Paroxetine for Somatic Pain Associated With Physical Illness: A Review

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Objective: The purpose of this article is to review the prevalence of somatic pain with and without depression or anxiety and the pharmacologic effects of the selective serotonin reuptake inhibitor paroxetine on pain in physical conditions with and without comorbid depression or anxiety.

Data Sources: MEDLINE and PsychLIT/PsycINFO database. Keywords included *depression*, *anxiety*, *pain*, *somatic*, *antidepressants*, and *paroxetine*. Only English-language publications and abstracts were considered.

Study Selection: More than 100 articles that reflected the prevalence of somatic pain in patients with physical illness with and without comorbid depression or anxiety and that evaluated the efficacy of antidepressants in this population were identified and reviewed.

Data Synthesis: Nearly two thirds of patients with major depressive disorder suffer from a physical illness, and about one fifth of patients with chronic physical illness are depressed. Both of these comorbidities pose diagnostic and therapeutic challenges. Therapeutic effects of antidepressants on pain improvement in patients with chronic physical illnesses and comorbid depression/anxiety have been attributed to the antidepressant or anxiolytic properties of these drugs. However, tricyclic antidepressants have demonstrated analgesic properties in patients with physical illness both with and without depression. The review looks at evidence for the efficacy of the selective serotonin reuptake inhibitor paroxetine on pain in physical illness with and without depression and the mechanisms for the relief of pain and depression.

Conclusions: The efficacy of paroxetine for depression and anxiety comorbid with physical illness looks promising. Studies also allude to evidence linking the analgesic properties of paroxetine with its serotonergic and noradrenergic activity. Large randomized controlled trials within specific antidepressant classes and also comparing dual-action antidepressants are warranted that could shed some light on the unique advantage of paroxetine over other antidepressants.

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It has been shown that there is an association between somatic complaints (including pain) and psychiatric disorders such as depression and anxiety.[1] Depression and anxiety disorders are frequently comorbid with each other and also physical illnesses in the middle-aged and elderly.[2] Epidemiologic surveys have demonstrated that approximately two thirds of patients with major depression are also suffering from a physical condition[3,4] and that around one fifth of patients with a chronic physical illness are depressed.[2] Such comorbidity is associated with an increase in the severity of both psychiatric and physical symptoms.[5]

Although depression/anxiety and chronic illness frequently copresent,[3,4] many patients are unwilling to admit the presence of psychiatric problems, while others just accept them as an inevitable consequence of physical illness. This poses a particular challenge for the physician, since the prognosis of patients with chronic physical illness is considerably worsened when there is comorbid depression or anxiety.[5]

The impact of comorbid depression on outcomes in physical illnesses, especially cardiovascular disease, has been extensively studied. This interplay between depression and comorbid physical illness is exemplified by the complex relationship between depression and cardiovas-

cular disease, with evidence to suggest that depression might actually predispose individuals to a first cardiovascular event[6–8] and result in increased mortality rates.[9]

In rheumatoid arthritis, depression has been known to lead to increased pain and disability,[10,11] while the presence of depression in patients with diabetes results in worse glycemic control and more complications than when depression is absent.[12] Studies have also demonstrated that depression and its associated symptoms constitute a major risk factor in the development of type 2 diabetes and may accelerate the onset of diabetes complications.[13] Complication of diabetes, especially diabetic neuropathy, may, in turn, exacerbate depressive symptoms.

Similarly, in patients with cancer, depression has a detrimental effect on prognosis and might even shorten survival times.[14–17] Psychophysiologic mechanisms linking depression and cancer progression include dysregulation of the hypothalamic-pituitary-adrenal axis, especially diurnal variation in cortisol and melatonin.[18] Depression also affects components of immune function; is correlated with pain, anxiety, and health-related quality of life; and may affect cancer surveillance.

For patients with Parkinson's disease, there is accumulating evidence suggesting that comorbid depression is secondary to the underlying neuroanatomical degeneration, rather than simply a reaction to the psychosocial stress and disability.[19] The incidence of depression is correlated with changes in central serotonergic function and neurodegeneration of specific cortical and subcortical pathways.

