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SECONDARY HYPERTENSION

Severe Paroxysmal Hypertension: Pseudopheochromocytoma

Samuel J Mann

ABSTRACT

Paroxysmal hypertension always engenders a search for a catecholamine-secreting pheochromocytoma (pheo). However, in 98% of cases, a pheo is not found, and the cause and management of the paroxysmal hypertension have remained a largely unstudied mystery. This review presents an approach to understanding and successfully treating this disorder, which is increasingly known as "pseudopheochromocytoma," or "pseudopheo." Patients with this disorder experience sudden, unprovoked, and symptomatic blood pressure elevations that are likely linked to stimulation of the sympathetic nervous system. Psychological characteristics associated with this disorder suggest a basis in repressed emotion related either to prior emotional trauma or to a repressive (nonemotional) coping style. Based on this understanding, successful intervention is possible in most of the cases. Hypertensive paroxysms can usually be managed acutely with an anxiolytic agent, such as alprazolam, an antihypertensive agent that targets the sympathetic nervous system, such as clonidine, or a combination of the two. Severe paroxysms may require an intravenous agent, such as labetalol or nitroprusside. In patients with severe and/or frequent paroxysms, recurrence of paroxysms can be prevented in most of the cases with an antidepressant drug. The importance of reassurance cannot be overstated. The possible role of psychotherapeutic intervention requires further study. Fortunately, with appropriately selected intervention, paroxysms can be effectively treated or eliminated in most patients.

Keywords: Catecholamines, Hypertension, Labile hypertension, Paroxysmal hypertension, Pheochromocytoma, Pseudopheochromocytoma.

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INTRODUCTION

Although paroxysmal hypertension is a textbook symptom of pheochromocytoma (pheo) and always engenders suspicion of a pheo, less than 2% of patients with this disorder actually have this tumor.[1] This is not surprising given the rarity of pheo.[2] Typically, diagnostic evaluation of paroxysmal hypertension reaches a dead end, leaving patients with an unexplained, difficult-to-treat, and often disabling disorder, reasonably called pseudopheochromocytoma (pseudopheo).

Although thousands of articles deal with management of patients who have a pheo, very few deal with the 98% of patients who do not have it. Doctors and researchers simply do not know what to do with these patients. In this article, the origin, mechanisms, diagnosis, differential diagnosis, and treatment of this disorder will be reviewed.

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CLINICAL DESCRIPTION OF PAROXYSMAL HYPERTENSION (PSEUDOPHEOCHROMOCYTOMA)

Characteristics of pseudopheo are summarized in Tables 1 and 2.[3,4] The frequency of paroxysms ranges from daily to less than once a month. The duration of the paroxysms can range from < 10 minutes to as long as 2 days. Physical

Table 1: Clinical presentation of paroxysmal hypertension in a series of 21 patients[3]

Sex (M/F)	5/16		
Age at onset:	50 (27–76)		
Reported duration of the disorder at time of first visit:			
< 6 months	9	18–36 months	5
6–18 months	4	> 3 years	3
Frequency of episodes:			
Daily	5	1–3/month	4
1–3/week	10	< 1/month	1
Duration of episodes:			
< 10 minutes	1	1–3 hours	6
10–60 minutes	6	3 hours–2 days	6
		Variable	2
Peak blood pressure during episodes:			
200/≥ 110	16	<200/≥ 110	2
≥ 200/< 110	2	< 200/< 110	1
Prior hospitalizations because of attacks:			
None	8		
One	5		
> Two	8		
Impairment of functioning:			
Little to none	1		
Mild to moderate impairment of usual activity	10		
Unable to work or perform usual activity	10		

Table 2: Symptomatology of pseudopheochromocytoma *vs* pheochromocytoma

Symptoms (% of patients)	*Pseudopheo Mann*[3] *(n = 21)*	*Pseudopheo Stein*[5] *(n = 28)*	*Pheo Stein*[5] *(n = 30)*	*Pheo Literature review*[5]
Chest pain	62	25	20	19–22
Headache	52	39	80	80–96
Dizziness/ lightheadedness	52	46	20	5–8
Diaphoresis	48	21	63	67–74
Nausea	48	25	23	10–42
Palpitations	43	39	60	62–70
Flushing	33	54	7	8–18
Dyspnea	29	11	13	10–19
Weakness	29	25	23	26–40

symptoms, such as chest pain, lightheadedness, headache, diaphoresis, nausea, palpitations, dyspnea, and weakness, typically accompany the blood pressure elevation. These symptoms are common to both pheo and pseudopheo, and do not reliably distinguish one from the other (Table 2). Paroxysms often result in emergency room (ER) visits and hospitalizations. The fear of recurrent attacks, which typically occur without warning, leads many patients to restrict their activity, and in some cases to leave their job. Thus, the disorder can have a considerable clinical and financial impact.

