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Review Article

Boxed Warnings in Dermatotherapeutics

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ABSTRACT

Boxed warnings (BWs), more commonly known as 'Black Box warnings,' are safety-related warnings assigned to medications by the Food and Drug Administration of the United States of America. Adverse events of the most serious kind and new data that emerged through post-marketing surveillance are highlighted. Furthermore, they implore the physician to pay heed to other important matters such as dosing, monitoring protocols as well as probable drug interactions. In the prescribing information document for any drug, special emphasis is placed on the BW by highlighting it with a black border and placing it on the top of the list of adverse drug reactions (ADRs). Commonly prescribed systemic medications for which BWs have been issued include azathioprine, itraconazole, cyclosporine, ciprofloxacin, tofacitinib, oral retinoids and rituximab. BW related to topical calcineurin inhibitors generated a lot of debate. The issues and challenges related to BW include financial and marketing aspects, undue apprehension in the minds of physicians and patients, medicolegal aspect. The onus is on the physician to be aware of such a warning and to assess the risks versus benefits before prescribing such drugs. Participation of the physician in post-marketing surveillance is essential in knowing about previously unknown ADRs. Through this article, the idea that these BWs are not to be viewed as complete contraindications but as an important guiding tool that should not be ignored has been explored.

Keywords: Boxed warning, Janus kinase inhibitors, Omalizumab, Rituximab, Topical calcineurin inhibitors, USFDA

INTRODUCTION

The safety data of newly approved drugs are based on short-term clinical trials conducted in limited study populations. It may not be applicable to the general population at large. When the drug is used by a large number of patients and for a longer period, new data related to adverse events emerge, mostly through post-marketing surveillance. Of these newly reported adverse events, the most serious type of adverse events is highlighted as Boxed Warnings (BWs).

WHAT DOES "BOXED WARNING" MEAN?

The Food and Drug Administration which is the drug control authority of the United States of America (USFDA) issues BW (previously known as Black Box Warning) on medications.

The producer's prescribing guidelines (often referred to as the package insert) has a black border around the BW, so that it is apparent and will be immediately seen by a prescriber, who can understand the gravity of the warning. Potential hazards are listed in descending order beneath the BW in the sections labelled 'Adverse Reactions', 'Warnings and Precautions' and 'Contraindications'.

A BW applies not to one specific drug, but rather to the entire class that it belongs to, as usually the grave risk is related to the mechanism of action and its unwanted effects on the body. At present, over 400 medications have BW, while up to 20% drugs are likely to acquire

new BW or be withdrawn from the market over the next 25 years.[1,2]

BW$_S$ ARE ISSUED FOR THE FOLLOWING THREE SITUATIONS

1. When an adverse reaction is serious enough (potentially permanently disabling or fatal reactions) compared to advantages of the drug, it is necessary to assess the risk versus advantage of the drug. For example, because of the risk of anaphylaxis, iron dextran injection should be judiciously used in cases having severe anaemia not responding to oral therapy.
2. Potential grave adverse events that may be prevented or intensity can be minimised by appropriate prescribing. This can be done by keeping patient under surveillance (e.g., liver function tests for valproic acid) or judicious case selection (e.g., avoidance of angiotensin-converting enzyme [ACE] inhibitors in pregnancy).
3. Mandatory restrictions to ensure safe use. For example, in the USA, physicians must complete a certification programme before prescribing isotretinoin. Other drugs, such as chemotherapeutic agents, may be administered only in supervised or inpatient settings.[3,4]

BW AND DRUGS

According to the USFDA's official website, 462 drugs were issued BW from January 1, 2015, to January 31, 2024. Two hundred and twenty-five out of 462 BWs were further analysed in a longitudinal analysis.[5] Of 225 BW analysed, 65 were newly added, the revision was done in 151 and 9 were deleted from the list. This was done based on post-marketing studies in 78% of BW, pre-marketing studies in 19% of BW and animal studies in 2% of BW.

