Versus Arthritis invites you to the 3rd Annual Pain Research in the UK Virtual Conference

Wednesday, July 14th, 2021

We are delighted to announce that our keynote lecture will be delivered by

Professor Emily Jefferson & Professor Tim Hales

University of Dundee

Hosted by

PAIN CENTRE VERSUS ARTHRITIS at the University of Nottingham

NIHR | Nottingham Biomedical Research Centre

PROGRAMME

Morning Session

Auditorium

9:00 – 9.30 Registration & Online orientation

9.30 – 9.40 Introduction - Professor David Walsh, Co-Director Pain Centre Versus Arthritis.

9.40 – 9.55 Welcome Address - Dr Neha Issar-Brown, Director of Research Versus Arthritis

10:00 – 10:40 Elevator Pitches x 1-4 (PRE-RECORDED 5min pitch + 3min questions)

10:40 – 11:00 Coffee

11:00 – 11:40 Elevator Pitches x 5-8 (PRE-RECORDED 5min pitch + 3min questions)

11.40 – 12.25 Oral Poster Presentations x 5 (PRE-RECORDED 5min presentation + 3min questions)

12.25 – 12.55 Networking Lunch & Oral Poster Prize Voting Opens

Afternoon Session

Break Out Rooms

12.55 – 13.25 Parallel Poster Presentations – Session 1 & 2 (3min presentation + 2min questions)

13.30 – 14.30 Workshops x 5

1. **Big data**
2. **Pain measurements, assessment, QST and outcome**
3. **Phenotyping**
4. **Molecular pain mechanisms**
5. **New approaches to treatment**

14.30 – 14.40 Coffee & Close of Oral Poster Prize Voting.

Plenary Lecture

14.40 – 15:40 Plenary Lecture - Professors Emily Jefferson & Tim Hales, University of Dundee**

Hosted by

Title: Big data for patient benefit: opportunities for pain research

Break Out Rooms

15.45 – 16.15 Parallel Poster Presentations – Session 3 & 4 (3min presentation + 2min questions)

Auditorium

16.20 – 16.30 Poster Prize Award

16:30 – 17.00 Workshop Round-Up and Conference Close

(** Sessions will be recorded)

Hosted by

Conference Introduction & Welcome

Prof David Walsh - Conference Chair

Co-Director Pain Centre Versus Arthritis

Director of the Advanced Pain Discovery Platform,

University of Nottingham, UK

It is my great pleasure to welcome all our delegates to the 3rd Annual Versus Arthritis Pain Research in the UK Conference, hosted by Pain Centre Versus Arthritis virtually from Nottingham. The ongoing Covid-19 pandemic has disrupted much but emphasised rather than abolished the huge need to better understand and manage chronic pain. As with previous conferences in this series, our programme demonstrates advances being made across the multidisciplinary spectrum. More than that, this is a meeting for interaction, and I encourage you to use the online chats, networking facilities, and the small group workshops to catch up with old friends and find new ones, to hatch and consolidate new ideas. Together we can crack the problems of chronic pain. I hope that by the end of this conference our conference organising team will have helped take you some small way in achieving that ambition.

A special thank you to our Conference Organising Committee

Clare Farmer – Versus Arthritis

Dr Sandrine Geranton – University College London

Professor Edmund Keogh – University of Bath

Professor Marzia Malcangio – Kings College London

Hosted by

Professor David Walsh – University of Nottingham

Professor Frances Williams – Kings College London

Dr Julie Jones-Diette – Conference Co-ordinator

Dr Stephanie Smith – Workshop Co-ordinator

Bismillah Kosser – Conference Administration

Rose Farrands-Bentley – Conference Administration

Hosted by

Versus Arthritis Welcome Address

Dr Neha Issar-Brown, Director of Research Versus Arthritis

Neha joined Versus Arthritis in February 2021 from Fight for Sight, where she was Director of Research, Policy and Innovation, supporting pioneering research to prevent sight loss. She also initiated the framework for the charity's first patient-centred research strategy.

