Pain Centre Versus Arthritis Annual Report

Executive Committee: Professors David Andrew Walsh and Victoria Chapman (Co-Directors), Duncan Hodkinson, Eamonn Ferguson, Federico-Dajas-Bailador, Roger Knaggs, Weiya Zhang

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Mission

Pain Centre Versus Arthritis pursues international excellence in multidisciplinary, translational research, thereby enhancing understanding of pain and improving its treatment

Introduction from the Co-Directors

This year, we continued to deliver fundamental research and capacity in research into chronic pain. We are proud of our unique, world-class, multidisciplinary research team, and privileged to share expertise with collaborators, and future generations of pain researchers. Our team covers key disciplines of neuroscience, orthopaedics, rheumatology, psychology, genetics, molecular biology, evidence-based medicine and clinical trials, biobanks, preclinical modelling, neuroimaging, education, and training. At the core of all our activities are the needs of people who experience chronic pain. Patients and the public are involved throughout our research by developing new ideas and delivering research through disseminating our findings to change practice and improve the lives of people who suffer pain. Since day one, the goal of Pain Centre has been to move towards bettering the lives of people with arthritis. To do so, we direct our efforts to identify novel treatment targets and new personalised interventions, which we test through randomised controlled clinical trials.

Our achievements this year are delivering our strategy expanding the expertise and techniques in pain research and identifying under-researched areas through international academic, commercial and stakeholder collaboration. We have conducted forward and backward translational research to integrate the breakthroughs from clinical and preclinical research with mechanistic pain models. We have achieved this through scientific exchange and developing more efficient preclinical models and resources. This year, our research has focused on musculoskeletal pain, including that of knee osteoarthritis and rheumatoid arthritis, and the worldwide problems of chronic opioid exposure. We have identified new biomarkers and tested the translation of new therapeutic approaches into clinical practice. We continue to research chronic pain from biological, clinical, psychological and socio-economic, perspectives.

Pain Centre Versus Arthritis is supported by a broad base of Government, charitable and commercial funding. We are grateful for the growing support from Medical Research Council (MRC), UK Research and Innovation (UKRI), Versus Arthritis, Wellcome Trust and Arthritis Research UK charity organisations, National Institute for Health Research (NIHR), Engineering and Physical Sciences Research Council, Biotechnology and Biological Sciences Research Council, Stroke Association, El Lilly & Co, Kennedy Trust and. Pfizer Ltd.

Pain Centre brings together stakeholder communities to address shared objectives. We encourage new collaborations and exchange of expertise by organising scientific internal and external meetings, and by building a united research community.

The Story So Far

Pain Centre Versus Arthritis came into existence in 2010 and has become an internationally recognised, translational research Centre. Since its day of inception, Pain Centre has aimed to enhance our understanding of chronic pain, improve therapeutic strategies and introduce novel treatments. We have striven to successfully implement our positive findings into clinical practice by influencing stakeholder agendas, including funding bodies, the government, and the public at large.

The multidisciplinary and translational strategy of Pain Centre Versus Arthritis has continued to sustain a high volume of novel research outputs, with 81 peer-reviewed publications and scholarly articles during its first 5 years and 456 to date.

The Pain Centre has also contributed to advances in translational research beyond arthritis. We have elucidated the links between arthritis pain and frailty, arthritis pain and the gut microbiome, pain and mental health and cognitive deficit, pain and fatigue, pain and personality, and osteoarthritis pain and socio-economic factors.

The Centre's Knee Pain and related health In the Community (KPIC) cohort has contributed both to understanding chronic pain, and by collating systematic data from pain-free (control) populations to facilitate an understanding of the benefits and adverse events of Sports and Exercise. Through NIHR funding we have established a large pain and frailty cohort (the Investigating Musculoskeletal Health and Wellbeing survey, IMH&W) with validated datasets on 8570 participants at baseline, and year 1, 2 and 3 follow-up surveys completed.

We are also responsible for the constant expansion of our biorepositories as we continue to collect blood, joint fluids, tissues, and serum from our patients which provides a useful foundation for lipidomics, proteomics, gene expression and imaging. This is of great importance in the search for new biomarkers that can help predict OA knee pain, or might indicate targets for novel therapeutics.

We have always sought to employ and develop diverse methodologies and recruitment strategies. Our KPIC and IMH&W cohorts have provided recruitment sources of phenotyped participants for efficient and stratified recruitment to other clinical research studies. We have demonstrated the appropriateness and efficiency of cohort-based recruitment to mechanistic and therapeutic clinical trials.

We have been pushing forward the exploration of deep brain electrical stimulation, already implemented in the management of depression, as a means to reverse abnormal brain processing of pain signals. We have been developing novel tools and techniques to perform successful phenotyping to advance the personalised management of chronic pain. We continue to elucidate the nature, mechanisms and impacts of existing treatments, such as opioid administration, developing strategies which could potentially solve the problem of side effects, tolerance, and limited efficacy of chronic opioid administration.

Outreach Activities:

The Pain Centre's continuing outreach activities engage local and national media and present our research findings and links to other patient and public resources through

our website (http://www.nottingham.ac.uk/paincentre). We work closely with trainees and staff to help them to develop skills in communicating beyond the scientific community. Our research is leading us to contribute directly to public and professional educational initiatives, in partnership with EULAR, EFIC and OARSI. We aim to increase understanding of the burden and mechanisms of arthritis pain, of what can best be done to relieve chronic pain, and of the cutting-edge research being undertaken within both the Centre and internationally, that should change the fate of people with arthritis in the near future. The Centre has contributed workshops or plenary sessions to national and international conferences, including the British Pain Society, EULAR, OARSI, EFIC, and SOPATE.

Training and Capacity Building:

Training, networking, and exchange of expertise benefit both early-career scientists and established researchers. Therefore, we enthusiastically organise internal and external events that bring together the members of our Centre and external researchers.

Each year, our internal scientific meetings aim to educate our members about the work of others within the Centre to encourage long-term collaborations, critical thinking, and exchange of expertise. Our Internal Scientific and Themed meetings provide an excellent opportunity for training and collaboration, in which researchers develop their soft skills and practise public speaking, communication, and creativity. Lessons learned during the Covid pandemic have led us to explore new meeting formats, including `in-person' meetings happening simultaneously at two university sites.

