

# The Measurement of Symptoms and Side Effects in Clinical Trials of Chronic Pain

Nathaniel Katz, MD

Current Address: 212 Winding Brook Road  
New Rochelle, NY 10804  
Telephone/Fax: 914-738-2560  
E-mail: [NatPaulKatz@aol.com](mailto:NatPaulKatz@aol.com)

## Introduction

Patients see doctors because they experience symptoms, and desire relief. Treatments prescribed to relieve symptoms may do so at the expense of causing other symptoms, now called side effects. The overall therapeutic result, i.e. whether patients are better off on treatment, depends upon a balance of symptom reduction and side effects (Fig 1). A medication that produces pain relief but also severe nausea will be less attractive than one that produces similar pain relief without the side effect. Global response measures may indicate the patient's overall integration of pain relief and side effects (and no doubt other factors); however, as yet there is no firm evidence in the analgesics field for this assertion[1]. It thus becomes an obligation of those conducting clinical trials in chronic pain to assess symptomatic side effects produced by the treatments under investigation, and ultimately to understand the therapeutic result that results from integration of symptom relief and symptom production.

Of course, other factors contribute to the determination of overall therapeutic result: convenience, cost, social values, expectations, etc. A treatment that produces symptom relief but requires daily visits to the hospital, or that is frowned upon due to social conventions, or that is unaffordable, will be less likely to produce overall benefit than a treatment without these limitations. Also, there are situations in which a highly toxic treatment will be desirable by virtue of meeting important therapeutic objectives, such as cancer chemotherapy. Conversely, a treatment on which patients feel fine may not be suitable for human use due to uncommon but severe consequences, as in the example of felbamate-induced hepatotoxicity. Despite these circumstances in which symptom integration during treatment is outweighed by other factors, understanding how patients feel while on treatment remains an important obligation.

This paper was written for the Second Meeting of the IMMPACT group, held in Washington, D.C. on April 10-11, 2003. The purpose of the meeting was to generate consensus on measurements to be considered by investigators for chronic pain clinical trials. This paper will describe the principles and practice of measuring symptoms and side effects in chronic pain trials.

## Definitions

A variety of overlapping concepts and terms must be clarified. A *symptom* may be defined as "Any morbid phenomenon or departure from the normal in structure, function, or sensation, experienced by the patient and indicative of disease." [2] The presence of a symptom may be called "*symptom occurrence*"[3]. The presence of a symptom may be further described in terms of *frequency* (how often it occurs in a person or a population), *onset* (when it starts), and *duration* (how long it lasts). There is generally something unpleasant about *symptoms*, and *symptom distress* may be defined as "the degree of physical or mental upset, anguish, or suffering experienced from a specific symptom" [4]. Like pain, a symptom may be rated by a patient in terms of its *intensity*. There is some

evidence that intensity and distress related to a symptom may be different dimensions [4], which may be analogous to the separation of pain into two factors: intensity and unpleasantness[5, 6]. To make things more complicated, patients may rate symptoms differently in terms of their *importance*, regardless of intensity[3, 7], described further below. It is likely that the distress experienced in response to a symptom, and the importance ascribed to a symptom, are determined in part by the meaning attributed by the patient to the symptom, demographics, and psychosocial factors [8].

Symptoms may be the result of diseases or of treatments, thus the language of symptom distress must be melded with the language of drug safety. An *adverse event* (AE) is any undesirable event that occurs in a subject on treatment or in a clinical trial. A *drug-related or treatment-related* adverse event is one that is attributed to treatment, although it is recognized that such attributions may be inaccurate. A *treatment-emergent* adverse event is one that was not present at baseline but which emerges after treatment is initiated, regardless of attribution. A *side effect* is a treatment-emergent adverse event that is attributed to the treatment in question. Adverse events, or side effects, may be symptomatic (i.e. headache), or not (e.g. asymptomatic hypertension or laboratory abnormalities). The correct designation of an adverse event implies a baseline assessment, analogous to the epidemiologic concepts of prevalence (presence of a variable regardless when it began) and incidence (new cases in subjects previously without the variable).

The decision to take a drug depends upon an analysis of all the potential risks and benefits, regardless whether they result in symptoms. For example, a rare but fatal side effect will not change how the vast majority of patients feel while taking the drug, but may well make taking the drug inadvisable. While clearly important, these drug safety considerations are beyond the scope of this paper. Here we are concerned with how to measure symptoms, and symptomatic side effects, with the goal of integrating these measurements with measurement of therapeutic symptom reduction, to determine how patients feel overall while on treatment.

## **Symptoms and Side Effects: Methods of Measurement and Reporting**

Several methods exist for capturing data about adverse events (symptomatic or otherwise) in the clinical trial setting. These may be arranged in increasing order of comprehensiveness (Fig. 2), and are discussed below.

### ***Passive Capture of Adverse Events***

In general, at least in clinical trials sponsored by the pharmaceutical industry, all AEs are recorded, in compliance with national and international regulations. These events are then coded, usually according to a standardized coding dictionary (e.g. COSTART or MedDRA), tabulated, and in the regulatory context reported in their entirety. The extent to which such AEs are reported in the medical literature, and the extent to which AEs are

captured and compiled by investigators outside the pharmaceutical industry, has just begun to be investigated systematically, but appears to be quite variable[9, 10]. Since this method of recording AEs does not involve any proactive effort on the part of the study staff, it will be referred to in this paper as “passive AE capture.”

