Psychiatric Consultations in Stiff-Man Syndrome

Joyce A. Tinsley, M.D., Elaine M. Barth, M.D.,
John L. Black, M.D., F.A.P.M., F.A.P.A., and Donald E. Williams, Ph.D.

Background: Stiff-man syndrome is a rare central nervous system disease first described nearly 40 years ago. Its cause has been attributed to both neurologic and psychiatric processes. In recent years, it has been accepted as a neurologic condition in which the γ-aminobutyric acid (GABA) system malfunctions, probably because of an autoimmune process. Published reports that have described psychiatric manifestations of the disease have relied on descriptions of one or two cases and literature reviews.

Method: We reviewed the medical records of 24 patients with confirmed stiff-man syndrome, 12 of whom had received psychiatric consultation. This review was done to better determine the psychiatric manifestations of stiff-man syndrome.

Results: Retrospective analysis of these 12 cases showed that the most common psychiatric symptoms were anxiety, depression, and alcohol abuse.

Conclusion: We speculate that the GABA system is involved in both the neurologic and psychiatric symptoms of these patients. Psychiatrists have a significant role in the management of patients with stiff-man syndrome and may be expected to manage anxiety, depression, and substance misuse.

(J Clin Psychiatry 1997;58:444–449)

Received May 14, 1997; accepted July 15, 1997. From the Department of Psychiatry and Psychology, Mayo Clinic and Mayo Foundation (Drs. Tinsley, Black, and Williams), and the Zumbro Valley Mental Health Center (Dr. Barth), Rochester, Minn.

Reprint requests to: Joyce A. Tinsley, M.D., Department of Psychiatry and Psychology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905.

Stiff-man syndrome (SMS) is a rare central nervous system disease characterized by continuous muscle rigidity and painful spasms that resemble a chronic form of tetanus. It was first described by Moersch and Woltman in 1956.[1] By 1991, 24 more cases that met a rigorous set of diagnostic criteria had been diagnosed at the Mayo Clinic. These patients have disabling stiffness and frequently fall. An increased prevalence of diabetes mellitus and autoimmune thyroid disease has been described in the patients and their families. Also, there is evidence that SMS is an autoimmune disease.[2] SMS is associated with an antibody to glutamic acid decarboxylase, an enzyme needed to produce γ-aminobutyric acid (GABA) from glutamic acid. An antibody to glutamic acid decarboxylase may produce a relative GABA deficiency, which in turn may prevent the inhibition of muscle rigidity.[3,4] The GABA agonists diazepam and baclofen have been effective in treating some patients. Diazepam, often used in high doses, is commonly a first-line treatment for SMS.[5] Other treatments include immunosuppressive agents and plasmapheresis.

Lorish et al.[6] stated that patients need to meet seven criteria for a definite diagnosis of SMS to be made. These are (1) a prodrome of stiffness and rigidity in the axial muscles; (2) slow progression of stiffness to include proximal limb muscles, making volitional movements and ambulation difficult; (3) a fixed deformity of the spine (most often, pronounced lordosis); (4) the presence of superimposed episodic spasms precipitated by sudden movements, jarring noise, and emotional upset; (5) normal findings on motor and sensory nerve examinations; (6) normal intellect; and (7) electromyographic findings typical of continuous motor activity that can be abolished by the intravenous administration of diazepam or a positive response to a therapeutic trial of orally administered diazepam.[6]

The literature that describes the psychiatric manifestations of SMS is scant. According to the earliest reports, patients with SMS may come to the attention of a psychiatrist before their neurologic disorder is recognized. Of the 14 patients reported by Moersch and Woltman[1] in 1956, 5 had first been given the diagnosis of a "functional condition." Subsequent reports described the diagnosis of conversion disorder as a clear misdiagnosis and neglected the possibility that psychogenic factors had a role in the patient's symptoms.[7,8] In 1960, Trethowan et al.[9] concluded that SMS had a neurologic cause, but they reported a case in which emotional disturbance led to exacerbation of symptoms. In 1961, Werk et al.[10] reported the first case with associated hyperthyroidism. They recorded a thorough psychiatric history and believed that the patient's personality and neurologic condition were interrelated. In 1965, Gold[11] returned to a psychogenic explanation, con-

cluding that "'stiff-man' can clearly be evidence of maladaptive, learned behaviour"(p284) or neurotic behavior. He reported a convincing case of an adult patient who had a history of hysterical blindness at age 14 that developed when his father became ill. Gold demonstrated the use of behavior modification to dramatically reduce the patient's stiffness.

