



# Harvard Mental Health Letter

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## Infection, inflammation, and mental illness

*The body's immune response to infectious agents may imperil the brain.*

For more than a century, researchers have explored whether infectious agents might trigger some types of mental illness, particularly schizophrenia. For the most part, however, these theories rested on studies that proved only an association between certain infections and mental disorders, not cause and effect.

But in the past decade, researchers have produced a growing body of observational and biological evidence suggesting that the body's defensive immune response, rather than the infection itself, may be what damages the brain. Further, chronic stress may activate a harmful immune response, even in the absence of infection. Although the research remains preliminary, the findings could suggest a new approach to treatment.

### Immune privileged—or influenced?

The immune system functions in part by unleashing inflammatory cells that identify and destroy viruses, bacteria, and other causes of disease. But this formidable firepower may kill healthy tissue along with foreign invaders.

In the brain, this would be devastating, because brain cells do not regenerate as well as cells located elsewhere in the body. The

traditional view has been that the brain is “immune privileged,” or protected in various ways from inflammation's onslaught.

But this view has been challenged on two fronts. First, consensus now exists that the brain's immune privilege is not absolute, but rather a regulatory system that sometimes malfunctions. One example is the neurodegeneration evident in multiple sclerosis, in which the immune system attacks the myelin sheath around nerve extensions.

Second, a growing body of research suggests that the immune system may support brain health in several ways. One study in mice, for example, found that the complement cascade, a biochemical pathway that helps clear disease-causing invaders from the body, may also help to prune synapses in the brain. Other research has found that an immune system enzyme, indoleamine 2,3-dioxygenase (IDO), affects circulating levels of tryptophan, an amino acid that is a precursor to the neurotransmitter serotonin in the brain. Such insights into the immune system's contribution to brain health have renewed interest in how its activation in response to infection or chronic stress might contribute to brain disorders.

### Sickness behavior and depression

Much of the research has focused on immune system proteins known as cytokines that initiate and orchestrate an inflammatory attack on viral or bacterial invaders. These proteins are also the main instigators of what researchers refer to as “sickness behavior”—loss of appetite, fatigue, sleep disruptions, and depressed mood.

Sickness behavior fosters healing, as it encourages people to slow down and allow the immune system to combat pathogens. ▶▶

### KEY POINTS

- Research suggests that the immune system supports brain health in several ways.
- Activation of certain immune system cells in response to an infection, or on an ongoing basis (chronic inflammation), may contribute to mental illness in different ways.
- Studies are under way to evaluate the use of anti-inflammatories in treating depression and schizophrenia.

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## Inflammation and mental illness *continued*

Given the similarity between sickness behavior and symptoms of depression, however, some researchers now think cytokines or other components of the immune system might also trigger at least some cases of this mood disorder.

**Evidence.** A link between immune system activation and depressed mood would help explain what many observational studies have reported: depression is more common in patients with type 2 diabetes, rheumatoid arthritis, and coronary artery disease—all of which involve chronic inflammation—than it is in people in the general population. It would also explain why interferon- $\alpha$ , a synthetic cytokine used to ramp up the immune system of patients with cancer or hepatitis C, causes depression in 30% to 50% of patients, depending on the dose used.

Of course, such observational studies document only an association between cytokine elevation and depression, not cause and effect. But a 2006 review identified 17 studies that reported elevated levels of various cytokines or other biological signs of inflammation in the blood or spinal fluid of patients with major depression who were otherwise healthy.

More recently, the Leiden 85-plus Study, a prospective longitudinal study in the Netherlands, measured blood levels of six biological markers of inflammation when each of the 267 participants first entered the study, at age 85. Five years later, the researchers found that elevated baseline levels of three blood markers of inflammation—C-reactive protein (CRP) and two cytokines—preceded the development of depression in participants whose mood had been normal when they entered the study.

**Possible mechanisms.** Cytokines and other immune system molecules may contribute to depression in several ways. For example, cytokines affect the synthesis, release, or reuptake of dopamine, serotonin, and other neurotransmitters. They stimulate the release of hormones involved in the hypothalamic-pituitary-adrenal axis, which underlies the stress

response. They also affect the brain's ability to nourish and support neurons and the synaptic connections between these brain cells, which enables learning and memory.

