trial, they were presented with the front of the medication package on a computer screen and could use the mouse to rotate the display to any of the package's six surfaces; thus, they were able turn the package to inspect the DFL if they wanted to. They were given no time constraints and could switch back and forth to different sides of the package freely. Participants made an appropriate/inappropriate judgement by clicking on one of two buttons on the screen that would

terminate the display of the medication and display a screen requesting they indicate their confidence in the prior appropriateness judgement on a 5-point Likert-Type scale.

After they indicated their confidence, the next trial began with a drift correction on the eye tracker followed by the next package. For this experiment, there were only two label treatments, the standard label and a novel label that included both highlighting and our novel FOP warning. There were 12 OTC medications, each of which appeared at each level of product labelling, providing 24 total trials. These were broken into two blocks of 12 trials, with each drug appearing once during each block. Within a block, half the trials were the standard label and half had the experimental label. Their responses allowed us to investigate the effect of label treatment on accuracy, and the eye tracking allowed us to evaluate which information they accessed in different trials and how that impacted accuracy.

Experiment 6 was identical to experiment 5 with two notable exceptions. First, it was run on new group of participants. Second, rather than use our mock brand names and relatively generic packing, we used the branded products on which the mock brands were based. Thus, these packages tended to be more colorful and busy and had the potential for brand familiarity. Again, there were two levels of package condition: one, the standard commercially available package; the second, the commercially available label with highlighting and our novel FOP warning added to the package front. In all other respects, the experimental methods were identical to Experiment 5.

Results

Results from our survey of 318 pharmacists suggest that three pieces of OTC information are critically important for consumer to make safe purchase decisions: the purpose/use of the medication, active ingredients, and warnings. These data provided important insights into the label designs used for subsequent experiments. Two pieces of information identified by the pharmacists (active ingredient, purpose/use) already appear on the front of packages, but warnings do not. Given prior work showing that consumers tend focus almost exclusively on the information on the front of the pack, this suggests that moving warning to the front of the pack may be beneficial.

Because space on the front of pack is limited, not all warnings could be placed there. However, we also had the pharmacists rank the 13 different subcategories of warnings required under 21 CFR 201. Rankings were analyzed utilizing a Content Validity Ratio (CVR), a statistic that indicates agreement among experts about the importance of content to a specific goal (Lawshe, 1975). There was broad consensus (see Figure 3) that two types of warnings ("ask a doctor or pharmacist before use if you are…" and "Do not use if…" or the drug/drug and drug/diagnosis warnings) were most important. Thus, we emphasized warnings from these two categories for our novel treatments (highlighting and FOP) in subsequent experiments. A more complete accounting of these findings are presented in the publication (B.A. Martin, et al., 2022) of the study.

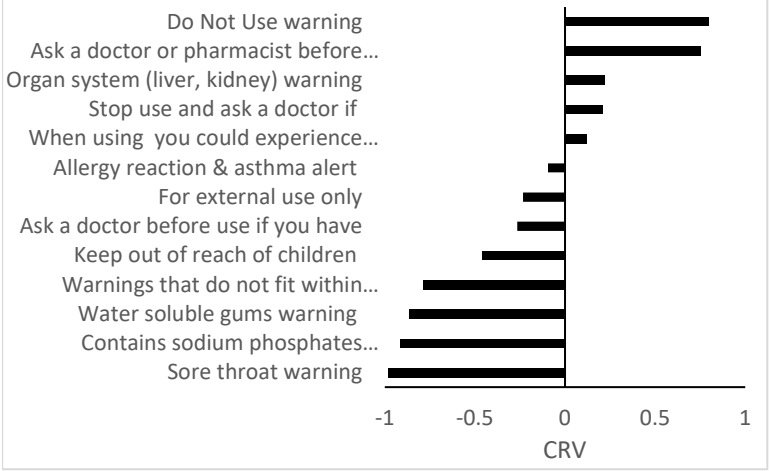

Figure 3 – CVR ratings of the 13 required warnings.