Going drug class wise, anticancer/immunosuppressants are the most common class for which BW is issued. This is followed by antimicrobials [Figure 1].[5]

The most common BW is related to drug addiction followed by drug hypersensitivity reactions [Figure 2].[5]

BWs related to some commonly prescribed drugs have been enlisted in Table 1.[5-9]

BWs related to various drugs prescribed commonly in Dermatology practice have been enlisted in Table 2,[10,11] with certain important ones being discussed in detail.

BW FOR DRUGS USED IN DERMATOLOGY PRACTICE

Topical calcineurin inhibitors (TCI)

In 2000 and 2001, the USFDA approved topical tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1%)

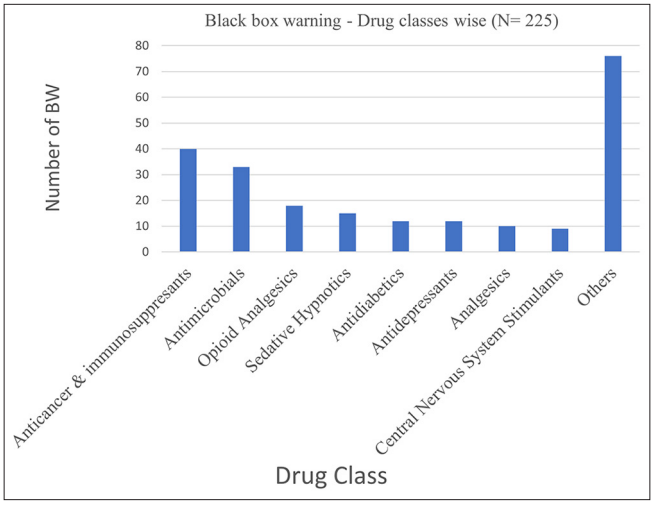

Figure 1: Boxed warning (BW) - drug classes wise (*n*=225).

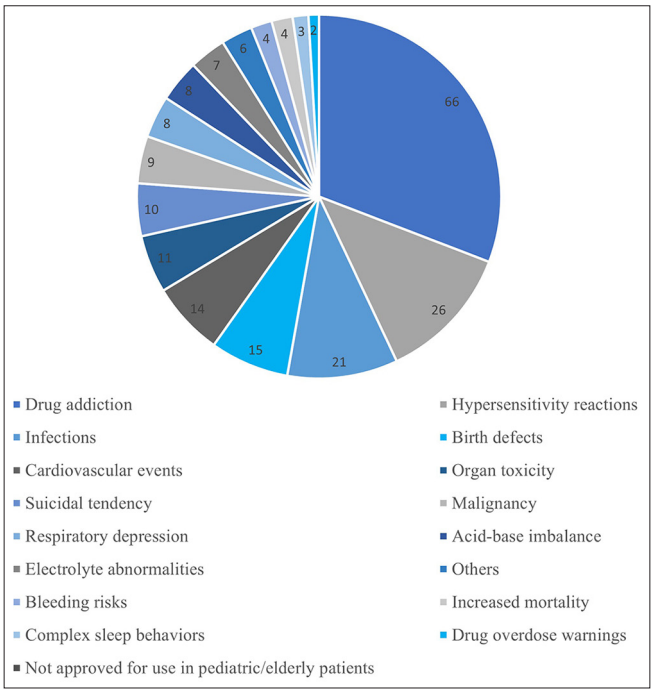

Figure 2: Types of boxed warnings.

respectively, as second-line agents for atopic dermatitis (AD) in children aged 2 years or above. By 2006, post-marketing surveillance revealed isolated case reports of heightened potential of lymphoma and cutaneous cancer, mainly in organ transplant recipients and in animal studies. However, in spite of no proof of a causal relationship, a BW was declared, mentioning that the long-term safety of TCIs had not been established.

As a result, less prescription generation from physician and cessation of its use by the patients were observed, ultimately leading to suboptimal control of AD.[12]

Table 1: Boxed warning – commonly prescribed drugs.

