

# The Association Between Panic Disorder and Coronary Artery Disease Among Primary Care Patients Presenting With Chest Pain: An Updated Literature Review

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**Context:** Although panic disorder is linked to hypertension and smoking, the relationship between panic disorder and coronary artery disease (CAD) is unclear.

**Objective:** To extend our understanding about the strength of the association between panic disorder and coronary artery disease and known cardiovascular risk factors.

**Data sources:** Potential studies were identified via a computerized search of MEDLINE and PsycINFO databases and review of bibliographies. MeSH headings used included *panic disorder with chest pain*, *panic disorder with coronary disease or cardiovascular disorders or heart disorders*, and *panic disorder with cholesterol or essential hypertension or tobacco smoking*.

**Study selection:** The diagnosis of panic disorder in eligible studies was based on DSM-IV criteria, and studies must have used objective criteria for CAD and risk factors. Only case-control and cohort studies were included.

**Data Synthesis:** Concerning the relationship between panic disorder and CAD, studies conducted in emergency departments found a relative risk [RR] of 1.25 (95% CI = 0.87 to 1.80), while those conducted in cardiology settings found an inverse relationship (RR = 0.19, 95% CI = 0.10 to 0.37). However, there is an inverse relationship between the prevalence of CAD in the study and the RR ( $r = -.554$ ,  $p = .097$ ), suggesting that, in primary care settings in which the prevalence of CAD is low, there may be a significant association between panic disorder and CAD.

**Conclusion:** The association between panic disorder and CAD has several implications for primary care physicians managing patients with chest pain. When comorbid, the panic attacks may cause the patient with coronary disease to seek care but could also provoke a cardiac event. If one condition is recognized, a search for the other may be warranted because of the potential consequences if left undetected. The treatment approach to the panic disorder should be adjusted in the presence of comorbid CAD.

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There are several reasons to consider that a relationship between panic disorder and coronary artery disease (CAD) might exist. First, panic disorder has been linked to other forms of cardiac disease. Second, the most likely source of the chest pain during panic attacks is ischemia. Finally, there is evidence that panic disorder may be associated with cardiovascular risk factors, such as hypertension, hyperlipidemia, and smoking.

Panic disorder is associated with several cardiac abnormalities. In addition to patients with panic disorder having elevated standing heart rates,<sup>1</sup> 10% have an arrhythmia.<sup>2</sup> Panic disorder is associated with increased left ventricular mass and diameter,<sup>3</sup> and patients with panic disorder have poorer cardiovascular fitness as demonstrated by lower maximum oxygen consumption and decreased exercise tolerance.<sup>4</sup> Patients presenting to the emergency department with panic attacks were found to have increased levels of B-type natriuretic peptide.<sup>5</sup> Conflicting studies concerning an association with idiopathic cardiomyopathy have been reported.<sup>6–8</sup> Case reports have linked panic disorder to a descending aortic aneurysm<sup>9</sup> and pulmonary hypertension secondary to an atrial septal defect with pulmonic valve disease.<sup>10</sup> However, the strongest association is between panic disorder and mitral valve prolapse (MVP). The panic-MVP relationship has been well documented,<sup>11</sup> but MVP is not likely to be the source of chest pain.<sup>12</sup> In addition, the significance of the panic-MVP relationship is unclear. Not only does the presence of MVP not alter psychiatric comorbidity<sup>13,14</sup> or treatment response,<sup>15</sup> but the source of the linkage is also unclear. There is no supporting evidence for a MVP-to-panic sequence as proposed.<sup>16</sup> Indirect linkages via autonomic vulnerability or dysfunction have also been proposed.<sup>17</sup> However, the most likely explanation is that the decreased left ventricular volume due to the tachycardia seen in panic disorder produces the MVP.<sup>18</sup> The

**Table 1. Prevalence of Panic Disorder in Patients With Coronary Artery Disease<sup>a</sup>**

| Setting                     | Prevalence of Panic Disorder, % (95% CI)     |
|-----------------------------|--|
| Emergency department        | 6 (3 to 9) <sup>30</sup>                     |
| No cardiac cause            | 34 (23 to 45) <sup>31</sup>                  |
| Referral populations        |  |
| Gastrointestinal laboratory | 49 (37 to 61) <sup>32</sup>                  |
| For cardiac testing         | 6 (0 to 13) <sup>33</sup>                    |
| For angiography             | 0 (not calculable) <sup>34</sup>             |
| Cardiology                  | 22 (7 to 37), 27 (14 to 40) <sup>35-37</sup> |
| Atypical chest pain         | 52 (34 to 70) <sup>38</sup>                  |
| Clinic                      | 10 (0 to 23), 5 (2 to 9) <sup>39,40</sup>    |
| Other                       |  |
| General                     | 7 (0 to 14) <sup>41</sup>                    |
| Post-myocardial infarction  | 6 (1 to 11) <sup>42</sup>                    |
| Microvascular angina        | 40 (15 to 65) <sup>43</sup>                  |

