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Observational Report

Low and Therapeutic Doses of Antidepressants are Associated with Similar Response in the Context of Multimodal Treatment of Pain

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Background: Antidepressants are prescribed in a wide range of doses to treat both depression and chronic pain, with optimal psychopharmacology individualized for each patient. In the past decade more antidepressants from different chemical classes have become available and are being used for the treatment of both chronic pain and depression.

Objective: To review the utilization pattern changes and compare response rates of different classes and doses of antidepressants for various pain conditions in the context of multimodal therapies.

Design: Chart review.

Methods: We reviewed 5,916 records at an outpatient multidisciplinary pain center. Of these, 379 records were for patients diagnosed with cancer pain. Because the mechanisms and treatment approaches to cancer pain can differ greatly from non-cancer chronic pain, these records were excluded from the analysis. We assessed 1,506 medical records for patients with chronic non-caner pain who had used at least one antidepressant, with the main outcome measure being the Numeric Rating Pain Scale, 0–10.

Results: Of the 5,916 charts reviewed, 1,506 (25.4%) chronic non-cancer pain charts recorded the prescription of at least one antidepressant. Most patients received a combination of medications and procedures. Of the 450 patients receiving secondary amines, favorable responses were recorded for 340 (76%) patients, while 103 (23%) did not respond and 7 had unknown responses. Of the 492 patients receiving tertiary amines, favorable responses were recorded for 375 (76%) patients, while 113 (23%) did not respond, and 4 had unknown responses. Of the 533 patients receiving SSRI/SNRIs, favorable responses were recorded for 382 (72%) patients, while 147 (28%) did not respond, and 4 had unknown responses. Of the 369 patients receiving atypical antidepressants, favorable responses were recorded for 272 (74%) patients, while 94 (25%) did not respond, and 3 had unknown responses.

Limitations: A retrospective study design and the use of antidepressants as a part of multimodal treatment of pain.

Conclusion: The data suggest that in the context of multimodal treatment for chronic pain, antidepressant therapy at both low and therapeutic doses demonstrates similar response rates. Tricyclic antidepressants (TCAs), which include secondary and tertiary amines, as well as SSRI/SNRIs and atypicals, all appear to show similar favorable response rates.

Key words: Antidepressants, chronic pain, multidisciplinary pain center, multimodal analgesia.

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Since the late 1950s, soon after tricyclic agents were established to have antidepressant properties, antidepressants have been used in the treatment of chronic pain. Kuhn published the first report describing the antidepressant properties of imipramine in 1958 (1); and, in 1960, Paoli et al published a report on the use of imipramine for the treatment of chronic pain (2). It is likely that antidepressants were originally used in chronic pain because of the belief that the patient's overall situation (3) could improve by relieving depression. Those who first studied tricyclic antidepressants (TCAs) had varying views on why antidepressants seemed effective in chronic pain. In 1964, Lance and Curran (4) performed the first placebo-controlled, crossover trial of amitriptyline in the treatment of tension-type headaches and concluded that amitriptyline was of value in relieving this type of pain. However, the primary mechanism of headache relief was not attributed to its antidepressant properties (4). They suggested vasodilatation as the mechanism by which amitriptyline produced relief from tension-type headaches. Subsequent studies have proposed an independent analgesic action of TCAs not related to vascular mechanisms (5,6).

With the publication of the gate-control theory of pain in 1965 (7), and the resulting implications for the role of central processes such as attention and mood in regulating pain perception, there has been increasing interest in the systematic study of the efficacy and mechanism of action of antidepressant drugs in the treatment of chronic pain. TCAs have been shown to provide effective analgesia for a variety of neuropathic pain syndromes, including diabetic neuropathy (8-13), post-herpetic neuralgia (14-16), and post-stroke pain (17). It is thought that TCAs are effective analgesics because they may act on inhibitory descending pathways that are mediated by norepinephrine and serotonin (5,6). However, drug interactions with TCAs and intolerable side effects have limited their use.

