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DOFETILIDE'S WARNING: STUDENT KNOWLEDGE & OPINION

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ABSTRACT

This cross-sectional study aimed to assess first-year pharmacy students' knowledge of dofetilide, with particular emphasis on its black box warning (BBW) for increased risk of supraventricular arrhythmias and the associated safety monitoring requirements. The study also sought to determine whether demographic factors—such as gender, level of education, undergraduate major, and pharmacy-related work experience—affect students' awareness and understanding of these safety considerations. **Methods:** A total of 46 first-year pharmacy students from a college of pharmacy completed an anonymous, electronically administered survey, yielding a 96% response rate. The survey included four sections: demographic information; familiarity and experiences with BBWs; opinion-based questions on dofetilide safety and monitoring; and knowledge-based questions evaluating understanding of key safety risks. Data was analyzed using SPSS (IBM Corp., Armonk, NY) with descriptive statistics and chi-square tests ($p < 0.05$) used to examine associations between demographic variables and survey responses. **Results:** Most participants were female, held a four-year degree in a basic or health science field, and had over three years of experience in a pharmacy-related setting. The majority reported prior awareness of BBWs and probable personal or familial experience with BBW-related adverse drug reactions. Opinion-based responses demonstrated strong agreement on the necessity of adhering to dofetilide's BBW, the importance of dose-related rehospitalization, the need for close monitoring in renal impairment, and universal patient counseling. While most students answered the knowledge-based questions accurately, one question revealed a notable gap in understanding. Statistical analyses showed that a higher level of education, greater pharmacy-related work experience, and a basic or health science undergraduate major were significantly associated with stronger

comprehension of BBW-related safety requirements and drug contraindications (e.g., clarithromycin co-administration, p = 0.046). **Conclusion:** These findings highlight critical gaps in pharmacy students' knowledge of black box warnings, using dofetilide as a representative example. The results underscore the importance of targeted educational interventions early in pharmacy education. Incorporating case-based learning and structured experiential opportunities into the curriculum may help address these gaps, ensuring that future pharmacists are better prepared to manage high-risk medications safely and effectively in clinical practice.

KEYWORDS: Dofetilide, Survey, Pharmacy, Students, Education, Black Box Warning, Arrythmia, Tikosyn.

BACKGROUND

Dofetilide, marketed under the brand name Tikosyn ®, is a class III antiarrhythmic agent approved by the U.S. Food and Drug Administration (FDA) on October 1, 1999, for the conversion and maintenance of sinus rhythm in patients with atrial fibrillation or atrial flutter lasting more than one week. It was specifically intended for use in highly symptomatic patients following pharmacologic or electrical cardioversion (Tikosyn™ [package insert] 2013; FDA, 1999).

Due to the drug's proarrhythmic potential, particularly its association with torsades de pointes, the FDA required that dofetilide be initiated in a hospital setting. The Black Box Warning—still in place today—mandates that therapy must begin with continuous ECG monitoring and renal function assessment for at least three days (FDA, 2013). The warning also emphasizes the importance of dose adjustment based on creatinine clearance and avoidance in patients with a baseline QTc > 440 ms.

To further safeguard patients, the FDA originally implemented a Risk Evaluation and Mitigation Strategy (REMS) requiring providers and facilities to complete training and certification before prescribing or dispensing dofetilide. This requirement was designed to minimize inappropriate use and educate clinicians about safe prescribing practices (FDA, 2016).

In March 2016, the FDA officially discontinued the REMS program, citing that the educational objectives of the program had been met, and that appropriate prescribing and

monitoring practices had become embedded in standard clinical guidelines. However, the agency maintained the boxed warning, recognizing the ongoing risk of life-threatening ventricular arrhythmias if the drug is misused (FDA, 2016).

These findings support its continued use in appropriately selected patients under proper monitoring protocols. Despite these risks, clinical trials such as the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND-CHF and DIAMOND-MI) studies found no increase in all-cause mortality with dofetilide use compared to placebo (Torp-Pedersen et al., 1999; Pedersen et al., 2001).