Drug	Summary of boxed warning
Abacavir sulphate/Lamivudine/ Azidothymidine	Haematologic toxicity, hypersensitivity reactions, lactic acidosis, myopathy and severe hepatomegaly with steatosis, Exacerbations of hepatitis B
Acetaminophen	• Hepatotoxicity, accidental ingestion, addiction, abuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome and risks from concomitant use with benzodiazepines • Majority of liver injury cases are due to acetaminophen use at higher than recommended maximum daily limits and multiple acetaminophen-containing products are usually involved. • Appropriate care should be taken while prescribing, preparing and administering injectable acetaminophen to avoid dosing errors which can lead to accidental overdose and death. • For over-the-counter use of acetaminophen, the maximum dose permissible is 325 mg per tablet, capsule or other dosage unit.
Alprazolam	Abuse, misuse, addiction, dependence, withdrawal reactions, risks from concomitant use with opioids
Aspirin	Abuse, misuse, addiction, accidental ingestion, life-threatening respiratory depression, opioid analgesic risk evaluation and mitigation strategy, neonatal opioid withdrawal syndrome
Bedaquiline fumarate	QT prolongation, increased mortality
Captopril	Foetal toxicity
Carbamazepine	• Aplastic anaemia and agranulocytosis • Serious dermatologic reactions and HLA-B* 1502 allele
Chlorpheniramine maleate	Risks when simultaneously used with benzodiazepines or other central nervous system depressants. Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children
Clonazepam	Risk when simultaneously used with opioids
Clopidogrel bisulphate	Patients with two loss-of-function alleles of the CYP2C1 9 gene (CYP2C1 9 poor metabolisers) have reduced antiplatelet effect.
Codeine phosphate	Risks when simultaneously used with benzodiazepines or other central nervous system (CNS) depressants. Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children
Diclofenac sodium	Risk of gastrointestinal events and cardiovascular events
Ethinylestradiol	Combination with hepatitis C drug leads to hepatic enzyme elevation
Febuxostat	Gout cases having cardiovascular (CV) disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol. It should be prescribed only in cases not responding or intolerant to allopurinol.
Furosemide	Fluid/electrolyte loss
Glipizide/Metformin hydrochloride	Lactic acidosis
Ibuprofen/Famotidine	Serious gastrointestinal bleeding, ulceration and perforation, serious cardiovascular thrombotic events
Iron Dextran	Anaphylactic-type reactions, Appropriate use
Isoniazid/Rifampicin	Hepatotoxicity
Levonorgestrel	Combination with hepatitis C drug leads to hepatic enzyme elevation.
Levothyroxine sodium	Not for the treatment of weight loss.
Lorazepam	Risks when simultaneously used with opioids
Montelukast sodium	Serious neuropsychiatric events, aggression, agitation, sleep disturbances, depression, suicidal thoughts and behaviour
Morphine sulphate/Naltrexone hydrochloride	Accidental ingestion, interaction with alcohol, addiction, abuse and misuse, opioid analgesic risk evaluation and mitigation strategy, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, risks when simultaneously used with benzodiazepines
Naproxen sodium	Serious gastrointestinal bleeding, ulceration and perforation, serious cardiovascular thrombotic events
Phenytoin sodium	Cardiovascular risk when rapidly infused
Propranolol hydrochloride	Cardiac ischaemia if abruptly discontinued
Tramadol hydrochloride	Addiction, abuse and misuse potential; risk of life-threatening respiratory depression
Zolpidem	Complex sleep behaviours such as sleep-walking and sleep-driving

HLA: Human leucocyte antigen

Table 2: Boxed warning – drug prescribed in dermatology practice.