DEFINITION OF THE SYNDROME OF PSEUDOPHEO

The following characteristic features are typically seen in patients with pseudopheo (Table 3):

- Hypertensive paroxysms that are characterized by sudden onset
  Patients typically describe an abrupt onset, with no particular setting or trigger.
- Blood pressure elevation is associated with physical symptoms, such as headache, flushing, fatigue, and dizziness
  Blood pressure elevation is not asymptomatic. The physical symptoms do not distinguish between pheo and pseudopheo.[5]
- Episodes are not triggered by emotional distress or by panic
  Unlike panic attacks, hypertensive paroxysms are not heralded by panic or emotional distress. Patients typically insist that paroxysms occur "out of the blue." However, once an episode has begun, the severe physical symptoms do characteristically provoke a fear of dying or stroke.
- Biochemical tests have been performed and do not support the diagnosis of pheochromocytoma.
  The possibility of a pheo must be considered in any patient with paroxysmal hypertension. This requires assessing blood or urine levels of catecholamines or catecholamine metabolites, as discussed below.
- In most cases, psychosocial inquiry reveals either a past history of severe trauma or abuse, or a defensive, very even-keeled personality style
  A characteristic psychological background is evident in most patients with pseudopheo, as discussed below. Its presence in a patient with normal catecholamine studies strongly supports the diagnosis of pseudopheo and adds reassurance that a pheo is not being missed.

Table 3: Clinical features of pseudopheochromocytoma

1	Hypertensive paroxysms that are characterized by sudden onset.
2	Blood pressure elevation is associated with physical symptoms, such as headache, flushing, fatigue, and dizziness.
3	Episodes are not triggered by emotional distress or by panic.
4	Biochemical tests have been performed and do not support the diagnosis of pheochromocytoma.
5	Nearly, in all cases, psychosocial inquiry reveals either a past history of severe trauma or abuse, or a defensive, very even-keeled personality style.

PSEUDOPHEO AND THE SYMPATHETIC NERVOUS SYSTEM

The sudden elevations in blood pressure in pseudopheo are linked to the sympathetic nervous system (SNS), which governs instantaneous changes in blood pressure. Evidence of increases in catecholamine levels during paroxysms and the other evidence of increased catecholamine levels support this notion.[4,6-8]

PSYCHOLOGICAL ROOTS OF PSEUDOPHEO

Despite the continuing mystery of the origin of pseudopheo and of the sympathetic nervous system (SNS) activation underlying it, the possibility of a psychosomatic etiology is widely overlooked. This is understandable since paroxysms are dominated by hemodynamic changes and physical symptoms and patients typically do not report or view stress or emotional distress as a contributory factor.

A breakthrough in understanding the origin of pseudopheo occurred with the observation that most patients, upon psychosocial inquiry, acknowledged a past history of unusually severe trauma or abuse, often from as long ago as childhood.[4] Remarkably, most patients claimed that they were free of any lingering emotional effects, which strongly suggest that they had repressed trauma-related emotions. They had vivid memories of the trauma, but did not feel or suffer from the powerful and painful emotions related to it. The clues lay in the story rather than in reported emotional distress.

Repression of painful emotion is a normal and valuable defense mechanism, and it is protective against overwhelming emotional distress. The ability to repress emotion in the aftermath of severe trauma offers an explanation for the resilience of some victims of severe trauma who survive without apparent psychological sequelae.[9]

The history of severe past trauma reported by most patients with pseudopheo suggested that the absence of overt psychological effects should not exclude a psychological basis for the disorder. This mind/body paradigm in pseudopheo is thus the opposite of the usual approach to understanding psychosomatic illnesses in that it focuses on the absence rather than the presence of emotional distress related to previous major events. Patients might have experienced severe emotional distress immediately following the trauma, but eventually repressed and no longer experience the related emotions. Unfortunately, the concept of repressed emotion and the possible role of repressed emotion in a hypertensive disorder are not widely considered, even though no alternative understanding or treatments of pseudopheo have emerged.

