The Value of the Black Box Warning in Dermatology

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Abstract

Boxed, or "black box" warnings are issued by the United States Food and Drug Administration (US FDA) as a means to label drugs associated with serious adverse events. However, there is no clear metric to determine how and when the boxed warning is applied. Inconsistencies in the review process, language, timing, and dissemination of these warnings impact dermatologists and their patients. Appropriate patient selection and monitoring can help minimize risk to patients when prescribing drugs with boxed warnings. Future changes in the manner in which the boxed warning is issued and in its subsequent clinical application may improve the utility of these warnings for dermatologists and ultimately, patient safety.

Clinical Case

A 63-year-old white male with diabetes mellitus type II returns to your clinic for follow-up of non-healing neuropathic diabetic foot ulcers. He has not responded to multiple wound care modalities and is interested in other therapeutic options. You consider adding becaplermin to your patient's current regimen. Becaplermin (0.01% Regranex® gel), recombinant human platelet-derived growth factor-BB that has been topically formulated, is indicated for chronic lower extremity diabetic ulcers. Currently, it is the only approved growth factor for use in wound healing. Multicenter, randomized, double-blinded placebo-controlled studies have shown statistically significant efficacy of becaplermin in increasing complete ulcer healing and in decreasing time to healing when combined with appropriate wound care.[1]

The most common side effects of becaplermin listed in its package insert are erythematous cutaneous eruptions and burning sensation at the application site.[2] In clinical trials, the most common adverse events observed were infection, cellulitis, skin ulceration, and osteomyelitis, none of which are included in the package insert.[1] Serious adverse events were demonstrated in similar percentages of the becaplermin gel (24%), placebo gel (25%), and good wound care monotherapy (28%) groups, and the majority of these events were thought to be related to common sequelae of diabetes or nonhealing diabetic ulcers, rather than to the becaplermin gel itself.[1]

Becaplermin also comes with a boxed warning which states, "Warning: Increased Rate of Mortality Secondary to Malignancy." The warning continues to note that "An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of Regranex® Gel in a postmarketing retrospective cohort study. Regranex® Gel should only be used when the benefits can be expected to outweigh the risks. Regranex® Gel should be used with caution in patients with known malignancy."[2]

This boxed warning was applied in 2008, when a long-term study of a medical claims database compared patients who had received becaplermin to matched comparators. In patients who were observed for a median of approximately 20 months in order to identify malignancies, patients using becaplermin had a relative risk (RR) of 2.7 for developing cancer compared to those receiving vehicle/standard of care (3% versus 1%, respectively).[2] The incidence of mortality from all cancers in patients using 3 or more tubes of becaplermin was 3.9 per 1,000 person years, whereas this incidence was 0.9 per 1,000 person years in the comparators (adjusted rate ratio of 5.2).[2] The FDA reviewed this data and "concluded that the increase in the risk of death from cancer in patients who used three or more tubes of Regranex was five times higher than in those patients who did not use Regranex®. However, the risk of getting new cancers among Regranex® users was not increased compared to non-users. The duration of follow-up of patients in this study was not long enough to detect new cancers. In response, the manufacturer of Regranex® has added this information and a Boxed Warning to the labeling for the product."[3]

Recently, long-term follow-up from the same database has been published and shows no overall elevated cancer mortality risk with becaplermin (RR 1.0). The study goes on to suggest that despite the original boxed warning, there is no statistically significant increase in mortality from all cancers in patients using more than 3 tubes of becaplermin (RR 2.4).[4] The study authors "found no convincing evidence that cancer incidence RRs are increased among becaplermin initiators relative to comparators who are similar but who did not receive becaplermin."[4]

