Journal of Advances in Medical and Pharmaceutical Sciences

15(1): 1-11, 2017; Article no.JAMPS.36666
ISSN: 2394-1111

Knowledge Level and Perceptions of Pharmacists and Prescribers Regarding Boxed Warnings

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Authors' contributions

This work was carried out in collaboration with all authors. Authors MLA, VBC and WDR designed the study. Author WDR collected the data and authors MLA, VBC and WDR wrote the first draft of the manuscript. Author WDR managed the statistical analyses of the study and wrote the results. Authors VBC and MLA wrote the initial discussion and implications. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMPS/2017/36666
Editor(s):
(1) Amr Ahmed El-Arabey, Pharmacology & Toxicology Department, Al-Azhar University, Egypt & University of Science and Technology of China (USTC), China.
Reviewers:
(1) Pradeep Jadhav, MGM Medical College, India.
(2) Yao Potchoo, University of Lomé and Sylvanus Olympio University Teaching Hospital , Lomé, Togo.
Complete Peer review History: http://www.sciencedomain.org/review-history/21353

Short Research Article

Received 7th September 2017
Accepted 3rd October 2017
Published 12th October 2017

ABSTRACT

Background: Black box warnings indicating harmful or potentially fatal adverse events are required by the Food and Drug Administration on certain drugs and chemical entities; however it is unclear if prescribing and dispensing habits are impacted by these warnings. This study investigates the knowledge and perceptions of prescribers and pharmacists regarding black box warnings.
Methods: A cross-sectional survey of self-reported behavior related to black box warnings was administered to prescribers and pharmacists across North Carolina between October 2010 and January 2011.
Results: A total of 867 pharmacists and prescribers completed the survey, including 715 pharmacists and 152 prescribers. Of the respondents, 54% were female and 92% described their ethnicity as Caucasian. Overall, pharmacists reported a greater change in behavior than did prescribers in relation to the presence of a boxed warning ($P < .01$). Pharmacists also demonstrated a significantly greater overall knowledge of boxed warnings compared to prescribers ($P < .01$). No differences in reported behavior or knowledge were observed between prescribers and pharmacists

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based on demographic factors.
Limitations: Solicitation through professional association mailing lists resulting in low response rates may impact findings.
Conclusion: Overall knowledge on information pertaining to boxed warnings was lacking. Impact in clinical practice due to the lack of understanding regarding boxed warnings may put patients at increased risk. To improve the overall knowledge of black boxed warnings, the FDA should adopt develop a publicly available central repository for all black box warnings. Curricula in schools of medicine and pharmacy as well as professional continuing education should include a focus on boxed warnings.

Keywords: Boxed warning; drug regulation; labeling knowledge; prescribing behavior; dispensing behavior.

1. INTRODUCTION

Boxed warnings, frequently called "Black Box warnings", are the strongest warning statements that the Food and Drug Administration (FDA) can require on a drug label [1]. These cautionary statements are placed predominately on the package insert and are called boxed warnings because of the actual box that surrounds the text. These warnings highlight potentially fatal or disabling adverse events that are typically identified from clinical data. However in the absence of clinical data, serious animal toxicity data may be utilized to support this cautionary labeling [1]. The FDA provides guidance for industry in conditions that may warrant a boxed warning. These conditions include life threatening adverse drug reactions and adverse drug reactions that can be prevented or reduced in frequency with appropriate drug use and monitoring, or with restricted distribution or use [2]. However, no clearly defined process or criteria exists for applying these standards to new drug applications or previously approved products [3].

The inclusion of a boxed warning, at approval or post-marketing, is designed to make health care providers aware of adverse events; however, according to the published literature, prescriber habits may or may not be affected by boxed warning recommendations [4-13]. The post-marketing addition of boxed warnings for antidepressants in pediatric and adolescent patients, and the use of antipsychotics in dementia patients caused a decline in the use of these drug classes for these specific populations [7-13]. Although some warnings result in a decrease in prescribing habits, residual inappropriate prescribing has been documented after the addition of some boxed warnings [4-6,14-16] Lasser et al. [4], reported that 1 in 10 ambulatory patients was prescribed at least 1 drug with a boxed warning, with approximately 7 in 1000 outpatients receiving a prescription for a drug that was in violation of the boxed warning. It is unclear if prescribers are unaware of the boxed warnings associated with these agents or utilize clinical judgment to assess a specific patient case.

