



THALIDOMIDE BLACK BOX WARNING AWARENESS AND PERCEPTIONS OF PHARMACY STUDENTS

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ABSTRACT

Background: Thalidomide, despite its history of severe teratogenicity, remains a vital treatment for multiple myeloma and leprosy. Its safe use is contingent upon strict adherence to Black Box Warnings (BBW) and Risk Evaluation and Mitigation Strategy (REMS) protocols. **Objective:** This study aimed to assess the baseline awareness and safety-related opinions of pharmacy-affiliated individuals and determine if educational level significantly impacts these factors. **Methods:** A cross-sectional survey was conducted (N=47). Data were analyzed using descriptive statistics and Pearson's Chi-Square tests ($p < 0.05$) to compare two education-based groups: Undergraduate and Postgraduate/Degree. **Results:** Findings revealed a significant knowledge gap, with 63.8% of respondents unaware of BBWs prior to their pharmacy program. However, a high professional consensus was found regarding safety; 95.5% agreed that patient counseling is essential and that BBWs significantly impact clinical decision-making. Chi-Square analysis showed no statistically significant relationship between education level and awareness ($p = .728$) or safety opinions ($p = .840$), though the limited sample size warrants cautious interpretation of these findings. **Conclusion:** While initial awareness of regulatory warnings is low, pharmacy education appears to align students and professionals toward a commitment to risk management. Strengthening early curriculum coverage of high-risk medications such as thalidomide may help address the initial knowledge gap identified in this study.

KEYWORDS: Thalidomide, Students, Pharmacy, Survey, Black box Warning, Risk Evaluation and Mitigation Strategy.

I. INTRODUCTION

Thalidomide represents one of the most significant cautionary tales in pharmacological history. Originally marketed in the late 1950s as a non-barbiturate sedative and anti-emetic for morning sickness, its widespread use led to a global epidemic of phocomelia and other severe congenital malformations. This tragedy affected over 10,000 infants worldwide, catalyzing a total overhaul of drug safety regulations, including the 1962 Kefauver-Harris Amendment, which established the modern requirement for drugs to be proven both safe and effective prior to approval. Despite its history, thalidomide has resurfaced as a potent therapeutic agent. It is currently FDA-approved for the treatment of erythema nodosum leprosum (ENL) and as a first-line treatment for newly diagnosed multiple myeloma in combination with dexamethasone. Pharmacologically, it acts as an immunomodulatory and anti-angiogenic agent, though its high volume of distribution and complex metabolism require close clinical monitoring.

The primary safety concern remains its extreme teratogenicity. A single dose taken during the critical period of organogenesis (20–37 days after conception) can cause life-threatening birth defects. Beyond fetal risk, thalidomide is associated with severe venous and arterial thromboembolism, peripheral neuropathy, and significant somnolence, leading the FDA to mandate a **Black Box Warning (BBW)**—its most severe safety alert.

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This binding leads to the degradation of specific transcription factors (such as SALL4), which are essential for limb and organ development. Additionally, its anti-angiogenic properties disrupt the formation of new blood vessels in the developing fetus, leading to the hallmark limb deformities seen in phocomelia. The consequences of thalidomide exposure are

irreversible and devastating. Clinically, this includes not only limb reduction defects but also internal organ malformations (cardiac, renal, and gastrointestinal) and sensory impairments. In adult populations, the risk of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) significantly increases morbidity, often requiring concurrent thromboprophylaxis. Current clinical literature emphasizes the necessity of the REMS (Risk Evaluation and Mitigation Strategy) program.

Studies by Kim & Scialli (2011) and Lansari et al. (2020) have demonstrated that while the drug is highly effective for oncological and dermatological conditions, the efficacy of the safety protocol relies entirely on the stringent execution of Elements to Assure Safe Use (ETASU, are specific, mandatory interventions within a Risk Evaluation and Mitigation Strategy (REMS) program established by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of certain high-risk drugs outweigh their risks) such as mandatory pregnancy testing and pharmacy certification.

