Progress in pain medicine

Colvin, Lesley A.; Rice, Andrew S. C.

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Editorial for Pain Special Issue

Progress in pain medicine: where are we now?

Authors:

Lesley A Colvin [1*]

Andrew SC Rice [2]

[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
Email:l.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

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 them[1]. 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 for[6]. 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 pain[9]. 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 guidelines[13]. 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 planning[22]. 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 ago[23-25]}. 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 result[27-29]. 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 medicine[30-32]. 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 way[38]. 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 anandamide[46]. 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 interventions[48-50]

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

1 Colvin LA, Rowbotham DJ. I. Managing pain: recent advances and new challenges. *British Journal of Anaesthesia* 2013; **111**: 1-3
2 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1211-59
3 GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1545-602
4 GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789 - 858
5 Rice AS, Smith BH, Blyth FM. Pain and the global burden of disease. *Pain* 2016; **157**: 791-6
6 Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015; **156**: 1003-7
7 Blyth FM, Huckel Schneider C. Global burden of pain and global pain policy-creating a purposeful body of evidence. *Pain* 2018; **159 Suppl 1**: S43-S48
8 Smith BH, Fors EA, Korwisi B, et al. The IASP classification of chronic pain for ICD-11: applicability in primary care. *Pain* 2019; **160**: 83-7
9 Mills SN, K.; Smith, B.H. Chronic Pain: a review of its epidemiology and associated factors in population-based studies. *British Journal of Anaesthesia* 2019
10 Taxonomy ITFo. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. *http://www iasp-pain org/AM/Template cfm?Section=Classification_of_Chronic_Pain&Template=/CM/HTMLDisplay cfm&ContentID=2687* 2012: 214
11 Charier DV, M.C.; Zantour, D.; Pichot, V.; Martins-Naltar, A.; Courbon, M.; Roche, F.; Vassal, F.; Molliex, S. Assessing Pain in the Postoperative Period: Analgesia Nociception Index™ (ANI) versus Pupillometry. *British Journal of Anaesthesia* 2019
12 Ledowski T. Objective monitoring of nociception – mission completed? A review of current commercial solutions. *British Journal of Anaesthesia* 2019
13 Fallon M, Walker J, Colvin L, Rodriguez A, Murray G, Sharpe M. Pain Management in Cancer Center Inpatients: A Cluster Randomized Trial to Evaluate a Systematic Integrated Approach - The Edinburgh Pain Assessment and Management Tool. *Journal of Clinical Oncology* 2018: JCO
14 Corradi-Dell'Acqua CF, M. Sharvit, G.; Trueb, L.; Foucault, E.; Fournier, Y.; Vuilleumer, P.; Hugli, O. Pain management decisions in emergency hospitals are predicted by brain activity during empathy and error monitoring. *British Journal of Anaesthesia* 2019
15 Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia—when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *The Lancet* 2019; **393**: 1558-68
16 Neuman MD, Bateman BT, Wunsch H. Inappropriate opioid prescription after surgery. *The Lancet* 2019; **393**: 1547-57
17 Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet* 2016; **387 (10028)**: 1644-56

