Friday 4 June 2004

# EAPC Research Forum Highlights

3rd Forum of Research Network of the European Association for Palliative Care (Onlus)

## Welcome to the 3rd EAPC Research Forum

**Franco de Conno, EAPC Executive Scientific Committee member, welcomed delegates to the EAPC's 3rd Research Forum on Friday morning with a moving presentation about the opportunities the congress will provide to further methodological research into palliative care.**

Franco de Conno first paid tribute to the late Frances Sheldon, a founding member of the EAPC and former Board member who sadly passed away in February.

Professor Vittorio Ventafridda spoke to delegates via a taped interview from hospital, where he is recuperating from a period of illness, and gave an inspiring message about the importance of research into palliative care treatment. Professor Ventafridda reminded delegates that palliative research is based on the observation of the quality of life of human beings, and has as its goals different emotional, social and spiritual evaluations that are the most important aspects of life. "It is essential to consider these moments, and important to offer relief to patients who are suffering in the last moments of life," said Professor Ventafridda.

Franco de Conno wished Professor Ventafridda a speedy recovery, and opened the first plenary session of the Forum.

## National Policy Needed to Ensure Choice of Opoids

**Tony O'Brien of Marymount Hospice and Cork University Hospital has called for national legislation to ensure that opioids and other drugs are accessible in a range of formulations and dosages and that pain management policies should be created by each institution based on internationally accepted principles.**

O'Brien said that different patients need different opioids as there is not only variation in how different individuals will react to an opioid but also how an individual will react to the same opioid at different times.

"Morphine has been considered the drug of first choice but there is no evidence from comparative trials that morphine is superior over other opioids as regards adverse effects and analgesia."

O'Brien questioned the practice of titrating an opioid with a normal release preparation and doubling the dose at bedtime. "Why not give a long-acting oral preparation with normal release preparations reserved for breakthrough pain?" he asked. O'Brien was speaking at the New Findings in Palliative Care- A European Approach to Palliative Care symposium.

As far as the future is concerned, O'Brien felt that the primary focus should be on pain as a public health issue and as a basic human right. "We also need to promote the use of opioids as a vital element in cancer pain management and ensure that we implement the guidelines that we already have."

## More Research Needed into Palliative Care

**Palliative medicine in Europe has come a long way, but care is still patchy, according to Eberhard Klaschik of Malteser Hospital, Bonn, Germany.**

Speaking at Friday's symposium on New Findings in Palliative Care- A European Approach to Palliative Care, Klaschik explained that since 1992, membership of the EAPC has risen from a few hundred to 50,000 and most countries in Europe now have professional palliative care associations. "On the negative side, however, only a few countries include palliative care as part of the curricula for medical students and in parts of Germany there are not enough palliative care specialists based in hospices."

Klaschik feels that research into palliative medicine has been neglected, as all too often patients are too ill and vulnerable to take part in clinical trials. "Research is indispensable for the further development and improvement of palliative medicine and we can do it if we ask the right questions, use the right methods and have a sensitive and empathic attitude towards our patients."

## Genetic Variability Explains Opiate Dose Differences

**Genetic variability appears to explain why one patient needs a higher dose of opioid for pain relief than another, according to Pal Klepstad, St Olave's University Hospital, Trondheim, Norway.**

Klepstad and his research team outlined details of genetic studies on 310 cancer pain patients using morphine that show how minor changes in single nucleotide polymorphism (SNIPs) can sometimes impair the function of the gene involved.

It seems that tiny genetic changes can alter the gene encoding for mu opioid receptors. Using mouse mu opioid receptors which are similar to a human's, Klepstad and his team found that alternative splicing in the receptors produced intra- and extra-cellular changes, leading them to speculate that a complex system of splicing may be responsible for the different analgesic effects of morphine between individuals.

Opioid receptors are not the only genetic differences that affect morphine sensitivity. Gene encoding for multidrug resistance transporters which carry opioids across the blood-brain barrier have also been implicated, as have genes encoding for proteins that are not directly involved in opiate pharmacology.

