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A Case Series

Treatment Challenges and Complications with Ziconotide Monotherapy in Established Pump Patients

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Background: The U.S. Food and Drug Administration (FDA) recently approved Ziconotide intrathecal infusion for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of, or refractory to, other methods of treatment, including intrathecal morphine. Ziconotide is approved as a monotherapy, but there are challenges associated with the decision to wean intrathecal opioids for Ziconotide alone. Maintaining adequate analgesia and managing opioid withdrawal symptoms may be difficult. Additionally, a variety of adverse physiological, cognitive and psychiatric events may be associated with this new drug. Patients with pretreatment psychiatric disorders may be at increased risk for treatment complications.

Objective: To present a report of a case series describing treatment challenges and complications associated with the decision to convert established pump patients from intrathecal opioid therapy to Ziconotide monotherapy.

Description of cases: Three established pump patients, refractory to intrathecal opioid therapy, were converted to Ziconotide monotherapy. All of these patients experienced significant emotional distress or psychological symptoms that threatened the success of the treatment. Achieving adequate analgesia, reducing Ziconotide to mitigate adverse physiological effects, managing opioid withdrawal symptoms, and supportive psychological consultation were combined to achieve successful outcomes in two of our three patients.

Conclusion: This report describes challenges associated with the decision to convert established pump patients from intrathecal opioid therapy to Ziconotide monotherapy. Inadequate analgesia, adverse medication effects, and opioid withdrawal symptoms can precipitate a stressful situation that may be perceived as dangerous or threatening by patients who are predisposed to anxiety. Screening patients for psychiatric disorders, anxiety-proneness and/or vulnerability to stress should be considered to reduce the risk of treatment complications. A multimodal approach is strongly advocated, including rapid responses of treating physicians and nurses along with strong psychological support.

Key Words: Ziconotide, adverse events, treatment complications, psychological distress, treatment outcome

On December 28, 2004, the U.S. Food and Drug Administration (FDA) approved Ziconotide intrathecal infusion for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of, or refractory to, other treatments, such as systemic analgesics, adjunctive therapies or intrathecal morphine.

Ziconotide is the synthetic equivalent of a naturally occurring conopeptide found in the venom of a marine snail known as *Conus magus*, a predatory sea creature that attacks its prey with harpoons loaded with a paralytic poison (1). Ziconotide is the first in a new class of non-opioid analgesics known as N-type calcium channel blockers (NCCBs), which target pre-synaptic calcium channels on nerves that ordinarily transmit pain signals (2). Fig. 1 illustrates what has been learned from animal models. Ziconotide blocks the N-type voltage-sensitive calcium channels and prevents release of the excitatory amino acid, glutamate, from the presynaptic terminal, thereby reducing the amount of stimulation at the dorsal horn neurons (3).

FDA approval of Ziconotide was based on the treatment of more than 1,200 patients and three Phase III pivotal clinical trials, which evaluated the efficacy and safety of this drug in chronic pain patients from a variety of populations, including patients with cancer, AIDS, and neuropathic pain (4, 5). This novel pharmaceutical development is non-addictive, so tolerance and withdrawal should not become treatment issues (3, 6). Ziconotide is an approved monotherapy (7), although many physicians are using this drug in combination with intrathecal opioids or non-opioids.

The most commonly reported adverse events associated with Ziconotide intrathecal infusion during clinical trials were dizziness, confusion, memory impairment, ataxia, abnormal gait, somnolence, asthenia, headache, nausea, diarrhea, and vomiting. Less frequently described adverse effects included postural hypotension, impaired verbal expression, abnormal thought processes, dry mouth, anxiety, peripheral edema, nystagmus, and elevated creatine phosphokinase among others (8).

The Ziconotide safety profile (7) warns that severe psychiatric symptoms and neurological impairment may occur during treatment with this drug.

