



PIOGLITAZONE'S ASSOCIATION WITH HEART FAILURE AND STUDENTS KNOWLEDGE AND OPINION

Pannell, Makiya¹, Pierce, Nlaysia², and Hailemeskel, Bisrat^{3*}

¹Bachelors of Health Science, Minor; Business, PharmD Student

²Bachelors of Biology, PharmD Student,

³B.Pharm., MSc, Pharm.D., RPh, ABAAHP, RPh., Professor & Vice-Chair

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Corresponding Author: Hailemeskel, Bisrat

Address: 2300 4th Street, NW, Washington, DC 20059.

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ABSTRACT

Pioglitazone is a thiazolidinedione antidiabetic medication that carries a black box warning for heart failure due to its potential to cause fluid retention. Despite this warning, pioglitazone remains clinically relevant in the management of type 2 diabetes. This study aimed to assess pharmacy students' knowledge and opinions regarding pioglitazone and its black box warning, as well as to evaluate whether demographic factors were associated with differences in knowledge or perceptions. **Methods:** A cross-sectional survey was administered to pharmacy students, collecting demographic information along with opinion-based and knowledge-based responses related to pioglitazone. Statistical analyses were conducted using SPSS and R. Descriptive statistics summarized knowledge and opinion scores. Group comparisons were performed using Welch's t-tests and one-way ANOVA, while cross-tabulation analyses utilized chi-square tests of independence, with Fisher's Exact Test applied when expected cell counts were small. Statistical significance was assessed at an alpha level of 0.05. **Results:** A total of 44 respondents were included in the analysis. The mean knowledge score was 43.3%, indicating limited overall knowledge regarding pioglitazone. In terms of knowledge-based items, 31 participants (55.4%) correctly identified that pioglitazone can cause fluid retention and worsen heart failure, while 17 participants (30.4%) incorrectly believed that patients do not require monitoring for edema. For opinion-based items, 39 participants (69.6%) agreed that pioglitazone can still be used despite its black box warning, and 37 (66.1%) agreed it should be prescribed with caution in patients with a history

of heart failure. Additionally, 36 participants (64.3%) agreed that patients should be monitored for edema, and 42 (75.0%) agreed that women of childbearing age should be counseled on risks. The mean opinion score was approximately 69.0%, indicating generally favorable perceptions toward its use with appropriate precautions. No statistically significant differences were observed between demographic variables and knowledge or opinion outcomes (all $p > .05$). **Conclusion:** Pharmacy students demonstrated relatively low knowledge but generally consistent opinions regarding pioglitazone and its associated black box warning across demographic groups. Although no significant demographic differences were observed, the low knowledge scores suggest opportunities for enhanced education on the clinical implications of pioglitazone use, particularly concerning cardiovascular risk and patient monitoring.

KEYWORDS: Pioglitazone, Type 2 Diabetes, Black Box Warning, Heart Failure, Pharmacy Student Knowledge, Cross-Sectional Survey, Cardiovascular Risk, Medication Safety.

INTRODUCTION AND BACKGROUND

Pioglitazone is an antidiabetic medication belonging to the thiazolidinedione (TZD) class and is used in the management of type 2 diabetes mellitus. Developed by Takeda Pharmaceuticals, pioglitazone received approval from the United States Food and Drug Administration (FDA) in 1999 under the brand name *Actos*. The medication is administered once daily and is intended to be used in combination with lifestyle modifications, including diet and exercise, to improve glycemic control in adult patients with type 2 diabetes.

The recommended starting dose ranges from 15–30 mg orally once daily and may be titrated to a maximum dose of 45 mg daily as monotherapy or in combination with other antihyperglycemic agents such as metformin or sulfonylureas. In addition to its approved indication, pioglitazone has been used off-label for the treatment of nonalcoholic steatohepatitis at doses of 30–45 mg per day (American Diabetes Association, 2024; FDA, 2024b).

