NeuPSIG

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NeuPSIG: Investing in solutions to the growing global challenge of neuropathic pain

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Running title – The global challenge of neuropathic pain

Abstract

Neuropathic pain is a common and distressing condition, for which treatment is often unsatisfactory. NeuPSIG, the Special Interest Group on Neuropathic Pain, is part of the International Association for the Study of Pain, and has been working hard to improve understanding and management of neuropathic pain since 1999. Chronic cancer-related pain arises through many different, often concurrent mechanisms, is often neuropathic, and affects the lives of a growing number of cancer survivors. Cancer-related pain was a focus of part of NeuPSIG's 6th International Congress on Neuropathic Pain. Two comprehensive reviews, arising from this Congress and published in this edition of the *Journal*, present state of the art appraisals of current knowledge of (1) pain in cancer survivors; and (2) chemotherapy-induced peripheral neuropathy.

Introduction

This issue of the Journal includes two excellent review papers discussing epidemiology, mechanisms and management of pain after cancer.[1, 2] These were presented in a workshop at the 6th International Congress on Neuropathic Pain, in June 2017, sponsored by the *British Journal of Anaesthesia* (BJA). Cancer pain is a distressing, chronic painful condition, which is generally under-recognized yet whose importance in society is increasing as cancer survivorship improves and people live longer with lasting side effects of treatment.[3]

In a wide-ranging and comprehensive review, Brown and Farquhar-Smith examine pain in cancer survivors, explaining the multifarious, often concurrent causes of pain to which this growing population is vulnerable.[1] In an additional detailed review, Flatters and colleagues focus on chemotherapy induced peripheral neuropathy (CIPN) that in some cases may be severe enough to present as a barrier to the optimal treatment with chemotherapeutic agents and is one of the most distressing conditions in cancer survivors.[2] These two reports on pain associated with cancer and its treatment highlight the emergence of novel clinical challenges as a sequel of therapeutic advances in the management of patients with cancer. The authors present state of the art reviews that include findings from the forefront of research on this important topic, from the bench to the bedside and beyond.

Neuropathic pain

Chronic painful conditions, such as cancer pain, cause, by far, the most disability globally and in every individual country.[4, 5] Although prevalence varies between countries and regions, large epidemiological studies found that approximately 20-30% of European adults have significant chronic pain, and that it is often managed unsatisfactorily.[6, 7] Its most successful management requires multi-disciplinary approaches including pharmacological, non-pharmacological and self-management techniques.

The International Association for the Study of Pain (IASP) exists to bring together scientists, clinicians, health-care providers, and policymakers to stimulate and support the study of pain and translate that knowledge into improved pain relief worldwide.[8] It includes 20 Special Interest Groups (SIGs), the largest of which is that for neuropathic pain (NeuPSIG). NeuPSIG's aim is to advance the understanding of mechanisms, assessment, prevention, and treatment of neuropathic pain.[9]

Neuropathic pain (NP) is pain caused by a lesion or disease affecting the somatosensory system.[10, 11] It is typified by positive and negative symptoms such paraesthesia, altered sensation and a shooting or crawling nature of the pain, and signs such as sensory deficits, allodynia, hyperalgesia and an

altered appearance of the skin over the affected area. Common causes of peripheral NP include diabetic neuropathy, postherpetic neuralgia and lumbar radicular neuropathy. Central NP can arise in association with strokes, multiple sclerosis and other neurological and metabolic conditions. In cancer, NP may be the result of surgery, chemotherapy and/or radiotherapy, as well as through other treatments or specific disease mechanisms.[1] Pain with neuropathic features is more prevalent than generally realized, with population-based studies finding that 7-10% of adults are affected.[12] NP is more distressing than nociceptive pain, with a greater impact on life and health,[13] and the impact is more dependent on its severity than its underlying cause.[14, 15] In one study, 17% of people with NP classified its impact on quality of life as "worse than death", using well validated instruments.[16]