**Treatment implications.** About one in three patients with depression experiences only partial relief of symptoms from current drug therapies—or does not respond at all (see *Harvard Mental Health Letter*, August 2008). Researchers now think that understanding the role of inflammation in depression may help them improve treatment.

Preliminary research suggests that patients with increased blood levels of inflammatory cells are less responsive than other patients to antidepressant treatment. Likewise, a handful of early studies suggest that some anti-inflammatory drugs might help treat depression.

For instance, two small studies have found that combining an antidepressant with some type of anti-inflammatory drug improves mood in patients with major depression more than an antidepressant alone. Larger and better-controlled studies are necessary, however, before clinicians will know whether this is something to recommend for their patients.

## Inflammation and schizophrenia

Over the years, researchers have linked many infectious agents to an increased risk of schizophrenia and other psychotic disorders. But it's never been clear which infectious agents were the most important, or how they might cause psychosis and other symptoms of schizophrenia.

A review of five studies, for example, showed that individuals with newly diagnosed schizophrenia were more likely than controls to have antibodies to Cytomegalovirus, which spreads through breast milk, saliva, and other bodily fluids. And multiple reports have implicated the influenza virus.

Meanwhile, a meta-analysis of 23 studies found that patients with schizophrenia were nearly three times as likely as controls to be infected with *Toxoplasma gondii*, a parasite transmitted through

cat feces or contaminated soil or water. More recently, scientists at the Walter Reed Army Institute of Research examined blood samples collected from soldiers both before and after a diagnosis of schizophrenia and compared them with blood samples from controls. Although they looked for evidence of nine types of infections, only a pre-diagnosis infection with *T. gondii* increased the chance of developing schizophrenia.

**Common pathology.** Because multiple pathogens have been implicated in schizophrenia, researchers started trying to identify a common pathological process that might occur in response to infection. As with depression, the focus has turned to inflammation.

One body of evidence suggests that prenatal exposure to maternal infection may activate cytokines and other elements of inflammation—in either the fetus or the mother. This short-term or “acute” inflammatory response has long-term consequences for the fetal brain, which is actively developing. Although the exact mechanism of damage is not known, one theory is that acute inflammation causes abnormalities in apoptosis, a form of programmed cell death that prunes unnecessary nerve cells, making brain functioning more efficient. The result could be the type of abnormal thinking seen in schizophrenia.

A separate body of evidence implicates chronic inflammation later in life, based on studies that have found that patients with schizophrenia have higher blood levels of inflammatory chemicals than controls do. The thinking is that chronic inflammation may contribute to symptoms of schizophrenia—particularly the difficulties in thinking that tend to emerge as the disease progresses—in one of two ways. Inflammation causes irregularities in blood flow (a condition known as vascular dysregulation), so that the brain may be deprived of sufficient oxygen and nutrients. Another leading theory is that

inflammation causes insulin resistance and other metabolic problems, so that the brain cannot adequately metabolize blood sugar for energy.

However, the research on the impact of chronic inflammation later in life has been inconsistent, with some studies finding no difference in inflammatory biomarkers that would differentiate patients from controls. This may reflect the heterogeneity of schizophrenia. And because inflammatory cells and proteins may become activated at times of mental distress, it's possible that elevated levels of inflammatory biomarkers are a consequence rather than the cause of schizophrenia.

It's also likely that some individuals are more vulnerable than others to damage from inflammation. A recent large genetic study found that patients with schizophrenia had alterations in the area of chromosome 6 that contains genes important for normal immune system functioning.

**Therapeutic implications.** Although it's not yet clear if chronic inflammation contributes to symptoms of schizophrenia, there is evidence that it may affect response to treatment. Preliminary studies in patients with schizophrenia have suggested that elevated markers of inflammation predict poorer response to medication and more severe symptoms.

For example, a study of 79 patients with schizophrenia found that those with higher baseline spinal fluid levels of a biological marker of inflammation, interleukin-2 (IL-2), were more likely than other patients to experience a worsening of psychotic symptoms after they temporarily stopped treatment with haloperidol (Haldol). Another study followed 78 patients with schizophrenia who were treated with risperidone (Risperdal) or haloperidol for 12 weeks. Patients whose baseline blood levels of IL-2 were lower were more likely to improve with drug treatment than those whose baseline levels were higher. In another

study, researchers found that patients whose blood levels of CRP were above the normal range had worse psychotic symptoms than those whose CRP levels were normal.

