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13. ABSTRACT *(Maximum 200 Words)*

Post-mastectomy pain syndrome, phantom breast pain, and post-lumpectomy pain are poorly understood chronic pain syndromes that occur following surgical procedures for breast cancer. These pain syndromes are not well studied, but there is appreciable evidence that patients can be significantly disabled by their chronic pain and can suffer from substantial reductions in quality of life. The primary aims of this research project were to identify risk factors for chronic pain following surgical procedures from breast cancer, characterize its natural history, and examine its impact on quality of life using a prospective research design. In this project, 114 women who had various surgical procedures for breast cancer were assessed with respect to hypothesized risk factors for chronic pain. These women were studied for one year following their surgery, with periodic assessment of pain, health-related quality of life, and psychosocial variables; this research method allows risk factors for chronic pain to be identified and its impact on quality of life to be determined. Results of interim analyses suggest that age, malignancy, pre-operative pain, early post-operative acute pain, higher pre-operative anxiety, and greater illness concern were risk factors for the development of chronic pain in univariate analyses. Age and pre-operative pain both contributed significantly to the prediction of chronic pain at three months post-surgery in a logistic regression analysis, but subsequent entry of psychological distress and illness concern measures did not significantly improve the fit of the model. Ongoing anlyses of the complete database will further examine these relationships. The pathogenesis of chronic pain following breast cancer surgery is unknown, and the identification of risk factors constitutes an important first step in understanding the processes by which chronic pain develops. This knowledge may lead to the development of more effective treatment approaches. By identifying risk factors, the results can also be used to design interventions aimed at preventing the development of chronic pain following surgical procedures for breast cancer. Moreover, the identification of risk factors will make it possible to determine which patients are most in need of such preventive efforts.

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Introduction

Post-mastectomy pain syndrome, post-lumpectomy pain, and phantom breast pain are poorly understood chronic pain syndromes that occur following surgical procedures for breast cancer. The primary aims of this research were to identify risk factors for these chronic pain syndromes following surgical procedures for breast cancer, characterize their natural history, and examine their impact on quality of life using a prospective research design. Women scheduled for mastectomy, lumpectomy, or excisional biopsy were assessed with respect to hypothesized risk factors for chronic pain and were then studied prospectively for one year. Periodic follow-up assessments of pain, health-related disability and quality of life, and selected psychosocial variables allow risk factors to be identified and the impact of chronic pain on quality of life to be determined. An important feature of this research was its detailed assessment of pre-operative, early post-operative, and chronic pain. In these assessments, sensory and affective aspects of pain, pain quality, and non-painful abnormal sensations are examined. By identifying risk factors for chronic pain following surgical procedures for breast cancer, the results of this research can be used to design interventions aimed at preventing the development of these chronic pain syndromes.

Body of Final Report

Chronic pain has been defined as pain that persists beyond the normal time of healing, a definition which includes most painful conditions that have lasted longer than three months (Merskey & Bogduk, 1994). Chronic pain is both a medical and a behavioral problem and it is accompanied by substantial economic costs to society as well as great personal suffering. The research described in this report was a prospective study of the development of post-mastectomy pain syndrome (PMPS), post-lumpectomy pain, and phantom breast pain. Current understanding of these chronic pain syndromes is limited, and of these different types of chronic pain following breast cancer surgery, post-lumpectomy pain has been the least well studied. It has been suggested that PMPS is caused by surgical injury to the intercostobrachial nerve (Foley, 1987; Vecht et al., 1989; Stevens et al., 1995; cf. Watson et al., 1989, who noted that in some patients the cutaneous branches of other intercostal nerves are also involved). The pathophysiology of phantom breast pain—as well as other phantom pains—remains obscure (Katz & Melzack, 1990; Melzack, 1990, 1996; Sherman, 1997).

In the most recent literature review, most reports of the prevalence of PMPS were within the range of 16% to approximately 50% (Kwekkeboom, 1996). Not included in this review were two studies of PMPS in which 39% of 181 patients reported pain at least one year after surgery (Wallace et al., 1996) and 20% of 95 patients reported "chronic, stable pain of long duration" beginning within days to weeks after surgery (Stevens et al., 1995, p. 63). Early studies of phantom breast pain (excluding non-painful phantom breast sensations) reported prevalences ranging from 18-54% (Jamison et al., 1979), and a recent study found phantom breast pain present in 13% of patients three weeks and one year after mastectomy and in 17% of patients at six years (Krøner, 1989, 1992).

Although the prevalence of PMPS and phantom breast pain might be expected to decrease with duration of time since surgery, the results of several studies indicate that this may

not occur (Krøner et al., 1989, 1992; Vecht et al., 1989; Maunsell et al., 1993). It has been suggested that women are often reluctant to report pain following mastectomy to their physicians, which may contribute not only to the impression that pain following mastectomy is rare but also to the variability in the results of studies of the prevalence of PMPS and phantom breast pain (Jamison et al., 1979, Abraham & Llewellyn-Jones, 1983; Staps et al., 1985). Importantly, both PMPS and phantom breast pain have been found to have a significant negative impact on psychological adjustment, the performance of daily occupational and domestic activities, and quality of life (e.g., Jamison et al., 1979; Christensen et al., 1982; Hladiuk et al., 1992; Maunsell et al., 1993; Stevens et al., 1995).

Very few studies have examined risk factors for pain following mastectomy, and no consistent relationships have emerged between the likelihood of persisting pain and age, type of mastectomy, cancer treatment, or post-operative sequelae (Jamison et al., 1979; Christensen et al., 1982; Krøner et al., 1989, 1992). In one recent study, women with pre-mastectomy breast pain were more likely to have phantom breast pain three weeks, one year, and six years after surgery than those without pre-mastectomy pain (Krøner et al., 1989, 1992). The results of studies of limb amputees are consistent with this finding (Jensen et al., 1985; Katz & Melzack, 1990; Weiss & Lindell, 1996). The results of these studies suggest that patients with pain before either a mastectomy or a limb amputation are at greater risk for the development of phantom pain. Moreover, the risk appears greatest for patients with more severe pain, and it has been hypothesized that phantom pain may develop when the combination of pre-amputation pain intensity and duration exceeds a critical threshold (Katz & Melzack, 1990).

The presence of psychosocial distress in patients with pain following mastectomy has been interpreted as evidence that psychosocial factors contribute to the development of pain (Woods, 1975; Jamison et al., 1979; Christensen et al., 1982). However, psychosocial distress can be a consequence of living with prolonged pain, and the absence of prospective studies has made it impossible to determine whether psychological abnormalities in patients following mastectomy and limb amputation are risk factors that preceded the development of chronic pain or are consequences of it (Sherman et al., 1987; Katz, 1992). Nevertheless, there is evidence that stress can precede increases in phantom pain (Arena et al., 1990), and the results of prospective studies suggest that psychosocial factors can be risk factors for other pain syndromes (Dworkin, 1997a) as well as for pain associated with cancer treatment (Syrjala & Chapko, 1995). It is therefore important to determine whether patients who have greater psychosocial distress before surgical procedures for breast cancer are more likely to develop chronic pain.

The theoretical approach on which this research was based is one in which the development of chronic pain is considered the result of an interaction between biological and psychosocial processes. The principal investigator and his colleagues have proposed that the results of chronic pain research are consistent with a diathesis-stress model (e.g., Dworkin & Portenoy, 1996; Dworkin & Banks, 1999). In this approach, an interaction between an organic condition (the diathesis) and various psychosocial factors (the stress component of the model) is hypothesized to account for the development of chronic pain. The diathesis-stress approach provides a heuristic model that can be used in the design of research on the development of chronic pain following breast cancer surgery. In such a model, a mastectomy or lumpectomy and the nerve damage associated with these procedures can be considered the diathesis for

chronic pain; various psychosocial factors constitute the stress (broadly defined) that results in a process whereby acute peri-operative pain becomes the chronic pain of PMPS, post-lumpectomy pain, or phantom breast pain.

The prospective study of mastectomy and lumpectomy patients has the potential to identify risk factors derived from this model for the development of chronic pain following surgical procedures for breast cancer. To identify risk factors, patients with pain at a 3-month follow-up interview are considered to have chronic pain (Merskey & Bogduk, 1994). Patients who do and do not develop chronic pain are being compared with respect to each of the measures in five families of variables assessed pre-operatively—demographic and medical/surgical, acute pain, health-related disability, psychological distress, and social support and life events.

Because the results of cross-sectional studies that have attempted to identify risk factors for chronic pain following breast cancer surgery within the demographic and medical/surgical domain have been inconsistent, it is hypothesized that there will be no significant risk factors within these families of variables. As reviewed in Dworkin (1997a), the results of a number of studies indicate that more severe acute pain and greater psychosocial distress are risk factors for the development of chronic pain. It is therefore hypothesized that acute pain intensity and duration and measures within the two families of psychosocial variables will be significant risk factors for PMPS, post-lumpectomy pain, and phantom breast pain.

A second aim of this research is to examine the psychosocial consequences of chronic pain following surgical procedures for breast cancer. It has been proposed that the assessment of chronic pain patients should be multidimensional (Turk & Rudy, 1987; Dworkin, 1997b). This approach has been used as a basis for selecting measures of the impact of chronic pain on psychological distress and quality of life. It is hypothesized that psychological distress, maladaptive illness beliefs, and health-related physical, role, and social disability will increase in patients with persisting chronic pain from the 3-month follow up through the final follow-up assessment at 12 months.

Methods

English-speaking women 18 years of age and older scheduled for mastectomy, lumpectomy, or excisional biopsy were recruited from the surgical service at Strong Memorial Hospital (SMH). The inclusion of patients scheduled for lumpectomy and excisional biopsy represents a modification to the original research protocol. This change was made based on the increasing reliance of surgeons on these more conservative surgical procedures for the treatment of early stage breast cancer. Approval for this modification was obtained from the U.S. Army Medical Research and Materiel Command and from the University of Rochester Research Subjects Review Board.

Women scheduled for breast surgery whose names and telephone numbers were released with their permission by their attending surgeon were being contacted and the study was described to them over the telephone. Those who agreed to participate had their pre-operative assessment scheduled within two weeks of surgery. At this assessment, the patient was asked to sign an informed consent form. A project coordinator conducted subject recruitment and the pre-

operative assessments. Most of these assessments were conducted in patients' homes to facilitate their participation. Some assessments are conducted at SMH, if the patient so desires or if it is deemed unsafe for the research personnel to visit the patient's home. Patients were reimbursed $80 for participation in the research in two installments—$40 at the conclusion of the pre-operative assessment, and $40 upon completion of the 12-month follow-up interview.

To date, 114 women were enrolled in the research and have had their pre-operative assessment; 6 are undergoing final follow-up assessments. This constitutes completion of Tasks 1, 2, 5, and 6 in the approved Statement of Work. However, it was not possible to recruit the anticipated sample size of 200 women undergoing surgical procedures for breast cancer. The explanation for this failure to recruit the anticipated number of women is unclear. At least in part, it would seem to be a result of fewer women undergoing mastectomy for breast cancer as well as a shift in referral patterns over the course of the study in the practice of Dr. Andrus's, the surgeon who was the soiurce of the patients studied in this project.

Post-operative pain and analgesic use were assessed in hospital visits or telephone interviews at 2 and 10 days after surgery. which makes it possible to examine the relationships between acute post-operative pain and analgesic equivalence levels (Steedman et al., 1992) and the development of chronic pain. At 1, 3, 7, and 12 months following surgery, telephone interviews were conducted in which surgery-related pain and disability, analgesic use, health status and treatment history since the previous assessment were assessed. Surgery-related pain at the 3, 7, and 12 month follow-up interviews is considered chronic pain (Merskey & Bogduk, 1994). The criteria of Watson et al. (1992) are being used to diagnose PMPS and the criteria of Krøner et al. (1989, 1992) are being used to diagnose phantom breast sensations and phantom breast pain. Use of these criteria ensures that PMPS and phantom breast pain are distinguished from other types of pain that may be present at these follow-up interviews, including radiation plexopathy and neuritis (e.g., Watson & Evans, 1982; Watson et al., 1989) and post-mastectomy scar pain (e.g., Krøner et al., 1989, 1992).

To examine whether persisting pain is accompanied by increasing psychosocial distress, the questionnaire measures of depression, anxiety, disease conviction, and somatization were also administered during the follow-up interviews. To the extent possible, these interviews were conducted by a member of the research team who did not conduct the initial assessments and who was therefore blind with respect to the patient's pre-operative psychological status. Because the identities of patients who do and do not develop pain will only become known at the follow-up interviews, the project coordinator conducting the pre-operative assessments was in all instances blind with respect to the data used to identify risk factors for chronic pain.

Measures

Demographic and medical/surgical measures. Basic demographic data—age, race, marital status, number of children, living arrangements, years of education, occupation, and current employment status—were assessed at the beginning of the pre-operative assessment. The subject's medical history was assessed by means of an expanded version of the physical health section of the Life Stressors and Social Resources Inventory (see below; Moos & Moos, 1994). Information regarding past and current illnesses and treatments, including past and

current painful conditions (based on the methods of S.F. Dworkin et al., 1990), was obtained from this interview.

Information regarding the patient's breast cancer history, type of surgery, and degree of sparing of the intercostobrachial nerve was obtained from the attending surgeon and operative report. The type and duration of operative and post-operative anesthesia and analgesia was recorded from the patient's hospital records, and information regarding the dosage and portal of entry of any radiation treatment following surgery was obtained from the patient's radiation oncologist. Collection of this information on the 114 subjects enrolled in the research is complete (Tasks 3 and 4 in the approved Statement of Work).

Pre-operative pain, early post-operative pain, and chronic pain. Comprehensive assessments of pre-operative pain, early post-operative pain, PMPS, post-lumpectomy chronic pain, and phantom breast pain were conducted using the Brief Pain Inventory Short-form (BPI; Cleeland & Syrjala, 1992) and the McGill Pain Questionnaire (MPQ; Melzack, 1975); the reliability and validity of both measures has been extensively documented. The BPI was developed specifically for use in assessing cancer pain, and the MPQ provides an assessment of both sensory and affective aspects of pain, as well as providing a characterization of pain quality. No previous studies of chronic pain following breast cancer surgery have distinguished the sensory and affective aspects of pain, a central component of current pain research (e.g., Fernandez & Turk, 1992; Chapman, 1993), nor have pain quality and abnormal but non-painful sensations in these syndromes been carefully assessed. Indeed, in some studes of phantom breast pain, painful and non-painful phantom breast sensations have not been clearly distinguished (e.g., Christensen et al., 1982; Karydas et al., 1986).

Many amputees describe phantom limb pain "as indistinguishable from the pain they experienced in the limb prior to amputation" (Katz, 1992, p. 282), and the MPQ will also be used to examine the hypothesis that the quality of any pre-mastectomy pain and the quality of PMPS and phantom breast pain are similar. In addition, administering the MPQ will make it possible to examine whether the predominant qualities of phantom breast pain remain the same in the year following surgery, as has been reported by Krøner et al. (1989).

