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Clinical note

Chronobiological characteristics of painful diabetic neuropathy and postherpetic neuralgia: Diurnal pain variation and effects of analgesic therapy

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Abstract

Clinical impressions suggest that neuropathic pain is often worse at night and significantly impairs sleep. However, the temporal pattern of neuropathic pain during waking hours has not been clearly characterized. Using clinical trial data, we have evaluated the diurnal variation of pain intensity before and during analgesic treatment in patients with diabetic neuropathy (DN) and postherpetic neuralgia (PHN). Pain intensity (0–10) measures throughout the day from a placebo-controlled trial of around-the-clock administration of gabapentin, morphine and a gabapentin–morphine combination in neuropathic pain patients were examined. Baseline data in untreated patients revealed no effect of day of week but a significant effect of time of day in both DN ($P<0.001$) and PHN ($P<0.001$) such that pain intensity progressively increases throughout the day. This temporal pattern is essentially preserved during treatment with gabapentin, morphine and their combination. Neuropathic pain intensity progressively increases throughout the day and this temporal profile appears to be unaffected by treatment with gabapentin and/or morphine. Advancing our understanding of the chronobiology of neuropathic pain may shed new light on various neurohormonal and neurophysiologic influences and lead to the identification of novel therapeutic targets. Furthermore, recognizing diurnal pain patterns may guide treatment strategies such as the targeted timing of analgesic therapies.

Keywords: Neuropathic pain; Chronobiology; Diurnal variation; Circadian rhythm; Chronotherapeutics; Analgesic clinical trials

1. Introduction

Pain due to several pathological conditions exhibits temporal variations in intensity throughout the circadian cycle. This diurnal variation is multifactorial and may be affected by endogenous fluctuations in neuroendocrine or other factors as well as external influences which affect touch-evoked pain and levels of physical activity. Clinical impressions suggest that neuropathic pain is often worse at night (Belgrade, 1999) and evidence indicates that it also significantly impairs sleep (Schmader, 2002). However, the temporal pattern of neuropathic pain during waking hours has not been clearly characterized.

Circadian patterns of pain experience have been studied in various clinical disease states. For example, pain in rheumatoid arthritis occurs mostly at the beginning of the day (Kowanko et al., 1982) whereas pain due to osteoarthritis occurs mostly at the end of the day (Bellamy et al., 1990). Rigas et al. (1990) studied the circadian rhythm of biliary colic in patients undergoing cholecystectomy for symptomatic biliary tract stones. In comparison with a control group of patients with renal colic (which showed no correlation to time of day), biliary colic showed a circadian rhythm, with significantly increased pain between 23:00 and 03:00 h. In another visceral pain condition, Aya et al. (2004)

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observed that labouring mothers reported higher pain at evening and night as compared to morning and afternoon. Solomon et al. (1992) reported that the incidence of migraine headaches showed a circadian pattern with more attacks occurring in the morning hours (08:00–12:00) compared to midnight. Also, the circadian pattern of dental pain sensitivity was studied by Pollmann and Harris (1978) whose results indicated that dental pain thresholds were maximal in the early afternoon and minimal in the early morning.

Unlike these other conditions, very few details have been reported on the diurnal variation of chronic neuropathic pain. Describing the chronobiology of neuropathic pain may serve to advance our understanding of pathophysiology, enhance diagnostic accuracy, and guide the improvement of pain management strategies. Using data from a recent clinical trial, we have evaluated the diurnal variation of pain intensity before and during analgesic treatment in patients with two variants of neuropathic pain, diabetic neuropathy (DN) and postherpetic neuralgia (PHN).

2. Materials and methods

This study was conducted using pain intensity data from a recently completed placebo-controlled crossover trial of patients with DN and PHN (Gilron et al., 2005).

