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Recent Clinical Trials of Pain Control: Impact on Quality of Life

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The understanding and treatment of pain is one of the oldest challenges for physicians, scientists and philosophers. Much of our present rationale of pain control is based on the Cartesian idea that pain mostly originates from external or internal noxious stimuli, which are transmitted to and interpreted in the brain. Consequently, removal (blocking) of the stimuli and modification of cerebral awareness have been the prime targets of analgesic interventions. Only recently has the relationship between pain and other physical, psychological and social aspects of illness been considered in the overall management plan. Most of the literature on pain control reveals the physical bias of measurement. Apart from simple but reliable tools such as visual analogue scales and Likert-type verbal scales, more sophisticated measures such as multidimensional pain inventories have also been used when it is necessary to characterise pain more specifically. In clinical studies, it is usual to ask the patient to report on his own pain, although proxy measures such as mobility, performance status and analgesic consumption are also often used. The hospice concept of "total pain", in which the psychological, social, spiritual and other aspects are emphasised, has been influential in our new approach to pain measurement. Particularly when it is chronic and related to advancing disease as in metastatic cancer, pain can interact significantly with many facets of daily living. A holistic model of quality of life in such patients should, therefore, include a multidimensional or modular assessment of these areas. Medical interventions themselves can affect quality of life in both positive and negative ways. Some side-effects may be so common as to be accepted as "normal", e.g. constipation or sedation with opioids: it is only by their careful evaluation, when comparing opioids with essentially similar analgesic potentials, that differential toxicities may be revealed. Simple recording of physical side-effects of drugs is really not sufficient, because analgesics as well as other therapies may be associated with mood changes and broader consequences for quality of life. Only in the past few years has quality of life been seriously addressed in palliation research. For example, standardised quality of life scales are now included almost routinely in oncological studies involving radiotherapy or chemotherapy by the Medical Research Council (MRC) of Great Britain. Trials of the new biphosphonates, which can reduce bone pain in metastatic cancer, have been enhanced by incorporating quality of life measures. Based on the experience from earlier efficacy/safety studies with the new transdermal route of drug delivery for the opioid fentanyl, important areas of life such as sleep and cognitive function have been addressed. Randomised controlled trials of analgesics which include quality of life endpoints are still rare, but should be encouraged as these represent the most rigorous way of evaluating new therapies. The current preoccupation with quality assurance in healthcare is directed, ultimately, to the delivery of a better quality of care, which should also be more cost-effective, for large populations. An important intermediate step towards that ideal is the collection of data on pain and other symptoms, but also validated quality of life parameters on well-defined groups. Only by widening the scope of analgesic studies to include these dimensions can we hope to define appropriate strategies for more rational healthcare.
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HISTORICAL VIEW OF PAIN

THE UNDERSTANDING and treatment of pain is one of the oldest challenges for physicians, philosophers and scientists. St Augustine (354–430) wrote: "The greatest evil is physical pain". In a similar vein, Milton (1608–1674) wrote in *Paradise Lost*:

> But pain is perfect misery, the worst
> Of evils, and excessive, overturns
> All patience.

Thus the classical view of pain has always been as not just a physical symptom, but also as a sensation which can undermine

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a person's general wellbeing, and is even capable of being seen as an evil force active against man's soul.

The seventeenth-century philosopher Descartes presented a new concept of pain, based on the principle of noxious stimuli which transmitted messages to the brain, which were interpreted there as a harmful sensation. This Cartesian view has dominated Western scientific thought on pain mechanisms, and to a large extent also influenced the approaches to control of pain [1]. Consequently, removal (blocking) of the stimuli and modification of cerebral awareness have been the prime targets for analgesic interventions. Only recently has the relationship between pain and other physical, psychological and social aspects of illness been considered in the overall management plan.

MEASUREMENT OF PAIN

Most of the literature on pain control reveals the physical bias of measurement. Early studies relied heavily on the researcher's own interpretation of pain in his subjects, and these were in turn based on the patients' verbal reports or on their behaviour. The first attempts at formalising pain estimation were in the form of simple scales, which could take the form of visual analogue scales (VAS), numerical scales or verbal measures. Of course, other symptoms and psychological parameters may also be assessed using these scales.

