BLACK-BOX WARNINGS:

How they can improve your clinical practice

A better understanding of these warnings leads to safer, more effective prescribing

Matthew A. Schreiber, MD, PhD
Staff Psychiatrist
Puget Sound VA Health Care System
Seattle, Washington
Assistant Professor
Department of Psychiatry and Behavioral Sciences
University of Washington School of Medicine
Seattle, Washington

Michelle Wiese, MD, MPH
PGY-3 Psychiatry Resident
University of Washington School of Medicine
Seattle, Washington

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Recently, the FDA issued "black-box" warnings, its most prominent drug safety statements, for esketamine,[1] which is indicated for treatment-resistant depression, and the Z-drugs, which are indicated for insomnia[2] (***Table 1, page 20***). A black-box warning also comes with brexanolone, which was recently approved for postpartum depression.[3] While these newly issued warnings serve as a timely reminder of the importance of black-box warnings, older black-box warnings also cover large areas of psychiatric prescribing, including all medications indicated for treating psychosis or schizophrenia (increased mortality in patients with dementia), and all psychotropic medications with a depression indication (suicidality in younger people).

In this article, we help busy prescribers navigate the landscape of black-box warnings by providing a concise review of how to use them in clinical practice, and where to find information to keep up-to-date.

What are black-box warnings?

A black-box warning is a summary of the potential serious or life-threatening risks of a specific prescription medication. The black-box warning is formatted within a black border found at the top of the manufacturer's prescribing information document (also known as the package insert or product label). Below the black-box warning, potential risks appear in descending order in sections titled "Contraindications," "Warnings and Precautions," and "Adverse Reactions."[4] The FDA issues black-box warnings either during drug development, to take effect

WEB EXCLUSIVES

More on black-box warnings

Supplemental tables summarizing the indications, off-label uses, and common adverse effects of:

- first-generation antipsychotics
- second-generation antipsychotics
- antidepressants
- mood stabilizers
- other psychotropic medications

ADAM NIKLEWICZ

Black-box warnings

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The FDA issues a black-box warning based upon its judgment of the seriousness of the adverse effect

Table 1

Recent black-box warnings for psychotropic medications

Medication(s)	Year issued	Black-box warning	Comments
Brexanolone	2019	Excess sedation Risk of sudden loss of consciousness	REMS with ETASU associated with warning, includes administration in specific care settings only (for monitoring)
Zolpidem Eszopiclone Zaleplon	2019	Sleep behaviors, possibly resulting in death	Single, specific adverse effect for a class of drugs (Z-drugs for insomnia)
Esketamine	2019	Sedation and dissociation Abuse and misuse Increased risk of suicide in younger patients	Multiple adverse effects and misuse potential for a single drug; REMS with ETASU associated with warning
Pimavanserin	2016	Increased risk of death in geriatric patients with dementia	Single, specific adverse effect for an entire class of drugs (all antipsychotics), but with an exception for Parkinson's disease psychosis specific to pimavanserin

ETASU: elements to assure safe use; REMS: Risk Evaluation and Mitigation Strategy

upon approval of a new agent, or (more commonly) based on post-marketing safety information,[5] which the FDA continuously gathers from reports by patients, clinicians, and industry.[6] Federal law mandates the existence of black-box warnings, stating in part that, "special problems, particularly those that may lead to death or serious injury, may be required by the [FDA] to be placed in a prominently displayed box" (21 CFR 201.57(e)).

When is a black-box warning necessary?

The FDA issues a black-box warning based upon its judgment of the seriousness of the adverse effect. However, by definition, these risks do not inherently outweigh the benefits a medication may offer to certain patients. According to the FDA,[7] black-box warnings are placed when:

- an adverse reaction so significant exists that this potential negative effect must be considered in risks and benefits when prescribing the medication
- a serious adverse reaction exists that can be prevented, or the risk reduced, by appropriate use of the medication
- the FDA has approved the medication with restrictions to ensure safe use.

Table 2 (*page 21*) shows examples of scenarios where black-box warnings have been issued.[8] Black-box warnings may be placed on an individual agent or on an entire class of medications. For example, both antipsychotics and antidepressants have class-wide warnings. Finally, black-box warnings are not static, and their content may change; in a study of black-box warnings issued from 2007 to 2015, 29% were entirely new, 32% were considered major updates to existing black-box warnings, and 40% were minor updates.[5]

Critiques of black-box warnings focus on the absence of published, formal criteria for instituting such warnings, the lack of a consistent approach in their content, and the infrequent inclusion of any information on the relative size of the risk.[9] Suggestions for improvement include offering guidance on how to implement the black-box warnings in a patient-centered, shared decision-making model by adding evidence profiles and implementation guides.[10] Less frequently considered, black-box warnings may be discontinued if new evidence demonstrates that the risk is lower than previously appreciated; however, similarly to their placement, no explicit criteria for the removal of black-box warnings have been made public.[11]

