

VIEW FROM THE OBSERVATORY

Changing technologies of cancer pain relief: case studies of innovation

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In a previous article (1), we presented the first phase of a project within the International Observatory on End of Life Care that is seeking to develop an analysis of the specific problem of cancer pain relief in its historical and cultural context (2). We offered a historical overview of major themes in cancer pain relief in the 20th century by exploring the interplay of regulatory, scientific, clinical, cultural and ethical dimensions – themes which continue to shape contemporary debate and practice. In this article, we present an overview of the second phase of the study in which we explore contemporary debate and practice in case studies of three fields of innovation that emerged from our earlier analysis of the history of cancer pain relief since 1945.

Routes of administration

Our focus here is on the methods available to clinicians for the administration of pain-relieving drugs in the context of advanced disease. We focus on key innovations such as the development of slow release formulations for morphine; the transfer of the syringe driver from other areas of medicine into palliative care; the use of transdermal

patches; and the rising importance of patient control and preference in the formulation and marketing of new technologies.

Pharmacogenetics

The variability of patients' responses to analgesic therapies has become a major issue in cancer pain management. The new field of pharmacogenetics has been hailed as a means of tailoring treatments to individual genetic profiles and of enhancing the efficacy and safety of drug administration. The potential benefits of these new technologies for cancer pain relief merit exploration.

Pain and the public

Cancer pain relief is of course an issue in the wider social context – beyond the health care facility or the laboratory. We are interested in the ways in which cancer pain has been presented as a public health issue and the extent to which associated programmes have had an impact. One particular aspect of this is the barriers to cancer pain relief that exist in different countries and settings and the cultural, governmental, political and economic factors that shape them.

Our analysis is based on a variety of approaches: extensive reviews of the published literature; searches of the grey literature and web-based sources; investigations in personal papers and archives; interviews with key individuals (3). In exploring these case studies, we have kept in mind some important principles about the nature of innovation. For example, there is a distinction to be made between 'invention' (the creation of a new product or process) and 'innovation' (the means through which inventions become an operational reality). There are also identifiable 'types' of innovation, for example: 'product' or 'process'; 'basic' or 'incremental'; and 'pseudo-innovation'. The relationship between 'innovation' and its environmental context is also important as is the relevance of organisational structure and culture to innovative activity. Marketing too has a special role in innovation processes (4).

Impact of changing routes of analgesic administration

Slow release formulations for morphine

Morphine, usually as sulphate or hydrochloride salts, is available in four oral formulations: (i) solution; (ii) immediate release tablets; (iii) sustained or controlled release tablets or capsules; and (iv) controlled release suspensions. The controlled release tablets are available in 12 or 24 hour release patterns. Controlled release capsules contain coated beads which can be sprinkled over food (5).

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The mechanism of sustained release (6) varies according to the medium in which the drug is prepared.

In sustained release tablet form, morphine is mixed with hydroxyalkyl-cellulose (7) and granulated. The granules are compressed into a tablet and given an enteric coating. This coating is broken down by gastric fluids, thus exposing the granules. As the hydroxyalkyl becomes hydrated during further digestion, morphine is released.

In sustained release capsules, a process of 'multiparticulate' technology is adopted. In this, powdered morphine is mixed with a powdered waxy material, which is slightly hydrophobic. The mixture is processed carefully to produce an evenly distributed mixture of particles containing morphine and wax. These particles are packed into capsule shells. The capsules dissolve within 15 minutes of entering the digestive system, and morphine is gradually released and the particles of morphine and wax are hydrated.

In sustained release solutions, morphine is mixed with resin to make a solution. The solution is drunk, and the morphine released slowly as the resin becomes hydrated. The resin is excreted.