As a dermatologist, reading the most recent medical literature reveals a better safety profile than anticipated from the becaplermin black box warning and package insert. Furthermore, in selected populations being treated for diabetic foot ulcers, the combination of becaplermin and good wound care may be cost effective.[5] Given that nonhealing neuropathic diabetic foot ulcers are often recalcitrant to treatment and have a limited set of treatment options as well as your patient's lack of improvement with other wound care approaches, you discuss the risks and benefits of becaplermin with him. He elects to proceed with this therapy. The typical treatment regimen is recommended, which involves applying becaplermin once daily until complete healing has occurred. This treatment may be modified if complete healing does not occur after 20 weeks or if the ulcer does not reduce in size by 30% after 10 weeks of therapy.[2]

Introduction

The US Food and Drug Administration (FDA) is charged with bringing drugs to market in a safe and efficient manner. The

majority of drugs are approved based on data from relatively short clinical trials conducted in specific patient populations that may not represent their ultimate market and clinical use. In addition, initial study data on novel therapeutic agents may change as newer, longer-term data demonstrates differing results. There is always the potential for new adverse events (AEs) to emerge, and post-marketing safety studies and passive surveillance using Adverse Event Reporting System (AERS) data collection are employed to monitor this risk.[1] This computerized database combines MedWatch, which is based on voluntary reporting by health care providers, and FDA-mandatory reports from pharmaceutical companies, that despite being mandatory are nonetheless comprised of spontaneously reported AEs. Additional safety information may come from FDA-conducted analyses of databases with information linking drugs to adverse events, commercial databases purchased by the FDA, as well as new case reports and clinical trials in the medical literature.[6]

It is well-known that AEs are underreported by both health care providers and pharmaceutical sponsors, yet AERS relies solely on spontaneous reporting.[7] The majority of boxed, or "black box" warnings, however, are based on this postmarketing surveillance, rather than on data from randomized controlled clinical trials. Today, this term has evolved to describe the most serious type of marketed prescription drug warning, the boxed warning.[8,9]

Approximately 400 drugs in the United States have a boxed warning and the number is growing, despite a relatively stable number of drug withdrawals.[10,11] It is estimated that the likelihood that a drug will acquire a new boxed warning or be withdrawn from the market over 25 years is 20%.[12] For dermatologists, the topical calcineurin inhibitors (TCIs) are a well-known class of drugs that carries a boxed warning, primarily based on animal toxicity and carcinogenic potential.[13] A decade after their initial approval, the manufacturers of onabotulinumtoxinA (Botox® and Botox Cosmetic®) were required to add a new boxed warning in 2009, notifying prescribers and patients of the potential for "distant spread of toxin effect," which was based on data in children with cerebral palsy being treated off-label for spasticity.[14] Table 1 lists common drugs used in dermatology that carry a boxed warning.[15]

As evidenced by the preceding examples, there is no clear metric to determine how and when a boxed warning is applied. Inconsistencies in the review process, language, timing, and dissemination of these warnings therefore impact both dermatologists and their patients.

Boxed Warning Guidelines

The boxed warning criteria were released by the FDA in 1979. Despite the vague nature of these criteria, they remain valid to this day: "The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data." Of note, a causal relationship between the drug and the adverse event does not have to be proven.[8] In 2006, further guidelines were released that provided "nonbinding recommendations" for the application and use of boxed warnings, but did not provide any specific criteria for their issue.[16,17] The FDA describes the boxed warning as a means to alert health care providers of three general situations: 1) when the risk of an AE is so serious that it may outweigh the benefits of a drug (eg, life-threatening, fatal, or can cause permanent disability), 2) when serious AEs may be prevented or their risk decreased with appropriate prescribing considerations including lab monitoring and suitable patient selection, and 3) the FDA approved the drug with mandatory restrictions or guidelines for safe use.[17] Boxed warnings may also be issued in other unspecified circumstances and in instances in which there may be an anticipated adverse reaction, such as in the contraindication of drugs during pregnancy due to evidence in humans or animals. [17] The boxed warning about the potential risk of cancer with the use of TCIs was based on their mechanism of action, animal studies, and postmarketing surveillance demonstrating 20 case reports of lymphoma in patients who had used TCIs worldwide.[18]

