A Prospective Study of Commonly Prescribed Drugs in the Management of Neuropathic Pain and its Medication Adherence Pattern.

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Citation

Shrestha R, Silwal P, Basnet N, Shakya Shrestha S, Shrestha R, Pokharel BR. A prospective study of commonly prescribed drugs in the management of neuropathic pain and its medication adherence pattern. *Kathmandu Univ Med J* 2016;53(1):47-53.

ABSTRACT

Background

Neuropathic pain is one of the common complains of patients visiting neurology and orthopedic departments in hospitals. Management of neuropathic pain is difficult and is often symptomatic rather than being curative. Adherence to medication is necessary for pain management to be effective. However, there are various factors related to patient, physician, drug regimen and other socio-economic affecting adherence.

Objective

To study commonly prescribed drugs in neuropathic pain management and the medication adherence pattern including its associated factors.

Method

Patients already diagnosed as neuropathic pain were interviewed using structured questionnaire and data entered in Microsoft Office Excel 2007. Informed consent was taken from the patients.

Result

Among the 84 patients in the study, 69% were females. Majority 53.6% of patients had low back pain as cause of neuropathic pain. Anticonvulsants were mostly prescribed (75%) followed by non-steroidal anti-inflammatory drugs (52.4%) and Methylcobalamin (47.6%). More than 50% (n=49) patients were not adherent to the prescribed medication and majority (61.2%) of them were housewives. Significant association was observed between patient's adherence to gender, occupation, polypharmacy, drug regimen, cost and availability of medicine.

Conclusion

Anticonvulsants were commonly prescribed drugs in patients with neuropathic pain. Neuropathic pain was seen more in females with low back pain. Majority of patients were non-adherent and forgetfulness was the major reason for missing dose in them.

KEY WORDS

Low back pain, medication adherence, neuropathic pain, non-adherence

INTRODUCTION

Neuropathic pain is a disease of global burden affecting more people than assumed.[1] It is associated with diversity of conditions, therefore, its epidemiology is difficult to study.[2,3] Few epidemiologic researches have shown its prevalence lower than ten percent in general population.[4-6] However, this percentage is believed to increase in future due to aging and higher survival rates from diseases associated with neuropathic pain like diabetes, cancer, HIV infection, herpes virus infection etc.[7] Neuropathic pain is a group of heterogeneous condition with chronic pain disorders that normally develops as result of lesion or disease affecting the somatosensory nervous system peripherally or centrally.[7-10] Researches made in human show that lesion of afferent pathway is important in developing neuropathic pain which ultimately results in numbness, weakness and loss of deep tendon reflexes in affected areas.[10,11]

There have been considerable advances in the understanding of neuropathic pain syndromes, however, it's management still challenges physicians.[12] In the year 2006, the European Federation of Neurological Societies came up with a solution and produced the guidelines on pharmacological treatment of neuropathic pain.[13] Since neuropathic pain is partially or completely unresponsive to primary analgesic treatments, adjuvant analgesics like antiepileptic drugs and antidepressants are required for better treatment.[14] Combination of two or more drugs are essential in achieving satisfactory pain relief but only few trials support this observation.[10]

In spite of many published guidelines and algorithms for management of neuropathic pain, it still serves as one of the major complains of patients. All these methods to manage pain become effective only when patients are adherent to them. Since adherence plays an important role in treating chronic illness, this study contributes to understanding treatment failure despite standard treatment strategies developed for management of neuropathic pain.

METHODS

A prospective study was conducted from May, 2015-February, 2016 in Dhulikhel Hospital, Kathmandu University hospital, Dhulikhel, Kavre after obtaining ethical clearance from Institutional Review Committee, Kathmandu University School of Medical Sciences (IRC approval no. 29/15). Patients above 18 years old visiting the Departments of Orthopedic and Neurology who were clinically diagnosed as neuropathic pain were included in the study. However, those patients who failed to provide consent were excluded from our study.

Patients with neuropathic pain conditions such as peripheral diabetic neuropathy, post-herpetic neuralgia, post-surgical pain, trigeminal neuralgia, carpal tunnel syndrome, peripheral neuropathy, cervical and lumbosacral radiculopathy were included in the study. Patients with nociceptive and mixed type of pain were excluded from this study. Patients meeting inclusion criteria were explained about the study and their role in it. After acquiring the consent, patients were interviewed using the structured questionnaire. The general information regarding their age, gender, occupation, literacy, cause of pain, site of pain and their prescribed drugs were obtained. Patients were followed after two weeks and further questions related to medication adherence were asked.