Health-related disability, quality of life, and psychological distress. At the pre-operative assessment, patients were administered the Medical Outcomes Study short-form health survey (SF-36; Ware et al., 1992) as well as the Functional Assessment of Cancer Therapy-Breast (FACT-B; Brady et al, 1997). The SF-36 provides measures of health-related physical, role, and social disability in the week immediately prior to surgery. The impact of post-surgical pain on quality of life at each of the follow-up interviews was assessed by readministering the FACT-B at the 1, 3, 7 and 12 month follow-up assessments.

Depression and anxiety have been found to be risk factors for chronic pain as well as consequences of chronic pain (Banks & Kerns, 1996; Dworkin, 1997a), and measures of both were administered at the pre-operative assessment and at the 1, 3, 7, and 12 month follow-up interviews. The Hamilton rating scales for depression and anxiety (Hamilton, 1959, 1960) were administered at the pre-operative assessment using structured interviews developed for these measures (Williams, 1988, unpublished manual). To complement these interview-based

assessments, two self-report measures of symptoms of depression and anxiety were also administered—the Beck Depression Inventory (Beck et al., 1961), a measure of depression that has been used in a large number of studies of chronic pain, and the State-Trait Anxiety Inventory, state version (Spielberger, 1977), a measure of the extent to which an individual feels anxious at the time of testing. The combined use of these interviews and questionnaires provides an assessment of the moderately severe forms of depression and anxiety that appear to be both risk factors for and consequences of chronic pain.

Several measures that reflect the individual's beliefs about physical illness and somatic symptoms were also administered at both the pre-operative assessment and at the 1, 3, 7, and 12 month follow-up interviews. These are the Illness Behavior Questionnaire disease conviction scale (Pilowsky, 1989), the Somatosensory Amplification Scale (Barsky et al., 1990), and the Somatic Symptom Inventory (Barsky et al., 1990). As reviewed in Dworkin et al. (1996), these measures have been reported to have important relationships with chronic pain in both cross-sectional and prospective studies. Their administration makes it possible to evaluate whether maladaptive beliefs about relationships between physical symptoms and illness and heightened awareness of physical symptoms are risk factors for or consequences of pain following mastectomy.

Social support and life events. Moos (1992) has argued that social supports and life events are closely interrelated and influence each other over time, and that an integrated approach to their assessment is therefore necessary. It has also been noted that whereas most existing measures of life events have focused on temporally discrete events, many psychological and physical disorders may be more closely associated with ongoing chronic stressors (e.g., Monroe & Roberts, 1990; Moos, 1992). Based on these considerations, Moos and his colleagues (Moos, 1992; Moos & Moos, 1994) developed a measure—the Life Stressors and Social Resources Inventory (LISRES)—that has been used in a variety of populations to provide an integrated assessment of chronic stressors, discrete life events, and social supports. The LISRES was administered at the pre-operative assessment to test the hypothesis that decreased social support and stressful life events are risk factors for the development of PMPS and phantom breast pain following mastectomy.

Results of Interim Analyses

As described in detail in the attached poster presentation (Appendix, Jung et al., 2002), the results of interim analyses suggested that age, malignancy, pre-operative pain, early post-operative acute pain, higher pre-operative anxiety, and greater illness concern were risk factors for the development of chronic pain in univariate analyses. Age and pre-operative pain both contributed significantly to the prediction of chronic pain at three months post-surgery in a mulitvariate logistic regression analysis, but subsequent entry of psychological distress and illness concern measures did not significantly improve the fit of the model. Analyses of the complete database will further examine these relationships.

Key Research Accomplishments

1. 114 patients have been enrolled in the research protocol and all but 6 have completed all follow-up assessments.

2. Two participants have withdrawn from participation in the study; four participants changed residences or telephone numbers and could not be contacted for follow-up.

3. Computer-scannable data collection forms were prepared to ensure accurate data entry and minimize the amount of effort required for data verification.

4. Information regarding breast cancer history, type of surgery, degree of sparing of the intercostobrachial nerve, type and duration of operative and post-operative anesthesia and analgesia, dosage and portal of entry of radiation treatment, and chemotherapy has been obtained from the patients' attending surgeon, operative report, and hospital records.

5. Interim analyses of the data have been conducted and presented at four conferences (Dworkin et al., 2000; Kulick et al., 2001; Jung et al., 2002a, 2002b), and publications related to the research have been prepared (Dworkin et al., 2001; Jung et al., submitted). Referecnes to these materials appear directly below in "Reportable Outcomes."

6. Data entry and verification are ongoing, and it is anticipated that the database will be locked in April 2003 and final analyses will be conducted immediately afterwards.

7. These accomplishments constitute completion of Tasks 1-6 and 8 and satisfactory progress on Tasks 7 and 9 described in the approved Statement of Work.

Reportable Outcomes

Dworkin, R.H., Kulick, D.I., Andrus, C.H., Hogan, L.H., Nagasako, E.M., Pennella-Vaughan, J., Perkins, F.M. Chronic pain following breast cancer surgery. Paper presented at the Department of Defense Breast Cancer Research Program Era of Hope meeting, Atlanta, Georgia, June 2000.

Dworkin, R.H., Nagasako, E.M., Galer, B.S. Assessment of neuropathic pain. In D.C. Turk & R. Melzack (Eds.), *Handbook of pain assessment* (2nd ed.). New York: Guilford Press, 2001.

Kulick, D.I., Hogan, L.H., Nagasako, E.M., Andrus, C.H., Dworkin, R.H. Chronic pain following breast cancer surgery: Prevalence and risk factors. Paper presented at the 21st annual scientific meeting of the American Pain Society, Phoenix, Arizona, April 2001.

Jung, B.F., Hogan, L.A., Kulick, D.I., Andrus, C., Dworkin, R.H. Chronic pain following breast cancer surgery: Prevalence and risk factors. Paper presented at the 7th annual scientific symposium of the James P. Wilmot Cancer Center at the University of Rochester, Rochester, New York, October 2002a.

Jung, B.F., Hogan, L.A., Kulick, D.I., Andrus, C., Dworkin, R.H. Chronic pain following breast cancer surgery: Prevalence and risk factors. Paper presented at the 5th International Conference on the Mechanisms and Treatment of Neuropathic Pain, Bermuda, November 2002b.

Jung, B.F., Ahrendt, G.M., Oaklander, A.L., Dworkin, R.H. Neuropathic pain following breast cancer surgery: Review and proposed classification. Submitted for publication.

Conclusions

The results of interim and ongoing analyses of the data suggest that age, presence of malignancy, presence of pre-operative pain and early post-operative acute pain, higher pre-operative anxiety, and greater illness concern may be risk factors for the development of chronic pain following surgical procedures for breast cancer. These risk factors and additional variables will be re-examined in final analyses of the complete locked database, at which time additional risk factors may also be identified.

Advances in the diagnosis and treatment of breast cancer, accompanied by improved disease control and increased survival time, will increase the challenge of controlling symptoms such as chronic pain and their negative impacts on quality of life. Chronic pain following breast cancer surgery—whether phantom breast pain, intercostobrachial neuralgia associated with mastectomy or lumpectomy, or scar pain—can be studied before the pain has developed in large patient samples. Such prospective studies will not only further increase understanding of the natural history of these chronic pain syndromes, but will also provide an important opportunity to investigate mechanisms accounting for the transition from acute to chronic pain. Knowledge of natural history, risk factors, and mechanisms will inform and enhance understanding of the processes by which chronic pain following breast cancer surgery develops and may lead to the development of more effective preventive interventions and treatment approaches for these disabling syndromes.

Personnel who have Received Salary Support from the Research Effort

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Chronic Pain Following Breast Cancer Surgery: Prevalence and Risk Factors

Beth F. Jung, EdD, MD, MPH, Laura A. Hogan, MS, NP, Dale I. Kulick, PhD, Carl H. Andrus, MD, and Robert H. Dworkin, PhD

University of Rochester Medical Center, Rochester, New York

Introduction

As many as 55% of women who undergo surgery for breast cancer develop post-surgical pain that may persist for months to years[1]. Although little is known about such pain syndromes once they have become chronic (i.e., at least three months following surgery), it is clear that patients can be significantly disabled and may experience substantial reductions in quality of life. The primary aims of this study are to identify risk factors for chronic pain following surgery for breast cancer, characterize its natural history, and examine its impact on women's quality of life.

Methods

Subjects

- 87 patients who have undergone breast surgery for cancer (150 anticipated by conclusion of study).
- English-speaking and at least 18 years of age.
- Recruited from surgical service at Strong Memorial Hospital, Rochester, NY.

Procedures

- Women scheduled for breast surgery for cancer who authorized the release of their names and telephone numbers to the study coordinator were contacted to describe the nature of the study and determine interest in participation.
- Those who agreed to participate were interviewed pre-operatively, within two weeks of surgery.
- A variety of interview and questionnaire measures of demographic, medical, pain, and psychosocial status were administered at this initial assessment.
- Post-operative pain and analgesic use were assessed via telephone interviews at 2 and 10 days after surgery.
- At 1, 3, 7, and 12 months following surgery, telephone interviews were conducted in which persisting surgery-related pain and disability, analgesic use, interim health status and treatment history, and psychological distress were assessed.
- The individuals conducting these follow-up interviews were blind with respect to the information collected during the initial assessment.

Measures: Initial assessment

- The present analyses are focused on comparing patients who did and did not report some degree of persisting pain at three months after surgery with respect to measures administered at the initial assessment.
- Age, presence of pre-operative breast pain, presence of malignancy, history of diagnostic core biopsy, type of surgery, acute post-operative pain (within 48 hours of surgery), self-reported overall pre-operative health, and four sets of psychosocial measures hypothesized to predict chronic pain were examined:

1. Depression: Hamilton Rating Scales - Depression (HAM-D)[2] and Beck Depression Inventory (BDI)[3]
2. Anxiety: Hamilton Rating Scales - Anxiety (HAM-A)[4] and State-Trait Anxiety Inventory, state version (STAI)[5]
3. Disease conviction: Illness Behavior Questionnaire disease conviction scale (IBQ)[6]
4. Somatosensory focus: Somatosensory Amplification Scale (SAS)[7]

Measures: Follow-up interview

- Chronic pain at three months after surgery was defined using two methods:
  - Method 1, denoting any pain: On 11-point numerical scales ranging from 0 to 10, any non-zero rating of either current pain or worst, least, or average pain within the past week.
  - Method 2, denoting moderate-to-severe pain: On a 0 to 10 numerical rating scale, a rating greater than 4 for worst pain within the last week. This method was based on the results of a recent study indicating that worst pain ratings 1-4 correspond with mild pain, 5-6 with moderate pain, and 7-10 with severe pain[8].
- 87 participants have been interviewed for the three-month follow-up as of April 1, 2001.

Results

- Two-tailed t-tests and chi-square tests comparing participants who did and did not develop chronic pain with respect to each of the measures from the initial assessment were used to test predictions based on previous prospective studies of the development of chronic pain syndromes[9].
- Based on Method 1, 43 (49%) participants reported some degree of pain three months after surgery, 44 (51%) did not.
- Based on Method 2, 13 (15%) participants reported moderate-to-severe pain three months after surgery, 74 (85%) did not.
- As can be seen from Table 1, participants who were younger as well as those who were diagnosed with cancer were significantly more likely to have developed some degree of chronic pain by three months after surgery.

Table 1: Demographic and Clinical Variables in Patients Reporting Various Levels of Chronic Pain Three Months After Breast Surgery

Measure	Pts. with no chronic pain (n=44)	Pts. with any chronic pain (n=43)	Pts. with no/mild chronic pain (n=74)	Pts. with mod/sev chronic pain (n=13)
Age (years)	60.1	55.1*	58.0	55.7
Malignancy (% pts.)	60.5	88.5*	66.2	92.3†
Type of surgery (%)				
Lumpectomy (n=64)	59.1	40.9	90.9	30.8
Lumpectomy w/nodes or mastectomy (n=43)	41.9	58.1	79.1	69.2
Biopsy taken (%)	65.9	69.8	66.2	76.9
Pre-op health (1-6)	2.2	2.2	2.1	2.4

Note. Statistical significance levels in the second and fourth columns reflect the results of two-tailed t-tests and chi-square tests:
† $p \leq .10$; * $p \leq .05$

- As can be seen from Table 2, participants who developed chronic pain reported greater pre-operative pain and early post-operative pain than participants who did not. Composite ratings refer to averages of current, least, worst, and average pain for the week prior to the pre-operative assessment and over the 24 hours prior to the early post-operative assessment.

Table 2: Pre-operative (week prior to surgery) and Early Post-operative (24 hours after surgery) Pain Ratings (0-10) in Patients Reporting Chronic Pain Three Months After Breast Surgery

Measure	Pts. with no chronic pain (n=44)	Pts. with any chronic pain (n=43)	Pts. with no/mild chronic pain (n=74)	Pts. with mod/sev chronic pain (n=13)
Pre-op average	0.1	0.7*	0.3	0.5
Pre-op composite	0.2	0.7*	0.4	0.7
Post-op 24-hr. average	2.6	3.2	2.6	4.2*
Post-op composite	2.4	3.1†	2.5	4.1*

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- As can be seen from Table 3, participants who developed moderate-to-severe chronic pain (according to Method 2) had greater pre-operative anxiety than those who did not develop chronic pain.
- Although the differences between groups were not significant for either measure of depression, patients who developed pain at three months (according to Method 1) showed a nonsignificant trend toward greater pre-operative depression than those who did not.

Table 3: Psychological Distress in Patients Reporting Various Levels of Chronic Pain Three Months After Breast Surgery

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BDI	4.5	6.6†	5.1	7.9
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Table 4: Illness Concern in Patients Who Developed Various Levels of Chronic Pain Three Months After Breast Surgery

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IBQ	3.6	4.7	3.9	5.5†
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Note. Statistical significance levels in the second and fourth columns reflect the results of two-tailed t-tests:
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- To further examine the relationships among the risk factors for the development of chronic pain, a logistic regression analysis was conducted in which age and presence of malignancy were entered first in the model, the two pre-operative and two acute post-operative pain ratings were entered second in stepwise fashion, and the independent contributions of psychosocial risk factors were examined last. As proposed by Hosmer and Lemeshow (1989)[10], measures were included in these analyses when their univariate tests had p values of <.25.
- Results of these analyses revealed that age and presence of malignancy both contributed significantly to the prediction of chronic pain at three months post-surgery, and that the fit of the model was significantly improved when the rating of average pre-operative pain over the week prior to the initial assessment (log-likelihood χ^2=6.24, df=1, p=.01) was entered in the analysis. Subsequent entry of psychological distress and illness concern measures did not significantly improve the fit of the model.

Conclusions and Implications

- Age, malignancy, pre-operative pain, early post-operative acute pain, higher pre-operative anxiety, and greater illness concern were found to be risk factors for the development of chronic pain following surgical procedures for breast cancer in the univariate analyses.
- Identification of risk factors for chronic pain syndromes following breast cancer surgery will enhance understanding of the processes by which they develop and may lead to the development of more effective preventive interventions and treatment approaches.