The *Drug and Therapeutics Bulletin* of 1981 reported on the introduction of 'morphine in slow release tablets', noting that:

Slow-release tablets containing 10 mg morphine sulphate (MST-1 Continus-Napp) have recently been introduced for the long-term management of patients with severe and intractable pain. Morphine is the analgesic of choice for severe pain in cancer, but when given by mouth as an aqueous solution it needs to be taken every four hours. This solution is convenient for most patients, but those who are forgetful, live alone or have poor eyesight may find their therapy difficult to manage. The aim of a slow release formulation of morphine is to allow a reduction in the frequency of analgesic administration, and given at bedtime it may also help patients who would otherwise wake in pain in the early morning.

It is noted in the *Bulletin* that the data sheet for MST-1 states that the usual dose is one or two tablets, and that since this dose is 'rather cautious, ... it would be an advantage to have a tablet size greater than the 10 mg now available' (8).

Two clinical studies to trial the new formulation are cited in the *Drug and Therapeutics Bulletin*. The first is by Robert Twycross and was reported briefly in *The Lancet* in 1981 (9). The second study is reported in *The Lancet* (10) and the *British Journal of Anaesthesia* (11). The lead author was Geoffrey Hanks, who was working at the Institute of Cancer Research and the Royal Marsden Hospital, in London. In his paper, Twycross *et al.* reported that 30 selected cancer patients were given MST, most of whom were

switched from morphine sulphate in solution to MST before leaving hospital. MST proved as effective in providing analgesia as the morphine in solution. Twycross *et al.* concluded cautiously that MST has a useful role to play, but cautioned against inappropriate use on an 'as required basis' and as an attempt 'to avoid the use of morphine by name' (12). In contrast, Hanks and his colleagues reported on the use of MST after dental extractions, finding this to be relatively ineffective although ascertaining that MST did produce sustained plasma concentrations. The work of Twycross and Hanks in evaluating MST was confirmed by Welsh, who reported in 1983 a comparative study of cancer patients receiving morphine sulphate solution and MST Continus tablets. In a later study, published in 1987, Hanks and Twycross (13) established that not only was MST as effective as immediate release morphine for patients with stable pain due to advanced cancer, it also provided a simpler and more convenient treatment regimen than a 4-hourly opioid for patients with cancer pain, once they had been stabilised with immediate release morphine, and contributed to better sleep. In a summary published in 1990 of the early trials of slow release morphine, Kaiko (14) identified that as well as these trials, there were also three articles published in Japan during 1987, a Scandinavian study published in 1985, a controlled but open prospective study published in 1984, five retrospective analyses of clinical experience published between 1981 and 1986, and two comparisons with diamorphine solution published in 1984 and 1986. There is no mention of Australian studies; this may be because of the reported delay in availability of controlled release morphine (15).

MST-Continus tablets rapidly gained in popularity, and it is clear that Napp responded promptly to the identified need for tablets in a wider range of strengths. Twycross became especially vigorous in his dissemination of the new approach to the use of opioids in cancer pain through teaching and textbook publication. By 1984, in one of a number of similar articles aimed at providing a guide to opioid administration for patients with cancer pain, he was able to report confidently that aqueous solutions of morphine are 'only one way of administering the drug', and that:

Controlled release morphine sulphate tablets are available in Britain in 10, 30, 60 and 100 mg strengths. These are of particular value in patients on a stable morphine regimen but who find a four hourly regimen difficult or impossible to manage. In most patients, a twice daily regimen is satisfactory (16).

Hanks later reflected that once controlled release morphine for oral use was introduced into the UK in 1981, it quickly became available world-wide, its use encouraged by the ease and simplicity of administration as well as acceptability to patients:

It has become an effective and convenient means of maintaining patients on morphine, if treatment is needed for long periods of time. Because of its acceptability to patients and because it simplifies morphine administration, the introduction of this formulation has encouraged the use of oral morphine in countries where such use was not well established (17).

