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Assessment and treatment of pain in thalassemia

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Abstract

Pain is a subjective symptom whose prevalence can be grossly underestimated. The high proportion of adults with thalassemia who experience chronic pain is evident from recent surveys. However, pain has not received enough attention in the overall management of thalassemia. The association of pain with the type and treatment of thalassemia or with its comorbidities is unclear. Abnormal spine imaging is seen in patients reporting pain, although the role of osteopenia has not been established. Pain becomes more frequent with age. The lower back is the most common site and can be particularly disabling and difficult to treat. Treatable causes, such as extramedullary masses or disc herniation or fractures, must be ruled out. Some adults experience increasing pain when the hemoglobin drops at the end of transfusion cycles. Interdisciplinary management of pain is necessary, while overreliance on medications can be counterproductive. The impact of chronic pain on the quality of life must be acknowledged. Physical therapy, psychological counseling, and vocational rehabilitation are vital to management. I recommend a proactive approach for prevention of pain by maintaining optimal bone density and an active lifestyle. I further propose that a universal tool be adopted to document and characterize pain at routine clinic visits.

Keywords

thalassemia; bone health; chronic pain

Introduction

Pain is an unpleasant and emotional experience whose prevalence is underestimated. Acute pain is generally of sudden onset and short duration, and usually has an underlying known etiology. Chronic pain is described as pain lasting > 3 months, which is difficult to treat and has known or unknown causes.

The perception and treatment of pain is influenced by (1) biological factors—extent of injury, other coexisting illnesses, pain tolerance; (2) psychological factors—anxiety, fear, anger, depression, and helplessness, which precede or follow the onset of pain; and (3) social factors—family support, work environment, cultural attitudes, and access to care.^{1–4}

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Conflicts of interest

The author declares no conflicts of interest.

Chronic pain can become a disease in its own right, overshadowing the underlying cause in the intense and overwhelming need to address its impact on all dimensions of life.¹ Chronic pain affects the individual's ability to maintain an independent lifestyle, productivity, and social relationships.⁴ There is real concern that, unlike cancer or other anatomically defined causes, the pain in thalassemia may be underrecognized and undertreated owing to its ill-defined pathogenesis.

Pain in thalassemia

Current management advances have extended life spans for individuals with thalassemia, which has exposed previously unidentified issues, including chronic pain.⁵⁻⁷ Many physicians caring for adults with thalassemia have encountered patients with chronic pain, which is at times severe and intractable.

Pain has been reported in thalassemia in multiple publications over the past 2 decades. The initial studies were case series highlighting complications of thalassemia that lead to chronic pain.⁸⁻¹¹ Papanastasiou *et al.* reported that scoliosis is more common in preadolescents with thalassemia.^{12,13} Among the subgroup of 43 patients who were evaluated again after a period of 10 years (mean age 12.5, range 13.5-39 at second visit), the number of patients with scoliosis greater than 10 ° did not change significantly. Only one patient had severe thoracic scoliosis (65 °) at first examination, which progressed on follow-up.¹³ The reason for this pattern of scoliosis in thalassemia is not clear, but bone marrow expansion and pubertal delays could contribute to these observations. In addition, deferoxamine is well known to produce metaphyseal changes in the long bones, reduction in growth velocity,¹⁴ and flattening of the thoracic and lumbar vertebral bodies.¹⁵ The effect of deferoxamine on growth is more severe when it is started before 2 years of age or given in high doses.¹⁴ Realization of these irreversible toxic effects has led to a marked change in chelation practices, with deferoxamine being avoided or used at very low doses in young children starting chelation.¹⁶ Bone changes attributed to expansion of bone marrow are more marked in patients starting transfusion later in life⁸ and in those who are undertransfused.¹⁷ Angastiniotis *et al.* reported that patients who were initially classified as thalassemia intermedia and started transfusions after 6th year of life had more expanded hypercellular bone marrow on magnetic resonance imaging (MRI), instead of the fatty replacement seen in well-transfused patients between 30 and 40 years of age. Hydroxyurea treatment was associated with modification of MRI signal and relief of pain in such cases.¹⁸ Low bone density is found in the majority of patients to varying degree,¹⁹ while extramedullary hematopoiesis with spinal cord compression are more common in non-transfused patients. However, in the absence of adequate transfusions, patients with thalassemia major have worse bone density and skeletal deformities than those who have baseline hemoglobin over 7 g/dL.¹⁷ MRI imaging of spine in patients who report back pain reveals more extensive degenerative disc disease than in patients with back pain who do not have thalassemia.⁹ These changes are severe, involve multiple intervertebral discs, and lack a predilection for L4/5 disc space that is observed in general population. Collapse or crush fractures of the vertebral body are uncommon unless associated with trauma.