Experiment 1: Change Detection

The results from our change detection experiment support three conclusions. First, the older adults we tested preferentially attended information on the front of packages. The evidence for this conclusion is that changes to both pieces of critical information (active ingredient and warnings) were found significantly faster (both $p<0.001$) when the change occurred on the front of the package than on the drugs facts label (DFL). Second, the FOP label itself effectively garnered attention. The evidence for this was that its presence competed for attention with the active ingredients, such that active ingredient changes were significantly ($p=0.007$) slower in the presence of a front-of-pack drug warning. Furthermore, changes to warnings were found more quickly ($p<0.001$) when they occurred in an FOP warning label than when they occurred in the DFL. Third, highlighting was an effective strategy. Changes to the active ingredients and changes to warnings were found significantly more quickly with highlighting than without (both $p<0.003$). Finally, we should note that these patterns appear consistently across different demographic variables. The only demographic variable that was significantly correlated with our accuracy was age, with older participants being overall less accurate ($p<0.001$). There was no evidence of speed or accuracy being affected by vision quality, Realm-R scores, sex, education (dichotomized into two groups: some college or more versus high school or less), or race.

It is worth noting that the benefits of FOP and highlighting were observed despite the fact that we used flattened packages; with three-dimensional packages, we would expect the effects of the FOP to be more pronounced for warnings, because seeing the warnings on those packages would require one to turn the package to that face. In short, these results suggest that both highlighting and use of a front-of-pack warning label may be effective at garnering attention to warning and active ingredient information among participants who are not explicitly looking for this critical information. A more detailed accounting of these findings appears in the published paper of the experiment (A.L. Harben, et al., 2021).

Experiments 2 & 3: Judgments Given Scenarios

These two experiments investigate how our label treatments impact the speed and accuracy of making an absolute judgement (3a – appropriate/inappropriate) or a cross-product judgements (which of two OTCs is appropriate) about the appropriateness of a specific OTC for a person with a specific condition or who takes a specific medication. Our data suggest that both highlighting and the addition of front of pack warning labels are beneficial to these appropriateness judgements.

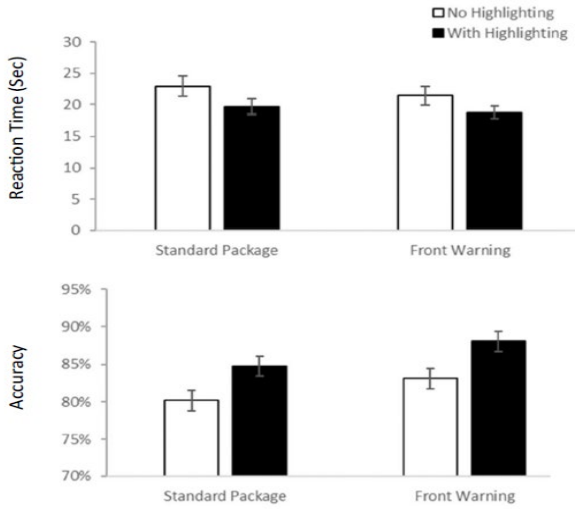

Figure 4. Reaction time (top) and Accuracy (bottom) as a function of label type for Experiment 2.

For instance, in Experiment 2 (absolute judgement), when the label warnings suggested the drug was contraindicated (see Figure 4), participants were faster ($p<.001$) with highlighting and were more accurate with both highlighting ($p<.001$) and the front-of-pack design ($p<.019$). In Experiment 3 (cross-product), accuracy was high for all conditions, suggesting that subjects were near ceiling. Even so, their accuracy was better with highlighting ($p<.006$), and both highlighting ($p<.001$) and FOP warnings ($p=.02$) produced

faster, accurate decision times. In short, both experiments suggest that both highlighting and front-of-pack warnings are beneficial to performance. A more detailed accounting of these findings appears in the published paper of the experiment (Becker, et.al, 2023).

Experiment 4: Here, we report preliminary analyses for Experiments 4-6. We anticipate publishing more comprehensive results of these experiments soon. Experiment 4 was designed to determine what information was required for people to make appropriate decisions about *their own* OTC use, given their health status. To this end, we asked people via survey whether they were familiar with the nine active ingredients we used in experiment 4 as well as whether the active ingredient was appropriate for them to take given their current health status and their confidence in that appropriateness decision. We also had the pharmacists indicate whether the correct response for each drug was appropriate or inappropriate given the individual subject's health and medication status.