<sup>a</sup>Reprinted with permission from Katerndahl.<sup>29</sup>

observation that the MVP disappears with remission of the panic disorder supports this sequence.<sup>19</sup> Thus, panic disorder has been linked to several forms of cardiac disease. In fact, this association is seen in studies from the United States<sup>20</sup> and around the world.<sup>21</sup> Although a relationship with MVP is probably the most common, an association with CAD would be the most significant.

Whether because of decreased heart rate variability, microvascular angina, or coronary artery disease, ischemia is believed to be the cause of chest pain during panic attacks. Smoller et al.<sup>22</sup> found an association between panic attacks and both ischemic and nonischemic chest pain among women undergoing Holter monitoring. In fact, in a large managed care database, an association between diagnoses of panic disorder and coronary heart disease was found even after controlling for covariates (odds ratio = 1.87, 95% CI = 1.80 to 1.91).<sup>23</sup> Similarly, women enrolled in the Women's Health Initiative Observational Study demonstrated an association between panic attacks and coronary heart disease (hazard ratio = 4.20, 95% CI = 1.76 to 9.99).<sup>24</sup> If this association is true, myocardial ischemia could cause panic attacks via increased catecholamines or cerebral carbon dioxide levels secondary to lactate.<sup>25</sup>

Finally, a relationship between panic disorder and CAD could exist through a relationship between panic disorder and cardiac risk factors. While Dammen et al.<sup>26</sup> reported no association with hypertension, diabetes, obesity, or hyperlipidemia, Bajwa<sup>27</sup> reported no association with BMI and Roy-Byrne et al.<sup>28</sup> reported no association with hypercholesterolemia. However, most studies have linked panic disorder with cardiac risk factors. In fact, people with panic disorder frequently have a family history of CAD and have a higher number of risk factors than controls.<sup>26</sup>

Not only would a panic-CAD association lead to serious consequences, but because the respective characteristics of the chest pain do not accurately distinguish be-

**Table 2. Prevalence of Coronary Artery Disease in Patients With Panic Disorder<sup>a</sup>**

| Setting                    | Prevalence of CAD, % (95% CI)               |
|----------------------------|---|
| Primary care               | 4 (0 to 8) <sup>28</sup>                    |
| Emergency department       | 55 (40 to 70) <sup>44</sup>                 |
| Cardiology                 | 44 (30 to 58) <sup>2</sup>                  |
| Atypical chest pain        | 27 (15 to 39) <sup>38</sup>                 |
| Other                      |   |
| General                    | 20 (0 to 41) <sup>41</sup>                  |
| Any cardiovascular disease | 8 (1 to 15), 21 (2 to 40) <sup>45, 46</sup> |

<sup>a</sup>Reprinted with permission from Katerndahl.<sup>29</sup>

Abbreviation: CAD = coronary artery disease.

tween them, panic symptoms could overshadow those typically linked to CAD, obscuring its presence. Although prior reviews have looked at the panic disorder-CAD relationship, none have focused on their association among primary care patients presenting with chest pain. The purpose of this review was to estimate the strength of the association between panic disorder and CAD in primary care settings, attempt to understand possible reasons for an association to exist, and translate that understanding into recommendations for management.

## LITERATURE REVIEW

This review extends the results from a systematic review previously reported.<sup>29</sup> Briefly, potential studies were identified via a computerized search of MEDLINE and PsycINFO databases, and review of bibliographies. MeSH headings used included *panic disorder with chest pain*, *panic disorder with coronary disease or cardiovascular disorders or heart disorders*, and *panic disorder with cholesterol or essential hypertension or tobacco smoking*. The diagnosis of panic disorder in eligible studies was based on DSM-IV criteria, and studies must have used objective criteria for CAD and risk factors. Only case-control and cohort studies were included. Using the same search and selection strategies, new studies were sought. Although the results of the original systematic review did not change, the synthesis has been extended to include an assessment of the limitations of the literature on which it is based, an estimation of whether there is a panic-CAD association in primary care settings, and suggestions of how these translate into management strategies.

