Iraq/Afghan veterans may feel isolated and alone, doubting that anyone understands what they experienced or how they feel.

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Current Psychiatry

TRAUMATIZED TROOPS

HOW TO TREAT COMBAT-RELATED PTSD

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Thousands of U.S. troops are seeking mental health care after being deployed in Iraq. Among 222,000 Army and Marine Iraq veterans, 35% sought treatment in the year after returning home—many for posttraumatic stress disorder (PTSD).[1] Other veterans also may have PTSD but do not recognize its symptoms or resist seeking mental health treatment.

We have described symptoms you may see in Iraq war veterans—including nightmares and intrusive thoughts, fears of losing control and hurting someone, and suicidal thoughts (*see Related resources*). In this article, we:

- recommend tools to screen for combat-related PTSD
- discuss psychotherapy, evidence on medications, and how to approach special problems such as insomnia and anger
- suggest resources to help you treat these patients in a community practice.

In a related article (*page 53*), we discuss the diagnosis and treatment of military sexual trauma, a form of PTSD.

continued

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Table 1

3 domains of posttraumatic stress disorder symptoms

Domain	Symptoms
Re-experiencing	• Recurrent, intrusive, distressing recollections or dreams of traumatic event • Acting or feeling as if the event were recurring • Intense psychological distress or physiologic reactions when exposed to internal or external cues
Avoidance and numbing	• Efforts to avoid thoughts, feelings, or conversations about the trauma or activities, places, or people that arouse recollections • Inability to recall an important aspect of the trauma • Markedly less interest or participation in significant activities • Feeling detached or estranged from others • Restricted range of affect • Sense of a foreshortened future
Increased arousal	• Difficulty falling or staying asleep • Irritability or angry outbursts • Difficulty concentrating • Hypervigilance • Exaggerated startle response

Source: DSM-IV-TR

PERSISTENT PATHOLOGY

The greater the intensity of an Iraq/Afghanistan veteran's combat experiences ("firefights"), the more likely the soldier is to develop PTSD.[2] Being wounded or witnessing someone being wounded or killed also increases PTSD risk. Symptom severity may be trauma "dose-related" and influenced by life experience, use of psychoactive compounds, psychosocial stressors, and conditioning.

Resiliency is the rule; more than one-half of veterans diagnosed with PTSD no longer meet DSM-IV-TR criteria at later follow-up.[3] In others PTSD persists, resists treatment, and impairs relationships, ability to work, and quality of life.[4]

Combat exposure's negative effects can persist for decades, as Prigerson et al[5] showed in 2,583 men ages 18 to 54 enrolled in the National Comorbidity Survey. Using standardized psychiatric interviews, they found combat experience associated with 30% of PTSD, 21% of spouse or partner abuse, 12% of joblessness, and 8% of substance abuse among U.S. men.

DIAGNOSIS AND SCREENING

DSM-IV-TR diagnostic criteria for PTSD[6] apply to combat veterans (*Table 1*), but they might not report their symptoms to you. Veterans most likely to meet PTSD criteria may minimize their symptoms to avoid mental health treatment.[2]

We recommend you screen all veterans for PTSD, using part of the Veterans Administration's Afghanistan & Iraq Post-Deployment Screen (*Figure, page 45*). The VA mails the full screen to recently discharged veterans who served in Iraq or Afghanistan to identify deployment-related medical and psychological problems, including depression, alcohol abuse, and PTSD (*see Related resources*).

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(Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of oral olanzapine (15+2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events—Dose-relatedness of adverse events was assessed using data from a clinical trial involving 3 fixed oral dosage ranges compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 56% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; Infrequent: atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation,* amenorrhea,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation,* glycosuria, gynecomastia, hematuria, impotence,* increased menstruation,* menorrhagia,* metrorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged,* vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been rarely reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

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Literature revised September 30, 2005

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Figure

PTSD screen for war veterans

Have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month, you …

1. Have had nightmares about it or thought about it when you did not want to?

   YES NO

2. Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?

   YES NO

3. Were constantly on guard, watchful, or easily startled?

   YES NO

4. Felt numb or detached from others, activities, or your surroundings?

   YES NO

Key: ≥2 "yes" answers is a positive screen.