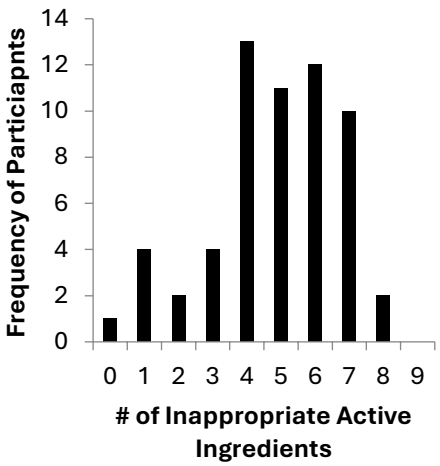

Figure 5. Histogram of the number of participants with each number of inappropriate active ingredients.

These data support three main conclusions. First, OTCs represent a significant risk of preventable ADEs for older adults. For the average participant, 4.83 (SE=.24) of the nine active ingredients were deemed inappropriate, with four or more of the active ingredients deemed inappropriate for the vast majority of our subjects (see Figure 5). Second, multilevel logistical regression analyses show that the likelihood of a participant rating an active ingredient as appropriate for them was strongly driven by familiarity with the active ingredient, b= 4.70, z=9.73, p<.001. Third, participants had little knowledge about what active ingredients they should avoid (see Figure 6). Indeed, the pharmacists' evaluation of appropriateness had no significant effect on the participants' responses, nor did it interact with familiarity, $c^2(2) = 2.17$, p=.338. In sum, when an active ingredient was familiar, it was rated as appropriate for consumption at a high rate, regardless of whether the active ingredient was, in fact, appropriate or not (See figure 6). Thus, based on the survey responses, it appears that familiarity breeds recklessness.

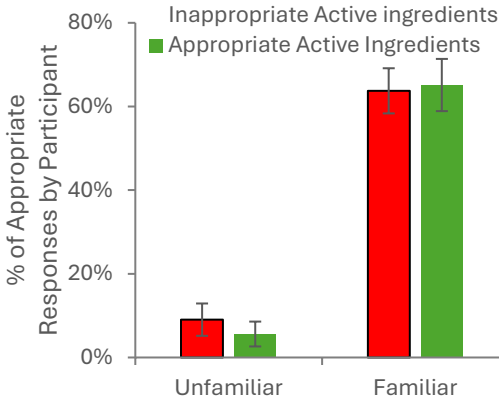

Figure 6. The percentage of appropriate responses as a function of participants' familiarity with the active ingredient and whether the pharmacist judged it to be appropriate or inappropriate.

The experimental data from Experiment 4, when subjects were asked to make an appropriateness judgment utilizing varied levels of information about a product, were analyzed using a multilevel logistic regression model in the 'lme4' package (Bates et al., 2015), with repeated measures nested within persons. Confidence intervals were generated via the bootstrap method. We regressed the participants response (Yes/appropriate=1; No/inappropriate=0) onto the experimental condition factor as a fixed effect. The experimental manipulations explained 17.8% of the variation in responses, $c^2(4) = 598.76$, p<.001. As seen in Figure 7, in the Brand condition, the chance of rating a drug as appropriate was only

8%, but the chance of rating a drug as appropriate was significantly higher in all other conditions, ranging from 48% to 77%. The other four conditions were not significantly different from one another. In addition, including the pharmacist's evaluation of whether the correct response should have been appropriate or inappropriate in the model did not explain a significant amount of variance in the participants' response, $c^2(1) = 2.07$, p=.149, and neither did its interaction with the experimental condition, $c^2(5) = 8.03$, p=.155. In sum, when given only the mock brand name, participants were unlikely to say the drug was appropriate for them to take, but when given any additional information, the likelihood of saying the drug was appropriate increased dramatically; in all experimental conditions, the likelihood of participants responding that a drug was appropriate was equivalent for appropriate and inappropriate drugs, suggesting that people were not able to discriminate safe from unsafe drugs.