In clinical trials involving patients with supra-ventricular arrhythmia, 8.7% of dofetilide patients discontinued treatment due to adverse events (vs. 8.0% with placebo), with ventricular tachycardia as the most common cause (2.0% vs. 1.3%). Common adverse effects included headache, chest pain, and dizziness. Despite the significant risks associated with dofetilide, research on healthcare professionals' knowledge and adherence to its warning remains limited. This gap in understanding may contribute to inappropriate prescribing and inadequate patient monitoring, increasing the risk of supra-ventricular arrhythmia and other adverse events.

Studies highlight the critical need for healthcare professionals to understand and adhere to dofetilide's black box warning. A 2020 study (Kibert et al.) demonstrated that interdisciplinary collaboration significantly improved safety outcomes, with baseline monitoring compliance increasing from 72.5% to 94% and clinical interventions rising from 0.58 to 3.34 per patient ($P < .01$), supporting the authors' conclusion that the increased interventions and improved adherence to monitoring parameters may allow for safer use of these agents.

Complementing this, a 2021 study (Cicirale et al.) revealed that 190 out of 224 patients were inappropriately initiated on dofetilide, leading to a significantly higher rate of adverse cardiac events, with the authors warning that patients are placed at a higher risk of adverse reactions when this potentially dangerous antiarrhythmic medication is not used according to the protocol set forth by the guidelines. Together, these findings reinforce the vital role of education, collaboration, and protocol adherence in mitigating the serious risks associated with dofetilide therapy.

The objective of this study is to assess the knowledge and perceptions of pharmacy students regarding the FDA-mandated risk information and Black Box Warning associated with dofetilide. Specifically, the study aims to evaluate students' understanding of the drug's proarrhythmic potential—particularly the risk of torsades de pointes—as well as their awareness of dosing requirements, renal function considerations, and monitoring protocols outlined in the prescribing guidelines. Additionally, the study explored students' attitudes toward the clinical use of dofetilide, including their confidence in counseling patients and collaborating with healthcare teams in managing this high-risk antiarrhythmic agent. The findings will help identify educational gaps and inform the development of targeted instructional strategies to strengthen pharmacovigilance competencies among future pharmacists.

METHODOLOGY

This cross-sectional study assessed first-year pharmacy students' knowledge and perceptions regarding dofetilide safety concerns and monitoring requirements. A total of 46 students from Howard University College of Pharmacy completed the electronic survey, yielding a 96% response rate. The survey was distributed via a secure online platform, with participants receiving the link through email and informed of the study's voluntary and anonymous nature. The survey comprised four sections: demographic information, familiarity and experiences with black box warnings (BBWs), opinion-based questions on dofetilide safety and monitoring, and knowledge-based questions evaluating comprehension of key safety concerns. Data was collected and analyzed using SPSS Statistics (IBM Corp., Armonk, NY). Descriptive statistics summarized demographic variables, knowledge scores, and opinions. Chi-square tests ($p < 0.05$) were conducted to assess associations between demographic characteristics and survey responses. This approach offered insight into the baseline understanding of BBWs among first-year pharmacy students and identified opportunities for targeted educational interventions.

RESULTS

Among the forty-six students who participated in the survey, the majority were female and held a four-year degree, either a Bachelor of Arts or Bachelor of Science. Most respondents had over three years of experience in a pharmacy-related profession.

Table 1: Sociodemographic Characteristics of Participants (N=46).

Variables		N (%)
Gender	• Male	13 (12.5%)
	• Female	34 (69.4%)
	• Prefer not to say	2 (4.1%)
Education (Highest level attended)	• 2 Years of College	3 (2.9%)
	• 4 Years/BS/BA	31 (29.8%)
	• MSC/MA or Higher	8 (7.7%)
	• Other (Specify)	4 (3.8%)
	• Prefer not to say	3 (2.9%)
Work Experience	• Worked in a healthcare related job	8 (16.3%)
	• Worked in a pharmacy related job	27 (55.1%)
	• Worked but in non-healthcare jobs	10 (20.4%)
	• No answer	4 (8.2%)
If worked, how many years	• <1 Year	6 (12.2%)
	• 1-3 Years	17 (34.7%)
	>3 Years	21 (42.9%)
	0 Years	5 (10.2%)

Table 2 shows among the forty-four respondents, most reported definite prior awareness of black box warnings before entering pharmacy school. Among the respondents, about one-third (n=17; 34.7%) reported that they had definitely not heard of Black Box Warnings (BBW) in general prior to entering the pharmacy program. However, in response to whether they or someone close to them had experienced an adverse drug reaction, three-fourth of them (n=36; 74%) answered yes, suggesting a high proportion of them had personal exposure to such incidents. Regarding undergraduate background, while the majority came from basic or health sciences, only one student came from social sciences or business disciplines.

