BLACK BOX WARNINGS OF ANTIBIOTICS: A NARRATIVE REVIEW

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Key Points:
• Boxed Warning is important to call attention to serious or life-threatening risks.
• The physician should decide whether to prescribe a drug with a boxed warning for the patient or no
• Black box warnings for Antibiotics are mainly for Aminoglycosides and Fluoroquinolones

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INTRODUCTION:
Boxed warning, commonly referred to as a “black box warning”, appears on the labeling of drugs and is important to call attention to serious or life-threatening risks. (1) The Boxed Warning is a risk mitigation. These warnings typically concern important safety issues with a potential for main effect on public health. (2) The responsibility of the prescribers is to give the patient information about relevant risks, and also the physician should decide whether to prescribe a drug with a boxed warning for the patient or no. (3)

Fuentes, AV et al provides a comprehensive information about the top 200 drugs prescribed in the US including information regarding black box warning (4).

Ganjizadeh-Zavareh, S et al reported that the Food and Drug Administration recently call attention to the increased risk of fibromyalgia associated with fluoroquinolones use (5) The mental health side effects to be included in the labeling across all the fluoroquinolones are disturbances in attention, disorientation, agitation, nervousness, memory impairment and delirium.

Additionally, the recent FDA review found instances of hypoglycemic coma where users of fluoroquinolones experienced hypoglycemia (6). In addition to the increased the risk of psychosis in some patients (7) and the risk tendinitis and tendon rupture (8).

FDA issued more than one black box warning for fluoroquinolone antibiotics, in addition to their effects in the tendons and their psychiatric effects, they also can lead to peripheral neuropathy (7).

Dixit, D et al reported that tigecycline antibiotic was associated with increase in all-cause Mortality (9). Brenner, SM et al stated that ondansetron could increase the risk of Q wave to T wave interval Prolongation and can cause arrhythmia (10).

Kwast, LM et al reported that one of the important causes of drug withdrawals and black box warnings is the immune-mediated drug hypersensitivity reactions (11). O’Connor, NR reported that many medications such as fluoroquinolones, salmetrol and oral sodium phosphate bowel preparation remain available treatment despite the black box warning of these medications, so it is the responsibility of physicians to decide whether to use these drugs or no (12) another study also showed the severe adverse effects of fluoroquinolones that for some medications lead to drug withdrawal such as the recent withdrawal of gatifloxacin due to dysglycemia (13). Moreover, the FDA advises the doctors to weigh the benefits and risks of fluoroquinolones because it can lead to serious adverse effects such as hallucinations, convulsions, torsade de points, clostridium difficile associated diarrhea and other effects (14).

Methodology
FDA mandates black box warning for many antibiotics. The first part of searching consist of searching Micromedex (15) for the medications under the category of "antibiotics" and found if there are black box warnings for these antibiotics or no. Then they were separated according to the category and finally the most common adverse effects or complications of antibiotics that call attention to serious risks were found.

The second part includes searching Web of Science (16) using the topic "antibiotics black box warning" without limitations.

RESULTS AND DISCUSSION:
Black box warnings are firmest labeling requirements that the FDA can command for prescription drugs. Generally, black box warnings are not certainly complete contraindications, but the health care providers should be aware of these safety worries when advising patients. In order to counsel patients, medication experts (pharmacists) should be familiar with the common black box warnings of the drugs. (17)

Searching Micromedex for antibiotics there are 123 antibiotics. Out of these antibiotics, the FDA issued black box warning for 30 medications (24.39%). The medications with FDA black box warning are showed in Table 1.
Black box warnings for antibiotics are mainly issued for aminoglycosides and fluoroquinolones. No any warning for tetracycline antibiotics; no any warning for cephalosporin antibiotics, there are warning to two macrolides and warning for one penicillin (penicillin G benzathine either alone or combined).