The data entered in Microsoft Office Excel 2007 and analyzed using Statistical package for social sciences (SPSS) version 16.0. All the quantitative data were expressed as percentage and mean ± standard deviation (SD) and the qualitative data were analyzed using chi-square test where p-value <0.05 was considered as statistically significant.

RESULTS

Among 84 patients diagnosed with neuropathic pain, majority 69.0 % (n=58) were females and 31.0 % (n=26) were males. The mean±SD age of patients was 45.6 ±15.6 years with 38.1% (n=32) patients belonging to age group 19-38 and 39-58. When categorized according to occupation, majority 42.9% (n=36) of patients were housewives. In 34.5% (n=29) of patients manual work was the major cause of their pain aggravation. In the present study, adjuvant pain management included physiotherapy in majority 48.8% (n=41) of patients followed by exercise in nine patients (Table 1).

Causes of neuropathic pain

Among the 84 patients under study, majority 53.6% (n=45) of patients had low back pain as cause for neuropathic pain. Peripheral neuropathy was the cause of neuropathic pain in 14.3% (n=12) of the patients followed by 10.7% (n=9) of patients had neuropathic pain due to radiculopathy. Among the studied population (n=84), the cause of pain was unknown in six patients (Fig. 1). In rest of the cases (14.3%), the main causes of pain were carpel tunnel syndrome, peripheral diabetic neuropathy, post-herpetic neuralgia, post-surgical neuralgia and trigeminal neuralgia (Fig. 1).

Types of prescribed drugs

Out of 84 patients, most of them were prescribed with anticonvulsants (75%) followed by Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (52.4%) and Methylcobalamin (47.6%). Likewise, Amitriptyline was prescribed in 11.9% of patients and muscle relaxant was prescribed in 5.9% of patients. Opioids were prescribed in 2.4% of patients (Fig. 2).

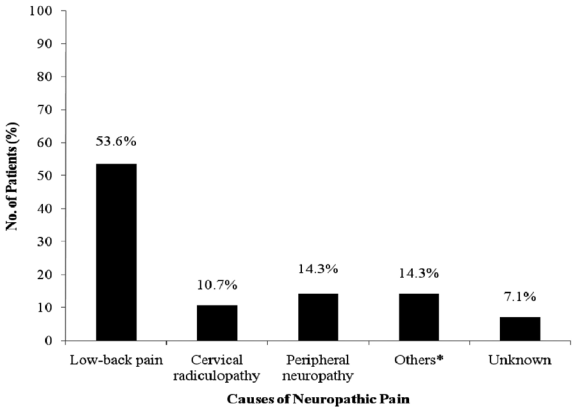
Adherence pattern

Out of 84 patients, about 42.0% (n=35) were adherent to

Table 1. Demographic factors and history of 84 patients with neuropathic pain.

	Total (n)	%
Gender		
Male	26	31.0
Female	58	69.0
Age (years)		
19-38	32	38.1
39-58	32	38.1
59-78	20	23.8
Occupation		
Service	10	11.9
Bussiness	10	11.9
Housewife	36	42.9
Farmer	15	17.9
Students/Unemployed	13	15.5
Pain aggravation		
Walking	15	17.9
Standing	6	7.1
Manual work	29	34.5
Sitting	5	6.0
Walking and manual work	9	10.7
Walking and standing	2	2.4
Walking, standing and manual work	11	13.1
Rest	7	8.3
Adjuvant Pain Management		
Physiotherapy	41	48.8
Exercise	9	10.7
Lumber belt application	2	2.4
Physiotherapy and immobilizer	1	1.2
Rest	2	2.4
None	29	34.5

drug treatment among whom 54.3% were female (Fig. 3, Table 2). Non-adherence was higher (40.8%) in patients with age group 30-58 years and 61.2% of them non-adherent patients were housewives. (Table 2).