In a landmark paper in 1967, Gordon et al.[12] reviewed the literature and asserted that SMS was not a "functional disorder"; however, they added that a neuropsychological explanation for it was hard to put to rest and suggested that metabolic or psychogenic influences, or both, may maintain the exaggerated activity of the suprasegmental centers. They also reported that psychiatric disturbances typically precede the disorder.[12] In 1974, Warneke[13] emphasized the need for psychiatrists to recognize the disorder because the majority of patients with SMS present with nonspecific symptoms of depression and anxiety. He noted that these patients may be considered "difficult." In addition, his paper purports that 70% of patients with SMS are male.[13] In 1977, Heiligman and Paulson[14] reported one case of SMS and reviewed four other cases to conclude that patients were found to have

> overly dependent personalities, childhood domination by an authoritarian parent, inadequate and unfulfilling psychosexual adjustment, a tendency to gambling and the achievement of specific secondary gains—ranging from a socially acceptable rationalization for not working, from the dismissal of gambling debts, to the "justified" avoidance of adult sexual responsibility.(p369)

However, their most important contribution was in emphasizing the interplay between organic and psychological factors. They recognized that attention to psychological factors could improve the patient's response to neurologic therapy. In 1991, McEvoy,[2] citing the Mayo Clinic experience, strongly emphasized the recognition and treatment of psychiatric problems in this population and pointed out that affective disorders and unusual personalities were common in these patients.

METHOD

A computer search of the Mayo Clinic record-keeping system (1976–1991) identified 37 patients who had the diagnosis of SMS. Of these patients, 24 met the rigorous seven-point criteria[6] for SMS. Twelve of these patients had been evaluated in psychiatric consultation, and 11 of those had the presence of anti-glutamic acid decarboxylase antibody (serum for testing was unavailable for Patient 4). A review of the medical records of these 12 patients was conducted by two of the authors (J.A.T., E.M.B.) in order to describe the psychiatric symptoms and complications seen in this population. The psychiatric symptoms, recorded family histories, psychiatric treatment, and follow-up (if available) of these 12 patients are summarized in Table 1. We provide 6 case reports that highlight the psychiatric symptoms encountered in these patients. Patients 1 to 4 are representative of the most commonly seen psychiatric problems, and Patients 5 and 6 illustrate the level of complexity a patient with SMS may present. All patients in our series were also under the care of a neurologist who prescribed appropriate treatment for SMS.

CASE HISTORIES

Patients 2, 4, and 10 were included in the study by Lorish et al.[6] from a rehabilitation perspective. Patients 9 and 10 were previously reported by McEvoy[2] from a neurologic perspective.

Patient 1 (Anxiety)

A 50-year-old woman presented for a second opinion of SMS. Her symptoms began 5 years earlier with a fall that resulted in fractures of her wrist and knee. Her stiffness progressed to the point that she needed a cane and a walker. SMS was diagnosed and treated appropriately with diazepam (40 mg daily) for 2 years prior to the second opinion. At that time, she was referred to psychiatry because of anxiety that had developed during the preceding year.

She described anxiety associated with a fear of falling. This resulted in avoidance of wide spaces of cement, parking lots, and shopping malls unless someone accompanied her. Although she could not right herself if she lost her balance, she felt that she was more fearful than was realistic. She avoided work situations if she had to walk across cement to get to a meeting, but she experienced no anxiety when walking on a soft surface. At times, she experienced symptoms of generalized anxiety, with a stomachache, a feeling of not being in control, jitteriness, muscle tightness in the back, generalized weakness, flushing, and perspiration. Also, she described excessive worry about the health of her family and work. Occasionally, she added an extra 5 to 10 mg of diazepam to deal with anxiety.

The consulting psychiatrist diagnosed an anxiety disorder. She was advised to use diazepam, as prescribed for treatment of SMS. It was recommended that a behavioral approach be added to treat her symptoms of anxiety.

Patient 2 (Depression)

A 40-year-old woman presented for medical evaluation because of progressive and disabling stiffness. The first episode occurred 2 years previously when she was attending the funeral of a close relative. At that time, she experienced incapacitating stiffness in her thighs and back. Shortly thereafter, she began to have episodes of anxiety, sweating, shortness of breath, and insomnia.