The most important advantage of passive AE capture is that it is not constrained by preconceived notions of the potential AEs associated with a specific treatment, since everything, in theory, is recorded. A second advantage is that passive AE capture is perceived to be performed throughout the pharmaceutical industry in much the same manner. This is consistent with the “level playing field” approach to pharmaceutical industry regulation, i.e. the medications produced by one company are subject to the roughly the same AE scrutiny as the next company. If one company, or one drug, were scrutinized for safety through a finer lens than another, it could potentially distort comparisons of the safety data of that drug to others, with negative scientific, clinical, and perhaps market consequences.

Disadvantages of passive AE capture are described in more detail below. In brief, this method has been shown under certain circumstances to fail to capture AEs of clinical significance. The consequence of this insensitivity is that clinical trials relying on passive AE capture may fail to reveal important differences between treatments, or may inaccurately describe the overall therapeutic benefit of a treatment. These conclusions should not be surprising, as other research has shown that there are numerous barriers to patients relating symptoms during encounters with their physician[11].

### ***Prompting***

A slightly more proactive form of AE capture involves asking the patient on a regular basis an open-ended question designed to elicit AEs without biasing the patient. For example one could ask, “Are you having any problems?” at the end of a clinic visit. The author is unaware of any published research comparing prompted vs. completely passive AE capture. However, it stands to reason that AEs are more likely to be reported if the patient, or the clinician, is prompted. If so, prompting would have the advantage of allowing the patient the opportunity to relate important symptoms, without suggesting any specific symptoms to the patient.

### ***Prospective Assessment of Specific Side Effects of Interest***

In certain clinical trials, a specific side effect or set of side effects may be of special interest[12-17]. For example, in a recent trial of a selective cyclo-oxygenase-2 inhibitor, rofecoxib, for patients with chronic low back pain, investigators chose to pre-specify outcomes related to the potential renovascular side effects of non-steroidal inflammatory agents[14]. The trial showed that in this population, the efficacy of rofecoxib 25 and 50 mg was similar, but there were greater renovascular side effects in the higher dose group, leading to the recommendation of 25 mg as the appropriate dose for this indication. Pure

passive AE capture might have failed to reveal this side effect difference in a trial of this relatively modest size. A more elaborate example comes from the treatment of gastroesophageal reflux disease (GERD). Several scales have been validated to measure the gastrointestinal symptoms, and associated distress, caused by this disorder[13, 15, 16]. Similar scales have been validated in several disorders[12, 18], and address the symptom clusters relevant to the disorders, and treatments, in question. The presumed advantage of these pre-specified symptom inventories is greater sensitivity and validity in detecting side effects of specific treatments, which may aid in dose-finding, or in comparison of two active treatments.

### ***Prospective Comprehensive Symptom Checklists***

A more complete approach involves administering a comprehensive symptom distress inventory, in order to measure all the symptoms, and associated distress, relevant to a particular clinical context[7, 19-28]. The comprehensive approaches that have appeared in the literature may be divided into two broad categories. The first category is symptom inventories designed to capture all symptoms relevant to patients with particular diseases - such as AIDS[28], breast cancer[27], lung cancer[7], cancer in general[22, 23, 25], or end-stage renal disease[18] – regardless whether symptoms are caused by the disease or its treatment. The purpose of symptom distress inventories in these settings is to identify symptoms requiring treatment, to provide an overall assessment of patients' clinical status, and to provide prognostic information.

The second category of comprehensive symptom distress inventories occurs in clinical trials, where the goal is to distinguish the side effects profile of various treatments. Such inventories may include only the potential side effects of the treatments being studied[29], or may in addition include the potential symptoms of the diseases being treated[19-21]. Symptom distress inventories have been used to provide an intuitive yardstick with which to judge changes in less intuitive quality of life scales[30]; symptom distress inventories have also been compared to the stress produced by contemporaneous real-life events in order to provide an even more intuitive yardstick with which to judge changes in symptom distress levels (and associated quality of life changes)[21].

Comprehensive symptom distress inventories have been sensitive measures to discriminate the effects of different treatments, in fact more sensitive than measures of efficacy, passively captured adverse event rates, and comprehensive quality of life batteries[19, 21, 31]. Comprehensive symptom distress inventories are much more sensitive in detecting symptoms than passive AE capture[19, 32, 33]; even symptoms that are extremely distressing to patients are routinely missed with passive AE capture. Symptoms picked up in this manner predict drop out, predict changes in psychosocial quality of life, and are comparable to levels of distress produced by contemporaneous stressful real-life events. In the cancer setting, symptom distress levels have been shown in multiple studies to predict survival, independently of performance status, disease severity, and psychosocial and other patient characteristics (for summary see [34]. The details of these findings will be presented below.

# **Evidence for the Importance of Symptoms and Side Effects**

## ***Symptom Distress Predicts Survival***

Symptom distress has been shown in multiple studies to be an independent predictor of survival in patients with cancer[26, 34-45]. Perhaps the most detailed such study, by Chang et al[26], confirmed in a large, heterogeneous cancer population that symptom distress as measured by the Memorial Symptom Assessment Scale predicted survival, after controlling in multivariate analyses for disease status, global quality of life, psychological state, and performance status. In fact, it has been proposed that previous studies, which demonstrated that quality of life ratings were predictive of survival, may have done so because the quality of life scales employed in these studies included measures of symptom distress[26].