Because so much evidence suggests some type of role for inflammation in schizophrenia, several research teams are currently exploring whether it's possible to improve treatment response by adding various anti-inflammatory drugs to antipsychotic therapy. So far, the results of preliminary studies have been mixed—but the research continues and may produce a clearer answer in the next few years.

### Other mental disorders

In the wake of the growing evidence of the role of infection and the immune response in depression and schizophrenia, scientists are also investigating the potential link with other mental disorders, including autism spectrum disorders and bipolar disorder. Whether a connection exists remains to be seen, but the question about the potential role of microbes in mental illness remains as provocative today as it was more than a century ago. ♥

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For more references, please see [www.health.harvard.edu/mentalextra](http://www.health.harvard.edu/mentalextra).

# Treating premenstrual dysphoric disorder

Options include drugs targeting serotonin and various types of hormone therapy.

Most women experience some degree of emotional or physical discomfort a few days before and just after their menstrual period begins each month. About 5% of women of childbearing age, however, experience premenstrual symptoms that are so severe they cause significant mental distress and interfere with work, school, or relationships—thereby meeting the criteria for premenstrual dysphoric disorder, or PMDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*; see box, page 5). Another 18% to 35% of women suffer from less severe, but nevertheless bothersome, premenstrual symptoms.

Although sometimes dismissed as trivial, PMDD can disrupt a woman's life and relationships so completely, she may despair that life itself is not worth living. About 15% of women with PMDD attempt suicide. Fortunately, treatment options exist for PMDD—but the most effective are not always prescribed.

## Risk factors and diagnosis

Brain areas that regulate emotion and behavior are studded with receptors for estrogen, progesterone, and other sex hormones. These hormones affect the functioning of neurotransmitter systems that influence mood and thinking—and in this way may trigger PMDD. But it's not clear why some women are more sensitive than others. Genetic vulnerability likely contributes. Other risk factors for developing PMDD include stress, being overweight or obese, and a past history of trauma or sexual abuse.

A key challenge in diagnosis is differentiating between mild premenstrual symptoms, which may be annoying but are not disabling, and those severe enough to interfere with daily life.

Partly for this reason, the *DSM-IV* includes PMDD in an appendix of conditions needing further study.

Two other common diagnostic schemes list different criteria and use different terminology. The World Health Organization's *International Classification of Diseases, Tenth Edition* describes a disorder called premenstrual tension syndrome, while criteria from the American College of Obstetricians and Gynecologists help to distinguish premenstrual symptoms severe enough to cause impairment.

Regardless of which criteria clinicians use, it's important to rule out other conditions that cause symptoms similar to PMDD, such as depression, dysthymia, anxiety, and hypothyroidism.

## Serotonin reuptake inhibitors

Antidepressants that slow the reuptake of serotonin are effective for many women with PMDD. Options include selective serotonin reuptake inhibitors (SSRIs) such as citalopram (Celexa) and fluoxetine (Prozac); the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor); and a tricyclic antidepressant that has a strong effect on serotonin, called clomipramine (Anafranil). Studies report that 60% to 90% of women with PMDD respond to treatment with drugs that block reuptake of serotonin, compared with 30% to 40% of those who take a placebo.

Other types of antidepressants, which target neurotransmitters other than serotonin, have not proven effective in treating PMDD. This suggests that serotonin reuptake inhibitors work in some way independent of their antidepressant effect—but their mechanism of action in PMDD remains unclear.

These drugs also alleviate symptoms of PMDD more quickly than depression, which means that women don't necessarily have to take the drugs ev-

## KEY POINTS

- Antidepressants that slow the reuptake of serotonin provide effective treatment for premenstrual dysphoric disorder (PMDD).
- These drugs alleviate PMDD more quickly than depression, which means that women don't necessarily have to take the drugs every day.
- Hormone therapies provide additional options, but are generally considered second-line treatments.
- Some dietary and lifestyle changes may also help relieve symptoms.

ery day. Instead, women can take them on an intermittent basis, also known as luteal-phase dosing because it coincides with the roughly 14-day span that begins just after ovulation and ends when menstruation starts.

