Healthcare Provider Perceptions of Boxed Warnings: Findings from Qualitative and Quantitative Investigation

Blair Coleman, PhD, MPH[1]; Sara Eggers, PhD[1]; Esther Zhou, MD, PhD[1]; Rachel Ingersoll, MPH[2]; Elise Bui, PhD[2]

[1] Center for Drug Evaluation and Research, U.S. Food and Drug Administration; [2] Fors Marsh

Introduction

Boxed Warnings (BWs) are an important risk management tool, intended to add prominence to risk information in FDA-approved prescribing information for human drugs and biologics.

While BWs are frequently utilized, information is limited regarding their influence on healthcare providers' assessment of a drug's benefits and risks, whether or how to prescribe the drug with a BW, and communications with patients about risk information.

The primary objective of this research was to explore how BW information fits within the context of providers' overall treatment decision-making and how they communicate with patients about BW information.

Methods and Materials

This research was conducted in two sequential phases:

(1) Qualitative individual in-depth interviews (IDIs) with providers to explore their knowledge and perceptions of BW generally and in the context of a specific prescribing scenario;

(2) A quantitative study (via online survey) to assess how BW information factors into providers' assessment of a drug's benefits and risk, decisions whether or how to prescribe the drug, and approach to communicating risk information with patients.

To understand the potential variable impact a BW may have in different treatment contexts, both study phases included two treatment scenarios:

- Estrogen vaginal inserts to treat vulvovaginal atrophy (VVA); and
- Direct-Acting Antivirals (DAAs) to treat chronic hepatitis C infection (HCV).

Participants within each study population included providers (general practitioners [GPs] and specialists) who treat patients in the scenarios (VVA and HCV), reported substantial time on patient care, and have prescribing authority.

Qualitative Data Collection

An online panel of health care professionals and patients (Lightspeed Health) was used to recruit participants for both VVA and HCV study samples.

Methods and Materials (Continued)

Interviews conducted via web conference software lasted up to 60-minutes and were led by a professional moderator.

A semi-structured interview guide was designed to elucidate how HCPs perceive BW information, how they factor this information into assessments of a drug's benefits and risk, and how they communicate with patients about risk information.

Three independent coders reviewed verbatim transcripts using NVivo v.11 software using a coding structure developed by investigators a priori. A thematic analysis was conducted to identify patterns/themes in the responses.

Quantitative Data Collection

The online survey was tailored to the two different treatment scenarios (VVA and HCV, respectively). Participants were presented with the survey that corresponded with their specialty – i.e., OB/GYNs and geriatricians were assigned to the VVA version; gastroenterologist, hepatologists, and infections disease specialists were assigned to the HCV version. Participants who were eligible for both scenarios were randomly assigned to one condition.

The survey instrument format and question structure for both survey versions included:

- Background and experience with the treatment condition (VVA or HCV) and prescribing history for estrogen vaginal inserts or DAAs, respectively.
- Pre-exposure benefit-risk assessment for treatment scenario medication
- Factors in prescribing decision-making, communication with patients about the medication, attitudes towards BWs and knowledge of medication risks
- Exposure to BW stimuli for treatment scenario medication (i.e., BW for DAAs or BW for estrogen)
- Post-exposure benefit-risk assessment of the medication
- General perceptions of BWs

Data were analyzed separately for each study population (VVA and HCV). Descriptive results were generated to examine demographic characteristics of the study population.

Means, standard deviations, and percentages were provided for scale items. For sub-group analyses, chi-square tests were conducted for categorical variables and logistic regression analyses were conducted for ordinal variables.

Results and Discussion

Qualitative Findings

Overall, there were 52 interview; n = 26 in the VVA scenario and n = 26 in the HCV scenario. Each study sample was evenly split by GPs and specialists.

HCPs in this study described BWs as only one of several factors that affect prescribing decision-making, and the presence of a BW is part of a broader context when considering the condition, patient factors (e.g., access to treatment, preferences, and adherence), and their prescribing experience.

HCPs across treatment scenarios expressed differences in their assessment of the BWs, where the BW content was viewed more favorably in the HCV scenario, compared to the VVA scenario where HCPs described the BW as "outdated" and overstates the risk for this drug*.

Quantitative Results

The study population consisted of 1,227 HCPs (n=614 in the VVA scenario; n=613 in the HCV scenario). The demographic composition of the sample was generally comparable to the physician demographic breakdown published by the AMA in 2020, however the current study population skewed slightly more male and older compared to the AMA population.

Across study conditions, the majority of participants reported being at least somewhat familiar with the BW information in their scenario (67% in VVA scenario; 73% in HCV scenario) with specialists being more likely to report "familiar" or "very familiar" compared to GPs for both scenarios.

Perceptions of BW Usefulness and Presentation of Risks:

In the **VVA scenario**, 51% reported that the BW was "useful" or "very useful", where specialists were less likely than GPs to assess the estrogen BW as useful (p = .001). Specialists were also more likely than GPs to report the BW strongly overstates the risks (37% vs. 10%, respectively).

In contrast, 75% of HCPs in the **HCV scenario** reported the BW information was "useful" or "very useful"; and opposite VVA, specialists in the HCV scenario were more likely to report the BW is very useful, compared to GPs. Participants most often reported that the DAA BW provides appropriate assessment of the risk information (83%).

Benefit-Risk Assessment – Pre/Post Exposure to the BW:

In the **VVA scenario**, following exposure to the BW, the proportion of participants who reported that the benefits outweigh the risks for most participants dropped from 72% pre-exposure to 60% post-exposure.
In the HCV scenario, 74% of participants pre-exposure to the BW indicated that the benefits of DAAs outweigh the risks; after exposure to the BW, 70% of participants reported that the benefits outweigh the risks for most patients – indicating few participants changed their benefit-risk assessment after viewing the BW information (Figure 1).

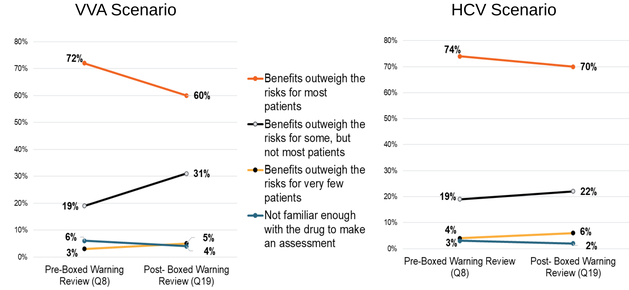

Figure 1. Assessment of Provider Benefit-Risk Assessment (by Treatment Condition) Pre- vs. Post- Boxed Warning

Lastly, across both prescribing scenarios, the majority of participants agreed or strongly agreed they would think carefully before prescribing a product with a BW if other treatments were available (65% in VVA scenario; 73% in HCV scenario), and likewise, agreed or strongly agreed they would counsel their patients differently when prescribing a product with a BW (60% in VVA; 66% in HCV).

Conclusion

This multi-modal study provided novel insight into how providers perceive, interpret and consider BWs in their prescribing decision-making.

Findings suggest BWs are only one of several factors influencing prescribing decision-making and that providers' perceptions of a BW likely vary in different treatment contexts.

*Of note, in 2019 and again in 2022 (following data collection for this study), labeling information for estrogen therapies was revised to more explicitly place the WHI findings in the context of the dose and mode of administration that was studied and convey uncertainty around how this evidence may translate to other formulations