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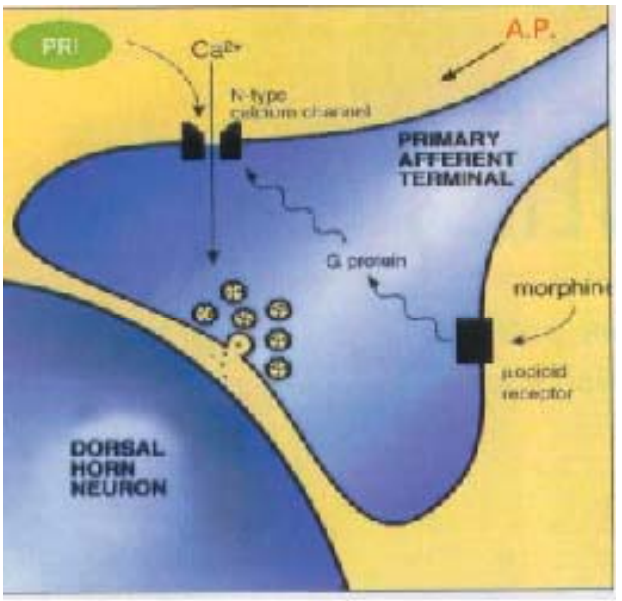

Fig. 1. Ziconotide Mechanism of Action

Patients with pretreatment psychiatric disorders may be at an increased risk. Ziconotide may cause or worsen depression with the risk of suicide in susceptible patients. Those with pre-existing history of psychosis should not be treated with Ziconotide. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. Additionally, Ziconotide does not interact with opioid receptors and will not prevent withdrawal symptoms in patients being weaned from opioids (9).

The emergence of significant emotional stress or psychological symptoms in chronic pain patients during their conversion from intrathecal opioid therapy to Ziconotide monotherapy can be an alarming worry for those patients and their families. Such complications obligate the pain physician to determine if the patient's psychological symptoms result from inadequate analgesia, adverse medication effects, opioid withdrawal or other psychological factors (10-12). Assessment of this complex clinical picture can be challenging. The following review cases describes our experience with three patients, who were the total number of participants in a Ziconotide effectiveness and safety trial in an interventional pain setting between July, 2004, and February, 2005.

Description of Cases

As shown in Table 1, the three individuals in this case report were established pump patients whose mixed neuropathic and mechanical back pain complaints were refractory to intrathecal opioid therapy. They include a 53-year-old female patient suffering from severe and intractable low back and bilateral leg pain, a 54-year-old female patient suffering from severe and intractable low back and lower extremity pain, and a 54-year-old male patient suffering from severe and intractable neck, shoulder, low back and left leg pain.

Prior to their involvement in the Ziconotide study, each of these patients had been implanted with a Medtronic SyncroMed (Medtronics, Minneapolis, MN) pump and spinal catheter system which delivered intrathecal infusion of morphine or similar opioid medications. The length of time that these patients were treated with intrathecal opioid therapy ranged from five to eight years. Each of them had complained of insufficient pain relief despite escalating dosing, and we suspected that they had plateaued on intrathecal opioids. Table 1 shows the maximum doses of intrathecal opioids received by our patients, which were the doses they were receiving at the time of conversion to Ziconotide. Pre-study numerical pain ratings for each patient ranged from 7 to 9 on a scale of 10. Psychologically, the three patients were free of emotional turmoil or significant psychological distress prior to their enrollment in the Ziconotide study. However, like many chronic pain patients, each of them had a history of depression and generalized anxiety that had been identified with pre-surgical psychological evaluation (13, 14) prior to pump implantation. One of them was on a daily maintenance dose of antidepressant medication.