TCAs and monoamine oxidase inhibitors (MAOIs) were the only group of antidepressants used in the treatment of depression or pain until 1981, when trazodone was introduced in the United States. The availability of fluoxetine in the late 1980s revolutionized the treatment of depression as the first of the selective serotonin reuptake inhibitors (SSRIs). Other antidepressants are classified as selective serotonin norepinephrine reuptake inhibitors (SNRIs) and finally atypical antidepressants (AAs) because of multiple sites of antidepressant action and chemical structures distinct from TCAs, SNRIs or SSRIs (18,19). AAs include bupropion, trazodone, nefazodone, and mirtazapine.

Since SSRI/SNRIs and AAs may be better tolerated and have different side effects than TCAs, they are used as first line agents for the treatment of depression and other syndromes thought to represent serotonin or norepinephrine disturbances. Their use in the treatment of chronic pain, however, remains limited. Studies have produced conflicting results with regard to the efficacy of AAs, SSRIs, or SNRIs in chronic pain (20). For example, although certain SSRIs may have a role in the prophylactic treatment of chronic daily headaches, they have not been proven effective for migraine headaches (21-24). Furthermore, it is difficult to generalize efficacy by the type of antidepressant. Studies have not supported the hypothesis that if one SSRI is proven effective for a particular chronic pain syndrome, then other SSRIs will also be effective (20). Because of the variability of reported responses to SSRI/SNRIs, along with the proven efficacy of TCAs in chronic pain, clinicians treating chronic pain have generally preferred to use low dose TCAs.

A survey in 1993 – 1994 reviewed the patterns of use of antidepressants in a multidisciplinary pain center (25). Findings from that survey showed the infrequent use of non-TCAs in patients with chronic pain, despite the availability of newer antidepressants (25). By 1993, fluoxetine was the most prescribed antidepressant in the USA, but other antidepressants were also used for depression, including sertraline, paroxetine, bupropion, and trazodone (20,26-28).

With recent reports of the efficacy of newer antidepressants in the treatment of chronic pain, we designed this study to evaluate the change in patterns of use of antidepressants in our multidisciplinary pain center since before the advent of Cymbalta (20-24,29-31). This response rate comparison was done in the context of additional multimodal therapies practiced in our clinic. Mood stabilizing drugs, such as lithium, were not evaluated.

Methods

After approval by the Committee on Clinical Investigation (Human Studies Institutional Review Board) at Beth Israel Deaconess Medical Center, we conducted an in depth chart review of 5,916 patients seen in the Arnold Pain Center from before the introduction

of Cymbalta. The retrospective review was conducted on consecutive patients seen over a 2-year period in 2001 and 2002. Of these patients, 379 (6.4%) had the diagnosis of cancer pain, and were excluded from the larger analysis. This decision was made because of the differences in natural history, treatment approaches, and mechanisms of cancer pain compared to non-cancer pain. The charts of 1,506 patients (25.4%) were identified as documenting the prescription of at least one antidepressant. The eligible antidepressant drugs were secondary amines (nortriptyline and desipramine), tertiary amines (amitriptyline, imipramine, clomipramine, and doxepin), SSRIs (fluoxetine, paroxetine, sertraline, and citalopram), an SNRI (venlafaxine), and AAs (trazodone, bupropion, nefazodone, and mirtazapine). The decision to use an antidepressant was typically based on the location, nature, and duration of the patient's pain and on the physician's preference. The patient's mood and sleep patterns were not uniformly characterized in the medical records.

Demographic data included age, primary diagnosis, presence of premorbid or comorbid depression, medical or procedural interventions, antidepressant used and dose, response to treatment, and side effects. A diagnosis of depression was made if the patient was receiving psychiatric treatment for depressed mood or if the treating physician, usually in consultation with the team psychologist, made a diagnosis of major depression, depression not otherwise specified, or dysthymia (32).

Each patient's chart was reviewed for documentation indicating that one or more of these antidepressants had been prescribed, as well as the observed and reported response to this treatment based on the numeric response pain scale 0–10. Reasons for stopping or changing a particular antidepressant drug were also noted.