FDA guidelines and the THALOMID REMS™ program mandate that only certified prescribers and pharmacies may handle the medication. Current standards of care require pharmacists to perform mandatory counseling at every dispense, verify negative pregnancy tests for females of reproductive potential, and ensure that patients are using two forms of effective contraception. Several recent studies have investigated BBW awareness among pharmacy students and healthcare trainees, highlighting a pattern of suboptimal regulatory knowledge at the early-career level. Andrevill et al. (2025) examined BBW awareness related to lithium among pharmacy students and found that while students demonstrated a general understanding of therapeutic benefits, awareness of specific regulatory risk warnings remained limited prior to formal clinical training.

Similarly, Beltran et al. (2025) assessed pharmacy students' knowledge and attitudes regarding fentanyl BBWs and reported gaps in awareness of specific safety protocols, particularly among students earlier in their programs. Acquah et al. (2025) investigated clozapine BBW awareness and found that targeted education significantly improved both knowledge and safety attitudes among pharmacy students. Collectively, these studies suggest that awareness of high-risk drug BBWs is not consistently established through general health education alone, and that structured pharmacy curricula play a critical role in building this knowledge base.

In the study, Andrevill, Boateng, Hailemeskel, and Fullas (2025) evaluate the proficiency of pharmacy students in navigating the complex clinical profile of lithium. The researchers emphasize that while lithium remains a gold-standard treatment for bipolar disorder, its narrow therapeutic index makes it a high-alert medication. The findings suggest that while students are generally aware of its therapeutic utility, there is a distinct need for more focused education regarding its black box warnings, specifically those involving lithium toxicity, renal dysfunction, and cardiotoxicity. The authors argue that future pharmacists must be more strictly trained in monitoring protocols to prevent the life-threatening complications associated with these risks.

Beltran, Hailemeskel, and Fullas (2025) investigate the knowledge and attitudes of pharmacy students concerning fentanyl, a potent synthetic opioid at the center of the current overdose crisis. The study reveals that students possess a solid understanding of fentanyl's clinical application for severe pain but exhibit varying levels of familiarity with the specific nuances of its black box warnings. The research highlights the importance of reinforcing the risks of fatal respiratory depression and the stringent requirements for patient selection and diversion control. The authors conclude that improving student attitudes and depth of knowledge is essential for ensuring that future pharmacists can safely manage and dispense this high-potency medication.

The publication by Acquah, Boateng, Hailemeskel, and Fullas (2025) explores the educational gaps regarding clozapine, a medication notable for carrying five separate black box warnings. The research focuses on the critical need for students to understand the Clozapine REMS (Risk Evaluation and Mitigation Strategy) program, which is designed to manage risks like severe neutropenia, myocarditis, and seizures. The authors find that while students recognize clozapine as a treatment for resistant schizophrenia, they require more rigorous training on the practical application of these safety mandates. The study suggests that a deeper mastery of these warnings is vital for pharmacists to play their role in preventing adverse drug events in psychiatric care.

A search of current literature reveals that the challenges identified in these three articles are part of a broader trend in pharmaceutical education. Research consistently shows that pharmacy students' ability to identify and describe black box warnings (BBWs) improves significantly as they progress through their didactic years, yet knowledge remains highly variable depending on the drug class. For instance, studies indicate that students are more

likely to remember warnings for high-profile medications than for those less frequently prescribed, suggesting a reliance on "common knowledge" rather than a systematic understanding of regulatory safety. Furthermore, the literature highlights that "alert fatigue" and the sheer volume of FDA-mandated warnings pose a challenge even for seasoned clinicians.

Studies in medical toxicology have shown that even practicing healthcare providers often fail to identify BBWs for the medications they prescribe most frequently. This underscores a global need for pharmacy curricula to transition from simple memorization of warnings to a more integrated, case-based approach. Experts suggest that by focusing on the clinical "why" behind a black box warning, students can better translate regulatory data into actionable patient counseling and safety monitoring in real-world practice. Pharmacists serve as the final gatekeepers in the medication-use process.