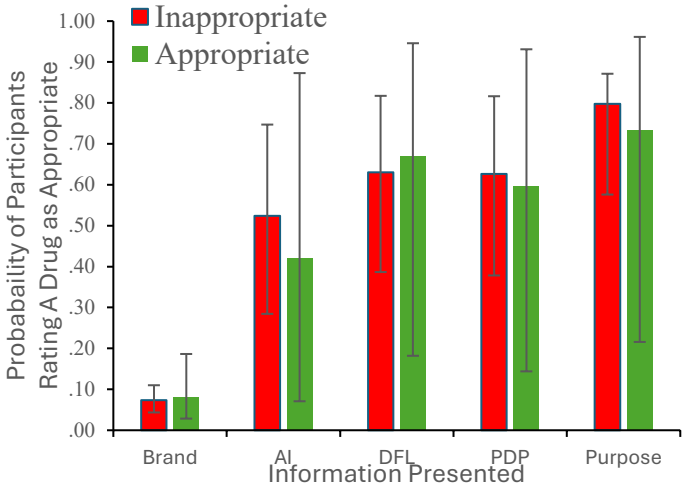

Figure 7. Probability of participants rating a drug as appropriate as a function of the type of information provided in the condition and whether the medication was actually appropriate or inappropriate for the participant. Error bars are 95% confidence intervals.

This failure to discriminate appropriate from inappropriate drugs was particularly striking when the participants were presented with the DFL. In that case, the provided label had all the necessary information to make a correct appropriateness judgement, yet people called inappropriate medications appropriate over 60% of the time. These high error rates provide strong evidence that the DFL in its current format is ineffective.

In sum, the results of Experiment 4 are extremely worrying. They suggest that many OTC medications are deemed inappropriate for many of our older participants by our learned intermediaries; yet, participants frequently judge these inappropriate medications to be appropriate.
People seem unaware of the active ingredients that are contraindicated for their health status, and that familiarity leads people to make more risky choices; even presenting people with the full DFL does not lead to more informed decision making.

Experiment 5. Eye tracking with Mock Brands-Preliminary

In experiment 5, people again made judgments about whether a given medication was appropriate for them to take given their health status. In addition, we tracked their eye movements and presented them with a digital model of the full package; they began by viewing the front of the package but could choose to inspect the different faces of the package. Furthermore, we presented each drug in two formats: a standard package and a package that included highlighting of critical information and a front-of-pack warning label.

We analyzed data separately for appropriate and inappropriate OTCs, as rated by the pharmacists. There were both practical and theoretical motivations for doing so. From a practical perspective, these inappropriate medications are the ones for which the participants could make a potentially dangerous drug decision and thus are of the most interest. From a theoretical perspective, when a drug is inappropriate, the critical indication that the drug should be avoided is presented on the label. By contrast, when a drug is appropriate, the information that lets a participant know the

medication is safe is not on the label (e.g., labels do not say "this is safe to take if you have hypertension."). Thus, these two scenarios map onto target-present and target-absent searches from the visual search literature. It is well documented that reaction times are usually faster and errors are usually higher for target-present than for target-absent searches. Thus, analyzing them separately is typical of visual search tasks.

For inappropriate drugs, a comparison of how often participants say the drug is appropriate (as a function of label condition) found that participants were less likely to make this type of dangerous decision with our experimental label (M= 48.48%, SE = .045) than with the standard label (M=51.97%, SE = .044); however, this difference was only marginally significant, t(57) = 1.62, p =.055 (one-tailed). Although the benefit of our label was only marginally significant in the overall analysis, we performed two subanalyses that provide additional evidence for its ability to support better decision making (see Figure 8).

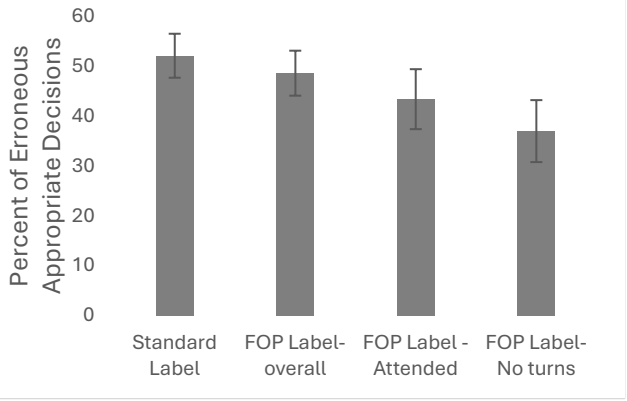

Figure 8. Percentage of erroneous appropriate responses as a function of label type and sub-analysis.