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Issuing a Boxed Warning

When a drug is identified to be high risk, the FDA commissioner may refer it to the Center for Drug Evaluation and Research (CDER), which may convene an advisory committee for further review.[19] However, boxed warnings are not required to undergo this process prior to implementation and are often issued without this type of evaluation. In the three-year time period from 2004-2006, 77 new black-box warnings were released, of which only 11 were discussed by advisory committees.[20] Advisory meeting transcripts often indicated confusion regarding the boxed warning and an emphasis on the potential impact of the warning rather than the content.[20] Same-class drugs do not all share the same safety information including a boxed warning.[21] Furthermore, the median time for a black box warning to appear on the label of another drug in the same class is 66 months (2-170 months).[21]

The language of boxed warnings is also variable. The wording of each warning is negotiated between the multidisciplinary FDA group, which includes pharmacologists, chemists, medical officers, and statisticians, who review scientific data and negotiate specific drug labeling with drug manufacturers.[22] A study evaluating the informativeness of warnings for drugs causing

TABLE 1.

Drugs Used in Dermatology With Boxed Warnings[16]*		
Drug Name	**Brand**	**Summary of boxed warning**
AbobotulinumtoxinA	Dysport®	Potential life-threatening distant spread of toxin effect after local injection
Acitretin	Soriatane®	Pregnancy and blood donation contraindicated; appropriate use by experienced physicians, considerations in women of child-bearing potential, alcohol avoidance, hepatotoxicity
Adalimumab	Humira®	Serious infection risk, malignancy risk
Azathioprine	Imuran®, Azasan®	Malignancy risk, mutagenic potential in males and females, hematologic toxicity
Bexarotene	Targretin®	Pregnancy contraindicated
OnabotulinumtoxinA	Botox®, Botox Cosmetic®	Potential life-threatening distant spread of toxin effect after local injection
Isotretinoin	Accutane®	Restricted use through iPLEDGE, pregnancy contraindicated
Intravenous immunoglobulin (IVIg)	Gammaplex®, Gammagard®, Gamunex®, Carimune NF®, Privigen®, Flebogamma®	Acute renal dysfunction/failure
Certolizumab Pegol	Cimzia®	Serious infection risk, malignancy
Ciprofloxacin	Cipro®, Cipro XR®	Risk of tendon rupture and tendonitis, avoid in myasthenia gravis
Chlorambucil	Leukeran®	Myelosuppression, carcinogen, mutagen/ teratogen, infertility
Chloroquine phosphate	Aralen®	Appropriate use for malaria and extraintestinal amebiasis
Clindamycin	Cleocin®	*C. difficile* associated diarrhea risk
Cyclosporine modified	Neoral®	Appropriate use in experienced physicians, immunosuppressant, bioequivalence, monitor drug levels, skin malignancy risk in psoriasis, hypertension and nephrotoxicity risks
Doxepin	Silenor®	Suicidality risk in children, adolescents, young adults
Drospirenone/ethinyl estradiol	Gianvi®, Loryna®, Ocella®, Syeda®, Vestura®, Zarah®, Yaz®, Yazmin®, Beyaz®	Smoking and cardiovascular events
Etanercept	Enbrel®	Serious infection risk, malignancy
Gemifloxacin	Factive®	Risk of tendon rupture and tendonitis, avoid in myasthenia gravis
Golimumab	Simponi®	Serious infection risk, malignancy
Hydroxychloroquine	Plaquenil®	Prescribers should be familiar with complete prescribing information
Infliximab	Remicade®	Serious infection risk, malignancy
Interferon alfa 2b	Intron A®	Fatal/life-threatening events
Itraconazole	Sporanox®, Onmel®	Contraindicated in ventricular dysfunction (CHF, CHF history) patients, potent CYP3A4 inhibitor
Ketoconazole	Nizoral®	Hepatotoxicity risk, potent CYP3A4 inhibitor
Levofloxacin	Levaquin®	Risk of tendon rupture and tendonitis, avoid in myasthenia gravis

