Introduction

Patients suffering from chronic pain with no identifiable organic cause (somatoform pain disorder) tend to be resistant to treatment and visit a number of medical institutions (“doctor shopping”). Chronic lower back and leg pain are the most frequent complaints. Because no organic cause can be identified, treatment plans for such patients are difficult to formulate. Depression may play a role in a chronically disabled patient. Antidepressants including tricyclic antidepressant amoxapine was investigated in 20 subjects suffering from somatoform pain disorder consisting of chronic lower back and leg pain with no identifiable organic cause and resistant to treatment. Evaluation of efficacy was made both prior to and 6 months after administration using the visual analogue scale (VAS) and self-rating depression scale (SDS). VAS and SDS improved significantly after amoxapine administration. If a VAS improvement rate ≥ 50% is defined as effective and < 50% as ineffective, then there were 10 subjects where the treatment could be rated as effective and 10 as ineffective. Correlations between pain response to amoxapine and subject background factors were consequently examined but no predictive factors could be identified. The onset of the effect was 1 week in 7 subjects and after 2, 3, and 4 weeks in 1 subject, respectively. The strongest effect tended to be shown in those subjects where the onset was earliest. These results indicate amoxapine administration may be an intervention worthy of consideration in cases of lower back and leg pain with no identifiable organic cause and resistant to other forms of treatment and that the efficacy can be evaluated in relatively short period of time.

Key words: chronic pain, chronic lower back pain, somatoform pain disorder, tricyclic antidepressant

Summary

The efficacy of the tricyclic antidepressant amoxapine was investigated in 20 subjects suffering from somatoform pain disorder consisting of chronic lower back and leg pain with no identifiable organic cause and resistant to treatment. Evaluation of efficacy was made both prior to and 6 months after administration using the visual analogue scale (VAS) and self-rating depression scale (SDS). VAS and SDS improved significantly after amoxapine administration. If a VAS improvement rate ≥ 50% is defined as effective and < 50% as ineffective, then there were 10 subjects where the treatment could be rated as effective and 10 as ineffective. Correlations between pain response to amoxapine and subject background factors were consequently examined but no predictive factors could be identified. The onset of the effect was 1 week in 7 subjects and after 2, 3, and 4 weeks in 1 subject, respectively. The strongest effect tended to be shown in those subjects where the onset was earliest. These results indicate amoxapine administration may be an intervention worthy of consideration in cases of lower back and leg pain with no identifiable organic cause and resistant to other forms of treatment and that the efficacy can be evaluated in relatively short period of time.

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the tricyclic class of agents (TCA) have been reported to be effective in a variety of chronic pain syndromes and the analgesic effects of these drugs are thought to result from both their antidepressant action and separate analgesic effect. These drugs are widely prescribed as analgesics for chronic back pain however there is no evidence that antidepressants are truly effective for patients with chronic lower back pain where the organic cause cannot be identified. The authors report a preliminary investigation of the analgesic effect of TCA on subjects with somatoform pain disorder consisting of chronic lower back and leg pain with no identifiable organic cause a condition difficult to both diagnose and treat.

**Materials and Methods**

In 24 of the 350 patients (7%) who attended our Lower Back Pain Specialty Clinic for the first time between 1998 and 2001 no organic cause for chronic lower back and leg pain could be identified despite intensive investigation including MRI and bone scintigraphy as well as functional assessments such as nerve root blocks and intervertebral discography and a diagnosis of somatoform pain disorder was made using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R. Subjects with fibromyalgia neuropathic pain and those with refractory pain due to underlying conditions such as malignancy and collagen diseases including rheumatoid arthritis were excluded. Out of these 24 patients TCA were administered to the 20 subjects for whom NSAIDs and various blocks had been ineffective and who were not visiting the Department of Psychiatry and who had not yet taken psychotropic medications including antidepressants. The clinical data for these 20 cases is summarized in Table 2. The subjects comprised 10 males and 10 females aged 58 ± 14 years (range 26-74 years) Duration of symptoms was 54 ± 38 months (range 12 years) and all subjects had visited other institutions for what is called “doctor-shopping” (1-5 institutions mean 2 ±). Seven subjects had previously undergone lumbar spinal surgery.
of them twice or more

The TCA used was amoxapine. Informed consent was obtained from the subjects after explaining the following points: 1) amoxapine would be administered not as an antidepressant but as an analgesic; 2) anticholinergic side-effects such as a dry mouth and constipation are common; 3) although extremely rare, there was a possibility of malignancy.