The usual interpretation of the association of symptom distress with survival is that patient-reported symptoms may be a sensitive measure of disease status, which provides information not fully captured by other measures of disease state. In this paradigm, the use of symptom distress measures would have obvious application in identifying symptoms requiring treatment, and in supplementing prognostic information, but treatment of symptoms alone would not be expected to prolong survival. Interestingly however, the only test of this hypothesis in the literature is a prospective, randomized clinical trial of intrathecal analgesics vs. standard analgesic approaches in patients with intractable cancer pain[46]. In this study, patients randomly assigned to receive intrathecal analgesics had similar pain ratings compared to those assigned to standard approaches, but had significantly reduced side effects, and, provocatively, prolonged survival. This finding suggests the possibility that at least in some circumstances, interventions to reduce symptoms alone may be associated with prolonged survival.

## ***Symptom Distress Predicts Clinically Important Outcomes***

Symptom distress has been associated in clinical trials with other important clinical outcomes survival. Testa and colleagues[21] studied 379 hypertensive men in a randomized controlled trial of captopril vs. enalapril for 24 weeks. Measurements included clinical variables, a comprehensive quality of life battery, Side Effects and Symptoms Distress Index, Life Events Index, and Stress Index. The Life Events Index consisted of 42 scales for major life events rated according to their level of stress. For example, very stressful events included death of a spouse and divorce; moderately stressful events included retirement and change in health of a family member; and less stressful events included minor violations of the law. The Symptom Distress Index contained 50 items relating to common side effects of antihypertensive medications.

Efficacy, passively captured AEs, overall dropouts, and dropouts due to AE were similar between groups. Quality of life results in general showed improvement in subjects on

captopril and declines in patients on enalapril, with the differences statistically significant (Fig. 3). To evaluate the clinical meaningfulness of these changes in QOL, the QOL scales were correlated with three indexes: the Symptom Distress Index, the Stress Index, and the Life Events Index. QOL scales were significantly correlated with all three indexes, with correlation coefficients ranging from 0.36-0.58 ( $p < .001$ ); Symptom Distress was most strongly correlated with QOL and explained most of its variance. A calibration model was constructed using regression analysis to relate the change in QOL to scores for stressful life events (Figure 4). The changes found in QOL were comparable in severity to moderately stressful life events, such as loss of a job or sexual difficulties. Thus, this study demonstrates, via an innovative approach comparing QOL and Symptom Distress to contemporaneous stressful real-life events, that the changes in QOL detected in this medication trial, driven primarily by Symptom Distress, were important to these patients based on comparison to the stress produced by real-life events. These important differences were not reflected in differences in efficacy or passive AE capture. The authors point out that the QOL battery they employed required a 30-40 minute response burden, and that less comprehensive QOL batteries may not have picked up these important differences.

In a study by Anderson and colleagues[19], 269 patients with hypertension were treated with either controlled-release verapamil or nifedipine for 10 weeks. Measurements included clinical variables, a QOL battery similar to that employed in the Testa study, and a Physical Symptom Distress Index (PSDI). The PSDI consisted of 71 symptoms associated with hypertension or the potential side effects of both drugs. Both treatments effectively lowered blood pressure. A greater proportion of patients treated with nifedipine dropped out of the study (31%) compared to those treated with verapamil (24%). Dropouts due to AEs were 9% on nifedipine and 7% on verapamil, with all of the difference accounted for by withdrawal due to pedal edema on nifedipine. The PSDI was significantly different between the two groups ( $p < .001$ ), with univariate differences detected for 7 symptoms (Fig. 5). Importantly, some of the between-treatment differences in change of symptom distress were due to reductions in distress in the verapamil group, suggesting that measurement of symptom distress at baseline is critical. Patients who dropped out reported significantly worse symptom distress than those who completed the trial. Worsening of symptom distress was highly correlated ( $p < .001$ ) with worsening of the General Health Status subscale of the psychosocial scales. There was no significant difference between treatments on the psychosocial QOL scales themselves. Again, however, QOL among dropouts was worse than completers, irrespective of treatment group.

There was a substantial difference between passively captured AEs and the symptom distress ratings by patients (Table 1). Passive AE capture picked up only a fraction of symptoms, even those associated with significant distress. Interestingly, one symptom, constipation, which was more frequent in the verapamil group as measured by passive AE capture, was not associated with differences in symptom distress. One may interpret these findings as indicating that prospective symptom distress measurement may clarify both false negative and false positive findings from passive AE capture. Alternatively, the symptom distress ratings may integrate perceptions of symptom importance not

reflected in simple frequencies. In any case, symptom distress measurement was the only measure that clearly differentiated the tolerability of the two treatments.

Hollenberg and colleagues later presented a more comprehensive analysis of these findings[31], from the hypertension study described above and from a similar study of angina patients treated with either verapamil, amlodipine, or an amlodipine-atenolol combination[47]. These analyses confirmed for both studies that neither drug efficacy nor psychosocial QOL batteries distinguished treatments. However, PSDI found significant differences between treatments. These studies also confirmed that changes in symptom distress were associated with changes in psychosocial QOL of the same magnitude that was associated with moderately stressful life events in the Testa study[21], which used the same QOL battery (Fig. 6).