Source: U.S. Department of Veterans Affairs. Afghan & Iraq Post-Deployment Screen, Attachment B. Screening for risk factors associated with development of post-traumatic stress disorder (PTSD)

Be especially vigilant for PTSD symptoms in troops who were wounded. Because 22% of Iraq/Afghan war casualties have head, neck, or face injuries,[7] consider possible traumatic brain injury; clinical findings will guide further testing[8] (*see "Traumatic brain injury: Choosing medications for neurobehavioral symptoms," page 57*). Sexual trauma also may cause or exacerbate PTSD[9] (*see "Military sexual trauma: How to identify and treat a unique form of PTSD," page 53*).

COGNITIVE THERAPY

Psychotherapy is the cornerstone of PTSD treatment; skilled therapists may achieve greater effi-

Table 2

VA's support services for veterans with PTSD

Entry points for referral information
County Veterans Service Officer
Readjustment Counseling Services Officer (Vet Center)
VA Web site for returning veterans (www.seamlesstransition.va.gov)
Programs offered
Substance abuse treatment
Military sexual trauma coordinator (for access to treatment programs)
Specialized PTSD programs
Outreach to veterans and their families
Vocational rehabilitation
Mental health clinic
Benefits for the veteran
Peer support
Integrated care
Applications for service-connected disability and compensation

VA: Department of Veterans Affairs

cacy and more-durable results than medications do. Evidence strongly supports cognitive behavioral therapy—including exposure therapy, anxiety management, and cognitive therapy.[10]

PTSD patients often feel isolated and alone, doubting that anyone understands what they experienced or how they feel. Though they may resist group therapy, it can be invaluable. In a group, they can safely discuss problems, feel less isolated, and validate experiences, while learning how to cope with trauma-related shame, guilt, rage, fear, doubt, and self-blame.

Help your patient find a program or individual therapist.[11] The VA provides specialized treatment programs, resources, individual counseling, and financial support for returning soldiers (*see Related resources and Table 2*).

Education and support. When a combat veteran returns, family therapy can help manage dysfunction in the home. Interventions—vocational support, community involvement, and appropriate medical and psychiatric treatment—may contribute to long-term symptom remission.[12]

Medication. We usually consider veterans' preferences and motivation for psychotherapy but strongly recommend using medications when:

- the patient has psychiatric comorbidities—such as depression, panic disorder, social phobia, and obsessive-compulsive disorder—that can be effectively treated by medications used for PTSD
- PTSD is severe and interferes with ability to engage in or tolerate psychotherapy
- special PTSD psychotherapy is not available.[13]

Our experience suggests that combining medication and psychotherapy may enhance clinical response, especially during acute treatment, but empiric evidence is lacking.

SSRIS: FIRST-LINE MEDICATION

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for PTSD (*see Related resources*). SSRIs cause relatively few adverse effects and are rarely associated with completed suicide. They also may treat PTSD's common psychiatric comorbidities.

Precautions. Treatment resistance rates with SSRIs are approximately 50% in PTSD clinical trials.[14] SSRI-induced sexual dysfunction can be problematic and lead patients to discontinue treatment. Counsel them about this side effect, or they might blame sexual problems on pre-existing marital or relationship difficulties.

Activation associated with starting an SSRI may worsen PTSD hyperarousal. Discuss this with patients as you start with low dosages and