After educating the patients about the potential benefits and possible side effects of Ziconotide, a written consent for treatment was obtained. Each patient's intrathecal opioid dose was

Table 1. *Pre-treatment descriptions of Ziconotide study participants.*

Patient #	Age/Gender	Medical Diagnosis	Intrathecal Opioid Dose	Numerical Pain Rating
1	53/Female	Lumbar spondylosis and Arachnoiditis	Morphine 9.0 mg daily Bupivicaine 6.0 mg daily	7-9/10
2	54/Female	Lumbar spondylosis with myelopathy and Thoracic spondylosis	Sufentanyl 32 mcg daily	7-8/10
3	53/Male	Lumbar spondylosis with myelopathy	Morphine 13.5 mg daily	8-9/10

decreased by 25% per week. Therefore, the weaning process from intrathecal opioids lasted four weeks. During the weaning process, patients were prescribed oral opioids in an attempt to mitigate the symptoms of withdrawal. Oral opioids used included methadone and hydrocodone. Their pumps were emptied, washed with preservative free normal saline solution, and then filled with Ziconotide 25mcg/ml. The initial daily dose of Ziconotide (2.4 mcg.) was slowly increased according to the study protocol.

Throughout the intrathecal opioid reduction phase, patients were closely monitored for signs of opioid withdrawal. Patients kept a daily log of their pain scores and signs and symptoms of withdrawal. They were instructed to document anything out of the ordinary. Each of them described a variety of opioid withdrawal symptoms, including nausea, vomiting, muscle aching, diarrhea, nervousness, restlessness and anxiety. During the final weeks of the intrathecal weaning process, two of our three patients escalated their prescribed doses of oral opioids. Their rationale was to treat "feelings of withdrawal." Verbal pain ratings remained high for all the patients.

During the Ziconotide titration period, patients were closely monitored for changes in reported pain severity, medication side effects, alterations in neurological and psychological functioning, and continued signs of opioid withdrawal. Each of our three patients reported or exhibited a number of adverse events, including confusion, dysesthesia, asthenia, diarrhea, nausea, blurred vision, and impaired verbal expression among others. These symptoms were believed to be treatment-emergent adverse events, although some were also consistent with opioid withdrawal. Following the initiation of Ziconotide, one patient reported reduced pain ratings almost immediately. The remaining two patients continued to complain of withdrawal symptoms, despite continuation of oral opioids, and did not report lower pain ratings until after one to two weeks.

After each patient reported lower pain ratings with Ziconotide, their doses of oral opioids were gradually reduced over the next several weeks. Each of our patients exhibited increased psychological distress as their oral opioids were tapered. For one person, this included anxiety with panic symptoms. For another, the psychological symptoms were anxiety, somatic hypervigilance, and increased avoidance behavior. The third patient exhibited anxiety, depressed mood, and over-reliance on oral pain medications. In all cases, the increased psychological distress was manifested by daily phone calls or faxes to report various somatic symptoms and perceived cognitive and/or speech impairments. One of the patients received short-term trials of novohydroxyzine 75mg and diazepam 15mg for persisting complaints of nausea, anxiety and insomnia. This same patient also obtained amitriptyline, nortriptyline and sertraline outside of our clinic, and reported that she had taken each for a few days. She was eventually prescribed a daily dose of escitalopram 10mg to assist in reducing her dysphoria.

All of the patients expressed misgivings about Ziconotide and questioned its role in their distress. In all three cases, the emotional distress was accompanied by variations in verbal pain ratings and a strong desire to discontinue treatment. In response to the noted complaints and concerns, each patient's daily infusion rate of Ziconotide was decreased to 2.4 mcg. After one to two weeks on this reduced dose, most adverse physiological and/or cognitive side effects were resolved, but significant psychological distress persisted for all three patients.