In summary, these studies reveal that, at least under these circumstances, symptom distress was the most sensitive discriminant between treatments, where efficacy, passive AE capture, and a comprehensive psychosocial QOL battery failed to reveal differences. A change of one step in overall symptom distress was associated with a change of psychosocial QOL (based on the Rand Mental Health Index) of 0.1-0.2 SD units, which had been shown to correspond to the distress associated with important stressful real-life events.

### ***Are All Symptoms Equally Important?***

To add another level of complexity, patient ratings of intensity of a symptom may be different than the distress associated with that symptom, and the importance of that symptom may be yet a different dimension. In one study of anti-emetic treatment for chemotherapy-associated emesis, “duration” of nausea correlated more with self-reported well-being than “intensity” or “frequency” of nausea/vomiting (described in [7]). In another study of patients with lung cancer [7], the order of symptoms as ranked by “intensity” was different than the order of the same symptoms as ranked by “importance” (Table 2). For example, the intensity of distress associated with “appearance” ranked fifth, but “appearance” ranked last in order of importance (Table 2). Thus, importance may be an important dimension of the symptom experience not captured in intensity or distress measures.

### ***Are Elicited Symptoms “Signal” or “Noise”***

One potential critique of prospectively administering symptom distress inventories is that numerous irrelevant symptoms would be elicited – after all, if the symptoms were sufficiently bothersome to the patient, would he/she not report them, so that they would be captured in a passive AE capture system? Are symptoms captured after they are “put into the head” of the patient meaningful? There are as yet no published data from an analgesic clinical trial that directly address this important question. However, numerous studies suggest that important levels of one symptom, pain, are frequently missed in routine clinical or investigational settings[48]. A number of barriers to adequate symptom assessment have been delineated[11], which have resulted in regulatory



approaches to ensure adequate assessment[49]. There is no reason to believe that these factors are less operant in the case of other symptoms. Furthermore, the studies described above suggest symptom distress not revealed by passive AE capture was associated with important treatment outcomes. An additional study directly compared symptom distress elicited from patient, spouse, and physician[20]. It was clear that even with detailed prompting, the physician missed important side effects. The extension of these findings to analgesic studies awaits further research.

## **Responsiveness of Symptom Distress Measures**

The only published experience of assessing symptom distress in a clinical trial for chronic pain is that of Jamison and colleagues[29]. These investigators conducted a randomized prospective clinical trial of naproxen, vs. fixed-dose opioids (up to four oxycodone-acetaminophen tablets per day) vs. titrated-dose opioids (controlled-release morphine plus oxycodone-acetaminophen as needed, titrated to optimal doses) in the treatment of chronic low back pain in 36 patients. A symptom distress inventory of 20 potential opioid side effects was administered weekly to these patients for 52 weeks. These authors found statistically significant differences in symptom frequency (Table 3) and symptom intensity (Table 4) between the three treatment groups, despite the small sample size. Curiously, while symptom frequency was highest in the titrated-dose opioid group, symptom intensity was greater in the fixed low-dose group than the titrated-dose group. While the responsiveness of this symptom distress inventory in this study was clear, the impact of symptom distress upon overall treatment response was not reported.

As noted above, in separate clinical trials of agents for hypertension and for angina, symptom distress inventories were the only measures that clearly separated the treatment groups, whereas AEs measured by passive capture, efficacy, and psychosocial QOL measures failed to differentiate the groups.

## **Global Ratings: Do Patients Integrate Side Effects?**

Patient global ratings of treatment, or of overall clinical status, have increasingly come into vogue in clinical trials of analgesics and other agents[1]. The purported advantage of global measures is that they give the patient an opportunity to integrate any perceived benefits with tolerability and other factors. In this manner, the overall treatment response, which consists of a balance between benefit and side effects, would be revealed. To date, however, there has been no reported evidence of the extent to which patients integrate side effects into their global assessment of treatment effect in any analgesic trial. Global ratings may be inflated at times by unwillingness to deprecate a new treatment or doctor, by the positive effects in a clinical trial setting of attention, free medical care, or other factors. Until more research on the drivers of patient global ratings is available, it would appear unjustified to assume that global ratings provide an accurate measurement of side effects of therapy, or of the balance between benefit and side effects as perceived by the patient.

## Available Symptom Distress Inventories

A number of comprehensive symptom distress inventories have appeared in the literature (Table 5). Most have been extensively validated, while some have simply been utilized. The only inventory published in the setting of chronic pain is that of Jamison and colleagues[29]; while this inventory showed discriminant validity in the single trial in which it appeared, further information on validity and reliability is not available. These authors also demonstrated the feasibility of capturing this symptom inventory in electronic diary format[50]. However, this inventory was composed of potential side effects only; potential symptoms of underlying disease were not incorporated, as was done by Anderson and colleagues[19, 31]. Thus, there are no “off-the-shelf” inventories available for application to chronic pain trials. Moreover, it is not clear that a standard questionnaire would be broadly applicable in chronic pain trials, since in the only other extensive experience applying comprehensive symptom distress inventories in the clinical trial setting, the investigators customized their approach for each clinical setting by combining the potential symptoms of the diseases and drugs being studied[19, 21, 31].