Table 2

Examples of categories addressed by psychotropic black-box warnings

Category	Examples of black-box warnings
A subset of patients is at elevated risk for severe adverse effects	Teratogenesis for pregnant patients with valproate Serious dermatologic reactions for patients with the HLA-B*1502 allele (highest risk with Asian ancestry) with carbamazepine
A drug or food interaction can result in critical safety issues	Food interaction: dietary tyramine with MAOI (tranylcypromine) resulting in hypertensive crisis Drug interaction: SSRI, SNRI, linezolid, methylene blue, phenylephrine and other medications, with MAOI (tranylcypromine)
Monitoring can provide early detection of a severe adverse effect	Toxicity with lithium Severe neutropenia with clozapine Hepatotoxicity with valproate
Behavioral risk for all patients	Risk of misuse and dependence with stimulants

MAOI: monoamine oxidase inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

When a medication poses an especially high safety risk, the FDA may require the manufacturer to implement a Risk Evaluation and Mitigation Strategy (REMS) program. These programs can describe specific steps to improve medication safety, known as elements to assure safe use (ETASU).[4] A familiar example is the clozapine REMS. In order to reduce the risk of severe neutropenia, the clozapine REMS requires prescribers (and pharmacists) to complete specialized training (making up the ETASU). Surprisingly, not every medication with a REMS has a corresponding black-box warning[12]; more understandably, many medications with black-box warnings do not have an associated REMS, because their risks are evaluated to be manageable by an individual prescriber's clinical judgment. Most recently, esketamine carries both a black-box warning and a REMS. The black-box warning focuses on adverse effects (***Table 1, page 20***), while the REMS focuses on specific steps used to lessen these risks, including requiring use of a patient enrollment and monitoring form, a fact sheet for patients, and health care setting and pharmacy enrollment forms.[13]

Psychotropic medications and black-box warnings

Psychotropic medications have a large number of black-box warnings.[14] Because it is difficult to find black-box warnings for multiple medications in one place, we have provided 2 convenient resources to address this gap: a concise summary guide (***Table 3, page 22***) and a more detailed database (***Table 4***, ***Table 5***, ***Table 6***, ***Table 7***, and ***Table 8***, available at MDedge.com/psychiatry). In these Tables, the possible risk mitigations, off-label uses, and monitoring are not meant to be formal recommendations or endorsements but are for independent clinician consideration only.

The information in these Tables was drawn from publicly available data, primarily the Micromedex and FDA web sites (see ***Related Resources, page 25***). Because this information changes over time, at the end of this article we suggest ways for clinicians to stay updated with black-box warnings and build on the information provided in this article. These tools can be useful for day-to-day clinical practice in addition to studying for professional examinations. The following are selected high-profile black-box warnings.

Antidepressants and suicide risk. As a class, antidepressants carry a black-box warning on suicide risk in patients age ≤24. Initially issued in 2005, this warning was extended in 2007 to indicate that depression itself is associated with an increased risk of suicide. This black-box warning is used

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Black-box warnings may be placed on an individual agent or on an entire class of medications

Black-box warnings

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There are no published, formal criteria for instituting black-box warnings

Table 3

Quick guide to black-box warnings for psychotropic medications

Black-box warning	Medication(s)	Possible risk mitigation
Increased risk of death in elderly patients with dementia-related psychosis	All antipsychotics, except when pimavanserin is used for Parkinson's disease-related psychosis	Shared decision-making with patient/family/caregivers
Severe sedation (including coma) after injection; must observe for 3 hours	Extended-release olanzapine	Risk and benefit discussion with patient; REMS
Aplastic anemia and agranulocytosis	Carbamazepine	Baseline CBC; CBC after drug initiation and at intervals as clinically indicated; monitor WBC and platelet count in particular
Severe neutropenia	Clozapine	Absolute neutrophil count monitoring; REMS
QTc prolongation leading to possible Torsades de Pointes	Droperidol Thioridazine	Baseline ECG; if inpatient, telemetry if available; assess for other QT prolongation risks
Myocarditis	Clozapine	Symptom discussion with patient, frequent check-ins, consider baseline ECG
Orthostatic hypotension	Clozapine	Symptom discussion with patient; baseline orthostatics
Seizures	Clozapine	Consider seizure disorder history; use lowest effective dose (dose-dependent)
Serious and sometimes fatal dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis)	Carbamazepine Lamotrigine	Symptom discussion with patient to stop medication if rash; discussion about medication adherence and risk; patients with HLA-B*1502 alleles should not be treated with carbamazepine; check for allele in patients with Asian ancestry
Hepatotoxicity	Valproate Naltrexone	Risk and symptom discussion with patient; baseline LFTs; LFTs after medication initiation and at intervals as clinically indicated
Pancreatitis	Valproate	Symptom discussion with patient, lab monitoring as clinically indicated
Teratogenicity	Valproate	Discussion of teratogenic risk vs clinical benefit in pregnancy; review of pregnancy prevention; pregnancy screen prior to medication initiation; pregnancy screens as clinically indicated
Suicidality in adolescents and young adults	All antidepressants Aripiprazole Atomoxetine Brexipiprazole Quetiapine	Shared decision-making with patient/parents; frequent follow-up upon initiation of medication
Suicidal thoughts and behaviors	Esketamine	REMS; shared decision-making with patient; frequent clinical contact
Sedation and dissociation	Esketamine	Shared decision-making with patient; information sheet, monitoring, REMS
Hypertensive crisis in combination with foods containing tyramine	Tranylcypromine (although potentially relevant to all MAOIs)	Nutrition review with patient; discussion of dietary restrictions; possible consultation with nutritionist
Thyroid toxicity (not to be used for weight loss/obesity)	Levothyroxine	Symptom discussion with patient; baseline TSH level; repeat TSH levels as clinically indicated
Subject to abuse, misuse, addiction, diversion	Methylphenidates Amphetamines Esketamine	Shared decision-making with patient/parents; frequent follow-ups; monitor for misuse or diversion; UDS as indicated