The diagnosis of SMS was made during her medical examination, and she was prescribed diazepam (40 mg

Table 1. Psychiatric Symptoms, Diagnosis, Treatment, and Follow-Up of 12 Patients With Stiff-Man Syndrome

Patient	Age (y)	Sex	Race	Psychiatric Symptoms at Consultation	Psychiatric Diagnosis at Consultation	Psychiatric Treatment Advised	Psychiatric Follow-Up	Family History
1	50	Female	White	Anxiety: generalized, phobic	Anxiety disorder	Behavior therapy	None	None
2[a]	40	Female	White	Depression, panic anxiety	Organic affective disorder	Fluoxetine, marital therapy	Temporarily improved	Suicide: son completed, mother attempted
3	50	Male	White	Alcohol abuse, phobic anxiety	Alcohol dependence, simple phobia	Abstinence from alcohol	Improved at 4 y	None
4[a]	55	Female	White	Rule out conversion disorder	None	None	None	None
5	45	Female	Black	Depression, panic anxiety	Rule out conversion disorder, history of alcohol abuse	Psychotherapy	Improved at 4 y	Depression in mother
6	45	Female	White	Depression, phobic anxiety	Rule out conversion disorder, personality disorder, history of alcohol dependence	None	Organic brain syndrome	None
7	45	Female	White	Stress	None	None	Depression, phobic anxiety at 4 y	None
8	50	Female	White	Anxiety	Adjustment disorder	Psychotherapy	None	None
9[b]	40	Male	White	Depression, anxiety	Alcohol dependence, depression, dependent personality	Fluoxetine	Improved at 3 y	Depression in father and brother, alcoholism in father
10[a,b]	35	Female	White	Depression, suicide attempt	Major depression	Fluoxetine	Suicide attempt at 2 y	Suicide in uncle, alcoholism in father
11	55	Male	White	Overmedication	Organic personality, marital problems	Decrease sedative if possible	Cardiopulmonary arrest at 1 y	Alcoholism: 2 brothers
12	30	Female	White	Phobic anxiety	None	None	Suicide at 1 y	Posttraumatic stress disorder in brother, depression in mother, alcoholism in parents

[a]The patient was included in the study by Lorish et al.[6]
[b]The patient was previously reported by McEvoy.[2]

daily), which provided some relief. However, 3 months later, she reported having depression for the first time. She had trouble accepting her diagnosis and the related disability, and there was family discord. The dosage of diazepam was increased to 60 mg, but this was followed by increasing mood lability. She was dysphoric, lost 20 lb (9 kg), and had passive death wishes.

A consulting psychiatrist diagnosed an organic affective disorder. Fluoxetine (20 mg) was prescribed and resulted in temporary improvement in her mood. Marital and family therapy was also recommended.

Patient 3 (Alcohol Dependence)

A 50-year-old man diagnosed with SMS presented for a second opinion. Ten years earlier, he had begun to experience stiffness that interfered with his ability to walk and play golf. He found that diazepam alleviated these symptoms. The diagnosis of SMS was made 2 years after the onset of his initial symptoms. At the time of the second opinion, his diazepam dose was 120 mg daily. He was referred for psychiatric consultation to address his alcohol abuse. He reported social drinking until 4 years earlier when he learned that alcohol further relieved his stiffness. He used alcohol to complete a golf game, before social functions, during and after work, and to tolerate air travel. Symptoms of alcohol dependence included failed attempts to control his drinking, efforts to hide his drinking, concern of family and friends, personality change when drinking, work-related problems, social embarrassment, tolerance to alcohol, and denial of the problem. He also complained of a fear of sidewalks after he fell several times. He viewed the fear as irrational because he avoided sidewalks even when the risk of falling was very low; he had sought relief from this fear through hypnotherapy.

The consulting psychiatrist diagnosed alcohol dependence and simple phobia. The patient was advised to abstain from alcohol. Diazepam (120 mg) was continued,

and prednisone (60 mg) was added to his treatment. Two months later, he reported abstinence from alcohol, which was confirmed by his wife. His level of alertness, the coherence of his speech, and his stiffness were markedly improved.

