PAIN MEDICINE
SECTION EDITOR
SPENCER S. LIU

The Impact of Therapy on Quality of Life and Mood in Neuropathic Pain: What Is the Effect of Pain Reduction?

Maneesh A. Deshpande, MSc, Ronald R. Holden, PhD, and Ian Gilron, MD, MSc, FRCPC

Department of Anesthesiology, Queen's University and Kingston General Hospital, Kingston, Ontario, Canada

Mood and quality of life (QOL) outcomes vary widely in neuropathic pain trials. This may be a result of variable analgesia and other treatment effects. We evaluated the relationship between pain reduction and mood/QOL in neuropathic pain. Pain, side effects, QOL, and mood from a trial of morphine, gabapentin, and a morphine-gabapentin combination were examined. Baseline QOL was impaired according to Short Form Health Survey (SF-36) scores. Baseline mood, according to Profile of Mood States scores, was comparable to that of a nondepressed population. Pain reduction with all three active trial treatments correlated with improved QOL. Pain reduction with morphine and with gabapentin correlated with improved mood. Pain reduction with a morphine-gabapentin combination correlated with improvement in only one of several domains of the Profile of Mood States. Severity of sedation, constipation, and dry mouth during any treatment did not correlate with mood/QOL changes. These results can be interpreted to imply that larger analgesic treatment effect sizes lead to more substantial improvements in QOL and/or mood. However, other beneficial or adverse treatment-related side effects may also affect mood/QOL. Therefore, future studies are needed to also evaluate the impact of treatment-related side effects on mood/QOL in analgesic trials.

(Anesth Analg 2006;102:1473–9)

Chronic pain resulting from peripheral nerve damage or disease is a frequent painful complication of cancer, diabetes, degenerative spine disease, human immunodeficiency virus/acquired immunodeficiency syndrome, and other infectious diseases (1) and exerts a profound negative impact on quality of life (QOL). For example, patients with painful diabetic neuropathy and postherpetic neuralgia have been shown to suffer from impaired mood, sleep, mobility, and physical functioning (2), and similar observations have been reported for chronic pain in general (3). It is widely accepted that the evaluation of multiple dimensions of QOL and mood is important in the psychological assessment of neuropathic pain patients (4). Such measurements of QOL and mood are not only valuable in guiding treatment strategies for individual patients but are also crucial in the setting of clinical trials for characterizing the therapeutic profile of novel analgesic therapies. Although pain is commonly a primary outcome in therapeutic trials, corresponding improvements in QOL and mood are expected to reinforce the inherent value of a given therapy. Indeed, a recent Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT – www.immpact.org) has identified physical functioning (health-related QOL) and emotional functioning (mood) as two of six core domains for clinical trials of chronic pain in general (5) and the European Federation of Neurological Societies has recommended the concurrent evaluation of QOL and mood for neuropathic in particular (6).

Several neuropathic pain trials of tricyclic antidepressants, anticonvulsants, and opioids that included secondary outcome measures of QOL and mood have been reported (7–9). Results from such clinical trials illustrate that effects of analgesic treatment on QOL and/or mood vary widely. As expected, most trials that fail to demonstrate analgesia also fail to show improvements in QOL or mood (10–12). However, among drug trials demonstrating analgesia superior to placebo, improvements in QOL and/or mood are not always observed (13–18). On closer consideration, the interpretation of mood and QOL as secondary outcomes in analgesic trials may be complicated by

Accepted for publication December 21, 2005.

Supported, in part, by CIHR Grant #MCT-38149. M.D. was supported by an HRF/CIHR Studentship in Medicine, I.G. is supported by a CIHR New Investigator Award and R.R.H. is funded by SSHRC.

Address correspondence and reprint requests to Ian Gilron, MD, MSc, FRCP(C), Associate Professor & Director of Clinical Pain Research, Department of Anesthesiology, Queen's University, c/o Kingston General Hospital, 76 Stuart Street, Kingston, ON, Canada K7L 2V7. Address e-mail to gilroni@post.queensu.ca.