Slow release morphine formulations are used when pain is fairly constant. Their administration reduces the number and frequency of doses that a patient needs to take. Following their introduction they were quickly recognised (18) as a 'significant departure' from the 'as required' form of administration of morphine. An early analysis of the use of sustained release morphine in a hospice setting in the US, reported that such preparations improved quality of life for patients and care givers (19). It has been suggested that slow release formulations avoid the peaks and troughs occasioned by immediate release formulations, and may also reduce the risks of drug errors, and improve compliance (20). Immediate release morphine needs to be given every 3–4 hours and, in the hospital sector in the UK, requires administration by two nurses. A study of a hospice ward in Glasgow reported in 1996 that it cost twice as much to administer a syringe driver as sustained release morphine tablets, because of the nursing resources required (21).

In 1989, Hanks published a review of the European experience of controlled release morphine in *Cancer* (22), establishing once and for all the equivalent potency and effectiveness of immediate release and controlled release formulations. This was followed in 1990 by the detailed review of controlled release morphine by Kaiko (14) and of Roxanol SR by Shepard (23). Hanks was involved in a survey of practice with strong analgesics for cancer pain relief in a variety of settings, published in 1991 (24). He and his colleagues reported that the majority of those who responded were using morphine in line with the World Health Organization (WHO) guidelines and were no longer concerned about addiction or tolerance. The more recently qualified doctors were using controlled release formulations readily, in spite of some remaining confusion about their use (25). It seems that, by the early 1990s, the use of slow release morphine was a vital part of the general pharmacopoeia of doctors charged with the care of patients in pain from cancer.

There are no 'true generic' (*i.e.* non-proprietary) titles for SR morphine. All products have brand names. Napp Pharmaceuticals (now Napp Pharmaceutical Holdings Ltd) launched MST tablets in 1980, prior to which only immediate release formulations (26) were available. Between 1980 and 1992, Napp held the patent for MST in the UK, and produced two more slow release formulations – MST suspension and MXL. Napp exports sustained release tablets but has no involvement in promotion, marketing or sales overseas. At 1 March, 2000 there were four suppliers of slow release morphine in the UK:

- * Napp: MST and MXL
- * Boehringer Ingelheim Limited: Oramorph SR (this was supplied between 1994 and 2000, but is no longer produced. It was produced as 'SRM Rhotard' by Farmitalia between 1991–1994)
- * Link Pharmaceuticals: Zomorph
- * Sanofi-Winthrop: Morcap SR.

MST tablets are produced in seven strengths, and are the only product offered in 5 mg and 15 mg packs. MXL and Morcap SR require once daily administration (24 hours), while the remainder of the formulations require twice daily administration.

MST is the market leader: seven of the 14 regional supply contracts in the NHS were held by Napp on a sole basis from March 2000, and all were for two or more years. Four further contracts were shared with Boehringer Ingelheim Limited.

The only other slow release opioids available are hydromorphone and oxycodone: these are not seen as 'first line' drugs but are used when patients cannot tolerate morphine (27). About 1–2% of patients (28) fall into this category. Slow release morphine has been incorporated into suppositories for rectal administration (29).

The transfer of syringe drivers from other medical specialties into palliative care

The subcutaneous route is commonly used in the management of symptoms, including pain, in palliative care. It is used when the oral route is impossible, when persistent nausea and vomiting are present, in intestinal obstruction and, more rarely, in dysphagia. Small, battery-powered syringe drivers are often used to deliver the infusion and these have established an important and lasting place in palliative care practice despite being developed for use in another clinical area.

The current popularity of the subcutaneous route represents a reversal of longer term trends. It was the first parenteral route to be used with the invention of the hypodermic syringe in the middle of the nineteenth century (30), but in the 1950s its use declined following reports of adverse effects (31). Interest in the sub-cutaneous route and in particular, continuous subcutaneous infusions (CSCI) revived in the 1970s among haematologists and paediatricians caring for children with the hereditary blood disorder, thalassaemia. Propper and his team in Boston established that deferoxamine, used to treat the condition, was effective by CSCI and that this represented the possibility of increased independence for sufferers as treatment could be undertaken at home (32). One of Propper's correspondents was Bernadette Modell, a paediatrician at University College Hospital, London. With an increasing population of children with thalassaemia to care for, she was keen to trial this approach. She

approached Martin Wright, a doctor and medical engineer whose inventions included the respirometer, Wright's Mini Peak Flow meter and the breath alcohol meter. She asked him to make her a portable device suitable for delivering CSCI to children and the syringe driver we know today was born.