Finally, with regard to epilepsy, recent studies have also revealed that a history of depression is associated with a 4- to 6-fold greater risk of developing the illness.[20] These data suggest either a possible "bidirectional" relationship between epilepsy and depression or at least the presence of common pathogenic mechanisms that facilitate the occurrence of one in the presence of the other.

One of the most studied physical illnesses with regard to comorbid anxiety and depression is irritable bowel syndrome (IBS). Indeed, nearly 70% to 90% of patients seeking treatment for IBS show psychiatric symptoms.[21] Comorbid psychiatric disorders are present in 50% to 60% of patients with IBS who present to gastroenterology clinics.[22] The relative prevalence of anxiety and depression in sufferers of IBS varies according to different patient populations (clinical vs. community). Patients recently referred to gastroenterology clinics generally experience more anxiety than depression (nearly 7% to 58% depending on the individual anxiety disorder), whereas chronic attendees experience less anxiety (10%) than depression (39%).[22,23] Interestingly, IBS sufferers who do not seek treatment—representing up to 50% of the IBS population[24]—tend not to display symptoms of psychiatric disorders.[21] In addition, nearly 30% to 60% of patients with psychiatric illnesses have comorbid IBS.[25]

The risks of patients with medical illness developing depression were quantified in the World Health Organization Collaborative Study on Psychological Problems in General Health Care (PPGHC).[26] For patients with 1 chronic medical condition, the odds ratio of developing depression was 4.7. This rose to 6.4 for patients with more than 1 chronic medical condition.[26] For individual physical illnesses, depression was present in 15% to 33% of patients with myocardial infarction, 26% to 34% with stroke, 33% to 35% with chronic pain, 9% to 27% with diabetes, 20% to 45% with cancer, 27% with IBS, and 15% to 36% with rheumatoid arthritis.[10,12,27,28]

In a recent cross-sectional survey of a random sample of 18,980 subjects from European countries,[29] chronic (≥ 6 months' duration) painful physical conditions (joint/articular, limb or back pain, headaches, or gastrointestinal diseases) were strongly associated with major depressive disorder (odds ratio = 3.6). Moreover, there is an association between the severity of pain and the severity of depression. A study investigating the relationship between low back pain and psychological distress has reported a statistically significant correlation between the 2.[30]

The ideal treatment for depression and anxiety in patients with a chronic physical illness would be a monotherapy that resolves depressive symptoms over the long term, is well tolerated, and does not adversely affect the severity or treatment of the concomitant physical illness. In view of the relationship between pain and depression, it would be particularly useful if such therapy also had an analgesic effect.

There is evidence to suggest that tricyclic antidepressants (TCAs) have analgesic properties in patients with chronic physical illness with and without depression.[31] Amitriptyline and imipramine were more effective than placebo at relieving painful peripheral diabetic neuropathy in 2 double-blind crossover studies.[32,33] In a 12-week study, amitriptyline provided superior analgesia compared with placebo for peripheral diabetic neuropathy, with no correlation between antidepressant effect and analgesia.[32] The analgesia described by nondepressed patients was similar to that in depressed patients, and it occurred in some depressed patients without associated changes in mood.[32] Similar results were achieved in a 5-week comparison of imipramine 100 mg daily versus placebo in 12 nondepressed patients with peripheral diabetic neuropathy.[32] Moreover, in a 3-week, double-blind, placebo-controlled trial of patients with noncardiac chest pain, imipramine was significantly superior to placebo ($p < .03$) in improving pain.[34] However, this analgesic property of TCAs has been overshadowed by the impact of their adverse tolerability profile, particularly when compared with newer antidepressants.[35–38]