DOI: 10.1213/01.ane.0000204295.90178.77

0003-2999/06

issues of: 1) statistical power (i.e., trials are powered for the primary outcome rather than for mood/QOL outcomes), 2) nonspecific 'placebo' effects associated with treatment expectations and other cues related to clinical trial participation (19), and 3) diverse treatment effects including analgesia (i.e., does pain reduction enhance mood/QOL?), other beneficial treatment-related effects (e.g., does improved sleep enhance mood/QOL?), and treatment-related adverse effects (e.g., does daytime sedation impair mood/QOL?). Although it would seem intuitive that therapeutic reduction of pain intensity should improve QOL and/or mood, one observational study involving multimodal pain therapy in a heterogeneous chronic pain population failed to demonstrate such improvements (20). Therefore, achieving a better understanding of the interactions between pain and QOL or mood in the setting of drug therapy is critical for the proper interpretation of these important secondary outcomes during pain management. Thus, the purpose of this investigation is to test the hypothesis that, in the setting of drug therapy, pain reduction is correlated with improvements in QOL and mood.

Methods

This study was conducted using pain, QOL, and mood data from a recently completed placebo-controlled crossover trial of patients with pain resulting from diabetic neuropathy or postherpetic neuralgia and no history of major depression (21). This trial involved 57 patients (35 diabetic neuropathy/22 postherpetic neuralgia; 32 male and 25 female), 41 of whom completed the entire trial.

The clinical trial from which the data were gathered was approved by the Queen's University Research Ethics Board and involved patients with diabetic neuropathy or postherpetic neuralgia who experienced daily moderate pain for at least 3 mo before study entry and who had no evidence of a serious mood disorder or history of significant drug/alcohol abuse. All patients gave written informed consent to participate in the study. The trial was a double-dummy, 4-period crossover comparison (5 wk per treatment period) of morphine, gabapentin, a morphine-gabapentin combination, and active placebo (lorazepam) whereby patients were randomized, in a double-blind fashion, to 1 of 4 possible sequences of these 4 treatments according to a balanced Latin square design. Within the first 3 wk 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. Before starting the study (baseline) and during the fourth week of each treatment period at MTD, patients completed various mood and QOL questionnaires.

Pain intensity was recorded as rated using the 0-10 cm visual analog scale (VAS) score of the Short Form–McGill Pain Questionnaire (SF-MPQ) (22). The SF-MPQ VAS was used because these scores were reported at the same session that mood/QOL questionnaires were completed. Treatment-emergent adverse effects were reported by patients as they occurred throughout the trial and rated on a 0-3 category scale as none = 0, mild = 1, moderate = 2, or severe = 3. QOL was rated using the Short Form (SF-36) Health Survey (23) and mood was rated using the Profile of Mood States (POMS) (24).

The SF-36 consists of 36 questions that are scored and combined to represent 8 QOL domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. These scores are presented as values on a 0-100 scale, with greater values representing better QOL. In addition to individual scale scores, we computed an aggregate value representing overall QOL, as has been done in previous studies (25). This was done by summing the individual SF-36 domain scores and adjusting them onto a 0-100 scale. We refer to this aggregate score of overall QOL as the SF-36 composite score.

The POMS consists of 65 measures of mood which are then organized into 6 mood scales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The individual scales are combined to achieve the mood disturbance score (MDS), an aggregate indicator of overall mood. A greater MDS value indicates greater mood disturbance.

All raw data were entered and scaled in Microsoft Excel 2000 (Microsoft, Redmond, WA). Individual POMS scales were omitted from the calculation if more than 10% of the component data from an individual patient were missing. As recommended by the SF-36 Health Survey Manual and Interpretation Guide (23), SF-36 scales were omitted from the calculation if more than 50% of the component data were missing. Descriptive statistics were tabulated as mean ± SD.

To examine the effect of pharmacological pain reduction on QOL and mood, placebo treatment pain intensity scores were subtracted from the pain intensity scores during each active treatment (i.e., gabapentin, morphine, and combination) to calculate treatment-induced change in pain intensity for each treatment. Changes in SF-36 and POMS scores for each treatment were calculated in a similar fashion. Primary analyses evaluated correlations between change in pain and changes in the aggregate mood or QOL scores (i.e., POMS-MDS and SF-36 composite). Correlations between pain and other mood/QOL domains were considered secondary analyses and, therefore, no corrections were made for multiple significance tests. Without correcting, the importance of these secondary