Pioglitazone exerts its therapeutic effect through activation of the peroxisome proliferator activated receptor gamma (PPAR- γ), a nuclear receptor involved in glucose and lipid metabolism. Activation of PPAR- γ enhances insulin sensitivity by increasing peripheral glucose uptake in skeletal muscle and adipose tissue while reducing hepatic glucose production. These mechanisms contribute to improved glycemic control in patients with

insulin resistance (Kolesar & Vermeulen, 2020). Despite its metabolic benefits, pioglitazone carries a United States FDA black box warning regarding the risk of new or worsening heart failure. The warning is primarily associated with the thiazolidinedione drug class and is related to fluid retention caused by PPAR γ activation. Increased sodium reabsorption within renal tubules promotes extracellular fluid expansion, leading to edema and potential exacerbation of underlying cardiac dysfunction. Consequently, pioglitazone is contraindicated in patients with New York Heart Association (NYHA) Class III or IV heart failure.

Clinical evidence suggests that while pioglitazone use may increase fluid retention and the risk of heart failure exacerbation, the medication has also demonstrated cardiovascular benefits, including reductions in myocardial infarction and stroke risk by approximately 16%. Previous investigations have reported that many cases of investigator-reported heart failure were manageable and not treatment-limiting (Nesti *et al.*). These findings highlight ongoing clinical debate regarding the balance between cardiovascular risk and therapeutic benefit associated with pioglitazone therapy.

Although substantial literature exists evaluating cardiovascular outcomes associated with pioglitazone, limited research has examined healthcare students' knowledge and perceptions regarding its black box warning and clinical safety profile.

Healthcare professionals have demonstrated limited awareness and cautious attitudes toward pioglitazone use. In one study, only 11% of providers reported prescribing pioglitazone for patients with diabetes and concurrent NASH, while 60% expressed concerns about adverse effects, particularly edema and heart failure (Alomar *et al.*, 2024). Additionally, 70% of providers were unaware of the most recent American Diabetes Association recommendations, suggesting gaps in knowledge and contributing to underutilization of pioglitazone despite evidence supporting its clinical benefits (Alomar *et al.*, 2024). This represents an important gap, as future healthcare providers play a critical role in medication safety, patient counseling, and risk-benefit decision-making. Therefore, assessing knowledge and perceptions surrounding pioglitazone's heart failure warning may provide insight into educational needs and clinical preparedness among pharmacy students.

Similar survey-based studies among first-year pharmacy students at Howard University have explored knowledge and attitudes toward other high-risk medications carrying FDA black box warnings. (Beltran, Hailemeskel, and Fullas 2025) investigated pharmacy students'

knowledge, perceptions, and experiences related to fentanyl's black box warnings, which highlight risks of addiction, life-threatening respiratory depression, and clinically significant drug interactions. In that study, 42 to 44 Doctor of Pharmacy students completed an electronic survey assessing both knowledge-based and opinion-based items.

The overall correct response rate was 66.6%, with students demonstrating strong understanding of fentanyl's pharmacokinetics (75–84% correct) but weaker performance on its drug classification and comparative safety relative to morphine (42– 50% correct). Opinion-based responses indicated broad consensus on the importance of accounting for fentanyl's high potency, short half-life, and addiction potential in clinical decision-making. These findings underscore a recurring theme across high-risk drug categories: pharmacy students tend to have foundational pharmacological knowledge but demonstrate gaps in specific safety and monitoring areas, highlighting the ongoing need for targeted educational interventions related to black box warnings.

OBJECTIVE

The objective of this study was to evaluate pharmacy students' knowledge and perceptions regarding the black box warning associated with pioglitazone and to assess whether demographic characteristics influenced understanding of its cardiovascular safety profile.

METHODS

Participants were selected as rows containing response data (excluding embedded codebook rows). Pioglitazone opinion items were coded on a 1-4 Likert scale (1=Strongly agree, 4=Strongly disagree) and were reverse-coded (5 - response) so that higher values indicate stronger agreement/support.