18 IASP. IASP Statement on Opioids. 2018. https://www.iasp-pain.org/Advocacy/Content.aspx?ItemNumber=7194, Accessed April 2019)
19 Hollmann MW, Rathmell JP, Lirk P. Optimal postoperative pain management: redefining the role for opioids. *The Lancet* 2019; **393**: 1483-5
20 Coluzzi F, Bifulco F, Cuomo A, et al. The challenge of perioperative pain management in opioid-tolerant patients. *Therapeutics and Clinical Risk Management* 2017; **13**: 1163-73
21 Wenzel JT, Schwenk ES, Baratta JL, Viscusi ER. Managing Opioid-Tolerant Patients in the Perioperative Surgical Home. *Anesthesiology Clinics* 2016; **34**: 287-301
22 Goel AA, S.; Weissman J.; Shanthanna, H.; Hanlon, J.G.; Samman, B. et al. Perioperative Pain and Addiction Interdisciplinary Network (PAIN) Clinical Practice Advisory for Perioperative Management of Buprenorphine - Results of a Modified Delphi Process. *British Journal of Anaesthesia* 2019
23 Macrae WA. Chronic post-surgical pain: 10 years on. *British Journal of Anaesthesia* 2008; **101**: 77-86
24 Macrae WA, Davies HTO. Chronic postsurgical pain. In: Crombie IK, ed. *Epidemiology of pain*. Seattle: IASP, 1999; 125-42
25 Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *The Lancet* 2019; **393**: 1537-46
26 Kemp HL, H.; Costello, A.; Brett, S.J. Chronic Pain in Critical Care Survivors. *British Journal of Anaesthesia* 2019
27 Moore RA, Derry S, Wiffen PJ. Challenges in design and interpretation of chronic pain trials. [Review]. *British Journal of Anaesthesia* 2013; **111**: 38-45
28 Moore RA, Straube S, Eccleston C, et al. Estimate at your peril: Imputation methods for patient withdrawal can bias efficacy outcomes in chronic pain trials using responder analyses. *Pain* 2012; **153**: 265-8
29 Moore RA, Derry S, McQuay HJ, et al. Clinical effectiveness: an approach to clinical trial design more relevant to clinical practice, acknowledging the importance of individual differences. *Pain* 2010; **149**: 173-6
30 Forstenpointner J, Otto J, Baron R. Individualized neuropathic pain therapy based on phenotyping: are we there yet? *Pain* 2018; **159**: 569-75
31 Smith SM, Dworkin RH, Turk DC, et al. The Potential Role of Sensory Testing, Skin Biopsy, and Functional Brain Imaging as Biomarkers in Chronic Pain Clinical Trials: IMMPACT Considerations. *J Pain* 2017; **18**: 757-77
32 Lotsch J, Ultsch A, Kalso E. Prediction of persistent post-surgery pain by preoperative cold pain sensitivity: biomarker development with machine-learning-derived analysis. *Br J Anaesth* 2017; **119**: 821-9
33 Davis KD, Flor H, Greely HT, et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nature Reviews Neurology* 2017; **13**: 624
34 Tracey I, Woolf CJ, Andrews NA. Composite Pain Biomarker Signatures for Objective Assessment and Effective Treatment. *Neuron* 2019; **101**: 783-800
35 Wanigasekera V, Wartolowska K, Huggins JP, et al. Disambiguating pharmacological mechanisms from placebo in neuropathic pain using functional neuroimaging. *Br J Anaesth* 2018; **120**: 299-307
36 Wanigasekera V, Mezue M, Andersson J, Kong Y, Tracey I. Disambiguating Pharmacodynamic Efficacy from Behavior with Neuroimaging: Implications for Analgesic Drug Development. *Anesthesiology* 2016; **124**: 159-68
37 Vase LW, K. . Pain, placebo and test of treatment efficacy. *British Journal of Anaesthesia* 2019
38 Themistocleous AC, Crombez G, Baskozos G, Bennett DL. Using stratified medicine to understand, diagnose, and treat neuropathic pain. *Pain* 2018; **159 Suppl 1**: S31-s42

39 Gabriel LY, J.; Hoesli, I.; Girard, T.; Dell-Kuster, S. Generalizability of randomized trials of the programmed intermittent epidural bolus technique used for maintenance of labour analgesia: a prospective cohort study. *British Journal of Anaesthesia* 2019
40 Sikandar S, Dickenson AH. II. No need for translation when the same language is spoken. *British Journal of Anaesthesia* 2013; **111**: 3-6
41 Rice ASC, Finnerup NB, Kemp HI, Currie GL, Baron R. Sensory profiling in animal models of neuropathic pain: a call for back-translation. *Pain* 2018; **159**: 819-24
42 Percie du Sert N, Rice AS. Improving the translation of analgesic drugs to the clinic: animal models of neuropathic pain. *Br J Pharmacol* 2014; **171**: 2951-63
43 Yamamoto GK, Y.; Sasaki, M.; Ikoma, M.; Baba, H.; Kohno, T. . The Neurosteroid Dehydroepiandrosterone Sulfate Enhances Pain Transmission in the Dorsal Horn in the Spinal Cord. *British Journal of Anaesthesia* 2019
44 van Amerongen GS, P.; Gurrell, R.; Dua, P.; Whitlock, M.; Gorman, D.; Okkerse, P,; Hay, J.L.; Butt, R.; Groeneveld, G.J. Analgesic potential of PF-06372865, an α2/α3/α5 subtype selective GABAA partial agonist, demonstrated using a battery of evoked pain tasks in humans. *British Journal of Anaesthesia* 2019
45 Zhou XLZ, C.J.; Peng, Y.N.; Wang, Y.; Xu, H.J.; Liu, C.M. ROR2 modulates neuropathic pain via phosphorylation of NMDA Receptor GluN2B Subunit. *British Journal of Anaesthesia* 2019
46 Abdella HO, A.; Hill, M.N.; Bras, J.T.; Lee, M.C.; Li, S.; Gossage, S.J.; van Drimmelen, M.; Morena, M.; Houlden, H.; Ramirez, J.D.; Bennett, D.L.H.; Srivastava, D.; Cox, J.J. Microdeletion in a FAAH pseudogene identified in a patient with high anandamide levels and pain insensitivity. *British Journal of Anaesthesia* 2019
47 Huggins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain* 2012; **153**: 1837-46
48 Benson N, Metelkin E, Demin O, Li GL, Nichols D, van der Graaf PH. A systems pharmacology perspective on the clinical development of Fatty Acid amide hydrolase inhibitors for pain. *CPT: pharmacometrics & systems pharmacology* 2014; **3**: e91
49 Fowler CJ. The Potential of Inhibitors of Endocannabinoid Metabolism for Drug Development: A Critical Review. *Handb Exp Pharmacol* 2015; **231**: 95-128
50 Edwards RR, Dworkin RH, Turk DC, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain* 2016; **157**: 1851-71