Table 1. Descriptive Statistics for Baseline Pain, Mood, and Quality of Life

Scale	Study patient data	Cronbach's alpha	Normative population data
Present Pain Intensity (0-10 cm visual analog scale)	5.0 ± 2.1	N/A	N/A
SF-36 Health Survey Domains			
Physical functioning	51.7 ± 23.4	0.87	88.2 ± 18.4*
Role-physical	48.2 ± 44.5	0.91	85.7 ± 30.2*
Bodily pain	52.1 ± 18.2	0.71	78.0 ± 22.3*
General health	61.5 ± 21.8	0.76	77.6 ± 17.7*
Vitality	49.5 ± 19.2	0.81	68.9 ± 17.1*
Social functioning	70.3 ± 24.2	0.73	88.3 ± 18.6*
Role-emotional	69.8 ± 42.3	0.91	87.0 ± 29.3*
Mental health	76.7 ± 16.4	0.76	79.0 ± 14.7*
SF-36 composite score	60.2 ± 15.6	N/A	75.7†
Profile of Mood States Subscales			
Tension-anxiety	6.0 ± 7.6	0.92	12.3 ± 7.0‡
Depression-dejection	9.7 ± 9.6	0.92	8.3 ± 8.7‡
Anger-hostility	8.1 ± 7.6	0.91	9.2 ± 8.3‡
Fatigue	10.5 ± 7.0	0.95	7.0 ± 5.7‡
Confusion-bewilderment	2.0 ± 4.1	0.76	6.7 ± 4.6‡
Vigor	17.3 ± 6.8	0.90	16.3 ± 6.3‡
Mood disturbance score	18.9 ± 35.6	N/A	27.2 ± 31.8‡

Values are mean ± SD. The study patient data presented are from 41 clinical trial completers.[21]
* These are data from a random sample of the Canadian population.[26]
† This composite score was calculated from the mean normative values of the 8 SF-36 domains, as described in the Methods.
‡ These data are from a male sample only, given that normative data were tabulated separately for males and females.[24] They are provided only for purposes of general comparison and not used in any analysis.

analyses is the magnitude of the observed effect sizes and their stability across different treatments. To examine the effect of adverse treatment effects on QOL and mood, only the most frequent (>10% of patients) adverse effects during MTD were considered, i.e., sedation, constipation, and dry mouth. Placebo treatment side effect severity scores were subtracted from the side effect severity scores during each active treatment (i.e., gabapentin, morphine, and combination) to calculate treatment-induced change in side effect severity for each treatment. Treatment-induced changes in side effect severity were similarly plotted against their corresponding changes in QOL and mood on separate plots (i.e., sedation severity versus SF-36 and sedation severity versus POMS). Correlation analyses were performed and Pearson correlation coefficients were calculated. All testing was 2-sided at the 0.05 α level and performed with version 12.0 of the Statistical Package for the Social Sciences (SPSS, Chicago, IL).

Results

Three of the clinical trial patients completed at least two treatment periods and were thus included in the trial's intent-to-treat analysis (21); however, these three patients were excluded from the present study because of missing mood/QOL data. Descriptive statistics of pain intensity, SF-36 and POMS pre-trial baseline scores from 41 trial completers are summarized in Table 1, along with previously published normative data. The mean SF-36 composite score in this study population is 60.2, compared with a calculated score of 75.7 from a random sample of the Canadian population (26), with higher values representing better QOL. The mean aggregate POMS-MDS in this study population is 18.9, compared with a previously reported normative value of 27.2 (24), with higher values representing a greater likelihood of depression. Pain intensity reduction was correlated significantly with changes in the SF-36 composite score (medium to large effect sizes for all three treatments) (27) as well as bodily pain and vitality domains for all three treatments (Figs. 1–3, Table 2). Morphine- and gabapentin-induced changes in pain intensity correlated significantly with changes in POMS-MDS scores (medium to large effect sizes for both treatments) (27) as well as depression-dejection and anger-hostility domains, whereas combination-induced changes in pain intensity were significantly correlated only with the POMS anger-hostility domain (Figs. 1–3, Table 2). Because correlations between mood (POMS-MDS) and QOL (SF-36 composite score) were statistically significant (-0.71, $P < 0.001$; -0.59, $P < 0.001$; and -0.70, $P < 0.001$ for morphine, gabapentin, and combination treatments, respectively), we also calculated partial coefficients for the correlations between pain reduction and change in mood (controlling for QOL) and between pain reduction and change in QOL (controlling for mood). The partial coefficients for the correlation of pain reduction and change in POMS-MDS (controlling for SF-36 composite scores) were -0.21