With the VAS, the subject is asked to make a mark at some point on a 10 cm line, whose ends are designated as "no pain" and "worst pain"; the distance from the "no pain" end represents the level of pain being experienced. The numerical scale is a modification of this approach, in which the patient is presented with a series of numbers, usually from 1–7 or 1–10, which are also anchored by "no pain" and "worst pain" at the two extremes. With the third type, the subject is asked how much pain he has, and has to choose his response from a series of verbal statements or categories, e.g. "no pain at all", "mild pain", "moderate pain", "severe pain". These three types of pain assessments are the most commonly used in studies of pain management, because of their ease of use and responsiveness to clinical change. Examples of these are given in Table 1.

VAS measures—also called linear analogue scale assessment (LASA)—seem superficially more attractive in that they directly yield numerical data (0–100 mm) [2]. However, two problems can arise in their usage. First, some people, especially elderly patients and those with limited cognitive function, are less able to translate their pain experience into a mark on the 10 cm line. Second, although "statistically" significant differences between two measures may be obtained in terms of change of linear score, the *clinical* significance of say, a 10 mm or 20 mm change, is more difficult to appreciate.

Table 1. Examples of pain measurement scales

a. *Visual analogue scale*

No pain ——— Worst pain

b. *Numerical scale*

1 2 3 4 5 6 7

No pain Worst pain

c. *Verbal scale*

Have you had any pain?

Not at all A little Quite a bit Very much

In an attempt to characterise the nature and different causations of pain, the McGill Pain Questionnaire was devised by Melzack and has been extensively used in clinical settings [3, 4]. This instrument has three verbal subscales which cover the sensory, affective and evaluative components of the pain experience. In addition, the patient is asked about the present pain intensity (using a hybrid 5-point numerical/verbal scale), and also about the frequency of pain. Although it has been used extensively in North America, it has had rather limited usage in European studies of analgesia, probably because it relies so heavily on extensive verbal lists.

The Memorial Pain Assessment Card (MPAC) is a somewhat simplified version of this approach, and consists of true VAS measures for "present pain intensity", "pain relief" and "present mood", along with a single set of verbal descriptors of pain severity. Because of its brevity and the single set of words, it is more readily incorporated into protocols which also require the patients to complete other questionnaires [5].

As well as direct questions on pain level, other physically oriented measures may be used in the evaluation of patients in analgesia studies. For example, since pain can limit daily activities, it may be relevant to know whether—as the result of an intervention—the patient becomes more or less mobile, and more or less independent [6]. For these parameters, ideally the standardised scales for performance status or activities of daily living should be chosen [7].

USE OF PROXIES

In clinical studies, it is usual to ask the patient to report on his own pain. If he is unable to comply, two options are available: the physician or nurse can estimate the pain level, usually by asking the patient and observing his behaviour; alternatively, and particularly if the patient is at home, a relative can act as proxy and record pain level on the patient's behalf. Neither option is ideal, as it has been shown that both professional staff and family members are often poor judges of the patient's experience [8]. However, in some situations it may be inevitable that proxy measures have to be used, in order to obtain any data at all.

In some pain trials the consumption of analgesics has been recorded as another type of proxy measure for pain control [9]. If intake is reduced, it is assumed that pain has improved, presumably as the result of the intervention under study, e.g. biphosphonate infusions for bone metastases. Although apparently easy to measure, there are two objections to this approach: first, many patients are poor historians of their drug consumption; and second, an improvement in pain does not always necessarily lead to a reduction in analgesia consumption, since patients may continue to take the same dose, but with a greater sense of relief. Indeed, one of the principles of opioid usage in palliative care is to encourage patients to take the drug regularly, in anticipation of pain rather than in reaction to it; an increased consumption of drug may, therefore, even be seen as a feature of better pain control!

IMPACT OF PAIN ON QUALITY OF LIFE

One of the central pivots of the new hospice philosophy in the 1970s was Saunders' concept of "total pain", in which the psychological, social, spiritual and other consequences of cancer pain were emphasised, as well as the obvious physical perception [10]. This enlightened view has been very influential in the new approach to chronic pain management. It helped to lead to a holistic way of regarding the cancer patient at a time when

society was rejecting the poor level of care for dying people which was prevalent in hospitals and at home, and while the hospice movement was becoming established. The "total pain" idea was readily accepted by doctors, nurses and psychologists who saw the limitations of the purely physical evaluation of pain, and was thus one of the first moves towards the modern way of taking into consideration the patient's quality of life.