Tables 1 and 2, respectively, show that panic disorder occurs in 0% to 53% of patients with CAD and that CAD occurs in 4% to 55% of patients with panic disorder. Although panic disorder is usually more common in people without CAD than with CAD,<sup>33-35,38,41</sup> it is still seen in a significant portion of those with CAD. In fact, Kane et al.<sup>32</sup> found more panic disorder in patients with CAD than without it among cardiac patients referred for esophageal motility studies.

Figure 1. Funnel Plot of Studies on the Panic–Coronary Artery Disease Association

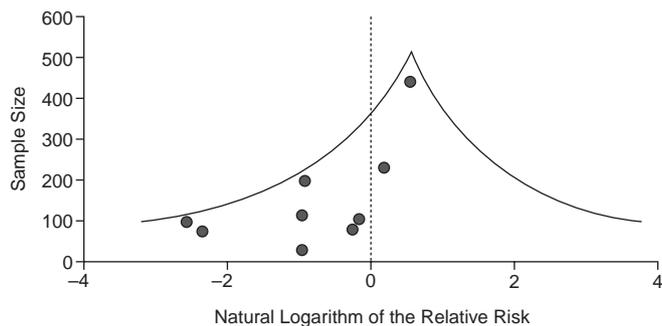
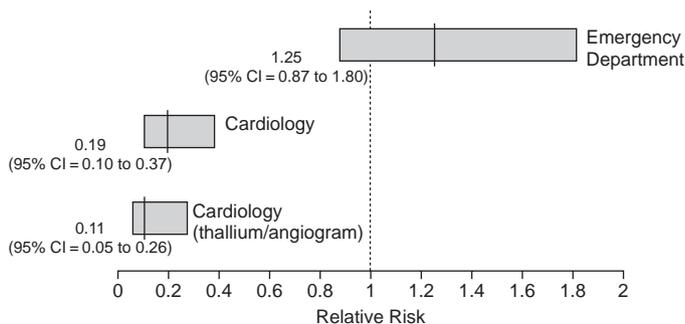


Figure 2. Association Between Coronary Artery Disease and Panic Disorder in Chest Pain



**LIMITATIONS OF THIS LITERATURE**

How reliable and valid is the literature on which this discussion is based? Reliability assessments have shown that the diagnoses of both spontaneous and situational panic attacks have good-to-excellent reliability.<sup>47</sup> The validity of the diagnosis of panic disorder in these studies is supported by several sources. First, subjects with panic disorder and noncardiac chest pain have decreased partial pressure of carbon dioxide levels suggestive of the hyperventilation commonly seen in panic disorder.<sup>48</sup> In addition, in studies of patients in whom the results of coronary angiograms are normal, the validity of the diagnosis of panic disorder is supported by the clinical description, family studies, lactate and CO<sub>2</sub> challenge tests, treatment response, and diagnostic stability in longitudinal studies.<sup>49</sup>

The concerns expressed by family physicians relate to the research settings and sample characteristics of studies in the literature. Few studies have been conducted in primary care settings. Most of the research has been conducted in emergency medicine, cardiology, and psychiatry settings. Although comparisons between patients

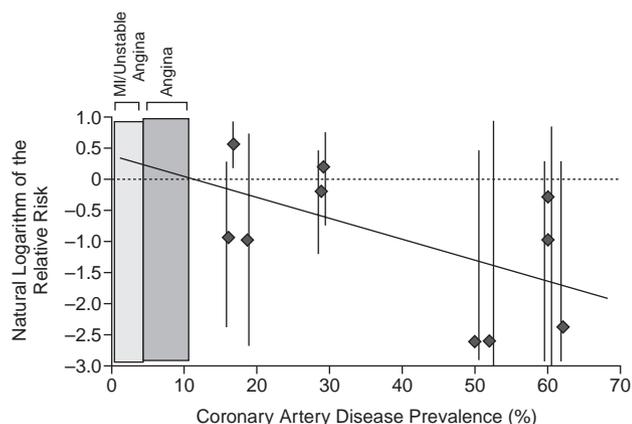
with panic disorder in primary care settings versus those in emergency medicine settings have not been done, patients referred to cardiology settings for chest pain often have personality disorders that, in turn, are associated with increased rates of avoidance and suicidality.<sup>50</sup> Similarly, comparing patients with chest pain in primary care versus cardiology settings, the prevalence of CAD is considerably higher in cardiology settings even when controlling for the number of cardiac risk factors.<sup>51</sup> The use of psychiatric settings is even more problematic. Not only did 22% of primary care patients with panic disorder referred to psychiatrists initially present with chest pain,<sup>52</sup> but previous work found that patients who see mental health professionals for panic attacks have more severe disease as measured by symptom severity and health care utilization.<sup>53</sup> Finally, although patients with chest pain in emergency medicine versus psychiatry settings do not differ in prevalence of generalized anxiety disorder, major depression, or suicidal ideation, those seeing psychiatrists have higher rates of agoraphobia, social and specific phobias, and posttraumatic stress disorder.<sup>54</sup> Thus, the literature may reflect the differences of patients seen in different settings and results may not apply to primary care settings.