Drugs Used in Dermatology With Boxed Warnings[16]*		
Drug Name	**Brand**	**Summary of boxed warning**
Methotrexate	Trexall®	Appropriate use, fetal death/congenital abnormalities, impaired drug elimination, concomitant NSAID use warning, hepatotoxicity, pulmonary toxicity, gastrointestinal toxicity, malignant lymphoma, tumor lysis syndrome, skin reactions, opportunistic infections, concomitant radiotherapy risks
Methoxsalen (8-methoxypsoralen)	Oxsoralen Ultra®, 8-MOP®, Oxsoralen lotion®	Appropriate use by experienced physicians, ocular/skin damage, skin cancer, non-interchangeable forms with other methoxsalen products
Moxifloxacin	Avelox®	Risk of tendon rupture and tendonitis, avoid in myasthenia gravis
Mycophenolate mofetil	CellCept®	Appropriate use by experienced physicians, risks in pregnancy, immunosuppressant
Norgestimate/ethinyl estradiol	Ortho Tri-Cyclen®, Ortho Tri-Cyclen Lo®	Smoking and cardiovascular events
Norelgestromin; ethinyl estradiol	Ortho Evra®	Smoking and cardiovascular events, venous thromboembolism risk, ethinyl estradiol pharmacokinetic profile
Norfloxacin	Noroxin®	Risk of tendon rupture and tendonitis, avoid in myasthenia gravis
Ofloxaxin	Floxin®	Risk of tendon rupture and tendonitis, avoid in myasthenia gravis
Pegylated IFN-alfa 2a	Pegasys®	Fatal/life-threatening events, warning with concomitant ribavirin
Pegylated IFN-alfa 2b	PEG-Intron®	Fatal/life-threatening events, warning with concomitant ribavirin
Pimecrolimus topical	Elidel®	Rare malignancies
Pimozide	Orap®	Dementia-related psychosis
Rituximab	Rituxan®	Fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, progressive multifocal leukoencephalopathy
Sirolimus	Rapamune®	Appropriate use, immunosuppressant, use not recommended in liver and lung tranplantation
Spironolactone	Aldactone®	Tumor risk
Tacrolimus topical	Protopic®	Rare malignancies
Thalidomide	Thalomid®	Restricted use through Thalomid REMS, embryo-fetal toxicity, venous thromboembolic events

*This list is not comprehensive but serves to provide a resource for commonly used dermatologic drugs with boxed warnings
Abbreviations: CHF – congestive heart failure; NSAID – nonsteroidal anti-inflammatory drug; REMS – Risk Evaluation and Mitigation Strategy

hepatotoxicity found that the labeling was highly variable and was affected by multiple factors, including recommendations made by different FDA drug review committees. In comparing drug labels with strategies for laboratory monitoring for hepatotoxicity, 12 different schedules were given for 15 drugs.[23]

Based on two national physician surveys, the FDA has recognized the need for revising the label format, and in June 2006 began a process to prioritize the positioning of information on the label. This includes placing the black box warning at the front of the prescribing information.[24]

There is no one official or central black box warning resource. Labeling information may be found in the Physicians' Desk Reference (PDR), Drugs@FDA.gov, manufacturer websites, and drug interaction databases. However, of the major drug interaction databases, Facts & Comparisons 4.0, MICROMEDEX DRUG-REAX, and Lexi-Comp Lexi-Interact, significant discrepancies in detecting boxed warning drug contraindications were found.[25] Furthermore, only half of newly discovered serious AEs are detected and documented in the PDR within 7 years after drug approval.[12] Therefore, clinicians are forced to consult a number of different sources for accurate information. The current package insert of a particular drug may be the most up-to-date and definitive resource for boxed warnings.[25]