Each demographic variable (Q1-Q7) was treated as a categorical predictor using the numeric codes present in the dataset. Because the outcomes are ordinal/limited-range and group sizes are small, nonparametric tests were used: Two groups: Mann-Whitney U (Wilcoxon rank-sum) Three or more groups: Kruskal-Wallis P-values are shown both unadjusted and adjusted within outcome using Benjamini-Hochberg false discovery rate (FDR).

A knowledge score (0-4) was computed using the answer key derived from the item stems: (36_1=True, 36_2=False, 36_3=True, 36_4=False). Group comparisons used Welch's t-test for 2group factors and one-way ANOVA for factors with 3+ groups ($\alpha=0.05$).

The opinion score was computed as the mean of 5 reverse-coded items (35_1 to 35_5). Pioglitazone knowledge items were True/False (1=True, 2=False).

Cross tabulation and Chi-Square Analysis Report

Cross tabulation analyses were conducted to assess associations between demographic variables and the ten individual pioglitazone opinion and knowledge questions. Chi-square tests of independence were performed, with Fisher's Exact Test applied when expected cell counts were small. No statistically significant associations were seen between any demographic variable and responses to individual opinion or knowledge questions (all $p > 0.05$).

RESULTS

Table 1 summarizes the demographic characteristics of the 44 respondents. Most participants were female and held a 4-year bachelor's degree. The majority reported pharmacy-related work experience, with nearly half of having more than three years of experience. Over half of respondents indicated probable ADR experience and familiarity with black box warnings.

Variable	Category	n (%)
Gender	Female	32 (72.7%)
	Male	12 (27.3%)
Education	4 Years/BS/BA	30 (68.2%)
	MSc/MA or Higher	8 (18.2%)
	Other (Specify)	4 (9.1%)
	2 Year College	2 (4.5%)
Work Experience	Worked in pharmacy-related jobs	27 (61.4%)
	Worked in non-healthcare jobs	9 (20.5%)
	Worked in healthcare-related jobs	7 (15.9%)
Years Worked	>3 Years	21 (47.7%)
	1–3 Years	16 (36.4%)
	<1 Year	6 (13.6%)
ADR Experience	Probably Yes	25 (56.8%)
	Definitely Yes	10 (22.7%)
	Definitely Not	8 (18.2%)
Heard Black Box Warning	Unsure	23 (52.3%)
	Yes	16 (36.4%)
	No	5 (11.4%)

Table 2 shows that students demonstrated low knowledge of pioglitazone. Most correctly identified its role in improving insulin sensitivity (69.6%) and its risk of fluid retention

(55.4%). However, fewer students correctly recognized the black box warning and the need for monitoring, indicating gaps in knowledge regarding safety and patient monitoring.

Knowledge Question	Answer	Correct n (%)
Pioglitazone is primarily used to improve insulin sensitivity in patients with type 2 diabetes	True	39 (69.6%)
The black box warning for pioglitazone is specifically related to its risk of causing liver damage	False	10 (17.9%)
Pioglitazone can cause fluid retention, which may exacerbate existing heart failure	True	31(55.4%)
Patients taking pioglitazone do not need regular monitoring of their weight or signs of edema	False	17(30.4%)
AVERAGE		24.25 (43.3%)

Table 3 shows that most students agree with appropriate safety and monitoring practices for pioglitazone. A majority supported continued use despite the black box warning, prescribing with caution in heart failure, monitoring edema, and educating patients on risks. Overall, responses indicate generally positive opinions and awareness of safe pioglitazone use.

