Pain symptoms in depression: definition and clinical significance

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ABSTRACT – This article presents the findings of a focused literature review and consensus meetings on the definition and clinical significance of painful symptoms in patients with depression. About 50% of depressed patients report pain, and many types of pain occur more frequently in people with depression than in those without. There is some evidence that pain in depressed patients is associated with a poor response to treatment. Pain and depression may share common pathways and may both respond to treatment with certain antidepressants. Doctors need to be alert to pain in depressed patients and be prepared to treat it.

KEY WORDS: comorbidity, consensus, definition, depression, pain

Depressive symptoms in patients with chronic pain are well recognised and extensively researched. However, pain symptoms in people with depression attract far less attention and may be under-recognised and inadequately or inappropriately managed. A literature review identified 59 studies on depression in pain patients but only 14 about pain in a depressive population.[1]

Literature reviews also highlight the lack of consistent terminology and definitions. This lack of precision may reflect conceptual issues about the nature of pain and depression. Experiences of pain and depression raise complex issues about mind:body distinctions. This is not reflected in much of the existing research which takes a relatively narrow, dualistic perspective. For example, depression rating scales, such as the Beck Inventory,[2] tend to be developed on 'pure' psychiatric populations without confounding physical problems and have not been validated on patients with pain.[3] Conversely, clinical trials of analgesics often exclude patients with psychological problems. Depression is often viewed as a disturbance of emotion, but its behavioural aspects such as social withdrawal are as important. Equally, pain is likely to affect a patient's mood, behaviour and sleep patterns.

The measurement of both pain and depression relies on patients reporting their symptoms, yet little research is done from the patient's perspective. Patients' descriptions of their symptoms, and professionals' responses to them, are likely to be affected by their beliefs about their illness and to what they attribute the symptoms. Studies attempting to classify patients according to the degree of 'somatising' have produced inconsistent results, but they at least illustrate the complexity of the spectrum of presentation from emotional to physical.[4,5]

While chronic pain is increasingly recognised as a problem in its own right, and the goal of therapy is often to reduce pain and improve functioning, pain may be a symptom of another condition. Doctors are thus faced with the dilemma of whether they should concentrate on relieving pain or on seeking its cause. Pain in patients with depression is often regarded as 'medically unexplained'. A recent joint report from the Royal Colleges of Physicians and Psychiatrists notes that the management of such patients is 'largely inadequate'.[6] The report also states that it is unhelpful to think of these symptoms in either purely physical or psychiatric terms and suggests that the term 'medically unexplained' may be a misnomer.

The aim of this position paper is to:

- review the evidence about pain in people with depression
- discuss its clinical significance, and
- make recommendations about its management.

Methods

Guidelines were drawn up following two meetings. They are evidence-based wherever possible, but in many cases clear evidence is lacking. The scope of the project was defined (by CK, CD, RP, SW and EW) at the initial meeting. Medline was then searched (1966 to July 2004) for studies about pain that recruited patients with a confirmed diagnosis of depression, excluding those that recruited chronic pain patients. Pharmaceutical companies working in this area were consulted and relevant publications requested. Reference lists of retrieved publications were also searched.

An outline was prepared (by EW, a medical writer), circulated to all participants and discussed at

the second meeting. Participants were chosen to represent the disciplines of psychiatry, general practice and clinical psychology, and included representatives from the Royal College of General Practitioners Mental Health Task Group and the Royal College of Psychiatrists Liaison Psychiatry Faculty. The outline was expanded into a draft after the second meeting (by EW), and successive drafts were circulated to all participants for comment until consensus was reached.

Findings

Prevalence of pain symptoms in people with depressive disorders

The interpretation of research into pain in people with depressive disorders is hampered by the lack of clear terminology. This problem is particularly apparent in epidemiological studies. Cohorts of people with depressive disorders may be drawn from a variety of settings, ranging from the general population who have not sought medical treatment to those who are hospitalised. It is thus likely that different definitions of pain and depression result in different estimates of their prevalence. Despite these difficulties, similar findings have emerged from recent studies and reviews (summarised in Table 1).

Depressed individuals are more likely to have painful symptoms than those without depression.[1] Studies of single pain types also suggest higher rates in depressed patients, for example, low back pain is almost twice as common in patients with depression than in those without.[11]

Association between pain symptoms and outcomes in depressed patients

The authors of a literature review on depression and pain noted that:

> *relatively few studies have specifically addressed how the presence of pain affects depression outcomes.*[1]

These studies, however, suggest that the presence of pain might be associated with a poor response to various types of treatment for depression, although results are inconsistent.