Made by Graseby Medical (then Pye), the syringe driver proved very successful in thalassaemia (33) and other potential markets began to be explored, including postoperative analgesia (34) and the management of myasthenia gravis (35). Wright approached his friend Dr PSB Russell and suggested he might find it useful in the management of cancer pain in his hospice, Michael Sobell House. Russell was impressed, whilst reinforcing the use of the oral route where possible (36). Twenty-five years later, Dr Russell could clearly remember the case of one of the first patients with whom he used a syringe driver, a young woman with cancer desperate to have a final holiday with her children. Unable to take oral medication, she had remained in the hospice for parenteral analgesia. The syringe driver enabled the holiday to go ahead successfully:

... and she came back really overjoyed with her holiday because she knew time was short and it had meant so much to her to have this holiday with those children ... and that has stayed in my mind ever since. For me, that was the moment when I knew this had a big future (37).

Following Russell's letter to the *British Medical Journal*, use of the syringe driver spread through the developing field of palliative care and established a place that it maintains today. However, during the 1990s concerns were raised about its indiscriminate and inappropriate use (38). This light-weight and relatively simple device which seemed acceptable to patients was now being used unnecessarily, probably in the belief that parenteral medication was inherently more effective. Inevitably, this led to problems for patients (39) and to the suggestion that practitioners were using these devices to justify specialty status (40). With increasing experience and education in the use of syringe drivers, this situation seems to be improving. Yet uncritical application of the device persists, with little in the recent literature related to level of use and the attitudes of patients to it. These areas warrant further investigation as the case of the syringe driver offers useful insights into the application of innovative technology within palliative care specifically and in healthcare generally.

The use of transdermal patches

Another key innovation in modes of administration of strong analgesics is that of the development of transdermal methods – an area of pharmaceutical science that is often underestimated (41). We explore here why such an alternative mode of administration was sought, the historical development of transdermal analgesia delivery, and physicians and patients' perceptions of it. We take the transdermal formulation of the drug fentanyl as an example.

In the 1960s and 1970s, pharmaceutical researchers were seeking an effective means of introducing drugs into the bloodstream by applying them to unbroken skin (42). The pharmaceutical vision was to move away from 'primitive' dosage forms – tablets, capsules, slow release preparations, time capsules, ointments, solutions and injectables – which 'dump' their drug content in the body and rapidly enter the bloodstream resulting in under or over medicated patients. In 1981, it was reported that, at any one time in the US, 10–15% of the patient population had a drug-induced disorder. Hence, a delivery method was sought which administered smaller drug doses more frequently (43). The US-based ALZA Corporation emerged as pioneers of the transdermal delivery system with their first product, a scopolamine patch for the treatment of motion sickness introduced in 1980 (44).

Potent drugs are necessary for transdermal delivery. Fentanyl, a synthetic short-acting opioid synthesised by Janssen and colleagues in 1962, is 50–100 times more potent than morphine and offered an opportunity to develop a transdermal system for the treatment of pain (45). The arrival of transdermal fentanyl as an alternative treatment for cancer pain was heralded as a promising advance in non-invasive continuous drug administration (46). In 1988, the marketing of the new technology in cancer pain relief was taken on by Janssen in an 'ideal collaboration' which utilised their drug and ALZA's technology (42) and, in 1990, Duragesic (Fentanyl Transdermal System) entered the 'cancer market'. Transdermal fentanyl gradually grew in popularity with patients and physicians alike. In 1995, nearly 95% of patients in a study were reported as wanting to continue with transdermal fentanyl, preferring opioid medication administered every 48–72 hours and greater independence from pain therapy. Minimal disruption on an individual's life allowed a normal life-style, which was considered an immense benefit, though a disadvantage with the long interval between applications was a prolonged adjustment phase, requiring patients to take morphine solution for a time (47).