Centre members interact closely with musculoskeletal researchers from other institutions integrating Pain Centre Versus Arthritis as a valued component of the wider UK and international research community. The Centre is contributing to the UKRI/Versus Arthritis Advanced Pain Discovery Platform through its research, collaborations, and programme directorship.

The Pain Centre, for the 4th consecutive year, organised this year's annual Versus Arthritis Pain Research in the UK conference which was held in London on the 27th of June. Positive feedback confirmed that we achieved our key objectives to deepen the delegates' knowledge of pain-related research by promoting a critical and in-depth discussion, ensuring equal participation from everyone present. The conference provided an opportunity to engage in fast-paced and absorbing conversations on topics of particular interest collated from the UK pain research community. based on a list of questions that were prepared in advance by our Facilitators. The five themes of focus for this year's conferences were: Psychological Aspects of Pain, Nociplastic Pain, 'Omics' in Pain, Mechanisms of Chronic Pain in the Periphery, and Comorbidities. Further information about the conference content can be found in the conference report here

https://www.nottingham.ac.uk/paincentre/documents/conferences/2022/versus-arthritis-conference-report-2022.pdf

A full list of meetings at Pain Centre can be found here:

https://www.nottingham.ac.uk/paincentre/meetings/pain-centre-versus-arthritis-meetings-2022.aspx

Training and educational activities on pain:

Centre members convene and contribute to pain in undergraduate courses at the University of Nottingham for undergraduate degrees in neurosciences, medicine, physiotherapy, nursing, and pharmacy, and Master's Courses in Pharmacy, Physiotherapy, and Neurosciences. The Pain Centre organises a programme of scientific meetings for its members and other interested researchers in its partner institutions. Please see the programme of the meetings below.

Date	Meeting
14/06/2021	Internal Scientific Meeting
14/07/2021	Versus Arthritis 3rd Annual Pain Research in the UK Conference 2021
15/10/2021	External Scientific Meeting: The mechanisms of physical activity and exercise in patients with chronic musculoskeletal pain
08/12/2021	Internal Christmas Research Seminar Meeting 2021
23/05/2022	Internal Scientific Meeting
27/06/2022	Versus Arthritis 4th Annual Pain Research in the UK Conference 2022
29/10/2022	Internal Scientific Meeting
14/10/2022	External Scientific Meeting: Comorbidities in Osteoarthritis
TBC	Internal Christmas Research Seminar Meeting 2022

Jo Stocks provides training for researchers on Public and Patient Involvement, and Eamonn Ferguson provides undergraduate and post-graduate training on cross-cultural health care, ethnic diversity, inequality and health. David Walsh has provided invited presentations on pain to the Scottish Pain Research Community (SPaRC), FRESCO@CNAP workshop, Aalborg, Denmark, Br Pain Soc ASM, British Society for Rheumatology, and the EFIC Academy. Member of the IASP Global Year Against Back Pain and OARSI Pain Education task forces. He is the author of EULAR online training modules in low back pain and musculoskeletal pain, chapters on spinal pain for the Oxford Textbook of Rheumatology, and on Rheumatologic conditions in Practical Management of Pain.

Name	Teaching activity details
David Walsh	Contributions to undergraduate and postgraduate training on pain, including contributions to text books, EULAR and other web-based materials.
Gareth Hathway	Director of BSc and MSci neuroscience degree programmes.
Joanne Stocks	Teaches on the BMedSci 'Patient and Public Involvement in Research' module

Eamonn Ferguson	Cross-cultural health care; ethnic diversity, inequality and health Masters in Public Health (Health Inequalities
Kavita Vedhara	Delivers two Master's modules in Health Psychology: - Chronic Illness, Disability and Stress - Biomedical Perspectives in Psychology and Health
Michelle Hall	Head for the following courses on the BSc Hons Physiotherapy and BSc Sport Rehabilitation programmes - Developing evidence- based practice - Physical Activity & Health - Rheumatology - Dissertation project BSc Physiotherapy - Sports Medicine & Sports Injuries (Epidemiology) - Long-term & Complex Conditions - Personal & Professional Development Teaching contribution to the MSc Physiotherapy Advancing Neuromusculoskeletal Practice
Paul Hendrick	Course coordinator for Research Development and Rehabilitation of Spinal Disorders and NMS 1 at UG level Course coordinator for the Masters Dissertation Module, Evaluation and Research Development in Health Sciences and Pain Rehabilitation at PGT level Teaches across a number of UG and PG modules including Management of musculoskeletal Disorders, Management of complex long-term conditions and the Pain module. Undergraduate teaching includes Early Clinical and Professional Development course
Richard Pearson	Translation PhD framework (nTRANS) lecture on "Ethics - Human Tissue and Research Governance".
Roger Knaggs	In addition to teaching on the MPharm undergraduate course he is the pharmacist lead for non-medical prescribing course (School of Nursing, Midwifery and Physiotherapy) and provides occasional lectures for other Learning Beyond Registration courses in Division of Nursing. He is also an an Honorary Senior Tutor on the MSc in Pain Management (Cardiff University).
Stefan Kluzek	Stefan teaches applied anatomy and functional anatomy to under and postgraduate students. Third year Communicating science (Undergraduate Ambassadors Scheme) module convenor Course coordinator for Research Development and Rehabilitation of Spinal Disorders and NMS 1 at UG level Course coordinator for the Masters Dissertation Module, Evaluation and Research Development in Health Sciences and Pain Rehabilitation at PGT level