Particularly when it is chronic and related to advancing disease as in metastatic cancer, pain can interact significantly with many facets of daily living. A comprehensive model of quality of life in such patients should, therefore, include a multidimensional assessment of these areas [11]. It is possible to identify several discrete "domains", such as physical symptoms, aspects of physical, social and role functioning, cognitive ability, mood state, sexuality and spiritual issues (Table 2). Although it is important in our multi-ethnic societies to be aware of racial and religious differences, it is interesting that the concerns of patients with advanced cancer tend to cross cultural boundaries: an exploration of patient's problems and needs for psychosocial intervention in India showed that although cancer pain was the commonest (68%), other concerns about physical symptoms (60%), finances (54%), worries about "the future" (52%) and work (40%) were also prevalent [12].

Other dimensions of cognitive, affective and behavioural relevance include autonomy/control, personality type and coping strategies. Although these could be interesting areas for pursuing research on the consequences of cancer pain on the individual's lifestyle, they are of less practical importance in analgesia studies.

Clinicians often make assumptions about the relative importance of pain and other factors which contribute to quality of life of their patients. It has been shown that physicians frequently fail to recognise the effect of age, and tend to underestimate the reporting of problems by younger compared with older patients [13].

IMPACT OF TREATMENT OF QUALITY OF LIFE

Medical interventions themselves can affect quality of life in both positive and negative ways. Some side-effects of treatment may be so common as to be accepted as inevitable or even "normal", e.g. nausea/vomiting, constipation or sedation with opioids [14]. It is only by the careful evaluation of adverse effects when comparing opioids with essentially similar analgesic potential, preferably in a randomised crossover trial design, that differential toxicities may be revealed. However, recording of only the physical side-effects of drugs is really not sufficient, because analgesics, as well as other therapies such as radiotherapy or surgery, may be associated with functional, mood and social changes with their consequential effects on quality of life.

Table 2. Domains of quality of life which are relevant to cancer patients

Physical symptoms (besides pain itself, these could include anorexia, weakness, fatigue, sleep quality, etc.)
Physical functioning (e.g. mobility, activity)
Social and role functioning (e.g. independence, ability to continue at work or maintain the housework, interference with hobbies and leisure pursuits)
Cognitive functioning (including concentration, memory, confusion and disorientation)
Emotional functioning (e.g. anxiety, depression, anger, guilt)
Sexual functioning (including body image, sexual desire and activity)
Financial problems (including those affecting other family members who are involved in caring)
Spiritual issues (e.g. uncertainty and fear of prognosis, doubts about self-worth; also *positive* aspects such as dignity, feeling at peace, valued)
Autonomy / control (e.g. ability to make own decisions, choice of type and place of care)
Satisfaction (including information, treatment, inpatient facilities, etc.)

Often two treatments with equivalent pain-relieving properties may have different requirements with respect to the place of care, e.g. in ambulatory patients, a choice of attending hospital for radiotherapy or nerve blocks versus receiving medical treatment in the patient's own home. Or for compliance, e.g. taking regular oral medication several times a day versus 24 h portable syringe driver infusions or longer duration skin patches. In these situations, adding a comprehensive quality of life evaluation and preferably some measure of financial burden, could increase the likelihood of identifying a superior approach. An important principle in establishing these comparisons is to design the evaluation of subjective measures when, from the point of view of analgesia, both treatment arms are equivalent; it is then valid to make statements regarding differential effects on quality of life.

WHAT ARE THE APPROPRIATE MEASURES OF QUALITY OF LIFE?

From the preceding discussion of the dimensions of "total pain" and its consequences on everyday living, it could be thought that a truly comprehensive quality of life assessment might be intolerably long and unwieldy in most clinical trial situations. Indeed, it would be inappropriate to design an evaluation which included all possible quality of life parameters: such a study would prove impossible to analyse as well as being a major burden on patients and data collectors. However, several well developed, reliable, validated and succinct quality of life scales which cover the most important domains are now available, and may be used in clinical trials where pain control is one of the endpoints [11, 15, 16].