Table 1. Prevalence of pain in patients with depression.

Source/population	No.	Prevalence (%)	Ref
Literature review		65 (range 15–100)	1
Telephone survey (Europe)	19,000	43	7
Primary care patients (Norway)	100	43	8
Inpatients (Sweden)	209	54	9
Inpatients (Sweden)	144	50 (21% severe pain)	10

Key Points

Pain symptoms are common in depressed patients

While depressive symptoms in patients with chronic pain have been well researched, pain in people with depression has attracted much less attention

Doctors should enquire about pain in their depressed patients and be prepared to treat it

Doctors need to understand more about pain management

The 'ARTIST' study assessed 573 depressed patients (73% meeting DSM-IV criteria for major depression) receiving one of three selective serotonin reuptake inhibitors (SSRIs) in primary care. The initial study concluded that SSRIs were equally effective in improving depression at nine months. A *post hoc* analysis examined the association between pain and treatment response at three months.[12] Two-thirds (69%) of the participants had some degree of pain at baseline. The presence of pain was associated with a poor response to treatment with an SSRI. Odds ratios for poor treatment response were 1.5 (95% confidence interval (CI) 0.8–3.2) for mild pain, 2.0 (CI 1.1–4.0) for moderate pain, and 4.1 (CI 1.9–8.8) for severe pain compared with patients without pain. This relationship between pain severity and treatment response was observed regardless of whether baseline pain was assessed from the Short Form (SF)-36 or the PHQ-15 questionnaires.

A study of 512 patients with major depressive disorder randomised to receive either placebo or the serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine also suggested that pain was correlated with poor treatment response in depression.[13] The mean pain scores, which indicated low overall levels of pain, were significantly lower in patients who achieved remission of their depressive symptoms (13 *vs* 23/100, compared with 27 at baseline, $p < 0.001$). Patients whose pain decreased by at least 50% were also significantly more likely to experience remission of their depressive symptoms than those classed as pain non-responders (36% *vs* 18%, $p < 0.001$).

Studies on the effect of pain on response to psychological treatments have been inconclusive. No good evidence was found about the relationship between pain and the chronicity of depressive symptoms, on the effects of pain on functional disability or on suicide in depressed patients. Research in this area is needed as these are important outcomes, and pain may have an impact on morbidity and suicide.

Healthcare resource use

Unsurprisingly, patients with depression and a painful condition such as fibromyalgia pose a greater economic burden to employers in terms of lost work time and healthcare resource use than those with depression alone.[14] This may not, however, simply reflect an overall increase in health needs. A cross-sectional US study of 1,500 community-dwelling adults with

major depression (of whom 938 reported at least one chronic painful condition) showed that the presence of pain was associated with significantly more intensive use of general medical services (eg 20% more visits to medical providers, $p < 0.01$) but *lower* rates of use of mental health services. Only 24% of patients with pain were seen by a mental health specialist compared with 30% of the depressed patients without pain.[15]

This study also found that depressed patients with pain were significantly more likely to use complementary/alternative medicine than those without pain (although the numbers remained relatively low: 24% *vs* 19%, $p < 0.05$), perhaps suggesting dissatisfaction with conventional treatments. Access to, and therefore use of, primary and secondary care services varies in different countries, so care must be taken in extrapolating these findings to other healthcare systems. However, other studies have shown that patients with pain often consult complementary/alternative medicine practitioners.[16]

Doctors may unwittingly contribute to increased resource use by pursuing unnecessary investigations into the cause of pain. One US study in the mid-1980s found that the cost of discovering an organic cause of headache or backache was over $7,000 per positive diagnosis.[17] In some cases, negative investigations may provide reassurance for patients and reduce anxiety that their pain has a malignant cause. A recent study found that offering magnetic resonance imaging (MRI) to patients with serious headaches, even in the absence of any clinical indication for scanning, may be cost-effective.[18,19]

Evidence for common pathways in depression and pain

Several authors have suggested that pain (particularly 'medically unexplained' pain) and depression share common pathogenic pathways, perhaps involving serotonin[20] or noradrenaline (norepinephrine).[21] Patients with depression and severe pain may also have lower levels of monoamine oxidase activity than depressed patients without pain.[10] Such mechanisms have also been proposed to account for the effects of some antidepressants on both affective and painful symptoms.[22-24]

It has also been suggested that low levels of serotonin and noradrenaline, which occur in depression, may affect pain modulating pathways. This might amplify minor pain signals and increase attention towards them, and could explain why people with depressive disorders often describe multiple pain symptoms.[1]