In 1996, an Expert Working Group of the European Association for Palliative Care published a review of modes of morphine administration in cancer pain. The group reported that transdermal fentanyl seemed effective and well tolerated but it was considered too early to determine where it would fit in the routine management of cancer pain. In line with contemporary WHO guidelines, oral administration was recommended as the preferred route of delivery, with the transdermal method acknowledged as an alternative to subcutaneous injection (48).

Reports of problems with transdermal fentanyl were appearing, however, and these involved physical withdrawal symptoms (49); temperature increase during delivery; unsuitability for patients with chronic skin disorders or limited dexterity (50); and some difficulties with adherence, especially in hot climatic regions.

Nevertheless, positive accounts of transdermal fentanyl outweighed the negative. In 1997, reports concluded several advantages over other modes of parenteral application; transdermal fentanyl was non-invasive; it had low technical and nursing requirements and excellent patient acceptance and compliance (52). A specific advantage was its uncomplicated delivery method without the need for expensive and complex infusion pumps (53). Transdermal fentanyl was considered a welcome addition to the armoury of drugs for treating pain in patients with cancer, and was said to be establishing its place in palliative care (54). The year 1998 saw transdermal fentanyl regarded as being as effective as oral opioids in relieving cancer-related pain, with an equal or better safety and side-effect profile. Patient acceptability was reported high with fewer stigmas attached to taking opioids in this form (55).

In 2001, transdermal fentanyl was reported as fitting into the third step of the WHO analgesic ladder as a strong opioid (56). Although a palliative care physician in India has raised concerns about the economics of transdermal pain relief: 'I am afraid the [pharmaceutical] industry is trying to push inexpensive things out in their effort to promote very expensive things ... many hospitals will not have morphine at all, but use transdermal fentanyl which is about six hundred times as expensive' (57).

Problems with application and removal of patches were highlighted by the US Food and Drug Administration (FDA) in 2001. Some patients were not applying patches directly to skin and others were not removing the inner liner to expose the adhesive and medication. Problems were reported where patients applied multiple patches at once and the risk for error increased when multiple caregivers are involved due to miscommunication about where the last patch was placed and when the next was due (58).

A consumer study published in 2002 established that patients' and caregivers' fear of addiction to and concern about morphine's side effects were major barriers to adequate pain relief in cancer patients. However, transdermal administrations of opioids in fentanyl patches did not evoke such fears. Patches were found to be associated with ideas relating to cuts, bruises, blisters and protection; whilst tablets, injections and infusions were linked with side effects, physicians and the hospital environment (59).

Looking to the future in transdermal pain therapy, Duragesic's developers disclose:

We have filed an NDA [New Drug Application] for our E-TransFentanyl product, and that is a little credit-card sized delivery system using electrical current to deliver the drug through the skin. It has fentanyl in it and patients can press the button just like they do when they use the PCA device, they'll get 40 micrograms of fentanyl in a dose ... in the field of analgesia I can't imagine many or any analgesic products coming to market in the future that doesn't have a delivery system

associated with it ... for whatever pain condition you're trying to treat, there is some profile that you're looking for, so I think that drug delivery systems are going to be associated with most products (42).

Developments in transdermal analgesia have taken place in a broad context. In addition to the pharmaceutical framework, drivers of innovation and market expansion are evident in the emerging hospice movement, WHO, and in shifting perceptions of opioid use in cancer pain from the notion of regular as irresponsible to recognition that regular use is therapeutically beneficial. Further, transdermal fentanyl's deceptively straightforward technology, which offered a non-invasive delivery method every 2–3 days, and with less constipation, ensured the product's popularity amongst patients and physicians alike. Reported difficulties with transdermal fentanyl application, the potential for error and misuse, and the expense of the product are barriers to its emergence as the ideal global solution for cancer pain. Nevertheless, as an alternative mode of administration, transdermal fentanyl has secured its position as an important innovation in the treatment of cancer pain.