The decision about whether to take a serotonin reuptake inhibitor every day or on an intermittent basis depends on the type of symptoms a particular woman experiences and if the symptoms of PMDD are superimposed on a more persistent depression. Intermittent dosing is sufficient for treating irritability or mood, but daily medication may be necessary to control somatic symptoms such as fatigue and physical discomfort.

Side effects of serotonin reuptake inhibitors are usually relatively mild and transient. Nausea, for example, typically subsides after several days of taking a drug for the first time—and the problem tends not to recur even when the drug is taken intermittently.

Sexual side effects, such as reduced libido and inability to reach orgasm, can be troubling and persistent, however, even when dosing is intermittent. Of course, PMDD can also lessen sexual desire, so as a practical matter, taking a serotonin reuptake inhibitor on an intermittent basis may still seem

like an acceptable strategy. (For information about how to deal with the sexual side effects of antidepressants, see *Harvard Mental Health Letter*, May 2008.)

If anxiety or insomnia are the prevailing symptoms, a clinician may prescribe a benzodiazepine, such as alprazolam (Xanax), in addition to an SSRI or SNRI. Just keep in mind that benzodiazepines may lead to dependency. This problem can be avoided by monitoring use and—in the case of patients with a history of substance abuse—by discussing risks specific to this subgroup.

### Hormone therapy

One of the most common PMDD treatments is progesterone supplementation, but the studies consistently find no evidence that a deficiency of this hormone contributes to the disorder.

The hormone therapies that do seem to work in PMDD act not by countering hormonal abnormalities, but by interrupting aberrant signaling in the hypothalamic-pituitary-gonadal circuit that links brain and ovaries and regulates the reproductive cycle. Largely because of side effects, however, the following strategies are considered second-line treatments for PMDD.

**Oral contraceptives.** Although frequently prescribed for PMDD because they regulate and stabilize reproductive hormones, oral contraceptives have seldom been studied for this purpose, and it's not clear if they are effective.

The one exception is YAZ, a contraceptive approved by the FDA in 2006 that combines ethinyl estradiol (an estrogen) with drospirenone. Clinical trials have demonstrated that this drug is effective for treating PMDD.

**Estrogen.** Another option is to inhibit ovulation with estrogen, which can be delivered via a skin patch or via a subcutaneous implant. Doses of es-

### Proposed criteria for premenstrual dysphoric disorder (PMDD)

- Five or more of the following symptoms (at least one related to mood) for most menstrual cycles in the past year:
  - Depression
  - Anxiety or tension
  - Sudden mood changes
  - Irritability
  - Loss of interest in daily activities
  - Difficulty concentrating
  - Decreased energy
  - Food cravings and appetite changes
  - Insomnia or sleepiness
  - Physical symptoms, such as breast tenderness or bloating
- Symptoms interfere with activities, work, school, or relationships
- Symptoms are not due to a cyclical exacerbation of another disorder
- Documentation by daily symptom ratings for at least two menstrual cycles

Source: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*

trogen tend to be higher than those prescribed for hormone therapy during menopause, but lower than those used for contraception in childbearing years. If estrogen is prescribed, it should be taken along with a progestogen to reduce risk of uterine cancer—except for women who have had a hysterectomy.

**GnRH agonists.** Gonadotropin-releasing hormone (GnRH) agonists, which are usually prescribed for endometriosis and infertility, suppress the hormonal cycle—and may be helpful for women whose PMDD symptoms have not responded to other drugs.

Examples of GnRH agonists include buserelin (Suprefact) and goserelin (Zoladex). But these agents can induce a menopausal state, triggering hot flashes and increasing risk of osteoporosis, so they are often supplemented with estrogen and a progestogen—which may trigger PMDD symptoms again in some women.

### Under investigation

Lifestyle changes and psychotherapies have not been well studied in PMDD, but a few have shown promise.

**Diet.** The usual dietary advice given to women with mild or even moderate premenstrual symptoms—such as consuming less caffeine, sugar, or alcohol, and eating smaller, more frequent meals—is unlikely to help women with PMDD.