Understanding the baseline knowledge and attitudes of pharmacy-affiliated individuals is vital for ensuring that thalidomide is managed safely. If significant gaps exist in awareness, it signals a need for enhanced curriculum focus on high-risk regulatory protocols like REMS. The primary objective of this study was to assess the level of awareness regarding BBWs and evaluate the opinions of pharmacy-affiliated individuals concerning thalidomide safety and monitoring. A secondary goal was to determine if educational level (Undergraduate vs. Postgraduate) significantly influences these safety perceptions and knowledge levels

METHODS

A descriptive cross-sectional study was conducted via an online survey (N=47). Demographic data including gender, education level, and work experience were collected alongside Likert-scale opinion variables (items 3.1–3.5) and a BBW awareness question (Q5). For inferential analysis, education was collapsed into two groups: Undergraduate/Other and Postgraduate/Degree. Data were analyzed using Pearson's Chi-Square tests in SPSS to identify significant associations ($p < 0.05$) between education groups and safety awareness and opinions.

RESULTS

The demographic analysis (Table 1) reveals a respondent pool that is largely female (70.8%) and undergraduate-focused (67.4%). Within the subset reporting work experience, the

majority (60.0%) worked in pharmacy-related settings, placing them at the front line of the thalidomide REMS dispensing process.

Table 1: Demographic Profile of Respondents.

Variable	Category	n	%
Gender (n=48)	Female	34	70.8
	Male	14	29.2
Education (n=45)	Undergraduate	38	82.6
	Postgraduate/Degree (MSc/MA, or Higher)	8	17.4
Work Experience (n=46)	Non-Healthcare-Related	10	22.2
	Healthcare Related	8	17.8
Years Worked (n=44)	>3 years	21	17.8
	1-3 years	17	38.6
	<1 year	6	13.6

Table 2 highlights a strong professional consensus regarding thalidomide safety protocols. Across all five opinion items, the majority of respondents agreed or strongly agreed with each safety-related statement. Agreement was highest for the importance of comprehensive patient counseling (95.5%) and the impact of BBWs on clinical decision-making (95.5%). Slightly lower but still substantial agreement was observed for the sufficiency of current management strategies (84.1%) and the effectiveness of monitoring requirements (86.4%), suggesting that while most respondents endorse current protocols, a meaningful minority believes further safeguards may be warranted.

Table 2: Opinion on Safety and Counseling (n=44).

Question	Strongly Agree	Agree	Disagree	Strongly Disagree	Total Agree
1. What is your stance on the continued use of thalidomide for treating certain medical conditions today, and do you believe its benefits justify its use despite its controversial past?	11 (25.0%)	29 (65.9%)	3 (6.8%)	1 (2.3%)	40 (90.9%)
2. How do you feel about the impact of black box warnings on patient and physician decision-making when considering thalidomide as a treatment option?	21 (47.7%)	21 (47.7%)	2 (4.5%)	0 (0.0%)	42 (95.5%)
3. Do you believe the current management strategies for thalidomide warnings are sufficient to protect patients, or should more stringent measures be implemented?	10 (22.7%)	27 (61.4%)	7 (15.9%)	0 (0.0%)	37 (84.1%)
4. What is your opinion on the effectiveness and necessity of the current monitoring requirements for patients prescribed thalidomide to ensure their safety?	18 (40.9%)	20 (45.5%)	5 (11.4%)	1 (2.3%)	38 (86.4%)
5. How important do you believe comprehensive patient counseling is when prescribing thalidomide, and what key elements should be included to ensure patient understanding and safety?	25 (56.8%)	17 (38.6%)	2 (4.5%)	0 (0.0%)	42 (95.5%)

Table 3 demonstrates a significant knowledge deficit prior to formal pharmacy education. Over 60% of respondents entered their professional training with little to no understanding of Black Box Warnings. This confirms that regulatory safety information is not a common part of general health literacy and must be explicitly taught within the clinical curriculum.

Table 3: Awareness of BBWs Prior to Program (Q5: Have you heard of black box warnings before coming to the pharmacy program?).

Awareness Category	n	%
Yes	17	36.2%
Unsure / No	30	63.8%

The inferential analysis (Table 4) yielded no statistically significant p-values ($p > .05$) for either comparison. No significant association was detected between education level and prior BBW awareness ($p = .728$) or between education level and safety-related opinions ($p = .840$). These results suggest that the two education groups did not differ meaningfully in their awareness or professional attitudes toward thalidomide safety within this sample, though the limited sample size restricts the conclusions that can be drawn from these tests.

Table 4: Inferential Statistical Analysis (Chi-Square).

