Current PSYCHIATRY

A cry for help: Treating involuntary emotional expression disorder

Pharmacotherapy can lessen the impact of uncontrollable laughing or crying

Mrs. R, a 68-year-old retired teacher, is referred to you for suspected mania after a closed head injury from a car accident. The referring physician reports that Mrs. R experienced mild anterograde amnesia that has resolved, but she continues to suffer from "persistent mood swings as evidenced by substantial inappropriate laughter."

Mrs. R is not manic. Her mood is normal, with a relatively euthymic affect. When asked about her accident or injury, however, she breaks into bouts of laughter that appear to be uncontrollable and last up to several minutes. These episodes include respiratory changes that make her laughter nearly indistinguishable from crying. Mrs. R explains that the episodes occur every time she discusses the accident—regardless of her efforts to prevent them—and complains they are extremely frustrating and embarrassing. She avoids situations that might trigger the episodes.

Patients with involuntary emotional expression disorder (IEED)—a neurologic disorder that manifests as brief bouts of uncontrollable crying, laughing, or both—may appear to have bipolar disorder, schizophrenia, depression, or another psychiatric disorder. Careful evaluation, however, can distinguish IEED from other conditions. Managing the disorder requires an understanding of IEED phenomenology, including:

- neurologic conditions that result in IEED
- underlying pathology
- diagnostic criteria
- effective treatments.

continued

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Clinical Point

If a patient presents with symptoms that suggest IEED, first determine the neurologic condition that is causing them

Table 1

Neurologic conditions associated with IEED

Amyotrophic lateral sclerosis
Multiple sclerosis
Traumatic brain injury
Stroke
Alzheimer's disease
Frontotemporal dementia
Parkinson's disease
Progressive supranuclear palsy
Multiple systems atrophy
Wilson's disease
Normal pressure hydrocephalus
Olivopontine cerebellar atrophy

Source: Reference 7

Table 2

Is it IEED? Diagnostic criteria

Presence of brain damage
Episodes of involuntary emotional motor output that: • represent a change from normal emotional reactivity • are independent or in excess of provoking stimuli • result in clinically significant distress or social or functional impairment
Disorder is *not*: • better accounted for by another neurologic or psychiatric disorder • caused by a physiologic substance

Source: Reference 1

Brain dysfunction alters affect

IEED was introduced as an inclusive term, replacing previous nomenclature such as pathologic laughing and crying, pseudobulbar affect, affective lability, and emotional incontinence.[1]

IEED can present as episodes of laughter, as in Mrs. R's case, but more commonly manifests as bouts of crying. Other presentations include a combination of laughing and crying, but episodic outbursts of other emotions that are out of the patient's control—such as anger—can be included in this syndrome.[2] IEED episodes can lead to embarrassment, frustration, and anger that eventually can affect mood and often cause patients to avoid social interaction.[3]

IEED can occur in any condition that damages and affects the brain areas critical to emotional motor output (***Box 1***).[4-6] The broad pattern of lesions that can result in IEED stems from many disease states. IEED is often observed in amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), stroke, and traumatic brain injury. It also may occur in dementia, Parkinson's disease, and other disorders (***Table 1***).[7]

Diagnosis can be elusive

Although IEED is not included in DSM-IV-TR, recently developed diagnostic criteria can help distinguish it from other disorders (***Table 2***).[1] As with DSM-categorized disorders, IEED must result in clinically significant distress or impairment in social or occupational function and must not be better accounted for by another disorder or caused by a physiologic substance.

The patient must present with symptoms caused by brain dysfunction from brain injury or neurodegenerative disease. Underlying brain damage might not be apparent when the patient first presents, but to our knowledge no case of idiopathic IEED has been described. If a patient presents with symptoms thought to be IEED, first determine what underlying neurologic condition is causing the symptoms and optimally manage this disorder.

To be considered IEED, the patient's symptoms must represent a change from his or her normal emotional reactivity. When interviewing patients and their families, compare the patient's current emotional reactivity with that from when he or she was free of all disease symptoms. Such considerations are important because a patient may have a life-long condition in which he or she is prone to emotional displays—such as essential crying—that is distinct from IEED.[8]

Symptoms must be incongruent with or in excess of the person's underlying mood and independent or in excess of the provoking stimulus. Inappropriateness of the emotional response is the hallmark of IEED.

Box 1

IEED: A consequence of brain pathology

Damage to the descending inputs to the pontomedullary area once referred to as the faciorespiratory center is most likely to result in release of bulbar function and, subsequently, involuntary emotional expression disorder (IEED). Therefore, because of the progressive upper motor neuron degeneration associated with amyotrophic lateral sclerosis (ALS), nearly 50% of ALS patients will eventually demonstrate pathological affect.[4]

The lesions that can result in IEED are diffuse, however, and have been described in a review of IEED neuroanatomy as including a cortico-limbic-subcortico-thalamo-ponto-cerebellar network.[5] Single lesions to white matter structures—such as the internal capsule—and gray matter structures—such as the thalamus, hypothalamus, basal ganglia, cerebellum, and several cortical locations—have been associated with IEED. Bilateral lesions are more likely to produce the disorder than single lesions.