The number of boxed warnings utilized may contribute to a lack of knowledge in healthcare providers. According to a historical review of the Physician's Desk References published between 1975 and 2000, a total of 548 new chemical entities were approved. Throughout this time period, boxed warnings were added to 45 chemical entities (8.2%) after initial FDA approval [2]. While these data do not include boxed warnings that were part of the first approved labeling, it does indicate frequent addition of new warnings added after widespread use.

1.1 Objective

The purpose of this cross-sectional study was to examine the health care provider's knowledge and perception of boxed warnings and to determine if behavior is affected by these warnings. The self-reported awareness, perceptions, and impact of boxed warnings on prescribing and dispensing habits of providers was evaluated via an electronic survey.

2. METHODS

In 2010, a questionnaire (Fig. 1) was distributed electronically via Zoomerang to all registered pharmacists and prescribers in North Carolina (NC) to evaluate the main outcome of self reported behavior and knowledge related to boxed warnings. All completed surveys from October 26, 2010 to January 1, 2011 were utilized in data analysis. In order to detect at

least a 10% difference between groups at 80% power with an alpha of .05 a sample of 540 participants was required. Pharmacist participants were recruited by email, via a list maintained by the NC Board of Pharmacy, and prescriber participants were recruited through a postcard delivered by the US postal services. The policy of the NC Board of Medicine prevented email contact with prescribers, but did allow the practice site mailing address to be purchased from a public database of all NC registered resident prescribers. The post card containing a URL linking prescribers to the survey was mailed to the address on file with the NC Board of Medicine. The post card described the study and invited prescribers to participate by visiting the link. Prescribers included physicians, physician assistants, and nurse practitioners. Study participants completed the online survey anonymously. Because the NC Board of Pharmacy does not disclose individual email addresses it was not possible to contact pharmacist non-respondents. Similarly, post cards sent out to prescribers did not contain a unique identifier; therefore, prescriber non-respondents could not be contacted. The decision to exclude an unique identifier was made by the research team in order to guarantee anonymity of the respondents but also prevented any utilization of incentives.

2.1 Data Sources

Several drug information databases were queried in June 2010 for drugs containing a boxed warning. These databases included Lexi-Comp, Facts and Comparisons, Clinical Pharmacology, Micromedex, and BlackBoxRX.com. All commercial products were then grouped by active chemical entity. Chemical entities no longer available in the United States were excluded. The remaining entities were then available for inclusion in the survey.

2.2 Ethics Approval

Potential participants who were invited to Participate in the study were provided with an electronic informed consent statement before the start of the survey. The informed consent statement indicated that participation in this study was completely voluntary and involved minimal risk. To access the electronic survey respondents were required to read and click “agree” to the informed consent document. Respondents who clicked “disagree” were redirected to a brief message thanking them for their time. All authors hereby declare that all experiments have been examined and approved by the university ethics committee (IRB) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.3 Survey Instrument

The survey questions were developed by the research team based on a review of the available literature and professional experience of the pharmacists conducting the study. Questions were reviewed by colleagues for face validity, but pretesting was not performed.

The survey collected demographic information regarding gender, ethnicity, years in practice, and practice type for all participants (Fig. 1). Pharmacists responded to a set of questions regarding their opinion of the influence which boxed warnings have on their practice. Prescribers responded to a similar set of questions regarding their opinion of the influence which boxed warnings have on their practice. All participants were asked to indicate how strongly they agree with each of three statements regarding the number of boxed warnings and the number of chemical entities with boxed warnings. For each of these statements participants could rate their opinion on a 5-point Likert scale. The scale consisted of the following: “Strongly Agree (5)”, “Agree (4)”, “Neutral (3)”, “Disagree (2)”, and “Strongly Disagree (1)”.

