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AMIODARONE SAFETY CONCERNS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction: The purpose of this study was to review Black Box Warning (BBW), specifically on Amiodarone, and to evaluate first-professional year students' knowledge of its safety profile and monitoring parameters. Additionally, the study examined students' familiarity with amiodarone's clinical use and sought to explore the way in which factors such as educational background and work experience influenced their perspectives of these safety considerations. **Methods:** The study utilized a cross-sectional study method that combined opinion-based and knowledge-based surveys. First-year pharmacy students were asked to respond to questions regarding the safety parameters of amiodarone, including BBWs, photosensitivity, monitoring requirements, and patient counseling. The students' baseline knowledge was assessed due to them being in their early stages of their education and not having yet gone through extensive pharmacy training. Assessing their knowledge and understanding around medication warnings and precautions, at this stage, offers useful insights into the impact that the summer prep courses have on the incoming students, and how the future curriculum can be tailored for their developmental success. Data were analyzed using descriptive statistics, mean scores, standard deviations, and the Chi-square test. **Results:** A total of 44 first-year pharmacy students participated in the survey. The opinion-based questions showed a strong consensus with 77% agreeing that amiodarone should be used as last-resort and its use should be limited due to its risks, 86.4% agreeing that the strategies to check amiodarone are effective and that patients should be counseled on photosensitivity side effects, and 88.7% agreeing that patients taking the medication should

have check-ups and routine lab work. On the knowledge-based surveys 81.8% of respondents correctly identified the warnings and risks of amiodarone. However, only 29.5% recognized other clinical uses of amiodarone and 18.2% understood the need for more frequent monitoring in patients on the medication. Students with higher levels of education or three or more years of work experience demonstrated a significantly higher level of knowledge pertaining to amiodarone's monitoring parameters (p-value <0.05). **Conclusion:** These findings highlight the need for targeted curriculum development and expanded hands-on experiences to improve pharmacy students' understanding of high-risk medications. Strengthening critical thinking skills, particularly in evaluating the balance between risks and benefits, is essential for optimizing patient outcomes. By using amiodarone's safety profile, monitoring parameters, and key patient counseling points as a model, this study brings attention to important gaps in students' knowledge of BBWs and underscores the urgency of addressing these areas in pharmacy education.

KEYWORDS: Amiodarone; Cordarone; Survey, Pharmacy, Arrhythmia; Knowledge; Opinion.

INTRODUCTION

Amiodarone (Cordarone®) is a Class III iodine-containing antiarrhythmic agent that was approved by the U.S Food and Drug Administration (FDA) in 1985 for the treatment of life-threatening ventricular arrhythmia in adults (Florek et al. 2023; Herendael et al 2010; and FDA 2018). It is often considered first line in certain instances and aside from the FDA approved indication, amiodarone is also used off-label for other types of arrhythmias such as supraventricular tachyarrhythmias including atrial fibrillation (AFib) (Florek et al. 2023). Amiodarone's primary mechanism of action works by blocking potassium channels in the heart and lengthening the action potential and refractory period to prevent abnormal rhythms Hondeghem et al. 1990). Additionally, amiodarone possesses the mechanisms of Class I (sodium channel blockade), Class II (adrenergic blockade), and Class IV (calcium blockade) but even though it is a highly efficacious agent, it is highly toxic. Approximately 15% of patients experience adverse effects within the first year of amiodarone therapy and 50% of patients experience them during long-term therapy. Amiodarone has BBWs (BBWs) for pulmonary, hepatic, and cardiac toxicity; along with other adverse effects such as thyroid dysfunction, and skin reactions (Florek et al. 2023).

The FDA has put an emphasis on closely monitoring amiodarone dosing, levels, and patients' organ functions throughout the treatment duration due to these risks (Liss et al. 1984). Adverse reactions such as pulmonary toxicity, being among the most fatal manifestation, and cardiac toxicity can occur as quickly as within the first year of initiation (Biancatelli et al. 2019). The close monitoring that needs to be done and the severity of which these effects can occur emphasize the importance of student pharmacists, and all healthcare professionals, having a strong grasp of amiodarone's safety profile.