Chronic pain was identified as pain persisting for more than 3 months. The patient's numeric rating pain score (NRPS) from 0–10 was recorded at the beginning of the antidepressant regimen, 3 to 4 months after initiating treatment, and again 6 months after initiating the treatment. If the NRPS did not decrease more than 20% after 6 months, the treatment was graded as "no response"; "mild response," if there was a 20% improvement in the pain score; "moderate" if there was 40% improvement; and "marked" if there was a 60% or greater improvement in subjectively reported pain scores. A "mild response," "moderate response," or "marked response" was considered a favorable response. A "no response" was an unfavorable response. The dosing of antidepressants was identified as "low," if the dose was less than conventionally recommended for the treatment of depression, and "therapeutic," if it was within the manufacturer's recommended range for treatment of depression (Table 1). Levels of dosing were examined among various antidepressants. The painful conditions were surveyed individually, but, for the purposes of analysis, pain conditions were grouped into 6 clusters: headache, neuropathic pain, non-radicular pain, radicular pain, myalgia, and cancer pain (Table 2).

Table 1. *Classification of daily dose of antidepressants.*

Antidepressants	Low Dose	Therapeutic dose
tricyclic antidepressant	<50 mg	≥50 mg
sertraline	<50 mg	≥50 mg
mirtazapine	<15 mg	≥15 mg
citalopram	<20 mg	≥20 mg
fluoxetine	<20 mg	≥20 mg
paroxetine	<20 mg	≥20 mg
fluvoxamine	<100 mg	≥100 mg
trazodone	<100 mg	≥100 mg
venlafaxine	<75 mg	≥75 mg
nefazodone	<100 mg	≥100 mg
bupropion	<150 mg	≥150 mg

Table 2. *Diagnostic categories.*

1. Headache
   a. Migraine headache
   b. Tension-type headache
2. Neuropathic pain
   a. Chronic Regional Pain Syndrome (CRPS) / Reflex Sympathetic Dystrophy (RSD)
   b. Neuropathic pain
3. Non-radicular spinal pain
   a. Low back pain (syndrome)
   b. Neck pain
   c. Spinal stenosis
   d. Post-laminectomy syndrome
   e. Facet syndrome
4. Radicular spinal pain
   a. Cervical radiculopathy
   b. Lumbar radiculopathy
5. Myalgia
   a. Fibromyalgia (FM)
   b. Myofascial pain (MFPS)
6. Cancer pain

Comparisons across categories of antidepressants were performed using the chi-squared and Fisher's exact tests using Stata v8.2 (StataCorp, College Station, Texas) statistical software.

Results

Of the 5,916 charts reviewed, 1,506 (25.4%) were of patients with non-cancer pain with a recorded prescription of at least one antidepressant. Patients ranged in age from 20 to 96 years, with 1,316 (87%) being younger than 70 and 1,040 (70%) falling between 30 and 60. Of the 1,506 patients, 66.4% were females and 33.6% were males.

Table 3. *Distribution and combinations of antidepressant drug use.**

Class or Combination	Number	Percent
Secondary amines (total)	450	
• As sole class	331	74%
• With tertiary amines only	9	2%
• With SSRIs only	65	14%
• With atypicals/SNRIs only	35	8%
• With two or more other classes	10	2%
Tertiary amines (total)	492	
• As sole class	346	70%
• With secondary amines only	9	2%
• With SSRIs only	96	20%
• With atypicals/SNRIs only	36	7%
• With two or more other classes	5	1%
SSRIs (total)	533	
• As sole class	280	53%
• With secondary amines only	65	12%
• With tertiary amines only	96	18%
• With atypicals/SNRIs only	79	15%
• With two or more other classes	13	2%
SNRIs/AAs (total)	369	
• As sole class	208	56%
• With secondary amines only	35	10%
• With tertiary amines only	36	10%
• With SSRIs only	79	21%
• With two or more other classes	11	3%

* This table includes patients with and without other treatments.
• 1,165 patients were receiving only one class of antidepressant.