Depression and chronic pain are also associated with similar predisposing social factors and childhood experiences[25-27] and may be perpetuated by mechanisms such as catastrophising and fear-based avoidance. Catastrophising is a processing bias which overestimates the threat of information, internal or external. Functional MRI studies in fibromyalgia have shown that 'catastrophisers' have increased activity in brain areas associated with the anticipation of pain, attention to pain and emotional aspects of pain,[28] suggesting that catastrophising can modulate the experience of pain. Similarly, patients who avoid movement because of unfounded fear of injury or increased pain may, by limiting physical and social activity, actually worsen both depressive and painful symptoms.[29]

Effects of antidepressants on painful symptoms

Reviews of antidepressants as analgesics have concluded that tricyclic antidepressants are effective, but evidence about SSRIs is less convincing.[23,24,30] However, no meta-analyses have examined the relative or absolute efficacy of different classes of antidepressants to treat pain in patients with depression. A randomised comparison of the effects of desipramine, amitriptyline and fluoxetine on pain in diabetic neuropathy suggested that the first two were equally effective in reducing pain in patients without depression but that fluoxetine was no better than placebo. The authors concluded that blockade of noradrenaline reuptake accounts for the analgesic effects of tricyclic antidepressants.[21]

Two studies with the SNRI duloxetine involving 500 patients with major depressive disorder and painful symptoms showed a statistically significant difference between duloxetine and placebo in relieving pain. Mean visual analogue scores for various measures of pain fell by 22–41% from baseline in the duloxetine group versus 5–18% in the placebo group. About 50% of the improvement in pain was independent of the improvement in depressive symptoms.[13] This led to the conclusion that improvements in pain severity were attributable equally to the direct effect of duloxetine on pain and to associated changes in depression severity.

Uncontrolled studies have suggested that the SNRI venlafaxine may be effective in reducing pain in depressed patients[31] and in fibromyalgia,[32] but no placebo-controlled studies have been performed in these populations. There is also some evidence that mirtazapine (which also has actions on both serotonergic and noradrenergic neurotransmission) can reduce pain in cancer patients with mild depression.[33] These findings need to be confirmed by larger, placebo-controlled trials.

Recommendations

Terminology and classification

Pain may be classified according to its site, nature or presumed mechanism. Such classification may not, however, be helpful in predicting treatment response. For example, both the burning and shooting pains associated with diabetic neuropathy have been shown to respond well to tricyclic antidepressants, dispelling the received notion that antidepressants should be used for burning pain and anticonvulsants for shooting pain.[34]

The traditional classification of diagnoses into organic or psychological and the use of terms such as 'functional', 'unexplained' and 'psychosomatic' to describe painful symptoms are both unhelpful.[35] It has been noted that:

> *For the vast majority of chronic pain sufferers, terms such as psychogenic pain and somatisation disorder produce only frustration and distress and offer little in terms of treatment, evidence-based or otherwise.*[36]

Although ICD-10[37] and DSM-IV[38] definitions of depression both mention pain, it is described as a secondary or uncommon symptom. For example:

Most other symptoms are either secondary to, or easily understood in the context of, such changes
Disturbance in mood is the predominant feature.

This emphasis on affective symptoms may contribute to under-recognition of pain in patients presenting with depression. The next revisions of the ICD and DSM classification systems should be constructed to reflect the extensive overlap between depressive and painful symptoms.

Clinical assessment in primary and secondary care

A large proportion of depressed patients will suffer from some sort of pain, and there is evidence that such painful symptoms have an adverse effect on clinical outcome. Therefore, both general practitioners (GPs) and psychiatrists should enquire about, and pay attention to, pain symptoms in patients presenting or diagnosed with depression. In assessing patients' progress, they should take account both of change in these symptoms and of their impact on the patient's life.

Clinicians should balance the need to exclude common causes or those with a serious prognosis against the danger of subjecting patients to unnecessary and costly tests. However, in the absence of explicable symptoms or when tests prove negative doctors should avoid 'normalising', that is, implying that the symptoms:

- are within a common acceptable range of experience
- do not indicate a serious disease, or
- are likely to be self-limiting.