Tobias Bast	Year 1 - Psychology of Addiction (PSGY1005). - Biological Psychology (PSGY1003). Year 2 - Neuroscience and Behaviour (PSGY2007/4029). Year 3 - Mechanisms of Learning and Psychopathology (PSGY3018). MSc Psychology (Conversion) MSc projects Year 3, Neuroscience, School of Life Sciences Sensational Neuroscience (LIFE3082). His teaching and lecturing at the University is to postgraduate students within the Taught course - Translation PhD framework (nTRANS) lecture on "Ethics - Human Tissue and Research Governance". He also lectures postgraduate students within the EPSRC Doctoral Training Centre in Regenerative Medicine on "Bone Grafts and Bone Substitutes" and students studying towards their MSc in Stem Cell Technologies on a number of topics including "Metals and Ceramics in Surgical Implants". Administrative duties include being the Person Designate for the Division of Orthopaedic & Accident Surgery under the Human Tissue Authority license.First year lab organizer Third year Communicating science (Undergraduate Ambassadors Scheme) module convenor
Weiya Zhang	Clinical study design (BMeSci undergraduates) Systematic review (N-trans postgraduates) Meta-epidemiology (Specialists)In addition to teaching on the MPharm undergraduate course he is the pharmacist lead for non-medical prescribing course (School of Nursing, Midwifery and Physiotherapy) and provides occasional lectures for other Learning Beyond Registration courses in Division of Nursing. He is also an an Honorary Senior Tutor on the MSc in Pain Management (Cardiff University).His teaching and lecturing at the University is to postgraduate students within the Taught course - Translation PhD framework (nTRANS) lecture on "Ethics - Human Tissue and Research Governance". He also lectures postgraduate students within the EPSRC Doctoral Training Centre in Regenerative Medicine on "Bone Grafts and Bone Substitutes" and students studying towards their MSc in Stem Cell Technologies on a number of topics including "Metals and Ceramics in Surgical Implants". Administrative duties include

	being the Person Designate for the Division of Orthopaedic & Accident Surgery under the Human Tissue Authority license.
Roshan das Nair	He is the Senior Research Tutor with the Trent Doctorate in Clinical Psychology. He has supervised 55 doctoral research projects to successful completion.In addition to teaching on the MPharm undergraduate course he is the pharmacist lead for non-medical prescribing course (School of Nursing, Midwifery and Physiotherapy) and provides occasional lectures for other Learning Beyond Registration courses in Division of Nursing. He is also an an Honorary Senior Tutor on the MSc in Pain Management (Cardiff University)
Stefan Kluzek	Stefan teaches applied anatomy and functional anatomy to under and postgraduate students. He has a number of postgraduate students and is leading big data projects, including all major US sport injury data depository and automated histology and clinical imaging projects. Stefan beliefs that all academics research requires skilled professionals who are confident and confident in gathering, managing and analysing large data sets and that those skills can be taught in a way that empowers learners from different backgrounds to study at their own pace in and outside of the classroom. He has been developing a data science skills training program with tools necessary to develop good research questions, training to think in this paradigm, and data literacy skills to answer these findings.He is the Senior Research Tutor with the Trent Doctorate in Clinical Psychology. He has supervised 55 doctoral research projects to successful completion
Victoria Chapman	Teaches undergraduate Neuroscience and Medical Students pain pathways, analgesics, mechanisms of chronic pain.

Public and Patient Involvement and Engagement (PPI/E):

Pain Centre Versus Arthritis has established open and reciprocal communication with patients, their carers and other members of the public, through our Patient and Public Advisory Group (PPAG). This partnership with the public and patients helps us to understand the needs, priorities, and expectations of those whose quality of life we aim to improve and to better communicate our increasing understanding of pain and its management. Our strategic priority is to drive forward PPI/E impact in research. We have created a supportive environment with effective and inclusive two-way communication between researchers, the public and patients. We have developed training and support that inspires participation in the PPI/E process. PPAG has been an invaluable source of information that helped us to direct our research to the specific needs of people with arthritis. Our novel research ideas grow from discussions with people with chronic pain and those who care for them. Our PPAG helps us to ensure

that each project addresses a key need of people with chronic pain, using methods that are feasible and acceptable to research participants. Patients and the public help us to communicate our findings, and to interpret their importance for people with chronic pain. We share our PPI/E activities with our partners across the School of Medicine, Nottingham University Hospitals NHS Trust, and Versus Arthritis to expand a network of mutual support and collaboration. We are currently merging our PPAG with NUH/BRC infrastructure so that together we can take PPI activities to the next level, ensuring that the needs and interests of people with chronic pain are central to our activities.

Research Themes

Pain Centre is engaged in a programme of linked studies investigating mechanisms and treatments for arthritis pain in the laboratory, clinic and in everyday life, using a comprehensive range of modern research methodologies. Our research spans across 5 major themes; (1) Biomarkers and Novel Therapeutic Targets, (2) Nociplasticity, and (3) Neurocognitive and Psychological Function. We have built upon this increased mechanistic understanding to undertake research that will transform (4) Treatment Efficacy and Real-World Evidence, and (5) Phenotyping and Personalised Medicine. Below, we report selected key publications from the 2021-22 period relating to these themes.

Theme 1: Biomarkers and Novel Therapeutic Targets

The transcranial magnetic stimulation of the primary motor cortex has been previously recognized as a promising treatment for chronic pain. Such non-invasive brain stimulation technique is believed to exert its long-lasting and potentially reversible analgesic effects by inducing cortical neuroplasticity. We used dynamic causal modelling (DCM) and Bayesian model selection (BMS) to test seven competing hypotheses and investigate the mechanism of action of such treatment technique **(Hodkinson et al., 2021)**. The results pointed to the effective connectivity between the primary motor cortex and the three cortical areas of the medial and lateral pain systems such as the insular cortex, anterior angular cortex, and the parietal operculum cortex. These findings support the hypothesis that the analgesic effects following the primary motor cortex stimulation are modulated by the top-down processes of intracranial modulation rather than spinal inhibition. What is more, an additional analysis recognised the pathway between the primary motor cortex and the insular cortex as the second-best model of plasticity following transcranial magnetic stimulation. Our findings provide a starting point for the research of the pathway-specific targeting by transcranial magnetic stimulation to improve the analgesic response.