Table 2: Participants familiarity and experience with black box warning (n=44).

Survey Questions	Response Choice	N (%)
Have you heard of black box warning before coming to the pharmacy program?	• Definitely Not	17 (34.7%)
	• Probably Yes	5 (10.2%)
	• Definitely Yes	24 (49.0%)
	• No answer	3 (6.1%)
Have you or any member of your family or friends experienced related adverse drug reactions in the past?	• Definitely Not	9 (18.4%)
	• Probably Yes	26 (53.1%)
	• Definitely Yes	10 (20.4%)
	• No answer	4 (8.2%)
What was your major as undergraduate student: - selected choice	• Basic or Health Science	30 (61.2%)
	• Social Sciences	1 (2.0%)
	• Business	1 (2.0%)
	• Other (Specify)	14 (28.6%)

	• No answer	3 (6.1%)
Others: Communications, Pre-Pharmacy, Animal Science, Biochemistry, Biological/Biomedical Sciences, Biology, Biomolecular Sciences, Chemistry, Pharmaceutical Science		

In the opinion-based questions, among the forty-four students who participated in the survey, the majority agreed on the importance of adhering to dofetilide's black box warning. Most respondents also supported the FDA formally recognizing dofetilide's use for life-threatening ventricular arrhythmia as an official indication. Additionally, the majority agreed that rehospitalization is necessary for patients receiving lower doses than those determined by the dosing algorithm. There was also strong consensus that patients with renal impairment should be closely monitored while on Dofetilide. Furthermore, the majority strongly agreed that all patients should receive counseling before initiating dofetilide therapy.

Table 3: Opinion-Based Question Results Summary.

Variables	Strongly Agree (N%)	Strongly Disagree (N%)	Mean + SD
As of 2016 dofetilide is no longer in the REMS program. Knowing that, do you think it is still necessary to adhere to the black box warning?	39 (88.6%)	5 (11.4%)	0.719
Dofetilide is known to be effective in the treatment of life-threatening ventricular arrhythmias. This is an off-label use. In your opinion, should the FDA make this an official indication?	36 (81.8%)	8 (18.2%)	0.802
Patients must be hospitalized for three days for every change in dose. Do you feel that rehospitalization is necessary for patients receiving doses lower than those determined by the algorithm?"	35 (79.5%)	9 (20.5%)	0.841
How strongly do you agree that dofetilide should be closely monitored for patients who have abnormal kidney function?	41 (93.2%)	3 (6.8%)	0.631
Is it important for all patients to be counseled before starting dofetilide?	43 (97.7%)	1 (2.3%)	0.55

A knowledge assessment of pharmacy students regarding dofetilide safety revealed varied understanding of key clinical facts. Most participants (93.2%) correctly identified that patients must be monitored during the first 3 days of initiating dofetilide therapy due to the risk of Torsade de Pointes. Additionally, 74.4% were aware that concomitant use of clarithromycin is contraindicated due to the risk of life-threatening arrhythmias.

However, only 68.2% correctly responded that missed doses should not be doubled, and just over half (52.3%) knew that dofetilide is not indicated for hypertension. Notably, only 36.4%

correctly answered that patients should not be monitored at home during initiation, highlighting a significant gap in understanding the requirement for inpatient monitoring.

The overall score across all knowledge-based questions was 66%, suggesting that while students generally understand major safety concerns associated with dofetilide, there remain critical areas—particularly around monitoring protocols and indications—where further education is needed.

Table 4: Knowledge-Based Question Responses Summary (n=43).