The potential for innovation resulting from pharmacogenetics

At a time when cancer therapies have managed to prolong life expectancy, the adequate control of pain in the context of cancer is paramount to guarantee a satisfactory quality of life to cancer sufferers. Yet, variability in response to analgesic medications represents a significant clinical problem (60,61). The unpredictability of how each individual may react to analgesics has two major implications: first, sub-populations of patients may not obtain benefits after taking the prescribed medicine, leading to therapeutic failure. Second, the appearance of clinically significant side effects jeopardises adequate levels of analgesia. Genetic inheritance as well as underlying pain mechanisms and neuroplasticity appear to be responsible for much of this unpredictability (62).

Pharmacogenetics investigates how genetic variations affect the way individuals respond to drugs (63). The attention recently given to the crucial role of genes in determining how individuals react to diseases and treatments has shifted the way in which drugs are researched and developed, with major implications for clinical practice and health care.

What developments in the pharmacogenetics of analgesia apply particularly to cancer pain relief? There are three dimensions to this question that we explore here: (i) changing patterns in drug research over the 20th century; (ii) current evidence from experts in the field of pain research and from relevant pharmacogenetics studies; and (iii) clinical, ethical and social implications of applying pharmacogenetics.

Initiated during the 1990s, the completion of the Human Genome Project is claimed as a major breakthrough of medical science with the potential to open up new understandings of human health and disease. Novel scientific disciplines have emerged which aim to unravel the complexity of pathological conditions at the molecular level, giving rise to the genomic approach to diseases and treatments. Driven by worrying levels of adverse drug reactions and therapeutic failures despite best evidence-based medical practice, pharmacogenetics is now bringing the hope of individual 'gene-tailored' medicines to patients (64). Pharmacogenetics seems to be the most effective strategy for delivering, in the near future, public health benefits promised by the Human Genome Project and related initiatives.

In this context of scientific and medical change, a pharmacogenetics approach to pain relief examines the following:

- the way in which gene activities modify the structure and function of selected drug targets
- ion channels, neuropeptide receptors and other transmembrane proteins relevant to pain mechanisms as new therapeutic targets
- the relevance of many of these targets in the action and behaviour of analgesic compounds in the human body, such as the cytochrome P450 enzymes
- the genetic basis of their function over time
- the relevance of gender, ethnicity, culture and other 'environmental' factors when considering any analgesic or other therapy.

Much of the information related to the pharmacogenetics of analgesia stems from animal models that explore acute or transient pain that may not apply to cancer pain. Investigations in animal models of cancer pain and human subjects have commenced only recently (65). The iterative nature of pharmacogenetics research, where clinical questions arise from genetic discoveries, requires the appropriate collection of clinical data and samples before research questions are formulated and studies are designed (66). This implies that cancer pain research arising out of pharmacogenetics studies will be dependent upon clinical data concerning pain and response to analgesics being included in studies conducted on tissue and sample banks. This has implications for the nature of the consent obtained from research subjects.

In the current context of drug development, commercial as well as scientific considerations determine progress (67). There has been a perception in the past that pain in general and cancer pain in particular are not commercially attractive areas of research and development. However, drugs with broad indications that include chronic and cancer pain have proved to be commercially valuable.

There is still some doubt, however, that the market is large enough to support developments which individualise therapy or introduce contra-indications based on pharmacogenetics information which further reduce the potential number of patients who would benefit from a new treatment.

A significant technological development has taken place to support the development of pharmacogenetics and related disciplines. The application of this technology to cancer pain research will bring further insights into disease mechanisms and safer prescribing practices. Although a pharmacogenetics approach to pain management appears attractive, there are many unsolved practical, social and ethical barriers which need to be addressed if patients with cancer pain are to benefit.

