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Progress in pain medicine

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Editorial for Pain Special Issue Progress in pain medicine: where are we now? Authors: Lesley A Colvin^{1*} Andrew SC Rice² ¹ Division of Population Health and Genomics University of Dundee Ninewells Hospital and Medical School Mackenzie Building Kirsty Semple Way Dundee, DD2 4BF, UK Tel: 01382 381880 Tel: 01382 38 1000 Email:1.a.colvin@dundee.ac.uk ² Pain Research, Department of Surgery and Cancer, Imperial College, London, United Kingdom Tel: +44 (0)20 3315 8816 Email: a.rice@imperial.ac.uk © 2019. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/

This current issue of the BJA has a special focus on pain medicine and presents a mixture of invited reviews and original research across a broad range of pain related topics. Looking back to the last BJA pain special issue, in July 2013, there has been progress in our understanding of the problems and how to address them¹. The challenge remains of translating these to clinical benefit, although there are steps in the right direction. In this editorial, we have tried to highlight some of the themes presented in this issue, within the context of current pain research.

The Global Burden of Disease Collaboration (http://www.healthdata.org/gbd) is a unique initiative to improve our understanding of the epidemiology of disease, which is essential in order to develop effective, cohesive policies to improve healthcare and reduce inequities. The most recent analysis shows that chronic pain and mental health impose a major burden at a global level, with low back pain being *the* leading cause of globally of number of years lived with disability, followed by headache (above diabetes and COPD). This also does not fully take account of the hidden burden of pain within other chronic diseases, such as diabetes and rheumatoid arthritis ²⁻⁵. It is only in the latest update to the International Classification of Disease (ICD) that chronic pain is properly recognized and coded for⁶. If used properly, this may be used to better inform future developments, although we do need to consider how best use this information to influence and implement effective pain management policies^{7,8}. Mills et al in this issue, give a useful update of risk factors and demographic associations in chronic pain⁹. Risk factors may require a number of approaches to modify them, both at an individual and also, perhaps more importantly, at a population based level, through public health policy, in order to impact on long term outcomes.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage", and nociception as "The neural process of encoding noxious stimuli." ¹⁰ One area where measurement of nociception, as a surrogate for pain may be useful, is in situations where communication is impaired (e.g under anaesthesia, critical care). For clinical utility, an objective measure of nociception would need to be reliable, consistently sensitive to analgesic interventions, and easy to use in different clinical situations. The effect of nociception on autonomic function (e.g., heart rate, blood pressure, pupil diameter) has been utilised in a number of monitors to provide a way to guide analgesia, in areas where self-report and pain assessment is difficult. Several papers in this issue emphasizes the need for rigorous evaluation of such devices in relevant clinical settings before widespread use ^{11, 12}.

Whilst an objective approach to nociception may be possible, assessment and, subsequent management of pain remains subjective, and often suboptimal, even with the use of defined protocols and guidelines¹³. Education of healthcare staff and improved understanding of what factors affect clinical decision making around analgesia is explored using neuroimaging. Empathy and risk taking were shown to be some of the factors impacting on how patients with pain were managed in the emergency department ¹⁴.

The management of patients with chronic non-malignant pain using long-term potent opioids has been the subject of much discussion, with concerns about increasing addiction and dependence rates, and the contribution that surgery may make to this problem ^{15, 16}. The IASP have produced a position statement around the use of opioids for chronic pain, which reflects these concerns, although ensuring continued, appropriate use of opioids in acute and cancer pain management is important, especially in lower and

middle income countries ^{17, 18} The increasing number of patients presenting for surgery who are already on a strong opioid, create challenges for acute pain management ¹⁹. Buprenorphine, used for chronic pain and, increasingly, for opioid replacement therapy (ORT) for dependence is a partial agonist, with concerns about ceiling analgesic effects. There is a limited evidence base for how to manage acute pain in this patient group when they present for surgery, and for post-discharge analgesia ^{20, 21}. Using a Delphi approach clinical recommendations have been developed, with key recommendations to continue buprenorphine throughout the peri-operative period, with careful consideration of discharge planning²². The importance of continued review and assessment of all patients on strong opioids after surgery may be one way to reduce longer term problems ¹⁶.

There has been a considerable amount of research on the progression of acute to chronic pain after surgery, with much greater understanding of this problem since it was first systematically studied, several decades ago²³⁻²⁵}. Interestingly research in this area for patients after critical care admission is identified as being much less advanced in the review by Kemp at al ²⁶. The majority of studies in this area have not used pain specific questionnaires, but more general quality of life measures, where there hasn't been a focus on persistent pain as a primary outcome, despite the fact that it may affect up to 77% of survivors. Future studies should utilise pain specific outcome measures, with extended follow up periods.