References

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Chronic Pain F

Beth

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ollowing Breast Cancer Surgery: Prevalence

F. Jung, EdD, MD, MPH, Laura A. Hogan, MS, NP, Dale I. Kuli
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Chapter 27

Assessment of Neuropathic Pain

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ELNA M. NAGASAKO
BRADLEY S. GALER

Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as pain "initiated or caused by a primary lesion or dysfunction in the nervous system" (Merskey & Bogduk, 1994, p. 212). Depending on where the lesion or dysunction is located within the nervous system, neuropathic pain is subdivided into *peripheral* and *central* neuropathic pain. As with other types of pain, a distinction is also made between *acute* and *chronic* neuropathic pain. Following the convention established by the IASP, neuropathic pain can be considered chronic when it has persisted beyond the normal time of healing; with nonmalignant pain, "three months is the most convenient point of division between acute and chronic pain," whereas for cancer pain, "three months is sometimes too long to wait before regarding a pain as chronic" (Merskey & Bogduk, 1994, p. xi). Unfortunately, many patients suffering from neuropathic pain have chronic pain.

In this chapter, we emphasize assessment methods developed specifically for neuropathic pain. Methods more commonly used for other types of pain are also discussed, with an emphasis on their role in the assessment of neuropathic pain. Although the research we discuss has been conducted primarily in patients with peripheral neuropathic pain, many of the techniques and results are also relevant to patients with central neuropathic pain and neuropathic pain associated with cancer (e.g., Allen, 1998; Berić, 1998). We devote more attention to the assessment of chronic, rather than acute, neuropathic pain, which reflects the greater emphasis on chronic pain in the literature as well as in the clinic. We do not review research on complex regional pain syndrome (CRPS) or the unique issues associated with it, because Chapter 28 by Bruehl, Steger, and Harden is devoted to this condition. Table 27.1 lists the more common neuropathic pain syndromes, distinguishing nonmalignant peripheral and central neuropathic pain from neuropathic pain found in patients with cancer. Bennett (1997) has provided estimates of the incidence of many of these neuropathic pain syndromes, and concludes that almost 1.7 million individuals suffer from neuropathic pain in the United States (if neuropathic back pain is included, the total becomes 3.8 million).

We begin by discussing general issues in the assessment of neuropathic pain, including the different models, contexts, and goals of assessment. Next, we review the aspects of neuropathic pain that should be included in a comprehensive assessment. We then discuss the methods most commonly used in assessing neuropathic pain—specifically, the history and neurological examination, patient self-report questionnaires, and various procedures (with an emphasis on quantitative sensory testing, or QST).

TABLE 27.1. Common Types of Neuropathic Pain

Peripheral neuropathic pain	Central neuropathic pain	Cancer-associated neuropathic pain
Carpal tunnel syndrome	Central poststroke pain	Chemotherapy-induced polyneuropathy
Complex regional pain syndrome (CRPS)	HIV myelopathy	Neuropathy secondary to tumor infiltration or nerve compression
HIV sensory neuropathy	Multiple sclerosis pain	Phantom breast pain
Meralgia paresthetica	Parkinson's disease pain	Postmastectomy pain
Painful diabetic neuropathy	Spinal cord injury pain	Postradiation plexopathy and myelopathy
Phantom limb pain	Syringomyelia	
Postherpetic neuralgia (PHN)		
Postthoracotomy pain		
Trigeminal neuralgia		

GENERAL ISSUES

Disease versus Mechanism Models of Neuropathic Pain

Until recently, the primary goal of pain assessment has been diagnosis—that is, determining what disease or condition is responsible for the patient's pain complaint. During the past several years, however, an alternative perspective for how best to conceptualize a patient's pain has emerged from the basic science literature and from the relatively limited clinical advances that have been made with the traditional disease-based approach. This alternative to classifying patients based on disease is a classification based on pain mechanisms. In this approach, the major goal of assessment is to attempt to identify the specific pathophysiological mechanisms of the patient's pain and to use these mechanisms to identify appropriate treatments (Arnér, 1998; Max, 1990, 1991; Meyerson, 1997; Woolf et al., 1998; Woolf & Decosterd, 1999; Woolf & Mannion, 1999).

The impetus for this novel approach comes from the identification of a large number of pain mechanisms in research on animals and humans (see, e.g., Bennett, 1994; Fields & Rowbotham, 1994; Fields, Rowbotham, & Baron, 1998; Wiesenfeld-Hallin, Hao, & Xu, 1997). In addition, there is a growing recognition that pain syndromes identified by disease—for example, postherpetic neuralgia (PHN) or painful diabetic neuropathy—most likely have mutiple distinct underlying pain mechanisms. There are several implications of this perspective. One is that patients with the same disease typically have differing pathophysiologies that result in different patterns of symptoms and physical findings. In other words, neuropathic pain syndromes include heterogeneous groups of patients who differ in their symptoms, treatment response, and prognosis. This heterogeneity may be conceptualized in terms of different subtypes of patients (see, e.g., Rowbotham, Petersen, & Fields, 1998) or as the co-existence of different mechanisms within patients that vary between patients in the extent to which they account for pain. It follows that patients with different diseases may be more similar to each other with respect to the mechanisms of their pain than they are to other patients with the same disease. For example, a patient with PHN may share underlying pain mechanisms with a patient with painful diabetic neuropathy, but not with another patient with PHN.

At present, it is not possible to directly identify the specific pathophysiological mechanisms that account for a report of pain or a patient's findings on physical examination. Therefore, although it is based on a considerable body of research, there is limited evidence that the mechanism-based approach to pain assessment has greater value than the disease-based approach. No large prospective clinical studies have been reported that assess whether mechanism-based assessment and treatment lead to improved patient outcomes. Clinical researchers are currently examining the extent to which pain mechanisms can be identified from patterns of symptoms, pain quality, physical findings, sensory testing, and response to pharmacological challenges (Galer & Jensen, 1997; Rowbotham, Petersen, & Fields, 1998; Woolf & Decosterd, 1999).

Because this mechanism-based perspective is becoming increasingly important in research on neuropathic pain and on its treatment, we discuss assessment from both the traditional disease-based perspective and the perspective of this new alternative conceptualization. It will be apparent that these different models of pain have important implications not only for understanding pathophysiology, but also for assessing pain, predicting treatment response, and examining the natural history of a patient's pain.

The Context and Goals of Neuropathic Pain Assessment

The assessment of neuropathic pain occurs within two broad contexts. One is the clinical context, in which patients are evaluated and treated. The second is the context of clinical research, in which typical studies seek to evaluate the efficacy of treatments or to describe the characteristics of patients and the natural histories of their pain syndromes. These different contexts are accompanied by different but partially overlapping sets of goals for the assessment of patients. In the clinic, the predominant goals are diagnosis and treatment. Thus a physician's goals in this context are to provide a thorough and precise assessment that will (1) improve the chances of making the correct diagnosis of a patient's pain condition (e.g., is this patient's chest pain PHN or Tietze's syndrome?), (2) guide the tailoring of treatment to a specific pain condition (e.g., will a tricyclic antidepressant or a series of nerve block injections provide the most pain relief?), (3) provide information regarding prognosis, and (4) provide a means of evaluating treatment outcome.

In clinical research, the goals of patient assessment often differ from the goals of assessment in the clinic. In clinical trials of treatment, for example, a major goal of assessment is to determine whether a patient meets criteria for inclusion in a particular study. Depending on whether the study has a disease-based or a mechanism-based perspective, criteria for inclusion in a study would include either the patient's diagnosis or the mechanism of the patient's pain. The mechanism-based approach to determining eligibility for a study can involve mechanisms at different levels of specificity—for example, neuropathic versus non-neuropathic pain, peripheral versus central neuropathic pain, central hyperactivity versus central reorganization, large-fiber versus small-fiber loss.

A second major goal of clinical research overlaps with an important goal in the clinical setting: that is, to reliably assess symptoms and physical findings as a means of establishing treatment efficacy or the natural history of a disease. In the traditional disease-based model of pain, the assessment of treatment outcome evaluates various aspects of the patient's pain syndrome—for example, pain intensity, pain quality, the staged severity of the disorder, and the impact of the pain syndrome on quality of life. In a mechanism-based approach, on the other hand, treatment outcome is assessed by evaluating the specific mechanisms of the patient's pain. For example, once pain mechanisms have been identified at a baseline visit, subsequent assessments will evaluate these mechanisms and determine whether they have been affected by treatment.

Although in the following review we emphasize the assessment of neuropathic pain in clinical research, much of what we discuss also has applicability within the clinic. One major reason for this is the steadily increasing attention to the necessity of documenting patient outcomes as a routine part of the daily evaluation and treatment of patients with pain.

WHAT SHOULD BE ASSESSED?

Continuous Pain and Abnormal Sensation

Before we describe specific measures and methods, it is important to review the types of pain (and other abnormal sensations) that should be included in a comprehensive assessment of neuropathic pain. In evaluating neuropathic pain, an initial distinction must be made between *stimulus-evoked* pain and *spontaneous* pain that is stimulus-independent (Bennett, 1994). Spontaneous pain and sensations are present in the absence of any stimulation, and can be further subdivided into *continuous* and *intermittent* types. Continuous pain is present all or almost all of the time, although patients usually report that it varies in intensity. Moreover, most patients describe more than one type of spontaneous pain; that is, their pain has several different qualities (e.g., burning, throbbing, cold-like; Galer & Jensen, 1997). The predominant qualities of continuous pain, which are discussed below, not only vary within patients but also between patients. The second type of spontaneous pain is intermittent pain, which is episodic and typically has a relatively short duration when it occurs. Intermittent neuropathic pain is often paroxysmal and described as shooting, stabbing, or electric-like in quality.

In addition to these two broad types of spontaneous pain, patients with neuropathic pain frequently report other spontaneous abnormal sensations. The term *dysesthesia* refers to an abnormal sensation that is unpleasant, whereas *paresthesia* refers to an abnormal sensation that is not unpleasant; each of these types of abnormal sensation can be either spontaneous or evoked (Merskey & Bogduk, 1994). Examples of dysesthesias and paresthesias commonly reported by patients with neuropathic pain are itching, numbness, tingling, and pins-and-needles sensations. It is unfortunate

that so little research has been devoted to these abnormal sensations in patients with neuropathic pain. The distinction between the sensations labeled as "painful" and the sensations that the same individual labels "unpleasant" or just "abnormal" is of particular interest in clinical trials. It is not uncommon that patients being screened for a neuropathic pain trial will describe disabling spontaneous and evoked sensations, but will refuse to call these symptoms "pain." Interestingly, this seems to occur most frequently in patients with polyneuropathy, as compared to, for example, patients with PHN. Identifying the physiological and psychological reasons why one patient refers to sensations as "pain" and another does not is an important area for future research—one that will have direct effects on patient care. It is possible that the sensory phenomena of paresthesias, dysesthesias, and pain lie on a continuum, and that individuals have different thresholds for what they consider painful along this continuum of abnormal sensation and perception. If this is true, then the most informative approach to the assessment of neuropathic pain would include a comprehensive assessment of all the abnormal sensations experienced by the patient, regardless of whether the patient calls them "painful," "unpleasant," or "abnormal."

Spontaneous continuous and intermittent pain (and abnormal sensations) vary not only in their intensity and quality, but also in their location and area, frequency, and duration. A comprehensive assessment of neuropathic pain must attend to each of these characteristics, which vary within patients as a function of time and treatment, as well as between patients. Although methods for assessing the intensity, quality, and location of spontaneous continuous pain have been the focus of a substantial number of studies, considerably less attention has been paid to the systematic assessment and interpretation of the frequency and duration of spontaneous intermittent neuropathic pain. In addition, relatively few studies have systematically examined the different qualities of neuropathic pain that patients describe. Many older textbooks differentiate *constant persistent pains* from *lancinating pains* and use this distinction for determining treatment (i.e., tricyclic antidepressants to treat the former and anticonvulsants to treat the latter); however, as we discuss below, the few prospective controlled clinical trials that have systematically assessed these pain qualities find little evidence of a differential treatment response.

Stimulus-Evoked Pain and Abnormal Sensation

The second broad type of neuropathic pain and abnormal sensation is *stimulus-evoked* pain (also termed *stimulus-dependent* pain). There is a consensus that the multiple types of stimulus-evoked pain present in patients with neuropathic pain provide important information about pathophysiology. Unfortunately, however, there is still a great deal of inconsistency in the terminology used to refer to the different types of stimulus-evoked pain. It is beyond the scope of this chapter to review these variations in terminology, and we adhere to the IASP definitions in discussing stimulus-evoked pain and abnormal sensation (Merskey & Bogduk, 1994).

As can be seen from Table 27.2, the different types of stimulus-evoked pain and abnormal sensation vary with respect to whether the provoking stimulus is normally nonpainful (i.e., *innocuous*) or normally painful (i.e., *noxious*). They also vary with respect to whether the patient's response is a report of pain or another sensation. These various types of stimulus-evoked pain and abnormal sensation can be conceptualized in terms of the stimulus–response curves relating stimulus intensity to the subject's response. These evoked sensations involve abnormal changes in the intercept and/or the slope

TABLE 27.2. International Association for the Study of Pain (IASP) Definitions of Pain Terms

Pain term	Definition[a]
Allodynia	Pain due to a stimulus which does not normally provoke pain.
Analgesia	Absence of pain in response to stimulation which would normally be painful.
Hyperalgesia	An increased response to a stimulus which is normally painful.
Hyperesthesia	Increased sensitivity to stimulation, excluding the special senses.
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
Hypoalgesia	Diminished pain in response to a normally painful stimulus.
Hypoesthesia	Decreased sensitivity to stimulation, excluding the special senses.

[a]The definitions are from Merskey and Bogduk (1994).

of these stimulus–response curves, as depicted in Figure 27.1.

The response portion of these stimulus–response curves involves the patient's report of normal sensation or pain, and relatively similar assessments of these responses can be used for different evoking stimuli. The stimuli that have been used in assessing stimulus-evoked pain are of many types, including thermal (cold or heat), vibration, static (punctate or blunt), dynamic (moving brush-evoked), and chemical (e.g., capsaicin, mustard oil). Importantly, it has become clear from research on the neurophysiology of pain that distinct mechanisms are involved in the response to these different types of stimuli. One broad and oversimplified distinction is between stimuli that normally activate Aβ-fiber mechanoreceptors and stimuli that normally activate Aδ- and C-fiber nociceptors. The characteristics of the major sensory fibers that are relevant to neuropathic pain and its assessment are presented in Table 27.3. The typical stimuli that normally activate each of these fiber types, and the different sensations that are normally experienced as a result of this activity, are also presented in the table. In patients with neuropathic pain, these relationships among evoking stimuli, activity in primary afferents, and sensory experience are often abnormal and can provide important information about the mechanisms of their pain (Bennett, 1994; Fields et al., 1998; Koltzenburg, 1995, 1996).