Table 3 continued

Black-box warning	Medication(s)	Possible risk mitigation
Misuse may cause serious cardiovascular adverse events and sudden death	Amphetamines	Shared decision-making with patient/parents; review and discuss cardiovascular risk
Contraindicated during alcohol intoxication; requires patient's full knowledge	Disulfiram	Risk discussion with patient focused on concomitant alcohol use; involve family/relatives in shared decision-making if possible
Respiratory depression; added risk with benzodiazepine/CNS depressants	Methadone	Shared decision-making with patient; available for prescribing through certified programs only
Complex sleep behaviors, some resulting in injury or death	Zaleplon Eszopiclone Zolpidem	Risk discussion with patient focused on dangers of sleep behaviors; advise patient to disclose to prescriber urgently if these occur
Excess sedation, sudden loss of consciousness	Brexanolone	Shared decision-making, monitoring, REMS program; administered in monitored setting only

CBC: complete blood count; ECG: electrocardiogram; LFTs: liver function tests; MAOIs: monoamine oxidase inhibitors; REMS: Risk Evaluation and Mitigation Strategy; TSH: thyroid-stimulating hormone; UDS: urine drug screen; WBC: white blood cell

Source: Micromedex (www.micromedex.com) and the FDA (www.fda.gov/drugs). Possible risk mitigations are not meant to be formal recommendations or endorsements but are for independent clinician consideration only

for an entire class of medications as well as for a specific patient population (age ≤24). Moreover, it indicates that suicide rates in patients age >65 were lower among patients using antidepressants.

Among psychotropic medication black-box warnings, this warning has perhaps been the most controversial. For example, it has been suggested that this black-box warning may have inadvertently increased suicide rates by discouraging clinicians from prescribing antidepressants,[15] although this also has been called into question.[16] This black-box warning illustrates that the consequences of issuing black-box warnings can be very difficult to assess, which makes their clinical effects highly complex and challenging to evaluate.[14]

Antipsychotics and dementia-related psychosis. This warning was initially issued in 2005 for second-generation antipsychotics and extended to first-generation antipsychotics in 2008. Antipsychotics as a class carry a black-box warning for increased risk of death in patients with dementia (major neurocognitive disorder). This warning extends to the recently approved antipsychotic pimavanserin, even though this agent's proposed mechanism of action differs from that of other antipsychotics.[17] However, it specifically allows for use in Parkinson's disease psychosis, which is pimavanserin's indication.[18] In light of recent research suggesting pimavanserin is effective in dementia-related psychosis,[19] it bears watching whether this agent becomes the first antipsychotic to have this warning removed.

This class warning has had widespread effects. For example, it has prompted less use of antipsychotics in nursing home facilities, as a result of stricter Centers for Medicare and Medicaid Services regulations[20]; overall, there is some evidence that there has been reduced prescribing of antipsychotics in general.[21] Additionally, this black-box warning is unusual in that it warns about a specific off-label indication, which is itself poorly supported by evidence.[21] Concomitantly, few other treatment options are available for this clinical situation. These medications are often seen as the only option for patients with dementia complicated by severe behavioral disturbance, and thus this black-box warning reflects real-world practices.[14]

continued

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REMS programs describe specific steps to improve medication safety, known as elements to assure safe use

Black-box warnings

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As a class, antidepressants carry a black-box warning for suicide risk in patients age ≤24

Varenicline and neuropsychiatric complications. The withdrawal of the black-box warning on potential neuropsychiatric complications of using varenicline for smoking cessation shows that black-box warnings are not static and can, though infrequently, be removed as more safety data accumulates.[11] As additional post-marketing information emerged on this risk, this black-box warning was reconsidered and withdrawn in 2016.[22] Its withdrawal could potentially make clinicians more comfortable prescribing varenicline and in turn, help to reduce smoking rates.

How to use black-box warnings

To enhance their clinical practice, prescribers can use black-box warnings to inform safe prescribing practices, to guide shared decision-making, and to improve documentation of their treatment decisions.

Informing safe prescribing practices. A prescriber should be aware of the main safety concerns contained in a medication's black-box warning; at the same time, these warnings are not meant to unduly limit use when crucial treatment is needed.[14] In issuing a black-box warning, the FDA has clearly stated the priority and seriousness of its concern. These safety issues must be balanced against the medication's utility for a given patient, at the prescriber's clinical judgment.