2.1. Neuropathic pain clinical trial design

The clinical trial from which the data were gathered was approved by the Queen's University Research Ethics Board and involved patients with DN and PHN who experienced daily moderate pain for at least 3 months prior to study entry, and who had no evidence of any psychiatric or substance abuse disorder. The trial was a double-dummy, four period crossover comparison (5 weeks per treatment period) of sustained-release morphine (taken twice daily as per a BID [bis in die] schedule), gabapentin (taken three times daily as per a TID [ter in die] schedule), a morphine–gabapentin combination, and active placebo (lorazepam) whereby patients were randomized, in a double-blind fashion, to one of four possible sequences of these four treatments according to a balanced Latin square design. Within the first 3 weeks of each treatment period, study drug dose was titrated to maximal tolerated dose (MTD) and then continued at MTD over the fourth week followed by a taper and washout period over the fifth and final week of each treatment period. Prior to starting the study (7 day baseline) and throughout the entire trial, patients rated their present pain intensity on a 0–10 numerical rating scale thrice daily at 8:00, 16:00 and 20:00. At the outset of the study, patients received extensive study teaching by the research coordinator explaining all details of the study protocol including timing of data entry ($+/-30$ min from each specified timepoint) in the daily pain diary. On each biweekly telephone contact, the research coordinator repeatedly encouraged patient compliance with study drug administration and entry of pain scores. If any data entries were missed by the patient, these were to be left empty and treated as missing data. Each patient's pain data were included in the analyses if more than 50% of the data were not missing.

2.2. Statistical analysis

Descriptive statistics (mean, SD) were used for demographics and baseline patient characteristics. Temporal pain patterns in untreated patients at baseline and in clinical trial patients during each treatment (placebo, gabapentin, morphine, and combination) were evaluated using a two-way (day of week by time of day) repeated measures analysis of variance (ANOVA). Using time point specific (i.e. 8:00, 16:00 and 20:00) pain scores averaged across the entire week of MTD for each treatment, effects of analgesic treatment on diurnal variation were evaluated using a two-way (time of day by treatment) repeated measures analysis of variance (ANOVA). Significant main effects from any of the above ANOVAs were explored further using Fisher's protected least significant difference (PLSD) test.

3. Results

3.1. Chronobiological characteristics of untreated neuropathic pain

Table 1 describes the demographics and characteristics of 85 patients (55-diabetic neuropathy; 30-postherpetic neuralgia) evaluated for eligibility for the related clinical trial (Gilron et al., 2005). No patients were excluded from this study because of missing data. Circadian (time of day)

Table 1
Demographics and characteristics of patients evaluated for trial eligibility

	Diabetic neuropathy ($n=55$)	Postherpetic neuralgia ($n=30$)
Age [year; median (range)]	61 (32–75)	73 (47–83)
Sex [*n* (%)]		
Male	29 (53%)	17 (57%)
Female	26 (47%)	13 (43%)
Race* [*n* (%)]		
Caucasian	53 (96%)	30 (100%)
Other	2 (4%)	
Duration of pain or time since zoster onset [year; mean (SD)]	4.8 (3.5)	4.1 (4.6)
Duration of diabetes [year; mean (SD)]	9.9 (7.7)	
Glycosylated hemoglobin [%; mean (SD)]	0.08 (0.02)	
Affected site: *n* (%)		
Trigeminal	5 (17%)	
Thoracic	19 (63%)	
Lumbar	3 (10%)	
Sacral	3 (10%)	
Current medications: *n* (%)		
None	34 (62%)	26 (87%)
TCAs	6 (11%)	2 (7%)
Anticonvulsants	6 (11%)	0 (0%)
'prn' opioids (codeine/oxycodone)	10 (18%)	2 (7%)

SD, standard deviation; NRS, numerical rating scale; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

and circaseptan (time of week) pain intensity patterns were analyzed only for patients receiving no analgesic treatment (34/55-diabetic neuropathy; 26/30-postherpetic neuralgia) based on a 7 day baseline pain diary. Fig. 1 describes the circadian/circaseptan pattern of pain in untreated painful diabetic neuropathy. Two-way (day of week by time of day) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$), but no significant effect of day of week ($P=0.64$), and no significant interaction ($P=0.96$). Fisher's PLSD test demonstrated significant differences between all three daily time points ($P<0.0001$) such that pain progressively increases throughout the day. Of the 34 untreated diabetic neuropathy patients, 25 had pain steadily increase across the three timepoints, five had similar scores across the three timepoints, three had lower pain at the 16:00 timepoint and one had pain steadily decrease across the three timepoints. Fig. 2 describes the circadian/circaseptan pattern of pain in untreated postherpetic neuralgia. Two-way (day of week by time of day) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$), but no significant effect of day of week ($P=0.91$), and no significant interaction ($P=0.96$). Fisher's PLSD test demonstrated significant differences between 08:00–16:00 and 08:00–20:00 ($P<0.0001$) and between 16:00 and 20:00 ($P=0.0006$) such that pain progressively increases throughout the day. Of the 26 untreated postherpetic neuralgia patients, 17 had pain steadily increase across the three timepoints, five had similar scores across the three timepoints, two had lower pain at the 16:00 timepoint and two had pain steadily decrease across the three timepoints.