As we move forward we need to consider novel approaches to the development and evaluation of interventions for chronic pain. It is acknowledged that there are deficiencies in the standard Randomised Clinical Trial (RCT) approach to assessing chronic pain, with potential to either over estimate treatment effects, or to miss signals of efficacy and abandon potentially promising new therapies as a result²⁷⁻²⁹. Different approaches to assessing novel analgesics, utilising biomarkers, may reduce required sample sizes, with increased sensitivity to detect signals of efficacy. The use of detailed sensory phenotyping is showing promise in predicting treatment efficacy or identifying individuals at increased risk of persistent pain, moving towards the holy grail of a personalized approach to pain medicine³⁰⁻³². Neuroimaging, and other physiological measures may contribute to this, improving our understanding of pain perception, how it is modulated by expectation, and impact of the placebo effect, although further work needs to be done before translation to clinical use ³³⁻³⁷. Understanding the molecular profile, aided by the use of large datasets such as the UKBiobank (www.ukbiobank.ac.uk/), is an additional important piece of the jigsaw that could improve clinical trial design, by accurate stratification of patients leading to individualisation of therapy ³⁸.

Whilst accurate stratification of patients is an important approach in assessing efficacy of novel analgesics, wider applicability needs to be assessed in a different way³⁸. Pragmatic clinical trials can be used to ensure broad applicability to the wider patient population that is manged in routine clinical practice, rather than the carefully selected ones in RCTs. For example, many obstetric studies are limited to nulliparous women, A more pragmatic trial found that while programmed intermittent epidural bolus techniques are useful in obstetric analgesia, shorter, but more intense labour, in multiparous women may require a modification of the approach evidenced in RCTs ³⁹.

Our understanding of pain neurobiology advances, with novel pathways and targets identified for future improvement in analgesia. However, especially in chronic pain, despite major investment these by and large have not been translated into clinically useful treatments. Whilst not being unique to chronic pain, the problem is largely one of limitations in the internal and external validity of pre-clinical sciences

approaches currently employed. 40-42 A number of potential novel targets are reported in this issue, with targets related to the inhibitory (e.g. GABA) / excitatory balance (NMDA)) well recognised as contributing to chronic pain states^{43, 44 45}. In additional to laboratory and experimental pain models, being used to identify novel targets, the case report of an individual with a congenital insensitivity to pain illustrates how astute clinical observation can be used to help understand pain mechanisms. In this case, the observation that minimal analgesia was required for a surgical procedure combined with a careful history resulted in further investigation of this individual and her family. Genotyping revealed the causative mutation in the Fatty Acid Amide Hydrolase pathway, reflected in corresponding abnormalities in the endogenous cannabinoid system, with high circulating levels of anandamide⁴⁶. It is refreshing that this serendipitous finding may be used to develop novel analgesics, emphasising the importance of a strong link between clinicians and academics. Not only is this essential in ensuring that research is relevant and important in the clinical setting, but it is a good illustration of how observations from the clinic can be used to drive and direct pain research. It is however, important to emphasise that careful evaluation of any new agent is needed, with early clinical studies of FAAH not showing any benefit in osteoarthritis pain ⁴⁷. There is ongoing interest in FAAH inhibitors as analgesics, but a precision medicine approach may be more suited to assessing these, and other novel interventions⁴⁸⁻⁵⁰

So, in conclusion, has there been progress in the field of pain research over the last 6 years? While the steps may seem slow, there is no doubt that there is incremental progress, in a number of areas. Advances in Information Technology allow us to effectively interrogate large clinical datasets, to improve understanding at a population level, whilst improvements in our understanding of individual mechanisms may take us a step closer to personalised medicine in the field of chronic pain. Collaborations need to be supported, to bring together the diverse expertise that will be needed to take full advantage of these approaches. The traditional view of "translational pain medicine" as basic science to the clinic needs to be revaluated to reflect this. A further area that we must consider, is how we can address the problem at a global level, developing simple and effective solutions that can be used in resource poor areas. New strategic funding opportunities such as those through the MRC-UK, and the Versus Arthritis Research Roadmap for Pain (see https://www.arthritisresearchuk.org/research/news-and-updates-for-researchers/research-newsletter/april-2018/research-roadmap-for-pain.aspx) are to be welcomed, and perhaps, at last, reflect a recognition of the public health challenge that is posed by chronic pain. It is with a feeling of optimism that we look forward to the future research developments that will be reported in the next Pain Special Issue of the BJA.

Authors' contributions

LC and AR : concept, design, writing and approval of final draft

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