Of the 1,506 patients selected, 1,165 patients received only one class of antidepressant medication (Table 3). Most patients received a combination of medications and procedures. Of the 450 patients receiving a secondary amine, favorable responses were recorded for 340 patients, while 103 did not respond and 7 had unknown responses. Of the 492 patients receiving a tertiary amine, favorable responses were recorded for 375 patients, while 113 did not respond and 4 had unknown responses. Of the 533 patients receiving an SSRI, favorable responses were recorded for 382 patients, while 147 did not respond and 4 had unknown responses. Of the 369 patients receiving an SNRI or atypical, favorable responses were recorded for 272 patients, while 94 did not respond and 3 had unknown responses.

Response rates varied depending on the patient's painful condition (Table 4). For headaches, neuropathic pain, and myalgia, tertiary amines had the higher response rate 77%, 75%, and 79% respectively. AAs and the SNRI (venlafaxine) had the highest response rate for nonradicular pain (80%) and radicular pain (85%). Secondary amines had the lowest response rate (62%) for headache; SSRIs had the lowest response rate for neuropathic pain (65%), non-radicular pain (72%), and myalgia (68%). AAs and the SNRI (venlafaxine) had the lowest response rate for neuropathic pain (57%). The response of headaches to tertiary amines was the most significant.

Also, combinations of antidepressants, a spectrum of interventional procedures, and medications such as NSAIDs, antiepileptic, and opioids were employed (Table 5).

Patients who were prescribed AAs or an SNRI and who also were receiving steroid injections had the highest response rate (87%). Tertiary amines had the highest response rate for patients who were also receiving NSAIDS (79%), antiepileptics (70%), and opioids (74%). Response rates to SSRIs when combined with steroid injections were (80%), NSAIDs (74%), antiepileptics (69%), and opioids (68%).

The overall rates of response to various classes of antidepressants, as well as the rates of response to low and therapeutic doses of antidepressants, are reported in Table 6. Low doses of secondary amines, SSRIs, and SNRIs/AAs had higher response rates (77%, 74%, and 75% respectively) than therapeutic doses (71%, 70%, and 72% respectively). For tertiary amines, therapeutic doses had a higher response rate (81%).

Table 4. *Rate of response to antidepressant class by diagnostic categories.*

Diagnosis	Secondary Amines N=558			Tertiary Amines N=617			SSRIs N=690			Atypicals/SNRIs N=461		
	Total	Responders	%	Total	Responders	%	Total	Responders	%	Total	Responders	%
Headache	29	18	62	44	34	77	82	57	70	69	45	65
Neuropathic	97	70	69	104	78	75	83	54	65	56	32	57
Nonradicular	208	162	78	213	160	75	253	182	72	166	133	80
Radicular	121	91	75	162	131	81	134	105	78	84	71	85
Myalgia	103	73	71	94	74	79	138	93	68	86	67	78

- N represents the number of patients from a certain category receiving a certain antidepressant class.
- Some patients were classified in more than one diagnostic category.
- Difference between response rates of the antidepressant classes is not statistically significant.

Table 5. *Rate of response to antidepressant class combined with other treatments.*

Antidepressant Classes	Secondary Amines			Tertiary Amines			SSRI s			Atypicals/ SNRIs		
	N	Responders	%	N	Responders	%	N	Responders	%	N	Responders	%
Steroid Injection	172	143	83	192	156	81	207	66	80	121	105	87
NSAIDs	218	166	76	272	215	79	292	216	74	185	144	78
Antiepileptics	164	115	70	171	120	70	222	153	69	173	119	69
Opioids	158	115	73	187	138	74	222	151	68	169	122	72

- N represents the number of patients from a certain category receiving a certain antidepressant class.
- Some patients were classified in more than one diagnostic category.
- Difference between response rates of the antidepressant classes is not statistically significant.