In 2018, Arthritis Research UK and Arthritis Care joined forces taking the best from both the legacy organisations to form Versus Arthritis, covering research, care, services, policy, influencing and impact for people living with musculoskeletal and related conditions. Alongside oversight of the entire research portfolio, Neha will be leading on developing the new organisation's first research strategy, putting the views of people with arthritis at its core. She aims to further enhance the organisation's profile, income and reach, using her network, skills and experience in building high-value, multi-sectorial partnerships. In her new role, Neha aims to ensure research discoveries are rapidly translated into life-changing treatments for people with arthritis and use Versus Arthritis' voice to ensure that the level of investment in arthritis research reflects the burden of the condition that impacts one in six people in the UK.

Her previous roles include Head of Population Health and System Medicine at the UKRI's Medical Research Council (MRC). Neha is an experienced Senior Executive with two decades of experience in health research, funding, governance, international development and policy sectors, spanning multidisciplinary areas including biomedical, health, physical, engineering, environmental, educational and social sciences. Neha has a broad skill base gained within the private, public and non-profit organisations internationally whilst accumulating vast experience of interacting successfully with senior leaders within Government, civil society, academia and industry.

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Elevator Pitches

Abstract 1-4

#1 Dr Maxim Freidin - Kings College London

Genetic and omics studies of pain at King's

Department of Twin Research and Genetic Epidemiology, King's College London, London, UK

Established in 1992 the TwinsUK register was set up to facilitate the study of the genetics of osteoarthritis and osteoporosis. Nowadays, the Department maintains the database of ~14,000 twins, 350,000 biological samples and is one of the most densely phenotyped and omic-typed cohorts in the world.

Early studies focused on estimating heritability in musculoskeletal complaints and common pain phenotypes such as migraine, and determining their risk factors. More recent studies have revealed genetic and epigenetic variants underlying musculoskeletal pain and lumbar disc degeneration and identified biomarkers of chronic pain syndromes using multi-omic approaches.

In collaboration with others, we have carried out the largest to date genome-wide association studies of back pain (BP) and chronic widespread pain (CWP) revealing new loci and providing evidence of genetic factors underpinning the biopsychosocial model of musculoskeletal pain. Serum glycome studies have shown occult inflammation present in BP and CWP. In the EU FP7 supported grant PainOmics, we showed potential biomarker capacity of glycome and proteome for BP. Metabolome studies have demonstrated that steroid hormones are involved in pathophysiology of CWP and the decreased levels of ω-3 fatty acids as a hallmark of fatigue in CWP. Exome sequencing study revealed new pathways underlying heat pain sensitivity. Epigenetic studies provided evidence of the impact of neurological pathways in CWP. The most recent microbiome study showed lack of diversity in the gut microbiome in CWP.

Utilising contemporary genomic techniques such as polygenic risk score, Mendelian randomization and phenome-wide association, we continue to investigate the mechanisms of BP and other musculoskeletal disorders.

#2 Professor Victoria Chapman – University of Nottingham

The impact of anxiety upon osteoarthritis pain and effects upon opioid analgesia

Background & Aims: Anxiety and depression are associated with increased pain responses in chronic pain states. The extent to which anxiety drives chronic pain, or vice versa, remains an important question that has implications for analgesic treatment strategies. To help address this question we undertook a clinical study and then modelled the interaction between anxiety and osteoarthritis (OA) in a rat strain with anxiety-like behaviours (Wistar Kyoto; WKY). WKY rats develop an augmented widespread pain phenotype in the monoiodoacetate (MIA) model of OA.