Selective serotonin reuptake inhibitors (SSRIs) have also been reported to demonstrate analgesic properties,[39]

although the results have been mixed. Fluoxetine has been shown to provide relief for low back pain and whiplash-associated cervical pain in nondepressed patients with similar efficacy to amitriptyline.[40] However, in a double-blind, placebo-controlled trial,[41] fluoxetine failed to separate from placebo in relieving abdominal pain in patients with IBS. A double-blind, randomized, placebo-controlled trial with citalopram in fibromyalgia[42] failed to show significant effects on pain symptoms after 4 months, and an open-label study in patients with IBS[43] suggested that citalopram might be effective in the treatment of abdominal pain. Venlafaxine and mirtazapine have been found to be comparable to amitriptyline for pain relief in double-blind studies, and their antinociceptive effect has been attributed to their opioid receptor subtypes.[44,45] Given the efficacy of tricyclics in treating pain syndromes, comparison studies of tricyclics and SSRIs or newer antidepressants are more common. However, there are no within-class comparisons of SSRIs evaluating the effectiveness of these medications for pain.

Over the last decade or so, there have been several studies that have demonstrated the analgesic effect of paroxetine in neuropathic pain, arthritic pain, noncardiac chest pain, and IBS-associated abdominal pain.[46–50] Paroxetine has proven efficacy in the treatment of depression and anxiety[51–57] with a good tolerability profile, particularly compared to TCAs.[35] Moreover, it has a simple metabolism with a half-life of approximately 1 day and no active metabolites, making drug interactions unlikely except in the case of saturation of the 2D6 isoenzyme.[56] Given the favorable profile of paroxetine, this review considers studies that examine the evidence for the effect of paroxetine on pain in patients with painful physical conditions, with and without comorbid depression or anxiety. MEDLINE and the PsychLIT/PsycINFO database were the data sources used. Keywords included *depression*, *anxiety*, *pain*, *somatic*, *antidepressants*, and *paroxetine*. Only English-language publications and abstracts were considered. More than 100 articles were identified and reviewed.

BENEFIT OF PAROXETINE FOR DEPRESSION IN PATIENTS WITH PHYSICAL ILLNESS

There is evidence that paroxetine has benefits for the treatment of comorbid depression in patients with physical illness and comorbid depression (Table 1). Paroxetine was well tolerated in a 12-week, double-blind, multicenter, randomized study of patients with human immunodeficiency virus (HIV).[58] The improvement in depressive symptoms as assessed by the Hamilton Rating Scale for Depression (HAM-D) was equivalent for paroxetine (mean daily dose = 33.9 mg) and the comparator imipramine (mean daily dose = 162.5 mg). However, patients taking imipramine experienced significantly more

Table 1. Details of Studies Showing the Effect of Paroxetine on Depression in Patients With Physical Illness

Study Reference	Physical Illness	Study Design	Dose of Paroxetine and Comparator	Depression Assessment	Effect on Depression
Elliott et al (1998)[58]	Human immunodeficiency virus	Double-blind, multicenter, randomized, placebo-controlled, vs imipramine Duration: 12 wk N = 75 Inclusion criterion: HAM-D score > 18	Flexible dosing Mean daily doses: Paroxetine, 33.9 mg Imipramine, 162.5 mg	HAM-D, CGI	Paroxetine and imipramine showed improvement in depression No significant difference between treatments Paroxetine was better tolerated
Nelson et al (1999)[36]	Ischemic heart disease	Double-blind, multicenter, randomized, vs nortriptyline Duration: 6 wk N = 81 Inclusion criterion: HAM-D score ≥ 16	Paroxetine, 20–30 mg/d Nortriptyline dose adjusted to maintain plasma concentrations at 50–150 ng/mL	Change from baseline in HAM-D score HAM-D score ≤ 8 (a criterion for remission)	Both groups showed improvement of depression with no significant difference Paroxetine was better tolerated Rate of discontinuation due to cardiac adverse events significantly greater with nortriptyline
Pezzella et al (2001)[37]	Breast cancer	Double-blind, multicenter, randomized, vs amitriptyline Duration: 8 wk N = 179 Inclusion criterion: MADRS score ≥ 16	Paroxetine, 20–40 mg/d Amitriptyline, 75–150 mg/d	MADRS total score CGI-Severity of Illness Patient Global Evaluation	Improvement of depression in both groups with no significant difference

Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

adverse events of dry mouth (p = .05), dizziness/postural hypotension (p = .04), and palpitations (p = .04) than those taking paroxetine.