The existing analgesics designed to address chronic pain in osteoarthritis have limited therapeutic potential and produce adverse effects. The novel therapeutic pathways, which are believed to reduce the progression of chronic illness by targeting inflammatory signalling, have been a focus of extensive research for the past decade. It has been hypothesised that an increased endogenous anti-inflammatory response may prove an effective alternative strategy to traditional analgesics. We focused on the therapeutic potential of epoxyeicosatrienoic acids (EETs) which are endogenous anti-inflammatory mediators and whose clinical relevance remained under-researched

until recently. EECs produce short-lived effects due to their rapid metabolism by soluble epoxide hydrolase (EH) to dihydroxyeicosatrieno acids. The current research aimed to assess the role of the EH-driven metabolism of EETs in chronic joint pain and its therapeutic potential. We investigated the association of chronic knee pain with circulating EETs and DHETs and single-nucleotide polymorphism (SNPs) in the soluble EH gene **(Gowler et al., 2021)**. The therapeutic potential of soluble EH-inhibitor was studied in a murine model of OA by assessing weight-bearing asymmetry, hind paw withdrawal thresholds, joint histology and circulating concentrations of EETs and DHETs. The study was the first one to report that SNPs of the soluble EH gene are associated with 3 different measures of chronic knee pain in human subjects with OA. Furthermore, the study reported circulating levels of EETs and DHETs that were also associated with 3 pain measures in 2 separate cohorts of subjects. In terms of the therapeutic importance of the pathway, the results suggest that systemic administration of EH-inhibitor (TPPU) produced acute and chronic alleviation of pain symptoms. The treatment also decreased levels of circulating DHETs which we previously found to be positively associated with chronic knee pain severity **(Valdes et al., 2018)**.

At present, patients with knee osteoarthritis turn to the General Practitioner, hospital specialist, physiotherapist or dietitian for advice on non-pharmacological interventions which are recognised as the primary treatments for osteoarthritis. Specifically, such interventions include patient education, exercise, and dietary or weight loss advice. However, in the current model of care, such therapeutic approaches are often overlooked due to the physicians' limited availability, lack of knowledge or focus on pharmaceuticals. We explored the possibility of a nurse-led non-pharmacological package of care for knee pain in osteoarthritis **(Nomikos et al., 2022)**. The primary question was whether nurses can undergo efficient training to deliver such complex non-pharmacological interventions and whether patients would accept such care from the nurses due to their expectation to be treated by a specialist. The results were promising as the patients considered the advice provided by the nurses to be easy to follow and understand. In general, the patients who received nurse-led holistic care for knee osteoarthritis were satisfied and reported a change in perception regarding the treatment of knee pain.

Another noteworthy achievement of the Centre, with collaborators at St George's Hospital, London, is the development of the new scoring system by **Koushesh et al., 2022**. This novel histological scoring system, the Osteoarthritis Bone Score (OABS), is aimed at human osteoarthritis-related bone marrow lesions (BMLs). Despite the fact that BMLs are a key feature of osteoarthritis pathology, the histological processes in subchondral bone in osteoarthritis BMLs require better understanding. We identified histopathological characteristics of BMLs, verified the OABS, and confirmed that subchondral pathological features can be evaluated using this scoring system, enhancing our understanding of histopathological changes associated with osteoarthritis BMLs.

Theme 2: Nociplasticity

Pain is modulated by nociceptive processing in the peripheral and central nervous system, and interfering with this could provide effective analgesic treatment options. Our research aimed to shed light on the mechanisms that govern central sensitization in the dorsal horn of the spinal cord which is partially responsible for neuropathic pain

(Lobo et al., 2022). Previous studies have pointed to a disturbance in the integrity of the spinal vascular network as a causative factor in the origin of neuropathic pain. However, the exact mechanisms remain under-researched. Therefore, we explored how vascular dysfunction could upregulate nociceptive processing at the level of the spinal cord through curtailed blood flow and hypoxia and thus clarify the role of the vascular system in the development of long-term pain hypersensitivity. The study used Type I diabetic and transgenic rodent models which presented with degenerated endothelium in the dorsal horn to demonstrate that vasculopathy at the level of the spinal cord leads to central sensitisation. Furthermore, the findings also show that hypoxia, which results from vascular rarefaction in the dorsal horn, is critical to neuronal activation and initiation of neuropathic pain through the upregulation of hypoxia-inducing genes and alterations in bicarbonate metabolism. The conclusion is that microvasculature at the level of the spinal cord is essential for healthy neuronal modulation. In contrast, impaired vascular support is associated with a hypoxic microenvironment in the dorsal horn and leads to diabetic neuropathic pain development. This research elucidates a novel and promising pathway of analgesic treatment.

Pain Centre is also studying central sensitization in the context of Rheumatoid Arthritis (RA) **(Ifesemen et al., 2021)**. RA is a chronic inflammatory autoimmune disease which presents with pain, stiffness and fatigue, affecting joints, hands and feet. It has been suggested that even when treatment succeeds at managing the inflammatory symptoms of the disease, central sensitization may continue, contributing to pain and fatigue. We argued that the current treatment strategy approaches RA patients in a non-specific manner, while a growing amount of evidence demonstrates a heterogeneous nature of symptoms in the RA population, pointing to the different targets for pain management and pain mechanisms. Accurate measurement and identification of these various targets are thus needed to allow stratification and delivery of precision treatment to the correct patient subgroups. The study is building on the premise that in a certain RA patient population, much chronic pain results from central mechanisms. Therefore, an administration of adjuvant treatment in this specific patient group would lead to more efficient treatment strategies for these individuals. The paper recognises the CAP-RA questionnaire as an important stratification tool in the clinical setting and aims to further develop and validate its uses for measuring central pain mechanisms in RA and targeted interventions. Our rationale behind this is to improve the process of assigning specific patient populations diagnosed with RA to a treatment that is optimal for them.

Theme 3: Neurocognitive and Psychological Function

Pain Centre recognises the significance of psychological function in chronic pain. This year, research has targeted a complex relationship between negative affect and the use of opioid analgesics in people with osteoarthritis **(Lillywhite et al., 2021)**. The significance of studying negative psychological states in this context arises from the worldwide overuse of opioid-based treatments for long-term pain conditions even if their therapeutic effectiveness appears to be limited for most people. In particular, high rates of over-prescription of opioid treatments to people diagnosed with osteoarthritis have been previously associated with an increased risk of adverse events, greater depressive symptoms and trait anxiety. Therefore, we hypothesised that alterations in endogenous opioid signalling may be responsible for the interaction between high anxiety, chronic pain and great opioid use. We used a translational relevant rodent

model of high anxiety and osteoarthritis-like pain, we found an altered endogenous opioid receptors function and phosphorylation of the residues that are responsible for morphine-mediated desensitization without previous exposure to exogenous opioids. Our findings suggest that a combination of anxiety, chronic pain and disturbed opioidergic tone leads to heightened pain responses and reduced the efficacy of opioid treatment.