Guiding shared decision-making. Clinicians are not required to disclose black-box warnings to patients, and there are no criteria that clearly define the role of these warnings in patient care. As is often noted, the FDA does not regulate the practice of medicine.[6] However, given the seriousness of the potential adverse effects delineated by black-box warnings, it is reasonable for clinicians to have a solid grasp of black-box warnings for all medications they prescribe, and to be able to relate these warnings to patients, in appropriate language. This patient-centered discussion should include weighing the risks and benefits with the patient and educating the patient about the risks and strategies to mitigate those risks. This discussion can be augmented by patient handouts, which are often offered by pharmaceutical manufacturers, and by shared decision-making tools. A proactive discussion with patients and families about black-box warnings and other risks discussed in product labels can help reduce fears associated with taking medications and may improve adherence.

Improving documentation of treatment decisions. Fluent knowledge of black-box warnings may help clinicians improve documentation of their treatment decisions, particularly the risks and benefits of their medication choices. Fluency with black-box warnings will help clinicians accurately document both their awareness of these risks, and how these risks informed their risk-benefit analysis in specific clinical situations.

Despite the clear importance the FDA places on black-box warnings, they are not often a topic of study in training or in postgraduate continuing education, and as a result, not all clinicians may be equally conversant with black-box warnings. While black-box warnings do change over time, many psychotropic medication black-box warnings are long-standing and well-established, and they evolve slowly enough to make mastering these warnings worthwhile in order to make the most informed clinical decisions for patient care.

Keeping up-to-date

There are practical and useful ways for busy clinicians to stay up-to-date with black-box warnings. Although these resources exist in multiple locations, together they provide convenient ways to keep current.

The FDA provides access to black-box warnings via its comprehensive database, DRUGS@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/). Detailed information about REMS (and corresponding ETASU and other information related to REMS programs) is available at REMS@FDA (https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm). Clinicians can make safety reports that may contribute to FDA decision-making on black-box warnings

by contacting MedWatch (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program), the FDA's adverse events reporting system. MedWatch releases safety information reports, which can be followed on Twitter @FDAMedWatch. Note that FDA information generally is organized by specific drug, and not into categories, such as psychotropic medications.

BlackBoxRx (www.blackboxrx.com) is a subscription-based web service that some clinicians may have access to via facility or academic resources as part of a larger FormWeb software package. Individuals also can subscribe (currently, $89/year).

Micromedex (www.micromedex.com), which is widely available through medical libraries, is a subscription-based web service that provides black-box warning information from a separate tab that is easily accessed in each drug's information front page. There is also an alphabetical list of black-box warnings under a separate tab on the Micromedex landing page.

ePocrates (www.epocrates.com) is a subscription-based service that provides extensive drug information, including black-box warnings, in a convenient mobile app.

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continued

Related Resources

- US Food and Drug Administration. DRUGS@FDA: FDA-approved drug products. www.accessdata.fda.gov/scripts/cder/daf/.
- US Food and Drug Administration. Drug safety and availability. www.fda.gov/drugs/drug-safety-and-availability. Updated October 10, 2019.
- BlackBoxRx. www.blackboxrx.com. (Subscription required.)
- Mircromedex. www.micromedex.com. (Subscription required.)
- ePocrates. www.epocrates.com. (Subscription required.)

Drug Brand Names

Amitriptyline • Elavil, Vanatrip
Amoxatine • Strattera
Amoxapine • Asendin
Aripiprazole • Abilify
Asenapine • Saphris
Brexanolone • Zulresso
Brexpiprazole • Rexulti
Bupropion • Wellbutrin
Carbamazepine • Tegretol
Cariprazine • Vraylar
Chlorpromazine • Thorazine
Citalopram • Celexa
Clomipramine • Anafranil
Clozapine • Clozaril
Desipramine • Norpramin
Desvenlafaxine • Pristiq
Dexmethylphenidate • Focalin
Dextroamphetamine/amphetamine • Adderall
Disulfiram • Antabuse
Doxepin • Prudoxin, Silenor
Droperidol • Inapsine
Duloxetine • Cymbalta
Escitalopram • Lexapro
Esketamine • Spravato
Eszopiclone • Lunesta
Fluoxetine • Prozac
Fluphenazine • Prolixin
Fluvoxamine • Luvox
Haloperidol • Haldol
Iloperidone • Fanapt
Imipramine • Tofranil
Isocarboxazid • Marplan
Lamotrigine • Lamictal
Levomilnacipran • Fetzima
Levothyroxine • Synthroid
Linezolid • Zyvox
Lisdexamfetamine • Vyvanse
Lithium • Eskalith, Lithobid
Loxapine • Loxitane
Lurasidone • Latuda
Maprotiline • Ludiomil
Methadone • Dolophine, Methadose
Methylphenidate • Ritalin, Concerta
Midazolam • Versed
Milnacipran • Savella
Mirtazapine • Remeron
Naltrexone • Revia, Vivitrol
Nefazodone • Serzone
Nortriptyline • Aventyl, Pamelor
Olanzapine • Zyprexa
Paliperidone • Invega
Paroxetine • Paxil
Perphenazine • Trilafon
Phenelzine • Nardil
Pimavanserin • Nuplazid
Prochlorperazine • Compro
Protriptyline • Vivactil
Quetiapine • Seroquel
Risperidone • Risperdal
Selegiline • Emsam
Sertraline • Zoloft
Thioridazine • Mellaril
Thiothixene • Navane
Tranylcypromine • Parnate
Trazodone • Desyrel, Oleptro
Trifluoperazine • Stelazine
Trimipramine • Surmontil
Valproate • Depakote
Varenicline • Chantix, Wellbutrin
Vilazodone • Viibryd
Venlafaxine • Effexor
Vortioxetine • Trintellix
Zaleplon • Sonata
Ziprasidone • Geodon
Zolpidem • Ambien