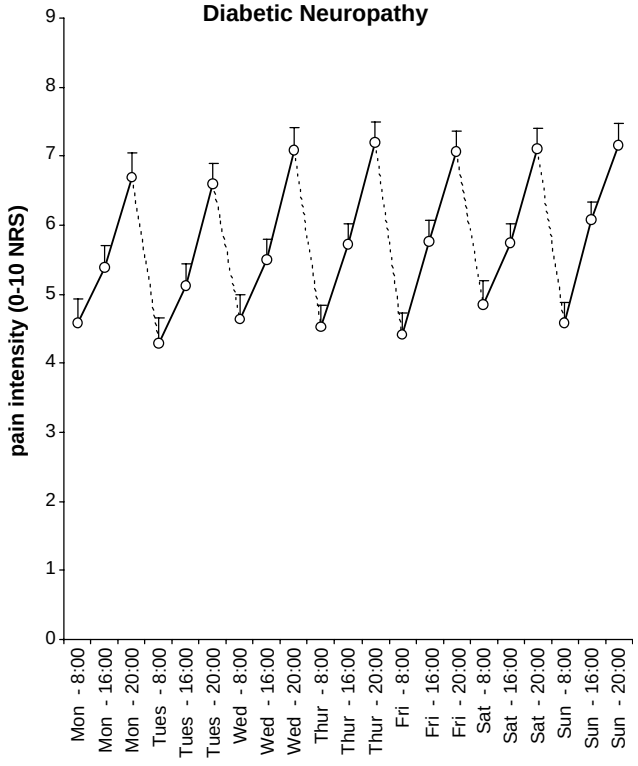

Fig. 1. Circadian/circaseptan pattern of pain in untreated painful diabetic neuropathy. Two-way (day of week by time of day) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$), but no significant effect of day of week ($P=0.64$), and no significant interaction ($P=0.96$). Fisher's PLSD test demonstrated significant differences between all three daily time points ($P<0.0001$) such that pain progressively increases throughout the day. Data represent mean pain scores of patients with untreated diabetic neuropathy. Error bars represent standard error of the mean.

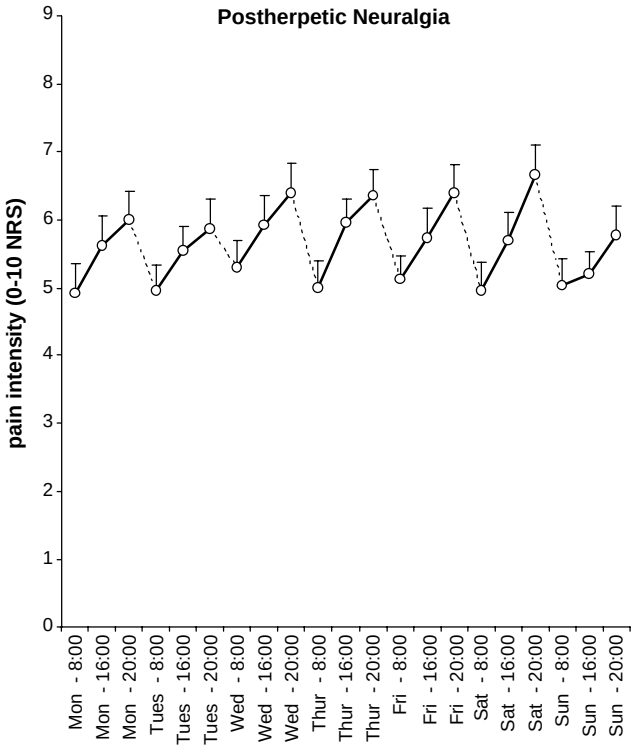

Fig. 2. Circadian/circaseptan pattern of pain in untreated postherpetic neuralgia. Two-way (day of week by time of day) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$) but no significant effect of day of week ($P=0.91$) and no significant interaction ($P=0.96$). Fisher's PLSD test demonstrated significant differences between 08:00–16:00 and 08:00–20:00 ($P<0.0001$) and between 16:00 and 20:00 ($P=0.0006$) such that pain progressively increases throughout the day. Data represent mean pain scores of patients with untreated postherpetic neuralgia. Error bars represent standard error of the mean.