Theme 4: Treatment Efficacy and Real-World Evidence

It is of great importance to seek an understanding of the nature, mechanism, and impact of existing treatments in our fight against chronic pain.
We recognise the problem that is posed by persistent opioid utilisation as it is linked to addiction and dependence and we also argue that persistent opioid utilization may be associated with opioid-related death in the UK. Therefore, we studied the association between opioid-related death and extensive use of opioids in the UK **(Chen et al., 2021)**. To do so, we carried out a nested case-control study and used primary care medical records from the UK Clinical Practice Research Datalink, linking the Office for National Statistics death registration. We found that persistent opioid prescription in any one of the three years before death is associated with a greater risk of opioid-related death, compared to non-persistent prescribing. Our study also found that tapering or stopping opioid treatment might increase the risk of opioid-related death. This supports a previously raised concern about the risks of terminating opioid treatment among persistent opioid users. To our knowledge, this is the first nested case-control study that focuses on the relationship between persistent opioid use and opioid-related deaths. We conclude that in the clinical setting, healthcare providers ought to take into consideration the history of persistent opioid utilization instead of considering the daily dose only. We also discovered that concurrent prescription of opioids with certain psychotropics such as tricyclic antidepressants, benzodiazepines or gabapentinoids is another risk factor for opioid-related death.

There has been an escalation in the use of opioids and their prescription needs to be carefully considered due to the increasing concerns of misuse, decreased efficiency and adverse effects. Constipation is one of such prevalent adverse events associated with opioid use. Despite producing significant adverse effects both on the patient quality of life and efficiency of the opioid therapy, healthcare providers underestimate the seriousness of this side effect and seem to have a very limited precautionary discussion before prescribing it. We employed a real-world dataset to characterise the burden of opioid-induced constipation in the UK healthcare system **(Morgan et al., 2021)**. We conclude that opioid-induced constipation greatly increases combined health costs when compared to those opioid users who are not diagnosed with opioid-induced constipation. We also emphasise the importance of recognising opioid-induced constipation as a serious side effect of opioid use and their consequences have to be taken into account prior to active opioid intervention.

Furthermore, we also emphasise that a commonly accepted arbitrary classification of opioids based on their strength, potency or efficacy should be stopped **(Crush et al., 2022)**. In fact, categorisation of opioids into either weak or strong may cause more harm and benefits since the opioids we term “weak” are more likely to lead to dependence. However, multiple problems which may arise from the use of weak opioids are often overlooked due to their perceived safety. We argue that there is a strong need for the development of a more generalised and patient-specific approach

which should be employed by the prescribers. What is more, such classification has outlived its usefulness to both healthcare providers, responsible for the prescriptions, and the patients.

In the review by **Kluzek et al, 2021**, we assessed patient-reported outcome measures (PROMs) which have become a popular measure in clinical practice when investigating the subjective factors of patients' conditions. These include, but are not limited to, pain intensity, activity limitations, and satisfaction or adherence to the treatment. This information provides a patient's perspective in the evaluation of the nature of the disease and the proposed treatment. However, the subjective nature of PROMs leads to potential limitations and biases which are frequently overlooked. We acknowledge the fact that PROMs are likely to be affected by several subjective factors such as mood, expectations, treatment context, socioeconomic situation and others. What is more, while judging the effects of treatments, patients tend to overestimate the benefits while underestimating the risks. As a potential strategy to improve the reliability of PROMs, we propose that blinding of patients would reduce the bias, unbalanced attrition or cointervention, whereas blinding healthcare providers decreased observer's bias. However, an element of objectivity should be added when blinding is not possible by combining PROMs with imaging and biochemical biomarkers. We also suggest that a placebo-controlled randomized controlled trial may be essential when evaluating the benefits or harms of ongoing treatment to ensure that evidence of efficacy is based solely on PROMs. Finally, we recommend carrying out numerous PROMs over time which would potentially overcome the simple measure variability.

We produced a systematic literature review of randomized controlled trials (RCTs) and performed a meta-analysis to quantify the effects of systemic glucocorticosteroids (GCs) on pain in RA **(McWlilliams et al., 2022)**. Short-term administration of low doses GCs is known to be effective in targeting pain symptoms. However, long-term exposure to GCs has been previously associated with major health problems including osteoporosis and cardiovascular risk. We recognise the need for a more accurate understanding of the benefits that result from this treatment. In order to assess the optimal use of systemic GCs, we took under consideration both clinical and evoked pain as well as, treatment durations, routes of administration and doses. We found that GCs produce effects that are most efficient shortly after initiation and may not produce clinically significant pain relief after 3 months. Therefore, we conclude that there is a strong need to introduce novel treatments to address pain in RA in long-term therapy.

Theme 5: Phenotyping and Personalised Medicine

Pain Centre Versus Arthritis recognises the importance of population stratification in medicine. There is a danger in treating the patient population as a homogenous sample since overgeneralisation may result in findings and effects that are overlooked. In contrast, by treating the patient population as a heterogenous sample and by classifying the sub-groups of people diagnosed with the same disease, we have a greater chance to identify markers of the disease and develop more patient-centred approaches. Stratification might become a more widely employed practice both in medical and research environments since it is uncommon for a patient population to display homogeneity in terms of their experience, symptoms, and disease progression patterns.

We extend this argument and apply it in the psychological context to explore how the personality-health effects vary as a function of different experiences of arthritis **(James et al., 2021)**. There are multiple aetiologies of arthritis with pain experience varied among different sub-groups depending on their specific pattern of pain progression. We recognised that it is not known how stratification of these sub-groups would affect the relationship between health and personality and we aimed to study how the effects of personality are regulated by disease heterogeneity. We carried out a longitudinal analysis over 14 years and looked at the predictive relationship between the Big 5 personality traits, pain and self-reported health while also stratifying them by different patterns of disease progression in arthritis. We obtained promising results showing that by modelling heterogeneity, we identified specific psychological traits, such as neuroticism, agreeableness, and extraversion. In contrast, these stratified personality effects remained undetected when the data was treated as homogenous. Our findings provide further evidence that there is a strong need for modelling heterogeneity on disease both for research and clinical purposes.