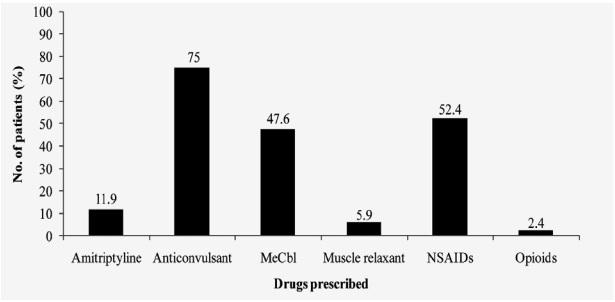
* Carpel tunnel syndrome, peripheral diabetic neuropathy, post-herpetic neuralgia, post-surgical neuralgia, trigeminal neuralgia.

Figure 1. Bar chart showing causes of neuropathic pain (n=84)

Table 2. Demographic characteristics and adherence pattern among 84 patients.

	n (%)	Adherent* (n=35; %)	Non-adherent** (n=49; %)	p-value
Gender				
Male	26 (31)	16 (45.7)	10 (20.4)	0.01
Female	58 (69)	19 (54.3)	39 (79.6)	
Age (years)				
19-38	32 (38.1)	13 (37.1)	19 (38.8)	
39-58	32 (38.1)	12 (34.3)	20 (40.8)	0.67
59-78	20 (28.6)	10 (28.6)	10 (20.4)	
Occupation				
Service	10 (12.0)	8 (22.9)	2 (4.1)	
Business	10 (12.0)	7 (20.0)	3 (6.1)	
Housewife	36 (42.8)	6 (17.1)	30 (61.2)	0.00
Farmer	15 (17.8)	6 (17.1)	9 (18.4)	
Students/Un-employed	13 (15.4)	8 (22.9)	5 (10.2)	

*Patients who had never missed or discontinued the medication
**Patients who had either missed or discontinued the medication



MeCbl Methylcobalamin

NSAIDs Nonsteroidal Anti-inflammatory drugs

Note: Sum of percentage exceeds hundred as more than one drug has been prescribed to the same patient in some cases.

Figure 2. Bar chart showing commonly prescribed drugs in management of neuropathic pain.

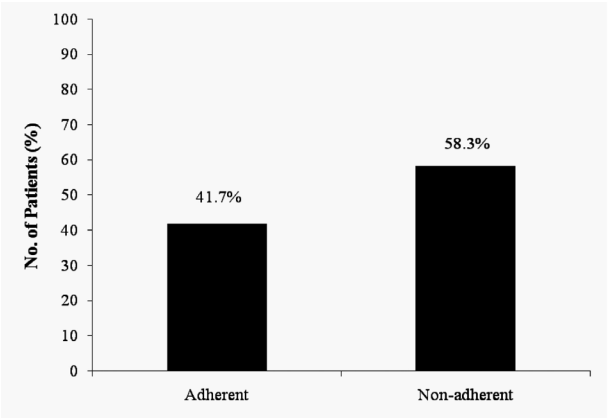


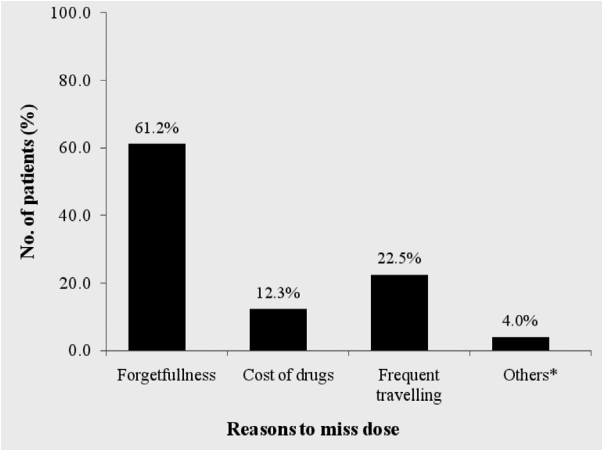
Figure 3. Bar chart showing adherence pattern in patients with neuropathic pain. (n=84)

In the present study, 58.3% (n=49) of patients were non-adherent to the treatment and forgetfulness was the main reason for missing dose in 61.2% (n=30) of patients and the association between adherence and reasons for dose miss was found to be highly significant (p =0.000; Figure 4). In similar manner, our study has shown a significant association with polypharmacy (p = 0.001), dosage regimen (p = 0.032), cost of medication (p = 0.009) and availability of medicine (p = 0.002). However, the study did not show association between adherence and patient's perception of disease, physician's attention, patient's satisfaction and complication of life due to pain management (Table 3).