Patient 4 (Rule Out Conversion Disorder)

A 55-year-old woman presented for medical evaluation. She had been mildly symptomatic with back spasms for 15 years. One year before her evaluation, her second husband became seriously ill, and his family criticized her care of him. Since that time, she experienced increased spasms, crying spells, depression, and significant weight loss. Her back spasms resulted in frequent falls and difficulty completing household tasks. Her developmental history was remarkable for losing her father at an early age, being in a concentration camp for 7 years during World War II, and marrying a man of privilege with whom she and her mother were deported.

She was referred for psychiatric hospitalization with the diagnosis of conversion disorder, but a neurologic consultation was obtained and SMS was diagnosed. She had a good response to 80 mg of diazepam daily.

Patient 5 (Complex)

A 45-year-old woman presented for psychiatric evaluation. She had been well until 8 years previously, when she began to have panic spells characterized by shortness of breath, palpitations, tremulousness, and "freezing" stiff. Early in the course of her illness, she began self-medicating her symptoms with alcohol. Gradually, stiffness in her lower extremities became so severe that she could not walk, and her activities of daily living were restricted to watching television or reading. During the preceding year, she used a bedpan instead of walking to the bathroom. She complained of severe depression with anhedonia, anorexia with a 20-lb (9-kg) weight loss, insomnia, and suicidal ideation. In addition to four psychiatric hospitalizations during the course of her illness, she had been evaluated by many psychiatrists and neurologists who prescribed various ineffective psychotropic medications.

When she presented to the Mayo Clinic, she was taking clonazepam (0.5 mg q.i.d.) for panic anxiety, and this was somewhat helpful. She and her husband reported marital discord during much of their 24-year marriage, in part because of her dependency. However, their relationship had improved as her condition deteriorated, and he spent more time attending to her needs. The mental status examination conducted while she was lying in her wheelchair was remarkable for severe regression. She was unkempt. Her speech was soft, her mood was dysthymic, and her affect was flat.

She was hospitalized with the preliminary diagnoses of conversion disorder, major depression, and anxiety disorder. In the hospital, neurologic evaluation led to the diagnosis of SMS. Symptoms of stiffness, depression, and anxiety responded to clonazepam (2.5 mg q.i.d.) along with physical therapy and supportive psychotherapy.

Patient 6 (Complex)

A 45-year-old woman with a history of depression and alcoholism presented for evaluation of stiffness. She reported having good health until 20 years previously when hyperthyroidism developed, which was treated with propylthiouracil and a tranquilizer. She began to walk cautiously because of mild stiffness. That same year a phobia to steps developed, which generalized to fears of cooking, walking, answering the door, and going out of the house. Four years later, back stiffness, depression, and insomnia developed, for which diazepam and a barbiturate were prescribed.

The next 15 years were marked by multiple psychiatric hospitalizations and attempts at sedative detoxification. Sedative detoxification was complicated by severe muscle spasms, hyperventilation, and anxiety. She substituted alcohol for sedatives in the amount of one case of beer daily. Electroconvulsive therapy and various types of psychotropic medications were tried unsuccessfully. She reported abstinence from alcohol for the 4 years before her evaluation for stiffness, but she took 150 to 300 mg of diazepam daily. At this dosage, neurologic evaluation was not suggestive of SMS, and she was referred to psychiatry.

On the psychiatry inpatient service, she was noted to be "incredibly regressed." Further history revealed a lifelong perfectionistic and dependent personality. The spasms worsened during family arguments. Inpatient detoxification was complicated by repeated episodes of falling, fecal incontinence, and a "pseudoseizure." During the fourth week, 2 days after her last dose of diazepam, she had a respiratory arrest, which later was thought to be due to hypoxia from respiratory muscle spasm. She required prolonged intensive care and was left with a mild organic brain syndrome. The diagnosis of SMS was finally made, and at hospital dismissal, she was taking diazepam (60 mg t.i.d.), and her condition was improved.

DISCUSSION

The common problems that the consulting psychiatrists were asked to evaluate in this group of patients were anxiety, depression, substance abuse, and the question of conversion disorder. Table 1 shows the symptoms exhibited by these 12 patients. The predominant symptom in the patients referred for psychiatric evaluation was anxiety, which was described in 9 (Patients 1–3, 5–9, 12) of 12 patients. Five (Patients 1, 3, 6, 7, 12) of these 9 anxious patients had phobic anxiety with avoidance behaviors. (The symptoms of anxiety and depression were

noted to have developed in Patient 7 at the time of follow-up.) They had specific fears of falling and fear of steps or cement. Although it may seem understandable that these patients would fear falling, their anxieties had become excessive. Of the 9 anxious patients, 2 had panic symptoms, 1 had anxiety associated with depression, and another had persistent but nonspecific anxiety. Four of the patients with anxiety disorder also abused alcohol, and 2 of the nonalcoholic patients self-medicated their anxiety with increased doses of diazepam. One patient reported a family history positive for anxiety in a brother who was reported to have posttraumatic stress disorder.