Additionally all participants were asked to rate their own awareness of boxed warnings using a 4-point Likert Scale consisting of the following options: “Extremely Aware (4)”, “Very Aware (3)”, “Somewhat Aware (2)”, and “Not at all Aware (1)”. All participants also answered a total of 14 knowledge questions that related to the actual number of chemical entities that possess boxed warnings, the type of event that warrants a drug or entity to receive a boxed warning, and the identification of common drugs that currently have a boxed warning.

2.4 Analysis

For behavioral questions related to the influence of boxed warnings (Fig. 1). The Likert-scale scores for each participant were combined to create a composite score ranging between 3 and 15. The composite score was then compared between pharmacists and prescribers using an

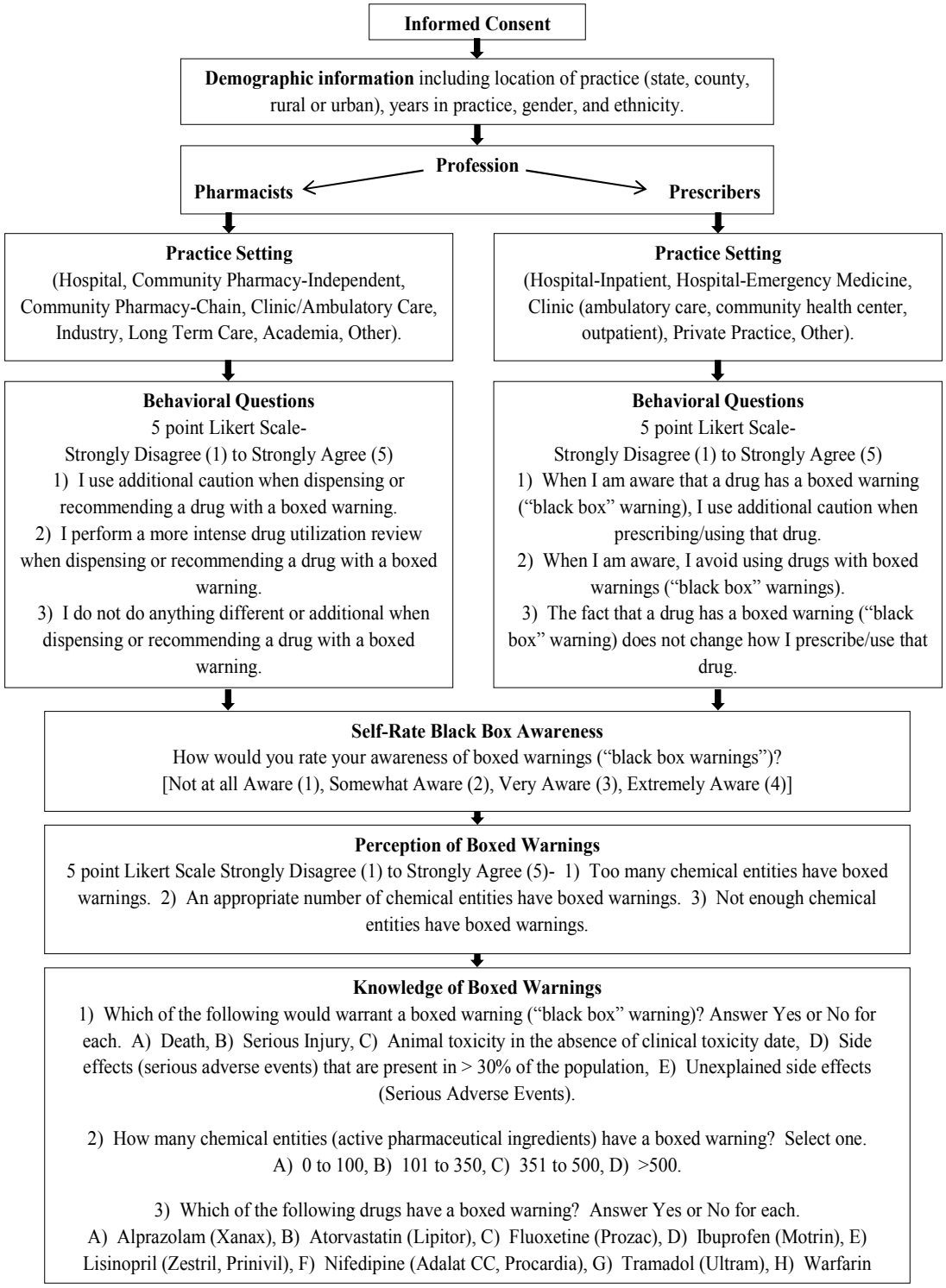

Fig. 1. Survey instrument

independent samples t-test. Each participant's knowledge of boxed warnings was evaluated through responses to questions in Fig. 1. Overall knowledge scores were calculated as the percent correct of the knowledge-based questions and compared between pharmacists

and prescribers using an independent samples t-test. One-way analysis of variance (ANOVA) was used to evaluate differences regarding both behavior and knowledge among prescriber practice type and among pharmacist practice type. P-values lower than 0.05 were considered significant. A reliability analysis was conducted for the behavioral questions (see Fig. 1) and a Cronbach's alpha of 0.87 was obtained indicating sufficient internal reliability. Descriptive statistics are provided for self-reported awareness. All analyses were carried out using SPSS/PASW 18.0. This study was approved by the Institutional Review Board at Campbell University College of Pharmacy & Health Sciences.

3. RESULTS