Table 3. Association between various factors affecting adherence in patients with neuropathic pain

	n (%)	Adherent* (n=35; %)	Non-adherent** (n=49; %)	p-value
Treatment characteristics				
Medication				
One drug	25 (29.8)	18 (51.4)	7 (14.3)	0.001
Two drugs	38 (45.2)	11 (31.4)	27 (55.1)	
Multiple drugs	21 (25.0)	6 (17.2)	15 (30.6)	
Dosage				
Once	20 (23.8)	13 (37.1)	7 (14.3)	0.032
Twice or more	64 (76.2)	22 (62.9)	42 (85.7)	
Patients factors				
Disease perception				
Curable	39 (46.4)	16 (45.7)	23 (46.9)	0.723
Non-curable	7 (8.3)	2 (5.7)	5 (10.2)	
Managed symptomatically	38 (45.2)	17 (48.6)	21 (42.9)	
Patient's belief				
Yes	74 (88.1)	31 (88.6)	43 (87.8)	0.909
No	10 (11.9)	4 (11.4)	6 (12.2)	
Complicated life				
Yes	68 (81.0)	27 (77.1)	41 (83.7)	0.452
No	16 (19.0)	8 (22.9)	8 (16.3)	
Clinician factor				
Physician's attention				
Yes	75 (89.3)	32 (91.4)	43 (87.8)	0.592
No	9 (10.7)	3 (8.6)	6 (12.2)	
Patient's satisfaction				
Yes	74 (88.1)	30 (85.7)	44 (89.8)	0.617
No	10 (11.9)	5 (14.3)	5 (10.2)	
Socio-economic factors				
Cost				
Yes	78 (92.9)	35 (100.0)	43 (87.8)	0.009
No	6 (7.1)	0 (0.0)	6 (12.2)	
Availability of medicine				
Yes	76 (90.5)	35 (100.0)	41 (83.7)	0.002
No	8 (9.5)	0 (0.0)	8 (16.3)	

*Patients who had never missed or discontinued the medication
**Patients who had either missed or discontinued the medication



*Availability of medicine, carelessness, physician attention

Figure 4. Bar chart showing reasons for missing dose in patients with neuropathic pain.

DISCUSSION

In our study, majority of patients having neuropathic pain were females. Different population based studies around the world also showed that neuropathic pain was more common in female than in male.[15-18] The reason for more females experiencing neuropathic pain may be due to their greater physical activities in workplaces.[19] However, because of higher participation in the labor force and in occupation involving lifting of heavy loads or whole body vibrations, few studies suggested neuropathic pain more common in male.[20] Low back pain was the main cause of neuropathic pain in our study which was the major reason for pain in females. Even though reliable prevalence rates are not available currently, chronic low back pain has been reported as one of the most common causes of neuropathic pain.[21] The long working hours without rest, poor posture, and improper technique of lifting or carrying loads have caused low back pain in females. Even from biological point of view, women are more prone to low back pain due to risk factors like pregnancy, contraceptive use and use of estrogen during menopause.[22] Most of these females were above nineteen years and from rural areas where early marriage and multiple pregnancies were supported by social values thus they had conceived at least once. Studies have shown that pregnancy lead to compression of nerve roots in lumbar spine that ultimately cause pain in lower back.[23,24] Therefore, pregnancy could serve one of the reasons for pain in females. However, there are no such literatures to support this. In contrast to our finding, a study in Indonesia reported that more males with low back pain had neuropathic pain.[12] The high proportion of male patients in that study was because they sought medical assistance more than females. Among the females with neuropathic pain in our study, most of them were housewives. A previous study has also reported that housewives in rural India work for hours without a regulated routine starting work early in the morning and

continuing till midnight which is also comparable with the working hour of housewives in Nepal.[22] The work a typical rural housewife has to do involves maintaining their home, collecting water, washing clothes, sweeping floor, lifting loads of water or hay, taking care of livestock and working in field that require repeated bending and twisting of spine. The increased work load due to combination of farming and household chores have contributed to the increased risk of neuropathic pain in housewives.[22] In the present study occupations of other patients were farming, business, and service and very few were students and elderly patients which indicated that occupation requiring long working hours developed neuropathic symptoms in people. A study has shown that patients with neuropathic pain could not go to work or had to even change their job due to pain.[15] However, such situations were not seen in the patients of our study but they did have difficulty working due to pain.