## Relationship Between Symptom Distress and Quality of Life

The growing interest in measuring outcomes from the patient’s perspective has also led to increasing emphasis on measuring “quality of life,” or more specifically “health-related quality of life” (HRQL). HRQL has been defined in a variety of ways, but generally consists of at least physical functioning, psychological functioning, and sometimes social and spiritual functioning, as well as global perceptions of function and well being. In the effort to assess these domains, most HRQL instruments include a number of items that address symptom distress. The Rotterdam Symptom Checklist[51], commonly viewed as a HRQL instrument for cancer patients, is essentially a symptom distress inventory. Conversely, most symptom distress inventories contain items related to the domains considered part of HRQL assessment. As noted above, symptom distress measures predict a large proportion of the variance of even psychosocial general well being instruments. Thus, symptom distress and HRQL are closely related, and further refinement of the constructs of symptom distress and HRQL will be needed in order to more clearly tease out the relationship between these two constructs.

## Current Recommendations

### 1. Passive AE capture

At a minimum, clinical trials for chronic pain should follow the procedure commonly employed in the pharmaceutical industry, which is to capture, code, and report passively captured AEs. Open-ended prompts should be employed. This author suggests the following minimum elements in the reporting of such AEs from any chronic pain clinical trial:

- Proportion of subjects in each group reporting  $\geq 1$  AE
- Proportion reporting  $\geq 1$  drug-related AE

- Proportion with  $\geq 1$  severe AE or “Serious Adverse Event” (the latter term has a specific regulatory definition; the former is an assessment by the investigator of clinical severity)
- Proportion who drop out due to an AE, and the specific reason for the dropout
- Proportion of subjects in each group who have each AE, and AE category (for example, the proportion with dyspepsia, abdominal pain, and other specific gastrointestinal AEs, as well as the overall proportion experiencing gastrointestinal AEs. Standard coding dictionaries are preferred.

Two methodologic issues must be mentioned. First, sensible accounting of AEs requires attention to the AE status at baseline. The better approach would be to measure symptoms prevalent at baseline, so that symptoms prevalent during or after the trial can be compared to baseline status. Alternatively, only “treatment emergent” (i.e. incident) AEs, that is, new symptoms/side effects not present at baseline, may be presented. Second, every effort should be made to assess dropouts for the reason for drop out, and for symptom distress levels in cases where symptom distress methods are employed. As indicated above, symptom distress levels in dropouts are likely to be different than in patients who complete the trial.

## **2. Prospective capture of AEs of interest**

All trials should consider whether certain AEs/symptoms/side effects may be of particular interest, and therefore should be measured prospectively, in addition to passive AE capture of all AEs. For example, a clinical trial of an agent suspected to alter neuropsychological function may choose to assess neuropsychological function prospectively, in addition to capturing all AEs passively.

## **3. Comprehensive symptom distress inventories**

At this point in time there is insufficient evidence to recommend routine use of comprehensive symptom distress inventories in all chronic pain clinical trials. However, there may be many circumstances in which important study hypotheses can be addressed only through such methods. For example, in trials that compare two active agents with similar efficacy (indeed, most analgesics within specific classes probably have similar efficacy at equi-analgesic doses), meaningful treatment differences may be discriminated only by comprehensively measuring symptom distress. Or, in assessing agents that may depend for overall therapeutic effect on a delicate balance between symptom reduction and symptom production, direct assessment of the symptom balance may be indispensable. When the symptom distress approach is employed, careful attention should be given to the relevant dimensions of the symptom experience, such as intensity, duration, frequency, distress, and importance.

## **4. Other options**

While investigators await further clarification, perhaps a simple way to move forward would be to introduce into analgesic clinical trials a simple question about overall symptom distress, e.g. “How bothered are you overall by side effects?” Moreover, when the balance between pain relief and side effects is pivotal, a simple determination of the patient’s perception of this balance could be useful. For example:

“Do you feel that the benefits of this treatment outweighed the side effects?”

- Yes, definitely
- Yes, probably
- Not sure
- No, probably not
- No, definitely not

## **Future Directions**

We need to understand how a patient determines overall benefit of a treatment: to what extent are global ratings driven by pain relief, by side effects, and by other factors, such as expectations, convenience, cost, etc. How much nausea is a patient willing to accept in order to reduce pain from severe to moderate? From moderate to mild? Are some side effects more distressing than others, and therefore less likely to be accepted as a trade-off for pain relief? How different are our treatments in terms of their side effects profiles? To what extent can aggressive management of side effects, e.g. by slow titration or by pharmaceutical management, improve overall treatment effect? Can we develop a standard approach to symptom distress measurement that will allow validated and reliable assessment of the construct of symptom distress, so that prediction of the overall therapeutic result in practice can be made from clinical trials in chronic pain?

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TABLES

Table 1. Frequency of symptoms found to differ between treatments from the Physical Symptom Distress Index, compared to the corresponding spontaneously reported adverse events, in a trial of verapamil vs. nifedipine for hypertension. Adverse events captured passively were of much smaller frequency than those captured proactively, despite both capture methods being present in the same study. Many patients with severe distress related to specific symptoms were not identified by passive AE capture. Constipation, which differed in frequency based on passive AE capture, did not differ in associated distress[19].