Psychological consultation was requested in order to gain a better understanding of the cognitive, emotional and behavioral factors possibly contributing to our patients' psychological symptoms, and to assist in the resolution of his or her emotional distress. Two of the patients were responsive to education about opioid withdrawal, and to psychological interventions with efficacy for treatment of anxiety, tension, depression and somatization in chronic pain patients (15-18), such as relaxation techniques and cognitive-behavioral coping strategies. They were then able to manage their anxiety and/or depression symptoms more effectively. Subsequently, these two patients progressed in their adaptation to medication side effects, enjoyed greater pain relief with Ziconotide, and continued acceptable levels of physical and social functioning. The third patient had difficulty accepting the physician's advice to address psychological contributions to her distress, including the cognitive and emotional effects of opioid withdrawal. She perceived the side effects of Ziconotide to be unbearable, and she believed her anxiety, somatic hypervigilance and avoidance behaviors were "normal" reactions to the toxic effects of this drug. This patient was unresponsive to educational and psychological interventions, as well as adjunct medications to reduce her anxiety. Despite reporting improved pain relief and mental clarity with Ziconotide, this patient opted to have the Ziconotide discontinued. Table 2 illustrates each patient's response to medical and psychological interventions, and overall treatment outcomes in terms of conversion from intrathecal opioid therapy to Ziconotide monotherapy.

Table 2. *Treatment responses and treatment outcomes*

Patient #	Ziconotide Dose	Change in Pain Rating	Emotional Distress	Response to Psych Consult	Treatment Outcome
1	7.0 mcg daily	7-9/10 to 2-5/10	Present	Negative	Failed Conversion
2	3.5 mcg daily	7-8/10 to 0-4/10	Present	Positive	Successful Conversion
3	5.4 mcg daily	8-9/10 to 2-6/10	Present	Positive	Successful Conversion

Discussion

Converting established pump patients from intrathecal opioid therapy

Table 3. *Psychiatric and cognitive event rates reported in clinical trials with Ziconotide*

Psychiatric Events	Percentage	Cognitive Events	Percentage
Hallucinations	12%	Confusion	33%
Anxiety	9%	Memory Impairment	22%
Paranoid Reaction	3%	Speech Disorder	14%
Hostility	2%	Aphasia	12%
Delirium	2%	Abnormal Thinking	8%
Psychosis	1%	Amnesia	1%
Manic Reaction	0.4%		

to Ziconotide monotherapy is a medical intervention that can offer significant relief to patients whose pain has been refractory to other methods of treatment, including intrathecal opioids. There are, however, challenges associated with this treatment decision, such as providing the patient adequate alternative analgesia during the process of weaning from intrathecal medications (9), managing opioid withdrawal symptoms, and minimizing the impact of medication side effects, including cognitive and psychiatric events. Table 3 lists the most commonly occurring CNS-related adverse psychiatric and cognitive events associated with Ziconotide during clinical trials with 1,254 patients (8).

When significant emotional distress or psychological symptoms are experienced during the conversion process, there may be an inclination on the part of some patients to attribute this to the new medication. This could lead to premature discontinuation of Ziconotide and treatment failure. Pain physicians should assess and address the relative contributions of inadequate analgesia, treatment-emergent adverse events, opioid withdrawal, and psychosocial factors to the psychological distress of their patients. In so doing, patients are given the greatest opportunity to benefit from this novel pharmaceutical intervention. If cognitive or psychiatric complications persist, or if the patient's psychological distress is unmanageable, Ziconotide should be discontinued. Ziconotide can be discontinued abruptly without evidence of withdrawal effects, and the various CNS-related effects of this drug are generally reversible within two weeks (8).

In each of our cases, significant psychological distress emerged several weeks after Ziconotide had been initiated and lower pain levels were reported, and at a point in time when oral opioids were being tapered. A review of symptomatic presentations following enrollment in the Ziconotide study revealed that each of our patients had first reported signs of dysphoria (nervousness, restlessness, and anxiety) during the intrathecal opioid reduction phase and prior to initiation of Ziconotide. The patients had been started on oral opioids to help them compensate for the reduction in intrathecal medication. Initially, it was unclear whether their dysphoria was a symptom of opioid withdrawal, or an indication of inadequate analgesia due to the differential effectiveness of oral versus intrathecal opioid administration (15,16). However, after Ziconotide was initiated and lower pain levels were reported, our patients continued to describe a number of psychological symptoms, including anxiety, nervousness, and "feelings of withdrawal." We concluded that inadequate analgesia did not explain the psychological symptoms seen with our patients, although it may have played a role in elevating their emotional distress initially.

