Idiopathic environmental intolerance (multiple chemical sensitivity)

AUTHORS: Donald W Black, MD, Scott Temple, PhD
SECTION EDITOR: Joel Dimsdale, MD
DEPUTY EDITOR: David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Apr 16, 2023.**

INTRODUCTION

Idiopathic environmental intolerance (IEI), formerly called multiple chemical sensitivity, is a subjective illness marked by recurrent, nonspecific symptoms attributed to low levels of chemical, biologic, or physical agents. These symptoms occur in the absence of consistent objective diagnostic physical findings or laboratory tests that define an illness [1,2]. Many experiments and observational studies consistently identify psychopathology in patients with IEI, and implicate behavioral or psychiatric causes for this illness [3]. This indicates that the underlying illness in many cases of IEI is actually a psychiatric disorder, such as a somatoform, depressive, or anxiety disorder [4,5].

This topic provides an overview of IEI, including clinical management of this condition. Related topics are discussed separately.

- (See "Somatic symptom disorder: Assessment and diagnosis" and "Somatic symptom disorder: Epidemiology and clinical presentation" and "Unipolar depression in adults: Assessment and diagnosis" and "Management of panic disorder with or without agoraphobia in adults" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Somatic symptom disorder: Assessment and diagnosis" and "Somatic symptom disorder: Epidemiology and clinical presentation" and "Unipolar depression in adults:

Assessment and diagnosis" and "Management of panic disorder with or without agoraphobia in adults" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Unipolar major depression in adults: Choosing initial treatment".)

- (See "Somatic symptom disorder: Assessment and diagnosis" and "Somatic symptom disorder: Epidemiology and clinical presentation" and "Unipolar depression in adults: Assessment and diagnosis" and "Management of panic disorder with or without agoraphobia in adults" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Somatic symptom disorder: Assessment and diagnosis" and "Somatic symptom disorder: Epidemiology and clinical presentation" and "Unipolar depression in adults: Assessment and diagnosis" and "Management of panic disorder with or without agoraphobia in adults" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Somatic symptom disorder: Assessment and diagnosis" and "Somatic symptom disorder: Epidemiology and clinical presentation" and "Unipolar depression in adults: Assessment and diagnosis" and "Management of panic disorder with or without agoraphobia in adults" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Somatic symptom disorder: Assessment and diagnosis" and "Somatic symptom disorder: Epidemiology and clinical presentation" and "Unipolar depression in adults: Assessment and diagnosis" and "Management of panic disorder with or without agoraphobia in adults" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Unipolar major depression in adults: Choosing initial treatment".)

DEFINITION AND BACKGROUND

Patients with idiopathic environmental intolerance (IEI) typically report sensitivity to multiple, chemically unrelated substances and becoming ill with heterogeneous, nonspecific symptoms when exposed to low concentrations of chemicals [6-8]. Patients attempt to minimize exposure by modifying their lives, sometimes in far reaching ways.

These "chemically sensitive" people are sometimes treated by "clinical ecologists" or "environmental clinicians" who believe the disorder is acquired, highly prevalent in the general population, and goes unrecognized by most other clinicians.

The most frequently used term for this condition is "multiple chemical sensitivity," but many other terms have also been used, including "environmental illness." The World Health Organization in 1996 proposed the term "idiopathic environmental intolerance" (IEI) be used instead, because it avoids unsubstantiated assumptions of etiology, and many people attribute symptoms to environmental agents other than chemicals, such as food or electromagnetic forces [9].

Criticisms of IEI as a distinct medical entity include the lack of reliable case definitions; the lack of consistent physical abnormalities and reproducible laboratory results; the use of unorthodox diagnostic procedures; and the use of unproven and potentially harmful treatments [10]. In addition, much of the research into IEI has been problematic due to excessive reliance upon surveys and self-reported symptoms, selection bias, lack of blinding, and inconsistent quality assurance of laboratory determinations [1].

Toxicity due to certain chemicals such as lead and arsenic is well established, including the signs, symptoms, and pathophysiology of the disease states that occur following exposure. No such information exists for IEI despite many years of research.

Prominent medical societies view IEI with marked skepticism [1,2,11-14]. As an example, the American Medical Association concluded that, "Until such accurate, reproducible, and well-controlled studies are available, the American Medical Association Council on Scientific Affairs believes that multiple chemical sensitivity should not be considered a recognizable syndrome" [14].

Psychiatric problems are present in most cases of IEI. The psychiatric basis for the illness does not negate the suffering and disability that occurs in these patients, and clinicians should remember that all psychiatric illness is ultimately a disorder of brain biology.

EPIDEMIOLOGY

Surveys show that many people report unusual sensitivity to everyday chemicals, but they do not tell us whether the complaints are clinically significant. As an example, the data do not distinguish between mild annoyance at cigarette smoke and a severe asthmatic reaction. Idiopathic environmental intolerance (IEI) covers a broad range of symptoms, and it is not at all

clear that people who report chemically sensitivities in a telephone survey resemble those who seek medical care for complaints of IEI.

A review found that IEI is reported only in Western industrialized societies and is unknown in other countries, despite the ubiquitous presence of chemicals to which the illness is attributed [15].

The only nationally representative study of IEI, conducted in Germany, found self-reported chemical sensitivity in 9 percent of the population, and a physician diagnosis of IEI in 0.5 percent [16]. Studies in United States communities found rates of self-reported chemical sensitivity ranging from 13 to 33 percent, and a prevalence of physician-diagnosed IEI in 3 to 6 percent [3,17-19].