In the present study the main approach in managing the pain was pharmacotherapy. Pharmacotherapy is believed to be the mainstay of treatment which is the ultimate choice of physician.[12] The commonly prescribed drugs were gabapentin and pregabalin. Non-steroidal anti-inflammatory drugs were the primary drugs being prescribed which was followed by methylcobalamin and antidepressants. Opioids were rarely prescribed in this study. This prescription pattern was similar to that of other studies.[12,13,15,25] Anticonvulsants and antidepressants (whose primary indication is not analgesia) that were commonly prescribed in many studies are the first line drugs for management of neuropathic pain.[13,26,27] Despite Nonsteroidal Anti-inflammatory Drugs (NSAIDs) being irrational drugs usually not effective in treating neuropathic pain, they were prescribed more than opioids and other second line drugs to treat neuropathic pain.[1] In the present study majority of patients were prescribed with more than one drug for pain management. Different drugs act synergistically on multiple sites to relieve pain thus drug combination was commonly practiced to get the best result.[28] However, the combination of two first line drugs were strictly avoided due to risk of cumulative adverse effects and were used only when appropriate.[13] When interviewed with the patients, the ones taking more than one drug reported better management of pain. Patients with ongoing and uncontrolled pain had poor quality of life.[29] Their pain was aggravated by various day to day activities. Many patients in the study reported that manual work worsened their pain while walking, standing and even sitting worsened pain in others. Patients could neither ignore nor prevent these causes thus were compelled to live a painful life. The positive impact on everyday functioning and well being of patients reflected the successful management of neuropathic pain thus; patients were advised adjuvant methods for pain management.[15] In our study, physiotherapy and exercise were advised to most of the patients with suggestion of lumbar belt to low back pain and wrist immobilizer for patients having wrist pain. In previous study, the adjuvant pain managements such as cognitive-behavioral therapy and physical therapy were also recommended.[30] All patients were advised to rest and take their medicine regularly to reduce their pain. Our study revealed that such approach has significantly reduced distress and disability.

Though, neuropathic pain is a chronic condition, the present study has shown the poor adherence to the prescribed medication. In agreement with this finding, a previous study has shown the higher rate of adherence among patients with acute conditions than those with chronic condition.[31] Our study has indicated that the poor adherence is due to patients missing dose during their treatment and forgetfulness being the major reason for missing dose. This finding was consistent to the findings of other studies on adherence to medication in chronic diseases.[32-34] The problem with adherence in patients with neuropathic pain was discontinuation of medication once they were symptom free which is also supported by other studies on the management of chronic diseases.[35,36] Moreover, medication adherence can be influenced by gender, personality and cultural factors and females are found to be more adhere to the prescribed medication than men,[31] which was also true in this study. However, current literatures lack evidence on the relation of the pain management in neuropathic pain with medication adherence. The current study shows that the higher number of females was non-adherent to the prescribed therapy than male which is contrast to the previous study.[31] The possible reason may be due to the higher enrollment of female patients in our study exceeding the number of males in both cases. However, our study shows the strong association between adherence and gender of patients. Housewives in this study were least adherent followed by farmers who were careless and missed their dose leading to non-adherence. Adherence was seen high in patients who had service as their occupation. These patients had routine to do everything thus rarely missed their dose. However, there are no published literatures to back up our findings yet, association between adherence and occupation of patients was found to be significant in this study.

The patients who were provided with the information about their disease and drug by their physician had better adherence than those who were ignored by their physician. Patient's relationship with the physician plays an important role in improving adherence.[31] Studies showed that higher patient- physician discordance led to decreased patient satisfaction which directly affected the adherence in them.[37-39] Patient's perception about their disease is also considered to be important and patients who believed their pain could not be cured were highly non-adherent to medication.[40] Majority of patients believed their pain could be managed symptomatically only. This of course was true because most of the treatment strategies were focused on providing symptomatic relief to patients rather than curing their disease.[41] Adherence can improve if patients believed that taking medicine regularly could treat their pain.[31] In our study most of the patients were prescribed

with polypharmacy and very few were prescribed with monotherapy. The patients who had to take only one drug per day were more adherent to medication than those taking more drugs. This might be because taking more than one drug a day is troublesome and patients tend to forget taking one of the prescribed drugs. With more drugs comes more adverse effects and patients stop taking medicine due to those effects too. Most of the patients in our study were from rural area with poor economic condition. Pain had affected their quality of life and the cost of medicine added economic burden to them. Since affordability of drugs is considered to be one of the barriers to achieving adequate adherence, their association was found to be significant in this study.[42,43]