As Ziconotide was slowly titrated and after lower pain ratings were reported, oral opioids were gradually reduced. During this treatment phase our patients reported a number of physical symptoms that could be associated with either Ziconotide or opioid withdrawal, such as nausea, diarrhea, and muscle aching. They also reported a number of other disturbing symptoms that were specific for Ziconotide, including dysesthesia, blurred vision, confusion and impaired verbal expression. It was at this time that more significant psychological distress was exhibited by our patients, including increased anxiety, panic attacks, depression, and somatic hypervigilance. Considering the possibility that their psychological symptoms might be the result of medication induced anxiety, the doses of Ziconotide were reduced. This step effectively decreased the physiological and cognitive symptoms of our patients, however, it produced no effect on the intensity of their psychological distress. While we recognized that the unpleasant physiological and cognitive side effects of Ziconotide had contributed to emotional distress in our patients, we were not convinced that their psychological symptoms were treatment-emergent adverse events.

Opioid withdrawal syndrome (17) was considered as a possible cause for the increased intensity of psychological symptoms in our patients. Clearly, each of them experienced withdrawal as they were weaned from intrathecal medication, although their symptoms were stabilized with oral opioids. However, when the oral opioids were tapered later in the conversion process, opioid withdrawal may have played a more significant role in the psychological distress of our patients. Subjective complaints of anxiety, restlessness, agitation, dysphoria, and increased pain sensitivity frequently characterize opioid withdrawal.

Psychological consultation was requested to investigate the possible contribution of psychosocial variables to the emotional distress seen with our patients. It is well known that one of the major sources of distress when treating chronic pain patients is psychopathology (18), and this is especially the case with anxiety, depression and somatization (19-24). Comorbid psychiatric disorders in these individuals may increase their vulnerability to stress and influence the manner in which stress is appraised and responded to (25, 26).

An analysis of pre-surgical psychological evaluation results was conduct-

ed. Each of our three patients had met the diagnostic criteria for a chronic depressive disorder and, perhaps more importantly, each had obtained higher than average scores on a measure of trait-anxiety (27). Anxiety is characterized by subjective feelings of tension, apprehension, nervousness, and worry, as well as by activation or arousal of the autonomic nervous system. Trait-anxiety refers to relatively stable individual differences in anxiety-proneness, that is, the difference between people in the tendency to perceive stressful situations as dangerous or threatening and to respond to such situations with elevations in the intensity of their anxiety reactions.

Any disruption of biological homeostasis may be perceived as stressful (28). Patients with a predisposition to respond with fear to bodily sensations are more likely to exhibit debilitating anxiety, as well as a tendency to misinterpret somatic sensations catastrophically and engage in avoidance or other illness behaviors (29-31). In the context of converting our established pump patients from intrathecal opioid therapy to Ziconotide monotherapy, disruption of biological homeostasis may have resulted from one or more physiological perturbations. That is to say, inadequate analgesia, adverse medication effects, and opioid withdrawal all may have played a role in precipitating a stressful situation for the three patients in this study. While no clear and specific causal relationship was established between any of these factors and the psychological symptoms exhibited by our patients, opioid withdrawal appears to have been most influential in terms of the patients' anxiety and increased pain sensitivity.

In the final analysis, we believe that the three established pump patients in this study were predisposed to anxiety, based on their pre-implant measures of trait-anxiety, and that they were vulnerable to the stress produced during the conversion from intrathecal opioid therapy to Ziconotide monotherapy, especially the stress associated with opioid withdrawal. Close monitoring and rapid responses by physicians and nurses along with supportive psychological services were instrumental in achieving successful outcomes with two of our three patients. In addition to superior pain relief and greater mental clarity, these individuals were able to adapt to the medication change and continue acceptable levels of physical and social functioning.