More recently, pain surveys have been undertaken in thalassemia, usually as part of health-related quality-of-life assessments. Pakbaz *et al.*,⁶ using the Dartmouth Care Cooperative Chart System (COOP) questionnaire, reported that 20% of both transfusion-dependent and non-transfusion-dependent patients had moderate pain, while severe pain was present in 14% and 5%, respectively. A subsequent survey in Europe using SF-36 revealed moderate pain in 61% and severe pain in 1%.²⁰ Trachtenberg *et al.*,⁷ also using SF-36 to examine pain prevalence in 265 adults/adolescents in North America, reported similar results. Body pain was reported by 69% of the sample, with 28% reporting moderate or severe pain. This study found that pain increased significantly with age and became more frequent than in the general population in patients older than 35 years. The prevalence of pain in children and young adults did not exceed that in the general population.⁷

Prevalence and characterization of pain in thalassemia

A comprehensive assessment of pain in thalassemia was conducted in patients living in North America by the Thalassemia Clinical Research Network.²¹ This survey utilized the Brief Pain Inventory (BPI),²¹ an instrument that has demonstrated validity over multiple cultures, languages,²² and diagnoses.²³ BPI assesses the pain perception (or sensory dimension) using questions on severity of pain and interference with daily life (reactive dimension), asking about general activities, mood, and sleep. There were 252 participants age 27 years (12–71 years) with a diagnosis of β -thalassemia major (81%), E β -thalassemia (11%), or hemoglobin H disease (6%), and 80% were on regular transfusions. This study revealed that the proportion of participants reporting pain in the last 7 days increased from 8% in the 12- to 17-years age group, to 36% among those 25–34 years and 56–58% among those older than 35 years (Fig. 1). Thus, this study clearly demonstrated the effect of age on pain prevalence in thalassemia. A majority of older patients reporting pain had experienced symptoms for longer than 1 year, were more likely to rate their pain as moderate to severe, and had more sites of pain than younger patients (Fig. 2). Similar to earlier reports, lower back was by far the most common site of pain, followed by legs, head, hips, and upper or mid-back. The most frequent pain trigger was low hemoglobin level, and relief was reported after blood transfusion. Only 8% of the entire group was on long-acting opioids, with another 17% using short-acting opioids. The same investigators later reported on the impact of pain on quality of life in a subgroup of participants who also completed the SF-36 and HADS questionnaires (Fig. 3).²⁴ The mean scores for most parameters worsened with increasing pain. Pain interference mean scores by BPI increased from 2.5 for mild pain to 7.0 for severe pain. On the SF-36, the QoL scores were 9 points lower in those reporting pain than those without pain. Participants with pain showed more symptoms of anxiety, with a trend toward more symptoms of depression. The impact of the number of sites of pain (from 0 to 4) on these three assessments is shown in Figure 3. A progressive worsening of QoL measures was observed with increasing number of sites of pain.

Comparison with general population

In the 2012 National Health Interview Survey, it was estimated that 56% of adults in the population report some pain in the previous 3 months, with 11% suffering from daily pain and 15% with category 3 or 4 pain.²⁵ Pain was assessed using the Washington Group on

Disability Statistics self-reported questionnaire, which categorized pain of increasing severity on a scale of 1 to 4 based on pain persistence and pain “bothersomeness.” Expressed in similar terms, the prevalence figures for thalassemia are 10–15% higher for both mild and severe pain. In the survey, race, ethnicity, language, sex, and age were associated with pain severity. Although individuals 18–44 years of age had a lower prevalence of category 3 or 4 pain than those in older age groups, no difference was seen between those 45–64 years and those older than 65 years. It is notable that instead of the age threshold of 45 years in the general U.S. population at which prevalence of pain increases, this increase is observed at 35 years of age in thalassemia.²¹ In the national survey, it was observed that individuals with category 3 or 4 pain have worse health status, use more health care, and suffer from more disability than those with less severe pain.²⁵ For instance, the number of bed disability days or inability to work for health reasons increases from < 10% with category 2 pain to nearly 40% with category 4 pain. While individuals with thalassemia have not been assessed with an identical questionnaire, current estimates of severe pain in thalassemia suggests that these comorbidities may affect over 25% of adults older than 35 years.