With such varied neuroanatomic substrates, predicting the underlying neurochemical pathology of IEED is difficult. Among the neurotransmitters considered in IEED pathology and treatment are serotonin, glutamate, and dopamine. The sigma-1 receptor system may also play a role.[6]

IEED episodes have characteristic clinical features (***Table 3***). They are brief—lasting seconds to minutes—and sudden in onset and conclusion. Episodes are likely to be stereotyped in severity and presenting type within patients, as well as in the triggering stimulus or set of stimuli. For example, patients often experience episodes when asked about the syndrome.[9] In severe cases, patients experience episodes with any interpersonal contact.[10]

Some characteristics support—but are not essential for—an IEED diagnosis:

- autonomic symptoms, such as flushing of the face and increased salivary production during episodes
- pseudobulbar signs, such as increased jaw jerk, exaggerated gag reflex, dysarthria, and dysphagia
- other emotional outbursts.

CASE CONTINUED

Reaching a diagnosis

After thoroughly interviewing Mrs. R, you exclude mood disorders such as depression or bipolar disorder. The paroxysmal, episodic nature of her emotional outbursts and the consistency of the eliciting stimulus, suggest IEED.

Distinguishing IEED from depression. Physicians may be quick to diagnose a patient with consistent, recurrent crying as having a depressive disorder. In IEED, the patient's family commonly (and inappropriately) will confirm this misperception, even if the patient claims otherwise. The hallmark distinctions between depression and IEED are:

- duration of crying
- associated mood state.

Major depressive disorder (MDD) is a persistent change in a patient's mood lasting weeks to months, accompanied by feelings of guilt, helplessness, hopelessness, and worthlessness, apathy, and anhedonia.[11] IEED is paroxysmal, with uncontrollable changes in affect without a corresponding sudden mood change. Patients may report mood changes during episodes, but between episodes return to an euthymic affect.

Patients who suffer from MDD, however, are not excluded from an IEED diagnosis. In 1 small study, almost one-half of patients with IEED also had major depression.[12] Differentiating these syndromes—even in patients who suffer from both— is important to ensure proper management and patient and

Table 3

Characteristics of IEED episodes

Paroxysmal, sudden onset with rapid offset
Brief (up to several minutes)
Stereotyped across patients (may manifest in similar fashion from patient to patient)
Stereotyped within patients (episodes often have similar type, severity, and eliciting stimuli)

Clinical Point

Inappropriate emotional response is the hallmark of IEED

Clinical Point

Education can help patients and families understand IEED and deal with embarrassment and other normal reactions

Table 4

IEED: Evidence for antidepressants

Drug	Study design/population	Dosage	Outcome
Tricyclics			
Amitriptyline	Schiffer et al;[13] double-blind crossover; 12 multiple sclerosis patients	Mean: 57.8 mg/d	8 patients showed significant improvement compared with placebo
Nortriptyline	Robinson et al;[12] double-blind, placebo-controlled; 28 stroke patients	≤100 mg/d	Patients receiving nortriptyline reported significantly greater improvement on PLACS at 4 and 6 weeks compared with placebo
Selective serotonin reuptake inhibitors			
Citalopram	Anderson et al;[14] double-blind, placebo-controlled crossover; 16 stroke patients	10 to 20 mg/d	Citalopram decreased the number of daily crying episodes by ≥50% compared with placebo
Fluoxetine	Choi-Kwon et al;[2] double-blind placebo-controlled; 152 patients	20 mg/d	Fluoxetine significantly improved measures of IEED and anger proneness but not depression
Paroxetine	Müller et al;[15] consecutive case series, comparison with citalopram; 26 patients with traumatic brain injury or stroke	10 to 40 mg/d	Both paroxetine and citalopram resulted in significant improvements in measures of emotionalism
Sertraline	Burns et al;[16] double-blind, placebo-controlled; 28 stroke patients	50 mg/d	Patients receiving sertraline had significant improvements in measures of emotionalism

IEED: involuntary emotional expression disorder; PLACS: Pathological Laughing and Crying Scale

family understanding of the condition. Lastly, although IEED is not a mood disorder, the embarrassment and frustration it causes can change a patient's mood over time.

Recommended treatment

Education. In our experience, education is critical to help patients and family members understand IEED and deal with embarrassment and other normal reactions they may experience. Explain that these emotional displays are not manic or psychotic episodes but periods of motor dyscontrol caused by a neurologic condition.

Teach them to cope with IEED by:

- identifying and avoiding stimuli that provoke IEED episodes
- ignoring the episodes and continuing with usual activities.