Conclusion

This case series provides a potential outline for physicians who may consider converting refractory patients from intrathecal opioids therapy to intrathecal Ziconotide monotherapy. This treatment decision is associated with a number of challenges, including providing adequate analgesia to patients as they are weaned from intrathecal opioids, controlling adverse medication effects, and managing opioid withdrawal symptoms. While many physicians advocate the use of Ziconotide in combination with intrathecal opioids, this practice has not been studied in blinded, placebo-controlled trials. We have demonstrated that it can be successful and efficacious in carefully selected established pump patients as a monotherapy. However, we strongly advocate a multimodal approach to these patients, with rapid responses of treating physicians and nurses and strong psychological support. Screening patients for psychiatric disorders, anxiety-proneness and/or vulnerability to stress should be considered to reduce the risk of treatment complications.

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References

1. Olivera B, Gray WR, Zeikus R, McIntosh JM, Varga J, Rivier J, de Santos V, Cruz LJ. Peptide neurotoxins from fish-hunting cone snails. *Science* 1985; 230: 1338-1343.
2. Mathur VS. Ziconotide: a new pharmacological class of drugs for the management of pain. *Seminar in Anesthesia* 2000; 19: 67-75.
3. Mathur VS, McGuire D, Bowersox SS, Miljanich GP, Luther RR. Neuronal N-type calcium channels: new prospect in pain therapy. *Pharmacology News* 1998; 5: 25-29
4. Staats PS, Yearwood T, Charapata SG, Presley RW, Wallace MS, Byas-Smith M, Fisher R, Bryce DA, Mangieri EA, Luther RR, Mayo M, McGuire D, Ellis D. Intrathecal Ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA* 2004; 291 (1): 63-70.
5. Chaplan SR. Neuropathic pain: role of voltage-dependent calcium channels. *Regional Anesthesia and Pain Medicine* 2000; 25 (3): 283-285.
6. Miljanich GP. Ziconotide: Neuronal calcium channel blocker for treating severe chronic pain. *Current medical Chemistry* 2004; 11:3029-3040.
7. Ziconotide [prescribing information]. San Diego, CA: Elan Pharmaceuticals, Inc. 2004.
8. Penn RD, Paice JA. Adverse effects associated with the intrathecal administration of Ziconotide. *Pain* 2000; 85: 291-296.
9. Webster LR, Fakata KL. Ziconotide for chronic severe pain. *Practical Pain Management* 2005; 5 (4):47-56.
10. Manchikanti L, Pampati VS, Fellows B, Beyer C, Damron K, Barnhill R, Burks T. Characteristics of chronic low back pain patients in an interventional pain management setting: A prospective evaluation. *Pain Physician* 2001; 4:131-142.
11. Manchikanti L, Pampati VS, Fellows B, Beyer C, Damron K, Barnhill R, Burks T. Comparison of psychological status of chronic pain patients with general population. *Pain Physician* 2002; 5:40-48.
12. Manchikanti L, Pampati V, Damron K, Beyer C, Damron KS, Barnhill R. Evaluation of psychological status in chronic low back pain; Comparison with general population. *Pain Physician* 2002; 5: 149-155.
13. Prager J, Jacobs M. Evaluation of patients for implantable modalities; Medical and behavioral assessment. *Clinical Journal of Pain 2001; 17: 206-214.*
14. Block, AR. *Presurgical Psychological Screening in Chronic Pain Syndromes:*

A Guide for the Behavioral Health Clinician. Lawrence Erlbaum Associates, Inc., Mahwah, New Jersey: 1966.