Drug	Summary of boxed warning
Azathioprine	• Malignancy risk • Mutagenic potential • Haematological adverse events
Azoles • Itraconazole	• Contraindications: Congestive heart failure • Drug interactions: Increases the plasma levels of drugs such as cisapride, pimozide, levacetylmethadol, quinidine which are metabolised by CYP3A4 pathway, leading to serious cardiovascular events.
• Ketoconazole	• Serious hepatotoxicity, including life-threatening complications requiring liver transplantation. • Drug interactions: Increases the plasma levels of drugs such as cisapride, pimozide, levacetylmethadol and quinidine which are metabolised by CYP3A4 pathway, leading to serious cardiovascular events.
Botox • Abobotulinum toxin A • Onabotulinumtoxin A	• Local injection of toxin may lead to distant spread and life-threatening complications like difficulties in breathing and swallowing
Calcineurin inhibitors (topical) • Pimecrolimus (topical) • Tacrolimus (topical)	• Rare malignancies • Rare malignancies (skin and lymphoma)
Clindamycin	*Clostridioides difficile* associated diarrhoea risk
Cyclosporine in psoriasis	• To be prescribed by experienced physicians. • Risk of cutaneous malignancies increases in cases previously treated with PUVA and to a lesser degree methotrexate, other immunosuppressive agents, UVB, coal tar or radiation therapy • Systemic hypertension and nephrotoxicity can occur at the recommended dose. • With increasing dose and duration of therapy, ADRs like renal dysfunction and structural kidney damage increase. • Regular renal function monitoring is compulsory.
Doxepin	• Suicidal risk in children, adolescents and young adults
Drospirenone/ethinyl estradiol	• Avoid in smokers and in those having cardiovascular events
Fluoroquinolones ciprofloxacin, Gemifloxaci, Levofloxacin, Moxifloxacin, Norfloxacin, Ofloxacin	• Risk of tendinitis and tendon rupture, avoid in myasthenia gravis • Peripheral neuropathy, central nervous system effects are additionally reported with ciprofloxacin
Hydroxychloroquine	• Baseline assessment of visual acuity before initiating long-term therapy
Intravenous immunoglobulin	• Acute renal dysfunction/failure • Thrombosis may occur in predisposed cases
Methotrexate	• Embryo-foetal toxicity, contraindicated in pregnancy • Hypersensitivity reactions - not to be used in cases with history of such reactions • Serious ADR - Closely monitor for adverse reactions of the bone marrow, gastrointestinal tract, liver, lungs, skin and kidneys.
Methoxsalen (8-methoxypsoralen)	• Photochemotherapy (Methoxsalen with ultraviolet radiation) • It should be restricted to cases with severe, recalcitrant, disabling psoriasis which is not controlled by other modalities of treatment • It should be used only by physicians experienced in the diagnosis and treatment of psoriasis and vitiligo • It should be constantly supervised by such a physician • Detailed information regarding inherent risks such as ocular damage, aging of the skin and skin cancer (including melanoma) should be disclosed to the patient.
Mycophenolate mofetil	• Apt use by experienced dermatologists • Risks in pregnancy • Immunosuppression

(Contd...)

Table 2: *(Continued).*

Drug	Summary of boxed warning
Retinoids • Acitretin (Retinoids) • Bexarotene (Retinoids) • Isotretinoin (Retinoids)	• Apt use by experienced dermatologists. • Significant foetal anomalies. • Strict avoidance of blood donation • Alcohol avoidance • Hepatotoxicity
	• Significant foetal anomalies. Contraindicated in females not using reliable contraception while on acetretin and etretinate and for at least 3-year post-treatment • Contraindicated in pregnancy • 2 forms of effective contraception, 1 month before treatment, while on therapy and 1 month post-treatment
Rituximab	• Fatal infusion-related reactions • Tumour Lysis Syndrome • Severe mucocutaneous reactions • Hepatitis B virus reactivation • Progressive multifocal leukoencephalopathy
Sirolimus	• Immunosuppression • Not to be used in liver and lung transplant cases
Spironolactone	• Tumour risk
Thalidomide	Teratogenicity: • Severe birth defects or embryo foetal death • Pregnancy is an absolute contraindication • Pregnancy must be excluded before start of treatment, pregnancy to be prevented by the use of two reliable methods of contraception • Even a single dose taken by a pregnant woman can cause severe birth defects • Venous thromboembolic events • Cases having multiple myeloma and receiving dexamethasone concomitantly are at a greater risk of deep vein thrombosis and pulmonary embolism
Tumour necrosis factor alpha inhibitors • Adalimumab • Etanercept • Infliximab	• Serious infection risk including tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens. • Risk of infection from Legionella and Listeria • Malignancy risk
Tofacitinib (oral)	• Increased chances of blood clotting and death in cases of ulcerative colitis receiving 20 mg daily oral dose
Omalizumab	• Anaphylaxis