We are also interested in the target identification of genetic markers associated with pain sensitisation and neuropathic-like pain phenotypes as these may explain the ongoing pain the patients experience after total joint replacement **(Kouraki et al., 2021)**. We carried out two genome-wide gene-based association studies (GWGAS) using pressure pain detection thresholds (PPTs) from the Knee Pain and related health in the community (KPIC) cohort. The aim was to identify genetic variants for distal and local sensitisation from distal and affected sites, respectively. We then explored genetic mechanisms implicated in the development of distal and local sensitisation in osteoarthritis pain by performing a genome-wide gene-based association analysis (GWGAS) and gene-set analysis with a focus on both PPT phenotypes. Furthermore, we also conducted a GWGAS to examine the genetic background related to the neuropathic-like pain phenotypes. Finally, we performed two gene-based meta-analyses by combining our neuropathic-like pain GWGAS findings with our results from distal and local sensitization GWGAS. Our objective was to identify the genes and genetic mechanisms common in distal and local sensitisation, and neuropathic-like pain phenotypes. We concluded that there might be distinct biological mechanisms responsible for distal and local sensitization, whereas distal sensitisation and neuropathic-like pain may arise from common genetic markers. It was the first study to conduct GWAS in the context of pain sensitisation and the first to perform a gene-based meta-analysis on pain sensitisation and neuropathic-like pain. Our findings have high clinical significance as identification of the genetic biomarkers and subsequent molecular processes are essential for the identification of therapeutic targets at early intervention.

Publications 2021-2022

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Organisational Structure

Co-Directors:

Name	School and Faculty	Position	Area of Expertise
Prof Victoria Chapman, Pain Centre Executive Committee Member	School of Life Science; Faculty of Medicine and Health Sciences	Co-Director of Pain Centre Versus Arthritis; Professor of Neuropharmacology	In vivo studies, pharmacological intervention, pain biomarkers, CNS function, forward and back translation.
Prof David Andrew Walsh, Pain Centre Executive Committee Member	School of Medicine; Faculty of Medicine and Health Sciences	Co-Director of Pain Centre Versus Arthritis; Professor of Rheumatology and Consultant Rheumatologist at Sherwood Forest Hospitals NHS Foundation Trust.	Pain phenotyping in arthritis, mechanistic pain modelling and assessment across preclinical and clinical studies, pharmacological and non-pharmacological therapeutic intervention, biorepositories.

Lead Investigators:

Name	School and Faculty	Position	Area of Expertise
Prof Abhishek Abhishek	School of Medicine;	Professor of Rheumatology Honorary Consultant Rheumatologist,	Autoimmune Rheumatic Disease Epidemiology, Gout, CPPD, OA clinical research, Clinical Trials -

	Faculty of Medicine and Health Sciences	Nottingham University Hospitals NHS Foundation Trust	CTIMPs, Pragmatic trials, Ultrasound imaging
Prof Ana Valdes	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Molecular and Genetic Epidemiology	Genetic epidemiology and musculoskeletal genetics
Dr Andrew Bennett	School of Life Science; Faculty of Medicine and Health Sciences	Associate Professor and Director of the FRAME Alternatives Laboratory	Molecular Biology /Biochemistry, models of inflammation in disease states, neuroinflammation and metabolic dysfunction
Prof Avril Drummond	School of Heath Sciences; Faculty of Medicine and Health Sciences	Professor of Healthcare Research	Healthcare research and occupational therapy, stroke rehabilitation and rehabilitation research
Prof Benjamin Ollivere	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Orthopaedic Trauma, Head of Division Rheumatology, Orthopaedics and Dermatology	Non-union, bone infection, trauma and major injury along with treatment of complex fractures and the complications of these treatments; interest in limb reconstruction
Prof Brigitte Scammell	School of Medicine; Faculty of Medicine and Health Sciences	Dean and Head of School of Medicine	Orthopaedic surgery, biology of fracture healing, osteoarthritis and biomaterials
Dr Cornelia De Moor	School of Pharmacy; Faculty of Science	Associate Professor in RNA Biology	Post-transcriptional mechanisms of gene expression in arthritis
Dr Dong-Hyun Kim	School of Pharmacy; Faculty of Science	Associate Professor	Analytical Bioscience
Prof Dorothee Auer	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Neuroimaging	Clinical neurosciences using advanced MRI techniques
Prof Eamonn Ferguson; Pain Centre Executive Committee member	School of Psychology; Faulty of Science	Professor of Health Psychology	Health psychology, cohort studies, statistical modelling, psychosocial impact

Dr Federico Dajas-Bailador Pain Centre Executive Committee Member	School of Life Sciences Faculty of Medicine and Health Sciences	Assistant Professor	Physiology Pharmacology and Neuroscience, regulation of axonal protein expression by selective degradation
Dr Galina Pavlovskaya	School of Medicine; Faculty of Medicine and Health Sciences	Associate Professor, Translational Imaging	Translational and Molecular Imaging
Dr Hareth Gathway	School of Life Sciences Faculty of Medicine and Health Sciences	Associate Professor, Director of Neuroscience Degrees	Science of pain and nociception, pain processing and chronic pain states
Dr Holly Blake	School of Health Sciences; Faculty of Medicine and Health Sciences	Associate Professor of Behavioural Science	Health psychology and behavioural science
Dr Joanne Stocks	School of Medicine; Faculty of Medicine and Health Sciences	Assistant Professor in Sport And Exercise Medicine	Healthy aging, focusing on the role of nutrition in frailty, osteoarthritis and pain
Prof Joe Kai	School of Medicine; Faculty of Medicine and Health Sciences	Clinical Professor and Head of Primary Care	Expertise in clinical and applied health research, teaching and service development
Prof Kavita Vedhara	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Health Psychology	Psychological stress, psychoneuroimmunology, patient expectations, placebo effect, psychological interventions, foetal programming hypothesis, psychological/behavioural interventions
Prof Lucy Donaldson	School of Life Sciences; Faculty of Medicine and Health Sciences	Professor of Sensory Physiology	Neurophysiology of acute and chronic pain, particularly in arthritis
Prof Marilyn James	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Health Economics	Applied economic and clinical evaluation