Once a warning is added, there is no official protocol for disseminating this information to prescribers. In recent years, however, the FDA has worked to improve drug safety. In 2004, the FDA issued the Development and Use of Risk Minimization Action Plans (RiskMAP Guidance) that describes how to minimize the risks of drugs and address specific risk-related goals and objectives.[26] A new black box warning may be accompanied by "Dear Doctor" letters sent by the manufacturer, press releases, postings on the company and/or FDA websites, notices to pharmacies or inclusion in commercial pharmacy databases, and detailing by pharmaceutical representatives directly to individual practitioners.[27] There are two separate parties involved in writing and communicating these warnings. While the FDA is the regulatory government body involved, the manufacturers are primarily responsible for sending letters, making press releases, and dispatching representatives to deliver information to individual physicians. RiskMAP Guidance also suggests the use of "Reminder Systems," which involve ways to prompt providers to double-check their prescribing procedures, and "Performance-Linked Access Systems," which link drug access to laboratory results or other documentation.[26]

The Food and Drug Administration Amendments Act (FDAAA) of 2007 gave the FDA the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, for certain high-risk drugs. This may include a Medication Guide, package insert, communication plan, implementation system, and timetable for future assessment of REMS, which are required 18 months, 3 years, and seven years after initial approval.[28] Under the FDAAA, the FDA can require post-approval trials to further investigate known AEs, assess AE signals, and to further identify future AEs. The FDA can mandate approved product labeling changes based on new safety data. It also allows for monitored access to drugs with known AEs that would otherwise be unavailable.[29]

Impact and of the Boxed Warning and Liability

The FDA's goal is to protect the public from serious adverse events, while the manufacturer stands to lose substantial revenue depending on how a boxed warning impacts physicians' prescribing habits. Although a boxed warning doesn't always reduce drug sales, the FDA's intention may be just that.[30] In the year after the antihistamine terfenadine (Seldane®) received a black box warning against its use in certain settings and for particular drug-drug interactions, its sales dramatically dropped from "around $700 to $450 million."[31] Terfenadine and terfenadine-containing drugs were later permanently withdrawn from the market.[32] Some medications with boxed warnings are withdrawn from the market, while others are still commonly used, such as the TCIs. However, the TCIs continue to have associated stigma from the warning, with usage and sales never again reaching levels of their 2003-2004 peak. In fact, insurance companies and third party payors responded to the boxed warnings on TCIs by changing reimbursement rates, formulary status, and requiring pre-authorization and other obstacles to prescription.[33]

In some cases, the warning may apply only to a specific patient population. In this scenario, even though a physician is aware of the boxed warning, it may be safe to continue prescribing the drug to patients outside of that group. However, the existence of any black box warning may have more widespread and unintentional effects. Patients' concerns and fears may lead to non-adherence to the prescribed regimen. With increased patient awareness of drug labeling, physicians may have to spend additional time counseling patients who may be appropriate candidates for the drug, but who are wary of using any medication with a "black box warning." This may potentially alter physician prescribing habits. Patients may therefore be denied access to a potentially beneficial drug with a boxed warning if physicians are unwilling to prescribe it due to concern about the time needed for additional counseling or even potential liability. The physician stands to be liable with or without a defendant drug manufacturer. For example, in a 1995 case, the court determined that the black box warning was sufficient to fulfill the "learned intermediary rule," protecting the manufacturer (Hoffmann-LaRoche) from product liability by informing physicians via a black box warning of the potential birth defects caused by Accutane® (isotretinoin).[8] However, some courts have more recently ruled that the learned intermediary doctrine does not apply in the setting of direct-to-consumer advertising.[34] Furthermore, the boxed warning provides little detail about the AEs including incidence information.