**ASSOCIATION BETWEEN PANIC DISORDER AND CAD**

This systematic review failed to document an overall association between panic disorder and CAD (RR = 0.77, 95% CI = 0.56 to 1.05). However, to assess whether publication bias exists, the sample size for each study was plotted against the natural logarithm of the relative risk (LnRR) in a funnel plot (Figure 1).<sup>55</sup> In an unbiased literature, studies should be uniformly distributed under the “funnel.” The lack of a right-hand “tail” suggests that the published literature is incomplete, lacking several small studies that would document a positive association between CAD and panic disorder.

This finding may be due to a relationship between study setting and RR (Figure 2). Although there were insufficient population-based or primary care studies to summarize, studies conducted in emergency departments found an RR of 1.25 (95% CI = 0.87 to 1.80). Because the CI includes 1.0, no significant association between panic disorder and CAD in emergency departments was found. Cardiology-based studies that excluded patients with prior evidence of CAD found an RR of 0.19 (95% CI = 0.10 to 0.37), while limiting studies to those in which the diagnosis of CAD was based on either thallium treadmill tests or angiography produced an RR of 0.11

Figure 3. Strength of Association Versus Coronary Artery Disease Prevalence



Abbreviation: MI = myocardial infarction.

(95% CI = 0.05 to 0.26). These results suggest an inverse relationship between the presence of panic disorder and CAD, strengthened by the fact that the RR decreases with increasing precision of CAD assessment. However, the selective nature of the samples prevents a strong conclusion about the association between CAD and panic disorder from being made.

Using all 10 studies conducted in patients with chest pain, there is an inverse relationship between the prevalence of CAD in the study and the RR found in the study ( $r = -.554$ ,  $p = .097$ ); thus, the more selective the sample, the lower the detected association (expressed as the LnRR) between panic disorder and CAD (Figure 3). The resulting regression equation is

$$\text{LnRR} = .296 - .033 (\text{CAD prevalence}).$$

Thus, based on the CAD prevalence in the study with the largest sample size as the best estimate of overall association in that setting,<sup>31</sup> the RR in emergency departments should be 1.75. Although previous primary care studies have not looked for a panic-CAD association, the prevalence for CAD in chest pain in primary care settings should be around 2% based on the 1.5% prevalence of unstable coronary artery disease<sup>56</sup> and the 2.9% prevalence of myocardial infarction (MI)<sup>57</sup> in 2 practice-based network studies. Using a CAD prevalence of 2% for primary care settings and the regression equation above, the expected panic-CAD RR should be 1.26 for primary care. Even the prevalence of angina in primary care populations with chest pain is about 10%,<sup>56,58</sup> the crossover point in the graph. These findings suggest that a significant positive association may exist between panic disorder and CAD in both primary care and emergency department settings. This association is consistent with the observation

that chest pain patients are diagnosed with psychopathology as a cause more often in primary care than emergency department settings.<sup>59</sup>

## PANIC DISORDER AND CARDIOVASCULAR RISK FACTORS

If there is an association between panic disorder and CAD, could they be linked through a relationship with cardiovascular risk factors? Systematic review found that there were insufficient numbers of homogeneous studies to quantitatively summarize the relationship, but several known cardiac risk factors have been reported present in people with panic disorder.