Studies of sociodemographic variables associated with IEI have found:

- The mean age for patients seen in clinical settings is typically in the 30s or 40s [19-37]. Adults 65 years and older are less likely to identify themselves as chemically sensitive, compared to those who are younger [7]. Patient-reported symptom onset is often 10 to 15 years prior to presentation [7,19].
- IEI is more prevalent in women than men [3,7,16,17,19-40].
- Individuals who never married are significantly less likely to receive a diagnosis of IEI by a physician, compared to those who are married (odds ratio 0.56) [17,36].
- Race and ethnicity has not been well studied. Hispanic ethnicity was significantly associated with physician diagnosis of IEI in one survey (odds ratio 1.82) [17].
- Employment, income, and education are variably related to IEI. While population surveys have generally found that employment, income, and education are not significantly associated with the prevalence of IEI [7,17], patients seen in clinical settings are typically middle to lower class and well educated [20-33,36].

Health care utilization — Controlled studies demonstrate that patients with IEI symptoms use significantly more health care resources [28,33]. A cross-sectional study found that significantly more patients with IEI symptoms than controls visited an outpatient physician at least six times during the prior year (26 versus 10 percent), visited an emergency department at least once (45 versus 21 percent), or were hospitalized at least once (16 versus 6 percent) [33].

Psychosocial functioning — Multiple studies show that functional impairment (occupation, relationships, and leisure) is significantly greater for patients with IEI symptoms than for

controls [28,33]. A prospective study found these differences persisted at 32 months post baseline [29]. Functioning is poor because attempts to avoid alleged chemical triggers often result in loss of work and isolation from family and friends.

A one-year prospective study of 49 patients with IEI symptoms and 54 controls found patients were significantly more likely to have lost a job or stopped working (22 versus 0 percent) [28]. Other studies found that 15 to 77 percent of patients had stopped working temporarily or left a job because of their chemical sensitivities [26,30,33-35].

Multiple studies have found that patients with IEI symptoms have significantly poorer social functioning compared to controls [26,33,36]. In one study, 91 percent of patients had reduced contact with friends and 63 percent had reduced contact with family [30].

Other serious disruptions can occur. Patients take special precautions at home, adhere to special diets, limit travel, experience difficulty shopping in stores or eating in restaurants, and change their residence [28,30].

ETIOLOGY AND PATHOGENESIS

Although there is some disagreement whether idiopathic environmental intolerance (IEI) is a toxigenic or psychogenic illness, the evidence strongly demonstrates there is no immunologic or other biologic basis for IEI and that psychopathology causes the symptoms of IEI in at least some if not most cases [15,41-47].

Toxicogenic mechanisms — Clinical ecologists have generated many hypotheses explaining how toxins cause IEI symptoms. However, controlled studies show that the immune system is not involved and that immunologic tests are not diagnostic of IEI [23,28]. In addition, there are no empirical data to support other proposed mechanisms involving toxicology or oxidative damage [2,48].

Multiple review studies have consistently failed to find a systematic connection between exposure to environmental triggers and onset of IEI symptoms [3,34,49,50]. Provocation studies that exposed patients with IEI to different substances found that patients could not distinguish between active and placebo substances when blinding or masking was adequate. Some patients with IEI exhibited severe reactions to sham provocations, which in one study were so extreme that the trial had to be terminated. These findings indicate that the biological properties of the various implicated chemicals do not cause IEI symptoms.

The notion that IEI symptoms result from toxic chemical substances is not consistent with the level of exposure, which is far below the established level of toxicity. In addition, the suspected chemicals are common in the environment and well tolerated by the general population.

While it is clearly established that infectious microorganisms, allergens, and toxins can cause diseases (eg, asthma, rhinitis) that are accompanied by objective changes of bronchial or nasal function, IEI is marked only by subjective symptoms [2].

Many studies have attempted to find biologic correlates or markers of IEI, eg, electroencephalography or brain imaging [51,52]. However, none of these studies carefully selected subjects or used appropriate controls, the results were not specific to patients with IEI, and the results have not been consistently replicated in patients with IEI symptoms.

Psychogenic mechanisms — The high prevalence of psychiatric morbidity observed in patients with IEI supports the theory that psychopathology causes at least some cases of IEI [43,47]. In addition, a study of family psychiatric history in patients with IEI found first-degree relatives of patients were significantly more likely than relatives of controls to have depression (17 versus 7 percent), alcoholism (20 versus 6 percent), and antisocial personality disorder (8 versus 0 percent) [53]. (See 'Psychiatric disorders' below.)

IEI symptoms appear to stem from underlying psychiatric disease rather than any acute effect of chemical exposure. This was demonstrated in a study of 59 industrial workers exposed to low doses of metals and solvents on a daily basis (control group) and 300 patients with IEI symptoms [54]. Although controls and IEI patients had similar serum concentrations of solvents and controls had higher urine metal concentrations, the patients had significantly higher rates of psychiatric diagnoses and distress.

Some clinical ecologists argue that IEI causes psychopathology in the same manner as a chronic disease such as diabetes. This is contradicted by the finding that psychiatric disorders typically occur prior to the onset of IEI [23,25,28,38,42]. One multicenter study found that mental disorders predated the onset of IEI symptoms by a mean average of 17 years [34].

There are several other plausible hypotheses explaining how psychogenic factors cause IEI. None of these are mutually exclusive.