More than 40% of surveyed dermatologists reported that over 20% of their atopic dermatitis patients were not adequately controlled since the boxed warning for TCIs was introduced.[35] The American Academy of Dermatology Association Task Force reported no causal proof that TCIs caused nonmelanoma skin cancer or lymphoma, and recommended their use for atopic dermatitis and other inflammatory disorders.[36] Those dermatologists who have been using alternative therapies to TCIs have resorted to chronic topical corticosteroids, systemic corticosteroids, cyclosporine, and other systemic immunosuppressive agents in addition to phototherapy.[35] These agents can

potentially pose greater risks than TCIs, particularly in light of decades of data which suggest that in transplant patients, oral calcineurin inhibitors are safer than oral systemic corticosteroids.[35]

"Greater transparency is needed in the administration and clinical application of the boxed warning."

The tumor necrosis factor-alpha (TNF-α) inhibitors are biologic agents (eg, infliximab, etanercept, and adalimumab) that are increasingly used for the treatment of psoriasis and other dermatologic diseases. A boxed warning was added to the entire class because of a potential malignancy risk based on AERS lymphoma reports in children and adolescents.[37] A recent meta-analysis of 63 randomized controlled trials and nearly 30,000 patients with rheumatoid arthritis, however, revealed no significant association between anti-TNF-α therapy and an increased risk of malignancy compared to other disease-modifying antirheumatic drugs or placebo.[38] After years of conflicting data leading up to this study, this new information may influence prescribing practices unless dermatologists rely only on the package insert given that despite this new data, the black box warning on anti-TNF-α agents remains.

Regardless of the black box warning's effect on legal liability, its intended purpose is to minimize severe adverse reactions in patients. Effective communication of new warnings to prescribers from both the FDA and manufacturers is the pivotal point in making the black box warning a successful risk management tool. The best strategy for disseminating a new black box warning is not known. Studies have shown that "Dear doctor" letters alone may have little impact on prescribing habits. These letters may be much more effective depending on their wording and whether they are accompanied by additional strategies such as media publicity.[27] The FDA is interested in improving its overall approach to this problem, and has made changes in recent years to improve physician and patient awareness of new drug information and labeling changes.[39]

Furthermore, adherence to boxed warnings is voluntary with no system of monitoring to guide use of drugs with such warnings. Ambulatory electronic health records with computerized order entry and prescribing alerts related to boxed warnings do not improve clinicians' overall adherence to boxed warnings, although do improve adherence in specific clinically important subcategories.[40] In a large study in outpatient practices, 0.7% of prescriptions (n=324,548) violated an aspect of a warning, such as a drug interaction, inappropriate patient selection, or inappropriate monitoring. This was observed to be more common in patients over 75 years old and in those with multiple prescriptions. Despite this, fewer than 1% of these events resulted in an AE.[41]

Future of the Boxed Warning

Greater transparency is needed in the administration and clinical application of the boxed warning. This was illustrated in the clinical case presented here using becaplermin. Many questions remain regarding black box warnings. For example, how well does the current system work? How do dermatologists learn about boxed warnings? How does the knowledge of a boxed warning change dermatology practice? Do dermatologists feel compelled to counsel patients more extensively before prescribing a drug with a boxed warning? Do dermatologists avoid prescribing these drugs altogether and choose alternative treatments to avoid the extra time needed for counseling and/or monitoring, or even to avoid potential liability? What is the magnitude of some of these unintentional effects of the boxed warning? What if there is no other effective alternative treatment available? Further research is needed to identify which methods of communication have the greatest impact on dermatologists' awareness of new boxed warnings as well as changes to warning data, thereby ultimately impacting patient safety.

In the context of prescribers' schedules, variable learning methods and practice styles, including use of electronic medical records and prescribing software, we would expect the "most effective" communication strategy to be a dynamic combination of multiple simultaneous and staggered outreach efforts. The ideal combination of modalities is likely to change over time, requiring frequent reevaluation and adjustment to maintain efficacy.

Disclosure

The authors have no conflicts of interest to declare.

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Editor's Note: Due to the important points raised, we thought it necessary to publish this letter as soon as possible. We hope to have a response from the FDA in an upcoming issue.