3.2. Effects of morphine and/or gabapentin on circadian/circaseptan variations in neuropathic pain

In the absence of analgesic treatment, both diabetic neuropathy and postherpetic neuralgia exhibited diurnal variations (above) and subgroup analyses of data from our recent clinical trial (Gilron et al., 2005) suggest that treatment effects on pain intensity are similar for both diabetic neuropathy and postherpetic neuralgia. Therefore, circadian (time of day) and circaseptan (time of week) patterns were described with a pooled analysis of diabetic neuropathy and postherpetic neuralgia patients based on

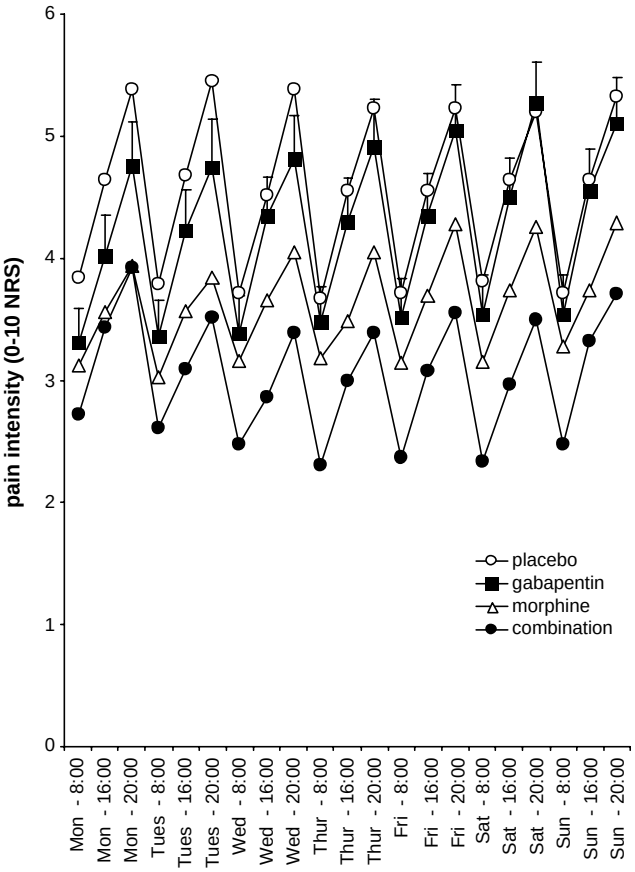

Fig. 3. Circadian/circaseptan pattern of pain painful diabetic neuropathy and postherpetic neuralgia during treatment with gabapentin and/or morphine. Two-way (time of day by treatment) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$) and a significant effect of treatment ($P=0.004$), but no significant interaction ($P=0.38$). Fisher's PLSD test demonstrated significant differences between all time points ($P<0.0001$) and upon comparisons between placebo–morphine ($P=0.03$), placebo-combination ($P=0.0009$), and gabapentin-combination ($P=0.008$). Two-way (day of week by time of day) repeated measures ANOVA of pain intensity scores for each treatment-placebo, gabapentin, morphine, gabapentin–morphine combination-revealed no significant effect of day of week ($P=0.99$, 0.97, 0.99 and 0.96, respectively) and no significant interaction with time of day ($P=0.99$, 0.99, 0.96 and 0.98, respectively). Data represent mean pain scores of patients with diabetic neuropathy and postherpetic neuralgia during treatment. Error bars represent standard error of the mean.