Cancer pain relief at the level of public debate and policy reform

In his classic work, *The Sociological Imagination*, published in 1959, C Wright Mills makes the distinction between 'private troubles' and 'public issues'; he explains some of the processes whereby a phenomenon thought to be uniquely individual and personally bounded in character can come to be seen as a matter for wider concern, requiring the mobilisations of collective action and planning and he notes the important interplay of these two dimensions for the social analyst (68). Just such a transformation, from 'private trouble' to 'public issue' is evident in the phenomenon of 'cancer pain' in the last quarter of the 20th century. During these years, the experience of pain associated with late-stage cancer shifted from something to be born by individual patients, with fortitude and a sense of fatalism ('there is nothing more we can do'), first to a site of specialist medical attention and then to a wider territory of public and professional concern. Indeed, the 1990s saw an explosion of interest in cancer pain, especially in North America, but also in other countries with 'advanced' health care systems, as well as in many resource-poor regions of the world.

To understand such developments in cancer pain, we must pay attention to the changing social construction of cancer as a disease in modern culture and move from there to an exploration of the ways in which it has been colonised by professionals, patients, policy makers and legislators (69). Within this, we can see one particular innovation of special significance: the promotion during the 1980s by the WHO of the so-called 'analgesic ladder'. This simple three-step approach to cancer pain relief provided both a clinical and a policy technology which would serve as a rallying call and catalyst, the effects of which would go well beyond the initial aspirations of its creators (70). The broader significance of this 'analgesic ladder' has been to act as a vector whereby cancer pain is relocated from the clinic to the polity. This, in turn, has led to a new construction of cancer and its meanings – pharmacologically, clinically, sociologically and commercially. In

due course, 'cancer pain' emerged from the gaze of the physician to become a site of 'partnerships' between health care workers, consumers, policy makers, activists, and the pharmaceutical industry itself. The 'total pain' described by Cicely Saunders (71) now becomes the route to 'total gain': where pain relief, commercial profits, and social reform are expressed as inter-related goals within a cancer world of increasing complexity.

Prior to the 1970s, cancer pain had received little international attention as a public health problem and was often regarded as an inevitable, not fully controllable, consequence of the disease. Subsequently, the spread of the modern hospice movement and the creation of the professional field of pain studies encouraged a small number of pioneering oncologists to organise the first *International Symposium on Cancer Pain* in 1978 (72). Research presented at this and subsequent conferences suggested that physicians had the means to relieve even severe cancer pain and that the principal factors contributing to poor pain management were legal barriers against opioid use and lack of knowledge in pain management. In 1982, the WHO enlisted the aid of palliative care leaders, cancer pain specialists, and pharmaceutical manufacturers in developing and disseminating a global *Programme for Cancer Pain Relief*, based on a three-step analgesic ladder with the use of adjuvant therapies, and incorporating the use of strong opioids as the third step (73). WHO representatives launched an international initiative to remove legal sanctions against opioid importation and use, relying on national 'co-ordinating centres' to organise professional education and the core principles of the 'pain ladder' were widely disseminated.

The WHO programme has met with only partial success, however. Opioid consumption between 1984 and 1993 rose dramatically in ten industrialised countries, but showed much smaller increases in the rest of the world (74). Significant differences in patterns and extent of opioid use have been observed within and between global regions (75). Even in the industrialised countries, there is great variation in the skills and attitudes of caregivers toward the use of opioid analgesia as well as in non-pharmacological methods to relieve cancer pain (76). The reasons for such problems have been captured in the term 'opiophobia' and a review of the European context in 1993 concluded that:

There is an urgent need to make opioid analgesics more available for patients with cancer pain. Apart from ill-founded fears about the promotion of addiction, major reasons for unsatisfactory treatment include a lack of concern by national governments and a failure to educate doctors, nurses and other health care workers in cancer pain management (77).

Nevertheless, for the moment, there seems to be no robust alternative to the WHO three-pronged strategy of focus-

ing upon drug availability, education and government policy; and this approach was endorsed by a consensus meeting of experts held in 1996 (78).

