Idiopathic recurrent stupor is a little-known sleep disorder characterized by periodic episodes in which a person becomes stuporous (i.e., arousal only by vigorous stimulation) for up to several days. When the stupor phase ends, the person’s sleep-wake patterns return to normal. The stupor phase may be preceded by agitation, aggression, depression, confusion, amnesia, difficulty forming words (e.g., slurred speech), ataxia (i.e., uncoordinated walking), and psychomotor slowing (i.e., thinking and moving slowly). Once the stupor phase ends, subsequent episodes of stupor may not recur until months or even years later. No factor appears to trigger the onset of the episode (hence, it is idiopathic), although some scientists suspect that overproduction of endogenous benzodiazepines — also called endozepines — may be a trigger.1 Other scientists question whether these molecules are truly the cause of the disorder.2

### Benzodiazepines: Synthetic & Endogenous

Benzodiazepines are a group of molecules that have anti-anxiety, sedative, hypnotic, anticonvulsant, and muscle-relaxant effects. Scientists did not understand how this class of drugs worked until 1977 when it was discovered that the drugs bind to specific sites on the gamma-amino-butyric acid (GABA) receptor found on the surface of a central nervous system (CNS) neuron.3 When a GABA molecule binds to its site on the receptor, negatively-charged calcium ions flood into the neuron. This raises the negative charge within the neuron (i.e., the neuron becomes hyperpolarized) and inhibits signal transmission in the neuron. Slowed signaling in the CNS results in sedation and relaxation. When a benzodiazepine molecule binds to its site on the GABA receptor at the same time that a GABA molecule is bound to the receptor, hyperpolarization is enhanced.

With the discovery of synthetic benzodiazepines (e.g., diazepam) affinity for the GABA receptor, scientists concluded that endogenous benzodiazepines must exist. However, finding an endogenous benzodiazepine was difficult until 1978 when scientists first discovered two factors in pig brain extract that seemed to be endogenous benzodiazepines.4 The factors, named by Greg D. Colello and colleagues as benzodiazepine competitive factor I (BCF I) and benzodiazepine competitive factor II (BCF II), displaced diazepam from its site on the GABA receptor.4 Each factor was thought to contain several polypeptides (i.e., molecules made up of more than one small protein). Because of this, Colello was uncertain whether each factor as a whole was an endozepine or if a constituent peptide of the factors could be the endozepine.

Further attempts to find endozepines led to the investigation of other molecules such as diazepam-binding inhibitor (DBI) and endozepine-4. DBI was found in rat brain extract and purified for the first time in 1983 by Alessandro Guidotti and colleagues.5 They determined that DBI was a polypeptide but suspected that it was a precursor molecule and that perhaps one or more of its constituents was the long-sought endozepine. Since that time, enzymatic degradation of DBI into its constituent peptides has led to the discovery of several peptides that could finally be called endozepines. Some examples of DBI-derived endozepines are triakontatetraneuropeptide (TTN) and octadecaneuroepeptide (ODN).6 In 1992, Jeffrey D. Rothstein and colleagues found three nonpeptide molecules in cerebellar granule cells that had an affinity for the benzodiazepine site.7 They suspected that these molecules were endozepines. One molecule in particular, endozepine-4, had the strongest affinity for the benzodiazepine site.

### The Endozepine Connection

Scientific focus on endozepines as a factor in idiopathic recurrent stupor began in the 1990s when reports began to appear in the medical literature of people who had repeated episodes of stupor or coma lasting a few hours to a few days.8,9 No factor such as toxicity, epilepsy, or metabolic dysfunction could explain the stupor. Symptoms of the stupor looked very similar to those of hepatic encephalopathy (i.e., brain dysfunction due to liver disease), although the patients had no liver dysfunction. In hepatic encephalopathy, ammonia and other toxins build up in the brain and other tissues as liver disease impairs the organ’s ability to breakdown harmful substances. As toxin levels in the brain rise, the person begins to have changes in thinking (e.g., slowed thinking), movement (e.g., ataxia), and behavior (e.g., agitation). As toxicity continues to increase, the person becomes increasingly sleepy and stuporous and ultimately comatose. Currently, flumazenil, a benzodiazepine antagonist drug, is used to quickly reverse stupor in people with hepatic encephalopathy.

In 1992 Paolo Tinuper and colleagues used flumazenil to resolve an episode of idiopathic stupor in a patient.8 During the stupor phase, Tinuper subjected the patient’s plasma and cerebral spinal fluid (CSF) to a radioreceptor binding assay. The test revealed that one molecule had an affinity for the benzodiazepine site, but it did not appear to be a synthetic benzodiazepine. From this, Tinuper proposed that excessive production of an endogenous
benzodiazepine-like substance may be involved in cases of idiopathic recurrent stupor.