In a 6-week, double-blind, multicenter, randomized study of patients with ischemic heart disease,[36] similar numbers of patients achieved remission (defined as a 50% reduction in the HAM-D score and a final HAM-D score of 8 or less) with paroxetine (20–30 mg/day) and nortriptyline (targeted to a therapeutic plasma concentration level of 50–150 ng/mL). In the intent-to-treat analysis, 61% of paroxetine patients (25/41) and 55% of nortriptyline patients (22/40) were classified as being in remission. However, while nortriptyline caused an increase in heart rate, a reduction in heart rate variability, and a decrease in ventricular premature depolarizations, paroxetine had no clinically significant effects on heart rate, blood pressure, cardiac conduction intervals, or cardiac rhythm.

In an 8-week, double-blind, multicenter, randomized study of patients with breast cancer,[37] paroxetine (20–40 mg/day) was as effective as amitriptyline (75–150 mg/day) in reducing the symptoms of depression as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS). The mean change from baseline in total MADRS score at study end was –10.5 for paroxetine compared with –9.4 for amitriptyline (95% confidence interval [CI] = –2.748 to 0.958, p = .345). However, paroxetine had a superior tolerability profile, particularly with regards to anticholinergic adverse events and sedation, compared with amitriptyline.

BENEFIT OF PAROXETINE FOR PAIN ASSOCIATED WITH CHRONIC PHYSICAL ILLNESS IN PATIENTS WITH COMORBID DEPRESSION OR ANXIETY

Improvement in somatic pain has been noted in studies of patients suffering from painful chronic physical disease for whom paroxetine was prescribed for the treatment of comorbid depression (Table 2). This analgesic effect of paroxetine has been quantified by improvements in specific pain assessments used in these studies to monitor improvements in the pain associated with physical illness.

In a study of patients with rheumatoid arthritis who received paroxetine (20–40 mg/day) or amitriptyline (75–150 mg/day) for 8 weeks (Table 2),[50] the Patient Global Pain Rating showed that, at baseline, 67.0% of paroxetine patients classified their pain as moderate and 22.3% classified their pain as mild. The corresponding figures for amitriptyline patients were 63.8% and 20.2%. During the study, there was an improvement in pain ratings for both treatment groups. At endpoint, only 46.8% of paroxetine patients had moderate pain and 40.4% had mild pain. In the amitriptyline group, 44.7% of patients had moderate pain and 41.5% had mild pain (Figure 1).

Table 2. Details of Studies Showing the Effect of Paroxetine in Patients With Chronic Physical Illness and Comorbid Depression or Anxiety

Study Reference	Physical Illness	Study Design	Dose of Paroxetine and Comparator	Effect on Anxiety or Depression	Effect on Pain
Bird and Broggini (2000)[50]	Rheumatoid arthritis	Double-blind, multicenter, randomized, vs amitriptyline Duration: 8 wk N = 191 Inclusion criterion: MADRS score ≥ 16	Paroxetine, 20–40 mg/d Amitriptyline, 75–150 mg/d	Both treatment groups showed significant reductions in MADRS scores compared with baseline	As assessed by the Patient Global Pain Rating, improvement in pain was seen in both groups with no significant difference between them
Masand et al (2002)[48]	Irritable bowel syndrome	Open-label Duration: 12 wk N = 20; 10 with comorbid anxiety (1 also with depression), 10 with no psychiatric condition (see Table 3) Inclusion criterion: diagnosis of irritable bowel syndrome according to Rome criteria	Paroxetine, 20–40 mg/d	Improvement in depression or anxiety not assessed	Remission (defined as ≥ 50% improvement from baseline to endpoint as measured by a telephone-based interactive voice system) of abdominal pain occurred for both severity and frequency of pain
Dickens et al (2000)[59]	Low back pain	Double-blind, randomized, placebo-controlled Duration: 8 wk N = 98 Inclusion criterion: MADRS score > 16	Paroxetine, 20 mg/d	Change from baseline to endpoint in MADRS score: –5.2 for paroxetine vs –2.9 for placebo	No significant differences were seen between paroxetine and placebo on the Pain Visual Analog Scale and the McGill Pain Questionnaire, but more patients taking paroxetine reduced their analgesic medication

Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

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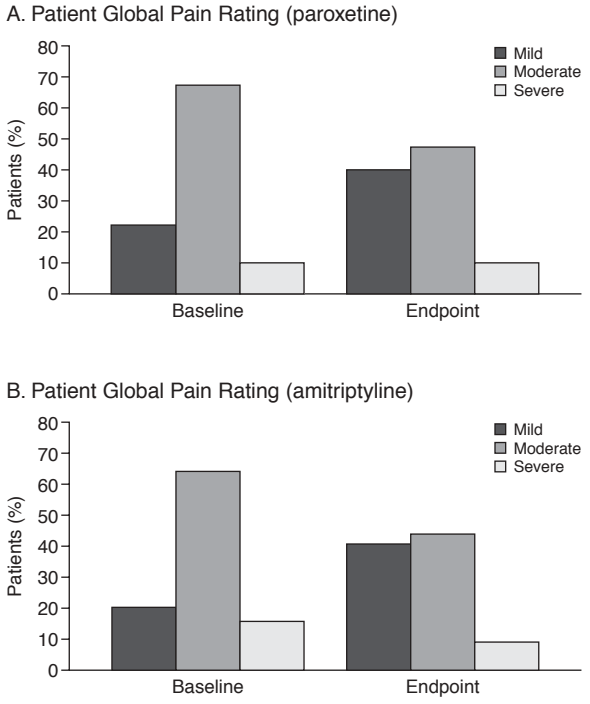
Figure 1. The Effect of 8 Weeks of Paroxetine (20–40 mg/day) or Amitriptyline (75–150 mg/day) on the Pain of Patients With Rheumatoid Arthritis (N = 191)[a]



[a]Data from Bird and Broggini.[50]

Both treatment groups also showed significant reductions in MADRS scores compared with baseline.

In a 12-week, open-label study of paroxetine (20–40 mg/day) in patients with IBS, 50% of the patients had comorbid anxiety (with 1 patient suffering from both anxiety and depression) and 50% had no comorbid psychiatric conditions.[48] Overall, 65% of patients receiving paroxetine experienced a ≥ 50% improvement in IBS-associated abdominal pain, 70% had improvements in pain severity, and 55% had improvements in pain frequency from baseline to endpoint as measured by a telephone-based interactive voice system. The psychometric validity of this system is comparable to that of the Structured Clinical Interview for DSM-IV diagnosis obtained by a trained clinician over the telephone.[60] Of the 50% of patients who had comorbid anxiety, 80% experienced a ≥ 50% improvement in abdominal pain and 70% reported an improvement in pain frequency.[48]

In a double-blind, randomized, placebo-controlled trial of paroxetine 20 mg/day for 8 weeks in sufferers of chronic low back pain, paroxetine showed no improvement in pain or depression compared with placebo; however, subjects randomly assigned to paroxetine were found to be more likely to reduce concomitant analgesic medication.[59] In the paroxetine group, 9% of patients (4/44) reduced their intake of analgesic medication and none increased it, compared with 2% of placebo patients (1/48) who reduced their analgesic medication and 11% of patients (5/48) who had to increase it ($\chi^2 = 8.7$, df = 2, $p < .01$). However, these results must be interpreted in the light of the low dose of paroxetine used.

BENEFIT OF PAROXETINE FOR PAIN ASSOCIATED WITH CHRONIC PHYSICAL ILLNESS IN PATIENTS WITH NO COMORBID DEPRESSION OR ANXIETY

In studies of paroxetine in patients with chronic physical illness and comorbid depression or anxiety, the therapeutic benefit in terms of any reported improvement in pain has frequently been attributed to the antidepressant or anxiolytic effects of the drug. However, paroxetine has also been shown to be effective in relieving pain when depression or anxiety is not present.