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As a class, antipsychotics carry a black-box warning for increased risk of death in patients with dementia

Bottom Line

Black-box warnings are the most prominent drug safety warnings issued by the FDA. Many psychotropic medications carry black-box warnings that are crucial to everyday psychiatric prescribing. A better understanding of black-box warnings can enhance your clinical practice by informing safe prescribing practices, guiding shared decision-making, and improving documentation of your treatment decisions.

Black-box warnings

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Black-box warnings are not static and can, although infrequently, be removed as more safety data accumulates

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Table 4

Black-box warnings for first-generation antipsychotics

Black-box warning: *Elderly patients with dementia-related psychosis treated with antipsychotic medications are at an increased risk of death*

Medication	Labeled indication(s)	Off-label use(s)	Common adverse effects
Chlorpromazine	Behavioral problems Bipolar disorder Hiccups Hyperactivity in children Nausea/vomiting Acute intermittent porphyria Psychotic disorders Restlessness and apprehension prior to surgery Tetanus (adjunctive)	Nausea/vomiting of pregnancy Psychosis/agitation associated with dementia	EPS Sedation QTc prolongation
Droperidol[a]	Postoperative nausea/ vomiting	Acute undifferentiated agitation	QTc prolongation Hypotension Sedation EPS
Fluphenazine	Psychotic disorders	Chorea of Huntington's disease Chronic tic disorders Psychosis/agitation associated with dementia	EPS
Haloperidol	Schizophrenia Tourette's disorder Behavioral disorders Hyperactivity	Hyperactive delirium Chemotherapy-induced nausea/vomiting Postoperative nausea/ vomiting Chorea of Huntington's disease OCD Psychosis/agitation associated with dementia Rapid tranquilization	QTc prolongation (especially IV formulation) EPS
Loxapine	Schizophrenia Agitation associated with schizophrenia or bipolar I disorder	Psychosis/agitation associated with dementia	EPS Hypotension Sedation Dysgeusia
Perphenazine	Severe nausea and vomiting in adults Schizophrenia	Psychosis/agitation associated with dementia	EPS QTc prolongation
Prochlorperazine	Schizophrenia Severe nausea/vomiting	Nausea/vomiting of pregnancy	EPS QTc prolongation
Thiothixene	Schizophrenia	Psychosis/agitation associated with dementia	EPS ECG changes
Trifluoperazine	Nonpsychotic anxiety Schizophrenia	Psychosis/agitation associated with dementia	Orthostatic hypotension EPS

[a]Droperidol has a second black-box warning for QTc prolongation leading to fatal cardiac arrhythmias. Similarly, thioridazine has this warning and is only available in the United States as a generic; mesoridazine also had this warning and was removed from the US market

ECG: electrocardiogram; EPS: extrapyramidal symptoms; OCD: obsessive-compulsive disorder

Sources: Micromedex (www.micromedex.com) and Up-to-Date (www.uptodate.com). Off-label uses and monitoring are not meant to be formal recommendations or endorsements, but are for independent clinician consideration only. This list is not intended to be exhaustive

Black-box warnings

Table 5

Black-box warnings for second-generation antipsychotics

Black-box warning: *Elderly patients with dementia-related psychosis treated with antipsychotic medications are at an increased risk of death*