Opinion Question	Agree n (%)	Disagree n (%)
Pioglitazone should still be used for managing type 2 diabetes despite its black box warning for heart failure.	39 (69.6%)	5 (8.9%)
Pioglitazone is best prescribed with caution in patients with a history of heart failure.	37(66.1%)	7 (12.5%)
Patients prescribed pioglitazone should be monitored for signs of edema.	36 (64.3%)	7 (12.5%)
Women of childbearing age should be informed about the potential risks of ovulation stimulation when taking pioglitazone.	42(75.0%)	2(3.6%)
Healthcare providers should educate patients about the early signs of toxicity associated with pioglitazone.	39 (69.6%)	5 (8.9%)
AVERAGE	39 (69.0%)	5 (9.3%)

DISCUSSION

The purpose of this study was to evaluate pharmacy students' knowledge and perceptions regarding pioglitazone and its associated black box warning for heart failure. Overall, findings from this study suggest that students demonstrated low overall knowledge (43.3%) but generally consistent opinions regarding the clinical use and safety considerations of pioglitazone. The absence of statistically significant differences across demographic groups indicates that understanding of pioglitazone's risks and benefits was relatively uniform among participants.

Results from the knowledge-based questions revealed that while most students correctly identified pioglitazone's role in improving insulin sensitivity, fewer participants demonstrated accurate understanding of monitoring requirements and adverse effect risks. Lower correct response rates related to edema monitoring and black box warning recognition suggest that certain safety considerations may not be fully emphasized during pharmacotherapy education. Because pharmacists play an essential role in identifying medication-related risks and counseling patients, gaps in knowledge surrounding adverse drug warnings may impact future clinical decision-making.

These findings are consistent with a parallel survey study conducted among first-year pharmacy students at the same institution examining knowledge of fentanyl and its black box warnings (Beltran, Hailemeskel, & Fullas, 2025). In that study, participants achieved an overall correct response rate of 66.6%, which is notably higher than the 43.3% knowledge score observed in the present pioglitazone study. This difference may reflect the greater public visibility of fentanyl due to the ongoing opioid crisis, which may prompt more informal exposure to information about its risks prior to formal pharmacy training.

In both studies, however, students demonstrated stronger knowledge in foundational pharmacological areas such as mechanism of action and pharmacokinetics while showing more pronounced gaps in drug safety classification and monitoring-specific content. Similarly, opinion-based responses in both studies revealed that students broadly recognized the clinical risks of the respective medications and supported cautious, monitored prescribing practices, even when their objective knowledge scores were limited. Taken together, these findings suggest that positive safety attitudes do not necessarily correlate with adequate knowledge, and that targeted curricular reinforcement of black box warning content including specific monitoring parameters and patient counseling responsibilities is warranted across high-risk drug categories.

Student opinions reflected general agreement that pioglitazone remains an appropriate treatment option when prescribed cautiously and with appropriate monitoring. Most respondents supported patient education regarding toxicity symptoms and monitoring requirements, highlighting recognition of the pharmacist's responsibility in medication safety. These findings align with existing clinical literature suggesting that although pioglitazone carries a heart failure warning, its therapeutic benefits may still outweigh risks when patients are appropriately selected and monitored (Nesti et al., 2021; FDA, 2024).

The lack of association between demographic variables and survey responses suggests that exposure to pharmacotherapy education may provide a relatively standardized understanding of pioglitazone across student groups. However, the low overall knowledge scores indicate opportunities for strengthened instruction related to black box warnings, cardiovascular risk assessment, and patient monitoring strategies. Enhancing education in these areas may better prepare future pharmacists to balance medication efficacy with safety considerations in clinical practice.

Current clinical practice guidelines further emphasize cautious use of pioglitazone in patients at risk for cardiovascular complications. According to recent American Diabetes Association (ADA) Standards of Care, antihyperglycemic therapy selection should prioritize comorbid conditions such as heart failure and cardiovascular disease when choosing treatment options (American Diabetes Association, 2024). Thiazolidinediones, including pioglitazone, are generally considered add-on therapies and should be avoided or used cautiously in patients with symptomatic heart failure due to the risk of fluid retention and cardiac decompensation (FDA, 2024; Kolesar & Vermeulen, 2020).