<table>
<thead>
<tr>
<th>Penicillin</th>
<th>Macrolides</th>
<th>Fluoroquinolone</th>
<th>Aminoglycoside</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G Benzathine</td>
<td>Erythromycin Telithromycin</td>
<td>Ciprofloxacin Delafloxacin Gemifloxacin Levofoxacin Moxifloxacin Norfloxacin Ofloxacin</td>
<td>Amikacin Gentamicin Kanamycin Neomycin Plazomicin Streptomycin Tobramycin</td>
<td>Bacitracin Bleomycin Chloramphenicol Clindamycin Lincomycin Metronidazole Mitomycin Polymyxin B Telavancin Tigecycline Tinidazole Trimetrexate</td>
</tr>
<tr>
<td>Penicillin G benzathine combined with Penicillin G Procaine</td>
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</table>

Aminoglycoside such as amikacin, gentamicin, kanamycin, neomycin, plazomicin, tobramycin and streptomycin should be used carefully because of the possible toxicity related to their use especially neurotoxicity, nephrotoxicity, and ototoxicity. In addition to an amplified risk of respiratory adverse reactions that can be result as a consequence of amikacin liposome use.

Fluoroquinolones, including ciprofloxacin, delafloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin, are associated with disabling and potentially long-lasting severe adverse reactions that have occurred together, including tendinitis, tendon rupture, peripheral neuropathy, and CNS effects.

Black box warnings for penicillin antibiotics consist of warning only for penicillin G benzathine either alone or combined with penicillin G procaine which should not be administered intravenously or admix with other intravenous solutions. Unplanned intravenous administration of penicillin G benzathine may result in cardiorespiratory arrest and death.

Black box warnings for macrolides include warning for erythromycin and telithromycin. Erythromycin estolate oral suspension should not be used for patients with a identified past history of sensitivity to this drug and for those with established liver disease. telithromycin can cause fatal and life-threatening respiratory failure.

Black box warnings for other antibiotics include:

Bacitracin: bacitracin can cause renal failure

Bleomycin: bleomycin can cause pulmonary fibrosis.

Chloramphenicol: chloramphenicol can cause serious and fatal blood dyscrasias.

Clindamycin Hydrochloride: clindamycin can lead to clostridium difficile associated diarrhea.

Lincomycin Hydrochloride: lincomycin can lead to clostridium difficile associated diarrhea.

Metronidazole: metronidazole should be used only when urgently required, it has been shown to be carcinogenic in mice and rats.

Mitomycin: mitomycin can cause bone marrow suppression and hemolytic uremic syndrome

Polymyxin B: polymyxin B can lead to neurotoxic reactions specially in patients with impaired renal function and/or nephrotoxicity.

Telavancin: telavancin may result in renal impairment

Tigecycline: tigecycline may lead to increase in all-cause mortality

Tinidazole: carcinogenicity has not been reported for tinidazole, nevertheless, unnecessary use of tinidazole should be avoided.

Trimetrexate: trimetrexate may lead to potentially serious or life-threatening toxicities, it must be used with leucovorin to avoid toxicity.

There are many adverse reactions that result in these black box warnings. Table 2 showed the main...
adverse reactions that result in these black box warnings.

Table 2. The main adverse reactions that result in these black box warnings

<table>
<thead>
<tr>
<th>Cardiovascular adverse reactions</th>
<th>Penicillin G Benzathine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological adverse reactions</td>
<td>Chloramphenicol, Mitomycin</td>
</tr>
<tr>
<td>Respiratory adverse reactions</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Aminoglycoside, Bacitracin, Polymyxin B, Telavancin</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Aminoglycoside, Fluoroquinolones, Polymyxin B</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>Aminoglycoside</td>
</tr>
<tr>
<td>Tendon rupture</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Gastrointestinal adverse reactions</td>
<td>Macrolides, Clindamycin, Lincomycin</td>
</tr>
<tr>
<td>Carcenogenic</td>
<td>Metronidazole, Tinidazole</td>
</tr>
<tr>
<td>An increase in all-cause mortality</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Others</td>
<td>Trimetrexate</td>
</tr>
</tbody>
</table>

CONCLUSION:
The major adverse reactions for warning include nephrotoxicity, neurotoxicity, gastrointestinal adverse reaction and ototoxicity.

It is the responsibility of the prescriber to educate the patient about serious adverse reactions and it is prescriber responsibility to weigh benefits and risks and to determine if the patient should take these medications or no according to patient case. If the patient take these medications he should know the important information about the drug, and the prescriber show follow the patient status continuously.

REFERENCES:
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