Anxiety — Several provocation studies indicate that some patients with IEI symptoms have a predisposition to anxiety disorders and that anxiety may be a causal mechanism in at least some cases of IEI [37,55-57]. One study compared 31 patients with IEI and 31 normal healthy controls by administering a single-breath inhalation of 35 percent carbon dioxide/65 per cent oxygen, a reliable trigger of experimental panic in patients with panic disorder [37]. Significantly

more patients with IEI suffered a panic attack compared to the healthy controls (71 versus 26 percent). A different provocation challenge study exposed 15 patients to their self-reported chemical "trigger" substances, which induced hyperventilation in 73 percent along with a rapid fall in pCO2 [55].

A genetic study found that the cholecystokinin B receptor allele 7, which is associated with panic disorder, was found in significantly more patients than controls (41 versus 9 percent) [58].

Conditioned response — Classic and operant conditioning may account for symptoms of IEI [1,15,59]. The theorized process begins with exposure to toxic or excess doses of a strong smelling chemical irritant that serves as the unconditioned stimulus. This is followed by the unconditioned response in the form of a physical or psychologic reaction. The same odor at a much lower concentration then serves as the conditioned stimulus and will trigger a conditioned response, with the same symptoms. Through stimulus generalization, different odors or irritants precipitate similar symptoms. Patients reduce their symptoms by avoiding the triggering chemicals and associated odors, and this negative reinforcement maintains the symptoms. Evidence supporting this hypothesis includes a prospective study that exposed patients with IEI (n = 18) and controls (n = 18) to low, nontoxic concentrations of an odorant (n-butanol) [60]. Patients with IEI rated the exposure as more intense and unpleasant, and the exposure elicited more symptoms (eg, irritation of the eye or skin, shortness of breath, and headache) over time.

Symptom amplification — Patients who learn about IEI may attribute their previously ill-defined chronic symptoms to this illness, which they regard as serious [61]. This misinterpretation intensifies the symptoms, which then leads to greater self-scrutiny [61]. Other ambiguous physical sensations are then viewed as further evidence of IEI. Thus, patient attention to benign but distressing physical sensations may be amplified through progressive preoccupation with symptoms, which is fueled by medical scrutiny, public health concern, and inappropriate media attention.

Iatrogenic — IEI may be iatrogenic in some patients because clinical ecologists assess patients with the goal of explaining symptoms in terms of their connection to environmental chemicals [1]. It is possible that some patients become convinced they have IEI through the power of suggestion [31].

A variety of studies have demonstrated that suggestion and expectation cause somatic symptoms in otherwise healthy volunteers [3,62,63]. One study demonstrated that in healthy volunteers who were exposed to an odor that was characterized as harmful, healthy, or neutral,

those who were informed the odor was harmful reported significantly more symptoms (eg, dizziness or headache) compared to those given a neutral or healthy bias [63].

In addition, the use of diagnostic tests and treatments may unintentionally reinforce symptoms or even increase the number of symptoms, thus exacerbating a patient's sense of illness [3,23].

Cognitive processing — Problematic cognitive styles may lead patients to somaticize when faced with adversity. Patients with IEI symptoms have externally oriented thinking and limited self-awareness, with a tendency to identify an environmental source of their symptoms and misattribute the symptoms to that external source [35]. In addition, biased attention and reasoning may lead to misattribution and misinterpretation of physical sensations [64-66].

Trauma — It is not known to what extent trauma is a risk factor for IEI. A study compared female patients with IEI symptoms to a control group of women who each had a chronic illness plus an anxiety or mood disorder [67]. Significantly more patients with IEI reported a history of sexual abuse (60 versus 25 percent) and physical abuse (50 versus 12 percent) [67]. However, a different study compared patients with IEI and controls, and found no significant difference in the number within each group who had a history of trauma (48 versus 41 percent) [68]. In addition, another study found that only 1 percent of 295 patients with IEI met criteria for posttraumatic stress disorder using a structured interview [35].

Coping mechanism — Some patients may avoid taking responsibility for their occupational, marital, and social problems and instead, cope with them by attributing them to IEI [27]. Assuming the sick role may provide certain rights and privileges that relieve the patient of undesired obligations. Somatization may be used as a means of communicating emotional distress. In addition, somatization may be used as a coping strategy in order to gratify dependency needs and the wish to be cared for by others, obtain social contact through doctor visits or support groups, manipulate interpersonal relationships, and compensate for having little control over others [69].

A study found that expressing feelings, especially negative ones, was significantly more difficult for patients with IEI compared to controls [27]. This supports the idea that patients with IEI express their emotional distress and seek help through physical symptoms, perhaps because there is less stigma associated with nonpsychiatric illnesses, or because patients have limited verbal skills and psychologic understanding [69]. A review found that IEI patients are more defensive, tend to deny psychopathology, and express distress through somatization [3].

CLINICAL FEATURES

Symptoms — The symptoms of idiopathic environmental intolerance (IEI) are diffuse, nonspecific, ambiguous, and common in the general population. There is no characteristic set of symptoms for IEI that can be distilled from the heterogeneous complaints involving a wide range of organ systems (table 1) [3,34]. In one study, 295 patients with IEI reported 252 different symptoms [35].

There are no essential differences in symptoms between patients who meet criteria for IEI and those who do not. A multicenter study of 290 patients treated at environmental medicine clinics compared the subset that met criteria for IEI according to their physician against the subset who did not [34]. There were no significant differences in the proportion of IEI patients versus non-IEI patients who reported respiratory (29 versus 30 percent), musculoskeletal (35 versus 39 percent), cardiovascular (14 versus 11 percent), gastrointestinal (38 versus 26 percent), dermatologic (24 versus 26 percent), head and sensory (34 versus 36 percent), and general (74 versus 68 percent) symptoms.