Prof Meritxell Canals Buj	School of Life Sciences; Faculty of Medicine and Health Sciences	Professor of Cellular Pharmacology	Interactions between G Protein-Coupled Receptors and intracellular proteins, and their consequences for receptor signalling and trafficking
Dr Michael Stocks	School of Pharmacy; Faculty of Science	Professor of Medicinal Chemistry and Drug Discovery. Associate Professor, Centre for Biomolecular Sciences	Drug Discovery, Design, Medicinal and Synthetic Chemistry
Dr Michelle Hall	School of Health Sciences; Faculty of Medicine and Health Sciences	Assistant Professor Physiotherapy and osteoarthritis	Musculoskeletal rehabilitation and rheumatology
Prof Paul Greenhaff	School of Life Sciences; Faculty of Medicine and Health Sciences	Professor of Muscle Metabolism	Physiology, Pharmacology and Neuroscience
Dr Paul Hendrick	School of Health Sciences; Faculty of Medicine and Health Sciences	Lecturer in Physiotherapy and Rehabilitation Sciences	Low back pain research, Pain Research, Clinical outcomes research
Dr Pavel Gershkovich	School of Pharmacy; Faculty of Science	Associate Professor of Biopharmaceutics	Biopharmaceutics, Pharmacokinetics, Pharmacodynamics, Bioanalytical Techniques, Oral Drug Delivery, Effects of Disease States on Pharmacokinetics and Pharmacodynamics
Prof Penny Gowland	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Physics	Developing quantitative MRI for biomedical applications
Dr Richard Pearson	School of Psychology; Faculty of Medicine and Health Sciences	Assistant Professor, Orthopaedics and Trauma Group	Quantified changes in bone associated with several disease pathologies
Dr Rob Lane	School of Life Sciences; Faculty of Medicine and Health Sciences	Associate Professor of Molecular Pharmacology	G protein-coupled receptors with a particular emphasis on novel approaches towards the development of

			improved therapeutics for CNS disorders
Dr Roger Knaggs; Pain Centre Executive Committee Member	School of Pharmacy; Faculty of Science	Associate Professor in Clinical Pharmacy	The appropriate use of analgesic medicines, and associated clinical outcomes and healthcare utilisation
Prof Roshan das Nair	School of Medicine; Faculty of Medicine & Health Sciences	Professor of Clinical Psychology and Neuropsychology	Multiple sclerosis, Acquired brain injury, Pain research
Dr Stefan Kzulek	School of Medicine; Faculty of Medicine & Health Sciences	Clinical Associate Professor	Sports and Exercise Medicine
Dr Tobias Bast	School of Psychology; Faculty of Science	Associate Professor	Brain mechanisms of cognition and behaviour, neuroscience and biological psychology
Prof Weiya Zhang; Pain Centre Executive Committee Member	School of Medicine; Faculty of Medicine & Health Sciences	Professor of Epidemiology	Epidemiology, evidence-based medicine, osteoarthritis, Gout research

Research Associates

Title	Name	School	Faculty	Position
Dr	Cottam, William	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Fuller, Amy	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Georgopoulos, Vasileios	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Goncalves, Sara	Life Sciences	Faculty of Medicine & Health Sciences	Research Fellow

Dr	Gowler, Peter	Life Sciences	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Hodkinson, Duncan	Medicine	Faculty of Medicine & Health Sciences	Senior Research Fellow. Pain Centre Executive Committee Member
Dr	Lillywhite, Amanda	Life Sciences	Faculty of Medicine & Health Sciences	Research Fellow
Dr	McWilliams, Daniel	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Nakerero, Georgina	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Smith, Stephanie	Medicine	Faculty of Medicine & Health Sciences	Research Fellow

Research Support

Title	Name	School	Faculty	Position
Mrs.	Rose Farrands-Bentley	Medicine	Faculty of Medicine & Health Sciences	Administrative co-ordinator
Mrs.	Vlada Yarosh	Medicine	Faculty of Medicine & Health Sciences	Administrative co-ordinator
Dr	Kelly, Anthony	Medicine	Faculty of Medicine & Health Sciences	Research Nurse
Mr.	Lott, Thomas	Medicine	Faculty of Medicine & Health Sciences	Musculoskeletal Data Administrator
Mr.	McLoughlin, Sean	Medicine	Faculty of Medicine & Health Sciences	Musculoskeletal Research Administrator
Dr	Millar, Bonnie	Medicine	Faculty of Medicine & Health Sciences	Musculoskeletal Project Manager
Mrs.	Naushahi, Fozia	Medicine	NUH	Research Nurse, Faculty of Medicine & Health Sciences

Mr.	Millns, Paul	Medicine	Faculty of Medicine & Health Sciences	Laboratory Technician
Dr	Shahtaheri, Seyed	Medicine	Faculty of Medicine & Health Sciences	Laboratory Technician
Ms	Taylor, Jennifer	Clinical Science	Research Administrator	
Ms	Widdowson, Kirsty	Research and Innovation, Nottingham University Hospitals NHS Trust	NUH	Patient and Public Involvement and Engagement Facilitator
Miss	Wilson, Deborah	Kings Mill Hospital	Sherwood Forest Hospitals NHS Foundation Trust	Research Nurse

PhD studentships

Pain Centre Versus Arthritis hosts a range of PhD studentships, proving training in diverse techniques while exploring diverse aspects of pain, including projects on;

- A biopsychosocial approach to understanding the contributors to chronic pain
- Prevalence and associated risk factors of foot/ankle osteoarthritis and neurodegenerative
- conditions in ex-professional footballers compared to general population
- Personalised approaches to the management of chronic musculoskeletal pain in people with Rheumatoid Arthritis
- Peripheral contributions to the development and maintenance of chronic OA pain.
- Arthritis damage and pain: VEGF involvement
- Investigating musculoskeletal pain and frailty

PhD students affiliated to the Centre during the 2021-22 academic year were: Afroditi Kouraki. Ahmed Thanoon, Ammar Khamis, Ashley Duncan, Asraa Thiyab, Aya Abd Elkhabir, Ayah Ismail, Bayan Aljilani, Dimitrios Amanitis, Isabel Ely, James Hudson, James Turnbull, Lauren Murrell, Monirah Shuaib, Nouf Al-Otaibi, and Ojasvi Mehta

