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FDA Boxed Warnings: Should Package Inserts Include Levels of Evidence?

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ABSTRACT

Many medications commonly used in dermatology come with package inserts that contain boxed warnings that are frequently not evidence-based. Boxed warnings are the most serious warnings that the US Food and Drug Administration (FDA) can issue for medications through various methods, like class labeling, despite the absence of factual, high-quality evidence. Currently, there are several medications labeled with these boxed warnings for which there is no evidence, and in many cases, there actually may exist refuting evidence. However, these warnings persist in the package inserts. This has led to much hesitancy in their use, contributing to the undertreatment, or even lack of treatment, of conditions for which these medications are efficacious. Furthermore, the negative physical and mental effects of the lack of effective treatment for patients with skin disorders are well-documented. The authors call for transparency regarding the evidence, or lack thereof, behind these boxed warnings on the part of the FDA.

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INTRODUCTION

New medications are continuously being developed for the treatment of various disorders. The US Food and Drug Administration (FDA) is the regulatory body responsible for protecting public and individual health, overseeing drug approvals, and ensuring food safety and vaccine oversight. Thus, the FDA certifies the safety, efficacy, and proper management of medications that are used in clinical care throughout the United States.

The FDA also oversees safety interventions, which include approving and revising package inserts (PIs). The PI includes information on indications, dosing, adverse effects, interactions, and safety warnings. This ensures that patients are protected by warning them of the potential adverse effects of medications when they are approved for use. However, FDA warnings can occasionally negatively impact patient care by making providers, patients, or both, hesitant to prescribe and use efficacious medications that may ultimately lead to undertreatment or a complete avoidance of a particular therapy. Frequently, FDA warnings, including the most serious boxed warnings, are not supported by clinical evidence. Making matters worse, the FDA is currently not obligated to reveal the fact that such warnings are not evidence-based. This controversial practice of issuing the most serious boxed warnings without clearly referencing the clinical or scientific evidence supporting them is relatively unique to the US FDA; the European Union (EU) and Japan do not follow this practice of issuing non-evidence-based warnings.

The following brief communication reveals this current reality in detail and communicates the authors' recommendations encouraging the FDA to be truthful and transparent about warnings that are not supported by clinical evidence.

Tacrolimus and Pimecrolimus

Boxed warnings are the most serious warnings the FDA can issue regarding a medication. However, within dermatology, there have been examples of the FDA issuing warnings with questionable scientific support, ultimately discouraging the use of many safe medications. One example is topical tacrolimus and pimecrolimus, which are FDA approved for the treatment of atopic dermatitis. Notoriously, the PIs of these medications contain boxed warnings about malignancy despite there being no human studies that support this risk being elevated with topical use. This has likely led to an increase in provider and patient hesitation and a resulting decrease in the use of these medications. Overall, this impacts clinical practices and likely contributes to the undertreatment of patients, especially amongst parents who are deciding on topical therapies for their children. After over twenty years of these medications being on the market, there remains no evidence that either contributes to an increased risk of cancer.[2] Nevertheless, the FDA has yet to retract the boxed warning about malignancy that continues to persist in PIs for these medications.

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Brodalumab

Brodalumab is another example of a medication with an FDA boxed warning that lacks scientific support. Brodalumab is an effective biologic approved approximately seven years ago for the treatment of moderate to severe plaque psoriasis. However, in a clinical trial of 4,464 patients worldwide, there were three cases of suicide, leading to a boxed warning about the increased risk of depression and suicide.[3] This also led to the burdensome requirement that physicians enroll in the FDA's Risk Evaluation and Mitigation Strategy (REMS) program when prescribing the medication. A closer evaluation of these cases of suicide in patients taking brodalumab reveals significant personal risk factors in all three cases that were present before the initiation of brodalumab. Additionally, brodalumab has a lower rate of reported suicide when compared to adalimumab, which does not have a boxed warning.[3] After approximately half a decade of worldwide use, there has only been one suicide documented in a terminal cancer patient in Japan, who may have only received one dose of brodalumab. This medication, arguably the most efficacious biologic at the time of its launch, has been severely under-utilized, likely due to this boxed warning and consequential REMS program.[4]

JAK Inhibitors

Another way the FDA justifies including boxed warnings without evidence is known as "class labeling." Through class labels, the FDA has the power to place warnings on medications that fall into the same class, even when they have a clean side effect profile with no worldwide clinical trial evidence that such risk is increased. A prime example is JAK inhibitors for atopic dermatitis, which have many boxed warnings despite clinical trials that have produced refuting evidence. Many patients and providers are reluctant to use JAK inhibitors because their PI consists of multiple boxed warnings, which include serious infections, all-cause mortality, malignancy, major adverse cardiac events, and thrombosis. Many dermatology providers are likely unaware that these boxed warnings are based on the ORAL surveillance study, which was a rheumatoid arthritis study (which contained no dermatology patients), in which tofacitinib was compared to adalimumab. Results of this study found an increased risk of serious infection, malignancy, and MACE when comparing tofacitinib to adalimumab, but this only reached statistical significance when patients who were both ≥ 65 years of age and smoked were included. After exclusion of these patients from analysis, these serious risks were quite similar between tofacitinib and adalimumab.[1,5] However, in several research studies, those treated with JAK inhibitors compared to placebo were only found to be at higher risk for herpes simplex infections.[6] In fact, a closer look at the data reveals that at week 16 of the clinical trial, those on the highest dose of JAK inhibitors for atopic dermatitis had a serious infection rate lower than those treated with placebo.[7,8] Besides herpes reactivation, none of the boxed warnings are supported by worldwide phase III clinical trial data for JAK inhibitors approved to treat AD.[1]

Additionally, even ruxolitinib the FDA-approved topical JAK inhibitor for AD and vitiligo, has these boxed warnings due to class labeling, despite acting locally and causing significantly less systemic absorption. Further, there are inconsistencies within class labeling that are not evidence-based; while topical ruxolitinib has a boxed warning, oral ruxolitinib does not.

Levels of Evidence

Dermatologists today may be hesitant to use these effective and potentially life-changing medications due to their boxed warnings. While it is of the utmost importance to prioritize patient safety and acknowledge all potential risks, ideally, the information included should be evidence-based. And if the warnings are not based on evidence, clinicians should be made aware of that fact. A useful way of considering what "evidence-based" actually means is to think about the levels of evidence. The quality of evidence depends on 1) whether a study was conducted and 2) how it was conducted. For example, prototypical level 1 evidence represents a higher quality of evidence drawn from a large-scale, randomized, placebo-controlled trial in humans.[9] In contrast, level 5 evidence, representing a lower quality of evidence, is synonymous with expert opinion only. The quality of our research influences the quality of our evidence, and it is the high-quality evidence that should be used to drive decision-making in medicine, especially when it comes to advising on serious adverse events of medications.

Recommendations

The authors are not recommending limiting the FDA's jurisdiction to issue warnings as it sees appropriate. However, for the sake of transparency, the authors recommend that the FDA clearly indicate whether boxed warnings are evidence-based, extrapolated from another medication through class labeling, or are purely speculative by explicitly stating the level of evidence that the warning is based upon. While the awareness of clinically significant risks is very important, serious warnings without evidence prevent the safe and efficacious treatment of patients with medications they desperately need if the FDA makes the clinician or the patient too hesitant to use them.

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