Preliminary evidence suggests that what *may* help is consuming more high-protein foods or complex carbohydrates to raise levels of tryptophan, a precursor of serotonin and other neurotransmitters.

**Aerobic exercise.** Although it has not been well studied for PMDD, a wealth of evidence concludes that aerobic physical activity, such as walking, swimming, or biking, tends to improve mood and energy levels.

**Supplements.** Vitamin B<sub>6</sub>, calcium, magnesium supplements, and herbal remedies have all been studied for use in PMDD—but as yet there is no consistent or compelling evidence leading to consensus about their efficacy. ♥

Cunningham J, et al. "Update on Research and Treatment of Premenstrual Dysphoric Disorder," *Harvard Review of Psychiatry* (April 1, 2009): Vol. 17, No. 2, pp. 120–37.\*

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For more references, please see [www.health.harvard.edu/mentalextra](http://www.health.harvard.edu/mentalextra).

# Lithium-induced kidney problems

*Serious problems are unusual, but monitoring is key.*

**L**ithium is one of the most effective treatments for bipolar disorder, not only helping to prevent relapse, but also reducing risk of suicide in these patients (see *Harvard Mental Health Letter*, January 2008). But clinicians and patients may be concerned about risks of long-term lithium use, including damage to the kidneys.

In the past few years, however, researchers have better defined what kidney problems might occur and how to guard against them.

## Excess thirst and urination

The most common lithium-induced kidney problem is impaired ability to concentrate urine, which may affect up to 60% of patients in the beginning of treatment, with the problem persisting in about 20% to 25%. The main symptoms—excessive thirst (polydipsia) and urination (polyuria)—are sometimes dismissed as unavoidable and even minor side effects of lithium treatment.

But these symptoms are evidence that the kidneys are not responding to the antidiuretic hormone that normally signals the kidneys to concentrate urine, a condition called nephrogenic diabetes insipidus.

Healthy people produce about one to two liters of urine per day. Anything more than three liters of urine output per day is considered polyuria. In patients with nephrogenic diabetes insipidus, urine output may reach up to 15 liters per day. If fluid intake does not match output, people may become so dehydrated that they develop neurological symptoms such as fatigue, headache, or lethargy. Furthermore, dehydration can also lead to toxic lithium levels, which in turn can damage the kidneys and other organs. (This is one reason clinicians advise patients taking lithium to ingest adequate amounts of liquid.)

**Initial treatments.** If a patient becomes excessively thirsty or urinates frequently while on lithium, the first step is to switch to a once-daily dose of the drug taken at bedtime, when urine production naturally slows. If this doesn't help, patients can increase fluid intake to avoid dehydration, while taking a lower dose of lithium.

**Switch drugs.** Patients can also try switching from lithium to a more kidney-friendly mood-stabilizing drug such as valproic acid (Depakote) or carbamazepine (Tegretol). Except in cases of lithium toxicity or acute kidney failure, it's important to reduce the lithium dose slowly rather than stopping it abruptly, to reduce risk of relapse and suicide.

**Take a diuretic.** If the benefits of lithium are so clear that it is desirable to manage a persistent urine-concentrating problem, patients can take a diuretic in addition to lithium. Although diuretics usually *increase* urine output, certain diuretics can affect how the kidneys handle lithium in a way that actually reduces urine output in people with nephrogenic diabetes insipidus.

The thiazide diuretic hydrochlorothiazide (Esidrix, Hydrodiuril) is one of these. If it is prescribed, the lithium dose is typically cut by half, because thiazide diuretics boost lithium levels in the blood and could cause toxicity. It's also important to monitor for imbalances of electrolytes, the salts that travel in the bloodstream. In particular, clinicians look out for low potassium levels—a potassium supplement may be necessary.

For this reason, the first choice is usually amiloride (Midamor), a potassium-sparing diuretic that may help patients avoid needing a potassium supplement. Another advantage to this drug is that it does not affect levels of lithium, reducing risk of toxicity.