Patients with IEI commonly report cognitive impairment. As an example, more patients with IEI reported poor concentration or memory in the year prior to assessment, compared with controls (87 versus 28 percent) [30]. However, objective assessment of neuropsychologic functioning with standardized tests in patients with IEI reveals little or no impairment [28,30,50,70]. As an example, a battery of nine tests, which evaluated attention, concentration, memory, mental flexibility, and visual motor speed, was administered to 41 patients with IEI. The results showed that all of the scores fell within an average range for age [28]. In addition, the scores were essentially the same compared to a control group of patients with chronic musculoskeletal injuries.

Some studies have identified differences between patients with IEI and non-ill controls. As an example, a prospective study exposed patients with IEI (n = 18) and controls (n = 18) to low, nontoxic concentrations of an odorant (n-butanol) [60]. Patients with IEI manifested a higher pulse and lower pulse rate variability. Other differences between those with IEI and comparison groups include sleep disturbance and daytime sleepiness [71] and sensitivity to loud noises [72].

Chemical exposure — IEI symptoms often develop following a single massive chemical exposure such as accidentally being sprayed with pesticides. Other patients report intermittent or chronic exposure to low levels of chemicals such as repeated sprayings of pesticides around the home, or exposure to new carpeting or new furniture. Thus, exposure may last anywhere from seconds to years [23].

Chemical sensitivities are generally attributed to numerous unrelated compounds, but emphasis is usually placed on volatile synthetic compounds such as gasoline, paints, and

perfumes. Foods, yeast, electromagnetic radiation, and metals such as mercury amalgam fillings have also been alleged to cause IEI symptoms.

In one study, patients reported sensitivity to a mean of 79 substances [19]. Many clinical ecologists attribute this to a "spreading phenomenon" in which sensitivity to one agent leads to additional sensitivities [73]. There is no plausible explanation for such a process.

CASE DEFINITIONS AND DIAGNOSIS

There is no definitive case definition or set of diagnostic criteria for idiopathic environmental intolerance (IEI). Several proposed case definitions for IEI emphasize reported sensitivity to multiple unrelated compounds, signs or symptoms in multiple organ systems, and symptom resolution upon withdrawal of the presumed chemical incitant [17,38,48,73,74]. Cullen's definition is one that is widely used (table 2) [74]. An alternative is the working definition of IEI developed at a symposium convened by the World Health Organization and German government agencies [9]:

- An acquired disorder with multiple recurrent symptoms
- Associated with diverse environmental factors tolerated by the majority of people
- Not explained by any known medical, psychiatric, or psychologic disorder

Neither these nor any other case definition has been established as valid diagnostic criteria. The reason is that identification of cases is extremely problematic and inconsistent, even when a set of uniform case criteria are applied. As an example, a federally sponsored research network of environmental medicine clinics at five academic centers collaboratively studied IEI [34]. The study developed an explicit protocol for physicians to identify cases using Cullen's case criteria (table 2) [74]. The proportion of clinic patients who were classified as meeting criteria for IEI varied between 0 to 81 percent among the five research centers.

Unvalidated testing — Clinical ecologists may conduct tests, such as elimination diets and oral food challenges to test for specific food sensitivities. Provocation-neutralization testing is also used to test for specific chemical sensitivities [23]. Small amounts of dilute chemical are taken sublingually, by injection, or through inhalation in a special glass booth. After this provocation, patients record their subjective symptoms, such as lightheadedness or shortness of breath. These symptoms are then "neutralized" by applying a smaller dose of the same substance. These tests have been criticized because they are rarely conducted in a blinded fashion or with the use of placebo controls [1,18,75].

Immunologic tests measuring serum immunoglobulins and complement levels may be conducted [2,76]. Assays of various chemicals including organic solvents, hydrocarbons, pesticides, and heavy metals are sought in samples of blood, urine, fat, hair, or other tissues. These testing procedures have been criticized because no laboratory abnormalities have been reliably linked to IEI.

PSYCHIATRIC DISORDERS

The belief that chemicals cause idiopathic environmental intolerance (IEI) symptoms is an overvalued idea, which means patients maintain their conviction despite substantial evidence to the contrary [27]. Multiple reviews of experiments and observational studies consistently implicate psychiatric causes for IEI symptoms [3,15,41-47]. (See 'Definition and background' above and 'Etiology and pathogenesis' above.)

Patients with IEI symptoms are heterogeneous, and not all cases can necessarily be attributed to psychogenic causes. Studies using standardized, structured clinical interviews showed that 25 percent of patients with IEI symptoms did not meet criteria for a current or past psychiatric disorder, and 24 percent did not have clinically significant psychiatric distress [28,35]. Thus, patients with IEI symptoms have significantly more psychiatric morbidity than is observed in control populations, but less than what is expected for a clinical psychiatric population [77]. As an example, a study of a nationally representative sample in Canada found that after adjusting for potential confounding factors (eg, age, chronic fatigue syndrome, and history of physical and/or sexual abuse) [78]:

- Unipolar major depression was more than twice as common among individuals with IEI, compared to individuals without IEI (odds ratio 2.4)
- Unipolar major depression plus generalized anxiety disorder was three times more common among individuals with IEI (odds ratio 3.1)
- Severe distress was more than twice as common among individuals with IEI (odds ratio 2.6)

Prevalence rates of psychiatric disorders reported in studies probably underestimate the true rates because many of the instruments used to assess psychopathology are transparent in their content and patients with IEI symptoms are often reluctant to acknowledge psychiatric symptoms and distress [36].