A comprehensive assessment of the different types of stimulus-evoked neuropathic pain and abnormal sensations must attend to their intensity, quality, location and area, frequency, and duration—all of which vary within patients as a function of time and treatment, as well as between patients. However, a comprehensive assessment of stimulus-evoked pain is not typically performed in clinical practice, and unfortunately has not often been conducted in clinical research. Separate analyses of intensity, duration, and area have rarely been reported in either the experimental or clinical literature;

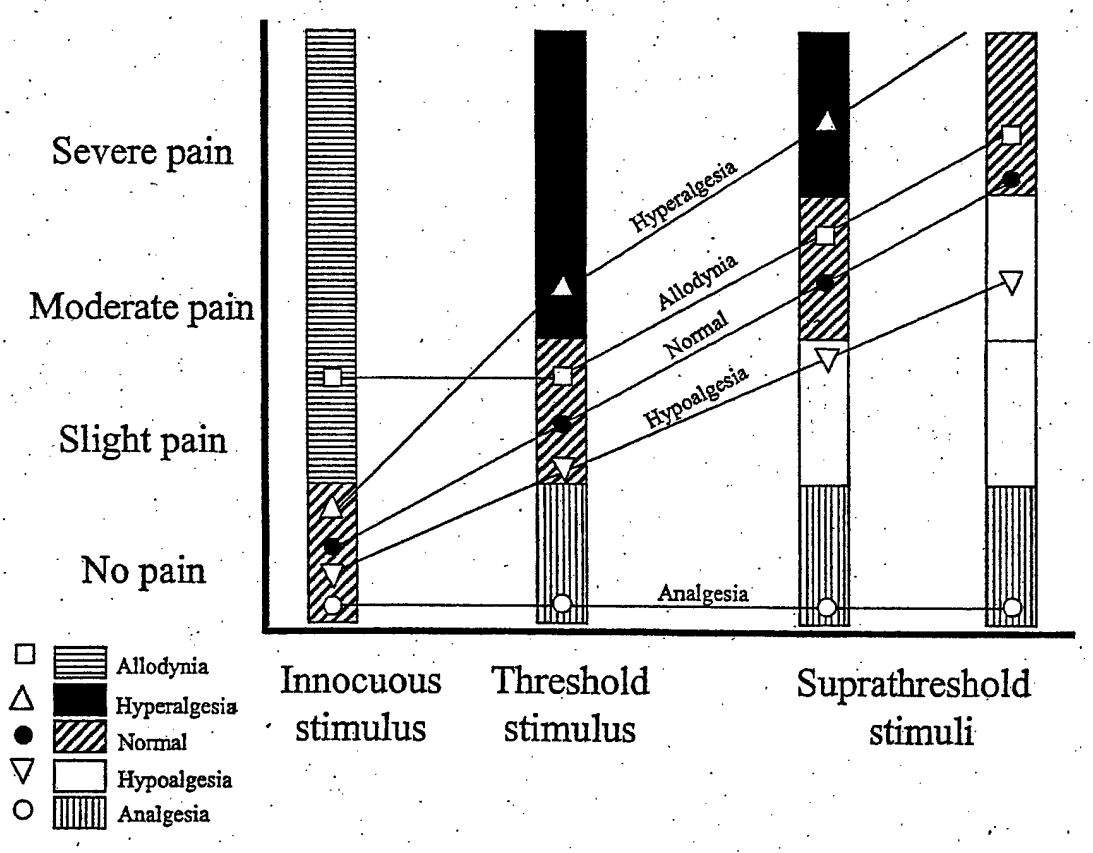

FIGURE 27.1. Stimulus–response curves for sensory abnormalities associated with neuropathic pain. Shaded regions indicate ranges of abnormal response to different stimulus intensities.

TABLE 27.3. Characteristics of Primary Sensory Neurons

Fiber class	Receptor type	Adequate stimulus	Perceived sensation	Myelination
Aβ	Low-threshold mechanoreceptor (e.g., Ruffini, Merkel receptors)	Maintained displacement	Sustained pressure	Myelinated
	Low-threshold mechanoreceptor (e.g., Meissner corpuscle)	Velocity of displacement	Flutter	Myelinated
	Low-threshold mechanoreceptor (e.g., Pacinian corpuscle)	Vibration	Vibration	Myelinated
Aδ	Low-threshold mechanoreceptor	Velocity of displacement		Myelinated
	Cooling thermoreceptor	Innocuous cooling	Cooling	Myelinated
	Mechanical nociceptor	Noxious mechanical stimuli	Sharp pain	Myelinated
	Thermal nociceptor	Noxious thermal stimuli	Sharp pain	Myelinated
C	Warming thermoreceptor	Innocuous warming	Warmth	Unmyelinated
	Cooling thermoreceptor	Innocuous cooling	Cooling	Unmyelinated
	Polymodal nociceptor	Noxious mechanical stimuli Noxious thermal stimuli Noxious chemical stimuli	Burning pain	Unmyelinated
	Mechanical nociceptor	Noxious mechanical stimuli		Unmyelinated
	Thermal nociceptor	Noxious thermal stimuli	Burning pain	Unmyelinated

Note. The information presented in this table has been drawn from Light and Perl (1993) and from Martin and Jessell (1991).

Bennett (1994) notes that this is unfortunate, because there is evidence that abnormalities in the intensity of stimulus-evoked neuropathic pain can be distinguished from abnormalities in its duration.

CLINICAL EVALUATION OF NEUROPATHIC PAIN

A careful history and physical examination play an essential role in the comprehensive assessment of neuropathic pain, and are as important in clinical research as in the clinic. There is a great deal of information relevant to the assessment of a patient's neuropathic pain that cannot be obtained from questionnaires or procedures such as quantitative sensory testing. Although clinical practice has evolved and refined the history-taking procedures and physical examinations conducted in patients with neuropathic pain, a systematic description of the information that should be obtained is not available. Because no standardized approach to

assessment exists, there is undoubtedly a great deal of variability among individuals who conduct assessments of neuropathic pain. This variability makes it very likely that the reliability of these clinical assessments is modest at best.

In psychiatry, inadequate interrater reliability among diagnosticians has been improved by the use of standardized diagnostic criteria (American Psychiatric Association, 1994) and structured clinical interviews to assess these criteria (e.g., First, Gibbon, Spitzer, & Williams, 1997). The IASP *Classification of Chronic Pain* (Merskey & Bogduk, 1994), based on the consensus of the expert members of a task force, is the first step in the direction of standardized diagnostic criteria for pain syndromes. This taxonomy includes many neuropathic pain syndromes, but few of the diagnostic criteria have stimulated research intended to refine them (for important exceptions, see Bruehl et al., 1999; Galer, Bruehl, & Harden, 1998; Harden et al., 1999). Much less effort has been devoted to systematically describing how to obtain the information in the history and physical examination that is needed to make these diagnostic evaluations. An interview guide for the assessment of chronic pain was published a number of years ago (Melzack, 1983), but it does not include information that is now known to be important in assessing neuropathic pain. Fortunately, several recent publications provide guidance on the clinical assessment of neuropathic pain from both disease- and mechanism-based perspectives (Backonja & Galer, 1998; Galer, 1998; Koltzenburg, 1998; Woolf & Decosterd, 1999), and efforts to specify the symptoms and signs that characterize different types of neuropathic pain can be expected to continue.

In recent research on diabetic neuropathy, considerable attention has been paid to the standardization of diagnostic criteria and the neurological history and physical examination (e.g., Diabetes Control and Complications Trial Research Group, 1995; Dyck, Melton, O'Brien, & Service, 1997). Pain is only one of the symptoms of diabetic neuropathy, and it is not present in all patients. Unfortunately, neither spontaneous nor stimulus-evoked pain has received a great deal of attention in these efforts to standardize diagnostic criteria and assessments in diabetic neuropathy. Typically, a detailed assessment of pain is not required, nor is the effect of pain on the patient's quality of life evaluated. Nevertheless, this research provides valuable examples of how the assessment of symptoms and signs that occur in patients with neuropathic pain could be standardized. We hope that future revisions of these instruments will include more comprehensive pain assessments.

The Total Symptom Score (TSS; Ziegler et al., 1995) is the briefest of these measures and the least comprehensive, but it nevertheless provides a clear example of how neuropathic symptoms may be assessed in a standardized manner when taking a patient's history. Four symptoms—pain, burning, paresthesias, and numbness—are each rated with respect to their intensity ("absent," "slight," "moderate," "severe") and their frequency ("occasional," "frequent," "[almost] continuous"). Each of the 12 combinations of the four levels of intensity with the three levels of frequency has been assigned a score ranging from 0 to 3.66, and each of the four symptoms receives one of these scores based on its intensity and frequency ratings. Scores on the TSS therefore range from 0 (no symptoms are present) to a maximum of 14.64 (all four symptoms are severe in intensity and [almost] continuously present). Although this measure assesses several important symptoms of diabetic neuropathy in a structured and efficient manner, the basis for the scores given to the various combinations of intensity and frequency is unclear (e.g., a severe symptom that is ocasionally present is assigned a score of 3.00, whereas a moderately intense symptom that is [almost] continuously present is assigned a score of 2.66). The TSS has not been used in clinical trials in which the primary endpoint is pain, but its separate assessment of symptom intensity and frequency is noteworthy and may provide important information that is not obtained with other measures.

The Neuropathy Symptoms and Change (NSC) questionnaire (Dyck, Peroutka, et al., 1997) provides a more comprehensive assessment of neuropathy symptoms than the TSS. The NSC instrument contains a series of 38 symptoms that are assessed as present or absent, and, if present, are rated as "slight," "moderate," or "severe." For each of these symptoms, a rating can also be made of whether the symptom is "the same," "better," or "worse" than was found in a previous assessment; for ratings of better or worse, the degree of change is rated as "slight," "moderate," or "much." The ratings are made for symptoms of weakness (e.g., "weakness of fingers when clasping or grasping objects"), sensory symptoms (e.g., "decrease or inability to feel pain, cuts, bruises, or injuries"), and autonomic symptoms (e.g., "dryness of the eyes which is not due to use of medication or known

eye disease"). For each of the sensory symptoms rated as present, a further rating is made of the part of the body that is affected. The NSC questionnaire provides relatively detailed instructions for the neurologist who is making these ratings, and it is an example of how the symptom assessments that are made during a history can be standardized with respect to both content and methods. However, because the NSC instrument is a measure of a variety of neuropathy symptoms, its assessment of neuropathic pain is not as comprehensive as would be desirable in a measure designed specifically for this purpose.

The Neuropathy Impairment Score (NIS; Dyck et al., 1995) contains a series of items in which muscle weakness, reflexes, and sensory function are rated on the right and left sides on the basis of a neurological examination. Each of the ratings of muscle weakness (e.g., wrist flexion, shoulder abduction) is made on a scale ranging from "normal" through varying degrees of weakness and movement to paralysis. The ratings of reflexes (e.g., biceps brachii, quadriceps femoris) and finger and toe sensation (e.g., pinprick, vibration) are made on a scale of "normal," "decreased," or "absent." Instructions are provided to the examiner indicating that anatomical site, age, gender, height, weight, and physical fitness should be considered when making the ratings. Although these ratings are based on the examiner's judgment of what is normal, the methods used in assessing touch pressure, pinprick, vibration sensation, and joint position are standardized. This approach to the neurological examination undoubtedly provides increased consistency in the content and methods of the assessments that are conducted. The NIS, however, does not include ratings of neuropathic pain signs such as allodynia and hyperalgesia, and it will need to be supplemented if a comprehensive assessment of neuropathic pain is required.

We have described the NSC and NIS measures in detail because we believe that these comprehensive and systematic measures of the symptoms and signs of neuropathy could serve as a guide in developing a similar approach to assessing neuropathic pain. To date, no structured history or physical examination has been developed for the comprehensive assessment of the symptoms and signs of neuropathic pain, although these would certainly be of great value. Fortunately, Backonja and Galer (1998) have provided a detailed review of the major components of an evaluation of patients with neuropathic pain. They emphasize that the assessment of pain is based on a traditional history, including a review of the chief complaint and a review of systems. In addition, they underscore the importance of paying particular attention to the specific elements of neuropathic pain, such as intensity, location, and quality of spontaneous and stimulus-evoked pain, as well as findings on physical examination of mechanical allodynia, thermal allodynia, and hyperalgesia. They also stress the importance of noting the temporal course of these symptoms.

In taking the history of a patient with neuropathic pain, there is much important clinical information that should be gathered, in addition to that which is specific to pain. This information is essential in conducting a comprehensive evaluation, and is needed to evaluate prognosis and develop a treatment plan. As with all other types of chronic pain conditions, the following should be assessed: psychiatric comorbidity (e.g., depression, anxiety disorder, posttraumatic stress disorder), sleep, work-related issues, illness conviction, rehabilitative needs, and the availability of a support system. Each of these factors can have a direct effect on symptoms, quality of life, and response to various therapies. For example, a patient with a work-related painful nerve injury who is also experiencing posttraumatic stress disorder, insomnia, depression, and the stresses of being unemployed in the workers' compensation system needs a very different therapeutic approach from that required by a retired person with PHN and no significant comorbid conditions.

The physical examination of the patient with neuropathic pain should include detailed sensory testing as well as a general neurological evaluation (Backonja & Galer, 1998). Positive and negative sensory signs, such as mechanical allodynia, thermal allodynia, and hyperalgesia, should be assessed. As Backonja and Galer (1998) stress, it is important for examiners to ask patients unambiguous questions and to observe and record patients' behavioral responses when stimuli are administered. *Mechanical allodynia*, which refers to the abnormal perception of pain evoked by a normally nonnoxious stimulus, can be subdivided into *dynamic* allodynia, which is pain evoked by a moving stimulus across the skin, and *static* allodynia, which is pain evoked by pressure applied to a single focus with a blunt object. Although the presence of mechanical allodynia can be elicited from a patient during the history, it is important to evaluate the patient's response to actual stimuli. In both clinical and research settings, dynamic allodynia can

be elicited by lightly rubbing the painful skin with a finger, cotton swab, or foam paintbrush. Static allodynia can be elicited by blunt pressure with a finger or von Frey filaments. *Thermal allodynia* is evoked by normally non-noxious thermal stimuli, either cold or hot, and it can be assessed in the clinic simply by heating or cooling a tuning fork or by applying ice briefly to the involved region. A more detailed and quantitative assessment of thermal sensation and perception can be performed via QST, which is discussed later in this chapter.

Hyperalgesia, by definition, is an exaggerated pain response evoked by a normally noxious stimulus. Unlike mechanical allodynia, the presence of hyperalgesia cannot be elicited during the history. *Summation* is an abnormally increasing painful sensation in response to a repeated stimulus while the actual stimulus remains constant; for example, as one continues to administer pinpricks to the involved skin, the perception of pain increases and becomes more painful than what would normally be experienced. *Aftersensation* is the abnormal persistence of a sensory perception provoked by a stimulus even though the stimulus has ceased, which may last for several seconds or even several minutes. In addition, patients who experience aftersensations may describe an enlarged region of pain (e.g., "The pain area got bigger and spread like a starburst").