Table 6. *Rate of response to different classes of antidepressants and to individual drugs.*

Antidepressants	Overall			Low Dose			Therapeutic Dose			
Class and Drug	Total	Responders	%	Total	Responders	%	Total	Responders	%	P-value
Secondary Amines	450	340	76	344	265	77	106	75	71	
• Nortriptyline	324	243	75	248	189	76	76	54	71	0.364
• Desipramine	126	97	77	96	76	79	30	21	70	0.298
Tertiary Amines	492	375	76	327	242	74	165	133	81	
• Amitriptyline	421	327	78	282	212	78	139	115	83	0.080
• Imipramine	18	14	78	8	6	75	10	8	80	1.000
• Clomipramine	6	4	67	6	4	67	0	-		-
• Doxepin	47	30	64	31	20	65	16	10	63	0.892
SSRIs	533	382	72	191	142	74	342	240	70	
• Citalopram	36	23	64	12	7	58	24	16	67	0.624
• Fluoxetine	197	149	76	70	60	86	127	89	70	0.014
• Paroxetine	127	92	72	52	37	71	75	55	73	0.787
• Sertraline	173	118	68	57	38	68	116	80	69	0.760
Atypicals/SNRIs	369	272	74	207	155	75	162	117	72	
• Venlafaxine	113	81	72	63	47	74	50	34	67	0.439
• Bupropion	79	62	79	38	30	79	41	32	78	0.923
• Mirtazapine	23	19	83	10	8	80	13	11	85	1.000
• Trazodone	120	87	73	77	57	74	43	30	69	0.616
• Nefazodone	34	23	68	19	13	68	15	10	67	0.914

- Total, represents the number of patients who received a certain antidepressant class.
- Responders = percent of patients that had a decrease in NRPS greater than 20%.
- Some patients receive more than one antidepressant.

Discussion

The results of this analysis highlight several important trends regarding utilization patterns in the treatment of chronic pain. First, the data supports our clinical impression that antidepressants are effective among patients with various chronic pain syndromes. Second, antidepressants appear to be effective at treating pain at doses lower than those needed for the treatment of depression. Finally, and most importantly, all the antidepressants analyzed had similar favorable response rates and there were no major differences in response rates between low and therapeutic doses.

Of the various classes of antidepressants used, TCAs have generally been found to have a higher rate of utilization, suggesting that this class with multiple mechanisms is still the first choice for pain relief; similar to what was found in the 1993 – 1994 study published in 1997 (25). Although TCAs were used more often at lower doses than therapeutic doses, the response rate was similar with both dosing regimens. Furthermore, amitriptyline is still the most common antidepressant used for chronic pain. However, amitriptyline, along with some other antidepressants, needs to be used with caution in the geriatric patients (33). TCAs often have the added benefit of sleep restoration, and this aspect may contribute to its beneficial effect. Furthermore, TCAs may still be used more often because of decades of clinical use for chronic pain.

The utilization rate of SSRIs was higher in this study than in the 1997 article (25) when only 12 of 1,145 patients were prescribed SSRIs. In this study, SSRIs were used in 533 patients, with an overall response rate of 72%. One of the important observations about these newer antidepressants is that they have been used more often at therapeutic doses rather than low doses, in contrast to TCAs.

Our data suggest that venlafaxine has a promising role in treating various types of chronic pain. Some other investigators have found similar results for venlafaxine (34-36). The effects of venlafaxine may be mostly serotonergic and akin to those of the SSRIs at lower doses, while at higher doses, it may be increasingly noradrenergic and more similar in action to that of TCAs. Mirtazapine and bupropion appear to have the highest rate of response among the AAs in this study. Other studies have also found promising results for mirtazapine (37-39) and bupropion (40,41). Bupropion is considered to be a dopamine and norepinephrine reuptake inhibitor with weak serotonin reuptake inhibition. These data also demonstrate the efficacy of trazodone and nefazodone in the treatment of chronic pain. This effectiveness does not support or rule out the possibility that these agents affect pain through changes in sleep.

Despite the validity of the findings pertaining to each antidepressant, one cannot generalize efficacy by type of antidepressant. For example, if one SSRI is effective for a certain type of pain, other SSRIs will not necessarily show similar efficacy. In this study, treatment response measured was the response to the overall treatment program with antidepressants utilized as part of a multimodal therapy. Interventional procedures were performed in the majority of patients, but the focus of this analysis was the use of antidepressants.