**The role of NSAIDs.** Nonsteroidal

anti-inflammatory drugs (NSAIDs) can reduce excess urination, but—as with some diuretics—this class of drugs also can boost the lithium in the blood, sometimes to toxic levels. The NSAID most often discussed in nephrogenic diabetes insipidus is indomethacin (Indocin). It inhibits prostaglandins, compounds that are involved with regulation of urine flow (among numerous other functions). Because of the risk of toxicity, using NSAIDs to control lithium-induced nephrogenic diabetes insipidus is worthwhile only when lithium is uniquely beneficial for managing a patient's psychiatric symptoms.

## Declining kidney function

Each kidney contains a million nephrons, tiny processing units that filter waste and produce urine. Nephrons have a complex structure, and—in a small proportion of patients—lithium causes enough damage to nephrons to gradually decrease function. Rarely, kidney failure occurs.

Kidney impairment is diagnosed with a combination of blood and urine tests. A standard measure of overall kidney function is the glomerular filtration rate (GFR). One frequently cited study analyzed reports of kidney function in 1,172 patients on lithium who had taken part in studies published from 1979 to 1986. It found that GFR was in the normal range in 85% of the patients, while it was only mildly decreased in the remaining 15%. But other researchers have noted that some patients on lithium experience a slow progressive decline in GFR or other subtle kidney damage that may elude clinical detection for years.

Taking lithium is not the only reason kidney function may become impaired. Kidney capacity gradually decreases with age, even in healthy people. And two common chronic conditions—high blood pressure and diabetes—can

further impair kidney function by damaging blood vessels.

The first sign of kidney deterioration is the detection of tiny amounts of the protein albumin in the urine. As kidney deterioration worsens, larger amounts of albumin and other proteins are found in urine. The next stage is chronic kidney disease, or gradually decreasing function. Those most at risk are patients taking lithium continually for at least 20 years. Untreated, chronic kidney disease could eventually lead to kidney failure.

Patients' kidney function should be evaluated before they take lithium and monitored regularly. The American

Psychiatric Association recommends testing kidney function every two to three months for the first six months of lithium treatment, and then following up with kidney function tests at least annually or semiannually afterward, unless more frequent testing is indicated medically. This can be done with simple blood tests taken at the same time as checking the lithium level.

If kidney function becomes moderately impaired (defined as a GFR of 45–59 ml/min/1.73m<sup>2</sup>), or seems to be declining steadily, it may be wise for patients to see a kidney specialist (nephrologist). Sometimes changes in

diet can help reduce the kidneys' workload, but other steps may be necessary—including stopping lithium treatment and switching to another drug. It's also important to keep blood pressure under control and take other steps to guard heart health, because high blood pressure is associated with worsening kidney function, and vice versa. ♥

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## In brief

### Drug fails to subdue repetitive behavior in children with autism spectrum disorders

People with autism spectrum disorders often engage in repetitive behaviors, such as flapping their hands or arms, turning in circles, or repeating words or sounds. Although studies had suggested that selective serotonin reuptake inhibitors (SSRIs) might help to reduce repetitive behaviors in adults with autism spectrum disorders, a recent randomized controlled study has found no such benefit for children taking one drug in this category—citalopram (Celexa).

Researchers at the University of Washington, Seattle, randomly assigned 149 children, ages 5 to 17, to citalopram or placebo. The children entered the study with moderate levels of repetitive behavior.

At the end of the 12-week study, about one in three children in both groups had improved, as measured by

the Clinical Global Impressions, Improvement subscale—a standard tool that assesses repetitive behaviors. But the children assigned to citalopram were significantly more likely to experience hyperactivity, insomnia, diarrhea, decreased concentration, and other adverse side effects during treatment.

The authors note that SSRIs may be helpful at alleviating depression or anxiety in children with autism spectrum disorders, but are likely not effective at reducing repetitive behaviors.

King BH, et al. "Lack of Efficacy of Citalopram in Children with Autism Spectrum Disorders and High Levels of Repetitive Behavior: Citalopram Ineffective in Children with Autism," *Archives of General Psychiatry* (June 2009): Vol. 66, No. 6, pp. 583–90.

### Supplement may ease compulsive hair pulling

Trichotillomania, a disorder that causes compulsive hair pulling, is not easy to treat. Cognitive behavioral therapy is effective, but symptoms tend to recur after therapy ends. And no medication has proven effective in controlled trials (see *Harvard Mental Health Letter*, April 2007).