The association of pain with treatment or complications of thalassemia

Previous studies show that hemoglobin level, bone density, iron status, and chelator use are not different between the groups with and without pain.²¹ The lack of identifiable risk factors is a hindrance to understanding the pathogenesis of pain in thalassemia. Nevertheless, there are recognizable triggers of pain among patients. Although average hemoglobin level is not significantly lower in individuals with pain, it may be very important in individual cases. A low hemoglobin, such as would occur at the end of a transfusion cycle, is the most frequently cited cause for worsening of pain (45%) that decreased after blood transfusion.²¹ Patients with delayed start of regular transfusions, and those with thalassemia intermedia, may be at higher risk for developing pain owing to continued hyperexpanded bone marrow.⁸ While the association of skeletal changes with undertransfusion in thalassemia is known, its relationship to development of chronic pain in adult life has not been studied. For many individuals, pain is triggered by prolonged standing, walking, and lifting heavy objects.

Bone changes are almost always observed when imaging is undertaken to investigate significant pain.⁹ These include abnormal vertebral morphology, scoliosis, and degenerative intervertebral disc changes.¹² In addition, most patients also have osteopenia, and many have vertebral body alterations from deferoxamine use at a young age.²⁶ Since these changes can also be observed in patients without severe pain, they seldom aid in the anatomic diagnosis of pain. It is also unknown if asymptomatic individuals with spine changes are at a greater risk of developing chronic pain in the future.

Acute pain in thalassemia

Acute pain can arise from multiple causes in thalassemia, many of which can signal an emergent situation or complication. For an overview of evaluation and management of acute onset pain, the reader is referred to guidelines for emergency management of thalassemia published by the Thalassemia International Federation.²⁷ These acute causes of pain are listed in Table 1.

Assessment of pain in thalassemia

The assessment of pain is a two-step process. First, it is necessary to establish the presence of pain, and second, to characterize the severity and frequency of pain and its interference in daily life (IOM). Since pain is a subjective symptom that may not have a physiologic correlate, the clinician may remain unaware of the problem unless the patient takes the initiative to disclose its presence. The corollary is that, unless a direct inquiry about the presence of pain is made, the prevalence of pain will likely remain underestimated. It is important that all adults with thalassemia should be asked about pain at routine clinic visits. Since clinicians may lack the skills to evaluate pain, the adoption of a simple universal tool to screen and categorize pain in the clinic is recommended. A simple question about presence and severity (rated 1–10) of any pain in the last 4 weeks, when asked directly during the clinical interview by an attentive physician, will identify nearly all affected individuals.²⁸ If pain is present, it should be probed in more detail and recorded either using the BPI²³ or the questions developed by the Washington Group on Disability Statistics.²⁵ BPI assesses pain in two dimensions by self-report (Fig. 4): the sensory dimension is assessed as pain severity or intensity, while the reactive dimension or the interference with daily function is a construct of seven items grouped in two subdimensions of REMS or affective and WAW or activity. The BPI assesses pain at its “worst,” “least,” “average,” and “now” (current pain).²⁹ In clinical trials, the items “worst” and “average” have each been used singly to represent pain severity. A composite of the four pain items (a mean severity score) is sometimes presented as supplemental information. The BPI is preferred over SF-36 as it characterizes pain in better detail, allows for comparison with other chronic illnesses, and has been validated across several cultural and language settings.³⁰

Management of chronic pain

Much of pain management takes place outside any healthcare setting. Individuals must respond to and attempt to control their own pain at home, at work or school, or when engaged in other activities.¹ The role of health professionals is largely guiding, coaching, and facilitating self-management, and hence must be patient centered. However, very few physicians are sufficiently prepared to perform this supportive role. Instead, providers from nursing or psychology are in a position to make a more significant contribution to management of pain. There may be barriers to obtaining support of health insurance providers for assessment by specialized pain teams.