7 days of pain intensity scores at maximal tolerated dose of the respective drug treatment completed (i.e. active placebo [lorazepam], gabapentin, morphine, and/or gabapentin–morphine combination). Fig. 3 describes the circadian/circaseptan pattern of neuropathic pain during these treatments. Two-way (time of day by treatment) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$) and a significant effect of treatment ($P=0.004$), but no significant interaction ($P=0.38$). Fisher's PLSD test demonstrated significant differences between all time points ($P<0.0001$) and upon comparisons between placebo–morphine ($P=0.03$), placebo-combination ($P=0.0009$), and gabapentin-combination ($P=0.008$). Two-way (day of week by time of day) repeated measures ANOVA of pain intensity scores for each treatment-placebo, gabapentin, morphine, gabapentin–morphine combination-revealed no significant effect of day of week ($P=0.99$, 0.97, 0.99 and 0.96, respectively) and no significant interaction with time of day ($P=0.99$, 0.99, 0.96 and 0.98, respectively). According to subgroup analysis of diabetic neuropathy patients, two-way (time of day by treatment) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$) and a significant effect of treatment ($P=0.003$), but no significant interaction ($P=0.57$). According to subgroup analysis of postherpetic neuralgia patients, two-way (time of day by treatment) repeated measures ANOVA of pain intensity scores revealed a significant effect of time of day ($P<0.0001$) and a significant effect of treatment ($P=0.02$), but no significant interaction ($P=0.81$).

4. Discussion

The results of this study suggest that pain intensity in both diabetic neuropathy and postherpetic neuralgia progressively increases throughout the day. Of note, pain intensity did not appear to vary significantly throughout the course of a 7 day cycle. It should also be noted that pain ratings were not made between 20:00 on 1 day and 08:00 on the following day. Therefore, the profile of pain intensity over this time interval remains unknown. Our observation of a progressive increase in pain intensity throughout the day is likely valid since it was A) made in patients receiving no analgesic treatments, B) statistically robust, and C) reproducible across several days and also across two different variants of neuropathic pain.

In a survey of patients ($n=105$) with painful diabetic neuropathy, Galer et al. (2000) reported that 53% of patients experience pain on a constant, daily basis and 30% experience pain daily, but intermittently so throughout the day. Furthermore, 52% of patients reported pain worse at night versus 17% worse in the daytime versus 28% equally intense day and night. Also of interest, 61% of patients reported that pain was worse when tired, and 46% reported pain worse when stressed (Galer et al., 2000). Other opportunities to measure diurnal pain variation include analgesic clinical trials where pain intensity is rated carefully throughout the trial most often on a daily basis (Turk et al., 2003). However, most neuropathic pain trials either rate pain only once daily (as a single present pain rating or a retrospective/cumulative 24 h pain rating) or report daily or weekly averages for the purposes of treatment effect analysis. Time point-specific analysis of pain intensity scores from our recently completed clinical trial (Gilron et al., 2005) has allowed for the description of diurnal neuropathic pain variation.

Attempts to explain the progressive increase in pain intensity throughout the day in neuropathic conditions may

advance understanding of pathophysiology and guide the development of future treatments. Modulation of nociception and pain experience by factors which vary throughout the circadian cycle include endogenous fluctuations in neurotransmitters and endocrine hormones, as well as extrinsic determinants which affect touch-evoked pain and levels of physical activity. Various preclinical studies in laboratory animals have demonstrated diurnal variations in pain sensitivity precipitating numerous hypotheses to account for this phenomenon. For example, endorphins, endogenous analgesic peptides that activate mu opioid receptors, have demonstrated circadian fluctuations (Hamra et al., 1993; Kerdeldhue et al., 1983) and, also, hyperalgesia induced by naloxone, a nonselective opioid receptor antagonist, was shown to follow a diurnal rhythm (Frederickson et al., 1977). Preclinical data have suggested a pro-nociceptive role for the pineal hormone, melatonin (Perissin et al., 2004), which exhibits a circadian rhythm such that secretion starts to increase at 21:00 with peak levels occurring at 03:00 (Kennaway and Voultios, 1998), although John et al. (1994) reported analgesic effects of melatonin and its ability to restore pain threshold variations in pinealectomized rats. Further studies are necessary to elucidate the ability of melatonin to modulate nociception, however, if melatonin is pro-nociceptive in humans, increased melatonin levels in the evening might explain higher pain intensity at this time of day. Finally, it also was suggested that changes in serotonin content might also account for diurnal pain sensitivity as frontal pole, but not hippocampal or amygdala, serotonin levels correlated with pain thresholds (Schlosberg and Harvey, 1978). To our knowledge, no preclinical study has demonstrated diurnal variations in pain thresholds in an animal model of neuropathic pain, although sleep disturbances thought to be a more valid measure of pain intensity have been reported compared control animals (Monassi et al., 2003).