Such 'normalisation' is a common and plausible response to unexplained symptoms in clinical practice but may cause patients to intensify their presentation (Table 2).[39]

Before assuming that negative results from investigations or simple explanations will give reassurance doctors should try to discover patients' views about their symptoms. Ensuring that patients feel their concerns and beliefs about their physical symptoms are fully understood and taken seriously by the health professionals is central to engaging patients in assessment and treatment. To communicate effectively with patients, doctors need to acknowledge and validate the patients' sense of suffering, provide tangible mechanisms to explain symptoms arising from patients' expressed concerns and offer opportunities for linking symptoms of depression and pain.[39]

Patients diagnosed with depression in primary care are usually referred to general adult mental health services, which often means that painful symptoms take second place behind affective symptoms or may even be ignored. Psychiatrists therefore need to be alert to their depressed patients' 'medical' problems, in particular to the prevalence and importance of painful symptoms.

Principles of management

Patients who present with multiple painful symptoms and depression are likely to be perceived by doctors as 'difficult' – the feeling may be mutual. Such patients report less satisfaction with medical care than patients without mental disorders and those who present with a single symptom.[40]

The author of a review on pain and depression has noted that:

Often patients are referred to specialists with expertise in treating pain or expertise in treating depression rather than to a provider who is comfortable treating both.[1]

Many general psychiatrists have little experience of treating pain. The division of psychiatric services into general adult and liaison psychiatry underscores and perhaps exacerbates this problem. Pain clinics, in contrast, usually offer access to psychological or psychiatric as well as physical treatments. We suggest that, just as psychiatrists attend pain clinics, pain specialists might usefully attend psychiatric clinics. Psychiatric teams should adopt a more multimodal, multidisciplinary approach on the pain clinic model since this 'biopsychosocial' model has been shown to be effective in the treatment of chronic pain.[41,42]

GPs may consider they lack the specialist knowledge to treat patients with depression and pain, but in fact they are ideally placed to do so, given their skill and experience in making sense of the undifferentiated, complex range of biological, psychological and social problems that their patients present (Table 3).

Taking patients' pain seriously may be therapeutic in its own right. Patients with complex problems often struggle to convey the reality of their symptoms.[45] If doctors appear to misunderstand or

Table 2. Types of normalisation displayed by general practitioners.[39]

Type	Features
Normalisation without explanation	Dismissal of disease Rudimentary reassurance Authority of negative test result
Normalisation with ineffective explanation	Tangible physical mechanism, unrelated to patient's concerns
Normalisation with effective explanation	Tangible mechanism grounded in patient's concerns Physical and psychological factors linked

Table 3. Key skills that can be acquired by general practitioners.[43,44]

Helping the patient to feel understood	Listening Taking physical complaints seriously Picking up cues of emotional distress Exploring illness concerns
Broadening the agenda	Opening up the consultation to discussion of physical and psychosocial issues in a negotiatory manner
Making links	Providing explanatory models for how physical and psychosocial problems may be linked
Negotiating treatment	Exploring concerns about treatment, including side effects that may be experienced

oversimplify these problems, patients may respond by intensifying their presentations – hence, paradoxically, generating further unnecessary somatic responses by doctors.[39] It is also important to assess the impact of pain on the patient's life since, in many cases, the goal of treatment is to mitigate this rather than to remove the pain itself.

Research

Our literature review revealed many areas in which there is little or no convincing evidence on which to base decisions or recommend best practice. The treatment of pain in patients with depressive disorders has received far less attention than the psychological problems of patients who present with chronic pain. There is evidence that antidepressants can reduce pain, but most studies have been relatively short or uncontrolled and patient populations poorly defined. Further large-scale, randomised trials of longer duration are therefore needed to determine the most effective treatments.

Research is also needed on the effects of pain on different types of treatment for depression, and also on the effects of pain on important outcomes such as disability and suicide.

There is little evidence that research has taken patients' concerns into account. Future studies should therefore consider outcomes that patients consider important. These are likely to include functional ability and the effects of pain on quality of life as well as direct measures of pain. Rigorous pharmacoeconomic evaluations would also be helpful to determine the most cost-effective management strategies.

Further education and training needs

Many psychiatrists and GPs feel poorly equipped to manage patients with complex presentations such as pain and depression. This suggests inadequacies in current medical training. However, as a good example of a problem that crosses boundaries, that of pain and depression lends itself well to a problem-based learning approach. We therefore recommend that such training should be incorporated into the medical curriculum. We also recommend further training in the recognition and management of depression and pain for most doctors, particularly those working in psychiatry and general practice.

Conclusions

Physicians need to understand more about pain management and should be alert to, and prepared to treat, pain symptoms in patients with depression.

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Competing interest statements

EW is a freelance medical writer who works for a number of pharmaceutical companies that produce analgesics and antidepressants; she is a former employee of Janssen-Cilag and GlaxoSmithKline.

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