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Issue 3

CLONAZEPAM

Prescription perspectives of clonazepam in cardiovascular conditions

LITERATURE REVIEW

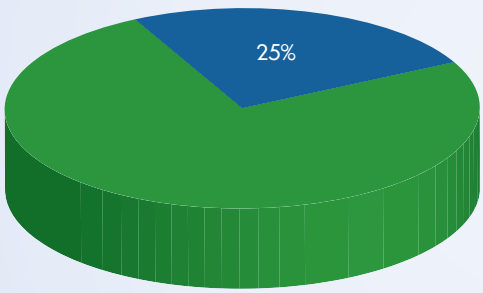
Picturing panic disorder with chest pain: Clinical implications

Association of chest pain with panic disorder

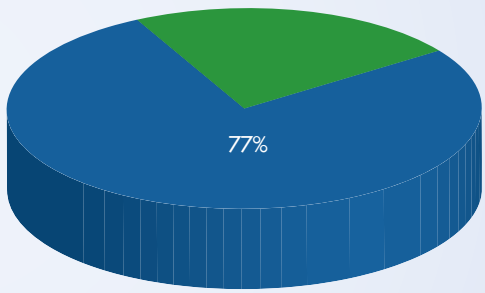
Panic disorder is a common chronic illness seen in individuals presenting to physicians, with significant physical symptoms that are similar to those of emergency medical conditions, for example chest pain. The disorder is characterized by the spontaneous and unexpected occurrence of panic attacks, during which patients usually refer to the emergency department, for unexplained respiratory or cardiovascular symptoms like chest pain.[1-3] In fact, it has been observed that approximately one quarter (25%) of patients who present to physicians for assessment and treatment of chest pain have panic disorder (Figure 1).[4,5] A recent study examined the prevalence of emergency department visits prompted by panic attacks in patients with non-cardiac chest pain, and used validated structured telephone interview to assess panic attacks and their association with emergency department consultation in 1327 emergency department patients with non-cardiac chest pain.[6] The authors noted that patients reported at least one panic attack in the past 6 months in 34.5% of cases, and about 77% of patients who reported panic attacks had visited the emergency department with non-cardiac chest pain following a panic

Figure 1: Prevalence of panic disorder in chest pain patients and their related emergency department visits

A. Approximate percentage of chest pain patients visiting emergency department and identified to have panic disorder



B. Approximate percentage of patients with panic attacks visiting emergency department with non-cardiac chest pain following a panic attack



Sources: **1.** Huffman JC, Pollack MH, Stern TA. Panic disorder and chest pain: Mechanisms, morbidity, and management. *Prim Care Companion J Clin Psychiatry.* 2002;4(2):54-62. **2.** Fleet RP, Dupuis G, Marchand A, et al. Panic disorder in emergency department chest pain patients: prevalence, comorbidity, suicidal ideation, and physician recognition. *Am J Med.* 1996;101(4):371-80. **3.** Foldes-Busque G, Denis I, Poitras J, et al. A closer look at the relationships between panic attacks, emergency department visits and non-cardiac chest pain. *J Health Psychol.* 2017:1359105316683785.

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attack (Figure 1). The results clearly indicated that panic attacks may explain a significant proportion of emergency department visits for non-cardiac chest pain. Nevertheless, the dilemma is that the disorder often goes unrecognized and hence untreated among this cohort of patients, leading to mismanagement, higher recurrence visits and considerable morbidity.

Mechanisms relating chest pain in panic disorder

It is proposed that panic attacks may lead to chest pain through diverse mechanisms, both cardiac and non-cardiac in nature, and multiple processes may converge to manifest this symptom in the same patient.[4] The cardiac mechanisms involve coronary spasm or ischemia, while non-cardiac mechanisms involve musculoskeletal, esophageal, or other processes unrelated to the heart.[4,7] Both autonomic activation and hyperventilation (via alkalosis) during panic attacks can lead to coronary artery spasm, which in turn can then lead to myocardial ischemia and cardiac chest pain. Hyperventilation during panic attacks may also lead to musculoskeletal chest pain, with strain or spasm of the intercostal chest wall muscles. In addition, the acute anxiety associate with panic attack may cause esophageal dysmotility, which may then lead to esophageal spasm, a well-described cause of non-cardiac chest pain.[4] Furthermore, existence of underlying comorbid conditions may also contribute in increased rate of chest pain in these patients. For instance, in patients with coronary disease, panic attacks can provoke ischemic pain simply by increasing myocardial oxygen demand through increases in heart rate and blood pressure (BP), mediated by the autonomic nervous system. This mechanism may be significant seeing that panic disorder is associated with elevated rates of cardiovascular diseases (CVDs), including hypertension, cardiomyopathy, and possibly, sudden cardiac death.