Patients with neuropathic pain also frequently experience motor symptoms and signs, and these should be routinely assessed. Backonja and Galer (1998) point out that such patients may suffer disability from weakness, hypotonia, tremor, dystonia, incoordination, ataxia, apraxia, and motor neglect. Although motor dysfunction is less common in certain neuropathic pain conditions, such as PHN (although it may occur when PHN involves a limb), motor abnormalities are not uncommon in polyneuropathies and CRPS. In fact, several recent studies of CRPS have shown that motor dysfunction is one of the most common symptoms in this disorder (Bruehl et al., 1999; Galer, Hendersen, Perander, & Jensen, in press; Ga' : & Jensen, 1999; Harden et al., 1999; Veldman, Reynen, Arntz, & Goris, 1993).

In their discussion of both the history and the physical examination, Backonja and Galer (1998) highlight the critical importance of a careful musculoskeletal and myofascial evaluation in all patients with chronic pain. *Myofascial pain syndrome* is defined as chronic pain that is maintained by chronic tightness and spasm of soft muscles and tissues. Patients who have this pain syndrome

> may describe their pain similarly as those with neuropathic pain, using terms such as burning, shooting, and aching. Myofascial pain may develop as a secondary phenomenon, evolving from disuse or overuse of musculature being caused by the primary neuropathic pain syndrome, although in some patients it is the primary origin of the chronic pain. Thus, even in patients with definite neuropathic pain syndromes, myofascial examination is critical to assess whether a secondary myofascial component is present, because myofascial pain requires a distinct treatment strategy. (Backonja & Galer, 1998, pp. 783–784)

If the clinician or clinical researcher fails to identify the presence of a myofascial component, then the evaluation of treatment outcome of a therapy for neuropathic pain would be misleading. (For a fuller discussion of myofascial pain syndrome, see Gerwin, Chapter 26.)

Backonja and Galer (1998) conclude their discussion of the assessment of patients with neuropathic pain by noting that the diagnosis is usually straightforward and is often based on a history of nerve injury, the patient's description of symptoms, and the presence of one or more neuropathic pain sensory signs on physical examination. Nevertheless, the diagnosis of neuropathic pain may also be given without a definite history of nerve injury in patients with symptoms and physical findings that are consistent with this diagnosis. For example, Backonja and Galer note that specific symptoms and signs are associated with a diagnosis of CRPS, and that these should be assessed whether or not there is a history of nerve injury, especially if a limb is involved. We have not reviewed these symptoms and their assessment, because they are discussed in detail by Bruehl and colleagues in Chapter 28. Patients with a painful polyneuropathy do not have a definite history of nerve injury and may also present with only paresthesia, dysesthesia, or pain in the toes or feet. If such a patient has a known exposure to a neurotoxin, such as the chemotherapeutic agent paclitaxel (Forsyth et al., 1997), or has a known medical condition where polyneuropathy is a complication, such as diabetes mellitus or HIV, then diagnosis is facilitated. However, making a diagnosis of polyneuropathy in a patient with painful feet without known risk factors for polyneuropathy can be more difficult. Yet, in patients with a history and examination findings consistent with this diagnosis, it is recommended that a diagnosis of polyneuropathy should be made.

SELF-REPORT METHODS FOR ASSESSING NEUROPATHIC PAIN

Pain Intensity

What comes to mind most often when pain specialists think of pain assessment are the diverse measures available for rating the intensity of pain and describing its quality. It is as important to assess the intensity of neuropathic pain as it is to assess the intensity of other kinds of pain, and this is no less true in the clinic than it is in research. There are a large number of measures of pain intensity available; these are comprehensively reviewed by Jensen and Karoly in Chapter 2, as well as in other chapters of this volume. These measures may be grouped into three broad types: Verbal Rating Scales (VRSs; e.g., "none," "mild," "moderate," "severe"), Numerical Rating Scales (NRSs; e.g., an 11-point scale anchored by "no pain" and "worst pain imaginable"), and Visual Analogue Scales (VASs; e.g., a 10-cm line anchored by "no pain" and "pain as bad as it could be"). Some measures of pain intensity do not fit readily into one of these categories (e.g., facial scales, pain thermometers), and others (e.g., the Descriptor Differential Scale; Gracely & Kwilosz, 1988) combine aspects of more than one of these types of measures. Nevertheless, most assessment of pain intensity is conducted with either VRSs, NRSs, or VASs.

The choice of one of these measures is most often based on the experience of the investigator. Although there are a number of studies in the literature that compare two or more of these different methods (e.g., Duncan, Bushnell, & Lavigne, 1989; Jensen, Karoly, & Braver, 1986; Price, Bush, Long, & Harkins, 1994), to our knowledge no study of this design has been conducted specifically with patients who have neuropathic pain. After reviewing this literature and comparing the advantages and disadvantages of different methods of measuring pain intensity in diverse samples of patients with chronic pain, Jensen and Karoly (1992) concluded in the first edition of this volume that "unless a particular clinician or researcher has a very strong rationale for using a VAS over other scales, we recommend against using the VAS as a *primary* (or sole) measure of pain intensity in adult clinical populations" (p. 140, original emphasis). They reach a similar conclusion in Chapter 2 of this volume.

This recommendation is based primarily on the difficulty that some patients have in understanding and using VAS measures of pain intensity. This problem may be particularly prevalent in elderly individuals (see, e.g., Carlsson, 1983; Kremer, Atkinson, & Ignelzi, 1981; Max, 1991), perhaps as a result of increased difficulty with abstraction (Walsh, 1984), which is consistent with our experience in using a VAS with older individuals. Because many common neuropathic pain syndromes are more prevalent in the elderly (e.g., PHN, painful diabetic neuropathy, central poststroke pain), use of a VAS may be limited in the assessment of neuropathic pain. Another obvious problem with using the VAS is that it cannot be administered in a telephone interview or to subjects who cannot indicate their pain with a written response (either because of limited motor function or because of the specific assessment situation—for example, during functional magnetic resonance imaging [MRI]).

Jensen and colleagues have conducted a series of studies comparing different measures of pain intensity (e.g., Jensen et al., 1986; Jensen, Miller, & Fisher, 1998; Jensen, Turner, & Romano, 1994). The results of these studies suggest that NRS methods of assessing pain intensity are somewhat superior to other approaches in the extent to which they are used accurately by subjects. In addition, it appears that a 21-point scale with numbers ranging from 0 to 100 in multiples of 5 may be the optimal measure. This is certainly consistent with our clinical and research experience, in which patients often respond with two adjacent numbers when administered a 0–10 scale orally, or indicate a point midway between two adjacent numbers when administered an 11-point scale in a written format. We therefore recommend the use of NRS methods (in preference to VAS and VRS methods) to assess pain intensity in research on neuropathic pain (see, e.g., Anderson, Syrjala, & Cleeland, Chapter 30, this volume; Jensen et al., 1998; but see also Price et al., 1994).

An important question regarding the assessment of pain intensity involves whether the pain rated by the patient is current, usual (average), worst, or least pain. In addition, when usual, worst, and least pain are assessed, a time frame for the ratings must be selected (e.g., past week, past 24 hours, today, since previous rating). Often these decisions will be determined by the specific clinical or research question. However, there are many situations in which the investigator must decide among these options, and there is unfortunately not a great deal of guidance in the literature in making these choices.

Pain Location, Frequency, and Duration

As noted above, less attention has been devoted to the systematic assessment of pain location and area, pain frequency, and pain duration. In assessing pain location and area, a common approach is to ask patients to indicate the area of their pain on drawings of the front and back of the human body. Such drawings may be analyzed in various ways, including total area of pain, number of body regions affected, and anatomical appropriateness or abnormality (for a review, see Jensen & Karoly, Chapter 2). With respect to neuropathic pain, it is possible to examine the total affected area not only of spontaneous pain but also of stimulus-evoked pain (e.g., the area of allodynia). There are various methods for doing this, including ratings by the investigator of the percentage of the dermatome(s) affected, and assessments of change in area using body maps, tracings of the affected area, and/or a polar planimeter. The most accurate assessment of variables such as total affected area and percentage of dermatome affected would be obtained by analyzing digital photographs, and the use of this approach is certain to increase in the coming years. Unfortunately, no published clinical trial has prospectively evaluated change in the size of the painful area with treatment. Yet, based on the evidence that prolonged neuropathic pain can be accompanied by an enlargement in receptive fields (e.g., Coderre, Katz, Vaccarino, & Melzack, 1993), it may be expected that a positive response to treatment could be manifested as the shrinkage of a painful area.

The systematic assessment of neuropathic pain frequency and duration has received little attention, although their importance has been emphasized by Bennett (1994). When measured, these aspects of pain have typically been assessed on an ad hoc basis. Several examples of questions for assessing pain frequency and duration are provided by Von Korff (Chapter 31). These could be readily adapted for use with both spontaneous and stimulus-evoked neuropathic pain.

Pain Quality

The assessment of different pain qualities has been an integral component of the assessment of neuropathic pain for many years, and has been emphasized in descriptive surveys (e.g., Bhala, Ramamoorthy, Bowsher, & Yelnoorker, 1988; Chan et al., 1990), clinical trials (e.g., Max et al., 1992; Watson & Babul, 1998), and research on pathophysiology (Baron & Saguer, 1993; Rowbotham, Petersen, & Fields, 1998). Often the quality of spontaneous and stimulus-evoked neuropathic pain has been assessed with simple questions and procedures (e.g., pinprick, cotton swab) developed specifically for a particular study. During the past several years, there has been an increased interest in improving the accuracy of assessments of pain quality. The reasons for this include the need for measures of treatment response that may be more sensitive than overall ratings of pain intensity, and the expectation that different pain qualities may reflect distinct pathophysiological mechanisms.

For the past 25 years, the preeminent method for systematically assessing the quality of a patient's spontaneous pain has been the McGill Pain Questionnaire (MPQ), which includes sensory, affective, and evaluative descriptors of pain (Melzack, 1975; see Melzack & Katz, Chapter 3). The MPQ has been as frequently used in the assessment of neuropathic pain as in the assessment of all other types of acute and chronic pain. Indeed, one of the earliest efforts to demonstrate the ability of the MPQ to discriminate among different types of pain included two examples of neuropathic pain, PHN and phantom limb pain (Dubuisson & Melzack, 1976).

Later studies using the MPQ included demonstrations that it could discriminate trigeminal neuralgia from atypical facial pain (Melzack, Terrence, Fromm, & Amsel, 1986), symptomatic diabetic neuropathy from non-neuropathic leg and/or foot pain (Masson, Hunt, Gem, & Boulton, 1989), diverse types of peripheral neuropathic pain from chronic benign pain (Boureau, Doubrère, & Luu, 1990), and chronic pain following complete spinal cord injury from chronic pain following partial injury (Defrin, Ohry, Blumen, & Urca, 1999). In the study conducted by Boureau and colleagues (1990), six MPQ Sensory adjectives were significantly more frequently chosen by patients with neuropathic pain ("electric shock," "burning," "cold," "pricking," "tingling," "itching"); of these, electric shock, burning, and tingling were the most common in the patients with neuropathic pain (53%, 54%, and 48%, respectively). These results provide important support for clinical observations that these adjectives are particularly valuable in identifying patients with neuropathic pain. However, several other adjectives typically considered characteristic of neuropathic pain did not discriminate the two groups (e.g., "lancinating," "shoot-

ing"). One very interesting finding in this study was that all of the MPQ Affective adjectives were less frequently chosen by the patients with neuropathic pain, and in some cases the differences were large (e.g., "fearful" was endorsed by 48% of the patients with non-neuropathic pain, but only 3% of the patients with neuropathic pain).

The MPQ has also been used to characterize changes in the quality of pain in specific neuropathic pain syndromes. For example, the quality of acute neuropathic pain in herpes zoster has been compared with the quality of chronic pain in PHN (Bhala et al., 1988; Bowsher, 1993). Sharp, stabbing pain was found to be more common in patients with acute herpes zoster than in patients with PHN, whereas burning pain was found to be more common in patients with PHN and was much less likely to be reported by patients with acute herpes zoster. Unfortunately, these results were based on cross-sectional studies of different groups of patients and not a prospective study of the same individuals. Interestingly, other data suggest that throbbing and burning pain should be examined separately in PHN. Patients with PHN who had received the antiviral agent acyclovir for treatment of their acute herpes zoster infection were found to be much less likely to report burning pain than patients with PHN who had not received acyclovir; reports of throbbing pain in these two groups, however, did not differ (Bowsher, 1992, 1993). Given the strong association between the adjective "burning" and neuropathic pain found in the study conducted by Boureau and colleagues (1990), one interpretation of these data is that antiviral treatment attenuates the development of one of the mechanisms of neuropathic pain in PHN.

Because the MPQ can be relatively time-consuming for some patients, Melzack (1987) has developed a short form of the MPQ (SF-MPQ). The initial studies of the reliability and validity of the SF-MPQ examined postsurgical, labor, and musculoskeletal pain, but did not include patients with neuropathic pain (Melzack, 1987). In subsequent research, however, this measure has been used in what are the two largest placebo-controlled clinical trials ever conducted for neuropathic pain. These studies reported beneficial effects of gabapentin treatment on SF-MPQ Total, Sensory, and Affective scores in patients with PHN (Rowbotham, Harden, Stacey, Bernstein, & Magnus-Miller, 1998) and painful diabetic neuropathy (Backonja et al., 1998). In additional analyses of the data from the PHN trial in which the individual SF-MPQ items were examined, treatment with gabapentin was associated with significantly greater pain relief for 10 of the 11 Sensory items and all four of the Affective items (Stacey, Rowbotham, Harden, Magnus-Miller, & Bernstein, 1999). In the results of a parallel series of analyses in which the SF-MPQ data from the diabetic neuropathy trial were examined, gabapentin treatment was associated with significantly greater pain relief for 9 of the 11 Sensory items, and nonsignificant improvement in all four of the SF-MPQ Affective items (Dworkin, 1999).

The results of these studies demonstrate the value of the MPQ and SF-MPQ in the assessment of patients with neuropathic pain. For assessing neuropathic pain, the greatest value of these measures may lie less in the Total, Sensory, and Affective scores and more in the ratings of the 11 Sensory descriptors. A similar conclusion was reached by the investigators of a multicenter study of the MPQ in 1,700 patients with chronic pain, who concluded that combining the MPQ descriptors into subscales may seriously limit the information obtained, because "information concerning the specific pain qualities endorsed by the patient is lost" (Holroyd et al., 1992, p. 309).

One possible interpretation of the results of the SF-MPQ analyses in the PHN and painful diabetic neuropathy gabapentin clinical trials, in which little discrimination among pain qualities in treatment response was found, is that the MPQ must be supplemented by more specific and sensitive measures when neuropathic pain is being assessed. Of course, the MPQ and the SF-MPQ were not developed specifically for the assessment of neuropathic pain. Galer and Jensen (1997) recently developed the Neuropathic Pain Scale (NPS; see Appendix 27.A), which was specifically designed to assess the different qualities of neuropathic pain in a questionnaire format. In initial studies of the validity of the NPS (Galer & Jensen, 1997), the measure discriminated patients with PHN from patients with three other types of neuropathic pain (i.e., complex regional pain syndrome, diabetic neuropathy, and peripheral nerve injury). The NPS also successfully assessed the treatment response to intravenous lidocaine and phentolamine infusions in a group of patients with central and peripheral neuropathic pain.