Psychiatric diagnoses — The prevalence of mental disorders in patients with IEI is high [43]. Studies using standardized, structured psychiatric interviews found that 65 to 75 percent of patients with IEI symptoms met criteria for a lifetime (current or past) psychiatric disorder [26,35]. This compares to a lifetime prevalence in the general population of 30 to 50 percent [79]. Patients may have more than one psychiatric diagnosis; in one study, 295 patients with IEI symptoms met criteria for 435 diagnoses (table 3) [35].

A review of five studies that each used standardized, structured diagnostic interviews found the most frequently identified psychiatric diseases in patients with IEI symptoms were [36]:

- Somatoform disorders
- Mood disorders
- Anxiety disorders

Somatoform disorder — Somatoform disorders are a group of illnesses, each of which is marked by physical symptoms that are not explained by a general medical condition [80]. The term somatoform disorders was used in Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) [80] and continues to be used in International Classification of Diseases-10th Revision (ICD-10) [81], but has been abandoned in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) because it is difficult to prove that a symptom is medically unexplained [82,83]. For patients with prominent somatic symptoms that cause distress and impair psychosocial functioning, DSM-5 has replaced the category of somatoform disorders with a category called somatic symptom and related disorders. Somatoform disorders, somatic symptom and related disorders, and changes in terminology in DSM-5 are discussed separately. (See "Somatic symptom disorder: Epidemiology and clinical presentation" and "Somatic symptom disorder: Assessment and diagnosis".)

Substantial evidence indicates that many patients with IEI symptoms actually suffer from a somatoform disorder. Studies using standardized, structured psychiatric interviews have found somatoform disorders in 26 to 69 percent of patients with IEI symptoms, and consistently found somatoform disorders significantly more often in patients with IEI symptoms than controls [24,27,32]. The clinical features of IEI often resemble the specific diagnosis of undifferentiated somatoform disorder (table 4) [4,80]. (See 'Clinical features' above.)

A study found that 54 patients with IEI symptoms and 44 patients with somatoform disorders did not differ significantly in clinical features such as number of visits to a family physician [32,84]. In addition, patients with IEI reported nearly the same number of somatic symptoms as the group with somatoform disorder, and significantly more somatic symptoms than the control group, both at baseline and at prospective follow-up 32 months post baseline [47].

Mood and anxiety disorders — Studies using the Structured Clinical Interview for DSM-IV found 17 to 30 percent of patients with IEI symptoms met criteria for either a current or lifetime mood disorder, while anxiety disorders were found in 17 to 22 percent [32,35,54]. One such study compared 309 patients with IEI symptoms and 59 controls and found significantly more patients had a lifetime mood disorder (30 versus 12 percent) or a lifetime anxiety disorder (20 versus 8 percent) [54].

Depression is most common. A structured telephone interview using standardized instruments found significantly higher rates of current depressive disorders in 169 military personnel with IEI compared to 3526 personnel without IEI (56 versus 11 percent) [38].

Other disorders

- Personality disorders – A study using a standardized, structured psychiatric interview compared 23 patients with IEI symptoms to 46 controls [26,27]. Significantly more patients than controls met criteria for at least one lifetime personality disorder (74 versus 28 percent). Specifically, IEI patients were more likely to meet criteria for schizotypal, histrionic, narcissistic, dependent, avoidant, and obsessive-compulsive personality disorders.

- Psychotic disorders – One study found the lifetime prevalence of psychotic disorders (primarily delusional disorder) in patients with more severe forms of IEI was 13 percent [36].

- Substance use disorders – Patients with IEI symptoms do not have an increased risk for substance use disorders [26,37,38,85]. A structured telephone interview using standardized instruments found little difference in the prevalence rate of alcohol abuse between 169 military personnel with IEI compared to 3526 personnel without IEI (17 versus 14 percent) [38].

Psychiatric distress — Many patients with IEI symptoms who do not meet criteria for a psychiatric disorder nevertheless have psychiatric symptoms and traits. One study using standardized, structured psychiatric interviews found a significantly greater mean number of psychiatric symptoms in 23 patients with IEI compared to 46 general population controls (28 versus 9 symptoms) [26].

Studies using standardized interviews and scales (eg, Minnesota Multiphasic Personality Inventory-2, Symptom Checklist 90-Revised) consistently identify somatic, depressive, and anxious features in significantly more patients with IEI symptoms than controls [27,28,30,34,37,54,77].

Patients with IEI symptoms may have externally oriented thinking, difficulty with self-reflection, and less emotional insight. This may lead to difficulties identifying and expressing feelings, sensations, and opinions [35].

MEDICAL EVALUATION

A comprehensive evaluation of patients with idiopathic environmental intolerance (IEI) symptoms includes a history, physical examination, and laboratory tests (table 5).

A thorough history should include the signs and symptoms which the patient attributes to IEI, the onset of the disorder, alleged triggering events, how the patient became aware of the diagnosis, the diagnostic techniques and treatments used, and the patient's response to treatment. The clinician also needs to make a detailed assessment of the patient's psychiatric history [86].

A detailed occupational and environmental history should be obtained because patients often report that symptoms stem from chemical exposures. Consultation with an occupational medicine specialist may be helpful.