REPRESSED EMOTION IN PATIENTS WITH PSEUDOPHEO: TWO PATTERNS

Two patterns of unawareness of emotion appear to be associated with pseudopheo: A past history of severe abuse or trauma and a personality characterized by a repressive coping style.

Roughly two-thirds of patients acknowledge a history of severe trauma, but strikingly insist that they suffer no lingering effects.[3] Their resilience and their ability to thrive in the aftermath of trauma can be attributed to repression of overwhelming emotion.[9] In most of the remaining patients, a repressive coping style is evident, which is characterized by a lifelong tendency to cope unemotionally with stress.[3,10] Such individuals tend to be very even-keeled, without experiencing ups and downs. Since they report little emotional distress, physicians rarely consider their medical condition to be linked to psychological factors. A repressive coping style is usually a pattern developed in childhood and it could be a result of psychosocial experience or inherent personality from birth. Such individuals are not buffeted by emotions, and the experience of depression or anxiety may be foreign to them.

DIFFERENTIAL DIAGNOSIS OF PSEUDOPHEO

Although paroxysmal hypertension can occur in many conditions, only a few truly resemble pseudopheo and need to be differentiated from it (Table 4). These include pheo, of course, as well as panic disorder and labile hypertension.

Table 4: Differential diagnosis of pheochromocytoma

- Pheochromocytoma
- Common conditions that resemble pseudopheo:
  - Panic disorder
  - Labile hypertension
- Other conditions in which paroxysmal blood pressure elevation can occur
  - Renovascular hypertension
  - Vasculitis
  - Hypertensive encephalopathy
  - Preeclampsia
  - Baroreflex failure
  - Hyperdynamic beta-adrenergic circulatory state
  - Paroxysmal tachycardia
  - Ingestion of sympathomimetics
  - MAO inhibitor + ingestion of tyramine
  - Clonidine withdrawal
  - Illicit drugs (e.g., cocaine)
  - Coronary insufficiency
  - Migraine
  - Intracranial mass lesion
  - Hypoglycemia
  - Porphyria
  - Carcinoid
  - Anxiety
  - PTSD

Pheochromocytoma

It is of course a priority to exclude the presence of a pheo. The measurement of plasma metanephrine levels has a high sensitivity and specificity for identifying a pheo, and it is widely employed for pheo screening.[11] If levels of plasma catecholamines or metanephrines are markedly elevated, radiological studies to identify a pheo are indicated. However, mild elevations are frequently encountered, which usually represent false positives, perhaps largely reflecting a 30% false-positive rate associated with lack of adherence to fasting state, supine position, and rest before sampling.[12] The increased sympathetic tone in patients with pseudopheo might also contribute to a higher false-positive rate. Thus, although radiologic imaging is sometimes obtained by physicians suspicious of a pheo in patients with normal or only mildly elevated metanephrines, an unending search for a pheo is unlikely to be of value.

Traditionally, a clonidine suppression test was performed in patients with mild elevation of plasma catecholamines.[13] However, this test currently is not widely employed.

Although there is no clearly established protocol with regard to further work-up, a reasonable approach would be to screen for pheo with plasma metanephrines in all patients with paroxysmal hypertension. Because of the rarity of pheo, magnetic resonance imaging should be

reserved for patients with metanephrine values that are markedly elevated or with persistent mild elevation on repeated testing and with severe manifestations or a high degree of physician concern.[14]

CONDITIONS THAT COMMONLY MIMIC PSEUDOPHEO

Panic Disorder

Both panic disorder and pseudopheo are characterized by sudden episodes of severely distressing physical symptoms, such as headache, dyspnea, dizziness, weakness, and diaphoresis. Thus, physical symptomatology does not allow the differentiation of the two disorders.