Medication	Labeled indication(s)	Off-label use(s)	Common adverse effects
Aripiprazole[a]	Bipolar disorder Irritability associated with ASD MDD (adjunctive) Schizophrenia Tourette disorder	Psychosis/agitation associated with dementia	Headache (12%) Akathisia (2% to 12%) Weight gain (17% to 22%) Metabolic syndrome (4% to 22%)
Asenapine	Bipolar disorder Schizophrenia	Psychosis/agitation associated with dementia	Drowsiness (13% to 26%) Insomnia (10% to 16%) Akathisia (4% to 15%) EPS (4% to 12%) Weight gain (1% to 22%) Metabolic syndrome (5% to 16%)
Brexpiprazole	MDD (adjunctive) Schizophrenia	Psychosis/agitation associated with dementia	Akathisia (4% to 14%) Increased triglycerides (8% to 13%) Increased weight gain (3% to 11%)
Cariprazine	Bipolar disorder Schizophrenia	MDD (adjunctive)	EPS (15% to 41%) Akathisia (9% to 20%) Headache (14%) Insomnia (9% to 13%) Nausea (7% to 13%)
Clozapine[b]	Schizophrenia (treatment-resistant) Suicidal behavior in schizophrenia or schizoaffective disorder	Bipolar disorder (treatment-resistant) Psychosis/agitation associated with dementia (treatment-resistant) Psychosis in Parkinson's disease	Neutropenia (<3%) Agranulocytosis (<1%) Myocarditis (<1%) Tachycardia (17% to 25%) Hypotension (9% to 13%) Hypertension (4% to 12%) Drowsiness (39% to 46%) Dizziness (14% to 27%) Vertigo (<19%) Sialorrhea (13% to 48%) Weight gain (4% to 31%) Constipation (14% to 25%) Nausea (5% to 17%)
Iloperidone	Schizophrenia	Psychosis/agitation associated with dementia	Tachycardia (3% to 12%) Dizziness (10% to 20%) Drowsiness (9% to 15%) Weight gain (9% to 18%) Hyperprolactinemia (26%)
Lurasidone	Bipolar depression Schizophrenia	MDD Psychosis/agitation associated with dementia	Drowsiness (8% to 26%) EPS (4% to 39%) Akathisia (7% to 22%) Increased fasting glucose (6% to 13%) Increased triglycerides (10% to 11%)

Table 5 continued

Medication	Labeled indication(s)	Off-label use(s)	Common adverse effects
Olanzapine[c]	Schizophrenia Acute mania associated with bipolar disorder Maintenance treatment of bipolar disorder Treatment-resistant bipolar I disorder MDD (in combination with fluoxetine)	Chemotherapy-associated acute and delayed nausea or vomiting prevention Chemotherapy-associated breakthrough nausea or vomiting Delirium Delusional infestation Psychosis/agitation associated with dementia PTSD Tourette syndrome	Metabolic syndrome (20% to 26%) Weight gain (22% to 64%) Increased appetite (3% to 24%) Orthostatic hypotension (5%) Dizziness (2% to 18%) Akathisia (5% to 27%)
Paliperidone	Schizophrenia Schizoaffective disorder	Delusional infestation	Tachycardia (3% to 14%) EPS (2% to 15%) Drowsiness (5% to 12%) Hyperprolactinemia (geriatric, 44% to 56%) Weight gain (3% to 9%) Metabolic syndrome (6% to 13%)
Pimavanserin	Parkinson's disease psychosis	None described	Peripheral edema (7%) Confusion (6%) Abnormal gait (2%) Nausea (7%) QTc prolongation
Quetiapine	Bipolar disorder Schizophrenia MDD (adjunctive)	Agitation Delirium Delusional disorder GAD MDD (monotherapy) OCD (adjunctive) PTSD Psychosis/agitation associated with dementia Psychosis in Parkinson's disease	Drowsiness (16% to 57%) Weight gain (3% to 28%) Metabolic syndrome (4% to 20%) Xerostomia (9% to 44%) Increased appetite (2% to 12%) Headache (17% to 21%)
Risperidone	Bipolar disorder (IM only) Bipolar mania Irritability associated with ASD Schizophrenia	Delusional infestation MDD PTSD Psychosis/agitation associated with dementia Tourette syndrome	Sedation (5% to 11%) EPS (2% to 35%) Headache (12% to 21%) Hyperprolactinemia (adults <4%, children 49% to 87%) Weight gain Metabolic syndrome
Ziprasidone	Acute agitation (IM only) Bipolar disorder Schizophrenia	Agitation Delirium Delusional infestation MDD Psychosis/agitation associated with dementia	Drowsiness (8% to 31%) EPS (1% to 31%) Headache (5% to 18%) Dizziness (3% to 16%) Nausea (8% to 12%)

[a]Aripiprazole also has a black-box warning for suicidality in adolescents and young adults
[b]Clozapine has other black-box warnings for agranulocytosis, myocarditis, orthostatic hypotension, and seizures
[c]A black-box warning also exists for extended-release olanzapine for severe sedation (including coma) after injection. Patients must be observed at the health care facility by a clinician for at least 3 hours

ASD: autism spectrum disorder; EPS: extrapyramidal symptoms; GAD: generalized anxiety disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: posttraumatic stress disorder

Black-box warnings

Table 6

Black-box warnings for antidepressants

Black-box warning: *Increased risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with MDD and other psychiatric disorders compared with placebo*