In a more recent study, the NPS was used to assess the prevalence of pain in patients with Charcot–Marie–Tooth (CMT) disease and to compare pain quality in CMT disease and several peripheral neuropathic pain syndromes (Carter et al., 1998). The results of this study demonstrated that pain intensity and pain quality in CMT disease and

in PHN, CRPS, diabetic neuropathy, and peripheral nerve injury were generally comparable, and they provided additional support for the value of the NPS in the assessment of neuropathic pain. Although the NPS is being widely used as a treatment outcome measure in neuropathic pain clinical trials, it remains to be seen whether the NPS is a more sensitive measure of treatment outcome than the MPQ or even a single overall pain intensity measure. In addition, future research will need to determine whether the different pain qualities assessed by self-report questionnaires such as the MPQ or the NPS actually reflect distinct pain mechanisms in patients with neuropathic pain.

It is important to emphasize that no measure of pain quality, whether the MPQ or NPS, was designed as a diagnostic tool for neuropathic pain. Studies using both of these measures have provided data suggesting that patients with different neuropathic pain syndromes may have significantly different profiles of pain qualities. For neither measure, however, are there data that support its use as a diagnostic tool to differentiate neuropathic pain from other types of pain, such as myofascial pain or arthritis. Such studies are currently being conducted for the NPS.

QUANTITATIVE SENSORY TESTING

The assessment of sensory thresholds provides a method of examining the function of peripheral nerve fibers and their central connections (Yarnitsky, 1997). Because different fiber groups participate in the perception of different stimulus modalities, the assessment of several modalities allows the characterization of function across a variety of fiber populations. Small fibers, whose function is not readily assessed by nerve conduction studies, are one of the fiber groups that can be readily examined (Triplett & Ochoa, 1990). The information that can be obtained from an assessment of sensory function can be used to document symptoms—for example, thermal testing in a region of reported heat allodynia. In addition, as understanding of different pain mechanisms has increased, sensory testing has become increasingly useful in identifying these mechanisms and differentiating between them (see, e.g., Dyck, Peroutka, et al., 1997; Fields et al., 1998). Sensory testing can also play a role in the diagnosis and staging of painful conditions (see, e.g., Dyck, 1988; Dyck et al., 1992); in research on the natural history of neuropathic pain syndromes (see, e.g., Cheng et al., 1999; Dyck, Davies, Litchy, & O'Brien, 1997); and in evaluating treatment response in patients with neuropathic pain (see, e.g., Attal, Brasseur, Parker, Chauvin, & Bouhassira, 1998; Eisenberg, Alon, Ishay, Daoud, & Yarnitsky, 1998; Zaslansky & Yarnitsky, 1998). In small-fiber neuropathies, thermal detection threshold may be the only means by which to document a neuropathy.

QST is a variant of conventional sensory testing wherein the goal is the quantification of the level of stimulation needed to produce a particular sensation. Measures for which there are normative data (based on age, sex, and body location) include warm and cold threshold, vibration threshold, and heat and cold pain threshold. In many cases, computer-controlled devices, which allow precise control of stimulus parameters, have made quantification possible. An example of this is the use of Peltier junctions in computer-controlled thermodes for the delivery of stimuli with known temperature and duration (Fruhstorfer, Lindblom, & Schmidt, 1976). However, the testing apparatus need not be complicated for stimulus quantification; von Frey filaments allow the estimation of tactile thresholds without the need for complicated instrumentation (Bell-Krotoski & Tomancik, 1987).

An important aspect of QST findings that must be considered in their interpretation is that the obtained thresholds reflect the functioning of the entire sensory system, including not only the peripheral sensory nerve but also central sensory and motor pathways. Although it has often been assumed that abnormal thresholds reflect abnormalities in specific peripheral afferent fibers, in order to obtain a threshold the stimulus energy must be transduced into energy in the peripheral nerve, which must then be perceived by the sensory cortex, which must then activate the motor system so that the subject can respond (typically by pressing a button). Although the major application of QST has been the identification of abnormal sensory thresholds, QST can also provide information regarding abnormal sensory perceptions, such as when cold stimulation causes an abnormal perception of burning and shooting pain that lasts for several minutes (aftersensations). Unfortunately, a standard method for assessing the abnormal sensory perceptions that can be evoked by different QST stimuli has not been developed.

In addition to the choice of stimulus modality and stimulus delivery method, another important element of QST is the choice of testing protocol (Gruener & Dyck, 1994; Yarnitsky, 1997). One example is the method of limits, which is com-

monly used with vibration and thermal modalities. In this method, the stimulus intensity is increased from a baseline value until the subject indicates that the stimulus is perceived. Although this method generally takes less time than other approaches and is straightforward with respect to patient instruction, it also includes a reaction time artifact (Dyck et al., 1993; Yarnitsky & Ochoa, 1990). There are many other testing protocols, each varying in complexity, repeatability, and test length. For a quantitative sensory test to be completely characterized, the modality, stimulus delivery method, and the testing protocol must be specified.

Types of Stimuli and Peripheral Nerve Fibers

QST typically encompasses use of the following stimulus modalities: warmth, cooling, heat pain, cold pain, vibration, static pressure, and brush-like stimuli. These modalities can be subdivided into the two broad categories of thermal and mechanical stimulation. Each stimulus modality can be tested either to locate the detection threshold or to determine the suprathreshold stimulus–response curve. Different receptor and fiber subpopulations are activated by the different stimulus modalities (Light & Perl, 1993; Triplett & Ochoa, 1990). In QST, the choice of the stimulus modality to be examined depends on the specific fiber subpopulation or symptom quality of interest. Although the focus of this section is on the relationship between stimulus modality and nerve fiber function in the periphery, it is important to recognize that the choice of stimulus modality also influences which central nervous system (CNS) pathway is preferentially activated. The measurement of patient response across various stimulus types is one method of investigating the function of different somatosensory pathways. Thermal and pain sensation thresholds are associated with the integrity of the spino-thalamic tract; vibration and tactile thresholds reflect the function of the dorsal column–medial lemniscal pathway. QST has been used in this context for the investigation of central pain (see, e.g., Berić, Dimitrijević, & Lindblom, 1988; Boivie, 1994).

Sensory fibers can be divided on the basis of the type of stimuli to which they preferentially respond (Light & Perl, 1993). Fibers are commonly classified as *low-threshold mechanoreceptors*, which respond preferentially to non-noxious skin displacement, velocity of displacement, or vibration; *thermoreceptors*, which respond preferentially to skin temperature changes; and *nociceptors*, which respond to noxious levels of skin deformation, heating, or cooling. Nociceptors may also respond preferentially to noxious chemical stimuli. Within these classes, fibers can be further divided according to the related properties of conduction velocity and fiber diameter. In order of decreasing fiber diameter and decreasing conduction velocity, the sensory fiber classes are Aα, Aβ, Aδ, and C. The A fibers are myelinated, and the C fibers are unmyelinated. As can be seen from Table 27.3, the primary thermoreceptors include C-fiber warm receptors and Aδ and C cool receptors. Noxious heat and noxious cold stimulate C and Aδ nociceptors. In specifications of these relationships between fiber types and the stimuli to which they respond, the integrity and function of the CNS is assumed to be normal.

After a fiber has been classified by modality and diameter, further divisions are possible based on the specific type of receptor with which it is associated. For example, low-threshold mechanoreceptors are predominantly Aβ fibers. Among the Aβ low-threshold mechanoreceptors are Pacinian corpuscles, Ruffini endings, and Meissner corpuscles. These fibers are respectively associated with preferential responses to high-frequency skin displacement (i.e., vibration), maintained skin displacement (i.e., static mechanical stimuli), and velocity of displacement (i.e., dynamic mechanical stimuli). Although each subgroup of fibers has an optimal mode of stimulation, other modes of stimulation can still cause excitation (e.g., fibers with Ruffini endings will also respond to cooling). This excitation may contribute to the perception of stimulus presence, but may not contribute to the perception of stimulus quality (e.g., warmth, cold). It is important to recognize that fiber populations grouped by stimulus modality or diameter are not homogeneous, and that even when a single modality is used, a variety of fiber subtypes can be activated.

Methods of Stimulus Delivery

Thermal Testing

Thermal testing is typically performed with a computer-controlled thermode. Thermodes can vary in size, temperature range, and rates of cooling and heating (Fruhstorfer et al., 1976; Gruener & Dyck, 1994). Although the thermode size and temperature range are typically fixed for a given

thermode, the rates of heating and cooling can usually be set by the user. A common thermode size is 3 cm × 3 cm; smaller stimulus areas are available, and these may be advantageous when one is testing restricted areas such as a single dermatome. It is important to recognize that the size of the thermode is critical when data from studies using different instruments are being compared; larger thermodes may activate greater numbers of fibers, and in so doing may lower the threshold that is obtained.

To prevent injury to the patient, the thermode's temperature is restricted, with a typical range being from 5° to 50°C. Rates of heating and cooling can usually be set by the user and range from 0.1°C/second to 4°C/second. When a testing protocol is used that is influenced by the subject's reaction time (e.g., the method of limits), a fast rate of stimulus change may lead to an overestimate of the threshold (Dyck et al., 1993; Yarnitsky & Ochoa, 1990). Although a slower rate is advantageous from this standpoint, a slow rate of stimulus change lengthens the testing protocol. Rates on the order of 4°C/second have been used in protocols in which reaction time artifact is not present (Dyck et al., 1993). As with thermode size, it is critical that the rates of temperature change be considered when the results of studies using different protocols are being compared.

Mechanical Testing

Mechanical stimuli may be divided into three categories—*static mechanical*, *dynamic mechanical*, and *vibration*. Static mechanical stimuli are those in which the deformation of the skin is maintained over time. With dynamic mechanical stimuli, the skin displacement changes with time (e.g., moving stimuli). Vibration stimuli also have a skin displacement that changes with time, but with a rapidly changing velocity. Low-threshold mechanoreceptors are predominantly Aβ fibers and less commonly Aδ fibers. As discussed above, each type of mechanical stimulus is optimally transduced by a different cutaneous receptor type. Although all of these mechanical stimuli involve excitation of Aβ low-threshold mechanoreceptors, a particular stimulus may be more suitable in a given situation, based on the symptoms described by the patient or the specifics of the testing environment.

Static Mechanical Stimuli. Various static mechanical stimuli have been used in QST, including von Frey filaments and pressure algometers. Stimuli vary in applied force and may also vary in surface area. The von Frey filaments consist of flexible filaments (initially horsehairs of different strength, but now plastic) of increasing diameters attached to a rigid rod (Bell-Krotoski & Tomancik, 1987). The free end of the filament is applied to the skin, and a force is applied to the rod until the filament begins to bend. This bending force increases with increasing filament diameter, allowing the application of a range of forces. Although the pressure applied is typically calculated by dividing the bending force by the contact area, the actual contact area may not be equal to the surface area of the fiber tip because of the bending of the fiber. Pressure algometers are another type of static mechanical stimulus used in QST.

A distinction is often made between sharp, punctate, or pinprick stimuli and pressure stimuli. However, the quality of a stimulus is not a fixed characteristic and depends on the amount of force used (Greenspan & McGillis, 1991). A given probe can produce sensations of dull pressure, sharp pressure, or sharp pain, depending on the force that is applied. The force needed for a perception of sharp pressure from a given probe falls between those needed for the perceptions of dull pressure and of sharp pain. When one is measuring mechanical allodynia in evaluating treatment outcome, it is critical that exactly the same body location is tested with the subject in the same position; for example, assessing allodynia on the dorsum of the foot may yield different results, depending on whether the person is standing or recumbent.

Vibration. Vibration thresholds are another measure of Aβ-fiber function (Goldberg & Lindblom, 1979). Vibration stimulators vary in surface area, applied frequency, range of displacement, and load weight. They usually consist of a small probe connected to a control unit, which is itself computer-controlled. A typical probe size is 1 cm^2. The applied frequency may be fixed (a typical value is 125 Hz) or controlled by the user. The frequency used may be chosen empirically as the frequency that gives the best test–retest reliability in the patient group of interest, or may be varied as one of the test parameters (Koltzenburg, Torebjork, & Wahren, 1994). The range of possible displacements is usually determined by the choice of stimulator. The load weight, which is determined by the stimulator configuration, is the amount of static force applied by the stimulator to the skin surface independent of the vibratory stimulation (Dyck et al., 1990; Goldberg & Lindblom, 1979). With

stimulators in which the probe is suspended over the area tested, the load weight can be reliably set to the same value over multiple tests. The load weight cannot be reliably determined with handheld stimulators, although a constant load weight can be approximated by allowing the stimulator to rest on the skin without additional applied pressure. A fixed load weight is desirable so that the static mechanical component of the stimulus is the same over repeated testing sessions. However, because it may not be feasible to suspend the stimulator over certain areas of the body, such as the back, a fixed load weight is not always possible.

Dynamic Mechanical (Brush-Evoked) Stimuli. The parameters involved in dynamic mechanical stimulation are the rate at which the source of stimulation is moved across the skin, the surface area that is applied to the skin, and the pressure applied to the skin. Although not specified in current testing protocols, another parameter that may be important in assessing dynamic allodynia is the direction in which the stimulus is moved. As in the visual system, it is possible that different movement directions are encoded differently in the brain. One method that is widely used in clinical trials for generating a dynamic stimulus makes use of a small paintbrush with a firm handle and a foam tip; camel's hair brushes have also been used. The surface area is determined by the dimensions of the tip, and the pressure is held approximately constant by pressing on the brush until the foam tip just begins to bend. The rate is determined by the administrator, who attempts to move the brush at the specified rate across the skin. Similarly, a cotton swab attached to a flexible metal strip has also been used to produce a dynamic mechanical stimulus (LaMotte, Shain, Simone, & Tsai, 1991), as has an electric toothbrush (see, e.g., Eide & Rabben, 1998; Nurmikko & Bowsher, 1990). All of these methods of producing dynamic mechanical stimuli can be applied to a predetermined area, or can be used to map out the borders of an area of abnormal sensation. Dynamic mechanical stimuli are preferentially transduced by Aβ low-threshold mechanoreceptors.

Stimulus Delivery and Response Collection Protocols

Although QST is defined with respect to the quantification of sensory stimuli, the protocols used for sensory testing are equally important. Many different aspects of the testing protocol influence the results obtained with QST, including subject and stimulus factors. For example, the subject's attentiveness and understanding of the protocol can play an important role; these may be monitored by the introduction of null stimuli. In addition, the magnitude and repeatability of the thresholds obtained may depend on the order in which the stimuli are presented (i.e., ascending, descending, random). In choosing a protocol, many other factors must also be considered, including the required accuracy of the results and pragmatic concerns such as the time available for testing and patient fatigue (for reviews of QST protocols, see Gruener & Dyck, 1994; Yarnitsky, 1997).