Unlike nociceptive pain, NP responds poorly to many of the standard analgesics, such as non-steroidal anti-inflammatory drugs.[17] Early diagnosis is therefore important, in order that treatment with more effective first-line medications, such as a tricyclic anti-depressant, a gabapentinoid, or a serotonin-norepinephrine reuptake inhibitor may be prescribed. However, even the most effective medicines have a number needed to treat of around 4 to 8 in order to achieve 50% reduction in pain relief, and often cause unacceptable side effects. Response to treatment seems to be less dependent on the underlying cause than on specific pain mechanisms,[18] and it is increasingly recognized that phenotyping and stratification according to factors such as sensory profiling [19] and endogenous pain modulation measures[20] might allow a precision approach to treatment selection. However, these techniques are a long way from the standard clinic, and it is important that research into mechanisms and management of this distressing condition is prioritised.

NeuPSIG

The Congress at which these papers were presented is NeuPSIG's biannual flagship. NeuPSIG includes over one thousand members from different scientific and clinical disciplines, and from 75 countries. It was formed in 1999 and has achieved much in the fight against NP. NeuPSIG prides itself in taking a rigorous, evidence-based approach to the initiatives to which it attends, and aims for products of the highest quality, to be adopted as standard by the international community. Examples of such outputs are shown in Box 1. They include evidence-based recommendations on various aspects of the assessment and management of NP, each based on detailed systematic reviews and expert interpretation and consensus. They also include a recent submission to the World Health Organization for inclusion of gabapentin in its Model Essential Medicines List – at present amitriptyline is the only medicine included for treating neuropathic pain. Previous NeuPSIG work has shown that even this was not always available, and that other effective medicines were of limited availability in many countries, particularly in the developing world.

In addition to these published outputs, NeuPSIG is committed to educating clinicians and the public about NP. It has led or contributed to training programmes in various countries including India, South Africa, Indonesia, Malaysia, and Chile. It has produced instructional videos on the neurological examination of central and peripheral NP, and of the cranial nerves. In 2015, NeuPSIG led IASP's Global Year Against Neuropathic Pain campaign,[21] which included educational material and events, for scientists, clinicians, the press and the public. Other educational initiatives have included satellite symposia to the World Congress on Pain at Santiago, Chile and Yokohama, Japan and special supplements to the journal *Pain,* with updated reviews focused on advances in basic and clinical aspects of neuropathic pain.

NeupSIG 2017

But the biannual Congress on Neuropathic Pain is where the front line of research on neuropathic pain is on display. Presentations range from basic science, through translational research and clinical trials to applied research in the clinic and the community. This year's Congress, the 6th, was attended by delegates from more than 50 different countries and included papers on: NP regulation by astrocytes, microglia and macrophages; emerging cell-based therapy for NP; psychological and genetic prediction of the placebo response; and the impact of NP on the global burden of disease. In addition, internationally recognized experts provided plenary overviews of the state of the art in important aspects of NP, including genetic research, clinical assessment, new treatments, and neuropathic itch.

NeuPSIG 2017 workshop on cancer-related pain

The *BJA*-sponsored workshop on cancer-related pain was exemplary in its range of material, from dorsal root ganglion and cellular mechanisms, to trials, treatment and translation. This work, and its dissemination at the Congress and in this Journal, will undoubtedly inform clinical practice and further research in this important area.