Medication	Labeled indication(s)	Off-label use(s)	Common adverse effects[a]
Selective serotonin reuptake inhibitors			
Citalopram	MDD	OCD Panic disorder PMMD Hot flashes	QTc prolongation (<2%) Diaphoresis (5% to 18%) Dizziness (14%) Headache (18%) Hip fracture (46%, geriatric)
Escitalopram	MDD GAD	OCD Panic disorder PMDD Social phobia	Diarrhea (6% to 14%) Nausea (15% to 18%) Reduced libido (3% to 7%) QTc prolongation
Fluoxetine	MDD OCD Panic disorder PMDD Bulimia nervosa Bipolar depression[b]	Body dysmorphic disorder Hot flashes Dysthymia PTSD Raynaud phenomenon	Diarrhea (8% to 18%) Indigestion (6% to 10%) Hyponatremia (<1%)
Fluvoxamine	OCD	MDD Eating disorder Panic disorder Social phobia	Nausea (34% to 40%) Xerostomia (10% to 14%) Diarrhea (11% to 18%)
Paroxetine	GAD MDD OCD Panic disorder PTSD PMDD Social phobia	Hot flashes Premature ejaculation	Palpitations (3%) Diaphoresis (5% to 14%) Constipation (16%) Diarrhea (18%) Nausea (26%)
Sertraline	MDD OCD Panic disorder PTSD PMDD Social phobia	Binge eating disorder Bipolar depression (adjunctive) Dysthymia GAD	Diarrhea (13% to 24%) Constipation (3% to 8%) Nausea (13% to 30%) Dizziness (6% to 17%) Headache (25%) Reduced libido (up to 11%) Hyponatremia (<1%)
Serotonin-norepinephrine reuptake inhibitors			
Desvenlafaxine	MDD	Anxiety disorders Bipolar depression PTSD Vasomotor symptoms	Diaphoresis (10% to 21%) Increased cholesterol (3% to 10%) Nausea (22% to 41%) Constipation (9% to 14%) Dizziness (10% to 16%) Reduced libido (3% to 6%)
Duloxetine	Diabetic peripheral neuropathy Fibromyalgia GAD MDD Chronic musculoskeletal pain	Chemotherapy-induced peripheral neuropathy Urinary incontinence	Hypertension (2%) Diaphoresis (6%) Constipation (10%) Diarrhea (9%) Nausea (18% to 23%)

Table 6 continued

Medication	Labeled indication(s)	Off-label use(s)	Common adverse effects[a]
Levomilnacipran	MDD	Fibromyalgia	Palpitations (6%) Diaphoresis (9%) Nausea (17%) Orthostatic hypotension (12%)
Milnacipran	Fibromyalgia	Depression	Hypertension (5% to 18%) Palpitations (7%) Constipation (16%) Nausea (37%)
Venlafaxine	GAD MDD Panic disorder Social phobia	Hot flashes ADHD Binge eating disorder Peripheral neuropathy OCD PTSD PMDD Dysthymia Tension headache (prophylaxis)	Hypertension (3% to 13%) Diaphoresis (7% to 25%) Constipation (15%) Nausea (21% to 58%) Weight loss (3% to 47%) Headache (25% to 38%) Blurred vision (4% to 6%) Hyponatremia
Atypical/other antidepressants			
Bupropion	MDD Depression associated with seasonal affective disorder	ADHD	Tachycardia (11%) Weight gain (9%) Weight loss (14% to 19%) Nausea (13% to 18%) Headache (25% to 34%) Agitation (2% to 9%)
Mirtazapine	MDD	Anxiety Dysthymia OCD Panic disorder	Increased appetite (17%) Increased liver enzymes (2%) Somnolence (54%)
Nefazodone	MDD	None described	Orthostatic hypotension (4%) Nausea (14% to 23%) Constipation (10% to 17%) Headache (26% to 52%) Dizziness (11% to 22%) Abnormal ECG
Trazodone	MDD	Insomnia	Nausea (21%) Xerostomia (14% to 34%) Dizziness (25%) Somnolence (45%) Hypotension (4% to 7%) Priapism Prolonged QTc
Vilazodone	MDD	None described	Diarrhea (29%) Nausea (24%) Premature ventricular beats (<1%)
Vortioxetine	MDD	None described	Nausea (21% to 32%) Hyponatremia

Black-box warnings

Table 6 continued

Medication	Labeled indication(s)	Off-label use(s)	Common adverse effects[a]
Tricyclic antidepressants			
Amitriptyline	MDD	Fibromyalgia Headache Irritable bowel syndrome Pain Postherpetic neuralgia Tinnitus	Weight gain Constipation Xerostomia Blurred vision Somnolence Dizziness Hypotension Prolonged QTc Tachycardia Cardiac dysrhythmia Agranulocytosis Hyponatremia
Amoxapine	MDD	Anxiety Insomnia	
Clomipramine	OCD	MDD ASD Panic disorder	
Desipramine	MDD	ADHD Diabetic neuropathy Postherpetic neuralgia	
Doxepin	Anxiety Depression Insomnia (Silenor only) Pruritus (limited settings)	Urticaria Insomnia (other than Silenor)	
Imipramine	MDD Nocturnal enuresis	Diabetic neuropathy Binge eating disorder Panic disorder Urinary incontinence	
Maprotiline	Bipolar depression MDD Dysthymia	Pain	
Nortriptyline	MDD	ADHD Diabetic neuropathy Neurogenic bladder Nocturnal enuresis Postherpetic neuralgia Smoking cessation	
Protriptyline	MDD	None described	
Trimipramine	MDD	None described	
Monoamine oxidase inhibitors			
Isocarboxazid	MDD	None described	Constipation Weight gain Increased LFTs Nausea Xerostomia Orthostatic hypotension Cardia dysrhythmia Hypertensive crisis with foods containing tyramine
Phenelzine	MDD	Agoraphobia Bulimia nervosa Social phobia	
Selegiline patch	MDD	None described	
Tranylcypromine[c]	MDD	None described	