However, the two conditions differ in that in panic disorder panic attacks are dominated by the emotional manifestation of panic, with less prominent elevation of blood pressure , usually averaging 20 mm Hg or less.[15] In contrast, pseudopheo is dominated by the autonomic manifestation of the blood pressure elevation (40–100 mm Hg or more), without panic attacks.[3] Panic does not trigger hypertensive paroxysms; it occurs as a result of the frightening physical symptoms. It was the perspective of viewing hypertensive paroxysms in pseudopheo as the autonomic equivalent of panic attacks that led to consideration of treating it with an antidepressant, in the same way that panic disorder is treated.

Labile Hypertension

Many individuals with essential hypertension experience considerable fluctuation in their blood pressure, often at times of stress or emotional distress. Blood pressure elevation can occur without physical symptoms or can be accompanied by symptoms, such as headache or palpitations.

Labile hypertension differs strongly from pseudopheo; in the former, most patients readily attribute their blood pressure fluctuations to stress and emotional distress. In some patients, blood pressure increases are associated with symptoms resulting from anxiety or hyperventilation.[16] Blood pressure lability is much more prevalent and should not be misconstrued as pseudopheo in the absence of the aforementioned characteristics.

Other Diagnoses

Many other conditions (some are commonly and others are rarely encountered) can also cause paroxysmal hypertension (Table 4). However, few present with paroxysmal hypertension as their only manifestation, without other signs or symptoms that are more typical of those conditions. In the absence of signs or symptoms characteristic of these conditions, they are unlikely to provide a diagnosis, whereas pseudopheo is overwhelmingly likely.

The use of illicit drugs, such as cocaine or amphetamines can cause severe blood pressure elevation. However, patients with pseudopheo are so symptomatic and frightened that they are highly unlikely to continue using, and deny that they are using, these drugs. The use of drugs, such as monoamine oxidase inhibitors or the sudden withdrawal from clonidine will be readily evident from the history.

Baroreceptor failure causes considerable blood pressure lability, but is unlikely to be seen in the absence of a condition predisposing to its development, such as prior neck surgery or irradiation.[17,18] In addition, marked blood pressure fluctuations of this disorder are regularly observed, while with pseudopheo, blood pressure elevations are seen only during paroxysms without abnormal lability or hypotension at other times.

Posttraumatic stress disorder (PTSD), like pseudopheo, is associated with prior trauma and with elevated plasma norepinephrine levels.[19] However, severe blood pressure elevation is not characteristic. Further, unlike patients with pseudopheo, patients with PTSD are very aware of prior trauma and its impacts.

Are tests to exclude these entities truly needed in the patient who presents with paroxysmal hypertension? Usually not, although each case must be assessed based on the accompanying clinical signs and symptoms. Further, as mentioned above, the presence or absence of the characteristic psychological profile of pseudopheo supports the diagnosis and argues for treatment directed at pseudopheo rather than endless testing for very unlikely causes. A clear response to treatment directed at pseudopheo then further supports the diagnosis.

APPROACH TO TREATMENT

The treatment of paroxysmal hypertension has been a major dilemma, and there is a paucity of treatment trials. Diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs) would not be expected to prevent hypertensive surges driven by the SNS. Further, it is difficult to prescribe an aggressive antihypertensive regimen in patients whose blood pressure is normal in between paroxysms, due to the risk of iatrogenic hypotension. Nevertheless, patients need treatment, and successful approaches based on understanding the origin of pseudopheo have been reported.[3,20] With these approaches, paroxysmal hypertension can be successfully managed in most patients, enabling their resumption of a normal life. Treatment involves acute treatment of paroxysms as well as preventive treatment (Table 5).

Table 5: Treatment

A. Acute management of paroxysms	
Goal:	
• To reduce blood pressure if severely elevated	
• To reduce symptoms	
• To avoid ER visits and hospitalizations	
Pharmacologic agents:	
Mild paroxysm:	Alprazolam
Moderately severe paroxysm:	Alprazolam ± clonidine
Severe paroxysm:	Intravenous labetalol and alprazolam
B. Preventive treatment	
Antihypertensive agents are of limited value:	
• Rx limited by normal blood pressure (BP) between paroxysms	
• Not proven to prevent paroxysms	
• Might reduce magnitude of BP spikes (unproven)	
• ACEIs, ARBs, diuretics unlikely to help	
• Role of combined α + β blockade remains to be determined	
• Role of chronic use of clonidine limited by adverse effects	
Psychopharmacologic agents:	
• Antidepressants highly effective in most patients	
• Various drug classes are effective; choice usually governed by side effects	