The starting dosage of amoxapine was 10 or 25 mg daily, increasing to 20-100 mg daily. All subjects took amoxapine at least for 6 months. No other medications that might affect pain were to be administered.

The degree of pain was assessed using the visual analogue scale (VAS), the level of depression by the self-rating depression scale (SDS) and psychological factors by the Ransford score (RS) using pain drawings.

For the VAS, a 100 mm horizontal scale was used, with a score in the left margin (a score of 0) representing no pain and to the far right (a score of 100) the worst pain imaginable.

For the SDS, a score of over 40 was considered to signify depression, over 48 moderate depression, and over 56 severe depression. A score of 3 or above in the RS was considered to signify psychological abnormality.

Evaluation of efficacy was made prior to and 6 months after administration using the VAS and SDS scores. The relationship between pain and degree of depression was evaluated by determining the correlation between rates of improvement from baseline (pre-treatment score) as calculated from the VAS and SDS scores prior to administration.
and 6 months after it. Statistical analyses were performed using the paired t-test and Pearson's correlation coefficient test.

**Results**

Daily maintenance dosages of amoxapine were 54 ± 27mg (range 20-100). Pre-treatment VAS scores were 81 ± 12 (range 62-100) at least 60 in all subjects and 90 or above in 5 who showed a tendency towards severe subjective pain. Pre-treatment SDS scores were 49 ± 9 (range 35-62) at least 40 (depressive state) was seen in 17 subjects (85%) and a severe depressive state with a score of 56 or above in 5 subjects (25%). The average RS was 2.5 ± 2.2 (range 0-8) and 6 subjects (30%) were shown to have an abnormal RS (≥ 3 points).

VAS and SDS improved significantly with the administration of amoxapine (VAS 81 ± 12 ± 43 ± 35 p=0.001; SDS 49 ± 9 ± 41 ± 9 p=0.131). A moderate correlation (r=0.58) was also observed between the improvement in VAS and SDS. However, results tended to be polarized into one group with markedly improved VAS scores and another group with little improvement including some cases of further deterioration.

The correlation was evaluated using the rate of improvement from the baseline (pre-treatment score) as calculated from the VAS and SDS scores prior to administration and 6 months following administration. A moderate correlation (r=0.58) was observed between the rate of improvement in VAS and SDS. However, results tended to be polarized into one group with markedly improved VAS scores and another group with little improvement including some cases of further deterioration. In other words, there was a correlation between amelioration of pain and depressive state. As can be seen in Figure 1, however, the results tended to be polarized into one group with markedly improved VAS scores and another group with little improvement including some cases of further deterioration. If we define a VAS improvement rate of 50% or more as effective and less than 50% as ineffective, then there were 10 subjects in whom the treatment could be rated as effective (VAS 81 ± 12 ± 12 ± 14) and 10 as ineffective (VAS 80 ± 13 ± 13 ± 15).
The degree of pain (VAS) improved significantly with the administration of TCA (amoxapine) in all subjects (VAS 81 ± 12 vs 43 ± 35 (p=0.001)) if we define a VAS improvement rate of 50% or more as effective and less than 50% as ineffective then there were 10 subjects in whom the treatment could be rated as effective (VAS 81 ± 12 ± 12 ± 14) and 10 as ineffective (VAS 80 ± 13 ± 74 ± 17).

Next the correlation between pain response to amoxapine and subject background factors was examined. Subjects in whom the treatment was rated as either effective or ineffective were compared according to pre-treatment VAS SDS and RS scores age gender duration of condition number of doctors previously seen and history of lumbar spine surgery. Statistical analyses were performed by Cohen’s effect size and Cramer’s V. No differences were detected between the two groups for any of these background factors and no factors predictive of the analgesic effect of TCA could be identified from the subjects of this study.