A few case reports have been conducted that showed an association between amiodarone and the development or rapid worsening of respiratory symptoms. One case report assessed two patients, one who was on amiodarone for two months prior to admission and one who was started on an amiodarone drip inpatient (FDA 2018). Both patients developed amiodarone-induced pulmonary toxicity which was confirmed by the immediate reversal of symptoms upon discontinuation and one patient was also given corticosteroid therapy. The second patient case highlighted the complexities surrounding diagnosis because they had respiratory symptoms prior to the drip treatment. Once all other possibilities were ruled out and it was revealed that the patient had a similar reaction to a previous administration of amiodarone, a diagnosis was made.

Further highlighting the complexities surrounding diagnosing amiodarone-induced pulmonary toxicities is a case report where physicians were unable to reach a diagnosis until the second week of the patient's hospitalization (Moeller et al. 2010). Once all the other possible diagnoses were ruled out and further evaluation was done, amiodarone was discontinued, and the patient began to show signs of improvement with the aid of a corticosteroid for the inflammation. This case report showed the worsening progression of the effects of amiodarone and noted the possibility of this being a dose-related adverse effect.

Amiodarone's BBW consists of toxicities in other organs such as the liver and the heart. A case report was conducted that demonstrated the effects of amiodarone on multiple organs, leading to multi-systemic toxicity involving the liver, lungs, thyroid, and eyes (Moeller et al. 2010). This patient was on a long-term treatment of amiodarone and the dose was titrated up and continued for approximately 2 years. Upon admission amiodarone was discontinued, systemic steroid therapy was initiated, and the patient began to show signs of improvement. The patient was able to be discharged after a month with most of the symptoms resolved. This case report highlights the importance of healthcare professionals having the knowledge

that amiodarone toxicity onset times are highly variable and can appear anywhere from the first few months to years after initiation.

Knowledge of BBWs and adverse effects and how to manage them are meant to be strengthened as students' progress through the curriculum. A cross-sectional survey was conducted among P1-P3 students to assess their familiarity with BBWs and medications that possess them. More than 90% of the P3 students identified that amiodarone had a BBW associated with it (Moeller et al. 2010). A positive correlation was seen between the depth of knowledge and the years spent in pharmacy school; however, a knowledge deficit was still noticed and a majority of the students reported not staying current on new warnings and risks. These findings emphasize the importance of early training on medication risk management and staying informed and drug safety profiles.

Furthermore, an exploratory, online physician survey was conducted with an aim to identify clinicians' variations in clinical decision-making and adherence to treatment guidelines with their use of antiarrhythmic agents in Afib management (Derington et al. 2022). The study found that even though clinicians were aware of the toxicity risks of amiodarone, 60%-80% of the respondents selected amiodarone as a typical treatment option across the examined comorbidities, even when guidelines recommended other antiarrhythmic agents first. However, 80% of respondents requested for routine monitoring at a higher instance for amiodarone than other antiarrhythmic drugs, which is suggestive that they are aware of its risks despite its frequent use.

Preventative strategies and patient counseling are very important to ensure patient safety is maintained during the treatment duration. Low dose amiodarone can help to reduce the risk of developing toxicities however it is still a possibility and proper routine monitoring must still take place. [12] Patients should also be counseled to avoid direct sunlight as much as possible and to wear sunscreen due to the increased risk of photosensitivity. A list of signs and symptoms of thyroid dysfunction should be relayed to patients before initiation, such as weight abnormalities, restlessness, hair thinning, temperature intolerance, etc.

While there is a better understanding of BBWs and medication risk management today, it is imperative that bridging the knowledge gap as early as possible in one's pharmacy journey can be beneficial to patient care. The current study assesses this gap by analyzing pharmacy students' knowledge of amiodarone's safety profile and monitoring requirements. This aligns

with the educational goal of aiding student pharmacists' preparedness for managing medication-safety risks and patient counseling.

METHODOLOGY

A cross-sectional study was conducted to evaluate the knowledge and opinions of first-year pharmacy students regarding the safety profile and monitoring parameters of amiodarone. A total of 44 students participated in the survey with a 99% response rate.

The survey was administered electronically through a secure online platform. Participants gained access through a survey link via email and were informed about the anonymity of the survey and that participation was voluntary. The survey consisted of four sections: sociodemographic information, prior knowledge and experiences with BBWs, knowledge-based questions assessing their understanding of the risks and monitoring of amiodarone, and opinion-based questions about effective counseling and clinical use.