A systematic review and meta-analysis of studies examining the epidemiology of cancer pain found that about 40% of cancer patients are affected by NP, and that 20% of this is related to cancer treatment, rather than the cancer itself.[22] As Brown and Farquhar-Smith point out, however, this relatively small proportion translates to a large and growing population presenting an increasing challenge to clinicians and society.[1] A cancer survivor – someone 'living with and beyond cancer'[23] – is likely to experience some of a number of lasting physical, psychological and social sequelae. Clearly, these will depend on the nature of the disease, its treatment and pre-existing and subsequent factors (also physical, psychological and social). With pain – particularly that of neuropathic origin – being one of the most lasting and distressing, it is important that we do our best to understand the causes and mechanisms, in order to target treatment and prevention effectively. Brown and Farquhar-Smith list the possible causes: pain from the tumour (including neuropathies associated with haematological malignancy); bone pain; post-surgical pain; neuropathy induced by chemotherapy, biological agents, monoclonal antibodies or aromatase inhibitors; and radiation-induced pain.[1] They describe the latest knowledge of the biological mechanisms of each of these, such as the host of cytokines and growth factors released by the tumour and stromal cells that lead to neuronal sensitization, and encourage us by indicating how this knowledge is leading to new potential treatments. Emphasising that a 'one size fits all' approach to treating pain in cancer survivors is unhelpful, they summarise the treatments available and the evidence for their effectiveness. They conclude that there are sufficient similarities in the approaches to management for them to propose the umbrella of 'chronic cancer-related pain' (CCRP) to promote investment of resources to further understand treatment and prevention.

Considering one of the main culprits of persistent pain in cancer treatment and survival, Flatters and colleagues note that the mechanisms of CIPN are poorly understood, and treatment is often unsatisfactory.[2] The arrival of CIPN often comes as a surprise to patients who have embarked on a course of chemotherapy, and its persistence disrupts their life which is increasingly likely to last for many years after treatment is complete. Early assessment is therefore essential, though not straightforward, as the variety of tools available for this purpose demonstrates. Similarly, understanding its biological mechanisms and responses to potential treatments are complex, one issue being the difficulty of developing ethical animal models that represent persistent CIPN in humans accurately. Nonetheless, the authors summarise important recent advances in understanding the roles of mitochondrial dysfunction, oxidative stress, immune cells, and ion

channels in causing CIPN, and the potential new treatments (or new combinations of existing treatments) that might reduce the burden of disease.

Conclusion

One common theme recurring through both of these reviews[1, 2] is the lack of evidence for effectiveness of treatments currently available, and the paucity of clinical research to date on possible new treatments. There are, of course, many reasons for these gaps, including the logistics and high costs of randomised controlled trials, difficulty in identifying and recruiting sufficient suitable trial participants, and the stage in the development pipeline at which newer drugs currently sit. Similar research gaps are identified for many established treatments available for NP more generally, particularly evidence on their long-term effectiveness.[17] However, there is little doubt that one reason is the relative lack of public and professional educational focus on chronic (neuropathic and/or cancer-related) pain, surprising and indefensible given the high prevalence and resultant disability worldwide.[4] It is essential that we, as a global society, invest more time, money, education and research into improving the understanding, assessment, management and prevention of chronic pain; and that a greater proportion of these resources that are currently available for cancer is devoted to cancer-related chronic pain. This is why the *BJA* sponsored this workshop, and is the primary mission of the IASP and NeuPSIG.

Authorship, funding and declaration of interests

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Box 1. Examples of NeuPSIG outputs

- Recommendations on pharmacological treatment of neuropathic pain in adults, first in 2007[24] updated in 2010,[25] and again in 2015 [17]
- Guidance for assessing neuropathic pain in primary care (2009)[26]
- Definition and a grading system for neuropathic pain, first in 2008,[27] updated in 2016[28]
- Guidelines for the assessment of neuropathic pain (2011)[29]
- Commentary on the need for systematic classification of neuropathic pain to ensure appropriate allocation of health care resources and implementation of evidence-based guidelines (2013)[30]
- Recommendations for conducting quantitative sensory testing for neuropathic pain in clinical practice and research (2013)[27]
- Recommendations on interventional management of neuropathic pain (2013)[31]
- An international consensus on phenotyping neuropathic pain for genetic studies (NeuroPPIC, 2015)[32]
- Instructional videos on neurological examinations of patients with neuropathic pain[9]
- A proposal to the World Health Organization (WHO) for inclusion of gabapentin in its Model List of Essential Medicines as treatment for neuropathic pain (2015)[33, 34]
- Definition of neuropathic pain for the WHO's International Classification of Diseases, forthcoming 11th revision (ICD-11)[35, 36]