Active Funding and Awards 2022

Pain Centre Versus Arthritis benefits from a broad foundation of funding sources, with current active grants totalling approximately **£32m**

Lead investigator(s)	Awarded by	Details	Period

Ana Valdes	Medical Research Council	Molecular signatures of endocannabinoid induced pain relief in humans: lifestyle interventions, systemic and localised changes.	05/2022-05/2025
Victoria Chapman, Ana Valdes, Dong-Hyun Kim	UK Research and Innovation	MICA: Exploiting specialised pro-resolution molecule mediated analgesia to identify novel targets for the treatment of chronic pain	05/2022-05/2025
Ana Valdes	UK Research and Innovation	Advanced Pain Platform ALLEVIATE Data Hub for Pain	06/2021-05/2024
Ana Valdes	Versus Arthritis	Synovial fluid to define endotypes by unbiased proteomics in OA	10/2010-12/2024
DA Walsh. D Auer, V Chapman, M Doherty, E Ferguson, S Kelly, B Scammell, K Vedhara, W Zhang	Versus Arthritis	Pain Centre Versus Arthritis	03/2015-06/2024
David Walsh	Kennedy Trust	STEpUP supplement (PROMS analysis)	2020
David Walsh	UKRI/Versus Arthritis	Advanced Pain Discovery Platform (APDP) – Programme Director	2020-2025
David Walsh	Ely Lilly & Co	Human validation for novel targets associated with OA pain.	2020-2022
David Walsh	Versus Arthritis	Lymphotactin in arthritis pain. 22452. Lead applicant: F Boissonade (Sheffield), Co-applicants: DA Walsh & V Chapman	2020-2022
David Walsh	Versus Arthritis	Improving pain outcomes in rheumatoid arthritis; detecting the	2020-2022

		contribution of central pain mechanisms.	
David Walsh	Pfizer Ltd	Improving pain outcomes in rheumatoid arthritis; detecting the contribution of central pain	2019-2022
David Walsh	Versus Arthritis	STEpUP, special programme grant. Lead Applicant Tonia Vincent, Oxford. Nottingham coapplicants Walsh, A Valdes. £150,000 allocated to Nottingham.	2019-2021
David Walsh	Versus Arthritis, Centre Initiative grant	Centre of Excellence in Mechanisms of Pain in Arthritis. Extension. Main applicant/Director: DA Walsh. Co-applicants: D Auer, V Chapman, M Doherty, E Ferguson, S Kelly, B Scammell, K Vedhara, W Zhang. Grant 20777.	2020
David Walsh	NIHR Programme Development Grant (PDG), NIHR202618	Support and treatment after joint replacement (STAR): translation into practice and long-term follow up	2021-2023
Dorothee Auer	Wellcome Trust	Midlands Mental Health & Neurosciences PhD Programme for Healthcare Professionals	10/2022-09/2029
Dorothee Auer	Engineering and Physical Sciences Research Council	Realising the potential of open MRI for dynamic studies of human anatomy and function	03/2021-03/2024
Dorothee Auer, David Walsh, John Gladman, Victoria Chapman, Paul Greenhaff	National Institute for Health Research	NIHR Nottingham Biomedical Research Centre	04/2017-11/2022

Joanne Stocks	QR Policy Support Fund	Understanding treatment outcomes in patients referred with musculoskeletal complaints. Pilot study on the implementation of an electronic PROM/PREM data collection system	12/2021-03/2022
Joanne Stocks	National Institute for Health Research	Development of an optimal physiotherapy intervention for arthrofibrosis following total knee replacement	02/2022-09/2023
Kavita Vedhara	Programme Grants for Applied Research	Promoting Activity, Independence and Stability in Early Dementia' (PrAISED)	2016-2022
Kim I Chisholm	University of Nottingham	Illuminating the spinal cord to understand chronic pain: In vivo imaging of somatosensory responses of spinal networks	07/2022-07/2025
Paul Greenhaff	Arthritis Research UK	Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis	01/2018-12/2022
Paul Greenhaff	Medical Research Council & Arthritis Research UK	MRC/Arthritis Research UK Centre for Musculoskeletal Ageing Research	08/2017-07/2022
Robert Lane	Biotechnology and Biological Sciences Research Council	New tools for acute spatiotemporal control of GPCR signalling in vivo	01/11/2020-31/10/2023
Roshan das Nair	Stroke Association	Nottingham Fatigue study-developing a fatigue programme. NotFAST2	12/2019-08/2021
Roshan das Nair	NIHR Programme Grants for Applied Research	Multicentre Research Programme to Enhance Return to Work after Trauma (ROWTATE)	03/2019-12/2024

Stefan Kluzek and Ana M Valdes	MRC	Molecular signatures of endocannabinoid induced pain relief in humans: lifestyle interventions, systemic and localised changes	02/2022 - present
Stefan Kluzek	Versus Arthritis	Biomarkers and Joint Pain in Military Osteoarthritis Study (Bio-Mil-OA)	12/2020 - present
Victoria Chapman, Gareth Hathway, Stephen Woodhams	MRC	Mechanistic studies of opioid-induced exacerbation of chronic pain responses	2022-2025
Victoria Chapman	Versus Arthritis	Harnessing the potential of 17-HDHA a novel biomarker of OA pain status	2021-2023
Victoria Chapman (PI)	Advanced Pain Discovery Platform UKRI Chapman	MICA: Exploiting specialised pro-resolution molecule mediated analgesia to identify novel targets for the treatment of chronic pain	2022-2025
Victoria Chapman (Co-I) Jones, Birmingham (PI)	Advanced Pain Discovery Platform UKRI	MICA: Synovial fibroblast pain pathotypes: A roadmap to understanding and targeting the complexity of patient-reported joint pain in osteoarthritis	2022-2025
Weiya Zhang	FOREUM Foundation	Comorbidities in osteoarthritis (PI)	01/10/2019-31/03/2023
Weiya Zhang	FA	Foot/ankle OA and neuro-degenerated conditions in ex-footballers versus general population (PI	01/05/2019-31/12/2023
Weiya Zhang	Health Technology Assessment	What is the clinical and cost-effectiveness of using a goal-directed allopurinol-based treat-to-target protocol in people with recurrent gout attacks? (CoI)	01/09/2018-30/04/2025