Management strategies for chest pain comorbid with panic disorders

Panic disorder has a negative long-term effect on both psychological and physical well-being of chest pain patients, emphasizing the necessity of correctly identifying these patients and offering them adequate treatment.[8] Fortunately, the disorder is treatable, and empirically validated interventions initiated in an emergency setting can be feasible and efficacious; both cognitive-behavioral psychotherapy and drug therapy [selective serotonin reuptake inhibitors (SSRIs), benzodiazepines) are effective in reducing the symptoms.[4,9] Preliminary studies have found that treatment of patients having panic disorder and chest pain with benzodiazepines results in both reduction of chest pain and relief of anxiety.[4] These medications have the advantage of a rapid onset of efficacy, and can be in fact be used to abort ongoing panic attacks. They are often used with SSRIs with aim to combine the rapid effects of benzodiazepines with long-term therapeutic effects of antidepressants.[4,10] Clonazepam, a high-potency benzodiazepine, has been shown to decrease anxiety levels and panic attack frequency in panic disorder patients with chest pain and normal coronary angiograms.[4,11,12] It has a long half-life that limits the frequency of dosing and reduces the likelihood of inter-dose rebound symptoms, making it useful for maintenance therapy. It can be started at 0.25 to 0.5 mg at bedtime and titrated upward; doses from 1 to 2 mg/day may offer the best balance of therapeutic benefit and tolerability.[4]

References

1. Esan OB, Baiyewu O. Panic disorder prevalence among patients referred for an electrocardiogram in a Nigerian teaching hospital. *Psychosomatics.* 2013;54(5):472-8.
2. Buccelletti F, Ojetti V, Merra G, et al. Recurrent use of the Emergency Department in patients with anxiety disorder. *Eur Rev Med Pharmacol Sci.* 2013;17 Suppl 1:100-6.
3. Foldes-Busque G, Hamel S, Belleville G, et al. Factors associated with pain level in non-cardiac chest pain patients with comorbid panic disorder. *Biopsychosoc Med.* 2016;10:30. eCollection 2016.
4. Huffman JC, Pollack MH, Stern TA. Panic disorder and chest pain: Mechanisms, morbidity, and management. *Prim Care Companion J Clin Psychiatry.* 2002;4(2):54-62.
5. Fleet RP, Dupuis G, Marchand A, et al. Panic disorder in emergency department chest pain patients: prevalence, comorbidity, suicidal ideation, and physician recognition. *Am J Med.* 1996;101(4):371-80.
6. Foldes-Busque G, Denis I, Poitras J, et al. A closer look at the relationships between panic attacks, emergency department visits and non-cardiac chest pain. *J Health Psychol.* 2017:1359105316683785.
7. Katerndahl DA. Chest pain and its importance in patients with panic disorder: an updated literature review. *Prim Care Companion J Clin Psychiatry.* 2008;10(5):376-83.
8. Bull Bringager C, Arnesen H, Friis S, et al. A long-term follow-up study of chest pain patients: effect of panic disorder on mortality, morbidity, and quality of life. *Cardiology.* 2008;110(1):8-14.
9. Pelland MÈ, Marchand A, Lessard MJ, et al. Efficacy of 2 interventions for panic disorder in patients presenting to the ED with chest pain. *Am J Emerg Med.* 2011;29(9):1051-61.
10. Rosenbaum JF, Moroz G, Bowden CL. Clonazepam in the treatment of panic disorder with or without agoraphobia: a dose-response study of efficacy, safety, and discontinuance. Clonazepam Panic Disorder Dose-Response Study Group. *J Clin Psychopharmacol.* 1997;17(5):390-400.
11. Katerndahl DA. Chest pain and its importance in patients with panic disorder: An updated literature review. *Prim Care Companion J Clin Psychiatry.* 2008;10(5):376–383.
12. Wulsin LR, Maddock R, Beitman B, et al. Clonazepam treatment of panic disorder in patients with recurrent chest pain and normal coronary arteries. *Int J Psychiatry Med.* 1999;29(1):97-105.

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Paroxysmal hypertension with panic disorder and role of clonazepam: A case report

Case report

An 82-year old female retired paramedic was referred to the hospital for evaluation of paroxysmal hypertension. Her husband had died about 20 years back, and she was currently living in an old-age home. The patient was a known case of hypertension and dyslipidemia, and reported history of mild hypertension and hyperlipidemia for many years. Until about six months back, her hypertension and hyperlipidemia were controlled with chlorthalidone and atorvastatin. However, as she started experiencing adverse effects related to chlorthalidone (confusion, weakness, irregular heartbeat, shortness of breath, numbness in hands), her physician replaced the diuretic with amlodipine. The switch-over was initially beneficial; but over next few weeks, she began to have frequent episodes of epigastric pain, flushing, weakness, light-headedness, and a feeling of warmth and anxiety.