Also in 1992, Rothstein and colleagues noted that during the stupor phase the level of endozepine-4 rose extremely high in the CSF and blood of three people with idiopathic recurrent stupor. The endozepine-4 level quickly fell back to normal once the stupor phase ended. Rothstein concluded that endozepine-4 may be the cause of, or at least contribute to, idiopathic recurrent stupor.

**Inconclusive Studies**

Studies of patients with suspected idiopathic recurrent stupor have produced mixed results. In 1998 Elio Lugaresi and colleagues reported their experience with 20 patients who they diagnosed with idiopathic recurrent stupor. The patients lived in different parts of Italy. Gas chromatography-mass spectrometry (GC-MS) performed on the blood of nine of the patients during the stuporous phase ruled out synthetic benzodiazepines and indicated that the endozepine-4 levels were high enough to induce a stuporous state. Based on this, Lugaresi concluded that an accidental overdose of benzodiazepines was not responsible for the recurrent episodes of stupor in the patients.

Lugaresi was later presented with a cluster of nine patients with idiopathic recurrent stupor. This time the patients lived in the same rural area and the onset of the stuporous attacks began at virtually the same time. Toxicological tests did not detect the presence of synthetic benzodiazepines, but liquid chromatography-mass spectrometry (LC-MS) revealed that the patients had high levels of lorazepam. This meant that they were being purposely poisoned, a finding that ultimately led to the arrest of the perpetrators.

LC-MS is more sensitive than GC-MS in testing for synthetic benzodiazepine. In GC-MS, lorazepam is virtually indistinguishable from endozepine. To avoid misleading results, Lugaresi suggests that patients with suspected idiopathic recurrent stupor have the LC-MS test performed rather than the GC-MS test.

In 2004 Granot and colleagues reported the case of a 71-year-old man who had experienced episodes of idiopathic recurrent stupor for 16 years. The attacks occurred every three to six months. Typically, the onset of the episode would begin with 20 minutes of increasing stupor. In some attacks the stupor would progress to coma. After 12 to 36 hours the patient would reawaken. The patient’s urine test was positive for benzodiazepines. However, the patient had been prescribed the benzodiazepine drug lorazepam by his physician, who suspected that stress may have been a factor in the stuporous episodes since they tended to occur during stressful times in the patient’s life. Despite this finding, Granot suspected that intermittent overproduction of endozepines may have been contributing to the patient’s recurrent episodes of stupor. Later it became apparent that the patient’s wife had been overdosing him intermittently for several years with lorazepam and oxazepam (a benzodiazepine). The wife was diagnosed with Munchausen by proxy syndrome (a disorder in which a caregiver invents, induces, or exaggerates illness in another to get sympathetic attention from medical staff, family, or others). Granot cautions that although the disorder Munchausen by proxy is uncommon, it needs to be considered as part of the differential diagnosis in a person with suspected idiopathic recurrent stupor.

**Uncertain Classification**

Having recurrent episodes of idiopathic stupor is considered rare since stupor is usually secondary to other factors such as liver or kidney dysfunction, drug toxicity, respiratory failure, and epilepsy. Because of its rarity, scientists remain uncertain whether the disorder exists. Reflecting this uncertainty, the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR)* by the American Psychiatric Association classifies idiopathic recurrent stupor as a type of recurrent central hypersomnia, but the most recent edition of the *International Classification of Sleep Disorders (ICSD-2)* by the American Academy of Sleep Medicine does not list this disorder.

The closest that the ICSD-2 comes to describing a hypersomnia involving recurrent episodes of idiopathic stupor is Kleine-Levin syndrome. In Kleine-Levin syndrome a person has recurrent episodes of hypersomnia in which he or she sleeps excessively (i.e., 18 or more hours per day for three or more days at a time). The person is rousable. When awake during the hypersomnia phase, the person may eat excessively, may be hypersexual or irritable, and may act confused. Once the episode is over, sleep-wake patterns return to normal. The electroencephalogram (EEG) of a Kleine-Levin sufferer shows slowed activity during the hypersomnia phase, whereas the EEG in an idiopathic recurrent stupor sufferer shows fast activity of 14-16 cycles/second during the stupor phase. This difference suggests that these may be two distinct sleep disorders.

**Conclusions**

Research continues on this rare condition as scientists struggle to understand what triggers the stupor phase. Recent studies have focused on treating idiopathic recurrent stupor. Flumazenil and modafinil have both shown encouraging results in preventing recurrent episodes. Areas for future research include determining the molecular structure of endozepines; standardizing the analytical methods that are used to detect and purify endozepines; and developing a more accurate differential diagnostic procedure. Gaining more clarity on these issues would help people who must live with the disabling consequences of idiopathic recurrent stupor.

**References**


*Continued on page 26...*


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