First, panic disorder is linked to elevations in both systolic and diastolic blood pressures.<sup>60,61</sup> Consistent across primary care and cardiology settings, hypertension is associated with both panic disorder<sup>2,27,46,52,62,63</sup> and panic attacks.<sup>62,64,65</sup> This association may explain why 9% to 32% of patients with chest pain and normal results of coronary angiograms have hypertension.<sup>66</sup>

Second, panic disorder is associated with lipid abnormalities. Specifically, total cholesterol levels are increased in those with panic disorder.<sup>26,67</sup> This association is supported by studies documenting elevated cholesterol levels in 8% to 55% of patients with chest pain and normal coronary angiograms.<sup>66</sup> In addition, the presence of panic attacks in patients with chronic obsessive-compulsive disorder was associated with elevated triglyceride and decreased high-density lipoprotein (HDL) levels.<sup>68</sup> Conflicting gender differences in lipid patterns have been found. In one study, women with panic disorder frequently have elevated low-density lipoprotein (LDL) levels with decreased HDL levels, while men with panic disorder frequently have elevated triglyceride levels.<sup>67</sup> However, Perez-Parada et al.<sup>69</sup> found elevated LDL levels in men in response to pentagastrin-induced panic attacks but not in women. But associations between panic disorder and lipid abnormalities are not always found<sup>70</sup> and, if found, are primarily seen in psychiatric settings and in studies with small sample sizes, as opposed to large studies conducted in primary care or cardiology settings, which have failed to document an association.

Finally, consistent across community, cardiology, and psychiatry settings, smoking is linked to panic disorder<sup>25,71,72</sup> uniquely among anxiety disorders<sup>73</sup> and this association is supported by the observation that 32% to 64% of patients with chest pain and coronary angiograms with normal results are smokers.<sup>66</sup> The nature of the panic-smoking relationship, however, is unclear.<sup>74</sup> Although 19% of patients with panic disorder report that they increased their smoking due to their panic,<sup>72</sup> panic attacks are not believed to induce smoking.<sup>71</sup> On the other hand, 72% of patients with panic disorder report smoking at the onset of their attacks, while 55% and 26% report having

Figure 4. Possible Mechanism Linking Panic Disorder and Coronary Artery Disease (model 1)

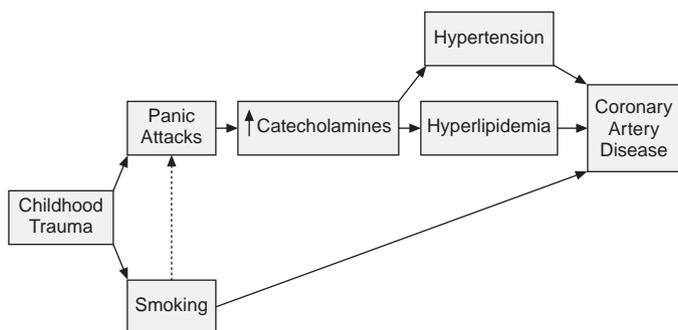
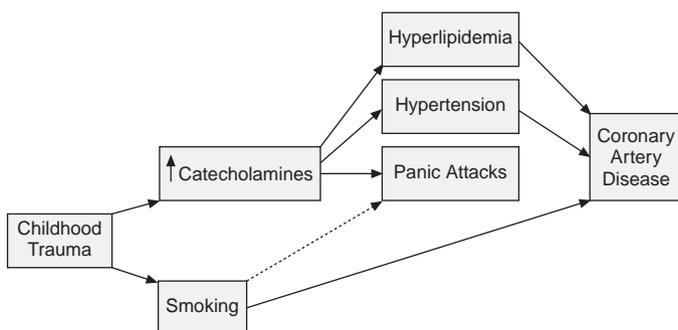


Figure 5. Possible Mechanism Linking Panic Disorder and Coronary Artery Disease (model 2)



decreased or stopped their smoking, respectively, in response to their panic.<sup>72</sup> Daily or continuous smoking is linked to the onset of panic, and the frequency of panic attacks correlates with the amount of smoking.<sup>71</sup> On the other hand, panic attacks have also started after acute smoking abstinence.<sup>75</sup> Although panic disorder has been linked to chronic obstructive coronary disease,<sup>76</sup> and it has been suggested that the smoking-panic association could be secondary to associated lung disease,<sup>71</sup> the weakness of this association refutes a causal relationship. Perceptions of health may moderate the smoking-panic association.<sup>77</sup>

To understand how these risk factors could be related to panic disorder, we must understand how catecholamines are involved. It is unclear whether the elevated levels of catecholamines seen in panic disorder<sup>6</sup> are a cause or effect of panic disorder. Elevations in cholesterol may be because of increased catecholamines<sup>27</sup> and may explain a correlation between total cholesterol and fear of dying in patients with panic disorder.<sup>78</sup> In addition, panic disorder may cause the increased catecholamines, which lead to hypertension and hyperlipidemia via activation of lipoprotein lipase.<sup>67</sup> Although childhood trauma is linked to panic disorder<sup>79</sup> as well as

to smoking and increased catecholamines,<sup>80-83</sup> it is only observed in 23% of people with panic disorder. Ultimately, these associations could yield at least 2 possible pathways linking panic disorder and CAD through cardiac risk factors.