	Percentage of Subjects Reporting									
	Edema		Palpitations		Increased Urination		Muscle Cramps		Constipation	
	COER- Verapamil	Nifedipine GIT8	COER- Verapamil	Nifedipine GIT8	COER- Verapamil	Nifedipine GIT8	COER- Verapamil	Nifedipine GIT8	COER- Verapamil	Nifedipine GIT8
Adverse events PSD Index†	1.4	12.8	1.4	2.8	0.4	1.1	0.7	3.2	14.9	8.2
Total	26.6	47.2	17.0	27.5	35.5	33.0	23.9	36.4	30.2	31.0
Distressed‡	12.4	33.8	7.3	13.4	17.4	23.0	12.0	22.7	25.1	18.2
Extremely distressed	2.4	12.2	0.4	1.9	1.9	7.0	1.2	2.2	6.1	5.5

Table 2. The ranking of symptoms by “intensity” (column 2) differed from the ranking of the same symptoms by “intensity” in a study of lung cancer patients[7].

Thurstone scale order	Intensity (mean) order
Outlook	Fatigue
Breathing	Outlook
Pain	Insomnia
Insomnia	Breathing
Cough	Appearance
Bowel	Appetite
Appetite	Pain
Fatigue	Cough
Appearance	Bowel

Table 3. Symptom frequency in a study of 36 patients with chronic low back pain randomly assigned to naproxen, fixed-dose opioids, or freely titrated opioids. Statistically significant separation of the three groups was found[29]

## Percent Reporting Symptoms

Adverse Effect	Value (%) for Indicated Group			
	Total (N = 36)	No Opioid (N = 12)	Set Dose (N = 13)	Titrated Dose (N = 11)
Dry mouth	26.1	19.3	26.0	34.7
Drowsiness	24.1	14.6	22.1	36.9
Headache	22.1	15.1	20.2	31.8
Constipation	19.1	10.4	17.8	30.1
Nausea	16.2	4.7	13.9	31.3
Itching	12.9	8.9	14.9	14.8
Dizziness	11.6	9.4	18.8	5.7
Sweating	6.8	6.8	9.6	3.4
Weakness	6.3	5.7	7.7	5.1
Sneezing	2.0	1.0	1.0	4.0
Muddled thinking	1.6	3.1	1.4	.0
Nightmares	1.2	1.0	1.0	1.7
Heart palpitation	.7	.5	.0	1.7
Visual distortions	.7	.0	1.9	.0
Memory lapse	.5	1.6	.0	.0

Note: Wilcoxon matched-pairs signed-ranks test: No opioid vs. set dose,  $z = -15.7$ ;  $P < 0.001$ . Set dose vs. titrated dose,  $z = -16.8$ ,  $P < 0.001$ . No opioid vs. titrated dose,  $z = -18.0$ ;  $P < 0.001$ .

Jamison RN et al, Spine, 1998

Table 4. Symptom intensity in a study of 36 patients with chronic low back pain randomly assigned to naproxen, fixed-dose opioids, or freely titrated opioids. Statistically significant separation of the three groups was found[29].

## Side Effect Intensities

Adverse Effect	Total (N = 36)		Intensity Ratio for Indicated Group		
	Frequency	Intensity Ratio*	No Opioid (N = 12)	Set Dose (N = 13)	Titrated Dose (N = 11)
Dry mouth	152	0.48	0.54	0.63	0.32
Drowsiness	139	0.40	0.46	0.44	0.35
Headache	127	0.45	0.60	0.53	0.32
Constipation	110	0.57	0.66	0.61	0.50
Nausea	93	0.33	0.40	0.36	0.30
Itching	74	0.45	0.74	0.43	0.29
Dizziness	67	0.41	0.43	0.41	0.34
Sweating	39	0.54	0.58	0.50	0.33
Weakness	36	0.49	0.60	0.52	0.29
Sneezing	11	0.34	0.50	0.23	0.33
Muddled thinking	9	0.43	0.46	0.37	—
Nightmares	7	0.29	0.28	0.35	0.25
Heart palpitation	4	0.24	0.35	—	0.20
Visual distortions	4	0.36	—	0.36	—
Memory lapse	3	0.38	0.38	—	—

\* Ratios from 1.0 to 0.0; sum of intensities/(no. of responses × 100).

Jamison RN et al, Spine, 1998



Table 5. A sampling of published symptom distress inventories.

INSTRUMENT	REFERENCES	POPULATIONS
Physical Symptoms Distress Index	Testa 1993[21] Anderson 1999[19] Hollenberg 2000[31]	Hypertension, angina
Opioid Symptom Checklist	Jamison 1998[29]	Chronic low back pain
Symptom Distress Scale	McCorkle 1978[52]	Cancer
Memorial Symptom Assessment Scale	Portenoy 1994[53]	Cancer
Edmonton Symptom Assessment System	Bruera 1991[54]	Palliative care, general cancer
Symptom Experience Scale	Rhodes 2000[3]	Cancer
Adapted Symptom Distress Scale-1,2	Rhodes 1984, 1987[4]	Cancer
MD Anderson Symptom Inventory	Cleeland 2000[22]	Cancer
Rotterdam Symptom Checklist	de Haes 1990[51]	Cancer
Memorial Symptom Assessment Scale – Short Form	Chang 2000[25]	Cancer, AIDS
Physical Symptom Distress Scale	Chiou 1998[18]	End-stage renal disease

## FIGURES

Figure 1. Treatment results depend, in terms of symptomatic benefit upon a balance of benefit (reduced symptoms) and side effects (produced symptoms). Overall treatment results depend on other factors as well, including non-symptomatic benefits and risks, convenience, cost, etc.