[a]Selective serotonin reuptake inhibitors: increased risk of bone fracture in geriatric population, increased bleeding risk, and hyponatremia
[b]In combination with olanzapine
[c]Tranylcypromine has another black-box warning for hypertensive crisis in combination with foods containing tyramine

ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; ECG: electrocardiogram; EPS: extrapyramidal symptoms; GAD: generalized anxiety disorder; LFTs: liver function tests; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PMDD: premenstrual dysphoric disorder; PTSD: posttraumatic stress disorder

Black-box warnings

Table 7

Black-box warnings for mood stabilizers

Medication	Black-box warning	Labeled indication(s)
Carbamazepine	Serious, sometimes fatal dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported, especially in patients with the inherited allelic variant HLA-B*1502 Aplastic anemia and agranulocytosis	Bipolar disorder Seizure disorder Trigeminal neuralgia
Lamotrigine	Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults	Bipolar I disorder Lennox-Gastaut syndrome Partial seizure Generalized tonic-clonic seizure
Valproate	Hepatotoxicity (some cases fatal), usually occurring during the first 6 months of treatment, has been reported in patients receiving valproate and its derivatives. Children age <2 and patients with hereditary mitochondrial disease are at a considerably increased risk of developing fatal hepatotoxicity Pancreatitis Teratogenicity	Bipolar disorder Migraine prophylaxis Absence seizure Complex partial seizure
Lithium	Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy	Bipolar disorder (acute and maintenance)

OCD: obsessive-compulsive disorder; TBI: traumatic brain injury

	Off-label use(s)	Common adverse effects
	Agitation Behavioral syndrome	Nausea Anemia Thrombocytopenia Dizziness Hyponatremia
	OCD Trigeminal neuralgia Refractory epilepsy Migraine	Rash (7% to 14%) Abdominal pain (5% to 10%) Blurred vision (24% to 49%) Nausea (7% to 25%)
	Juvenile myoclonic epilepsy Myoclonic seizure Generalized tonic clonic seizure Agitation associated with TBI	Alopecia (6% to 24%) Rash (6%) Weight gain (4% to 47%) Diarrhea (12% to 23%) Nausea (22% to 48%) Headache (5% to 31%) Hyperammonemia
	None described	Acne Hypothyroidism Hyperparathyroidism Weight gain Nephrotoxicity Leukocytosis Xerostomia Increased thirst (28%) Bradyarrhythmia

Black-box warnings

Table 8

Black-box warnings for other medications

Medication(s)	Black-box warning(s)	Labeled indication(s)
Methylphenidate Dexmethylphenidate	Subject to misuse, abuse, addiction, or diversion	ADHD Narcolepsy (methylphenidate)
Dextroamphetamine/ amphetamine Lisdexamfetamine	Subject to misuse, abuse, addiction, or diversion; misuse may cause serious cardiovascular adverse events and sudden death	ADHD narcolepsy (dextroamphetamine/ amphetamine) Binge eating disorder (lisdexamfetamine)
Naltrexone	Hepatotoxicity	Alcohol use disorder Opioid use disorder
Disulfiram	Contraindicated during alcohol intoxication; requires patient's full knowledge	Alcohol use disorder
Midazolam	Respiratory depression	Procedural sedation Induction of general anesthesia Status epilepticus
Methadone	Death due to rapid titration; QT prolongation; abuse and misuse; neonatal syndrome; use in certified programs only	Opioid use disorder (detoxification and maintenance) Pain
Zolpidem Zaleplon Eszopiclone	Complex sleep behaviors	Insomnia (short-term)
Levothyroxine	Life-threatening thyroid toxicity; ineffective for weight reduction	Hypothyroidism
Esketamine	Suicidal behavior; sedation and dissociation; abuse and misuse; available only with REMS	MDD (treatment-resistant, adjunctive)

ADHD: attention-deficit/hyperactivity disorder; MDD: major depressive disorder; REMS: Risk Evaluation and Mitigation Strategy; TBI: traumatic brain injury

Off-label use(s)	Common adverse effects
Geriatric depression Post-TBI fatigue	Increased systolic blood pressure Increased heart rate Weight loss Increased appetite Headache Anxiety
Geriatric depression Post-TBI fatigue	
Drug withdrawal Morphine adverse reaction Premenstrual syndrome Self-injurious behavior	Nausea Myalgia Headache Anxiety Hepatotoxicity
None described	Hepatitis Liver failure Optic neuritis
Postoperative nausea/ vomiting Seizure	Somnolence Hiccups Headache
Neuropathic pain	Hypotension Nausea Sedation Prolonged QTc
Insomnia (long-term) Catatonia (zolpidem)	Dizziness Visual disturbance Abnormal sleep behaviors Anaphylaxis (rare)
Augmentation of antidepressant	Palpitations Sweating Weight loss Insomnia Anxiety
None described	Nausea (28%) Emesis (9%) Dizziness (29%) Vertigo (23%) Anxiety (11%)