Klepstad acknowledged that his sample size of 300 was not very large and that he had studied only Norwegian patients. 'However, a new study, the European Pharmacogenetic opioid study aims to include 3000 patients and will examine several opioids in different populations, so hopefully this will answer some of the remaining questions.'

## Bone Pain Caused by Cancer has Unique Characteristics

**Evidence from animal studies indicates that cancer induced bone pain (CIPB) has unique characteristics, unlike pain due to neuropathic or inflammatory causes.**

Anthony Dickenson, University College Hospital, London, England, explained how MRMT-1 mammary tumour cells can be injected into the medulla of a mouse tibia to mimic cancer-induced bone pain. The reactions of these MRMT-1 mice to electrophysiological stimuli mimicking natural mechanical, thermal and cold are then compared with those of 'sham' or control mice that have had media only injected.

Electrical responses of superficial and deep dorsal horn neurones were also studied. 'Results showed that receptive fields were significantly enlarged in the MRMT-1 animals and they also had significantly increased responses to mechanical, thermal and other stimuli. The alterations seen in the dorsal horn have not been reported in neuropathic or inflammatory pain, adding to the evidence that cancer-induced bone pain is a unique pain state.'

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# Opening Plenary Session Examines Cachexia Methodology and Existential Issues in Palliative Care

**The first plenary session of the 3rd Research Forum of the EAPC began with a presentation from Ken Fearon, University of Edinburgh, United Kingdom, and focused on research methodologies in cachexia.**

The multifactorial origins of this condition have limited the nature, extent and arguably the usefulness of clinical trials conducted to date around cachexia, potentially hindering developments for patients with this devastating condition.

Fearon explained the problems with the standard measures of energy expenditure ratings, in that they were artificial and intrusive to patients, as well as heterogeneous. As such, he suggested that a revised approach is required in palliative care, combining a patient's total physical activity with their resting energy expenditure.

The gold standard in measuring total energy expenditure, is the doubly labelled water test, a biological response marker which has opened possibilities for new clinical trials in cachexia. "This non-invasive technique enables physicians to give patients a glass of water, and, 2 weeks later, assess how much energy has been expended," explained Fearon.

Within a clinical trial setting, existing entry criteria tend to rely on a non-robust, crude definition of cachexia, often focusing on a single factor. The disadvantage of this approach is that it may not be appropriate to all aspects of the target population. Fearon also explained that clinical trials have traditionally focused on nutritional status, rather than functional status, an increasingly important indicator with regards to regulatory bodies.

The importance of appropriate trial endpoints was also discussed within the presentation. With regards to cachexia, the ability to record data easily in the field, reproducible studies and endpoints reflecting the fundamental impact of cachexia were described as essential. The importance of clinical vs. statistical results was also discussed. For example, when patient weight gain is used as an endpoint, subsequent weight gain that is due to a build up of fluid, rather than tissue re-growth, has no functional effect within a clinical setting. Weight gain is also susceptible to a significant placebo effect.

The second of Friday morning's plenary sessions, presented by William Breitbart, Memorial Sloan-Kettering Hospital, described the psychosocial and existential issues in palliative care. Breitbart explained that concepts of adequate palliative care must be expanded in their focus beyond pain and physical symptom control to include psychiatric, psychosocial, existential and spiritual aspects. The growth of interest and appreciation of these elements in a patient's overall end of life care treatment strategy has highlighted the need for further detailed research in these areas.

Breitbart provided an overview of the range of diagnostic processes used to measure these existential issues, as well as an overview of the tests and explained a range of existing problems with regards to depression and delirium. Breitbart discussed the recently developed intervention programme at Memorial Sloan-Kettering for meaning-centred psychotherapy, designed to support patients at the end of life.

## Measuring Pain in Patients with Cognitive Failure

**Jon Havard Loge, Augusto Caraceni and Fabrizio Benedetti gave a series of presentations looking at the measurement and understanding of pain in patients with varying degrees of cognitive failure stemming from a range of underlying conditions.**

Jon Havard Loge examined the ways that clinicians define "agitation" and "confusion" and the plethora of meanings that these symptoms can have. The lack of consistency in our understanding of both confusion and agitation leads to a difficulty in accurately measuring pain in patients with cognitive failure, he suggested. Loge recommended that both doctors and nurses need improved strategies for detection of pain, and that clinicians must learn to trust relatives as informatives.