TCAs may remain the first-line antidepressants used for the treatment of neuropathic pain and migraine because of their proven efficacy. Some of the newer antidepressants may be used in conjunction with low dose TCAs to augment the effects of TCAs or by providing more favorable side-effect profiles. At higher doses, the newer antidepressants are better tolerated. Given that the elderly tend to be more sensitive to the adverse effects of TCAs, newer antidepressants may prove a more appropriate first-line intervention in geriatric pain management. Additional research is warranted to shed further light on the effectiveness of TCAs, SSRIs, SNRIs, and AAs in the treatment of chronic pain.

There are limitations to this chart review which are typical of the retrospective design with respect to the collection and analysis of data. Many patients were also receiving other treatments (such as epidural steroid injections, physical therapy, etc.) which may have affected their response rates. Approximately 22% of the patients did not respond to therapy. A number of patients were also receiving two or more antidepressants. The other treatments and patients taking more than one antidepressant may be confounding factors affecting the response rate. However 1,165 out of 1,506 (77%) patients were receiving only one antidepressant. Still another issue is the potential bias of the physician with respect to choice of antidepressant and evaluation of efficacy.

A further retrospective clinical trial using a control group not receiving antidepressant medications may yield insights into the best design for a prospective randomized trial. Prospective randomized trials should be done to evaluate the effects of antidepressants when used in combination with other interventions.

Conclusion

The data suggest that antidepressants are effective among patients with various chronic pain syndromes. In the context of multimodal treatment for chronic pain, TCAs which include secondary and tertiary amines, as well as SSRI/SNRIs and atypicals, all appear to show similar favorable response rates. Furthermore, our data suggest that antidepressant therapy at both low and therapeutic doses demonstrates similar response rates.