Figure 4 presents one of several possible pathways linking panic disorder with CAD through the cardiac risk factors. The key to this pathway is the initial childhood trauma and/or smoking behavior. In this pathway, childhood trauma and possibly smoking trigger the onset of panic attacks that, in turn, increase catecholamines. These high levels of catecholamines produce hypertension and hyperlipidemia. However, this sequence does not account for the observation that the diagnosis of hypertension is usually made prior to the onset of panic attacks.<sup>62</sup>

An alternative model is presented in Figure 5. In this model, childhood trauma is linked to both smoking and increased catecholamines.<sup>81-83</sup> While the increased catecholamines produce hyperlipidemia and hypertension, they and/or the smoking trigger panic attacks as well. In this model, the association between panic disorder and CAD is not causal but rather because of the increased catecholamines that they have in common. Because this pathway requires childhood trauma as the initial step, it could only apply to a portion of those with panic disorder.

### IMPLICATIONS

If a panic-CAD association exists in primary care, what would be the implications for health outcomes, evaluation, and management? The comorbidity between CAD and panic disorder could have serious consequences. Not only can diagnosing panic disorder result in failure to recognize CAD, but panic disorder itself is often unrecognized,<sup>44,84</sup> leading to increased social disability, medical costs, and disease progression.<sup>84</sup> Men with panic disorder have an increased rate of cardiovascular mortality.<sup>85</sup> The tachycardia observed during a panic attack could potentially lead to an acute MI in someone with underlying CAD. This may reflect the increased sudden death and fatal cardiovascular disease observed in patients with anxiety in general. In fact, phobic anxiety is a stronger predictor of fatal cardiovascular events than are cardiovascular risk factors such as smoking, systolic blood pressure, and hypercholesterolemia.<sup>86</sup>

### EFFECT ON EVALUATION

Which primary care patients with chest pain and panic disorder should be further evaluated for CAD? The most

defensible strategy is to consider working up panic disorder patients who have any cardiac risk factors, particularly males and postmenopausal women. Because patients with both CAD and panic disorder tend to exhibit distress due to the panic attacks,<sup>31</sup> the panic attacks may serve a valuable role in convincing the patient with CAD to seek care, alerting the physician to the possibility of CAD. Because MVP can produce an exercise treadmill test (ETT) with false positive results, either perform a thallium ETT on all patients with panic disorder or use the Bruce ETT as a screening test to be followed by a thallium ETT if the results of the Bruce ETT are abnormal. Cardiac workups should not be performed to convince patients that they do not have cardiac disease, because chest pain patients continue to have symptoms and disability after reassurance<sup>87</sup> or a coronary angiogram with normal results.<sup>88</sup> The disease conviction of patients with panic disorder may explain why only 56% of emergency department patients with chest pain begun on paroxetine therapy for panic are still taking it 1 month later.<sup>89</sup>

### EFFECT ON MANAGEMENT OF CAD AND PANIC DISORDER

#### Treatment of CAD

CAD and cardiac risk factors must be treated aggressively. Some cardiac treatments may potentially affect panic anxiety and its management. Smoking cessation and exercise can improve both CAD and panic disorder. Although cholesterol reduction is important, statin therapy has rarely been associated with increased anxiety. Similarly, because there is evidence that verapamil<sup>90</sup> and clonidine<sup>91,92</sup> have some antipanic activity, these drugs may play a specific role in the treatment of hypertension in patients with panic disorder. Although propranolol is recommended post-MI and may reduce panic symptoms<sup>93</sup> it has also been linked to exacerbation of panic disorder.<sup>94</sup> Finally, the combination of tricyclic antidepressants (TCAs) with nitrates and vasodilators can result in significant orthostatic hypotension<sup>95</sup>