Variables	Correct Answer	Participants with the Correct Answer N (%)
If a dose is missed, doses of dofetilide should be doubled so the regimen stays on track.	FALSE	30 (68.2%)
Patients must be monitored during the first 3 days of taking dofetilide because it may cause Torsade's De Pointes.	TRUE	41 (93.2%)
During the initiation dose of dofetilide, patients may be monitored at home by a trusted family member.	FALSE	16 (36.4%)
Dofetilide can be used for hypertension.	FALSE	23 (52.3%)
It is not recommended to take clarithromycin with dofetilide as it may increase the risk of life-threatening cardiac arrhythmia."	TRUE	32 (74.4%)
TOTAL SCORE		66%

In table 5, a series of chi-square analyses were conducted to evaluate factors influencing the understanding of patient consultation requirements prior to initiating dofetilide therapy. A significant association was found between education level and comprehension of this necessity ($p = 0.031$), with individuals holding at least a four-year degree demonstrating higher accuracy. Similarly, those with over three years of professional experience exhibited a better understanding compared to their less experienced counterparts. Furthermore, undergraduate major significantly impacted responses; participants with backgrounds in basic or health sciences were more likely to answer correctly than those from social science, business, or other fields ($p < 0.001$). Additionally, when assessing opinions on whether the FDA should officially approve dofetilide for treating life-threatening ventricular arrhythmias—currently an off-label use—individuals with basic or health sciences majors showed stronger agreement ($p < 0.001$). Notably, while dofetilide is primarily approved for atrial fibrillation and flutter, its off label use for ventricular arrhythmias has been explored, though it carries a risk of serious ventricular arrhythmias, including torsade's de pointes.

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

Demographics	Opinion based question	P-Values
Education (Highest level attended)	Is it important for all patients to be counseled before starting dofetilide?	0.031
If worked, for how many years?	Is it important for all patients to be counseled before starting dofetilide?	0.058
What was your major as undergraduate student (selected choice)	Is it important for all patients to be counseled before starting dofetilide?	< 0.001
	Dofetilide is known to be effective in the treatment of life-threatening ventricular arrhythmias. This is an off-label use. In your opinion, should the FDA make this an official indication?	< 0.001

Table six shows a Chi-square analysis was conducted to assess the relationship between undergraduate major and awareness of the contraindication of co-administration clarithromycin with dofetilide due to the increased risk of life-threating cardiac arrhythmia. The results demonstrated a statistically significant association ($p = 0.046$), with individuals who majored in basic or health sciences more frequently recognizing this contraindication compared to those with majors in social sciences, business, or other fields**.**

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

Demographics	Knowledge based question	P-Values
What was your major as undergraduate student (selected choice)	It is not recommended to take clarithromycin with dofetilide as it may increase the risk of life-threatening cardiac arrhythmia.	0.046

DISCUSSION

This study highlights pharmacy students' knowledge of dofetilide's black box warning, its risk for supra-ventricular arrhythmias, and monitoring requirements. Most participants were female (69.4%), held a four-year degree, and had over three years of pharmacy-related experience. While the majority answered key safety-related questions, a significant proportion struggled with one specific aspect. There was strong agreement on the importance of adhering to the black box warning, rehospitalization for dose adjustments, and monitoring patients with renal impairment.

Statistical analyses showed that education level, work experience, and undergraduate major significantly influenced understanding. Students with a four-year degree and over three years of experience demonstrated stronger knowledge of patient counseling requirements. Those with health or basic science backgrounds were more likely to recognize contraindications, such as the interaction between dofetilide and clarithromycin. These findings suggest that

targeted curriculum enhancements and clinical training could help address knowledge gaps and improve adherence to safety guidelines.

This study contributes to the existing body of knowledge by shedding light on pharmacy students' understanding of dofetilide, particularly its black box warning, adverse drug reactions (ADRs), and contraindications. Given the limited research on healthcare professionals' knowledge of dofetilide safety, this study helps close that gap by identifying areas where pharmacy education may need reinforcement. The findings emphasize the importance of proper adherence to dofetilide's safety guidelines, reinforcing the need for comprehensive education on high-risk medications.