Table 3

Target symptoms guide choice of second-line agents for PTSD*

Symptoms	Medication options	Recommended dosing†
Insomnia, nightmares	Prazosin	2 to 10 mg at bedtime
	Temazepam	15 to 30 mg at bedtime
	Trazodone	25 to 300 mg at bedtime
	Zolpidem	10 to 15 mg at bedtime
	Atypical antipsychotics	
	Aripiprazole	10 to 30 mg/d
	Olanzapine	10 to 20 mg/d
	Quetiapine	25 to 300 mg/d
	Risperidone	1 to 6 mg/d
Irritability, anger, aggression, impulsivity, bipolar comorbidity	Atypical antipsychotics	(see above)
	Mood stabilizers	
	Carbamazepine	600 to 1,200 mg/d
	Lamotrigine	50 to 200 mg/d
	Lithium	900 to 1,500 mg/d
	Valproic acid	750 to 2,000 mg/d
Paranoia, hallucinations, severe flashbacks	Atypical antipsychotics	(see above)
Refractory depressive/ anxiety symptoms	Antidepressants	
	Mirtazapine	15 to 45 mg/d
	Venlafaxine	150 to 225 mg/d
	Benzodiazepines	
	Clonazepam	0.5 to 6 mg/d
	Lorazepam	0.5 to 6 mg/d
	Atypical antipsychotics	(see above)

• Selective serotonin reuptake inhibitors are considered first-line therapy.

† Recommendations based on references 14, 24-26,28, 32.

increase gradually as needed. Insomnia may respond to an additional medication such as trazodone. Akathisia has been reported with SSRIs, sometimes with suicidal behavior.

Starting antidepressants has not been shown to increase suicidality in patients with PTSD.[15] Even so, we strongly recommend close monitoring because of PTSD's association with major depression and increased risk for suicidal behavior.[16] At minimum:

- talk with patients by phone or in person within 2 weeks of starting treatment
- schedule a follow-up appointment within 1 month.

Evidence of efficacy. Sertraline and paroxetine are FDA-approved to treat PTSD,[14,17] and fluoxetine has shown efficacy in a controlled clinical trial.[18] No large-scale controlled trials have examined citalopram or fluvoxamine in PTSD.

Sertraline. All three PTSD symptom clusters improved with sertraline in two double-blind, placebo-controlled trials totalling 395 civilians.[19,20] Mean dosages were 133.3 ± 59.2 mg/d and 146.3

± 49.3 mg/d, respectively. Effects were modest as measured by the Clinician Administered PTSD Scale (CAPS),[14] and women showed greater response than men.

A third double-blind, placebo-controlled trial examined sertraline in combat-induced PTSD. Compared with most civilian studies, baseline symptoms were more severe in these Israeli military veterans and sertraline was less effective.[21] Sertraline given for 10 weeks (mean final dosage 120 mg/d) was more effective than placebo, but the difference was not statistically significant. Using higher dosages might have improved outcomes in this pilot study.

Paroxetine, 20 to 50 mg/d, also was efficacious and safe for PTSD symptoms in two large, multisite, double-blind, placebo-controlled trials.[22,23] More than 800 men and women were enrolled in the 12-week studies. All three PTSD symptom clusters improved significantly more with paroxetine than with placebo, as measured by CAPS.

Fluoxetine. In a randomized, double-blind, controlled trial,[18] 301 patients with PTSD received fluoxetine, 20 to 80 mg/d (mean 57 mg/d), or placebo for 12 weeks. Most were white men, and 48% had experienced combat.

Depression, anxiety, hyperarousal, and other PTSD symptoms improved significantly more in the fluoxetine group—particularly in younger subjects with combat trauma—compared with placebo.

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JANUARY 2006

These findings may apply to Iraq and Afghanistan veterans with PTSD, who tend to be young and to have had symptoms for brief durations.

Prescribing SSRIs for PTSD. Provide acute-phase treatment at least 12 weeks (longer for severely ill veterans). We recommend:

- fluoxetine, 20 to 60 mg/d
- paroxetine, 20 to 50 mg/d
- sertraline, 75 to 200 mg/d
- citalopram, 20 to 60 mg/d.

Because no PTSD studies have compared the SSRIs, consider patient history of response and the drugs' side effects, ease of titration, and potential for drug-drug interactions. Treat responders for 6 to 12 months to prevent relapse. If your initial choice does not produce an adequate response, a reasonable option would be to try another SSRI.

Other medications. No other medication is a clear option for patients who do not tolerate or respond to an SSRI. We target symptom clusters such as insomnia, irritability, hallucinations, or refractory depression/anxiety (*Table 3*).[14,24-26]

Benzodiazepines. Although widely prescribed for PTSD, benzodiazepines offer little benefit, may worsen core symptoms,[27] and pose a risk of misuse or addiction.