Antidepressants are first-line pharmacotherapy for IEED. Studies and case reports have shown efficacy for tricyclic antidepressants (TCAs) such as nortriptyline and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (***Table 4***).[2,12-16]

These agents have IEED-specific therapeutic effects through a mechanism independent of their antidepressant action. In patients with IEED and depression, antidepressants may resolve IEED while depression remains refractory.[2,12] Potential drawbacks include anticholinergic effects with TCAs and sexual and gastrointestinal side effects with SSRIs. Nevertheless, these agents are the optimal first-line therapy for IEED among currently available options.

Other agents. Small studies have investigated other agents, but the data are insuffi-

continued on page 110

trials: ***Body as a Whole***—asthenia, back pain, accidental injury, chest pain; ***Cardiovascular***—hypertension; **Digestive**—dry mouth, increased appetite, thirst, constipation, increased salivation; ***Metabolic and Nutritional***—weight gain, peripheral edema, edema; ***Nervous System***—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; ***Respiratory***—pharyngitis, dyspnea; ***Skin and Appendages***—sweating, acne, dry skin; ***Special Senses***—amblyopia, abnormal vision; ***Urogenital***—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5-10 mg/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: ***Body as a Whole***—asthenia; ***Cardiovascular***—hypotension, postural hypotension; ***Nervous System***—somnolence, dizziness, tremor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism (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 this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

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).

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.

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 (8661 patients, 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 (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, 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 reported.

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

Literature revised October 1, 2007

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continued from page 104

Box 2

2 scales for measuring IEED treatment efficacy

Among scales that measure involuntary emotional expression disorder (IEED) severity, 2 have been used in studies of IEED therapeutic efficacy (see ***Related Resources***):[12,19,20]

- **Pathological Laughing and Crying Scale (PLACS)** developed by Robinson et al[12] is an interviewer-administered, 18-item tool that has been validated in IEED patients with stroke,[12] dementia,[22] and traumatic brain injury.[23]
- **7-item Center for Neurologic Study-Lability Scale (CNS-LS)** is a self-report measure that has been validated in IEED patients with amyotrophic lateral sclerosis[24] and multiple sclerosis.[25]

Although these scales have been used primarily for research, you can use them clinically to establish a baseline of IEED severity and gauge treatment efficacy. Improved scores generally correlate with successful treatment; if a patient fails to show adequate response on 1 of these scales, consider changing treatment.

cient to warrant recommendations for clinical practice. One study found that the novel antidepressant mirtazapine improved symptoms in 2 patients who did not respond to SSRIs.[17] In another study, levodopa therapy resulted in improvement in 10 of 25 patients.[18]

A combination dextromethorphan and quinidine (DM/Q) is being evaluated for IEED. This compound has demonstrated efficacy in IEED patients with ALS[19] and MS[20] and is in Phase III clinical development. DM/Q is thought to be a potent activator of the sigma-1 receptor system as well as an *N*-methyl-D-aspartate antagonist.[21]

CASE CONTINUED

Effective pharmacotherapy

After diagnosing IEED, you start Mrs. R on sertraline, 50 mg/d. She experiences a nearly immediate reduction in the number of daily IEED episodes. As a result, she feels more comfortable engaging in social activities.

Recommendations. We recommend using pharmacologic therapy for IEED. Because of the presence of underlying brain damage, IEED patients are likely to require treatment for other chronic or progressive conditions. Choose first-line therapy based on the patient's medication regimen and comorbid conditions, as well as the drug's side-effect profile.

Effective pharmacologic intervention can greatly improve patients' quality of life.[19,20] Use scales that measure IEED severity to gauge treatment effectiveness (***Box 2***).[12,19,20,22-25] Because treatment failure is a realistic possibility,[17] you may need to try a variety of agents to determine which regimen provides the greatest efficacy and therapeutic effects.

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Related Resources

- Involuntary emotional expressive disorder (for healthcare professionals). www.ieed.org/hp.
- Pathological laughing and crying scale (PLACS). Robinson RG, Parikh RM, Lipsey JR, et al. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am J Psychiatry* 1993;150:286-93.
- Center for neurologic study—lability scale (CNS-LS). Moore SR, Gresham LS, Bromberg MB, et al. A self report measure of affective lability. *J Neurol Neurosurg Psychiatry* 1997;63:89-93.

Drug Brand Names

Amitriptyline • Elavil, Endep
Citalopram • Celexa
Dextromethorphan/quinidine • Zenvia*
Fluoxetine • Prozac
Levodopa • Larodopa
Mirtazapine • Remeron
Nortriptyline • Aventyl
Paroxetine • Paxil
Sertraline • Zoloft

* IN PHASE III DEVELOPMENT

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Clinical Point

First-line treatment is pharmacotherapy with tricyclic antidepressants or selective serotonin reuptake inhibitors

Bottom Line

Inappropriate emotional response is a hallmark of involuntary emotional expression disorder (IEED). If a patient's symptoms suggest IEED, determine the neurologic condition that is causing the symptoms and optimally manage that disorder. Pharmacotherapy with tricyclic antidepressants or selective serotonin reuptake inhibitors can improve patients' symptoms and quality of life.