In a double-blind, randomized, crossover study of patients with diabetic neuropathy who showed no symptoms of depression at baseline,[46] improvements in pain on the Neuropathy Observer Scale were significantly greater for paroxetine than placebo (Table 3). The median single item scores for pain on the Neuropathy Observer Scale were reduced to 0.52 and 0.49 for paroxetine and imipramine, respectively, compared with 1.47 for placebo. In a single-blind dose-escalation study of paroxetine (30–70 mg/day) in patients with diabetic neuropathy and no comorbid psychiatric conditions, maximum pain relief as measured by a self-rating 100-mm vertical visual analog scale was achieved when plasma concentrations of paroxetine were higher than 300 to 400 nM.[49] The study also found considerable interindividual variations (10–800 nM, median of 195 nM). The therapeutic effect observed during the study appeared to increase gradually as the plasma concentration increased. Moreover, the beneficial effect was maintained during an additional 1-month open-label treatment period with optimum doses of paroxetine.

Paroxetine has also been studied in the treatment of noncardiac chest pain. Noncardiac chest pain describes angina-like pain for which cardiac catheterization or cardiac stress tests revealed no apparent etiology. In a 9-week, double-blind, placebo-controlled study of patients with noncardiac chest pain, for which 1 of the inclusion criteria was the absence of depression,[47] paroxetine (20–50 mg/day) was significantly ($p < .05$) superior to placebo in terms of improvement according to the physician-rated Clinical Global Impression of global improvement scale (CGI-I) and pain severity scale (CGI-S). At study endpoint, 67% of paroxetine patients showed a robust improvement (CGI-I score ≤ 2) and 59% achieved remission or near remission of pain symptoms (CGI-S score ≤ 2) compared with 52% and 43% of placebo patients, respectively.

Table 3. Details of Studies Showing the Effect of Paroxetine on Pain in Patients With Chronic Physical Illness and No Comorbid Depression or Anxiety

Study Reference	Physical Illness	Study Design	Dose of Paroxetine and Comparator	Pain Assessment
Sindrup et al (1990)[46]	Diabetic neuropathy	Double-blind, crossover, randomized, vs imipramine Duration: 6 wk N = 20 No depression at entry	Paroxetine, 20–40 mg/d Imipramine, 75–150 mg/d	The pain section of the Neuropathy Observer Scale showed imipramine to be significantly better than paroxetine
Sindrup et al (1991)[49]	Diabetic neuropathy	Single-blind, dose-escalation Duration: 4 wk N = 24 Depression and anxiety not assessed	Paroxetine, 30–70 mg/d	As assessed by a self-rating 100-mm vertical visual analog scale, maximum pain relief was achieved when plasma concentrations of paroxetine were above 300–400 nM
Masand et al (2002)[48]	Irritable bowel syndrome	Open-label Duration: 12 wk N = 20; 10 with no psychiatric condition	Paroxetine, 20–40 mg/d	Remission (defined as ≥ 50% improvement from baseline to endpoint as measured by a telephone-based interactive voice system) of abdominal pain occurred for both severity and frequency of pain
Doraiswamy et al (2002)[47]	Noncardiac chest pain	Double-blind, placebo-controlled Duration: 9 wk N = 50	Paroxetine, 20–50 mg/d	Paroxetine significantly superior to placebo as assessed by the physician-rated CGI-I and CGI-S

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

In an open-label study of patients with IBS,[48] of the 50% of patients who had no comorbid psychiatric conditions, 50% experienced a ≥ 50% improvement in abdominal pain and 40% reported an improvement in pain frequency.