In human studies, Petraglia et al. (1983) found a circadian rhythm to beta-endorphin concentrations which peaked at 08:00 h and were lowest at 20:00 h. Hindmarsh et al. (1989) reported that beta-endorphin levels were significantly higher in the morning compared to the afternoon in both human adults and neonates. In addition, an early clinical study reported that naloxone decreased diurnal variation in pain sensitivity evoked by electrical stimulation (Davis et al., 1978). Given that exogenous mu-opioid agonists are known to reduce neuropathic pain (Gilron et al., 2005; Watson and Babul; 1998), fluctuations in endogenous opioids such as beta-endorphin may, in part, explain our results. Alternatively, endogenous secretion of the glucocorticoid, cortisol, also exhibits a circadian rhythm such that peak levels are generally observed at 08:00 h (Schimmer and Parker, 1996). This temporal profile together with the potential analgesic efficacy of corticosteroids in neuropathic pain (Kotani et al., 2000) may implicate cortisol variations as a possible explanation for our observed diurnal pain intensity pattern.

Some external time-relevant factors which may affect pain experience include repeated somatic stimulation, physical activity and fatigue. Neuropathic pain conditions are commonly associated with allodynia-defined as pain evoked by a normally innocuous stimulus (Merskey and Bogduk, 1994). Careful psychophysical experiments have shown that allodynia can exhibit temporal summation-that is, repeated application of an innocuous mechanical stimulus elicits a progressively more intense pain response with each subsequent application (Price et al., 1989). Using the example of a patient with thoracic postherpetic neuralgia, repetitive brushing of a shirt over the allodynic area may become more painful over time (e.g. with repeated brushing of the shirt) and lead to progressively higher pain levels towards the end of the day. Given that over half of our trial's patients suffered from allodynia (Gilron et al., 2005), this feature of neuropathic pain may play an important role in the diurnal variation observed in this study. Whereas touch-evoked pain appears to play an important role in postherpetic neuralgia, movement-evoked pain related to physical activity may be more prominent in diabetic neuropathy. Similar to our own findings, other investigations have demonstrated that neuropathic pain often restricts walking and mobility (Coplan et al., 2004; Galer et al., 2000). This would imply that physical activity either evokes or exacerbates neuropathic pain and, as with temporal summation of allodynia, cumulative activity throughout the day may lead to progressive increases in pain. Since we did not collect data on touch-evoked or movement-evoked pain or levels of physical activity throughout the day, it should be noted that these are speculations which require further study.

Additional data from this study indicate that the pattern of progressively increased pain throughout the day is unaffected by around-the-clock treatment with gabapentin and/or morphine. That is to say, these treatments decreased pain scores to a similar degree at all study time points. These observations were based upon pain measurements made at maximally tolerated steady-state drug doses. Although the temporal pain pattern during treatment with gabapentin and/or morphine appears similar to that with no analgesic treatment, it should be noted that drug absorption and distribution may also vary throughout the circadian cycle. For example, Gourlay et al. (1995) reported that the peak concentration (Cmax) of morphine was higher when the drug was administered at 18:00 than at 10:00. Therefore, future studies evaluating effects of drug treatment on diurnal pain variation should also include measurements of systemic drug levels. Nevertheless, the preservation of diurnal pain patterns during treatment with gabapentin and/or morphine suggests that neither of these drugs have an important effect on pain mechanisms which contribute to progressive pain increases throughout the day. However, in patients who start the day with lower and tolerable pain intensity, delayed dosing of these drugs to later in the day

may be a useful strategy to avoid daytime sedation and cognitive dysfunction.

In conclusion, these data suggest that neuropathic pain intensity progressively increases throughout the day and this temporal profile appears to be unaffected by treatment with gabapentin and/or morphine. In addition to replicating these results, future studies are needed to characterize the temporal profile of pain experience during normal sleeping hours. While gabapentin and morphine do not appear to affect the diurnal variation of neuropathic pain, it would be useful to similarly evaluate the effects of other antineuropathic agents in order to identify treatments effective against more severe evening and/or nighttime pain. Finally, other investigations examining neurohormonal and neurophysiologic influences on neuropathic pain may further lead to the identification of novel therapeutic targets.

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