ADR: Adverse drug reaction, PUVA: Psoralene plus ultraviolet A radiation, UVB: Ultraviolet B radiation

Following this, a Prospective Paediatric Longitudinal Evaluation to Assess the Long-Term Safety (APPLES) of Tacrolimus Ointment for the Treatment of AD cohort of children exposed to tacrolimus ointment for AD was conducted over a period of 10 years. It was concluded that the cancer incidence was in close proximity with an age and sex-matched control population. As per APPLES, there was a lack of proof supporting the potentially heightened risk of cancer in children treated with tacrolimus ointment for AD.[13] Regardless of FDA's BW, till date, there are no published data about the heightened risk of cancer due to TCIs in either children or adults.[14]

As per the opinion of The Canadian Society of Allergy and Clinical Immunology (CSACI), advantages of TCIs should be judiciously assessed against the theoretical risks while prescribing. CSACI also accepts the need for long-term studies. TCIs are important steroid-sparing agents, not having any site or time restrictions and are free from atrophogenicity, and hence, they have a significant place in the management of chronic inflammatory dermatoses like AD.

The European Academy of Dermatology and Venereology position statement cites that the occurrence of Lymphoma in cases treated with TCI was no greater than in the general population.[15]

The basis of the warning is theoretical and not supported by epidemiological and clinical data. The American Academy of Dermatology thus opines that this warning is not necessary and is misleading. TCIs when used rationally are not dangerous.

Janus kinase (JAK) inhibitors

On the basis of post-marketing surveillance data on the safety of tofacitinib in cases of rheumatoid arthritis (RA), FDA placed BW related to the risk of venous thromboembolism (VTE) to tofacitinib label in 2019.[16]

Long-term safety data collected as a part of FDA-mandated post-marketing phase IIIb-IV study suggests that the risks of malignancy, VTE and major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction and stroke) were higher with tofacitinib as against TNF inhibitor in cases having comparable baseline co-morbidities. This prompted FDA to place a BW on all approved JAK inhibitors in 2021.

Baseline risk factors such as history of VTE, age above 65 years, smoking, hypertension or coronary artery disease and hormone replacement therapy/oral contraceptive use considerably escalate the chances of VTE or MACE in cases on JAK inhibitors.[17] The limitation of studies carried out in RA cases is that RA itself is associated with risk of MACE, VTE and malignancy.[18-21]

In dermatology practice, tofacitinib is mainly prescribed for alopecia areata (AA), vitiligo and AD. The patient population is younger and has fewer co-morbidities as compared to RA cases. Other studies have also revealed that tofacitinib use in dermatologic conditions such as AA, AD, vitiligo and psoriasis was not associated with the elevated risk of VTE provided they have no high-risk factor for the same.

The punch line is that JAK inhibitors should be used only if there is a clear indication and after meticulous screening for risk factors.