Methods: Pressure pain detection thresholds, anxiety, and depression were assessed in people with (n = 130) or without (n = 100) painful knee OA. Separately, knee pain and anxiety scores were also measured twice over 12 months in 4730 individuals recruited from the general population. A preclinical investigation of a model of OA pain in normo-anxiety Sprague-Dawley (SD) and high-anxiety Wistar Kyoto (WKY) rats assessed underlying neurobiological mechanisms. 4 experimental groups were used: Anxiety+OA (WKY/MIA); anxiety+no pain (WKY/saline); no anxiety+OA (Wistar/MIA); no anxiety+no pain (Wistar/saline). Adult male rats received a unilateral intra-articular injection of 1mg MIA or saline, and alterations in pain behaviour (paw withdrawal thresholds) and anxiety status (elevated plus maze) were assessed over 21 days. Responses to cumulative doses of systemic morphine were then assessed via in vivo single unit spinal recordings. In a separate group of rats, spinal expression of spinal mu opioid receptors (MOR) was assessed via Western blotting.

Results: Higher anxiety, independently from depression, was associated with significantly lower pressure pain detection thresholds at sites local to ($P < 0.01$) and distant from ($P < 0.05$) the painful knee in patients with OA. Separately, high anxiety scores predicted increased risk of knee pain onset in 3274 originally pain-free people over the 1-year period (odds ratio = 1.71; 95% confidence interval = 1.25-2.34, $P < 0.00083$). WKY rats display a basal anxiety-like phenotype. MIA injection did not significantly alter anxiety in either strain. Augmented pain behaviour in the WKY-MIA model was associated with increased wind-up of spinal neurons, and a decreased response to systemic morphine, demonstrating increased spinal excitability in this model. Ex vivo analyses reveal alterations in MOR expression and increased glial fibrillary acidic protein immunofluorescence in pain-associated brain regions, identifying supraspinal astrocyte activation as a significant mechanism underlying anxiety-augmented pain behaviour.

Conclusions: Pain pressure thresholds and anxiety scores in people with knee OA are highly associated, and anxiety at baseline predicts future knee OA 1 year later. Our clinical data support the investigation of new targets for treating pain in high-

anxiety patients with OA. Morphine has reduced efficacy in rats with anxiety-like behaviour and augmented OA-like pain, with potential implications for clinical prescription of opioids.

#3 Dr Lidia Sanchez-Riera – Pfizer

Measuring patient and healthcare impact of moderate to severe pain associated with OA

Authors: Hannah Stevenson[1], Rachel Russell[1], Greg Coates[1], Peter Clewes[1]; Robert Wood[2]; Theo Tritton[2], Roger Knaggs[2], Alastair Dickson[3,4,5], David Walsh[6]. Presenter on behalf of the working group: **Lidia Sanchez-Riera[1]**

1Pfizer UK, Tadworth, UK; 2Adelphi Real World, Bollington, UK; 3Primary Care Rheumatology & Musculoskeletal Medicine Society, York, UK; 4The North of England Low Back Pain Pathway, Teesside University, Middlesbrough, UK; 5AD Outcomes Ltd, York, UK; 6University of Nottingham, Nottingham, UK

Osteoarthritis (OA) is one of the leading causes of pain and disability in the UK. Nearly three quarters of people with OA report persistent or chronic pain, and many have one or more relevant comorbidities, which may exacerbate pain and functional decline. Pain and disability negatively affect functional independence and daily activities, leading to the reliance on informal care and social services. Most people with moderate to severe OA pain experience work productivity impairment, accounting for an enormous economic loss. However, management of OA pain is heterogeneous in the UK. Patients often cycle in and out of secondary care services multiple times prior to receiving secondary care interventions.

In Pfizer we have an interest in understanding the whole journey of a patient with chronic pain due to OA and identify major gaps for care improvement. To inform on cost-effective healthcare strategies, we are conducting real world evidence research based on primary and secondary care data from the UK. The main objectives are: to describe the total healthcare resource use and direct healthcare costs associated with moderate-to-severe chronic pain in OA; to describe the demographics and clinical characteristics of patients with moderate-to-severe chronic pain in OA; to describe treatment patterns of moderate-to-severe chronic pain in OA in primary and secondary care; to determine time to first surgery in patients with moderate-to-severe chronic pain in OA.