The first considered only trials for which the participants never turned beyond the front panel of the package that was displayed at the beginning of the trial. We chose this subanalysis because prior work suggests that people often fail to turn beyond the front panel when making medical decisions. Consistent with that observation, across participants, there were 900 trials with inappropriate drugs. Of these, participants made a decision without ever rotating the package to any other face on 353 (~40%) trials. An analysis of these "no turn" trials found a large effect of the FOP, with a significantly lower likelihood of rating the inappropriate medication as appropriate for FOP label trials (M= 36.89%, SE=.062) than the standard trials (M= 47.51%, SE = ,066), t(30) = 2.85, p = .004 (one-tailed).

The second analysis examined the subset of trials in which eye tracking indicated that the participants *looked at the FOP* warning label. Of the 450 trials with FOP warnings for which the drug was deemed inappropriate by pharmacists, participants fixated on the FOP on 182 trials, or a little over 40% of the time. Comparison of performance on these trials for which the FOP warning was attended (M= 43.28%, SE=.06) to performance with the standard label (M=50.72%, SE = .05) found fewer problematic errors in trials that had the FOP warning, t(47) = 2.01, p = .025 (one-tailed). These analyses suggest that the presence of a highlighted, front-of-pack warning can reduce the number of potentially dangerous medication decisions, particularly when the decision is made without turning to other areas of the package, and when the FOP warning label is attended.

However, an analysis of the medications deemed appropriate by the pharmacists also found that the presence of a front-of-pack warning reduced the number of correct appropriate drug responses. In the overall analysis, the percentage of trials in which participants correctly rated the drug as appropriate was lower for the front-of-pack label (M=57.18%, SE = 5.06) than for the standard label (M=62.80%, SE = 4.59), t(58) = 2.32, p =.012. The fact that the presence of an FOP label increased inappropriate responses even for appropriate drugs suggests, like Experiment 4, that the FOP warning label might increase the participants' bias to say inappropriate rather than an increase in the ability to discriminate between healthy and unhealthy drugs. To further investigate this issue, we ran a 2 (appropriate/inappropriate drugs) x 2 (FOP label/standard Label) within-subjects ANOVA. There was a main effect of appropriateness, with more participants making appropriate decisions for appropriate (M= 59.3%, SE = .047) than inappropriate (M= 50.2%, SE = 4.3) drugs, F(1, 57) = 7.168, p = .01, η_p^2= .11.

There was also a main effect for label type, $F(1, 57) = 6.36$, $p = .014$, $\eta_p^2 = .10$, with more appropriate decisions for the standard (M=57.1, SE = 4.2) than front-of-pack (M=52.5, SE = 4.4) labels. However, the two factors did not interact, $F(1, 57) = .623$, $p = .43$. The failure to find an interaction is consistent with the notion that the presence of a front-of-pack label reduces the likelihood of responding appropriate to a similar extent, regardless of whether the correct response is appropriate or inappropriate, supporting the view that the FOP label makes people more cautious in general rather than improving the ability to discriminate appropriate from inappropriate drugs. Even so, making people more conservative may reduce the likelihood of selecting an inappropriate medication, thereby reducing preventable ADEs.

Experiment 6. **Eye tracking with Commercial Products** - **Preliminary**

Experiment 6 was identical to Experiment 5 except that we used commercially branded labels rather than mock versions of those medications. We performed analyses similar to those in experiment 5. In total, drugs were rated as inappropriate by the pharmacists on 63.8% of the trials, again highlighting that the possibility of preventable ADEs due to OTC medications is prevalent for older adults.

Like Experiment 5, for inappropriate OTCs, the likelihood of the participant erroneously judging the medication to be appropriate was numerically lower for the FOP condition (M=58.32%, SE = 3.90) than the standard package (60.39%, SE = 3.95), but the effect was only marginally significant, $t(62) = 1.38$, $p = .086$ (one-tailed). With these branded products, participants often made their appropriateness responses without turning beyond the front panel of the package. For the 1,024 trials with inappropriate medicines, participants failed to turn beyond the front of pack on 633 trials (62%).