In Europe, the most commonly used scales are the European Organization for Research and Treatment of Cancer (EORTC) modular questionnaire [17, 18], and the Rotterdam Symptom Checklist (RSCL) [19]. They share a similar format, being based on verbal categorical questions with most items having four response categories (Table 3). The EORTC questionnaire also has items asking about the patient's own global assessment of physical condition and quality of life, using a 7-point numerical scale. Both of them have been translated into most of the European languages.

The current version of the EORTC Core Questionnaire is 30 items long (EORTC QLQ-C30); a 33-item version is being tested by the EORTC Study Group on Quality of Life. It is referred to as the "core questionnaire", because it is designed to cover the central essential issues experienced by most cancer patients. The modular design of the EORTC approach encourages the use, together with the core questionnaire, of other short tumour- or treatment-specific modules which can be focused on the trial's specific research questions [20]. The current RSCL is also 30 items long; it is an older instrument and unfortunately different versions have appeared.

It is crucial to appreciate that none of the published scales for

Table 3. Sample items from two cancer-specific quality of life scales

a. EORTC QLQ-C30

Please circle

3.	Do you have any trouble taking a *short* walk outside the house?	No	Yes
4.	Do you have to stay in bed or a chair for most of the day?	No	Yes
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	No	Yes

During the past week	Not at all	A little	Quite a bit	Very much
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall physical condition during the past week?

1 2 3 4 5 6 7
Very poor Excellent

How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7
Very poor Excellent

b. Rotterdam Symptom Checklist

2. *A number of activities are listed below. We do not want to know whether you actually do these, only whether you are able to at the moment. Please will you indicate how you managed last week*

	Able	With difficulty	Only with help	Unable
Care for myself (wash etc.)				
Walk about the house				
Light housework/household jobs				

quality of life should be adapted or amended by removing or adding items, without discussion with their authors. This is not so much for copyright reasons, but rather because altering the content and even the order of items in a psychometrically validated scale could render it invalid. One result of this practice could be a rejection for publication of a trial which used a "manipulated" quality of life instrument.

From North America, other quality of life instruments include the Functional Assessment of Cancer Treatment (FACT) [21] and the Functional Living Index–Cancer (FLI-C) [22]. These are both multidimensional questionnaires with good records of reliability and validity in cancer trials. The FACT is based on verbal categorical responses and has the attraction of enabling the patient to give his own weighting for the relative importance of different domains. The FLI-C is an older instrument and uses a hybrid of verbal and numerical analogue response sets. It also is able to yield a single overall score for quality of life, which clinicians may find less useful than separate domain scores, but which could be used in other mathematical formulae, e.g. by health economists in preparing quality of life adjusted years (QALYS).

The instruments mentioned so far are all disease-specific, i.e. quality of life scales devised for use in patients with malignancy. Tools for use in broader diagnostic groups are called generic scales. These include the Sickness Impact Profile (SIP) [23], Nottingham Health Profile (NHR) [24] and most recently, the Medical Outcomes Study Short Form 36 (SF-36) [25]. The SIP and NHP are older instruments and have been used in cancer pain studies, but the SF-36 is too new to have been tested in this area.

LINKING QUALITY OF LIFE TO QUALITY OF CARE

The current preoccupation with quality assurance in healthcare is directed, ultimately, to the delivery of a better quality of care for individuals, which should also be more cost-effective across large populations. An important intermediate step towards that ideal is the collection, in carefully controlled trials using well-defined groups, of data not only on pain and other symptoms, but also validated quality of life parameters [26, 27].

A reasonable *a priori* assumption is that with patients at an early stage having curative and adjuvant therapies, physical and role functioning will be relatively important. Similarly it may be argued that patients with advanced and terminal malignancies will be largely concerned with physical symptoms but also have greater need of social and spiritual support. Only by widening the scope of analgesic studies to include these dimensions can we build up a detailed picture of the patients' needs at different stages of cancer, and thus hope to define appropriate strategies for healthcare policies.