From a practical standpoint, this study highlights the necessity of integrating dofetilide-specific content into pharmacy curricula to ensure future pharmacists are well-equipped to counsel patients and prevent medication errors. Theoretically, it underscores the role of targeted education in improving medication safety and reducing adverse outcomes. In terms of policy, these findings support the need for stronger training requirements on black box warnings and high-risk drug monitoring in pharmacy programs. By increasing awareness and understanding of dofetilide, this study ultimately contributes to improving patient safety and ensuring adherence to critical prescribing guidelines.

This study has several limitations that should be considered when interpreting the findings. The small sample size of 46 students, with only 44 completing the survey, resulted in a dropout rate of approximately 4.35%, which may affect the generalizability of the results. Additionally, the study was conducted exclusively at Howard University College of Pharmacy, limiting its applicability to a broader population of pharmacy students. There was also a risk of non-responsiveness and attrition bias, as some students may have chosen not to participate or complete the survey due to various factors. Furthermore, the potential for survey error, including misinterpretation of questions or response bias, could have influenced the accuracy of the results.

Despite these limitations, this study raises important questions that future research should address. It remains unclear how pharmacy students at other institutions compare in their knowledge of dofetilide and its black box warning. Additionally, further studies should explore whether targeted educational interventions, such as case-based learning or simulation exercises, improve students' understanding and adherence to safety guidelines. Investigating

how knowledge retention changes over time and how it translates into clinical decision-making would also provide valuable insights. Expanding research to include practicing pharmacists and other healthcare professionals could further clarify gaps in education and real-world application, ultimately enhancing patient safety.

CONCLUSION

This study assessed first-year pharmacy students' knowledge and perceptions of dofetilide, a high-risk anti-arrhythmic drug with a black box warning for life-threatening arrhythmias. The findings revealed that while students generally demonstrated awareness of black box warnings and showed favorable attitudes toward dofetilide's safety protocols, knowledge gaps still persist—particularly regarding specific contraindications and monitoring requirements. Notably, students with higher levels of education, more extensive pharmacy-related experience, and undergraduate backgrounds in basic or health sciences were more likely to answer knowledge-based questions accurately and express stronger alignment with current clinical recommendations.

These results highlight the need for targeted educational interventions within pharmacy curricula that emphasize the clinical implications of black box warnings. Leveraging case-based learning, simulation, and early experiential education may enhance student comprehension and ensure that future pharmacists are better equipped to recognize and manage the risks associated with high-alert medications like dofetilide. Addressing these knowledge gaps early in pharmacy education is critical to promoting safe and effective medication use in clinical practice.

RESOURCES

1. Cicirale, C., Jackson, J., & Gothard, D. Safety of Inpatient Dofetilide Initiation per Cardiology Services: A Retrospective Review. Journal of Pharmacy Practice, 2021; 35(4): 593–598. https://doi.org/10.1177/08971900211000212
2. Kibert, J. L., Franck, J. B., Dietrich, N. M., Quffa, L. H., & Franck, A. J. Impact of a pharmacy-cardiology collaborative management program during initiation of antiarrhythmic drugs. Journal of the American College of Clinical Pharmacy, 2019; 3(1): 30–35. https://doi.org/10.1002/jac5.1143Pedersen OD, Bagger H, Keller N, et al. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: A Danish Investigations of Arrhythmia and Mortality on Dofetilide

(DIAMOND) study. Circulation, 2001; 104(3): 292–296. https://pubmed.ncbi.nlm.nih.gov/11457747/

3. Tikosyn™ [package insert]. Pfizer Labs Division of Pfizer Inc., NY, NY, 2013.
4. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med., 1999; 341(12): 857–865. https://doi.org/10.1056/NEJM199909163411201
5. U.S. Food and Drug Administration. Approval Package for: Tikosyn (Dofetilide) NDA #020931. October 1, 1999. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20-931_Tikosyn.cfm
6. U.S. Food and Drug Administration. Tikosyn (Dofetilide) Prescribing Information. Revised August 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020931s007lbl.pdf
7. U.S. Food and Drug Administration. Information for Tikosyn (dofetilide) – Discontinuation of REMS Program. March 2016. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-tikosyn-dofetilide