Invitations to participate were mailed to 26,153 prescribers with 49 post cards returned as undeliverable. Invitations to participate were emailed to 9,873 pharmacists with 297 returned as undeliverable. Of the pharmacists and prescribers solicited 1,126 accessed the survey. Of those who accessed the survey 77% responded to the survey and provided main outcome data related to behavior and knowledge pertaining to boxed warnings (715 Pharmacists and 152 prescribers) (Table 1). For the 867 respondents 54% were female, 46% were male, 92% described their ethnicity as Caucasian and 8% described themselves as non-Caucasian.

3.1 Prescribers and Pharmacists

An independent-samples *t* test was conducted to evaluate the difference in reported behavior between prescribers and pharmacists in relation to the presence of a boxed warning (Table 2). The test was significant, $t(865) = 4.65$, $P < .01$. Pharmacists on average reported a significantly greater change in behavior than did prescribers when dealing with products with a boxed warning (mean scores, 11.44 versus 10.34, respectively). An independent samples *t* test was conducted to

Table 1. Demographic characteristics

	Pharmacists	Prescribers	Overall
Gender [No. (%)]	415 (58)	50 (33)	465 (54)
Women	300 (42)	102 (67)	402 (46)
Men			
Race [No. (%)]			
American Indian or Alaskan Native	7 (1)	1 (1)	8 (1)
Asian	29 (4)	7 (5)	36 (4)
Black or African American	14 (2)	10 (7)	24 (3)
Hispanic or Latino	0 (0)	4 (2)	4 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
White (Caucasian)	665 (93)	130 (85)	795 (92)
Pharmacist Practice Site [No. (%)]			
Hospital	201 (28)		
Community-Independent	103 (14)		
Community-Chain	202 (28)		
Clinic/Ambulatory Care	52 (7)		
Industry	45 (6)		
Long Term Care	26 (4)		
Academia	17 (2)		
Did Not Report	69 (10)		
Prescriber Type [No. (%)]			
Physician		117 (77)	
Physician Assistant		34 (22)	
Nurse Practitioner		1 (1)	
Prescriber Practice Site [No. (%)]			
Hospital-Inpatient		23 (15)	
Hospital-Emergency Medicine		12 (8)	
Clinic		38 (25)	
Private Practice		61 (40)	
Other		18 (12)	