She mentioned that there episodes were sudden in origin, and lasted for about 30 to 40 minutes, during which she typically had high blood pressure (BP; paroxysmal hypertension). At current presentation, she was having approximately one episode per day. The patient further narrated that about 3 months back, she had one prolonged hospitalization for 2 weeks, during which, she underwent an extensive workup for secondary causes of hypertension, including pheochromocytoma. However, the workups yielded negative results, except the finding of a right renal artery stenosis. The renal artery stenosis was surgically treated with insertion of a stent, and her treatment regimen was later modified to clonidine, carvedilol and hydrochlorothiazide. Nevertheless, despite this surgical + medical intervention, there was no noticeable effect on the panic attacks.

On current hospitalization, a diagnosis of panic disorder was made considering the physiology of panic attacks, the role of hyperventilation as a trigger for physical symptoms, and role of catastrophic thinking in escalating a vicious cycle of increasing anxiety, increased physical symptoms and their interpretations. As follow, she was treated with a brief session of psychoeducation, and was instructed in paced breathing as a technique for stress reduction. In addition, she was prescribed clonazepam 0.5 mg twice daily. The patient complied well with the instructions, and continued practice of breathing relaxation with concomitant drug therapy, which was well-tolerated and resulted in complete remission of her symptoms. At one month, she was symptom-free and her BP was well-controlled.

Discussion

Paroxysmal hypertension, or pseudopheochromocytoma, is a quite common problem in clinical practice that may occur due to interaction of several factors in any one individual.[1-3] In most cases, the clinical syndrome includes paroxysmal (malignant) hypertension, and other physical symptoms related to sympathoadrenal overdrive, including tremor, palpitation, sweating, chest pain, headache, nausea, and dizziness. These episodes of clinical symptoms and complaints may last from minutes up to hours. Generally, the symptoms due to sympathoadrenal overdrive seen in paroxysmal hypertension are not related to emotional stress; however, in some patients, anxiety or panic disorder may be one of the major causes. Therefore, the clinical entity often bears resemblance to panic disorder.[1,2,4] Accordingly, three forms of intervention, alone or in combination, appear successful in many of these patients: antihypertensive therapy with agents directed at the sympathetically mediated BP elevation (e.g., combined alpha- and beta-blockade or central alpha-agonists such as clonidine); psychopharmacologic interventions including anxiolytic and/or antidepressant agents; and psychological intervention, including reassurance and increased psychological awareness.[5] As an appropriately selected intervention can reduce or eliminate attacks in most patients, use of drugs effective for treatment of panic disorder can be helpful in managing patients with identifiable panic disorder.[6]

References

1. Vaclavik J, Krenkova A, Kocianova E, et al. 7B.04: effect of sertraline in paroxysmal hypertension. *J Hypertens.* 2015;33 Suppl 1:e93.
2. Páll A, Becs G, Erdei A, et al. Pseudopheochromocytoma induced by anxiolytic withdrawal. *Eur J Med Res.* 2014;19(1):53.
3. Manger WM. The protean manifestations of pheochromocytoma. *Horm Metab Res.* 2009;41(9):658-63.
4. Eisenhofer G, Sharabi Y, Pacak K. Unexplained symptomatic paroxysmal hypertension in pseudopheochromocytoma: a stress response disorder? *Ann N Y Acad Sci.* 2008;1148:469-78.
5. Mann SJ. Severe paroxysmal hypertension (pseudopheochromocytoma). *Curr Hypertens Rep.* 2008;10(1):12-8.
6. Papadopoulos DP, Mourouzis I, Votteas V, Papademetriou V. Depression masked as paroxysmal hypertension episodes. *Blood Press.* 2010;19(1):16-9.

Panic disorder in patients presenting to the emergency with chest pain

Patients with panic disorder experience several symptoms likely to have a cardiovascular origin, such as palpitations, chest pain, dizziness, and breathlessness, and may present to the emergency department for evaluation of possible medical emergency. However, the recognition of panic disorder within the emergency remains low. In a recent observational study, investigators sought to establish the prevalence of panic disorder in patients presenting to emergency department for investigation of potential acute coronary syndrome (ACS), and to characterize the cohort in terms of presenting symptoms, risk factors, medical history and major adverse cardiac events. The study included 338 adult patients (average age 50.2 years, 37.9% female) presenting to the emergency department of a tertiary hospital. The findings revealed that 30-day major adverse cardiac events occurred in 7.7% of the cohort. The clinical diagnosis of panic disorder was made in 5.6% of patients. Patients with panic disorder were slightly more likely to report that their pain felt heavy than those without panic disorder (73.7% and 48.9%, respectively), though all other reported symptoms were similar in the two groups. The authors concluded that clinical signs or symptoms routinely collected as part of chest pain workup cannot be used to distinguish patients with and without panic disorder.

Patients with panic disorder were slightly more likely to report that their pain felt heavy than those without panic disorder (73.7% and 48.9%, respectively)

Source: Greenslade JH, Hawkins T, Parsonage W, Cullen L. Panic Disorder in Patients Presenting to the Emergency Department with Chest Pain: Prevalence and Presenting Symptoms. *Heart Lung Circ.* 2017 Feb 16. pii: S1443-9506(17)30063-X.