### Overall Treatment Result

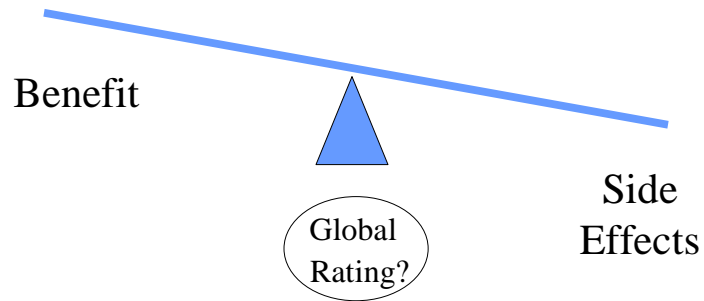


Figure 2. Several methods have been employed for capturing adverse events in clinical trials.

## Symptom Assessment

- Passive capture of adverse events
- Open-ended questions
- Specific AEs of interest
- Comprehensive symptom checklists
  - Frequency
  - Duration
  - Intensity
  - Distress
  - Impact on daily function
- Symptom Importance



Figure 3. Mean  $\pm$  SE changes in the quality of life subscales from baseline to end point in the patients assigned to captopril or enalapril in patients with hypertension in a 6-month trial. Changes were measured in responsiveness-index units representing the standard deviation of the change from weeks 18-24 [33].

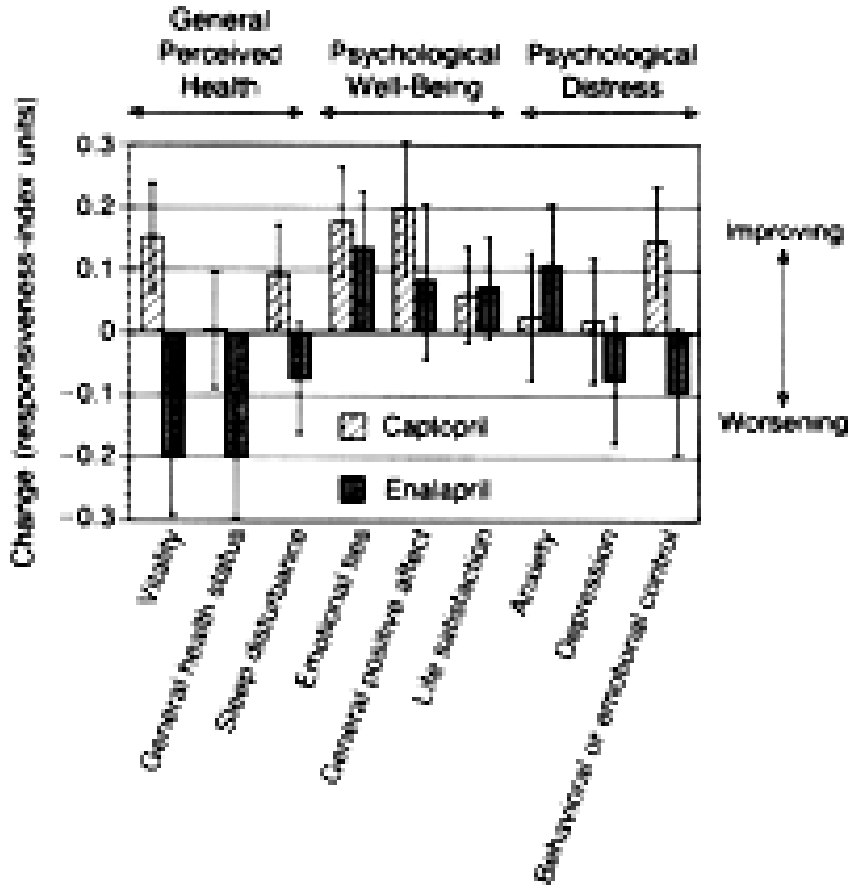


Figure 4. Linear trends on the General Perceived Health Scale as a function of the Life Events Index, in a study of captopril vs. enalapril for hypertension. Changes in the range of 0.10 to 0.20 responsiveness-index units, a magnitude of change found in the study, was comparable in associated distress to moderately stressful life events, such as loss of a job or sexual difficulties[21].