#### Treatment of Panic Disorder

Traditionally, panic disorder is treated with either cognitive behavioral therapy (CBT), pharmacotherapy (antidepressants, high-potency benzodiazepines), or both. A recent survey of family physicians found that, of their patients with panic disorder who were not referred to mental health providers, 73% received selective serotonin reuptake inhibitors (SSRIs), 23% received high-potency benzodiazepines, and 18% received CBT.<sup>96</sup> Comparison of CBT in primary versus secondary care settings found a more rapid response in primary care settings.<sup>97</sup> In fact, previous studies have shown that, after 20 minutes of instruction in the emergency department, exposure therapy decreases depression, avoidance, panic attack frequency,

**Table 3. Potential Cytochrome P450 Effects Between SSRIs and Cardiovascular Medications<sup>a</sup>**

| CYP450 Isoenzyme | SSRI        | Inhibition Potency | Cardiovascular Medications Affected    |
|------------------|-------------|--------------------|--|
| 2D6              | Fluoxetine  | High               | Beta blockers<br>Ca++ channel blockers |
|                  | Paroxetine  | High               | Beta blockers<br>Ca++ channel blockers |
|                  | Sertraline  | Moderate           | Beta blockers<br>Ca++ channel blockers |
| 3A3/4            | Fluvoxamine | High               | Metoprolol<br>Ca++ channel blockers    |
|                  | Nefazodone  | High               | Metoprolol<br>Ca++ channel blockers    |
|                  | Fluoxetine  | Moderate           | Metoprolol<br>Ca++ channel blockers    |
| 1A2              | Fluvoxamine | High               | Verapamil?<br>Propranolol?             |
| 2C9              | Fluoxetine  | High               | ARBs                                   |
|                  | Fluvoxamine | High               | ARBs                                   |
| 2C19             | Fluvoxamine | High               | Propranolol                            |
|                  | Fluoxetine  | Moderate           | Propranolol                            |

<sup>a</sup>Adapted from Ereshefsky et al.<sup>122</sup> and Cozza and Armstrong.<sup>123</sup>

Abbreviations: ARBs = angiotensin receptor blockers,

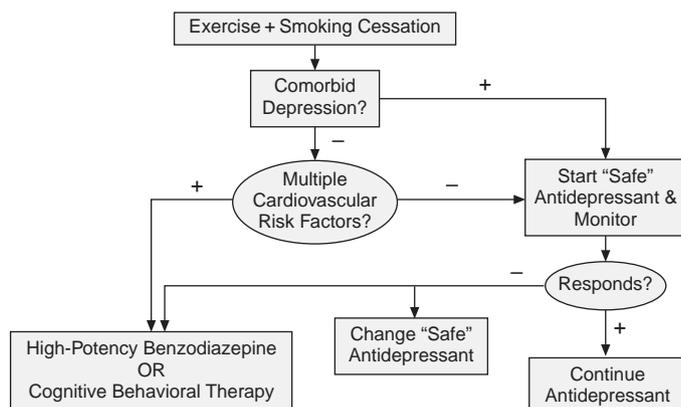
Ca++ = calcium, CYP450 = cytochrome P450, SSRI = selective serotonin reuptake inhibitor.

and emergency department visits.<sup>98</sup> Thus, CBT may be useful in the management of panic disorder in the presence of CAD.

Pharmacotherapy for panic disorder in CAD patients is more complicated. Although TCAs are effective in panic disorder, their cardiotoxicity precludes them as first-line agents in the presence of CAD. In fact, tricyclic use has been linked to the development of MI.<sup>99</sup> In addition, imipramine therapy for panic disorder increases cardiovascular mortality risk secondary to increased blood pressure and heart rate.<sup>95</sup>

SSRIs and nonselective serotonin reuptake inhibitors (NSRIs) may be appropriate for patients with both panic disorder and CAD, but they may affect cardiac risk factors. Although angina and hypertension are rare side effects of SSRI therapy, studies have shown that SSRIs are safe in patients with ischemic heart disease,<sup>100</sup> post-MI patients, and patients with unstable angina.<sup>101,102</sup> In patients without cardiac risk factors, SSRI use does not increase the risk of a first MI.<sup>103</sup> In fact, SSRI use in patients with known CAD is associated with a reduction in cardiovascular morbidity and mortality.<sup>104</sup> In addition, paroxetine use is associated with a reduction in the normal stress-induced rise in blood pressure among CAD patients.<sup>105</sup> However, as a group, SSRIs may increase cholesterol levels in patients with panic disorder.<sup>106</sup> More specifically, SSRIs may increase total, LDL, and HDL levels from baseline.<sup>107</sup> Although sertraline and possibly paroxetine may increase LDL cholesterol,<sup>108,109</sup> this effect may be offset by SSRI-linked attenuation of platelet activity and increase in endothelial nitrous oxide, which further inhibits platelet