The collected data were compiled and analyzed using SPSS Statistics Software (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize demographic characteristics, knowledge scores, and opinion responses. Chi-square tests were utilized to determine if there were statistically significant associations between demographic characteristics and survey responses (p-value <0.05). This approach provided insight into the P1 students baseline knowledge of amiodarone and helped highlight areas for educational interventions for the curriculum.

RESULTS

A total of 44 pharmacy students completed the survey (Table 1). The sociodemographic profile of the participants is summarized in Table 1, indicating that most of the participants are females, held a 4-year bachelor's degree, and worked in a pharmacy related job.

Table 1: Sociodemographic Characteristics of Participants (N=44).

		Column N %
Gender	Male	12 (27.3%)
	Female	32 (72.7%)
	Non-Binary/Third Gender	0 (0.0%)
	Prefer Not To Say	0 (0.0%)
Education (Highest Level Attended	2 Year College	2 (4.5%)
	4 Years/BS/BA	30 (68.2%)
	MSC/MA or Higher	8 (18.2%)
	Other (Specify)	4 (9.1%)

Work Experience	Never Worked	0 (0.0%)
	Worked In Healthcare Related Jobs	7 (16.3%)
	Worked In A Pharmacy Related Job	27 (62.8%)
	Worked But In Non-Healthcare Jobs	9 (20.9%)
If Worked, How Many Years?	<1 Year	6 (14.0%)
	1-3 Years	16 (37.2%)
	>3 Years	21 (48.8%)

Table 2 shows the participants familiarity and experience with black-boxed warnings in general. More than half of the students (52.3%) reported that they had definitely heard of BBWs before entering the pharmacy program, while 36.4% had definitely not heard of them, highlighting a mix of prior exposure to critical drug safety information. When asked about personal or family experiences with adverse drug reactions (ADR), a striking 81.4% indicated that they or someone they knew had experienced an ADR, suggesting that firsthand encounters with medication risks were common among the respondents.

Regarding academic backgrounds, the majority (63.6%) had an undergraduate degree in basic or health sciences, while very few came from social sciences (2.3%) or business (2.3%), and a notable 31.8% reported majors categorized as "other."

Table 2: Participants' familiarity and experience with BBW.

Survey Questions	**Response Choices**	**Column N %**
Have you heard of BBW before coming to the pharmacy program?	Definitely Not	16 (36.4%)
	Probably Yes	5 (11.4%)
	Definitely Yes	23 (52.3%)
Have You or Any Member of Your Family or Friends Experienced ADR in the Past?	Definitely Not	8 (18.6%)
	Probably Yes	25 (58.1%)
	Definitely Yes	10 (23.3%)
Undergraduate Major	Basic Or Health Sciences	28 (63.6%)
	Social Sciences	1 (2.3%)
	Business	1 (2.3%)
	Others*	14 (31.8%)
*Others: Communications, Biology, Biochemistry, Animal Science, Pre-pharmacy, Chemistry Major, Biomolecular Science, Pharmaceutical Science/Pre-pharmacy with a minor in Biology, Biological/Biomedical Science.		

The survey assessed pharmacy students' opinions on best practices regarding the use and monitoring of amiodarone, comparing their responses to established clinical standards. Overall, 83.2% of respondents agreed with the correct practices, while 16.8% disagreed, suggesting a strong but not perfect alignment with recommended guidelines.

Specifically, 77.3% of students correctly agreed that amiodarone should be used as a last-resort medication, and the same percentage recognized that the risks associated with amiodarone use should be limited—both in line with clinical best practices, though a notable 22.7% still disagreed or were uncertain. Encouragingly, 86.4% correctly believed that current strategies for monitoring amiodarone use are effective, and an even higher 88.6% agreed that patients on amiodarone should undergo regular appointments and lab work, which aligns strongly with standard patient safety protocols. Additionally, 86.4% recognized the importance of informing patients about photosensitivity risks, an essential aspect of patient education with amiodarone therapy.

While the majority of students demonstrated strong alignment with correct practices, the roughly 17% disagreement rate across questions highlights an opportunity for further education and reinforcement, especially regarding the cautious use and risk communication associated with high-risk medications like amiodarone.

Table 3: Opinion-Based Questions.