Though, the present study is first of its kind to address the issue in neuropathic pain, there are some limitations. This study has been conducted as a mono-centered study and specific conclusion can't be drawn without conducting such study in multi-center study sites. Nevertheless, the present study has tried to shed light on various factors related to neuropathic pain and could be one of the potential areas for research especially in Nepal where it seems to be present in higher population than assumed.

CONCLUSION

Most of the patients in the study were females having low back pain as the major cause of neuropathic pain. The management of neuropathic pain was challenging and patients did not achieve satisfying response even when treated with best strategy available. Anticonvulsants were commonly prescribed and combined therapy approach has been a better option in the effective management of neuropathic pain. However, non-adherence to medication was the major problem in managing neuropathic pain which greatly impaired the quality of life of patient. The patients prescribed with monotherapy were more adherent to treatment than those prescribed with polypharmacy. Among the non-adherent patients forgetfulness was the main reason for missing dose. There were factors like patient's perception about disease, occurrence of adverse effects and physician's role that affected adherence. The factors like occupation of patients, cost and availability of drugs had significant association with adherence.

REFERENCES

1. Tan E, Akinci A, Ayvaz G, Erbas T, Ertas M, Guc O, et al. Irrational drug use in neuropathic pain treatment: a two year data analysis. *Int J Med Biomed Res*. 2013 2(3): 202-6.
2. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain* 2002;18: 350-4.
3. Verma S, Estanislao L, Simpson D. HIV-associated neuropathic pain: epidemiology, pathophysiology and management. *CNS Drugs* 2005; 19: 325-34.
4. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237-51.
5. Taylor RS. Epidemiology of refractory neuropathic pain. *Pain Pract* 2006;6: 22-6.
6. Torrance N, Smith BH, Bennett MI et al. The epidemiology of chronic pain of predominantly neuropathic origin: results from a general population survey. *J Pain* 2006; 7: 281-9.
7. Dworkin R. An overview of neuropathic pain: syndromes, symptoms, signs, and several mechanisms. *Clin J Pain* 2002:18:343–9.
8. Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain* 2000; 16: S12–20.
9. Baron R. Mechanisms of Disease: neuropathic pain-a clinical perspective. *Nature Clinical Practice Neurology* 2006; 2: 95-106.
10. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9:807–19.
11. Gilron I, Flatters SJL. Gabapentin and pregabalin for the treatment of neuropathic pain: A review of laboratory and clinical evidence. *Pain Res Manage* 2006 11(SupplA): 16A-29A.
12. Purwata TE, Sadeli HA, Anwar Y et al. Characteristics of Neuropathic Pain in Indonesia: A hospital based national clinical survey. *Neurology Asia* 2015;20(40): 389-394.
13. Attal N, Cruccu G, Haanpa M et al. EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13: 1153–69.
14. Chong MS, Bajwa ZH. Diagnosis and Treatment of Neuropathic Pain. *Journal of Pain and Symptom Management* 2003;25:5S.
15. McDermott AM, Toelle TR, David J. Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: results from a cross-sectional survey. *European Journal of Pain* 2006;10:127–35.
16. deMos M, deBruijn AG, Huygen FJ et al. The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007;129:12–20.
17. Hall GC, Carroll D, Parry D, McQuay HJ. Epidemiology and treatment of neuropathic pain: The UK primary care perspective. *Pain* 2006;122:156–62.
18. Sandroni P, Benrud-Larson LM, McClelland RL et al. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003;103: 199-207.
19. Koley S, Singh G, Sandhu R. Severity of disability in elderly patients with low back pain in Amritsar, Punjab. *Anthropol* 2008;10(4):265-8.