Table 2. Behavioral and perception questions mean scores

	Pharmacists Mean ± SD (# of respondents)	Prescribers Mean ± SD (# of respondents)	P-value
How many years have you been in practice?	18.99 ± 13.27 (715)	20.31 ± 11.69 (152)	.26
Additional caution is used when dispensing/recommending/prescribing a drug with a boxed warning.[a]	3.95 ± .89 (715)	4.24 ± .81 (152)	< .01
I perform a more intense drug utilization review when dispensing or recommending a drug with a boxed warning.[a]	3.76 ± .94 (715)	N/A	N/A
When I am aware, I avoid using drugs with boxed warnings (“black box” warnings).[a]	N/A	2.66 ± 1.14 (152)	N/A
I do not do anything different or additional when dispensing/ recommending/prescribing a drug with a boxed warning.[a]	3.79 ± 1.07 (715)	3.43 ± 1.14 (152)	<.01
Combined Score for Behavioral Questions	11.44 ± 2.67 (715)	10.34 ± 2.49 (152)	< .01
How would you rate your awareness of boxed warnings ("black box warnings")?[b]	2.62 ± .64 (670)	2.63 ± .67 (144)	.81
Too many chemical entities have boxed warnings.[a]	3.18 ± .97 (670)	3.15 ± 1.05 (144)	.78
An appropriate number of chemical entities have boxed warnings.[a]	2.98 ± .87 (670)	2.94 ± .83 (144)	.69
Not enough chemical entities have boxed warnings.[a]	2.54 ± .85 (670)	2.58 ± .90 (144)	.55

Note: a. Responses,5-point Likert Scale; b. Responses, 4-point Likert Scale, N/A = Not Applicable

evaluate the difference in overall mean score for knowledge between pharmacists and prescribers. Pharmacists demonstrated a significantly greater overall knowledge [$t(868) = 3.18$, $P < .01$] of boxed warnings than did prescribers (Table 3).

No differences in either reported behavior or knowledge were observed between prescribers and pharmacists based on demographic factors such as gender, ethnicity (white versus non-white), or location.

3.2 Among Prescribers

A one-way ANOVA was conducted to evaluate the relationship between reported behavior related to boxed warnings and practice type of prescribers. The independent variable, practice type, consisted of four levels: Hospital – Inpatient, Hospital – Emergency Medicine, Clinic, and Private Practice. The dependent variable was the composite score of reported behavior related to boxed warnings. The ANOVA was significant, $F(3, 130) = 2.977$, $P = .03$.

Pair-wise comparisons demonstrated the differences among the means. Tukey post-hoc analysis confirmed that prescribers who indicated their practice type to be Hospital – Emergency Medicine had a higher overall composite score related to behavior than all other practice types included in the study. The 95% confidence intervals as well as the means and standard deviations for the practice types are reported in Table 4.

A one-way ANOVA was conducted to evaluate the relationship between knowledge of boxed warnings and practice type of prescribers. The independent variable, practice type, consisted of four levels: Hospital – Inpatient, Hospital – Emergency Medicine, Clinic, and Private Practice. The dependent variable was the composite score for knowledge of boxed warnings. The ANOVA was not significant. No differences were observed regarding reported behavior and demographic factors such as ethnicity or gender.

3.3 Among Pharmacists

A one-way ANOVA was conducted to evaluate the relationship between reported behavior related to boxed warnings and practice type of pharmacists. The independent variable, practice type, consisted of seven levels: Academia, Community Pharmacy – Independent, Community Pharmacy – Chain, Hospital, Clinic/Ambulatory Care, Long Term Care, Industry. The dependent variable was the composite score of reported behavior related to boxed warnings. The ANOVA was not significant.

A one-way ANOVA was conducted to evaluate the relationship between knowledge of boxed warnings and practice type of pharmacists. The independent variable, practice type, consisted of seven levels: Academia, Community Pharmacy– Independent, Community Pharmacy – Chain, Hospital, Clinic/Ambulatory Care, Long Term Care, Industry. The dependent variable was the composite score for the knowledge questions. The ANOVA was not significant. No differences were observed regarding reported behavior and demographic factors such as ethnicity or gender.