Variables	Agree	Disagree	
	n (%)		Mean ± SD
1: Do you believe that amiodarone should be used as a last-resort medication?	34 (77.3%)	10 (22.7%)	1.84± 0.939
2: Do you believe the risk associated with taking amiodarone should be limited?	34 (77.3%)	10 (22.7%)	1.95± 0.834
3: Do you believe the strategies for checking amiodarone are effective?	38 (86.4%)	6 (13.6%)	1.80± 0.734
4: Patients taking amiodarone should have appointments and lab work done.	39 (88.6%)	5 (11.4%)	1.68± 0.740
5: Do you think patients should be informed about photosensitivity and its risks while taking amiodarone?	38 (86.4%)	6 (13.6%)	1.64± 0.780
AVERAGE	**83.2%**	**16.8%**	

Table 4 shows knowledge-based responses. It revealed that while students demonstrated strong understanding in several key safety areas related to amiodarone, important knowledge gaps remain. A high percentage of participants (81.8%) correctly recognized that amiodarone's BBWs include pulmonary toxicity, hepatotoxicity, and thyroid dysfunction, and the same percentage knew that the drug should be discontinued immediately if pulmonary toxicity develops. Similarly, 81.8% correctly identified the need to counsel patients about photosensitivity risks associated with amiodarone. However, only 29.5% correctly answered that amiodarone is not exclusively indicated for ventricular arrhythmias, indicating a misunderstanding of its broader use for atrial fibrillation. Even more concerning, just 18.2%

correctly knew that liver, thyroid, and pulmonary monitoring should be done more frequently than every 1–2 years, highlighting a major gap in knowledge about appropriate long-term monitoring. Overall, while participants showed strong awareness of the drug's major risks, there is a critical need to strengthen education around appropriate indications and monitoring schedules.

Table 4: Knowledge-Based Questions.

Variables	Correct Answer	Participants with Correct Answer N (%)
1: Amiodarone is only indicated for ventricular arrhythmias and not for atrial fibrillation.	False	13 (29.5%)
2: Amiodarone's BBWs include risks for pulmonary toxicity, hepatotoxicity, and thyroid dysfunction.	True	36 (81.8%)
3: It is recommended to discontinue amiodarone immediately if pulmonary toxicity is detected.	True	36 (81.8%)
4: Monitoring liver, thyroid, and pulmonary function should be done every 1-2 years for patients on long-term amiodarone therapy.	False	8 (18.2%)
5: Patients should be counseled to avoid excessive sun exposure while taking amiodarone due to the risk of photosensitivity.	True	36 (81.8%)

Table 5 indicates significant associations between specific demographics and opinion-based questions. Participants with a 4-year degree/BS/BA were significantly more likely to agree that the strategies for checking amiodarone are effective. Those with more than 3 years of work experience were significantly associated with agreeing that patients on the amiodarone should have appointments and lab work done.

Table 5a: Demographics and Opinion-Based Questions with Statistical Significance.

Demographics	Opinion-Based Questions	P-Values
Education (Highest Level Attended	Do you believe the strategies for checking amiodarone are effective?	0.010
If Worked, How Many Years?	Patients taking amiodarone should have appointments and lab work done.	0.008

The data in Table 6 demonstrates a significant association between years of work experience and knowledge-based questions about amiodarone. Participants with more than 3 years of work experience were significantly more likely to recognize the correct answer regarding the monitoring parameters regarding amiodarone and liver, thyroid, and pulmonary function.

Table 6: Demographics and Knowledge-Based Questions with Statistical Significance.

Demographics	Knowledge-Based Questions	P-Values
If Worked, How Many Years?	Monitoring liver, thyroid, and pulmonary function should be done every 1-2 years for patients on long-term amiodarone therapy.	0.004

DISCUSSION

This study evaluated pharmacy students' baseline knowledge of amiodarone's safety profile, including their familiarity with black box warnings (BBWs), key safety risks, and perspectives on clinical use and patient counseling. Sociodemographic analysis revealed that the majority of participants were female, held a four-year bachelor's degree, and worked in pharmacy-related jobs. Notably, most students had prior awareness of BBWs before matriculation, although a portion entered the program without this background knowledge. Students with higher educational attainment and more than three years of work experience were significantly more confident in their opinions regarding amiodarone's monitoring strategies, suggesting that both academic advancement and hands-on experience play an integral role in preparing pharmacy students for clinical decision-making.