ACUTE MANAGEMENT OF HYPERTENSIVE PAROXYSMS

In the acute management of paroxysms, there is a role for antihypertensive agents, psychotropic agents, or a combination of both. The choice of treatment depends on the severity and frequency of paroxysms. For paroxysms with severe blood pressure elevation, treatment with a rapid-acting intravenous agent, such as labetalol, or, rarely, nitroprusside, may be needed. Concomitant treatment with a quickly effective anxiolytic agent like alprazolam can be helpful in shortening the duration of the paroxysm and the severity of blood pressure elevation.[3,21]

For milder paroxysms, oral treatment is usually appropriate and effective, consisting of an oral sympatholytic agent, such as clonidine, an anxiolytic agent, such as alprazolam, or a combination of both. In patients with a history of previous uncomplicated paroxysms and who are known to have responded to these agents, self-treatment at home, rather than management in an ER or hospital, is a realistic option. Oral labetalol is another alternative, although it might not be effective in rapid metabolizers of lipophilic beta-blockers.[22] Agents, such as ACEIs, ARBs, and diuretics do not appear well suited for acute treatment of SNS-mediated blood pressure elevations.

PREVENTIVE MANAGEMENT

There is no compelling evidence that antihypertensive agents can prevent paroxysms. It is also unclear whether or not they mitigate the magnitude of the blood pressure spike during paroxysms. Further, dosing of antihypertensive agents is often limited by the normal blood pressure between paroxysms.

The efficacy of the alternative of prescribing an antidepressant agent was originally suggested by the similarity of pseudopheo to panic disorder. This promise has been borne out in reports indicating that antidepressant drugs are highly effective in preventing paroxysms in most patients, at dosages used in treating panic disorder, and are the most effective treatment available for preventing paroxysms.[3,4,20] Initially, the high response rate reported in two retrospective case series was recently confirmed in a prospective study in which the antidepressant sertraline, given at a 50 mg dose, eliminated paroxysms in 61% of patients, and reduced or eliminated them in 90% of patients.[20] These results also strongly support the suggested psychosomatic basis of this disorder.

Which patients are candidates for long-term treatment with an antidepressant agent? In patients who have mild or infrequent paroxysms or who improve with psychological intervention (see below), it is reasonable to initially limit treatment to acute management of paroxysms with alprazolam or clonidine. However, in patients who continue to experience severe symptoms, severe blood pressure elevations, or frequent paroxysms that interfere with their functioning, an antidepressant agent is very likely to be effective and should be strongly considered. There is no evidence that any class of antidepressant agents is more effective than any other.

PSYCHOLOGICAL INTERVENTION

There are no trials regarding the psychological aspects of treating patients with pseudopheo. However, attending to psychological aspects of treatment appears to play an important role in the management of patients with pseudopheo.[3,4] Reassurance appears to be very helpful. Less commonly, psychological intervention centered on a shift in awareness regarding the role of past events might lead, in some cases, to a dramatic reduction or cessation in paroxysms, as discussed below.

REASSURANCE

The following are the three aspects of reassurance that appear to play an important role:

- Reassurance that a hypertensive paroxysm is highly unlikely to cause stroke or sudden death
  Symptomatic hypertensive paroxysms are terrifying to patients, regularly provoking fear of suffering a stroke or of dying during a paroxysm. Many treating physicians share that fear. However, the occurrence of acute cardiovascular events during a paroxysm has not been reported, supporting the likelihood that the

risk of an event is very low. Similarly, regular weightlifting causes acute and severe elevation in blood pressure, with peak mean arterial pressure averaging 160 mm Hg (equivalent to a systolic/diastolic pressure of 220/130) in normotensive weightlifters, yet it has not been reported to be associated with acute stroke.[23] Reassurance by a physician that stroke or death is very unlikely to occur during a paroxysm can be extremely helpful in reducing the fear of the patient and the sympathetic stimulation that is aggravated by fear.