These data suggest that paroxetine may have an analgesic effect in the treatment of pain that is unrelated to its antidepressant or anxiolytic effects. Indeed, patients in these studies had no apparent depression or anxiety at baseline and no significant changes in depression ratings as measured with the Beck Depression Inventory.[46,47] Moreover, results from the study of patients with IBS, with and without comorbid anxiety, showed that the presence/absence of anxiety was not predictive of remission of pain (≥ 50% improvement).[48]

POSSIBLE MECHANISMS FOR THE ANALGESIC EFFECT OF ANTIDEPRESSANTS

Some TCAs (imipramine, amitriptyline, and nortriptyline) have been shown to relieve pain in peripheral diabetic neuropathy in double-blind, crossover studies.[32,33,61] Imipramine has also been shown to significantly reduce the frequency and severity of noncardiac chest pain.[34] The antidepressant action of TCAs is possibly mediated through inhibition of the reuptake of serotonin and norepinephrine. It is unclear which of these mechanisms is involved in analgesia, but it has been suggested that the action could be mediated via the endogenous pain-suppressing system, which is dependent on serotonergic and possibly also noradrenergic receptors.[62] In addition, an analgesic effect of the H_1-histaminergic receptor blocker diphenhydramine has been described in an early experimental study.[63]

It is now well established that dysfunction in serotonergic and noradrenergic pathways is implicated in depression and anxiety disorders.[64] Serotonergic cell bodies, which are located in the raphe nucleus, send projections to areas of the brain controlling mood, movement, and emotions (frontal cortex, basal ganglia, and limbic system, respectively),[65] and also to the hypothalamus,[64] which regulates activities such as eating, sex, and pleasure. Noradrenergic cells in the locus ceruleus also send projections to the frontal cortex, basal ganglia, and limbic system, as well as to a specific area of the frontal cortex that deals with attention and cognition and to the cerebellum, which regulates motor control.[65,66] Reproducible increases in serotonergic function and decreases in noradrenergic function accompany treatment with antidepressants, and these alterations may be necessary for antidepressant efficacy.

In addition to the ascending serotonergic and noradrenergic pathways, neurons in the raphe nucleus and locus ceruleus project to the spinal cord.[67] These descending pathways can inhibit input from the intestines and skeletal muscles. The inhibitory effects are normally modest, but, during times of stress, they can completely inhibit painful stimuli; for example, the phenomenon of not feeling pain at the height of an accident.[67] Therefore, dysfunction at the level of these neuron cell bodies will affect both ascending and descending pathways resulting in psychological, somatic, and physical painful symptoms.[68] Hence, antidepressant drugs acting

on the serotonergic and noradrenergic system may not only improve mood and other psychological symptoms but also improve physical symptoms such as pain.

Further evidence for the implication of serotonin reuptake blockade as a mediator of pain sensation comes from a single-blind study of clomipramine and amitriptyline in the treatment of severe pain.[69] This comparison between clomipramine, the most potent 5-HT reuptake blockade TCA, and amitriptyline, a less powerful 5-HT reuptake blockade TCA, showed that clomipramine was better than amitriptyline in treating trigeminal neuralgia and tension headache after 3 months of treatment.

Inhibition of serotonin reuptake as a factor in pain relief is further supported by a study that showed the SSRI zimelidine to be superior to placebo in the treatment of chronic pain patients, in terms of both pain relief and reduction in need for analgesics.[70] For chronic neuropathic pain such as postherpetic neuralgia and diabetic neuropathy, studies have shown that dual-action antidepressants such as TCAs and venlafaxine were effective, whereas SSRIs in general were not.[71] Paroxetine and citalopram did demonstrate efficacy: less, however, than the dual-action antidepressants. The inhibitory effect of serotonin and norepinephrine on pain perception occurs in the spinal cord, and, at this level, there is an intimate interaction between serotonergic and noradrenergic neurons.[68] It is possible that SSRIs may also exert an effect on noradrenergic synapses.