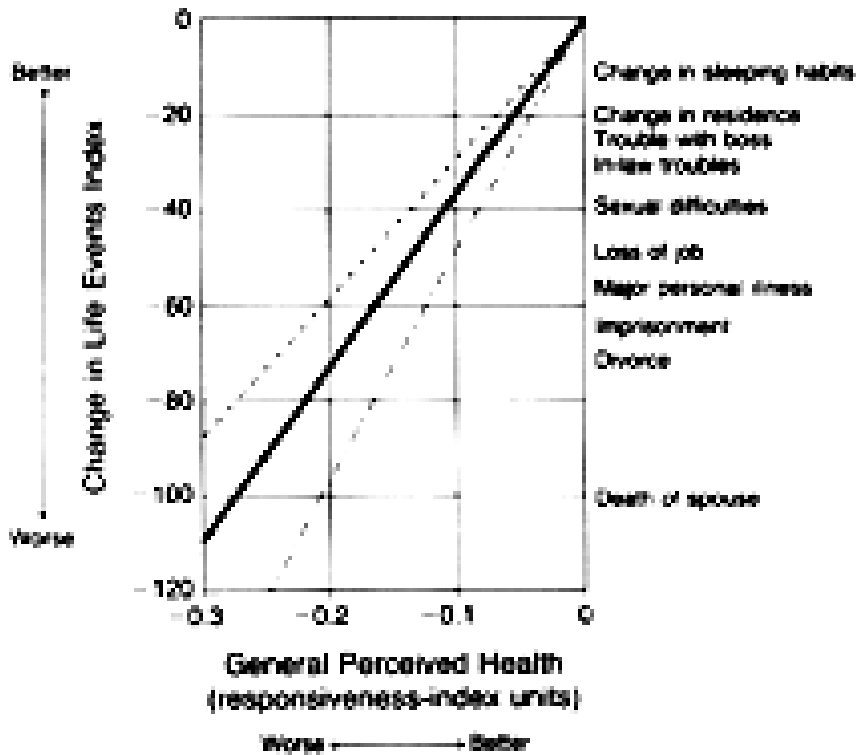


Fig. 5. Physical Symptom Distress Scores in a study comparing verapamil to nifedipine for hypertension. Change from baseline in SD units for individual symptoms demonstrating a significant univariate treatment effect by treatment group (positive change reflects reduced distress;  $p=.002$  for multivariate analyses of variance). COER indicates controlled onset, extended release; GITS, gastrointestinal therapeutic system.

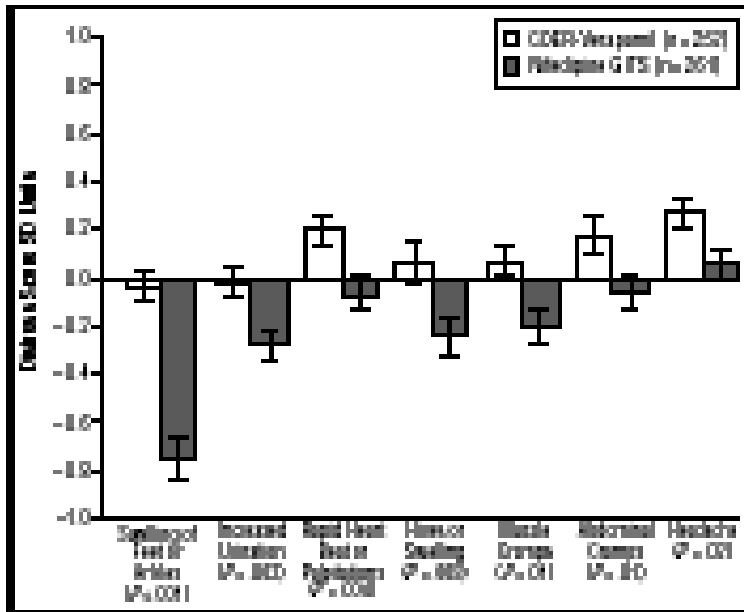
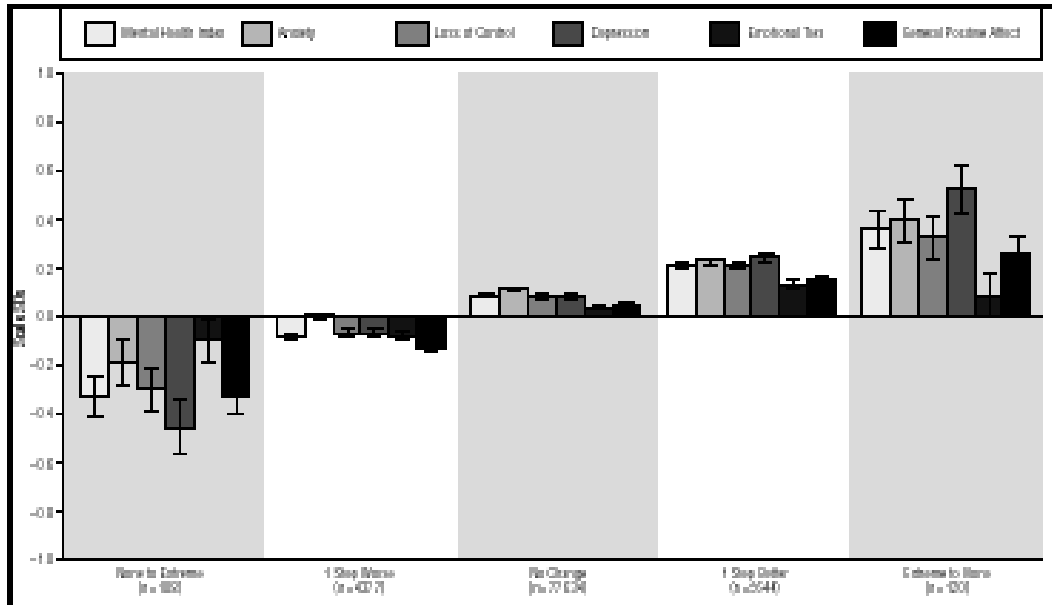


Fig. 6. Relationship between change in symptom distress during drug treatment of angina pectoris and accompanying change in quality of life in units of SD, in a study of three drug treatments for angina [31]. The relationship was essentially identical in a study of different agents for hypertension (data not shown).



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