- Reassurance that the patient will be able to resume a normal life

  Many patients have come to view themselves as chronically ill with no hope of improvement or return to a normal life. The reassurance that the disorder can usually be successfully treated and that they will be able to resume a normal life would seem to be, and in clinical experience, helpful to patients.
- Reassurance that the patient is psychologically healthy. Many patients resist an explanation of the disorder as having psychological roots, partly because it implies psychological weakness or illness. This concern also provokes resistance to consideration of the psychopharmacologic interventions that offer the best chance of clinical improvement.

  The fact that many patients with pseudopheo are successful survivors of severe trauma actually offers testimony of psychological strength, not weakness, rooted in successful repression that enabled avoidance of the severe and long-standing psychological sequelae that might otherwise have resulted from the trauma. Reassurance that the disorder is not indicative of psychopathology or psychological weakness increases the likelihood of patients' acceptance of its psychodynamic origin. This reassurance might increase patients' acceptance of the psychosomatic etiology of the disorder as well as treatment with an antidepressant.

AWARENESS

In treating physical symptoms that result from psychological distress, the usual paradigm of psychological intervention consists of stress reduction techniques or psychotherapy to relieve emotional distress. This paradigm does not fit pseudopheo, which is characterized by the absence of perceived emotional distress. Strikingly, in pseudopheo, it is a shift to conscious awareness of painful emotion that might be helpful in ameliorating the disorder.[21] However, most pseudopheo patients do not appear to be interested in, or capable of, dealing with trauma-related emotions; further, such interventions may be unhelpful and could perhaps be harmful.[9,21] Many successful survivors of severe trauma depend on repressing trauma-related emotions.[9] Of necessity, they continue to defend against awareness and probably benefit from doing so.[9] Thus, they are unlikely to be interested in, or to benefit from, psychotherapy aimed at emotional awareness.[21] This is analogous to the lack of benefit and the risk of harm associated with efforts to bring up trauma-related emotions in successful trauma survivors.[9] The dictum that it is always best to deal with the past is not inherently true.

In the absence of adequate study, the wisest course might be to reassure the patient that the disorder can be successfully managed and normal life can be resumed. If the patient wishes to pursue the psychological origin of the disorder, it can be encouraged. If not, then psychological discussion and psychotherapy should not be urged.

OBSTACLES TO SUCCESSFUL TREATMENT

Barriers to treatment with antihypertensive agents include the ineffectiveness of ACEIs, ARBs, and diuretics, and the normal blood pressure between paroxysms that limits the aggressiveness of antihypertensive therapy. Further, an antihypertensive regimen is unlikely to prevent paroxysms.

Barriers to treatment with antidepressants include patients' antipathy to the idea of taking one and intolerance to agents that are tried. Some patients will refuse to try an antidepressant no matter how severely symptomatic they are because its use implies a psychological cause. However, many such patients will eventually agree to try one because they are severely symptomatic and no other treatment has helped. The newer serotonin-specific reuptake inhibitors (SSRIs) are well tolerated in most, but in some patients, it is difficult to reach an effective dose of any drug.

Finally, there are major barriers to acceptance of a psychological origin of the disorder. Because the manifestations of pseudopheo are physical rather than psychological and are not triggered by obvious current stressors, its emotional basis is usually not suspected by either patient or physician. Further, many trauma survivors need to avoid psychological discussion or awareness. This is the reason why psychological awareness is not an option for most.

Clearly, the treatment of pseudopheo is a challenge and an art. However, fortunately, in most cases, successful treatment is achievable, and a normal quality of life can be restored.

CONCLUSION

Despite all the attention given to pheochromocytoma, >98% of patients with paroxysmal hypertension have

pseudopheo, whose origin and treatment have received remarkably little attention. The obscurity of its origin is attributable to its link to repressed emotion, a phenomenon essentially unrecognized by patients, physicians, and even psychologically oriented medical clinicians and researchers. Further, it is a disorder for which patients seek out physicians, not psychologists, and therefore, it has remained under the radar of psychologists.

If catecholamine studies are normal, the characteristic psychological background usually allows a confident diagnosis and greatly reduces concern that a pheo or other obscure cause is being missed. Treatment is successful in most patients. The main components are treatment at the time of paroxysms with an anxiolytic agent and/or an antihypertensive agent directed at the SNS, usually clonidine, and preventive treatment with an antidepressant agent.

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