If one limits the analysis to those trials for which the participant never turned beyond the front panel of the package, the benefit for treatments that contained an FOP warning was significant, $t(46) = 1.87$, $p = .034$ (one-tailed), with fewer erroneous appropriate judgements in trials with an FOP warning (M= 52.0%, SE = 5.2) compared to those with standard packages (M= 58.7%, SE= 5.2). If we perform a subanalysis that restricts the experimental label data to trials in which the participant fixated on the FOP warning label and compared that to the standard label, participants made fewer erroneous appropriate decisions with the front-of-pack label (M=56.2%, SE = 5.0) than the standard label (M=61.0%, SE=4.2); again, this difference was only marginally significant, $t(54) = 1.29$, $p = .10$ (one-tailed).

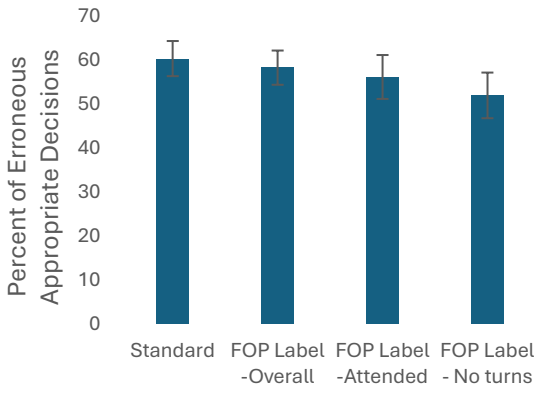

Figure 9. Percentage of erroneous appropriate responses in Experiment 6 as a function of label type and sub-analysis.

Like Experiment 5, the benefit conveyed by the front-of-pack warning label seems to result from a shift in the bias to say that a product is safe rather than an increase in the ability to accurately discriminate between safe and unsafe medications. For appropriate medications, the likelihood of correctly identifying the medication as appropriate was lower for the front-of-pack warning (M= 70.0%, SE= 4.5) than standard label (M=74.2%, SE=4.2), although the effect was only marginally significant, $t(62) = 1.64$, $p = .053$ (one-tailed). A similar 2 (appropriate/inappropriate medication) x 2 (FOP/standard Label) repeated measures ANOVA found a main effect of appropriateness, $F(1, 62) = 12.10$, $p < .001$, $\eta_p^2 = .163$, with more appropriate responses when the drug was in fact appropriate (M=72.1%, SE=4.2) than when it was inappropriate (M=59.4%, SE = 3.9). There was a marginally significant main effect of label type, $F(1, 62) = 3.49$, $p = .067$, $\eta_p^2 = .053$, with fewer appropriate responses with the front-of-pack warning (M=64.2, SE=3.7) than the standard label (M=67.3%, SE=3.6). Like Experiment 5, the interaction was not

significant, $F(1, 62) = .689$, $p = .41$, suggesting that the front-of-pack warning makes people less likely to identify a drug as appropriate regardless of whether the drug is in fact appropriate or not.

In general, though the front of pack warning label does seem to have a small effect of reducing the likelihood of misidentifying an inappropriate drug as appropriate, the effect is somewhat muted for these commercial packages relative to the somewhat generic mock brands used in Experiment 5; again, the effect of the front warning label seems to decrease the likelihood of identifying a drug as safe rather than increase the ability to accurately discriminate appropriate from inappropriate medications.

Conclusions and Implications

Our results clearly and consistently demonstrate that many OTC drugs may be contraindicated for older adults – on average over half the OTCs we tested were inappropriate for our participants based on their medical status. Also, our results consistently show that our participants often believe these inappropriate medicines are appropriate for consumption, thus raising the frequent possibility of preventable ADEs.

It is clear from our results that participants are relatively unaware of the active ingredients that they should avoid, that the currently mandated DFL does little to help determine whether a drug should be avoided, that participants often make their decisions without ever looking at the DFL, and that familiarity with a medicine makes people believe it to be safe. All these findings highlight the need for better methods of communicating the information that is critical for participants to identify OTCs that they should avoid.