Rituximab-BW

- Infusion-related reactions (IRRs)
  - It can result in serious/life-threatening IRR, usually while administering the first infusion within 30–120 min.
  - The manifestations and sequelae of IRR include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events or death.
- Severe mucocutaneous reactions with potentially fatal outcomes
  - These reactions include paraneoplastic pemphigus, Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis and toxic epidermal necrolysis.
  - Such reactions are observed during 1–13 weeks after infusion.
- Progressive multifocal leukoencephalopathy (PML)
  - In cases having haematologic malignancies or autoimmune diseases, JC virus infection with resultant PML and death can occur. The majority of cases having haematologic malignancies and diagnosed with PML received rituximab along with other chemotherapeutic agents or as a part of haematopoietic stem cell transplant.
  - Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.
- Hepatitis B reactivation
  - It can result in fulminant hepatitis, hepatic failure and death in cases who may or may not be hepatitis B surface antigen positive.
  - It can also occur in cases who appear to have resolved hepatitis B infection.
  - It is often followed by hepatitis.
- Infections
  - Grave/life-threatening bacterial, fungal and viral (new or reactivated) infections can occur while on therapy or up to 1 year after completion of therapy. Viruses such as cytomegalovirus, herpes simplex virus, parvovirus B19, varicella-zoster virus, West Nile virus and hepatitis B and C are reported to cause infections. In cases of severe infections, discontinuation of rituximab is essential.

Omalizumab

- Receiving omalizumab can lead to anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria and/or angioedema of the throat or tongue.
- Anaphylaxis is reported not only after the first injection of omalizumab but it is also reported beyond 1 year after initiating the therapy.
- Omalizumab therapy should be instituted in a healthcare setup having facility to manage life-threatening events like anaphylaxis.
- Educate patients about the signs and symptoms of anaphylaxis and advise them to seek urgent medical care when such symptoms occur.

TAKE HOME MESSAGE

- Assess the risk v/s benefits and prescribe the drug only if benefits outweigh the risks and if the disease is not controlled by the safer alternatives.
- Counsel and educate the patient regarding potential side-effects and take informed consent.
- Follow the baseline assessment protocol before initiating the drug in question.
- Pre-medicate the patient, if recommended.

- Administer the drug safely as per the guidelines.
- Be fully aware of ADRs and identify them at the earliest.
- Be prepared with emergency measures.
- Report the ADRs to pharmacovigilance programmes.

CONCLUSION

The USFDA does not control the practice of medicine. The onus is on the prescribing physician to weigh benefit versus risk of the drug and take the decision in the best interest of the patient. BWs are not absolute contraindications for drugs, but the main purpose is to make the clinician aware about the potentially serious side effects. Nevertheless, there is no precise metric to establish when and how to apply the BW.

Multiple Choice Questions

1. Boxed warnings assigned to medications are related to:
   a) Allergic reactions
   b) Teratogenicity
   c) Carcinogenicity
   d) Most serious type of adverse events
2. What is the site of Boxed warnings on package insert?
   a) Top
   b) Centre
   c) Bottom left
   d) Bottom right
3. How many boxed warnings have been issued in the past decade by USFDA?
   a) 662
   b) 262
   c) 62
   d) 462
4. What is the basis of updating boxed warnings?
   a) Post-marketing studies
   b) Pre-marketing studies
   c) Animal studies
   d) All of the above
5. Which is most common class of medications that have been issued boxed warning?
   a) Opioid analgesics
   b) Anticancer and immunosuppressants
   c) Antimicrobials
   d) Sedative hypnotics
6. The most common boxed warning issued is related to-
   a) Drug addiction
   b) Hypersensitivity reaction
   c) Infections
   d) Cardiovascular events
7. Which of the following is the boxed warning issued for topical calcineurin inhibitors?
   a) Peripheral neuropathy
   b) Rare malignancies
   c) Thrombosis may occur in predisposed cases
   d) Hypersensitivity reactions
8. Which of the following is not a boxed warning for azathioprine?
   a) Malignancy risk
   b) Mutagenic potential
   c) Haematological adverse events
   d) Congestive heart failure
9. "*Clostridioides difficile* associated diarrhoea risk" is a boxed warning associated with which drug?
   a) Clindamycin
   b) Cyclosporine
   c) Ciprofloxacin
   d) Calcineurin inhibitors
10. "Risk of infection from Legionella and Listeria" is boxed warning associated with which drugs?
    a) Adalimumab
    b) Etanercept
    c) Infliximab
    d) All of the above

Answer key:
1 - d, 2 - a, 3 - d, 4 - d, 5 - b, 6 - a, 7 - b, 8 - d, 9 - a, 10 - d

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