Augusto Caraceni spoke about methods of pain assessment in elderly patients with and without cognitive failure. Older patients with cancer pain have a lower chance of being treated with strong opioids, which is due at least in part to communication difficulties stemming from cognitive failure, suggested Caraceni. Elderly patients tend to underreport pain for a number of reasons, whether sociocultural or due to degenerative brain conditions. Compliance with pain assessment scales varies with the degree of cognitive failure, and Caraceni recommended that the best approach is for clinicians to be flexible and to use more than one tool to help patients determine which scale is easiest for them to understand and use. We should combine observational tools with subjective measures, as cognitive failure does not prevent pain measurement, but does impact upon it. Caraceni suggested that there is a need to approach research on the study of pain in patients with cognitive failure beyond the descriptive level.

Fabrizio Benedetti provided a look at how the brain processes pain differently according the type of degenerative disorder, by examining the neurophysiological responses of patients to painful stimuli. Patients with Alzheimer's disease had a modified emotional response to pain stimuli, whilst their pain threshold and tolerance remained normal, due to the lack of impact of Alzheimer's on the sensory cortex. There was a reduction in autonomic responses, including anticipation of pain and reaction to stimuli. Conversely, patients with vascular dementia have a changed response to pain processing dependent on the location of the lesions within the brain, which can lead to either increased or decreased perception of pain. Patients with frontotemporal dementia have a loss of awareness of pain – they feel pain but do not have a normal emotional reaction. Parkinson's disease patients demonstrated different subjective and autonomic responses. Whilst stimulus detection, pain threshold and pain tolerance remained normal compared to controls, the autonomic response of these patients showed a reduction in both anticipatory and pain stimuli responses. These autonomic responses were improved, however, following the use of deep brain stimulation in the subthalamic region.

## What is the Best Methodology for Determining Effectiveness of Palliative Care?

**This was the central question at the heart of Friday afternoon's session on health services research in palliative care, which was chaired by Geoffrey Hanks and featured presentations from Stein Kaasa, Furio Zucco and Margaret Robbins.**

Stein Kaasa explained the many methodological, ethical and clinical challenges related to research that seeks to provide valid information on a scientifically sound level about the effectiveness of palliative care. He also raised questions for the audience about appropriate endpoints for randomised clinical trials (time in hospital versus time at home, QoL, place of death, etc). Palliative care is strongly influenced by the structure and organisation of the health service in which it is delivered, so how do we differentiate between the various models (eg. free-standing hospices versus hospital units) in research? The measurement tools in palliative care are inadequate, argued Kaasa, to be able to take into consideration the wide degree of heterogeneity and provide an answer that would enable successful clinical trials in this area.

Furio Zucco provided an update on the progress of palliative care service development in Italy, demonstrating the significant achievement that has been made to ensure that Italians have a wide range of services available across their regions. One element of note was that the majority of Italian palliative care has focussed on home care with 77% of palliative services now delivered in the home through both NHS and private services.

Margaret Robbins gave a thorough review of the experience of the Bristol Hospital group in the development and rollout of a randomised clinical trial looking at hospital based palliative care interventions. The study took over 5 years from conception to publication, and failed to deliver statistically significant results, although it did show a trend towards the full service intervention arm of the trial. Robbins considered whether or not using a randomised controlled trial was a wise approach for evaluating a service-level intervention, and suggested that there is an inherent gulf between the sort of data that clinicians would ideally like to capture about the effectiveness of palliative care interventions, and the data that it is actually possible to collect.

The discussion section of this workshop focussed on the challenges of methodology, and it was suggested that perhaps one of the key considerations when beginning research should be to consider the audience for the final data. Stein Kaasa argued that it is politicians that need to be influenced in order to secure funding for palliative care services. This was echoed by Furio Zucco, who suggested that "we need to convince by the heart, not by science," to encourage greater support for palliative care.

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