The timing of the onset of effect (≥ 50% VAS improvement rate) was 1 week in 7 subjects and after 2, 3, and 4 weeks in 1 subject respectively with a tendency for a strong effect being shown in those subjects in whom the onset was earliest. Efficacy was sustained in these subjects throughout the period of amoxapine administration (8-55 months mean 32 months). In 1 subject the pre-treatment SDS score was normal (35 points) but a powerful effect became evident within 1 week of TCA administration with a VAS 100% improvement rate 6 months later.

Adverse events including a dry mouth constipation and drowsiness were reported in 15 subjects (75%). No cases of serious adverse reactions such as malignancy or urinary retention were observed.

**Discussion**

In a primary care setting more than 30% of patients are reported to present with unexplained somatic complaints (USC)
somatic factors later identified in some 20% of these cases. Primary care doctors in orthopedic departments where many patients present with pain as their primary complaint are required to continue investigating for a possible organic cause even if a somatic cause is unclear at the first assessment. However, in 16-42% of USC patients not only is no organic cause found but also no psychological explanation can be confirmed. In other words, in some cases of chronic pain, neither organic nor psychiatric causes can be identified. For these patients with chronic pain, conventional analgesics are often ineffective which makes the doctor’s explanation to the patient and treatment difficult. Unable to obtain an acceptable diagnosis or effective treatment, such patients will go to a multitude of medical institutions including specialized pain clinics. There is strong evidence that depression is related to pain and antidepressants with analgesic properties have been used as a treatment option for chronic pain. Various randomized controlled trials concerning the efficacy of antidepressants for chronic lower back pain have produced conflicting results. So their therapeutic value is inconclusive. This controversy may be the result of a lack of strict inclusion criteria in previous studies. We therefore limited our investigation of the analgesic effect of TCA to subjects with somatoform pain disorder consisting of chronic lower back and leg pain with no identifiable organic cause and a resistance to treatment. It was challenging to strictly select such subjects and so the number in this study was limited. However, our preliminary results show that TCA may possibly be effective for this condition and that there is a correlation between improvements in pain and the degree of depression. Although the causal relationship is still unclear.

One possible mechanism of the analgesic effect of antidepressants, apart from pain relief secondary to their antidepressant effect, has been believed to be a direct analgesic effect caused by their action on central neurotransmitter functions particularly those mediated by the catecholamine and indolamine systems. The onset of analgesia with TCA in chronic pain states has been reported to be more rapid than the usual onset of an antidepressant effect in the same clinically depressed patients (3-7 days vs. 14-21 days). Moreover, chronic pain relief with TCA has also been reported in patients without depression. These reports support the direct analgesic effect theory. In this study, the effect of TCA was observed at 1 week in 7 subjects and in one patient whose condition improved there was no evidence of a pre-treatment depressive state. The size of this study was small but the result suggests that a direct analgesic effect of TCA may possibly be an intervention worthy of consideration in cases of lower back and leg pain with no identifiable organic cause and resistance to other treatments whose efficacy can be evaluated after a rela-
tively short period of time to show stronger evidence for the efficacy of TCA and to run a predictive probability analysis for efficacy in a randomized double-blind trial with a large number of patients is necessary.

References


5) Fey SG. Chronic pain. Psychosom and Rehabilitation 1987 1 1-129.


24) Soja PJ, Sinclair JG. Evidence that Noradrenaline Reduces Tonic Descending Inhibition of Cat Spinal Cord Nociceptor-Driven...
Neurones Pain 1983 15 71–81

26) Tulder MW Goossens M Waddell G et al Conservative treatment of chronic low back pain In Nachemson AL Jonsson E ed Neck and Back Pain The Scientific Evidence of Causes Diagnosis and Treatment Philadelphia FL Lippincot Williams & Wilkins 2000 271–304

27) Zung WWK A self-rating depression scale Arch Gen Psychi 1965 12 63–70