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Review Article

# Strategies for the Prescription of Psychotropic Drugs with Black Box Warnings

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**Background:** *The Black Box Warning (BBW) is the Food and Drug Administration's highest level of drug warning. It signifies that a medication has serious (or potentially life-threatening) side effects and is prominently displayed on a medication's package insert. It literally consists of the medication warning and is surrounded by a bold black border.* **Objective:** *This article aims to review data related to BBWs on psychotropic medications currently used in clinical practice, with special attention to clinical situations and questions relevant to consultation-liaison psychiatrists.* **Results:** *We review 3 clinical advisories or BBWs for psychotropic medications (i.e., antidepressant medication and suicidality in the pediatric population, stimulant medication and sudden death in the pediatric population, and antipsychotic medication and increased mortality in the elderly) and discuss the effect they have had on prescribing practices. We provide a table of current BBWs relevant to psychotropic medications.* **Conclusions:** *BBWs can have unintended and far-reaching consequences, albeit with a limited ability to target specific populations and practice patterns. Although it is critical for clinicians to be aware of these serious potential side effects and to inform patients about these warnings, medications with boxed warnings remain Food and Drug Administration-approved and may have critically important therapeutic roles.*

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The Black Box Warning (BBW) is the most serious labeling change that the Food and Drug Administration (FDA) can issue. BBWs are intended to be a safety tool, created to communicate potentially serious safety information about a particular medicine. Usually, the BBW is located at the beginning of the labeling with a rectangle surrounding its boldface text, so that it stands out and is readily seen by a prescriber. To put it simply, it is a way to urge physicians to carefully consider the risks and benefits before prescribing a drug that has a potentially disabling or fatal reaction.

Most psychotropics in current use carry a boxed warning (Table); several psychotropics have more than 1 BBW (e.g., clozapine has 5 and valproic acid has 3). As the FDA has reached out beyond providers to the general public to publicize BBWs, it is increasingly common for physicians to encounter questions from patients about serious medication risks before definitive information is available.[1] The psychiatrist who tries to prescribe "around" boxed warnings would work from a vastly reduced pharmacopeia (e.g., buspirone, gabapentin, oxcarbazepine, and benzodiazepines), which could hamper effective care. Therefore, consultants who practice psychosomatic medicine are mindful of, but not paralyzed by, these warnings.

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**TABLE. Black Box Warnings on Available* Psychotropic Medications**

| FDA boxed warnings | Drug classes or medications included |
|---|---|
| Suicidal thinking and behavior in children and adolescents | All selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), atomoxetine, quetiapine, and aripiprazole |
| Subject to misuse, abuse, addiction, or diversion | All methylphenidates and amphetamines |
| Misuse may cause serious cardiovascular adverse events and sudden death | All amphetamines |
| Increased risk of death in elderly patients with dementia-related psychosis | All first-generation (typical) and second-generation (atypical) antipsychotics |
| Aplastic anemia | Carbamazepine |
| Agranulocytosis | Clozapine and carbamazepine |
| Myocarditis | Clozapine |
| Orthostatic hypotension | Clozapine |
| Seizures | Clozapine and flumazenil |
| Stevens-Johnson Syndrome | Lamotrigine |
| Lithium toxicity | Lithium |
| Pancreatitis | Valproic acid |
| Teratogenicity | Valproic acid |
| Hepatotoxicity | Naltrexone, dantrolene, and valproic acid |
| QTc prolongation; Torsades de Pointes | Thioridazine, mesoridazine, and droperidol |
| Life-threatening thyroid toxicity; ineffective for weight reduction | Levothyroxine |
| Certified programs only | Methadone |
| Contraindicated during alcohol intoxication; needs patient's full knowledge | Disulfiram |
| Respiratory depression | Midazolam |

* Does not include psychotropics already withdrawn from the market because of safety concerns (e.g., pemoline, nefazodone, or propoxyphene).

Psychiatrists today face the conundrum of how to responsibly prescribe FDA-approved medicines that are needed by often vulnerable patient populations in the face of FDA warnings about drug safety. What does a clinician have to do when he/she learns that a medication he/she prescribes has received a BBW? Specifically, what does a clinician have to discuss with a patient about a drug with a BBW? How should one respond when an adverse event occurs after prescribing a drug with a BBW? And, in such a case, what liability might there be? These questions frame our discussion of an attempt to generate a strategy for the prescription of drugs with BBWs in general, and psychotropics in particular. To this end, we review 3 BBWs for psychotropic medications and discuss the effect they have had on prescribing practices. We also provide a reference table of BBWs relevant to psychotropic medications.

## WHAT DOES IT TAKE FOR THE FDA TO LABEL A DRUG WITH A BBW?

Imposing a BBW has significant ramifications for product liability. Within the section dealing with warnings, the Code of Federal regulations[2] states:

> Labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved…Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. 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.

After a drug is approved, and so as to monitor its safety, the FDA seeks a commitment from the pharmaceutical company to conduct specific postmarketing clinical trials (phase 4 studies). Established in 1969 as a postmarketing surveillance tool, the Adverse Event Reporting System (AERS) detects previously unidentified adverse drug events that often occur.[3] The AERS is a computerized database that combines the voluntary adverse drug reaction reports submitted to the FDA by health care professionals to the MedWatch program with the mandatory reports from