CURRENT STUDIES

Only in the past few years has quality of life been seriously addressed in research on palliation. For example, standardised quality of life scales are now included almost routinely in oncological studies involving radiotherapy or chemotherapy by the Medical Research Council (MRC) of Great Britain [27]. The standard package of measures used by the MRC consists of the RSCL and the Hospital Anxiety and Depression (HAD) scale. A trial of the new biphosphonate pamidronate to reduce bone pain in metastatic cancer was enhanced by incorporating the

Table 4. Differences in adverse effects between oral morphine and TTS-fentanyl in an open study (based on [31])

	Morphine phase (VAS score)	TTS-fentanyl phase (VAS score)	*P*
Pain	34.1	37.5	0.287
Constipation	0.33	0.19	0.022
Nausea	0.42	0.25	0.034
Vomiting	0.19	0.08	0.016
Sleep quality*	48.5	58.1	0.034
Morning vigilance	60.7	51.7	0.018

* Higher value is better.

RSCL [9]. Increasingly European multicentre trials organised by the EORTC incorporate a quality of life evaluation, which is usually based on the EORTC's own core questionnaire, together with other tumour-specific modules or separate instruments to broaden the scope [20].

In an attempt to survey the extent to which quality of life parameters have been used in cancer pain studies, the author has recently conducted a comprehensive search of MEDLINE. A total of 53 172 articles were found with "pain" as a subject heading. "Pain measurement" was found in 4985. The key words "quality of life" yielded 11 054 references. However, articles with both "pain" and "quality of life" numbered 275. After eliminating those on non-malignant pain and review articles, references with "pain measurement" and "quality of life", which represent the most detailed work on these areas, numbered only 34. One hopes that this figure will increase substantially over the next few years, now that the issue of quality of life is alive in our society.

Clearly many clinicians and researchers find the prospect of trying to measure quality of life as well as pain in analgesia studies a daunting one. Up until 5 years ago, it would have been possible to claim that no good standardised measures for cancer trials were available: that is no longer tenable. On the other hand, it is worth being cautious before embarking on quality of life studies. The organisational problems, which require a significant infrastructure of data collectors and clinic nurses as well as committed doctors, can easily lead to the downfall of a trial which tries but fails to accrue quality of life data [28].

To see how increasingly more comprehensive evaluations can give added value to clinical research in pain control, it is helpful to follow the published studies of the new transdermal (TTS) application of the relatively old opioid agonist fentanyl. Since it was first introduced in the U.S.A. and then into Germany, the earlier studies concentrated almost exclusively on its efficacy in terms of pain control [29]. One of these early trials was noteworthy in that it was randomised, double-blind and included 56 subjects [30]. In this study, patients on active TTS-fentanyl not only had less pain, but also reported less tension and anger, as measured by the Profile of Mood States Scale. Arising from the accumulated clinical and trial experience, it emerged that TTS-fentanyl may have a different and potentially improved side-effect profile from morphine, even though both are thought to operate on the same mu-receptors.

This potential advantage became a focus of another smaller open study, the first using TTS-fentanyl in the U.K., which compared the symptom and side-effect profile of oral morphine in 40 patients with stable cancer pain, with the same parameters experienced after 9 days of TTS-fentanyl patches [31]. Because of the comprehensive battery of measures used, mostly based on visual analogue and verbal scales, differences emerged which were statistically significant and looked clinically useful (Table 4). For example, against a background of equianalgesic action of morphine and fentanyl, the latter agent was associated with less constipation; less nausea and vomiting; improved sleep quality and yet increased morning vigilance.

In 1993, a second, much larger, U.K. trial was set up expressly to investigate these differences, which were thought to be due to differential opioid adverse effects. The trial was designed as a randomised crossover comparison between slow release morphine, which is the most commonly prescribed tablet formulation, and TTS-fentanyl. Each arm of the study lasted for 15 days, which is sufficiently long enough to allow adverse effects to develop (or recede) to their full extent. The study was distinguished by recruiting 202 subjects through a strong collaboration between 46 U.K. hospices which are specialist in-patient facilities recognised for providing high quality palliative and terminal care, but not previously associated with multicentre trial work. One of the factors which gained its acceptance by collaborators was undoubtedly the strong emphasis placed on quality of life outcome measures. In this study, the EORTC QLQ-C30 questionnaire was employed, as well as VAS and verbal scales concentrating on constipation, sleep and alertness. The trial closed in December 1994. The results are eagerly awaited by those interested not only in the control of pain, but also in the complex relationship between pain, its treatment and the wider problems of coping with advancing malignancy.

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