The currently available treatment options have limited effectiveness for severe chronic pain (Table 2).³¹ Interdisciplinary assessment and management of chronic pain are essential, while overreliance on pharmacotherapy is counterproductive.³² In all adults with thalassemia who have chronic pain, a 3- to 6-month trial seeking to raise the pretransfusion hemoglobin by 1–1.5 g/dL should be considered. Hydroxyurea can be tried in transfused patients if it is felt that the expanded bone marrow is contributing to the pain.⁸

Use of analgesic medicines

The general principle is to begin with non-opioid drugs followed by stepwise escalation of potency. For many patients with intermittent pain, sufficient control is achieved with

nonsteroidal anti-inflammatory drugs (NSAIDs) or codeine/acetaminophen. For more severe pain, intermittent opioids are prescribed, such as beginning with a week of short-acting hydrocodone or morphine. At this stage, the adverse effects of opioids should be reviewed with the patient,³³ including overdose, dependence, depression, cognitive impairment, sexual dysfunction, constipation, and risk of motor vehicle accidents.

If long-term opioid use is deemed necessary, it is recommended to start with a 1-month trial. The physician and the patient should identify the functional goals of the treatment, instead of aiming for complete relief from pain. For continued long-term use, the lowest effective opioid dose should be used combined with NSAIDs for increased efficacy and managing breakthrough pain. Any of the controlled-release preparations of morphine or oxycodone can be used, with methadone being a suitable alternative.

While escalation of dose may be needed for better efficacy, caution must be used if the prescribed doses are getting very high.³⁵ The use of high doses of opioids has unproven benefits and increased side effects, and may indicate overreliance on drugs at the expense of other supportive and psychological remedies. In general, when the dose reaches 50–100 mg morphine equivalents per day (or methadone 20 mg or oxycodone 60 mg), it is time to re-evaluate the entire management plan.³⁴ It is suggested to seek pain clinic referral for evaluation and management guidance.

For many patients with chronic pain, there are periods when the pain can get worse and become unbearable, necessitating larger doses of analgesics, or even a hospital admission. These pain flare-ups are usually brief and do not require an escalation of an otherwise stable analgesic regimen.

A proactive approach towards preventing pain

Since established chronic pain can be an intractable problem, we provide some recommendations for prevention despite the absence of prospective data. Management decisions made at a young age may have bearing on the development of pain after several decades. The spine should be considered a target for complications of thalassemia. The prevention of skeletal deformities and osteopenia may reduce or delay degenerative changes in the spine. This should be a factor in deciding whether a patient with thalassemia intermedia who has visible skeletal changes from bone marrow expansion should be placed on regular transfusions. In patients who are on regular transfusions, morphologic changes in bones may be reduced by maintaining adequate hemoglobin level to prevent marrow expansion and avoid growth delays; avoiding high-dose deferoxamine at a young age; preventing hypogonadism; promoting good nutrition with emphasis on vitamin D, calcium and zinc; and encouraging an active lifestyle with regular exercise. Strategies for the prevention of pain during adulthood should begin during childhood.

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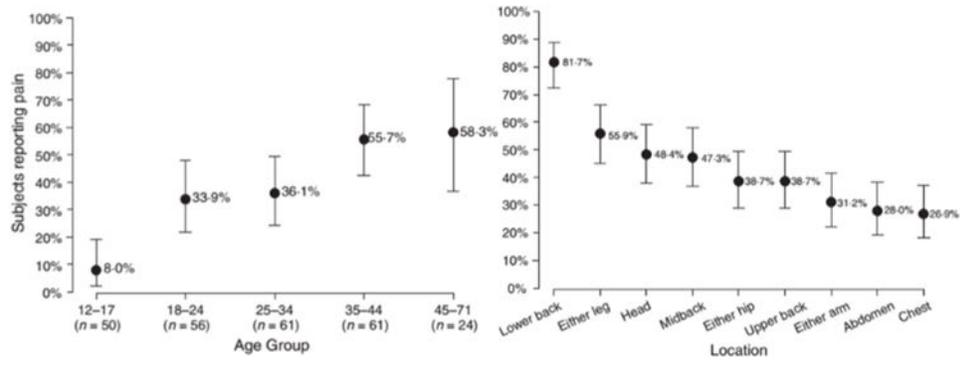


Figure 1. Prevalence of pain in thalassemia. (A) The proportion of patients reporting pain rises after 35 years of age. (B) The lower back is the most frequent site of pain. Reproduced with permission from Ref. 21.