Antipsychotics. Adjunctive olanzapine[28] risperidone,[29] quetiapine,[30] and aripiprazole[31] may help patients with treatment resistance, comorbid psychosis or bipolar disorder, or sleep disturbance. Because large randomized, controlled trials are lacking in PTSD, however, we cannot recommend using atypical antipsychotics. Their metabolic effects are a concern because veterans with PTSD have relatively high obesity rates.[12]

SPECIAL TREATMENT ISSUES

Sleep disturbance. PTSD-related insomnia, nightmares, poor sleep quality, and sleep disruption are common and can be difficult to treat. One strategy is to add trazodone, 25 to 300 mg at bedtime, to SSRI therapy. Little evidence supports this practice, but a

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survey of PTSD patients suggests that trazodone may help PTSD-related insomnia and nightmares.[32] Inform patients about the risk of priapism, orthostatic hypotension, and oversedation with trazodone.

Sleep disturbance is a core PTSD symptom, but sleep-disordered breathing—such as obstructive sleep apnea (OSA)—is prevalent in veterans.[33] OSA risk factors include obesity, alcohol use, and smoking. Request a sleep study for those who acknowledge snoring, daytime sleepiness, hypertension, morning headaches, depression, or memory problems. Treating OSA can improve sleep quality, well-being, nightmares, and PTSD.[34]

Anger. Angry veterans may respond poorly to PTSD treatment[35] and may have maladaptive coping skills. Review for developmental and abuse history, violence, weapons access, substance abuse, depression, mania, and head injury. Choose medications for underlying disorders, and refer to anger-management and other programs as needed.

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Screen all veterans for PTSD, using the VA's postdeployment questions. Special PTSD psychotherapy, especially in group therapy, is the cornerstone of treatment. When medications are indicated, SSRIs are first-line; target symptoms guide the choice of second-line medications. The VA system offers many support services.

Bottom Line

continued

Continued brief summary of prescribing information from previous page.

Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules

provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 2
Treatment-Emergent Adverse Events[1] Occurring During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
No. of Patients with AEs				
Total	84%	94%	85%	68%
Primary System Organ Class/ Adverse Event Preferred Term				
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

[1]Events, regardless of causality, for which the incidence was at least 5% in a Focalin XR group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

Two other adverse reactions occurring in clinical trials with Focalin XR at a frequency greater than placebo, but which were not dose related were: Feeling jittery (12% and 2%, respectively) and Dizziness (6% and 2%, respectively).

Table 3 summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of Focalin XR in the treatment of ADHD.

Table 3
Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

Adverse Events with Other Methylphenidate HCl Dosage Forms
Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia

Gastrointestinal: abdominal pain, nausea

Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura

Metabolism/Nutrition: anorexia, weight loss during prolonged therapy

Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis

Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: leukopenia and/or anemia

Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma

Psychiatric: transient depressed mood, aggressive behavior

Skin/Subcutaneous: scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class
Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

Abuse, Dependence, and Tolerance
See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE
Signs and Symptoms
Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Poison Control Center
The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

Recommended Treatment
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of dexmethylphenidate from Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis for Focalin overdosage has not been established.

Focalin™ XR is a trademark of Novartis AG

This product is covered by US patents including 5,837,284, 5,908,850, 6,228,398, 6,355,656, and 6,635,284.

REFERENCE
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DRUG BRAND NAMES

Carbamazepine • Carbatrol
Fluoxetine • Prozac
Lamotrigine • Lamictal
Lithium • Lithobid, others
Mirtazapine • Remeron
Paroxetine • Paxil
Prazosin • Minipress
Sertraline • Zoloft
Trazodone • Desyrel
Temazepam • Restoril
Valproic acid • Divalproex, others
Venlafaxine • Effexor
Zolpidem • Ambien

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products. Drs. Lineberry, Bostwick, and Rundell served on active duty in the U.S. Air Force. Dr. Ramaswamy is staff psychiatrist, Omaha Veterans Administration. and Director of Psychopharmacology Research, Creighton University, Omaha, NE.