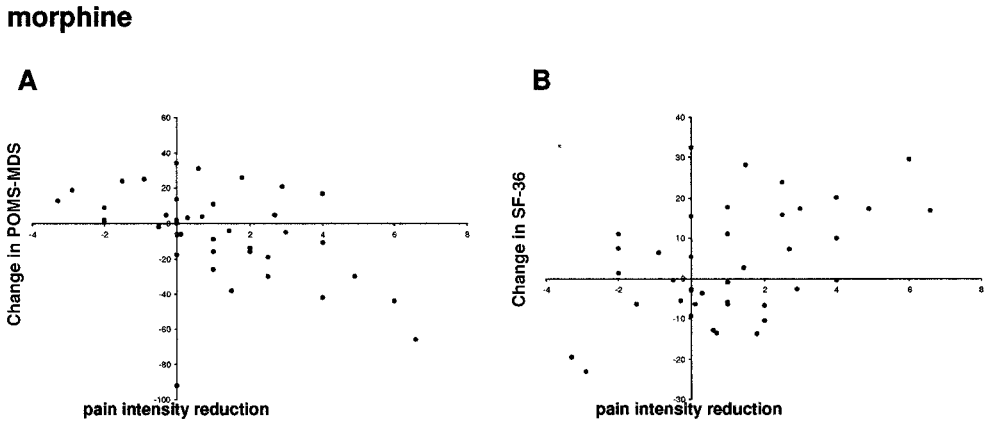

Figure 1. These plots describe the relationship between pain reduction and change in quality of life/mood during therapy with morphine. Each study patient is represented as an individual point on each of the 2 presented scatter plots (n = 41). The horizontal axis represents treatment-induced reduction in pain intensity while the vertical axis represents the corresponding change in (A) Profile of mood states - Mood disturbance score (POMS-MDS) and (B) SF-36 composite (SF-36) score.

Table 2. Correlations Between Pain Intensity Reduction and Improvement in Quality of Life/Mood

	Morphine		Gabapentin		Combination	
	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value
Aggregate scales						
POMS-MDS	−0.47	0.002*	−0.43	0.005*	−0.28	0.077
SF-36 composite	0.48	0.001*	0.53	<0.001*	0.47	0.002*
SF-36 domains						
Physical functioning	0.15	0.344	0.22	0.169	0.17	0.302
Role physical	0.27	0.092	0.31	0.049*	0.27	0.089
Bodily pain	0.55	<0.001*	0.68	<0.001*	0.49	0.001*
General health	0.28	0.077	0.24	0.126	0.02	0.922
Vitality	0.52	0.001*	0.49	<0.001*	0.50	0.001*
Social functioning	0.36	0.025*	0.26	0.097	0.48	0.001*
Role emotional	0.13	0.442	0.33	0.036*	0.16	0.323
Mental health	0.21	0.180	0.35	0.025*	0.34	0.033*
POMS domains						
Tension-anxiety	−0.20	0.213	−0.32	0.042*	−0.09	0.584
Depression-dejection	−0.40	0.010*	−0.43	0.005*	−0.21	0.194
Anger-hostility	−0.57	<0.001*	−0.44	0.004*	−0.31	0.050*
Fatigue-inertia	−0.41	0.008*	−0.21	0.192	−0.30	0.058
Confusion-bewilderment	−0.17	0.300	−0.01	0.926	−0.02	0.883
Vigor-activity	0.40	0.010*	0.29	0.064	0.23	0.130

* Statistically significant.
The Pearson correlation coefficient and p value (2-tailed) are shown for the correlation between pain intensity and each of the presented psychometric scales. Significant correlations with absolute values more than 0.50 and 0.30 constitute large and medium effect sizes, respectively.[27]
POMS = Profile of Mood States; MDS = Mood Disturbance Score.

(P = 0.20), −0.17 (P = 0.29), and 0.08 (P = 0.63) for morphine, gabapentin and combination treatments, respectively. The partial coefficients for the correlation of pain reduction and change in SF-36 composite scores (controlling for POMS-MDS) were 0.24 (P = 0.15), 0.38 (P = 0.02), and 0.40 (P = 0.01) for morphine, gabapentin, and combination treatments, respectively. Treatment-induced changes in the severity of sedation, constipation, and dry mouth were not significantly correlated with changes in POMS-MDS or SF-36 scores (Table 3).