IEI should be distinguished from objectively defined physical illnesses, such as allergies and contact dermatitis. In addition, the differential diagnosis includes medical disorders with nonspecific motor and sensory abnormalities or transient or equivocal signs (eg, multiple sclerosis, systemic lupus erythematosus, acute intermittent porphyria, and hemochromatosis) [87].

The value of a proper assessment was illustrated by a study of 264 patients with IEI symptoms who were evaluated at an outpatient environmental medicine clinic [4]. Standard procedure included an extensive case history, physical examination, routine laboratory tests, and monitoring for toxic substances. The evaluation identified various diseases (eg, polyneuropathy, multiple sclerosis) in many of the patients.

Laboratory and medical tests — The assessment should include a complete blood count, serum electrolytes, serum glucose, and urine analysis.

The selection of other tests will be guided by the patient's signs and symptoms. For example, patients with prominent respiratory tract complaints may need referral for pulmonary function tests to rule out the presence of reactive airway disease. If the patient's symptoms appear to be caused by specific allergies, or if the patient has received a diagnosis of "environmental

allergies" or "immune dysregulation," routine skin testing and/or in vivo assays can help to rule out the presence of an allergic state [88].

The legitimate use of tests needs to be balanced against excessive testing that is repetitious or not indicated. Physicians should thus use caution in ordering tests and obtaining specialty consults for the purpose of reassuring the patient [61]. A review found that negative findings do not reassure most patients with chronic medically unexplained symptoms and may paradoxically increase anxiety.

Psychiatric assessment — The psychiatric assessment will probably yield evidence of a somatoform, mood, anxiety, or other disorder. The clinician can use a brief screening instrument to assess patients, such as the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (table 6) [89]. This instrument screens for and provides categorical DSM-IV diagnoses for somatoform, depressive, anxiety, alcohol, and eating disorders. It was specifically designed for use in primary care, is fully self-administered by the patient, has good diagnostic validity (sensitivity 75 percent, specificity 90 percent), and the median physician time to review the results is one to two minutes.

Self-report instruments have the advantage of saving interviewer time but are more prone to false positive diagnoses. Alternatively, clinicians may use a structured diagnostic interview such as the Structured Clinical Interview for DSM-IV, which enables the interviewer to clarify ambiguous or contradictory responses, but are labor intensive and generally reserved for specialized treatment or research settings.

Neuropsychological testing will be useful in patients who report significant memory impairment or problems in attention or concentration.

TREATMENT

There are a few case reports of treatment for patients with idiopathic environmental intolerance (IEI) symptoms and no controlled trials [3]. Selection of treatment is largely based upon evidence from studies of somatoform disorders. Psychotherapy is the primary treatment and pharmacotherapy may be used as adjunctive treatment for certain symptoms such as anxiety or insomnia.

Clinicians should focus on relief of symptoms and improving occupational and interpersonal functioning. Another aim of treatment is to help the patient understand the cause of the symptoms as less rooted in the environment and centered more on psychiatric issues, but this

is not possible for all patients. In addition, it is not clear that the success of psychotherapy depends upon whether patients relinquish their belief that IEI is due to toxic causes.

Identified psychiatric disorders such as major depression, dysthymia, or panic disorder should be treated with medications and/or psychotherapy.

- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Management of panic disorder with or without agoraphobia in adults".)
- (See "Overview of psychotherapies".)

General principles for clinical management — In our clinical experience, there are many general principles for guiding clinical management of vague, nonspecific, medically unexplained symptoms [1,3,15,61,87]:

- Schedule regular visits
- Establish a therapeutic alliance with the patient
- Acknowledge and legitimize symptoms
- Limit diagnostic testing and referrals to specialists
- Provide consistent, limited reassurance that grave medical diseases have been ruled out
- Provide psychoeducation about coping with symptoms of IEI
- Make functional improvement the goal of treatment

Clinicians should schedule regular appointments at a frequency that mitigates the occurrence of crises and urgent telephone calls or visits.

A patient's belief in chemical sensitivity and IEI will generally be long-standing and firmly held. Patients with IEI symptoms also feel their mainstream physicians do not understand them or take their complaints seriously [3,27]. Thus, the clinician should refrain from directly challenging the patient's belief in IEI and avoid undermining the relationship with the patient.

Patients diagnosed with a psychiatric illness can be informed that their condition is most likely treatable, especially mood and anxiety disorders. Clinicians should assure patients that the presence of a psychiatric disorder does not negate the reality of their suffering and is not so much the cause of the IEI symptoms, but rather, the psychiatric disorder is exacerbating and perpetuating the IEI symptoms [61]. This approach may facilitate the patient's acceptance of a

formal psychiatric intervention. Patients may nevertheless react defensively if clinicians raise the possibility that there is psychopathology that needs to be addressed and treated.

Some patients will refuse to work with clinicians unless they view IEI as a distinct, valid medical entity. Clinicians need not collude with such patients, and should take a long-term perspective and inform them that the clinician is always available to provide treatment when the patient is ready.

Clinicians should emphasize the restoration and maintenance of functioning at work, home, and in social circles and deemphasize curing and eliminating symptoms [61]. Clinicians should discourage patients from assuming the sick role and instead, patients should take an active role in treatment by setting and working on specific, realistic, incremental goals that include observable behaviors. One example is a graduated exercise program.

Treatment recommendations depend upon the extent of the patient's illness belief and degree of impairment. Some patients will be interested only in specific treatment for a specified disorder, such as antidepressant medication for depression. Other patients may be receptive to entering a formal behavior modification program to improve their social and occupational functioning.