References

1. Kuhn R. The treatment of depressive states with G 22355 (imipramine hydrochloride). *Am J Psychiatry* 1958; 115:459-464.
2. Paoli F, Darcourt G, Corsa P. Note pre`liminaire sur l'action de l'imipramine dans les e`tats douloures. *Revue de Neurologie* 1960; 2:503-504.
3. Watson CP. Antidepressant drugs as adjuvant analgesics. *J Pain Symptom Manage* 1994; 6:392-405.
4. Lance JW, Curran DA. Treatment of chronic tension headache. *Lancet* 1964; 1:1235-1238.
5. Bouckoms AJ, Hackett TP. Pain patients. In: Cassem NH (ed). *Massachusetts General Hospital Handbook of General Hospital Psychiatry.* 4th ed. St. Louis: Mosby-Yearbook, 1997; p 367-413.
6. Hyman SE, Cassem NH. Pain. In: Dale DC, Federman DD (eds). *Scientific American Medicine*. New York: Scientific American, 1994; p 1-18.
7. Melzack R, Wall PD. Pain mechanisms: A new theory. *Science* 1965;150:971-9.
8. Kvinesdal B, Molin J, Froland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. *JAMA* 1984; 251:1727-1730.
9. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, Dubner R. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1987; 37:589-596.
10. Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, Dubner R. Efficacy of desipramine in painful diabetic neuropathy: A placebo-controlled trial. *Pain* 1991; 45:3-9.
11. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; 326:1250-1256.
12. Sindrup SH, Ejlersten B, Froland A, Sindrup EH, Brosen K, Gram LF. Imipramine treatment in diabetic neuropathy: Relief of subjective symptoms without changes in peripheral and autonomic nerve function. *Eur J Clin Pharmacol* 1989; 37:151-153.
13. Sindrup SH, Gram LF, Skjold T, Froland A, Beck-Nielsen H. Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990; 47:509-515.
14. Max MB, Shafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline but not lorazepam relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1988; 38:1427-1432.
15. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith I, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology* 1982; 32:671-673.
16. Watson CP, Chipman M, Reed K, Evans RJ, Birkett N. Amitriptyline versus maprotiline in postherpetic neuralgia: A randomized, double-blind, crossover trial. *Pain* 1992; 48:29-36.
17. Leijon G, Boivie J. Central post-stroke pain: A controlled trial of amitriptyline and carbamazepine. *Pain* 1989;3 6:27-36.
18. Hirsch M, Birnbaum, RJ. Pharmacology and use of antidepressants. *Up To Date* 2004; 12.2:10-19.
19. Horst WD, Preskorn SH. Mechanisms of action and clinical characteristics of three atypical antidepressants: Venlafaxine, nefazodone, bupropion. *J Affect Disord* 1998; 51:237-254.
20. Ansari A. The efficacy of newer antidepressants in the treatment of chronic pain: A review of current literature. *Harvard Rev Psychiatry* 2000; 7:257-277.
21. Saper JR, Silberstein SD, Lake AE III, Winters ME. Double-blind trial of fluoxetine: Chronic daily headache and migraine. *Headache* 1994; 34:497-502.
22. Saper JR, Silberstein SD, Lake AE III, Winters ME. Fluoxetine and migraine: Comparison of double-blind trials [Letter]. *Headache* 1995; 35:233.
23. Markeley HG, Gasser PA, Markley ME, Pratt SM. Fluoxetine in prophylaxis of headache: Clinical experience. *Cephalalgia* 1991; 11(suppl 11):164-165.
24. Sosin D. Clinical efficacy of fluoxetine vs. sertraline in a headache clinic population [Abstract]. *Headache* 1993; 33:284.
25. Richeimer SH, Bajwa ZH, Kahraman SS, Ransil BJ, Warfield C. Utilization patters of tricyclic antidepressants in multidisciplinary pain clinic: A survey. *The Clinical Journal of Pain* 1997; 13:324-329.
26. Richelson E. Antidepressants: Pharmacology and clinical use. American Psychiatric Association Task Force on Treatments of Psychiatric Disorders. Washington D.C.: *American Psychiatric Association*, 1989; 3:1773-1786.
27. Danish University Antidepressant Group. Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Dis* 1990; 18:289-299.
28. Kishore-Kumar R, Schafer SC, Lawlor BA, Murphy DL, Max MB. Single doses of the serotonin-agonists buspirone and m-chlorophenylpiperazine do not relieve neuropathic pain. *Pain* 1989; 37:223-227.
29. Goldenberg D, Mayskiy M, Mossey C, uthazer R, Schmid C. A randomized, double-blind crossover trail of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996; 39:1852-1859.
30. Goodnick PJ, Jimenez I, Kumar A. Sertraline in diabetic neuropathy: Preliminary results. *Ann Clin Psychiatry* 1997; 9:255-257.

31. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. *Headache* 1992; 32:101-104.
32. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* revised 3rd ed. Washington D.C.: American Psychiatric Association; 1987.
33. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. *Arch Intern Med* 2003; 163:2716-2724.
34. Kadiroglu AK, Sit D, Kayabasi H, Tuzcu AK, Tasdemir N, Yilmaz ME. The effect of venlafaxine HCl on painful peripheral diabetic neuropathy in patients with type 2 diabetes mellitus. *J Diabetes Complications* 2008; 22:241-245.
35. Zissis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, Georgiadis G, Karageorgiou K. A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. *Cephalalgia*.2007; 27:315-324.
36. Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. *Pharmacotherapy* 2007; 27:1571-1587.
37. Freynhagen R, Muth-Selbach U, Lipfert P, Stevens, MF, Zacharowski K, Tölle TR, von Giesen H-J. The effect of mirtazapine in patients with chronic pain and concomitant depression. *Curr Med Res Opin* 2006; 22:257-264.
38. Samborski W, Lezanska-Szpera M, Rybakowski JK. Open trial of mirtazapine in patients with fibromyalgia. *Pharmacopsychiatry* 2004; 37:168-170.
39. Bendtsen L, Jensen R. Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. *Neurology* 2004; 62:1706-1711.
40. Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. *Neurology* 2001; 57:1583-1588.
41. Semenchuk MR, Davis B. Efficacy of sustained-release bupropion in neuropathic pain: An open-label study. *Clin J Pain* 2000; 16:6-11.