Now more than ever, COVID has demonstrated a clear link between health and economy. NHS England has prioritised musculoskeletal health as the UK recovers from the pandemic. Understanding the challenges affecting health and wealth in society at large is therefore imperative. Besides looking at the physical health of OA patients, at Pfizer we are interested in how their poor health impacts the economy. Consequently, we have looked at quantifying the employee burden of chronic OA pain to an employer through absenteeism and early retirement. And, how such factors cause significant fiscal impact to the government due to lost tax revenues and increased public transfer costs, such as disability and personal independence payments.

Some available results of our research will be shown in poster format.

#4 Professor Nidhi Sofat – St Georges University of London

Identifying biomarkers for pain: What can we learn from Clinical Studies?

Chronic pain covers a wide range of conditions, including primary neurological, rheumatological and psychological disorders. Each condition demonstrates features of chronic pain that can have distinct characteristics, such as central and/or peripheral sensitisation, wet biomarkers and response to therapies. How to identify relevant biomarkers in specific stages of chronic pain which could aid in pain stratification is a major challenge in clinical pain research, which will be explored further in this talk.

Abstracts 5-8

#5 Professor Tony Pickering – University of Bristol

Bristol Anaesthesia, Pain and Critical Care research group – A painful but mercifully transient pitch from an elevator.

Tony Pickering, Professor of Neuroscience and Anaesthesia, University of Bristol.

Our pain research has built from a base in fundamental neuroscience into a multidisciplinary, translational and collaborative grouping. At this meeting we will be presenting studies on primary afferent neuronal properties, mechanisms of transduction and transmission in rodents and humans using novel electrophysiological approaches that will be introduced by Jim Dunham, Anna Sales, Aidan Nickerson and Graeme Newton [1]. We are also interested in how pain is centrally represented and regulated and have deployed opto- and chemo-genetic approaches to investigate the endogenous noradrenergic & opioidergic systems and the involvement of prefrontal cortex in chronic pain models [2-4]. To identify human homologues of these mechanisms we have undertaken a series of functional imaging studies to examine the role of endogenous analgesia and its pharmacology in health and disease [5-9]. This has been extended to include novel translational pain models as assays for analgesic/anti-neuropathic agents as part of the EU IMI Biopain project in collaboration with Eli Lilly. Our human work has developed to include clinical trials of novel anti-neuropathic agents, to harness the power of the 'Children of the 90s' for recall by genotype/phenotype studies and to develop outreach QST methods. We will soon launch a large NIHR funded RCT to try to prevent the development of post-herpetic neuralgia (ATHENA) involving recruitment of 850 patients with shingles from primary care. Finally, we are delighted to be part of the Psycho-Social consortium led by Bath within the Advanced Pain Discovery Platform to which we will be aiming to identify integrative and translational applications from the experimental medicine and cohort workstreams. Our work is currently funded by Wellcome Trust, MRC, BBSRC, Versus Arthritis, Above and Beyond, Eli Lilly and Lateral Pharma.

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#6 Dr Ben Seymour – Oxford University

Why brain learning is central to understanding chronic pain

Abstract: Pain acts as a teaching signal that shapes our normal response to an injury. If you've hurt yourself, pain teaches you what you should and shouldn't do. This learning occurs at multiple levels – nociceptor, dorsal horn, and in the brain. This is good learning - it drives protective and recuperative behaviour that allows us to recover. There is growing evidence to suggest that this process goes wrong in chronic pain, and effectively these mechanisms are over-sensitive and amplify pain i.e. what was an adaptive process becomes maladaptive and prolongs the pain state. We are now starting to understand how the brain contributes to this, and this reveals a new concept of chronic pain as an information-rich state. The significance of this is that it suggest that relearning, and not drugs, is the key to recovery.