Although many patients with IEI may be pursuing workmen's compensation or some other benefit, proper treatment extends beyond the recognition that patients may be malingering [1,23].

Psychotherapy — Several forms of psychotherapy can be used depending upon the patient's motivation and insight. These include behavioral desensitization, cognitive-behavioral therapy, psychoeducation, supportive therapy, stress management, biofeedback, and psychodynamic psychotherapy [42]. These can be provided individually or in a group format. Some clinicians use a variety of approaches, which in one case series resulted in improved functioning in nearly 75 percent of patients [90].

Guidelines for short-term psychotherapy in patients with IEI symptoms include [90]:

- Clearly explain the structure of the treatment plan
- Teach meaningful skills relevant to daily life
- Training in these skills should continue until they are mastered in the therapist's office
- Patients should practice these skills outside of the office
- Clinicians should encourage the patient to attribute improvement to the patient's increased skills

Behavioral desensitization — This treatment is based upon a behavioral model of the etiology of IEI (see 'Etiology and pathogenesis' above). A review suggests desensitization and graduated exposure can extinguish maladaptive responses to odors or other triggers in patients with IEI symptoms, and help patients overcome avoidance behaviors [15]. One report described the successful use of desensitization in two patients who remained nearly symptom-free for several years [57].

Desensitization involves patients exposing themselves to odors and fumes found in typical home and work situations. Exposure begins with relatively benign odors and progresses to increasingly noxious stimuli. In addition, the frequency and quantity of exposure are gradually increased as treatment progresses. Exposure is conducted in the clinician's office initially, followed by self-exposure homework in the natural environment [91]. Treatment may be condensed into five consecutive days for two hours on each day, or spread out over several weeks. Desensitization is often incorporated as part of cognitive-behavioral therapy. (See 'Cognitive-behavioral therapy' below.)

Cognitive-behavioral therapy — Although a cognitive-behavioral treatment model has been described [92], no controlled trials have tested the efficacy of cognitive-behavioral therapy (CBT) specifically for patients with IEI symptoms. Nevertheless, systematic reviews have found CBT was efficacious for treatment of somatoform disorders and medically unexplained symptoms [93,94]. Furthermore, there was more evidence to support the use of cognitive-behavioral therapy than any other intervention. The behavioral techniques include response prevention, systematic desensitization, progressive muscle relaxation, and graduated exercise programs [61]. (See 'Behavioral desensitization' above.)

A review of 31 controlled trials of CBT for patients with somatoform disorders found that in 71 percent of the studies, physical symptoms improved significantly more in the CBT patients than the controls [95]. Psychologic distress improved significantly more in CBT patients in 38 percent of the studies, and functioning improved significantly more in 47 percent of the studies.

A practical guide for providing CBT is available (table 7) [15,96]. The use of CBT is limited by an inability to rationally discuss cognitive distortions [42].

Family therapy — Involving family members in treatment can help clinicians better understand the patient's symptoms, and address how family members unintentionally reinforce the patient's problematic behaviors. Difficulties with specific family functions and processes such as communication and problem solving may also exacerbate the patient's illness. In addition, family members may be struggling to cope with the patient's illness and may require help for themselves.

Antidepressants — There are a few individual case reports that adjunctive selective serotonin reuptake inhibitors may be helpful for treating IEI symptoms [97-99]. Citalopram 60 mg per day or paroxetine 20 to 40 mg per day was successfully used to treat patients with IEI symptoms plus a depressive or anxiety disorder. In addition, one patient received citalopram 10 mg/day plus transcranial magnetic stimulation (20 sessions) for IEI symptoms and co-occurring unipolar major depression; the IEI symptoms improved and the depressive syndrome remitted [100]. In all of these cases, good results persisted for six months to four years during maintenance pharmacotherapy. However, the United States Food and Drug Administration issued warnings that citalopram causes dose-dependent QT interval prolongation that can lead to arrhythmias, and thus recommends that the maximum dose should not exceed 40 mg per day [101,102]. Additional information about the citalopram warnings and cardiac effects of SSRIs is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

In addition, systematic reviews of controlled trials for treatment of somatoform disorders and medically unexplained symptoms have found evidence to support the use of antidepressant medication [93,94]. A meta-analysis of 94 controlled trials compared antidepressants with placebo and non-antidepressant medications, and found a large clinical effect with antidepressants [103]. As an example, one study found significantly more patients responded to amitriptyline (12.5 to 37.5 mg two hours before bedtime) than placebo (74 versus 49 percent of patients) [104]. Based upon the Diagnostic and Statistical Manual, Fifth Edition (DSM-5), most patients who were previously diagnosed with somatoform disorders or medically unexplained symptoms are now diagnosed with somatic symptom disorder [82]. (See 'Somatoform disorder' above.)

Some patients with IEI symptoms may resist taking "chemicals" to treat their psychiatric disorders and others will report intolerance to relatively low levels of medication. Doses of psychotropic agents should start low and be increased slowly as tolerated to achieve a therapeutic dose.

Unproven therapies — The variety of treatments dispensed by clinical ecologists is limited only by their imagination and resourcefulness [26]. These include avoidance of chemicals, environment changes, special diets, over-the-counter or prescribed medications, sublingual ingestion or subcutaneous injection of small doses of an alleged offending chemical, and detoxification procedures. Some interventions cause iatrogenic effects and can seriously disrupt the lives of patients. There is no justification for these treatments.