Six (Patients 2, 5–7, 9, 10) of the 12 patients had symptoms of depression. Another patient committed suicide. In 3 patients, it was thought that treatment with diazepam or prednisone contributed to the depression. Five of these 6 patients received treatment with antidepressants. Three were given fluoxetine, which was reported to be well tolerated. Other antidepressants taken by this group of patients included trazodone, nortriptyline, doxepin, amitriptyline, and imipramine. One patient believed that trazodone ameliorated the stiffness. One patient reported that amitriptyline worsened stiffness, and 1 reported that imipramine worsened stiffness. Clomipramine aggravates stiffness when injected into patients with SMS.[15] Two of the 6 patients with depressive symptoms reported that family members had depression, and 2 other patients reported a family history positive for suicide.

Four patients (Patients 3, 5, 6, 9) had an alcohol use disorder. Three other patients reported family histories positive for alcohol problems. All patients with alcohol abuse reported self-medicating their stiffness with alcohol. Two of the nonalcoholic patients self-medicated their symptoms of anxiety by increasing the dosage of diazepam beyond the prescribed dosage. Another patient was thought to be overmedicated with diazepam. One patient reported sexual dysfunction related to diazepam treatment. It is important that patients who require large doses of benzodiazepine to manage symptoms of SMS not be detoxified in the same way as a typical sedative-dependent patient. As reported in Patient 6, detoxification may be a life-threatening procedure in these patients because of the involvement of the respiratory muscles. It is important to diagnose alcoholism when it exists and to manage it as a treatable condition.

Conversion disorder was diagnosed in 3 of 12 patients. Two other patients were evaluated for a stress-related problem. In 7 patients, there was a clear association between psychological stress and increased stiffness. Sensitivity to emotional stimuli has been confused as a sign of psychogenic disorder. In these patients, a complex interplay of both neurologic and psychogenic symptoms may have developed. Conversion disorder may not be the blatant misdiagnosis as often presumed but may be an example of how psychological factors can affect a physical disorder. Such examples may be seen in Patients 4 and 5 above.

CONCLUSION

Conclusions drawn from our study differ in three important ways from those of previous reports. First, in their landmark paper, Gordon et al.[12] reported that psychiatric symptoms usually precede the diagnosis of SMS. In our group of patients, in no case did psychiatric symptoms consistent with an Axis I disorder begin before the emergence of symptoms attributable to SMS. There were long-standing personality problems in 2 patients (Patients 6 and 9). Second, according to earlier reports, 70% of patients with SMS are male.[13,14] Our patient group consisted of 9 females and 3 males. Lorish et al.[6] reported on 7 males and 6 females in 13 confirmed patients of SMS at the Mayo Clinic. Furthermore, a computer search of the Mayo Clinic record-keeping system identified 37 patients with a diagnosis of SMS, nearly half of whom were female. Clearly "stiff-man" is a misnomer, as pointed out as early as 1958.[7] Gordon et al.[12] reported that the ethnic backgrounds vary in patients with SMS, and in 1971, the first case of SMS in a black person was reported.[16] One of our patients was also black. Third, the prominence of depression and unusual personality traits has been remarked on in patients with SMS,[2,13] but ours is the first report to emphasize the significance of anxiety disorders and substance abuse in patients with SMS.

The interplay between psychiatric and neurologic symptoms has been the object of speculation in SMS since its first description. We propose five possible interactions between psychiatric and neurologic symptoms found in SMS.

1. Psychiatric symptoms may exacerbate stiffness. In most of our patients, emotional stimuli increased muscle stiffness.
2. SMS may contribute to the development of psychiatric symptoms, such as the development of a simple phobia after a traumatic fall.
3. Treatments for SMS may produce psychiatric symptoms, as when diazepam or prednisone contributes to an organic affective disorder.
4. There may be a concurrent but unrelated psychiatric disorder, as when personality disorder precedes any evidence of SMS.
5. Concurrent and related syndromes may exist. It has been suggested that SMS,[3,4] anxiety,[17,18] alcoholism,[19,20] and depression[21] are all disorders that represent a dysfunction of the GABA system.