Relationship Tested	χ^2	p-value
Education vs. BBW Awareness	1.307	.728
Education vs. Safety Opinions	0.838	.840

DISCUSSION

The findings of the present study suggest that pharmacy education plays an important role in bridging the knowledge gap regarding high-risk medications. While pre-program BBW awareness was low (Table 3), strong consensus on the importance of BBWs and counseling (Table 2) was observed across both education groups (Table 4). This pattern implies that a safety-oriented professional mindset is cultivated through pharmacy training regardless of prior educational background. However, the 63.8% rate of initial unawareness highlights a need for earlier, more explicit coverage of regulatory warnings in undergraduate health sciences curricula, particularly for REMS-regulated drugs such as thalidomide. current sample may reflect differences in cohort composition, particularly the inclusion of postgraduate and non-traditional education backgrounds. Across all four studies, however, a substantial minority of incoming students lacked prior BBW familiarity, supporting the broader conclusion that BBW awareness is not consistently established through pre-pharmacy education.

The strong consensus on safety opinions observed in the present study (95.5% agreement on counseling importance and BBW impact on decision-making) closely parallels findings from the comparator studies. Andrevill *et al.* (2025) reported 82.7% combined agreement on the importance of patient education for lithium, and Acquah *et al.* (2025) found that 88.6% of students agreed or strongly agreed on the importance of monitoring for clozapine. Beltran *et al.* (2025) similarly reported strong consensus among PharmD students on the clinical importance of considering fentanyl's pharmacokinetic risk profile. This recurring pattern — high agreement on safety principles regardless of the specific drug — suggests that pharmacy programs effectively instill a generalized safety-conscious professional mindset early in training.

The finding that education level was not significantly associated with awareness or safety opinions ($p = .728$ and $p = .840$, respectively) contrasts with the longitudinal pattern documented by Schwarcz *et al.* (2010), who found that BBW knowledge increased markedly from P1 to P3 students. The discrepancy is likely attributable to two factors: first, the present study compared broad educational categories (Undergraduate vs. Postgraduate) rather than year-in-program, and second, the limited sample size of the current study reduces the power to detect such differences. Targeted, drug-specific knowledge (such as that examined by Schwarcz *et al.*) may show clearer educational gradients than the broader awareness and opinion items examined here.

While this study provides valuable insights into thalidomide BBW awareness and safety perceptions among pharmacy-affiliated individuals, several limitations must be acknowledged. The effective analytical sample was small ($n=44-47$ for key variables), which substantially limits the statistical power of the Chi-Square tests to detect potentially meaningful differences between education groups. Most cells in the chi-square analyses had expected counts below five — a condition that compromises the reliability of the test — and as such, the non-significant results should be interpreted as inconclusive rather than as confirmation that no difference exists.

Additionally, the high proportion of incomplete responses across demographic variables suggests that many participants may have been early-year students with limited clinical exposure, which may not fully represent the views of more experienced pharmacy professionals. As with any survey-based study, self-reporting introduces the possibility of social desirability bias; given the high-stakes nature of thalidomide safety, respondents may

have selected more affirming responses regarding counseling and monitoring than their practical knowledge of REMS protocols would otherwise support. Finally, the study population was drawn from a specific institutional context, which limits the generalizability of findings to other pharmacy programs, geographic regions, or practice settings where curricula and REMS exposure may differ considerably.

The thalidomide BBW awareness rate observed in this study (36.2% reporting prior awareness) is consistent with the patterns reported by Andrevill *et al.* (2025) and Acquah *et al.* (2025), both of whom found that approximately 52% of first-year pharmacy students at the same institution had heard of BBWs prior to entering the program. The somewhat lower awareness rate in the

CONCLUSION

This study found that while baseline awareness of BBWs is low among pharmacy-affiliated individuals prior to entering formal training, strong professional consensus regarding thalidomide safety protocols is present across both undergraduate and postgraduate respondents. Education level did not significantly predict BBW awareness or safety-related opinions, though this finding must be qualified by the study's limited sample size. The results underscore the importance of pharmacy education in establishing safety-conscious professional values and point to a need for earlier and more explicit engagement with high-risk regulatory frameworks such as REMS in undergraduate health sciences training.

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