Based largely on WHO principles, there are documented examples of 'cancer pain' strategies and alliances and these seem to have proliferated during the 1990s, particularly in the US. For example, results of a 3-year evaluation which shows improvement in US state policies governing pain management and the use of pain medications have been produced by means of a 'progress report card' that grades states on the extent to which their policies contain language that potentially enhances or impedes pain management (79). Across the US can now be found some 44 'state cancer pain initiatives' composed of voluntary interdisciplinary groups involving physicians, nurses, pharmacists, social workers, psychologists, educators, clergy, drug regulators and representatives of state government working towards the improvement of cancer pain management (80). Similarly, 'Partners for Understanding Pain' is an example of a consortium of professional and consumer organisations that have an interest in pain, including the American Academy of Nurse Practitioners, American Cancer Society, American Chronic Pain Association, Intercultural Cancer Council, National Black Women's Health Project and the National Urban League. The consortium recognised September 2003 as Pain Awareness Month and held a symposium in Chicago to examine the specific ways in which pain has an impact on the economy and the health care system (81).

Central to much of this kind of thinking has been the work of the Pain and Policy Studies Group at the University of Wisconsin. This has been recognised by the International Narcotics Control Board (INCB) itself which in its 2002 report (82) re-affirmed the support of international narcotics regulatory officials for efforts to improve the availability of opioids for the relief of pain. The report praised the continued work of WHO through its regional workshops on palliative care held during 2002 in Africa, the Americas and Eastern Europe and noted progress to improve opioid availability in Latin America. Previously, the INCB recognised WHO efforts to address regulatory impediments to opioid availability in India and Italy. The Board has also endorsed the use by countries of the Pain and Policy Studies Group document *Achieving balance in national opioids control policy: guidelines for assessment*. It is this question of balance – between availability for medical purposes and regulation to avoid diversion and misuse – that has become the central theme of policy making on opioid availability in recent years. It is a debate which has taken on some very public dimensions, notably in the moral panic that has surrounded the diversion of the prescription drug OxyContin into misuse within a number of economically deprived areas in the US (83). How the debate progresses may well depend as much upon cultural and ethical considerations as on either the

evidence base for effective pain relieving interventions or epidemiological data about unrelieved pain at the population level.

Conclusions

Looking around the world today, the field of cancer pain displays several important characteristics. Within the clinical area, there are continuing innovations directed towards improvement in the application of known drugs such as morphine, and trials of new ‘me too’ opioids that make claims to apparently marginal benefits over morphine. Considerable energy has gone in to the development of new routes of administration. We have looked here at some of the most established examples (slow release formulations taken by mouth in tablet or solution; sub-cutaneous infusions; and transdermal delivery systems); but there is also growing interest in other approaches such as the use of sub-lingual lozenges and suppositories. Although the clinical evidence base for these methods is growing, there are remarkably few studies that pay attention to patients’ perceptions of these technologies and the meanings they attach to them. Meanwhile, attention focuses on the possible benefits which might come from pharmacogenetics: in particular, pain relief regimens that are tailored to the individual and which take account of genetic predispositions that influence susceptibility to pain and variable responses to standard analgesics. Again, these might be seen as offering relatively minor benefits in patient populations already well served by the established approaches. Beyond this, lies the question of why it is that large numbers of those experiencing cancer pain fail to access appropriate analgesia. There is evidence that similar barriers to cancer pain relief are in existence in a variety of settings: ‘opiophobia’ on the part of regulators, clinicians and patients; variable levels of knowledge and expertise in cancer pain relief; and problems of regulated manufacture and supply. There is some evidence that this is being addressed as a public issue capable of attracting broadly-based community interest. As a major non-communicable form of life-threatening disease, cancer has attracted huge investment on the part of the biomedical industry, most of it focused on screening and, in particular, acute treatment. Despite notable successes in the clinic, the laboratory and the policy arena, however, much remains to be done if the modern ‘cancer journey’ is to be one free of unnecessary pain and suffering.

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