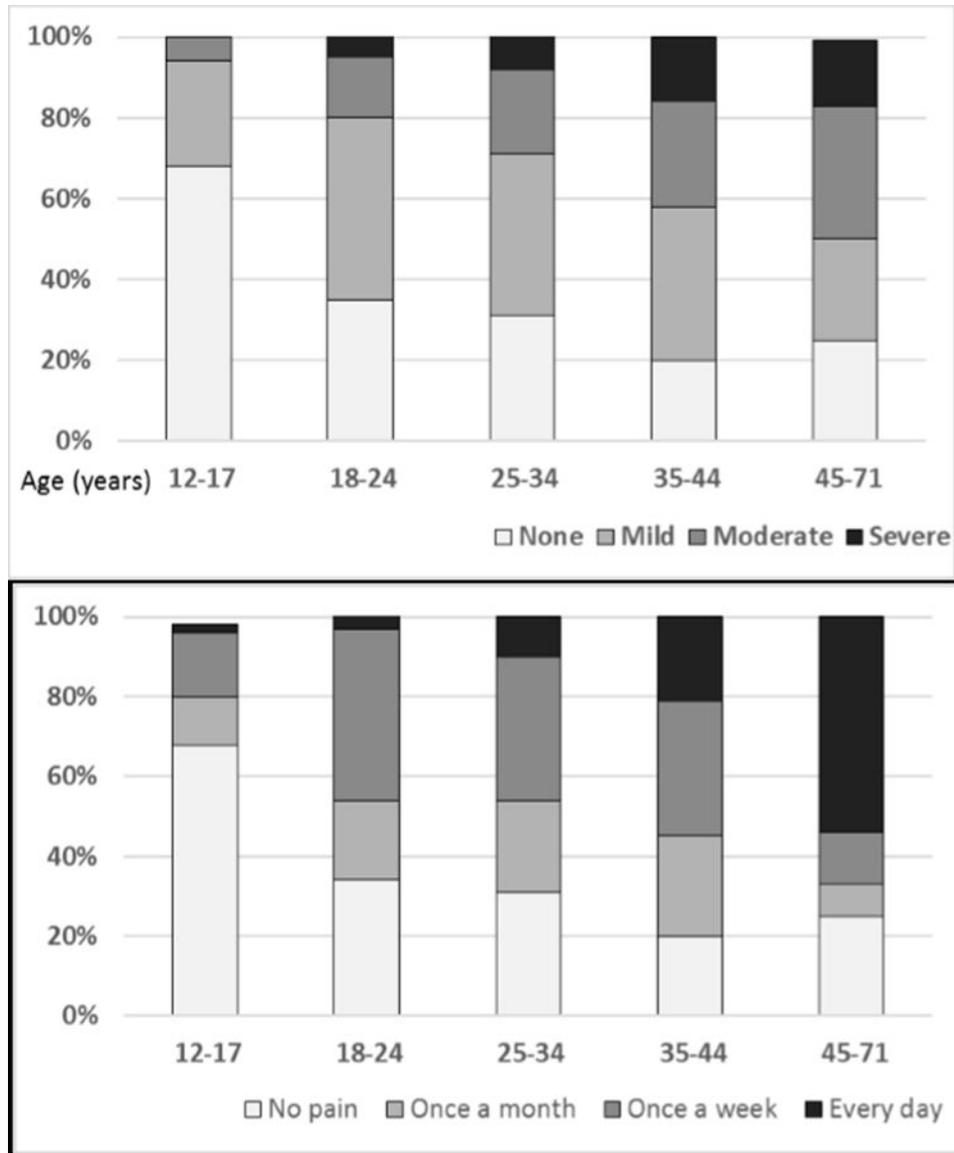


Figure 2. Frequency and severity of pain. Effect of age on (A) severity of pain and (B) frequency of pain. Adapted from Ref. 21.