15. Turner JA, Jensen MP. Efficacy of cognitive therapy for chronic low back pain. *Pain* 1993; 52: 169-177.
16. NIH Technology Assessment Panel. Integration of behavioral and relaxation approaches to the treatment of chronic pain and insomnia. *JAMA* 1996; 27: 313-318.
17. Turk, DC Okifuji A. A cognitive-behavioral approach to pain management. In Wall PD, Melzack R (eds). *Textbook of Pain; Fourth Edition*. Churchill Livingstone, London, 1999.
18. Morley S, Eccleston C, Williams AC. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 1999; 80: 1-13.
19. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Buchser E, Catala E, Bryce DA, Coyne PJ, Pool GE. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival. *Journal of Clinical Oncology 2002; 20 (19): 4040-4049*.
20. Hassenbusch SJ, Portenoy RK, Cousins M, Buchser E, Deer TR, DuPen SL, Eisenach J, Follett KA, Hildebrand KR, Krames ES, Levy RM, Palmer PP, Rathmell JP, Rauck RL, Staats PS, Stearns L, Willis KD. Polyanalgesic Consensus Conference 2003: an update on the management of pain by intraspinal drug delivery – report of an expert panel. *The Journal of Pain Symptom Management* 2004; 27 (6): 540-563.
21. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. *American Psychiatric Association*, Washington DC: 2000.
22. Gatchel RJ, Dersh J. Psychological Disorders and Chronic Pain: Are There Cause-and-Effect Relationships? In Turk DC, Gatchel RJ (eds). *Psychological Approaches to Pain Management: A Practitioner's Handbook*. The Guilford Press, New York, 2002, pp 30-51.
23. Tollison CD, Satterthwaite JR. Chronic benign pain: Diagnosis and behavior management. *Journal of Musculoskeletal Medicine* 1991; 8:55-66.
24. Sullivan M, Katon W. Somatization: The path between distress and somatic symptoms. *American Pain Society Journal* 1993; 2:141-149.
25. Gamsa A. The role of psychological factors in chronic pain. I. A half century of study. *Pain* 1994; 57:5-15.
26. Fishbain DA. Somatization, secondary gain, and chronic pain: Is there a relationship? *Current Review of Pain* 1998; 6:101-108.
27. Dickens C, Jayson M, Creed F. Psychological correlates of pain behavior in patients with chronic low back pain. *Psychosomatics* 2002; 43:42-48.
28. Manchikanti L, Fellows B, Singh V, Pampati V. Correlates of non-physiological behavior in patients with chronic low back pain. *Pain Physician* 2003; 6:159-166.
29. Admundson GJG, Wright KD. Biopsychosocial Approaches to Pain. In Hadjistavropoulos, T. Craig KD (eds). *Pain: Psychological Perspectives*. Lawrence Erlbaum Associates, Inc., Mahwah, New Jersey: 2004.
30. Sullivan MD, Turk DC. Psychiatric Illness, Depression, and Psychogenic Pain. In Loeser JD, Butler SH, Chapman CR, Turk DC (eds). *Bonica's Management of Pain; Third Edition*. Lippincott Williams & Wilkins, Philadelphia, 2001, pp 483-500.
31. Spielberger CD. State-Trait Anxiety Inventory (Form Y). Mind Garden, Palo Alto, CA. 1983.
32. Melzack, R, Katz J. The Gate Control Theory: Reaching for the Brain. In Hadjistavropoulos T, Craig KD (eds). *Pain Psychological Perspectives*. Lawrence Erlbaum Associates, Inc., Mahwah, New Jersey: 2004.
33. Asmundson GJG, Wright KD, Hadjistavropoulos HD. Anxiety sensitivity and disabling chronic health conditions: State of the art and future directions. *Scandinavian Journal of Behavior Therapy 2000; 29: 100-117*.
34. Asmundson GJG. Anxiety sensitivity and chronic pain: Empirical findings, clinical implications, and future directions. In Taylor S (ed). *Anxiety sensitivity: Theory, research and treatment of the Fear of Anxiety*. Lawrence Erlbaum Associates, Inc., Mahwah, New Jersey: 1999, pp 269-285.
35. Asmundson, GJG, Taylor S. Role of anxiety sensitivity in pain-related fear and avoidance. *Journal of Behavioral Medicine* 1996; 19; 577-586.