If additional confirmatory, studies prove this, these disorders are related in cause and they share an underlying pathogenesis.

We report the largest series of psychiatric consultations conducted in patients with confirmed SMS. Drawing conclusions from a retrospective study of medical records can be problematic. We relied on unstructured interviews that

were recorded by several different psychiatrists. We have reported psychiatric symptoms and not diagnoses because the diagnostic criteria used were not standardized. The attention paid to past psychiatric histories and to family histories also varied among the psychiatrists involved. However, the cases reported here refute some of the conclusions of the earlier literature and identify common psychiatric problems seen in patients with SMS. Clearly, in our practice, psychiatrists have a significant role in the management of patients with SMS. Psychiatrists who see patients with SMS may be expected to manage anxiety, depression, and substance misuse.

Drug names: amitriptyline (Elavil and others), baclofen (Lioresal), clonazepam (Klonopin), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac), imipramine (Tofranil and others), nortriptyline (Pamelor and others), prednisone (Delta-Dome and others), trazodone (Desyrel and others).

REFERENCES

1. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm ("stiff-man syndrome"): report of a case and some observations in 13 other cases. Proceedings of the Staff Meetings of the Mayo Clinic 1956;31:421–427
2. McEvoy KM. Stiff-man syndrome. Mayo Clin Proc 1991;66:300–304
3. Solimena M, Folli F, Denis-Donini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med 1988;318:1012–1020
4. Solimena M, Folli F, Aparisi R, et al. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990; 322:1555–1560
5. Howard FM Jr. A new and effective drug in the treatment of the stiff-man syndrome: preliminary report. Proceedings of the Staff Meetings of the Mayo Clinic 1963;38:203–212
6. Lorish TR, Thorsteinsson G, Howard FM Jr. Stiff-man syndrome updated. Mayo Clin Proc 1989;64:629–636
7. Asher R. A woman with the stiff-man syndrome. BMJ 1958;1:265–266
8. Price TML, Allott EN. The stiff-man syndrome: preliminary report of a case. BMJ 1958;1:682–685
9. Trethowan WH, Allsop JL, Turner B. The "stiff-man" syndrome: a report of two further cases. Arch Neurol 1960;3:448–456
10. Werk EE Jr, Sholiton LJ, Marnell RT. The "stiff-man" syndrome and hyperthyroidism. Am J Med 1961;31:647–653
11. Gold S. Psycho-genesis in the "stiff-man" syndrome. Guys Hospital Reports 1965;114:279–285
12. Gordon EE, Januszko DM, Kaufman L. A critical survey of stiff-man syndrome. Am J Med 1967;42:582–599
13. Warneke L. Stiff-man syndrome. Canadian Psychiatric Association Journal 1974;19:399–403
14. Heiligman R, Paulson MJ. The stiffman syndrome: a psychiatric disease? Int J Psychiatry Med 1977;7:363–371
15. Meinck HM, Ricker K, Conrad B. The stiff-man syndrome: new pathophysiological aspects from abnormal exteroceptive reflexes and the response to clomipramine, clonidine, and tizanidine. J Neurol Neurosurg Psychiatry 1984;47:280–287
16. Shah DM, Rubinstein HM. Stiff-man syndrome: report of a case. Indian J Med Sci 1971;25:41–44
17. Shekhar A. GABA receptors in the region of the dorsomedial hypothalamus of rats regulate anxiety in the elevated plus-maze test, I: behavioral measures. Brain Res 1993;627:9–16
18. Shekhar A, Sims LS, Bowsher RR. GABA receptors in the region of the dorsomedial hypothalamus of rats regulate anxiety in the elevated plus-maze test, II: physiological measures. Brain Res 1993;627:17–24
19. Zorumski CF, Isenberg KE. Insights into the structure and function of GABA-benzodiazepine receptors: ion channels and psychiatry. Am J Psychiatry 1991;148:162–173
20. Littleton J, Little H. Current concepts of ethanol dependence. Addiction 1994;89:1397–1412
21. Petty F, Kramer GL, Gullion CM, et al. Low plasma gamma-aminobutyric acid levels in male patients with depression. Biol Psychiatry 1992;32: 354–363