MECHANISMS OF THE ANALGESIC EFFECTS OF PAROXETINE

Interestingly, paroxetine, which is currently classified as an SSRI on the basis of its very high affinity for the 5-HT transporter ($K_i = 0.065$ nmol/L), also shows moderate affinity for the norepinephrine transporter ($K_i =$ 40–85 nmol/L).[72–75] This in vitro effect of paroxetine has also been confirmed in vivo, in animal studies[76] and in patients with major depressive disorder.[77] Importantly, both in vitro and in vivo data demonstrate that paroxetine inhibits the norepinephrine transporter in a concentration-dependent manner. In a study in rats, serum paroxetine concentrations between 100 and 500 ng/mL inhibited the norepinephrine transporter by an average of 21%, whereas serum concentrations > 500 ng/mL resulted in an inhibition of 34%.[76] This concentration-dependent inhibition of the norepinephrine transporter was also seen in an open-label, parallel-group, forced-titration study of 52 outpatients with DSM-IV major depressive disorder.[77] Administration of paroxetine resulted in an inhibition of the norepinephrine transporter of 27% at an average serum concentration of 100 ng/mL and produced 43% inhibition at 200 ng/mL.[77] Therefore, paroxetine may also act as a serotonin/norepinephrine inhibitor at higher doses or serum concentrations.

The role for serotonin in the control of pain also comes from physiologic studies that suggest that serotonin plays a vital role in mediating both sensory and reflex responses to gastrointestinal stimuli.[78] It is estimated that 90% of serotonin in the human body is present in enterochromaffin cells and in myenteric interneurons. It follows that exogenous substances that act on serotonin receptors have enormous therapeutic potential in the control of abdominal pain and discomfort as well as the rectification of gastric motility.[78] Moreover, the comorbidity of depression and/or anxiety with IBS and the absence of an identifiable organic cause of IBS suggest that underlying anxiety disorders might be causally related to IBS. SSRIs such as paroxetine have been shown to be effective in the treatment of both anxiety disorders and IBS, indicating that serotonin might be implicated in both disorders.[25]

For example, the brain-gut axis links the cognitive centers in the brain, the enteric nervous system, and the immune system, making a good case for the common role of serotonin in obsessive-compulsive disorder (OCD) and IBS. Gastrointestinal motility, secretion, and nociception appear to be influenced by the 5-HT_3 and 5-HT_4 receptor subtypes.[79] Serotonin may also play a central role in endorphin mediation of analgesia, possibly by "gating" afferent signals.[80]

It is thought that SSRIs, some of which may have activity at the 5-HT_3 receptor,[81] could improve both IBS symptoms and mood disorders in comorbid patients.[82,83] There is certainly evidence for the benefits of treatment with SSRIs such as paroxetine for IBS patients.[48] Moreover, the improvement in IBS symptoms with paroxetine is independent of the presence or absence of anxiety disorders.[48] Serotonin (5-HT_3) antagonists such as granisetron have also been found to be effective for the treatment of gastrointestinal motility disturbances.[84] Serotonin appears to be the common neurotransmitter link between OCD and IBS; however, the exact receptor subtypes common to both disorders still need to be delineated. There is a lack of reliable and sufficiently specific tools to explore the serotonin receptor subtypes, unlike the dopamine receptors for which the process is more advanced.

There is considerable evidence that serotonin and norepinephrine are involved in the analgesic properties of antidepressants such as paroxetine, although the precise mechanism still needs to be elucidated.

CONCLUSIONS

The efficacy of paroxetine in depression and anxiety comorbid with physical illness, given the evidence discussed above, looks promising. Paroxetine has demonstrated improvement of pain symptoms in physical illness comorbid with depression and anxiety. The findings of the studies presented in this review suggest that paroxe-

tine might have an analgesic effect that is unrelated to its antidepressant or anxiolytic properties.

This review reveals that there is evidence linking the analgesic properties of paroxetine with its serotonergic and noradrenergic activity. Larger placebo-controlled trials are required to determine whether pain scores improve more significantly than other physical illness symptoms in patients with and without comorbid psychiatric illness who are treated with paroxetine. Additionally, randomized controlled trials within specific antidepressant classes and also comparing dual-action antidepressants may help clarify the unique advantage of paroxetine over other antidepressants.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac and others), granisetron (Kytril), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor).

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