20. Punnett L, Pruss-Utun AP, Nelson DI, Fingerhut MA, Leigh J, Tak SW et al. Estimating the global burden of low back pain attributable to combined occupational exposures. *Am J Ind Med* 2005;48(6):459-69.
21. Sissi W, Arnaout A, Chaarani MW et al. Prevalence of neuropathic pain among patients with chronic low back pain in the Arabian Gulf Region assessed using the leeds assessment of neuropathic symptoms and signs pain scale. *J Int Med Res* 2010;38(6): 2135-45.
22. Gupta G, Nandini N. Prevalence of low back pain in non working rural housewives of Kanpur, India. *IJOMEH* 2015;28(2):313-20.
23. To WW, Wong MW. Factors associated with back pain symptoms in pregnancy and persistence of pain two years after pregnancy. *Acta Obstet Gynecol Scand* 2003;82(12):1086-91.
24. Wijnhoven HA, de vet HC, Smit HA, Picavet HS. Hormonal and reproductive factors are associated with chronic low back pain and upper extremity pain in women- The MOR-GEN study. *Spine* 2006;31(13):1496-502.
25. Wiklund I, Holmstrom S, Stoker M et al. Are treatment benefits in neuropathic pain reflected in the self assessment of treatment questionnaire? *Health and Quality of Life Outcomes 2013;*11:8.
26. Moulin DE, Clark AJ, Glivon I, Ware MA, Watson CP, Sessle BJ et al. Pharmacological management of chronic neuropathic pain – consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007.12:13-21.
27. O'Connor AB. Neuropathic Pain Quality-of-Life Impact, Costs and Cost Effectiveness of Therapy. *Pharmacoeconomics* 2009;27: 95-112.
28. Kalso E, Aldington DJ. Drugs for neuropathic pain. BMJ 2013;347: f7339.
29. Katz N. The Impact of Pain Management on Quality of Life. *Journal of Pain and Symptom Management* 2002;24(1).
30. Chetty S, Baalbergen E, Bhigjee AI, Kamerman P, Ouma J, Raath R, Raff, M, Salduker S. Clinical practice guidelines for management of neuropathic pain: expert panel recommendation for South Africa. *S Afr Med J* 2012;102(5): 312-25.
31. immy B, Jose J. Patient Medication Adherence Measures in Daily Practice. *Oman Medical Journal* 2011;26(3): 155-9.
32. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient adherence: A meta-analysis. *Med Care.* 2007;45: 521-8.
33. Shrestha SS, Shakya R, Karmacharya BM, Thapa P. Medication Adherence to Oral Hypoglycemic Agents Among Type II Diabetic Patients and Their Clinical Outcomes with Special Reference to Fasting Blood Glucose and Glycosylated Hemoglobin Levels. *Kathmandu Univ Med J* 2013;43(3): 226-32.
34. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999;47: 555–67.
35. Rapoff MA, Bartlett SJ. Adherence in children and adults. In: Bartlett SJ, ed. Clinical care in the rheumatic diseases. Atlanta: *American College of Rheumatology* 2006;279–84.
36. Pauwels RA, Buist AS, Calverley PM et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J RespirCrit Care Med* 2001;163:1256-76.
37. Haynes RB, taylor DW, Snow JC, Sackett DL. Annotated and indexed bibliography on compliance with therapeutic and preventive regimens, Baltimore: John Hopkins University Press, 1979;337-474.
38. Francis V, Korsch BM, Morris MJ. Gaps in doctor-patient communication Patients' response to medical advice. *N Engl J Med* 1969;280 (10): 535-540
39. Sherbourne CD, Hays RD, Ordway L, DiMatteo MR, Kravitz RL. Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. *J Behav Med* 1992;15(5): 447-68.
40. Restrepo RD, Alvarez MT, Wittnebel LD et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis.* 2008;3:371-84.
41. Backonja M, Woolf CJ. Future directions in neuropathic pain therapy: closing the translational loop. *Oncologist* 2010;15:24-29.
42. Cramer JA, Bradley-Kennedy C. Scalera A. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease. *Canadian Respiratory Journal*. 2007;14(1):25–29. ISSN 1198-2241.
43. Jung E, Pickard AS, Salmon JW et al. Medication adherence and persistence in the last year of life in COPD patients. *Respiratory Medicine.* 2009;103(4): 525–534. ISSN 0954–6111.