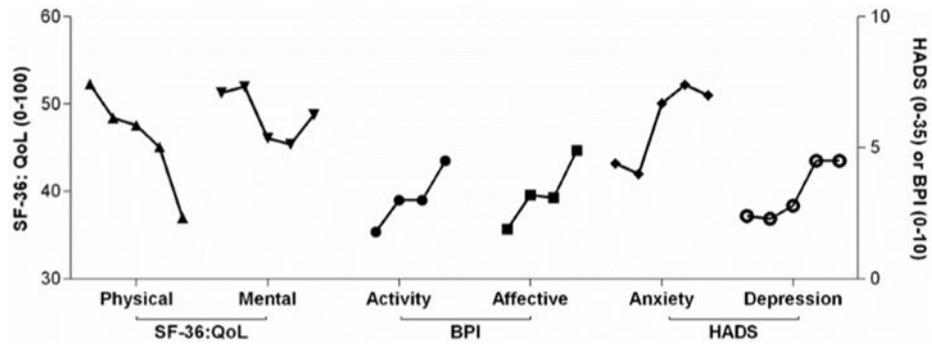


Figure 3. Effect of number of sites of pain on quality of life. The number of sites ranged from 0 to 4 for SF-36 and HADS measures, and 1–4 for BPI measures. Adapted from Ref. 24.

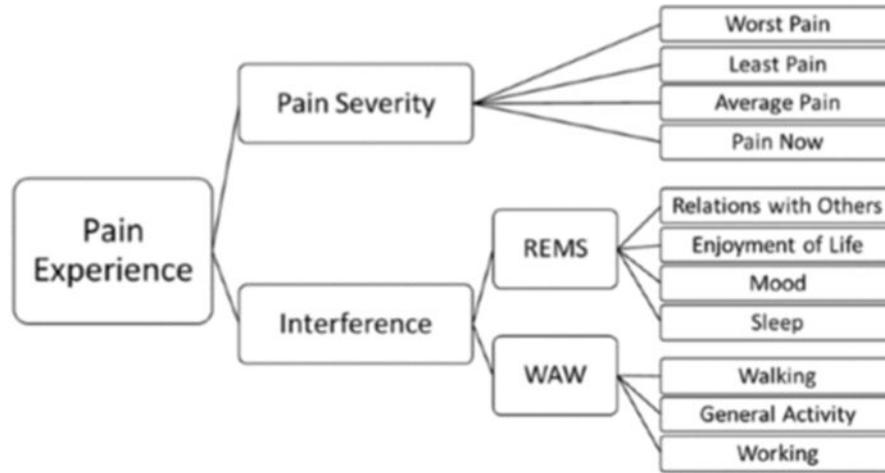


Figure 4. Pain assessment with the Brief Pain Inventory. Items are on the right side and constructs on the left side. Figure modified from Ref. 29.

Table 1

Etiology of acute pain in thalassemia

• Nerve compression
- Extramedullary masses
- Disc herniation or fractures.
- Fractures
- Feet, ribs, and vertebrae
• Headache
- Depression, fatigue
- Infections:
▪ Upper respiratory
▪ CNS: higher risk with iron overload and/or neutropenia
- Extramedullary hematopoietic masses
• Acute chest pain
- Pulmonary embolism
- Rib fracture
- Pericarditis
• Abdominal pain
- <i>Yersinia</i> infection
- Cholelithiasis
- Nephrolithiasis
- Congestive cardiac failure
- Intra-abdominal thrombosis (portal vein, mesenteric)
• Cyclic throbbing back pain towards end of transfusion cycle

Note: Modified from Ref. 27.

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Table 2

Options for management of chronic pain.

Hematological	Pretransfusion exacerbation of pain may respond to raising transfusion threshold by 1–1.5 g/dL. A trial of hydroxyurea is recommended if expanded bone marrow may be responsible.
Surgical	Consultation with surgery; only a minority of cases are candidates for surgery, alleviating direct nerve pressure, significant deformity.
Pharmacologic	Opioids and NSAIDs, epidural steroid injections
Treatment of osteoporosis	Bisphosphonates, parathyroid hormone analogues
Non-pharmacologic	TENS (transcutaneous electrical nerve stimulation), chiropractor, massage, acupuncture
Physical therapy	Targeted to increasing mobility and improving muscle strength
Psychological assessment	Counseling, antidepressant drugs, behavioral and cognitive therapies
Other	Workplace and lifestyle adjustments, vocational rehabilitation

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