The opinion-based questions provided critical insight into students' clinical judgment regarding amiodarone. Most participants emphasized the importance of routine monitoring and thorough patient counseling. A strong majority (77.3%) agreed that amiodarone should be used as a last-resort medication and similarly endorsed limiting its use due to safety concerns. This suggests an awareness of the drug's significant risk profile and an inclination toward favoring safer alternatives. The relatively moderate mean scores (around 1.84–1.95) reflect a solid but cautious consensus, supporting the notion that while students recognize amiodarone's efficacy, they remain wary of its risks.

Students also demonstrated strong agreement (86–88%) with the need for scheduled appointments, routine lab work, and counseling about photosensitivity risks associated with amiodarone. The strongest consensus (mean score of 1.64) was found in the belief that patients should be counseled on photosensitivity risks. These findings highlight students' understanding of the critical importance of ongoing patient education and monitoring in mitigating adverse outcomes, aligning well with clinical guidelines.

However, the knowledge-based questions revealed important gaps. While a majority of students (81.8%) correctly identified amiodarone's BBWs and the appropriate action to take when pulmonary toxicity develops, substantial weaknesses were evident in understanding the

full range of amiodarone indications and monitoring frequency. Only 29.5% correctly answered that amiodarone is indicated for both atrial and ventricular arrhythmias, and only 18.2% accurately recognized the need for more frequent monitoring of liver, thyroid, and pulmonary function tests. These results suggest that while students grasp major safety concerns, finer clinical details, especially around routine management and secondary indications, need greater emphasis in pharmacy education.

Importantly, work experience and educational background were significantly associated with stronger knowledge and opinions. Students with a four-year degree were more likely to view amiodarone monitoring strategies as effective ($p=0.010$), and those with over three years of professional experience were more likely to advocate for regular appointments and labs ($p=0.008$). Additionally, greater clinical exposure correlated with better knowledge of appropriate monitoring intervals ($p=0.004$), emphasizing the value of real-world practice in building clinical competence.

Overall, these findings reinforce the importance of assessing baseline knowledge among student pharmacists and integrating case-based learning early in pharmacy curricula. Enhancing critical thinking skills, particularly around medication safety and monitoring, is essential for preparing future pharmacists to manage high-risk therapies like amiodarone. Moreover, the results suggest that continuous education, incorporating real-world case reports and strategies for ruling out differential diagnoses, is crucial for maintaining safe prescribing and monitoring practices throughout a pharmacist's career.

LIMITATION

This cross-sectional study has several limitations to be considered. Even though the response rate was high, the sample size was small, which could restrict the generalizability of the findings. The demographics showed that the study comprised of respondents who are mostly female and have a pharmacy related job with backgrounds in basic or health sciences, which is not a reliable representation of the population across different pharmacy schools. The study was only conducted with first professional students, which could be a factor in their baseline scores, leading to the assumption that more BBWs educational interventions need to be made across the curriculum for all years which may not be the case.

Moreover, the study only focuses on the safety concerns and monitoring parameters of amiodarone and other drugs or drug classes. This poses limits on where the findings can be

used and applied. Potential biases that could exist for this study are recall bias, response bias, and social desirability bias due to the self-reporting aspect. Studies that encompass more agents and look more in depth on these effects could enhance pharmacy students training and knowledge surrounding BBWs and medication risk management.

CONCLUSION

The study identified gaps in pharmacy students' knowledge surrounding the safety concerns and monitoring parameters of amiodarone, particularly regarding the multi-organ toxicities, indications, photosensitivity, and routine lab work. While many students showed prior familiarity with BBWs and well-known risks, their overall understanding remained limited, which is most likely reflective of their early stage of pharmacy training.

The findings emphasize the importance of introducing case-based learning and targeted educational interventions in the curriculum to better address BBWs and monitoring. By implementing these interventions, pharmacy programs can better prepare their students with the knowledge and skills necessary to ensure safe and effective medication therapy, resulting in enhanced quality of life for patients.

Ethics Approval and Consent to Participate: This study was approved by the institutional Investigational Review Board and was conducted in accordance with ethical standards. As the survey contained no identifiers, formal ethics approval was deemed unnecessary. All participants provided informed consent to participate.

Consent for Publication: Participants provided consent for the publication of findings from this study. The survey did not include any personal identifiers.

Availability of Data and Materials: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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