Discussion

Based on the observed raw correlations, these results suggest a significant correlation between neuropathic pain reduction and improvements in QOL during treatment with gabapentin, morphine, or their combination and mood, during treatment with gabapentin or morphine. These results can be interpreted to imply that larger analgesic treatment effect sizes lead to more substantial improvements in QOL and/or mood. However, although partial correlations of pain with QOL (controlling for mood) remained significant

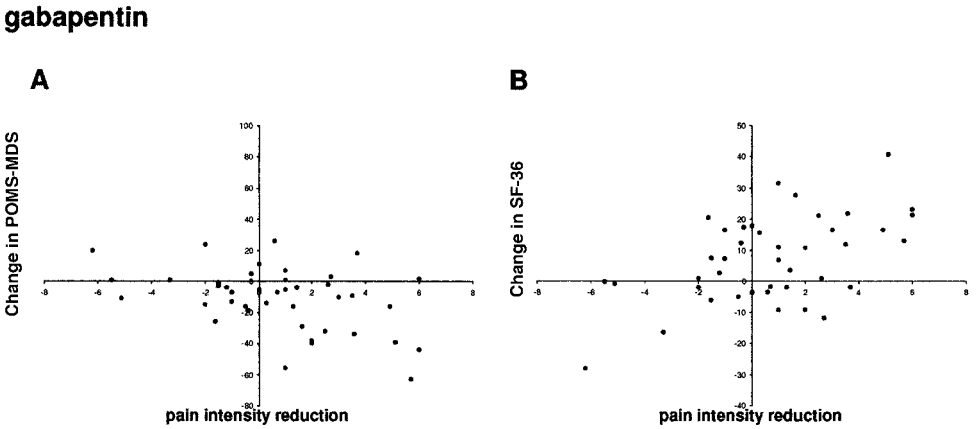

Figure 2. These plots describe the relationship between pain reduction and change in quality of life/mood during therapy with gabapentin. Each study patient is represented as an individual point on each of the 2 presented scatter plots ($n = 41$). The horizontal axis represents treatment-induced reduction in pain intensity while the vertical axis represents the corresponding change in (A) Profile of mood states - Mood disturbance score (POMS-MDS) and (B) SF-36 composite (SF-36) score.

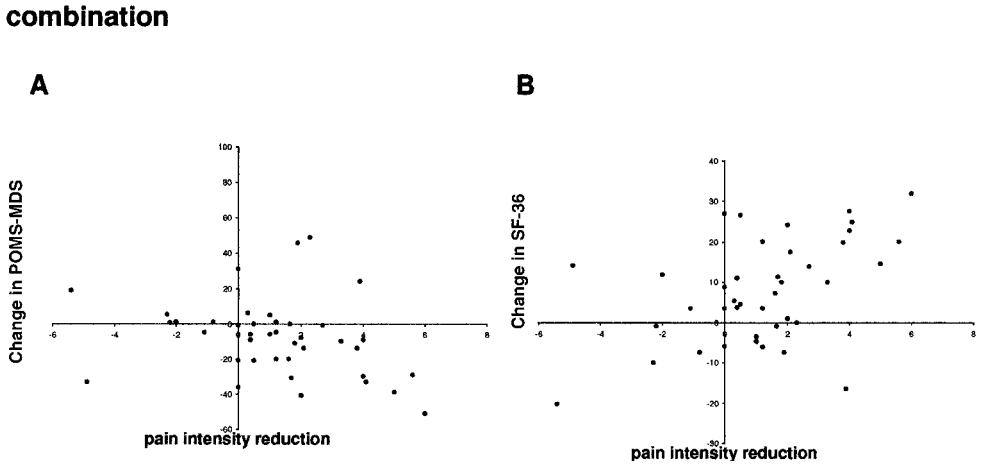

Figure 3. These plots describe the relationship between pain reduction and change in quality of life/mood during therapy with a morphine-gabapentin combination. Each study patient is represented as an individual point on each of the 2 presented scatter plots ($n = 41$). The horizontal axis represents treatment-induced reduction in pain intensity while the vertical axis represents the corresponding change in (A) Profile of mood states - Mood disturbance score (POMS-MDS) and (B) SF-36 composite (SF-36) score.

for gabapentin and combination treatments, partial correlations of pain with mood (controlling for QOL) failed to reach significance for any treatment. The fact that some raw correlations become nonsignificant partial correlations could be because mood and QOL overlap (in that they both reflect adaptive functioning), are correlated themselves, and/or because of insufficient statistical power of our sample size. Interestingly, the partial correlations between changes in pain and QOL (controlling for mood) remain significant for gabapentin and combination confirming that the SF-36 reflects various constructs other than mood.