Our survey of pharmacists suggests that there is consensus among experts concerning which subset of information from the DFL would be most important for older consumers to notice and comprehend to reduce preventable ADEs, namely the drug-drug and drug-diagnosis warnings. Leveraging this information, we designed front-of-pack warning labels that presented this critical information and could include highlighting. Our empirical evaluation of these labels suggest that they garner more attention to this critical information than the traditional DFL and that they can improve rapid and accurate decisions when the participants must evaluate medications based on scenarios about a specific medical condition or specific active ingredients. Thus, these labels do seem to be more effective at communicating critical information. However, when we turned away from scenario-based experiments and had participants evaluate whether a given OTC was appropriate for them to take, the benefit of the labels became less robust. The pattern of data seems to suggest that the presence of our novel warning label made people more cautious, increasing their likelihood of rating a drug as inappropriate. This shift could reduce problematic decisions (when a participant rated an inappropriate drug as appropriate), but this reduction did not result from the labels producing a better ability to differentiate appropriate from inappropriate drugs; the same pattern of reduced appropriate judgements occurred for drugs that were, in fact, appropriate.

From a practical standpoint this shift toward caution might be beneficial, but from an information processing perspective the fact that the novel labels do not increase people's ability to accurately discriminate which drugs would be appropriate verse inappropriate for them to take is problematic. Furthermore, it is noteworthy that these novel labels were effective at increasing discrimination for scenarios but not when people were making judgments about medications for their own use. We speculate that this difference may result because the scenarios presented a specific active ingredient or warning that participants must look for in the label. By contrast, given that our older participants often had polypharmacy and multiple medical conditions, evaluating whether a drug is appropriate for them to take required a search for multiple types of potentially nonspecific information, which may overwhelm the ability to effectively search.

In any case, though our labels may drive people to be overall more cautious about selecting over-the-counter medications, the fact that they did not improve drug discriminations when deciding

which drugs would be appropriate for their use suggests that this approach is not a panacea. Instead, it seems that other approaches may be required, such as augmented reality systems that can compare an OTC to an individual consumer's medication history and provide them with a real-time evaluation of whether that drug would be appropriate or not for their use. This approach is something that we have begun investigating and that seems to show promise.

LIST OF PUBLICATIONS AND PRODUCTS

Bolded authors indicate Graduate students; *Italicized authors indicate Undergraduate Students*; Underlined authors are lead.

Becker, MW; Kashy, D; **Harben, AL; Venkatesan, K; Rodriguez, A;** *Kebede, M;* Martin, B; Breslow, R and Bix, L A novel labeling strategy to enhance attention to, and comprehension of, information critical for the safe and effective use of over the counter medications by older adults: Analytical evaluation supports strategy for more effective labeling." Health Science Reports. January, 2023 6:1. https://doi.org/10.1002/hsr2.1062 Accessed June 21, 2024.

Martin, B; Breslow, R; Sims, A; **Harben, A;** Bix, L and Becker, M. "Identifying Information to Prioritize for the Purpose of Reducing Adverse Drug Reactions in Older Adults." *Journal of the American Pharmacists Association.* 23:S1544-3191(21)00360-5. doi:10.1016/j.japh.2021.08.019 PMID: 34503908. August, 2021. Accessed June 21, 2024.

(Article was Featured by *US Pharmacist* Magazine: https://www.uspharmacist.com/article/heres-how-to-get-older-adults-attention-before-they-use-otc-drugs)

Harben, AL; **Esfahanian, S;** Kashy, D; **Liu, L**; Bix, L and Becker, M. Using Change Detection to Objectively Evaluate whether Novel Over-The-Counter Drug Labels Can Increase Attention to Critical Information in Older Adults. Cognitive Research: Principles and Implications (CRPI): Special issue: Visual search in real-world and applied contexts. 6: 40. https://doi.org/10.1186/s41235-021-00307-z May 2021. Accessed June 21, 2024.

Bix, L. Invited Speaker, PROTECT Initiative, US Centers for Disease Control and Prevention (CDC) PROTECT Annual Meeting. Standardization for Error Prevention. Quantifying the efficacy of labeling strategies: Techniques and results to improve OTC labeling. November 13, 2021.

Becker, MW, Bix, L. Invited Speakers, Center for Quality and Innovation and Patient Safety (CQuIPS) Meeting, Quantifying the Efficacy of Labeling Strategies: Techniques and Results to Improve OTC Labeling. October 14, 2021.

Becker, MW and Bix, L. Invited Speakers, Expert Panel convened by the Office of Non-Prescription Drug Products- Center for Drug Evaluation and Research (CDER) United States Food and Drug Administration. "Packaging and Personalized Labeling." OTC Drug Facts Label in a Changing Consumer Marketplace 2021 Conference. Silver Spring, MD. June 9, 2021.

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