4. DISCUSSION

Overall, knowledge of the justification and requirements for a boxed warning, number of chemical entities with a boxed warning, and individual agents that have a boxed warning was lacking. On the knowledge-based questions, prescribers scored on average 56% while pharmacists scored on average 59%, indicating a gap in knowledge for both groups.

An incomplete understanding of criteria for the addition of a boxed warning to a chemical entity related to significant animal toxicity, even in the absence of human data, existed. Only 16% of survey respondents identified the animal toxicity as appropriate criteria for a boxed warning. However, the recent approval of liraglutide (Victoza – Novo Nordisk A/S) included a boxed warning for increased risk of thyroid C-Cell tumors that has only been observed in rodents [17]. The human risk, although the extent is currently unknown, was significant enough to warrant this labeling.

Wang et al. [18] evaluated the consistency of 3 commonly used databases in detecting an interaction in drugs contraindicated to be used concurrently. Each of the 3 interaction screening databases reported less than half of the expected interactions. The authors noted that the information regarding severity and evidence for contraindicated drug combinations, specifically addressed in boxed warnings, is quite variable between databases. Inconsistencies between databases and product

package inserts have also been documented [19]. These inconsistencies may contribute to lack of knowledge since many prescribers or pharmacists typically have access to only one or two databases in daily practice. A contributor to this problem may be related to the lack of a FDA maintained list of all drugs/entities with a boxed warning.

The two drugs in our survey that were most frequently correctly identified by prescribers as having a boxed warning were warfarin and fluoxetine (78% and 74%, respectively; Table 3). One reason for increased awareness for fluoxetine may be related to the intense lay media coverage of the announcement by the FDA to include a boxed warning due to the increased potential of suicide in children and adolescents on all antidepressants [20]. While lay media coverage of boxed warnings may be an avenue to communicate the risks, one study indicates that FDA and lay media reports of boxed warnings emphasized different information that is thought to be related to the different reasons for reporting the information [21]. These differences identified included an under reporting in the lay media of the generic names, research methods, clinical recommendations, and instruction to seek health care provider advice and an increased reliance on expert testimonials and personal stories from patients [21]. A similar effect attributed to the lay press was documented in Moeller et al. [22] for paroxetine and estrogen.

Table 3. Knowledge results

	Pharmacists no. (%)	Prescribers no. (%)	P-value
Which of the following would warrant a boxed warning ("black box" warning)?			
--Death [a]	623 (93)	134 (93)	
--Serious Injury [a]	619 (92)	125 (87)	
--Animal toxicity in absence of clinical toxicity data [a]	104 (15)	25 (17)	
--Side Effects (Serious Adverse Events) that are present in >30% of the population	410 (61)	96 (67)	
--Unexplained side effects (Serious Adverse Events)	304 (45)	73 (51)	
How many chemical entities (active pharmaceutical ingredients) have boxed warnings ("black box" warnings)?			
0 to 100	271 (40)	37 (25)	
101 to 350	256 (38)	67 (47)	
351 to 500 [a]	96 (14)	22 (15)	
>500	48 (7)	18 (12)	
Which of the following drugs have a boxed warning ("black box" warning)?			
Alprazolam (Xanax-Pfizer US Pharmaceutical Group)	107 (16)	42 (29)	
Atorvastatin (Lipitor-Pfizer US Pharmaceutical Group)	237 (35)	49 (34)	
Fluoxetine (Prozac-Eli Lilly & Co.) [a]	536 (80)	107 (74)	
Ibuprofen (Motrin) [a]	285 (42)	51 (35)	
Lisinopril (Zestril-AstraZeneca, Prinivil-Merck Sharp & Dohme) [a]	218 (32)	58 (40)	
Nifedipine (Adalat CC-Schering-Plough Corporation, Procardia-Pfizer US Pharmaceutical Group)	151 (23)	43 (30)	
Tramadol (Ultram-Janssen)	210 (31)	62 (43)	
Warfarin (Coumadin-Bristol-Myers Squibb Company) [a]	598 (89)	113 (78)	
Overall Mean Percent Score ± SD	59 ± 13	56 ± 15	< .01
Total Complete Respondents	671 (82)	144 (18)	

a Correct answer

Table 4. Comparison of mean composite scores for reported behavior of prescribers by practice type