The detrimental effects of neuropathic pain on mood and QOL are well known (2), and although clinical intuition would suggest that reducing neuropathic pain would improve these broader indices of well-being (28), current evidence indicates that pain reduction is not always accompanied by improved mood and/or QOL (13–18, 20). Such discrepancies could be explained by adverse treatment effects and/or concurrent chronic illness; however, proper interpretation of recently proposed mood/QOL trial outcomes (6,29) requires a better understanding of the quantitative relationship between pain intensity reduction and improvement of mood and QOL. These data from completers of our recent clinical trial (21) confirm that neuropathic pain reduction is correlated with improvements in both QOL and mood. It should be noted that, during treatment with a gabapentin-morphine combination, pain reduction was significantly correlated with improvement in only one of several domains (anger-hostility) of the POMS. Despite an apparent trend seen in the scatterplot of combination-induced pain reduction versus improvement in the aggregate POMS-MDS (Fig. 3A), the resulting correlation coefficient failed to reach statistical

Table 3. Correlation of Treatment-Emergent Side Effect Severity with Changes in Mood/Quality of Life

	Change in POMS-MDS		Change in SF-36 composite	
Treatment	Correlation coefficient	*P* value	Correlation coefficient	*P* value
Sedation				
Morphine	0.05	0.747	−0.04	0.783
Gabapentin	−0.01	0.968	−0.13	0.423
Combination	−0.20	0.214	0.17	0.301
Constipation				
Morphine	0.14	0.393	−0.14	0.371
Gabapentin	−0.12	0.451	0.04	0.811
Combination	−0.23	0.153	0.11	0.52
Dry Mouth				
Morphine	0.08	0.612	−0.07	0.646
Gabapentin	−0.05	0.776	−0.05	0.755
Combination	−0.01	0.930	−0.10	0.524

The Pearson correlation coefficient and *P* value (2-tailed) are shown for the correlation between side effect severity and each of the presented psychometric scales.

POMS = Profile of Mood States; MDS = Mood Disturbance Score.

significance ($P = 0.077$), which could be in part attributable to inadequate statistical power.

The ability to generalize our results requires the assumption that the population studied is representative of neuropathic pain patients with respect to pain, QOL, and mood. In this study, mean baseline present pain intensity, measured by a 0-10 cm VAS of the SF-MPQ, was 5.0, which is consistent with at least moderate pain. Average baseline QOL, estimated by the SF-36 composite score, was 60.2, which is substantially reduced from that of 75.7 (Table 1) for a normative population (26). This is consistent with previous evidence that neuropathic pain impairs QOL (2). The average baseline mood was within normative limits (Table 1) for the patients studied according to the POMS-MDS (24). These observations are reflective of our clinical trial's exclusion criterion of depression. Therefore, the results of this study should be viewed exclusively in the context of nondepressed patients with neuropathic pain. Further considering generalizability of these results, the interactions between pain reduction and mood/QOL changes were observed in the context of treatment with gabapentin and/or morphine and do not necessarily hold for other treatments. Future studies are needed to evaluate the effects of pain reduction on mood/QOL with other pharmacological and nonpharmacological treatments.

The correlation of treatment-induced pain reductions with mood suggests that reducing pain may elevate mood in the absence of clinical depression. The secondary analysis of individual POMS domains indicated that pain reduction correlated with improvements in depression-dejection and anger-hostility. Previous clinical trials using the POMS as a secondary measure have shown these specific subscales to improve significantly with analgesic drug therapy (30,31). The secondary analysis of individual domains of the SF-36 Health Survey indicate that vitality and, not surprisingly, bodily pain are significantly correlated with pain reduction during all three trial treatments. Previous studies have shown significant improvement in each of these scales that is thought to be, at least in part, attributable to treatment-induced analgesia (30–32).

The adverse impact of analgesic therapy on QOL has been evaluated in other areas such as cancer pain (33) but has received limited attention in neuropathic pain. In this study, the severity of sedation, constipation, and dry mouth (the most frequent adverse effects encountered) did not significantly correlate with changes in mood and/or QOL. However, this clinical trial was not statistically powered to detect differences in side effect severity, and thus no conclusion can be made about the impact of these treatment-related symptoms on mood or QOL.

In addition to reducing pain intensity, improving QOL, mood, and ultimately patients' degree of function are vital goals in the management of neuropathic pain. This study suggests that the magnitude of pain intensity reduction critically impacts on a particular treatment's effect on QOL and mood. Therefore, secondary outcomes of QOL and mood from analgesic clinical trials must be interpreted, in part, in the context of the magnitude of each treatment's analgesic efficacy. Furthermore, the effect of treatment-related side effects (both adverse and beneficial) on QOL and/or mood requires further investigation. Therefore, future studies should also evaluate the impact of treatment-related side effects on QOL and mood in analgesic trials.

The authors wish to thank Joan Bailey, RN, MEd, for her assistance with this study.

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