QST protocols also define the responses from which a subject can choose. In the case of threshold determination, the responses are usually limited (e.g., "yes" or "no"). For suprathreshold protocols, the subject is given a range of response choices. For example, an 11-point NRS or a VRS (e.g., "nothing," "slightly warm," "warm," "hot," "very hot") may be used.

The selection of a specific protocol for QST depends on the goals of the assessment. Protocols may be divided into *threshold determination* protocols and *suprathreshold* protocols. Threshold determination protocols are designed to quantify the stimulus intensity needed for detection of the stimulus, whereas suprathreshold protocols are designed to determine the magnitude of the subject's responses to a set of stimulus intensities above the perception threshold. The sensation of interest may either be a pain sensation or an innocuous sensation.

Threshold Determination Protocols

Method of Limits. In the method of limits (Fruhstorfer et al., 1976), the stimulus intensity is increased or decreased until the subject indicates that the stimulus is perceived. Typically, the average of 3–10 trials is taken as the threshold value. This method has the advantage of relatively straightforward subject instructions and a short testing time. Its primary disadvantage is the influence of the subject's reaction time on the threshold value, which can cause spuriously elevated thresholds at fast rates of stimulus increase (Dyck et al., 1993; Yarnitsky & Ochoa, 1990).

Method of Constant Stimuli. In methods in which constant stimuli are used, the stimuli are increased or decreased to fixed target values (Yarnit-

sky & Ochoa, 1990). At the termination of each stimulus, the subject indicates whether the stimulus was perceived or not. Subsequent stimulus values depend on the subject's response—values ascend until perception is indicated, then descend until perception is lost—and the step sizes used vary with the specific protocol (Dyck et al., 1993; Yarnitsky & Ochoa, 1990). The threshold can be defined as the mean of the intensities where ascending or descending perception occurred, the mean of the "turnaround" points (where perception is achieved and lost), or the value where perception occurs with a specified probability (e.g., greater than 50% of the time). Null stimuli may also be presented; repeated indications that a null stimulus has been perceived suggest subject inattention or lack of comprehension of the instructions. Subject response time is not a factor in this method. Although the testing time using the method of constant stimuli will vary, depending on the criterion for threshold, in general this method takes longer than the method of limits (but less time than the forced-choice method).

Forced-Choice Method. The forced-choice method is one of the most robust protocols used in QST (Dyck et al., 1990). In this protocol, the stimulus is presented in one of two intervals. After both intervals conclude, the subject is asked to select the interval in which the stimulus occurred. There is a 50% chance of guessing correctly without any stimulus perception. The threshold value is defined as the stimulus intensity at which the subject's "hit" rate reaches a predefined level above 50%. Reaction time is not a factor in this protocol, and random presentation of stimuli can reduce the subject's anticipation of stimuli. The primary disadvantages of the protocol are the length of time it can take to achieve the desired accuracy level and the complexity of the task. The length of the test session depends on the accuracy level selected and on the subject's sensitivity.

Suprathreshold Protocols

In suprathreshold protocols, the focus is on the determination of the subject's stimulus–response curve for the specific stimulus modality examined. For this reason, the subject's responses must be derived from a rating scale. Suprathreshold testing protocols differ in the order of stimulus presentation and in the scales used for the subject's responses.

Stimuli may be presented in ascending order or in random order. In principle, although a descending order may be used, this is not usually done because of the possibility of sensitization from the initial presentation of high-intensity stimuli. In the nonrepeating ascending stimulus protocol (Dyck et al., 1996), the stimulus intensity is increased in discrete steps, and the subject response is collected at each step. When a predetermined level of response is reached, the test is terminated. This test is useful for heat pain stimuli when multiple presentations of moderately painful stimuli are not required. With randomly presented stimuli, the test is not terminated at a particular response level, although a maximum response level is often set and no stimuli are administered that would produce responses greater than that level (Attal, Brasseur, Parker, et al., 1998). In suprathreshold protocols, subject responses are collected for each stimulus presentation, and any one of the different methods of rating pain intensity can be used.

Signal Detection Theory Protocols

One of the major ways in which signal detection theory (SDT) protocols differ from the other QST methods is that the subject's ability to discriminate stimuli is assessed in addition to the subject's criterion for response (Green & Swets, 1966). In these protocols, stimuli of fixed intensity are presented randomly, and the subject is asked to choose a response from a preselected rating scale. This approach distinguishes the sensory-discriminative aspects of subjects' responses from the extent to which subjects report their sensory experience as painful. SDT methods yield two measures: an index of sensory discrimination (d' or $P(A)$), which is interpreted as reflecting the functioning of the neurosensory system, and a measure of response criterion (Lx or B), which is interpreted as reflecting the subject's affective response to the sensory experience—that is, how readily he or she reports pain (Clark, 1974). Clark and Yang (1983) propose that the major advantage of these methods is that "at a descriptive, or qualitative, level, the sensory and emotional components of pain have long been recognized. SDT now permits the quantification of these two components into indices of discriminability and pain report criterion" (p. 23).

Interpretation of Findings

QST may be conducted for a variety of reasons. These include clarifying the nature of the sensory abnormalities present (Bouhassira, Attal, Willer, &

Brasseur, 1999); documenting the extent of the abnormalities for comparisons over time (Apfel et al., 1998; Attal, Brasseur, Parker, et al., 1998; Eisenberg et al., 1998); suggesting pain mechanisms that may be present in the patient (Rowbotham, Petersen, & Fields, 1998); and indicating possible diagnoses (Borg & Lindblom, 1986; Dyck et al., 1987). The role of QST will continue to evolve as more is discovered about the mechanisms of neuropathic pain and as more is learned about selectively treating pain symptoms, whether from a disease- or mechanism-based perspective. If the traditional disease-based treatment of pain continues to predominate in the future, the goals of symptom documentation and disease diagnosis will remain primary. If a mechanism-based model of pain treatment becomes more widespread, however, the goal of identifying the mechanisms of the patient's pain will become paramount.

Quantifying Symptoms

Neuropathic pain may be associated with a variety of sensory abnormalities (e.g., for PHN, see Nurmikko & Bowsher, 1990; Rowbotham, Petersen, & Fields, 1998). Some deficits may only become apparent on sensory testing, although other abnormalities may form a large part of the patient's complaint. Alterations of sensory function that are distressing to the patient can be quantified with respect to both their area and their severity, and these measures can be used to monitor treatment efficacy (see, e.g., Apfel et al., 1998; Attal, Brasseur, Parker, et al., 1998; Eisenberg et al., 1998; Lang et al., 1995). Less prominent alterations of sensory function can assist in diagnosis (Borg & Lindblom, 1986) or may predict disease course (Baron, Haendler, & Schulte, 1997).

The patient's responses to a given set of stimuli may be characterized using a stimulus–response curve (see Figure 27.1). The stimulus intensity axis will have the units of the relevant stimulus parameter (e.g., force or pressure, temperature, displacement). The response axis may have a numerical scale (e.g., VAS length in millimeters, NRS numerical ratings) or may be anchored by categorical descriptors. Multiple points on the curve may be determined via suprathreshold testing; alternatively, only a single feature, such as the detection threshold, may be assessed. Although the details of the stimulus–response curve will differ by testing method, modality, and subject, some broad characteristics of these curves may be defined.

The slope of the stimulus–response curve determines how much the patient's response increases for a given increase in stimulus intensity. *Hyperesthesia*, an increased responsiveness to stimuli, would be reflected in a curve with a steeper slope. If the stimuli under consideration are normally noxious, the steeper slope indicates an increased pain response to normally noxious stimuli, and the more specific term *hyperalgesia* can be used. A reported or observed increase in stimulus-evoked pain response can be investigated by performing a suprathreshold measurement of response to painful stimuli. Thermal hyperalgesia is often documented in such a manner, with protocols such as the heat pain nonrepeating ascending stimulus algorithm (Dyck et al., 1996). The use of von Frey filaments allows mechanical hyperalgesia to be documented in a similar manner (Attal, Brasseur, Parker, et al., 1998). Because calibrated dynamic mechanical stimuli have been less available, most QST approaches to the assessment of dynamic mechanical allodynia have used a single stimulus intensity to map out the affected area (e.g., a foam brush with fixed bending force and approximately constant rate of movement). Rather than a suprathreshold mapping of the stimulus–response curve, such an approach maps out the size of the area of the body where allodynia in response to a single stimulus is present or absent.

Sensory thresholds correspond to the minimum level of sensation that can be detected by the subject. In practice, sensory thresholds are specified in terms of the minimum stimulus level needed to produce a particular sensation. Typical thresholds used are the sensation detection threshold and the pain detection threshold, but thresholds can also be defined in terms of the stimulus needed to reach a particular pain rating. Threshold changes may be referred to directly or may be described with the same terms used for changes in the slope of the stimulus–response curve. Raised thresholds may be referred to as *hypoesthesia* and lowered thresholds may be referred to as *allodynia* or *hyperesthesia*, depending on whether the threshold in question is a pain threshold or a detection threshold. Thresholds for dynamic mechanical stimulation are less easily determined than thresholds for thermal, static mechanical, and vibration stimuli, because of the lack of calibrated methods for administering dynamic stimuli.

The quantitative documentation of sensory abnormalities allows a comparison between subgroups of patients with a given syndrome, which may help illuminate pathophysiology (e.g., Bouhas-

sira et al., 1999; Eide & Rabben, 1998). In one recent example, QST has been used to compare patients with painful and painless HIV sensory neuropathy (Bouhassira et al., 1999). Mechanical allodynia and hyperalgesia were found in the patients with painful neuropathy but not in the patients without pain, and these abnormalities correlated with the intensity of spontaneous pain. Such findings can provide a basis for evaluating the contribution of peripheral and central mechanisms to the altered processing of mechanical stimuli in this peripheral neuropathic pain syndrome.

Using QST to compare painful and painless subtypes within a particular syndrome has also been done in the context of central pain (Andersen, Vestergaard, Ingeman-Nielsen, & Jensen, 1995; Vestergaard et al., 1995). A consecutive series of patients with acute stroke was examined in the first week after admission, with follow-up testing at 1 and 6 months and 1 year after stroke. Patients with sensory deficits but without pain were compared to patients with both sensory deficits and pain. It was found that although some sensory deficits, such as decreased tactile sensation, were present in both the pain and nonpain groups, thermal abnormalities were significantly more frequent in the pain group. This result suggests that central poststroke pain is associated with injury to the spino-thalamic tract.

Identification of Mechanisms

As attention to the mechanism-based approach to pain assessment and treatment continues to increase, the use of QST for the identification of pain mechanisms can be expected to increase as well. At the present time, however, there is limited evidence to support the use of QST in everyday practice to identify pain mechanisms in individual patients and then select treatments based on these mechanisms. Although patterns of QST findings in patients with the same diagnosis have been used to identify different pain mechanisms and thereby to define different subgroups of patients (e.g., Rowbotham, Petersen, & Fields, 1998), few prospective studies have been reported in which treatments are matched to pain mechanisms. Furthermore, although numerous mechanisms of neuropathic pain have been identified in studies of animal models and human clinical syndromes (see, e.g., Bennett, 1994; Fields & Rowbotham, 1994; Woolf & Mannion, 1999), the role of QST in identifying many of these pain mechanisms requires further clarification.

There is considerable evidence that in many patients stimulus-independent neuropathic pain reflects abnormal activity in primary afferent nociceptors (e.g., for reviews, see Bennett, 1994; Koltzenburg, 1996). QST is commonly used to examine fiber function in the periphery, and can provide information about mechanisms of both stimulus-independent and stimulus-dependent neuropathic pain. As discussed above, however, QST findings do not simply reflect abnormalities in the peripheral nervous system, but also reflect sensory and perhaps motor function at peripheral, spinal, and cortical levels in the nervous system. Moreoever, the results of a QST assessment are very likely to be affected by more than one of the pain mechanisms occurring at a given level. For this reason, it is possible to have the same pattern of QST findings arising from very different neuropathic pain mechanisms. For example, dynamic mechanical allodynia occurring together with thermal sensory deficits may indicate deafferentation-induced sprouting of non-nociceptive Aβ fibers within the dorsal horn. Alternatively, it is possible that nociceptors disconnected from the skin are spontaneously active, and maintain a state of central sensitization while being unresponsive to cutaneous pain stimuli (Fields et al., 1998). In addition, the well-documented alterations that occur throughout the neuraxis following peripheral nerve injury suggest that a single pathophysiological event in the periphery results in a cascade of CNS alterations that can also become mechanisms of pain. Because multiple mechanisms can generate similar patterns of QST findings, it is essential that other sources of information be used in the interpretation of the results of a QST assessment.

Additional important complications in the interpretation of QST findings are that several different pain mechanisms may be involved in a single disease, and that the same pain mechanism may arise from more than one disease. It is for precisely these reasons that mechanism-based models of pain treatment are currently attracting a great deal of attention (Woolf et al., 1998). However, these multiple and overlapping relationships among diseases, symptoms, signs, and pain mechanisms make the identification of mechanisms with QST difficult to implement in practice. A particular patient may have several mechanisms active at a given time. Each of these mechanisms can contribute to the QST results, leading to an amalgam that may be difficult to interpret. In addition, the mechanisms present in a particular patient may change over time as the disease progresses or is modified by treatment.

At the most general level, QST evaluates whether there are any abnormalities in the patient's stimulus–response curve for a relatively standard selection of stimulus modalities. In the interpretation of the results of a QST assessment (see Table 27.4), several more specific questions should be addressed, including these:

- *Are any nonpainful detection thresholds elevated?* The presence of sensory deficits in these thresholds provides information about losses in various fiber populations.
- *Is dynamic mechanical allodynia present?* Dynamic mechanical sensation normally activates non-nociceptive Aβ low-threshold mechanoreceptors. The presence of pain in response to normally non-noxious dynamic mechanical stimuli suggests that central changes may be present that make second-order pain transmission neurons responsive to stimulation of Aβ low-threshold mechanoreceptors (Koltzenberg et al., 1994).
- *Is cold allodynia present?* Cold allodynia accompanied by an increase in the cold detection threshold may indicate disinhibition due to a selective loss of cool-specific Aδ fibers (LaMotte & Thalhammer, 1982).
- *Is static mechanical hyperalgesia or heat hyperalgesia present?* These symptoms are generally thought to reflect peripheral sensitization of nociceptors (Koltzenburg, Lundberg, & Torebjork, 1992; LaMotte, Lundberg, & Torebjork, 1992).
- *Are there abnormal perceptions associated with the stimuli?* For example, a cold stimulus that evokes the perception of sharp, shooting pains that last for several minutes may reflect different pathophysiological mechanisms in the nervous system from those associated with abnormalities in sensory thresholds.