These recommendations highlight the clinical importance of pharmacist awareness regarding medication safety warnings, reinforcing the need for strong educational preparation among pharmacy students. Although statistically significant differences were not observed across demographic groups, the clinical relevance of these findings lies in the identification of knowledge gaps related to medication safety warnings, which may influence future prescribing decisions and patient counseling practices.

Several limitations should be considered when interpreting the findings of this study. First, the sample size was relatively small and consisted of pharmacy students from a single academic institution, which may limit the generalizability of the results to other student populations or healthcare disciplines. Differences in curriculum structure or clinical exposure at other institutions may influence knowledge and perceptions differently.

Second, data were collected using a self-reported survey instrument, which introduces the potential for response bias. Participants may have selected answers they perceived as socially or academically appropriate rather than reflecting their true level of understanding. Additionally, survey-based assessments evaluate theoretical knowledge and opinions rather than real-world clinical decision-making.

Another limitation involves the cross-sectional study design, which captures responses at a single point in time and does not assess changes in knowledge as students' progress through pharmacy training. Longitudinal studies may provide greater insight into how education and clinical experiences influence understanding of medication safety warnings over time.

Finally, the knowledge assessment included a limited number of questions related specifically to pioglitazone, which may not fully represent overall competency in managing medications with black box warnings. Future studies incorporating broader assessment tools and larger participant populations may provide a more comprehensive evaluation of pharmacy student preparedness.

Findings from this study emphasize the importance of pharmacist awareness regarding patient specific risks associated with pioglitazone therapy. Certain patient populations require increased caution due to the medication's potential to cause fluid retention and exacerbate heart failure (FDA, 2024; Nesti et al., 2021). Individuals with a history of heart failure, ischemic heart disease, or cardiac arrhythmias may experience worsening cardiac function when treated with pioglitazone. Additionally, obese and elderly patients may demonstrate increased susceptibility to fluid retention and reduced cardiac reserve, further elevating clinical risk.

Pioglitazone therapy also presents important considerations for premenopausal women with anovulatory conditions, as treatment may stimulate ovulation and increase the risk of unintended pregnancy (Kolesar & Vermeulen, 2020). Appropriate patient counseling and contraceptive education should therefore be considered when initiating therapy in this population. The medication is not approved for pediatric use.

Appropriate monitoring remains essential to ensure safe use of pioglitazone. Patients should undergo regular assessment of glycemic control, including pre-prandial blood glucose levels and hemoglobin A1c measurements. Healthcare providers should also monitor early signs of toxicity such as edema, rapid weight gain, myalgia, bone fractures, sinusitis, and headaches, which may indicate fluid retention or adverse drug effects.

Pharmacists play a critical role in patient counseling and early detection of complications. Patients should be educated on medication administration, expected onset of therapeutic effect, and warning symptoms requiring medical attention, including shortness of breath,

unexplained weight gain, bone pain, or jaundice. Routine monitoring of body weight, liver function, hemoglobin levels, and ocular health may further support safe long-term therapy.

Recent guideline updates also recommend prioritizing alternative glucose-lowering agents, such as SGLT-2 inhibitors or GLP-1 receptor agonists, in patients with type 2 diabetes who have established cardiovascular disease or heart failure risk. These agents demonstrate cardiovascular benefit without promoting fluid retention, further supporting careful patient selection when considering pioglitazone therapy. These clinical considerations reinforce the importance of adequate pharmacotherapy education, as improved student understanding of monitoring and counseling requirements may translate into safer prescribing practices and enhanced patient outcomes.

CONCLUSION

This study demonstrated that pharmacy students possess generally consistent perceptions but low knowledge regarding pioglitazone and its associated black box warning for heart failure, with an average knowledge score of 43.3%. While awareness of cautious prescribing and monitoring was evident, opportunities remain to strengthen education related to medication safety warnings. Future studies involving larger and more diverse student populations may further evaluate educational preparedness related to high-risk pharmacotherapies.

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