Figure 6. Treatment Algorithm for Panic Disorder in the Presence of Coronary Artery Disease



aggregation and produces vasodilatation.<sup>110,111</sup> In addition, beta blockers, typically used to treat CAD, have been shown to potentiate SSRI activity.<sup>112</sup> Paroxetine can interact with digitalis to increase the risk of toxicity.<sup>113</sup> In addition, citalopram may be associated with atrioventricular blocks.<sup>114</sup>

Similarly, NSRIs (venlafaxine, nefazodone, and mirtazapine) can be effective in the treatment of panic disorder. However, high-dose venlafaxine (> 300 mg/day) has been associated with hypertension in 5% of cases;<sup>115</sup> doses up to 225 mg can reduce heart rate variability more than paroxetine<sup>116</sup> which, in turn, may increase oxygen demand and ischemia,<sup>37</sup> and a case of acute ischemia occurring within 1 week of venlafaxine onset has been reported.<sup>117</sup> Although generic nefazodone has antipanic activity, and electrocardiogram changes are rare,<sup>118</sup> its potential hepatic toxicity limits its use. In addition, nefazodone may increase the risk of rhabdomyolysis in patients on simvastatin therapy.<sup>119</sup> Finally, mirtazapine may also be considered. Although there is some evidence that mirtazapine is effective in panic disorder, there are case reports suggesting that, when combined with clonidine,<sup>120</sup> mirtazapine can induce hypertension. While no effect of mirtazapine on HDL or LDL has been documented, it may increase total cholesterol secondary to weight gain.<sup>121</sup> Finally, the role of antidepressants in the management of panic disorder in patients with CAD may depend on their potential interactions with medications for CAD (beta blockers, angiotensin receptor blockers, and calcium channel blockers) via their cytochrome P450 (CYP450) effects (Table 3). Generally, based on their CYP450 profiles, sertraline, venlafaxine (and presumably duloxetine), citalopram, escitalopram, and mirtazapine are felt to have a good margin of safety.<sup>123</sup>

Finally, high-potency benzodiazepines should also be considered. Alprazolam treatment of panic disorder

actually decreases total cholesterol<sup>124</sup> and catecholamine response to exercise.<sup>125</sup> In addition, although alprazolam does not decrease the frequency or severity of anginal attacks in CAD patients taking propranolol, it does decrease symptom severity and reduce nitroglycerin use.<sup>126</sup> Other potential cardiovascular benefits of low-dose benzodiazepines include decreased myocardial contractility and increased blood flow.<sup>127</sup> In fact, benzodiazepines were found to delay onset of ETT-induced ischemia<sup>128</sup> and to reduce MI rate<sup>129</sup> in patients with CAD. However, benzodiazepines should generally not be used in elderly patients or those with a history of substance abuse or personality disorders.

Thus, in the presence of CAD, panic disorder should be treated with an SSRI, a high-potency benzodiazepine, or CBT. Figure 6 presents the treatment algorithm recommended for patients with panic disorder and comorbid CAD. Exercise and smoking cessation are recommended for all patients. If not contraindicated, patients with comorbid depression should be started on an antidepressant therapy with few CYP450 effects (sertraline, venlafaxine, citalopram, escitalopram, mirtazapine). Patients without depression should be treated based on their number of cardiovascular risk factors. Patients with few or no risk factors should be started on citalopram or escitalopram therapy. Patients with multiple cardiac risk factors or an SSRI-exacerbated risk factor are probably best treated initially with a high-potency benzodiazepine or CBT.

## CONCLUSION

Although both are independent causes of chest pain, panic disorder and coronary artery disease may coexist, particularly in primary care settings. When comorbid, the panic attacks may cause the patient with coronary disease to seek care but could also provoke a cardiac event. Distinguishing between the 2 disorders can be difficult when based on clinical criteria alone. If one condition is recognized, a search for the other is warranted in particular patient subgroups. All patients with comorbid panic disorder and CAD should be treated with exercise and smoking cessation. Treatment with a "safe" antidepressant, high-potency benzodiazepine, or CBT depends on the presence of comorbid depression and cardiovascular risk factors.

**Drug names:** alprazolam (Xanax, Niravam, and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), metoprolol (Toprol, Lopressor, and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), propranolol (Innopran, Inderal, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), verapamil (Verelan, Covera, and others).

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