A survey of over 900 people with self-reported IEI, published in 2003, counted more than 100 types of commonly used treatments [39]. Patients spent a mean total of 7000 United States

dollars on treatments in the prior year, accounting for 15 percent of household income. The mean number of treatments ever tried for patients with mild IEI was 25 and for those with severe IEI was 33. The treatments most highly rated by patients were creating a chemical-free living space, avoiding chemicals, and prayer [39].

PROGNOSIS

Most of the information on the natural history of idiopathic environmental intolerance (IEI) comes from follow-up studies lasting less than three years. These data indicate that the condition is highly stable and most patients remain chronically ill. A prospective study of 49 patients with IEI symptoms found that 92 percent remained ill after one year [47,84]. In addition, patients reported more somatic symptoms than a control group at baseline and at 32 months post baseline. Other studies have found that 54 to 96 percent of patients with IEI symptoms were unchanged or worse when they were reassessed several months to two years after their initial evaluation [19,23].

IEI is thought to represent a severe form of a concept called "chemical intolerance," and individuals with chemical intolerance also appear to have stable symptoms. A general population study identified people with chemical intolerance based upon self-reported negative reactions to common airborne chemicals, with symptoms (eg, headache or fatigue) and daily life adjustments (eg, not using public transportation) [105]. Among individuals with chemical intolerance (n >500) at baseline, follow-up five years later found that chemical intolerance was present in nearly 70 percent.

A study conducted at an occupational health clinic found that a longer elapsed time from onset of IEI symptoms until the first clinic appointment was significantly associated with a poorer prognosis [19].

Greater rates of improvement may occur over longer periods of time. A psychiatrist interviewed 18 patients with IEI symptoms nine years after their initial interview, and rated 2 patients as remitted, 14 as improved, and 2 as unchanged or worse [106,107]. Whereas all 18 patients were initially in treatment with a clinical ecologist, only 7 were at the time of follow-up. However, all 18 remained convinced that IEI was a valid medical entity, and they continued to have problems with somatization, obsessive-compulsiveness, and hypochondriasis.

There are no data on the rate of recurrence among patients who recover from symptoms of IEI.

SUMMARY AND RECOMMENDATIONS

- Idiopathic environmental intolerance (IEI) or multiple chemical sensitivity is a subjective illness marked by recurrent, vague, nonspecific symptoms attributed to low levels of chemical, biologic, or physical agents. (See 'Definition and background' above.)

- IEI is not a distinct, valid medical entity. Symptoms lack specificity, there is no reliable case definition or set of diagnostic criteria, and there are no consistent objective diagnostic physical findings or laboratory tests. (See 'Definition and background' above.)

- Many patients with IEI symptoms undergo unorthodox diagnostic tests and unproven and potentially harmful treatments by clinicians who refer to themselves as clinical ecologists or environmental clinicians. (See 'Definition and background' above.)

- Estimates of the prevalence of IEI vary widely. Self-reported chemical sensitivity is found in 9 to 33 percent of the general population. IEI symptoms are more common in women. (See 'Epidemiology' above.)

- Different hypotheses regarding the etiology of IEI involve learned behavior, anxiety, classic and operant conditioning, symptom amplification, and skewed cognitive processing. None of these are mutually exclusive. (See 'Etiology and pathogenesis' above.)

- Many patients with IEI symptoms have one or more psychiatric disorders that predate the onset of IEI symptoms. The most frequently identified psychiatric illnesses are somatoform, mood, and anxiety disorders. The clinical features of IEI often resemble the specific diagnosis of undifferentiated somatoform disorder. (See 'Psychiatric diagnoses' above.)

- The history conducted as part of the medical evaluation should include questions about occupational and environmental exposure. The evaluation should attempt to exclude objectively defined physical illnesses. (See 'Medical evaluation' above.)

- A brief screening instrument can be used to assess patients for psychiatric disorders. The Primary Care Evaluation of Mental Disorders Patient Health Questionnaire screens for and provides categorical DSM-IV diagnoses for somatoform, depressive, and anxiety disorders. (See 'Psychiatric assessment' above.)

- There are many general principles for guiding clinical management of vague, nonspecific, medically unexplained symptoms. These include scheduling regular visits, establishing a therapeutic alliance, acknowledging symptoms and not challenging the patient's beliefs regarding IEI, evaluating and treating patients for diagnosable medical diseases including psychiatric disorders, limiting diagnostic tests and referrals to specialists, providing limited

reassurance that grave medical diseases have been ruled out, and providing psychoeducation about IEI. (See 'General principles for clinical management' above.)

- Treatment for patients with IEI symptoms is largely based upon evidence from studies of somatoform disorders. Clinicians should focus upon relieving symptoms rather than curing them, and improving occupational and interpersonal functioning. In patients with IEI who are amenable to treatment, we suggest psychotherapy as the primary option (**Grade 2C**). In patients who are unwilling to undergo psychotherapy but willing to accept medications, treatment with antidepressants is a reasonable alternative.

- A number of forms of psychotherapy have been tried. We suggest cognitive-behavioral therapy (CBT) (**Grade 2C**). Alternatives include behavioral desensitization and family therapy. (See 'Cognitive-behavioral therapy' above.)

- In patients being treated with CBT, we suggest additionally treating with antidepressants (**Grade 2C**). (See 'Antidepressants' above.)

- IEI is highly stable and most patients remain ill with impaired occupational and social functioning during follow-up studies that last one to three years. (See 'Prognosis' above.)

Topic 7764 Version 15.0

→