The results of QST provide information regarding both central and peripheral mechanisms of neuropathic pain. These mechanisms may be further distinguished according to whether existing connections are maintained, but with altered function of pre- and postsynaptic neurons, or whether new structural connections have developed. In Table 27.5, we present several important mechanisms of neuropathic pain and representative patterns of QST findings that are thought to reflect them. Peripheral sensitization occurs when primary sensory fibers increase their firing rate or their responsiveness to stimuli changes due to injury or environmental factors (LaMotte et al. 1992). Nociceptor sensitization is believed to contribute to static mechanical hyperalgesia (Koltzenburg et al., 1992) and to heat hyperalgesia (LaMotte et al., 1992). If there is decreased input from peripheral neurons to the dorsal horn instead of increased input, and if the involved neurons play a regulatory role in the perception of another sensory modality, disinhibition can occur. For example, cold allodynia in the presence of an elevated

TABLE 27.4. Putative Peripheral and Central Mechanisms of Sensory Abnormalities

	Response to innocuous stimuli		Response to painful stimuli	
Stimulus type	Hypoesthesia	Hyperesthesia/allodynia	Hypoalgesia	Hyperalgesia
Mechanical				
Static mechanical	Aβ loss	Peripheral sensitization		Peripheral sensitization
Dynamic mechanical		Central sensitization Central reorganization Disinhibition Phenotypic switching		
Punctate		Central sensitization	Aδ loss	Central sensitization
Vibration	Aβ loss			
Thermal				
Heating	C loss	Peripheral sensitization		Peripheral sensitization
Cooling	Aδ loss	Aδ cool-specific loss Central sensitization		Aδ cool-specific loss Central sensitization

TABLE 27.5. Examples of Patterns of Sensory Abnormalities Associated with Proposed Peripheral and Central Mechanisms of Neuropathic Pain

Mechanism	Thermal sensory abnormalities	Mechanical sensory abnormalities	Anesthetic infiltration
1. Central sensitization (maintained by sustained nociceptor input)	Minimal deficit or heat hyperalgesia	Dynamic mechanical allodynia	Decreased pain
2. Deafferentation-induced central reorganization	Thermal sensory deficits	Dynamic mechanical allodynia	Decreased allodynia (short duration)
3. Differential loss of cool-specific fibers	Cooling detection deficit Cold allodynia		
4. Deafferentation-induced central hyperactivity	Thermal sensory deficits	No dynamic mechanical allodynia	No change
5. Spino-thalamic tract injury	Thermal sensory deficits	None or less marked than thermal deficits	

Note. Some of the information presented in this table has been drawn from Rowbotham, Petersen, and Fields (1998).

cool detection threshold may be explained by disinhibition (LaMotte & Thalhammer, 1982). Because cooling-sensitive Aδ fibers determine the cool detection threshold and also inhibit the response to cold-responsive nociceptors, a disproportionate loss of Aδ fibers relative to C nociceptors will raise the cool detection threshold while decreasing the cold pain threshold.

Central sensitization of neurons in the spinal cord can be caused by sustained nociceptive input from the periphery. When this nociceptive activity is a result of neurons that have remained connected to the skin, the resulting symptoms will be associated with preserved thresholds in the relevant stimulus modality (Fields et al., 1998). The nociceptive input may also arise from activity in injured neurons that are no longer connected to the skin surface, which would be associated with sensory deficits in the relevant modality. The central sensitization that is maintained by these types of abnormal peripheral input causes central pain transmission neurons to become responsive to afferent neurons that normally transduce non-noxious stimuli, and this is believed to be an important mechanism of dynamic mechanical allodynia (Kolzenburg et al., 1994; Simone et al., 1991).

Central reorganization is another putative mechanism of dynamic mechanical allodynia (Devor & Wall, 1981). A loss of peripheral nociceptive input caused by damage or destruction of primary nociceptors can cause Aβ fibers to sprout into areas of the dorsal horn associated with pain transmission (Woolf, Shortland, & Coggeshall, 1992). The pattern of QST findings that would be expected from this mechanism is dynamic mechanical allodynia accompanied by decreased sensitivity to thermal stimuli (Fields et al., 1998).

The use of QST to investigate pain mechanisms is not restricted to peripheral neuropathic pain syndromes. Sensory thresholds have been used in conjunction with laser-evoked potentials to investigate the mechanisms responsible for central pain following cerebral or brainstem infarction. One hypothesis attributes central pain to a lesion-induced increase in the excitability of spinothalamic tract neurons. In one study, thermal and static mechanical thresholds and laser-evoked potentials were assessed in patients with unilateral pain (Casey et al., 1996). Comparison of the results from both sides showed that many patients with thermal and pain sensation deficits also had a reduction in laser-evoked potential amplitude on the affected side. The authors suggested that these results reflect a reduction in spino-thalamic tract function rather than increased CNS responsivity.

The Role of QST in the Comprehensive Assessment of Neuropathic Pain

The results of a QST assessment, no matter how extensive, do not alone provide a basis for diag-

nosing or evaluating neuropathic pain (Dyck et al., 1998). When included with other methods for evaluting a patient's symptoms and signs, however, QST provides valuable information that can be used in a variety of research and clinical situations. Zaslansky and Yarnitsky (1998) have reviewed the clinical applications of QST across a range of disorders, including endocrine, metabolic, compression, toxic, infection-associated, immune-related, and hereditary neuropathies, as well as CNS diseases and trauma.

Of these diverse disorders, diabetes is the one in which the role of QST has been most frequently studied and most clearly elaborated. This research has examined the prevalence and natural history of sensory deficits in patients with diabetes, the relationships between QST and other methods of assessing diabetic neuropathy, and the role of QST in predicting prognosis and evaluating therapeutic reponse (see, e.g., Dyck et al., 1992; Zaslansky & Yarnitsky, 1998). Importantly, in a number of studies various methodological aspects of QST have been examined, including the determination of normal values and differences in sensitivity and test-retest reliability between testing protocols (e.g., Dyck, 1993; Dyck et al., 1991, 1995; Zaslansky & Yarnitsky, 1998). We believe that this research on diabetic neuropathy and QST serves as an excellent example of how QST can be incorporated in research on other types of neuropathic pain.

The results of recent open-label studies of the effectiveness of anticonvulsant medications provide an additional example of how QST can augment the information obtained in an assessment of neuropathic pain. In these studies, spontaneous continuous pain, spontaneous intermittent pain, stimulus-evoked pain, and QST were examined. Attal and colleagues reported that 6 weeks of open-label gabapentin treatment reduced continuous pain, intermittent pain, and dynamic allodynia, and increased cold pain thresholds in patients with peripheral and central neuropathic pain (Attal, Brasseur, Parker, et al., 1998). There were, however, no changes in heat and tactile detection thresholds or in heat and punctate pain thresholds. A somewhat similar pattern of findings was reported by Eisenberg and colleagues (1998) in an open-label study of lamotrigine in painful diabetic neuropathy. As in the research reported by Attal and colleagues (1998), continuous pain decreased (as did cold allodynia), cold pain thresholds increased (although this was not statistically significant), and there were no changes in heat and tactile detection thresholds and heat and punctate pain thresholds (intermittent pain was not assessed in this study). However, because mechanical allodynia was minimal, the effect of lamotrigine on dynamic allodynia could not be assessed, in contrast to the reduction in dynamic allodynia reported in two gabapentin studies (Attal, Brasseur, Parker, et al., 1998; Caracenti, Zecca, Martini, & De Conno, 1999). Although the results of these studies must be interpreted with caution because they were not placebo-controlled, such patterns of findings can provide valuable information about mechanisms and treatment response of neuropathic pain.

In concluding this section, it is important to emphasize that although QST allows clinicians and researchers to obtain important information regarding the functional status of different parts of the nervous system, its ability to identify distinct pain mechanisms in individual patients has not been established. Indeed, it is possible that the mechanisms involved in the development and maintenance of human neuropathic pain are so complex that additional approaches to the assessment of such pain will need to be developed before pain mechanisms can be reliably determined in individual patients. Certainly, more research is needed before QST can be recommended for routine use in the daily clinical care of patients with neuropathic pain.

OTHER PROCEDURES

Various other procedures can provide valuable information in the assessment of neuropathic pain. These include skin punch biopsies (Holland et al., 1997; Oaklander et al., 1998; Rowbotham et al., 1996); electromyography and nerve conduction studies (see, e.g., Benedetti et al., 1998; Dyck, 1988; Wolfe et al., 1999); nerve blocks and infusions (see, e.g., Dellemijn, Fields, Allen, McKay, & Rowbotham, 1994; Galer & Jensen, 1997; Galer, Miller, & Rowbotham, 1993); laser Doppler flowmetry (Baron & Saguer, 1993, 1994; Kurvers et al., 1996); and positron emission tomography and MRI (see, e.g., Attal, Brasseur, Chauvin, & Bouhassira, 1998; Barón, Baron, Disbrow, & Roberts, 1999; Iadarola et al., 1995).

All of these procedures can provide important information regarding mechanisms of neuropathic pain. However, all require specialized training for administration and interpretation. In addition, these procedures are generally more invasive and considerably more expensive than the other approaches to the assessment of neuropathic pain discussed in this chapter. For these reasons, these approaches

should not currently be used on a routine basis in the assessment of neuropathic pain, either in the clinic or in research. Nevertheless, it can be expected that as research using these procedures in patients with neuropathic pain continues, their use will contribute to our understanding of neuropathic pain and have greater application in its assessment. Although detailed discussion of these procedures is beyond the scope of this chapter, many of them are discussed elsewhere in this volume.

CONCLUSIONS

The assessment of neuropathic pain requires that the person conducting the assessment evaluate his or her specific needs. What is the setting of the assessment—patient care or research? What should be assessed? What is the level of detail required for this particular assessment? Such questions must be answered prior to the actual assessment. It has only been over the last decade, and especially in the past several years, that specific tools to evaluate neuropathic pain have been developed and systematically studied. The continued development of neuropathic pain measures—such as sensory symptom questionnaires (e.g., the NPS; Galer & Jensen, 1997), sensory examination procedures (e.g., for assessing dynamic mechanical allodynia), and QST—will increase our understanding of the mechanisms of neuropathic pain. Furthermore, the identification of subgroups of patients who share the same symptoms, physical examination findings, or QST profiles has the potential to dramatically alter the way neuropathic pain is treated.

The point we would most like to emphasize in concluding this chapter is that a comprehensive assessment of neuropathic pain must examine a variety of symptoms and signs, and that the use of a single measure or method is inadequate. Although this is undoubtedly obvious to many readers, we believe that it must be emphasized, because it can be tempting to assess neuropathic pain in a less comprehensive manner. One recent example of an inadequate assessment of neuropathic pain is provided by a randomized, double-blind, placebo-controlled clinical trial of the analgesic effect of lamotrigine (McCleane, 1999). In this otherwise generally well-designed study, patients were diagnosed as having neuropathic pain and were enrolled in the trial if they had three of the following five "cardinal symptoms" of neuropathic pain: shooting/lancinating, burning, numbness, allodynia, and paresthesia/dysesthesia. No information was provided regarding the methods used for assessing these five symptoms. Although the results of studies reviewed above suggest that many (perhaps all) of these symptoms may be more common in patients with neuropathic pain, we have also emphasized that all of these symptoms can be found in patients with non-neuropathic pain. The validity of the diagnoses of neuropathic pain made in this study are therefore questionable, and the results must be considered uninformative with respect to the efficacy of lamotrigine in neuropathic pain.

In this chapter, we have discussed the assessment of neuropathic pain and not the assessment of patients with neuropathic pain. The assessment of such patients involves much more than the assessment of their neuropathic pain. As with the comprehensive evaluation of any patient with chronic pain, the assessment of a patient with neuropathic pain should include an evaluation of the impact of the pain on psychological function (e.g., depression, coping) and quality of life (e.g., sleep, occupational disability, activities of daily living, social relationships), and may also include an examination of health care utilization and costs, depending on the assessment context and goals (see, e.g., Dworkin, 1997a, 1997b; Dworkin et al., 1997). We have not discussed these aspects of the assessment of the patient with neuropathic pain, because they are comprehensively reviewed elsewhere in this volume.

A fitting conclusion to this chapter is to underscore the complex nature of neuropathic pain and its impact on the patient. As Backonja and Galer (1998) emphasize,

> It is the rule rather than [the] exception that patients who have chronic neuropathic pain have more than one type of pain. For example, a man who has PHN at high and midthorax may have constant ongoing pain that keeps him awake all night; mechanical allodynia and hyperalgesia that prevent him from wearing any clothing so he cannot be active and socialize; secondary myofascial pain in the shoulder so that use of that arm is limited; and after a few short weeks of his pain, the patient is by now sleep deprived, depressed, anxious, and very irritable. (p. 785)

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APPENDIX 27.A. NEUROPATHIC PAIN SCALE

Instructions: There are several different aspects of pain which we are interested in measuring: pain **sharpness, heat/cold, dullness, intensity,** overall **unpleasantness,** and **surface vs. deep** pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how intense your pain is. Place an "x" through the number that best describes the intensity of your pain.

No pain — The most intense pain sensation imaginable

0	1	2	3	4	5	6	7	8	9	10

2. Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing," or "like jolts."

Not sharp — The most sharp sensation imaginable ("like a knife")

0	1	2	3	4	5	6	7	8	9	10

3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."

Not hot — The most hot sensation imaginable ("on fire")

0	1	2	3	4	5	6	7	8	9	10

4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching," and "like a bruise."

Not dull — The most dull sensation imaginable

0	1	2	3	4	5	6	7	8	9	10

5. Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

Not cold — The most cold sensation imaginable ("freezing")

0	1	2	3	4	5	6	7	8	9	10

(cont.)

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive										The most **sensitive** sensation imaginable ("raw skin")
0	1	2	3	4	5	6	7	8	9	10

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe very itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy										The most **itchy** sensation imaginable ("like poison oak")
0	1	2	3	4	5	6	7	8	9	10

8. Which of the following best describes the time quality of your pain? Please check only one answer.

( ) I feel a background pain *all of the time* and occasional flare-ups (break-through pain) *some of the time.*
Describe the background pain: _____
Describe the flare-up (break-through) pain: _____

( ) I feel a single type of pain *all the time.*
Describe this pain: _____

( ) I feel a single type of pain only *sometimes.* Other times, I am pain-free.
Describe this occasional pain: _____

9. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how **unpleasant** your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant										The most unpleasant sensatio imaginable ("intolerable")
0	1	2	3	4	5	6	7	8	9	10

10. Lastly, we want you to give us an estimate of the severity of your *deep* versus *surface* pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No deep pain										The most intense deep pain sensation imaginable
0	1	2	3	4	5	6	7	8	9	10

HOW INTENSE IS YOUR *SURFACE* PAIN?

No surface pain										The most intense surface pain sensation imaginable
0	1	2	3	4	5	6	7	8	9	10

Note. From Galer, B. S., and Jensen, M. P. (1997). Development and preliminary validation of a pain measure specific to neuropathic pain: The Neuropathic Pain Scale. *Neurology, 48,* 332–338.