Now a small randomized controlled study has concluded that N-acetylcysteine, an amino acid found in health food stores, was significantly more effective than placebo. In double-blind fashion, investigators randomized 50 people, ages 18 to 65, to 12 weeks of treatment with the amino acid or a placebo.

At the end of the study, 56% of those assigned to the amino acid said they felt much improved, compared with 16% of those assigned to placebo. A clinical as-

essment found that N-acetylcysteine reduced frequency of hair pulling by a mean of 41%—about equal to that reported by other studies of cognitive behavioral therapy alone or in combination with medication. The people taking the amino acid did not experience significant side effects.

N-acetylcysteine may help subdue compulsive hair pulling by modulating glutamate, the brain's key "excitatory" neurotransmitter. But the investigators caution that nearly half of patients in the amino acid group saw no improvement, and that longer-term studies are needed.

Grant JE, et al. "N-Acetylcysteine, a Glutamate Modulator, in the Treatment of Trichotillomania," *Archives of General Psychiatry* (July 2009): Vol. 66, No. 7, pp. 756–63.



**Q** To prevent post-traumatic stress disorder, is it helpful to provide psychotherapy to everyone who has been exposed to a significant trauma?

**A** The research so far says no. By the end of the 1990s, investigators had demonstrated that a single “critical incident stress debriefing” group session did not reduce the risk of developing post-traumatic stress disorder (PTSD) for individuals who had been exposed to a trauma. This technique, which became popular in the 1980s for emergency service workers, such as firefighters and police officers, involved reviewing traumatic experiences in a group setting. Not only was it ineffective for preventing PTSD, in some instances it appeared to increase the incidence of psychological distress.

A review published recently by the Cochrane Collaboration revisited the question to determine whether or not more extended psychotherapeutic approaches might succeed where debriefing failed. The authors reviewed randomized controlled trials of interventions that involved at least two sessions, were provided within three months of a traumatic incident, and were aimed at reducing the risk of PTSD. They sought studies where participants had an experience that met the criteria for a trauma described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)—that is, the individuals had been directly confronted by a frightening loss of life, a life-threatening injury, or a grave threat.

The authors pointed out that, whereas many practitioners advocate providing care selectively, large-scale trauma often triggers public demand to offer an intervention to everyone who has been exposed. Thus the review was designed to consider studies where everyone exposed to a given threat was randomized either to a particular treatment or a control condition, such as a waiting list or usual care.

The eight studies that met review criteria used treatments representing a range of established techniques: cognitive behavior therapy, stress management, relaxation, eye movement desensitization and reprocessing, teaching of coping skills, or providing general psychological information. These studies were conducted in various countries and involved a range of traumatic

events, such as physical assault, armed robbery, traumatic births, and traffic accidents.

Unfortunately the reviewers were unable to find evidence that any of the treatments were effective for preventing symptoms of PTSD, anxiety, or depression. And, as with debriefing, some individuals may have gotten worse.

It is disappointing but ultimately helpful to learn that there is as yet no “best practice” after a far-reaching traumatic event. Therefore it is unreasonable in times of crisis to zealously mobilize a large mental health force charged with providing an intervention for every affected individual.

A mental health professional’s intuition is usually to urge people in distress to talk. But some PTSD experts believe talking may backfire after a traumatic experience by reinforcing and intensifying memories that may better be forgotten—or at least attenuated in some way.

The interventions reviewed involved general support, reassurance, teaching of coping skills, and relaxation techniques that are not intended to get trauma victims to focus on their memories and would seem to be benign and helpful. But when every member of a traumatized population is treated, the simple act of attending a group session may cause some individuals to rehearse traumatic events who would not otherwise have done so. Others may fall into conversation about events during non-technical, social portions of an encounter. In other words, the increase in PTSD symptoms in those who became worse may be a true side effect of psychotherapy.

For now, the research indicates that it is not helpful to provide psychotherapy to everyone exposed to a trauma. The review authors rightfully call for more research to help clinicians decide what intervention is best for each individual and—perhaps more important—when to intervene.

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