Practice type	M	SD	Mean Diff. (Hospital-Emergency)	95% CI for Diff. of Means
Hospital-Emergency	12.42	2.43		
Hospital-Inpatient	10.09	2.25	2.33[a]	.02-4.64
Clinic	10.24	2.67	2.18[a]	.03-4.33
Private Practice	10.16	2.47	2.26[a]	.21-4.30

Note: [a]P < .05

The effect caused by the existence of a boxed warning is mixed. In a study conducted by Lasser et al. [4], 7 out of 1000 outpatients received a prescription drug in violation of a boxed warning. However, an even higher rate of non-compliance with boxed warnings has been documented [14,16,23,24]. Of particular note are studies that examine the contraindicated use of metformin in patients with heart failure and/or renal failure due to the increased risk of lactic acidosis in this population [14,25,26]. Another area of documented non-compliance with a boxed warning occurred in the monitoring of patients taking lithium, carbamazepine, and valproate [27]. However, the rate of antidepressant use in children did diminish after the addition of a boxed warning to this class of drugs [13]. Also, changes to the use of antipsychotics in patients with dementia decreased after the addition of a boxed warning [10]. The reasons for non-compliance to a boxed warning or the absence of change in usage after the addition of a boxed warning are not known. Our data indicate that there may be a lack of knowledge of which agents have a particular type of boxed warning and this may be related to the large number of agents that include such a warning and database inconsistencies. These results suggest a need for additional black box education in schools of medicine and pharmacy in addition to professional continuing education focused on boxed warnings. Another effort to improve the overall knowledge of boxed warnings would be one central repository for all agents with boxed warnings. Consideration should be given to prominence and consistency of black box warning placement on literature provided with all medications prescribed to patients with additional information provided to prescribers that describe the evidence base which led to the boxed warning in the first place. If prescribers and patients are able to consistently find and review these warnings then prescribers may consider alternative medications in some instances. At the very least providing the evidence base will allow prescribers to consider appropriate prescribing in context of the individual patient.

5. LIMITATIONS

The study is limited by the sample surveyed. Only prescribers and pharmacists in NC were recruited to participate. The inability to gain direct access to respondent names and email addresses prevented effective follow up for the majority of the population solicited; therefore, a follow up request and an evaluation of non-responders was not possible. The inclusion of a web link in the email solicitation to pharmacists likely contributed to the stark contrast in response rates (715 pharmacists vs. 152 prescribers). The extra step required for prescribers to respond consisted of typing in a web link from the post cards perhaps inhibiting response rates in this group. Additionally, since the respondents were utilizing the internet to complete the survey, references could have been used to assist with the completion of the knowledge based questions. This could over-estimate the mean knowledge scores of participants. This study utilized self-reported data, which may not translate into actual practice behaviors. Formal pretesting was not performed on the survey tool. The actual wording of survey questions between prescribers and pharmacists differed slightly, which may contribute to some of the differences observed. Lastly, the small proportion of prescriber respondents limits the power of the analysis – particularly for sub-group analysis.

6. CONCLUSION

Knowledge on justification and requirements for a boxed warning, number of chemical entities with a boxed warning, and individual agents that have a boxed warning was deficient with a mean score less than 60%. Low overall knowledge may indicate a barrier to communicating the purpose and reasoning for the addition of a boxed warning to a drug label. Impact in clinical

practice due to the lack of understanding surrounding boxed warnings may put patients at an increased risk for serious adverse reactions.

CONSENT

As per international standard or university standard, participants' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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The peer review history for this paper can be accessed here:
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