

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

^aDroperidol 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%)
Brexipiprazole	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%)
lloperidone	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%)

^aAripiprazole also has a black-box warning for suicidality in adolescents and young adults

^bClozapine has other black-box warnings for agranulocytosis, myocarditis, orthostatic hypotension, and seizures

^cA 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 PMDD 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
Amoxapine	MDD	Anxiety Insomnia	Prolonged QTc Tachycardia
Clomipramine	OCD	MDD ASD Panic disorder	Cardiac dysrhythmia Agranulocytosis Hyponatremia
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
Phenelzine	MDD	Agoraphobia Bulimia nervosa Social phobia	Weight gain Increased LFTs Nausea
Selegiline patch	MDD	None described	Xerostomia
Tranylcypromine ^c	MDD	None described	Orthostatic hypotension Cardia dysrhythmia Hypertensive crisis with foods containing tyramine

^aSelective serotonin reuptake inhibitors: increased risk of bone fracture in geriatric population, increased bleeding risk, and hyponatremia

^bIn combination with olanzapine

^cTranylcypromine 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
Geriatric depression Post-TBI fatigue	Increased heart rate Weight loss Increased appetite Headache Anxiety
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%)