#7 Dr Cathy Price - University of Southampton

Interventional Pain Medicine Research for MSK disorders in the UK

Cathy Price 1, Vikki Wylde 2

1 University of Southampton, 2 University of Bristol

Interventional Pain Medicine (IPM) is the management of painful conditions through invasive techniques to block nerves to a painful area through a variety of methods. These offer attractive alternatives to pain medicines, which have multiple issues, when routine conservative care is failing. High quality clinical trials have been lacking leading to withdrawal of funding for certain procedures. Research methods have been inconsistent and the community divided on the outcomes as a result. In the UK there are 6 centres consistently participating in trials, funding is sporadic hindering development of robust methodologies and there has been an undue focus on placebo comparators leading to recruitment difficulties. Active comparators, the use of blinded re-interventions and improved consensus processes on pathways and techniques with robust cost effectiveness analyses will improve confidence in the outcomes (Price 2020, Wilby 2021). To develop further there needs to be greater between-centre collaboration to reduce set up times improve quality of applications and better communication with funders to unlock the potential of IPM.

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#8 Dr Jennifer Beierlein – NIH

NIH HEAL Initiative: National Institute of Neurological Disorders and Stroke's Early Phase Pain Investigation Clinical Network (EPPIC – Net)

Authors: Jennifer Beierlein, PhD, Barbara I. Karp, MD, Rebecca Hommer, MD, Marlene Peters Lawrence, RN, Tjerignimin Adissa Silue, PhD, Clinton Wright, MD

The NIH HEAL (Helping to End Addiction Long-term) SM Initiative is an aggressive, trans-NIH effort to speed scientific solutions to stem the national opioid public health crisis. Within the HEAL initiative, NINDS developed the Early Phase Pain Investigation Clinical Network (EPPIC-Net) to focus on understanding pain mechanisms and developing effective, non-addictive treatments for pain by carrying-out phase 2 clinical trials of novel, non-addictive pain therapies. Ultimately, EPPIC-Net will reduce reliance on opioids by accelerating development of non-addictive pain therapeutics. What is EPPIC-Net?

EPPIC-Net was set up to provide a robust and readily accessible infrastructure with a network comprised of pain experts who provide design, conduct, and data analysis for phase 2 trials built around submitted potential pain therapeutic assets at no cost to the asset provider. EPPIC-Net infrastructure includes a Clinical Coordinating Center, a Data Coordinating Center, and 12 Specialized Clinical Sites with access to broad, inclusive patient populations to provide phase 2 clinical trials incorporating proof-of-concept testing, biomarkers validation, novel study design, and protocol development and implementation.

What type of pain therapeutics can EPPIC-Net accept?

EPPIC-Net seeks innovative non-addictive treatments for any pain condition that lacks adequate treatment. EPPIC-Net evaluates new, as well as repurposed, small molecules, biologics, drugs, natural products, and devices submitted by industry, academic, or other partners for studies across the age and pain condition spectrum. The ideal asset has adequate data to support a phase 2 clinical trial and has an existing IND/IDE or is IND/IDE-ready.

What to know about applying?

EPPIC-Net accepts applications on a rolling basis. The applicant is expected to provide the asset and matched placebo for the study. The asset owner retains intellectual property rights to their asset. It is anticipated that successful phase 2 trials will enable the applicant to continue to phase III studies and further development of the asset outside of EPPIC-Net. Academic and industry researchers from the USA and internationally are welcome to apply.

Oral Poster Presentation

The following will be presenting their work as an oral poster presentation. Voting for the poster prize will be by closed and anonymous delegate vote. Voting will open at the end of this session and run until the end of the afternoon coffee break at 14.40pm. The winner to be announced at 16.20pm

Abstracts

#01 Dr Joao de Sousa Valente – Kings College London

Studying the anti-inflammatory and analgesic effect of Transient Receptor Potential Canonical 5 (TRPC5) agonist (-)-Englerin-A

Authors: Joao de Sousa Valente1, Khadija Alawi1, Sabah Bahrde1, Xenia Kodji1, Dibesh Thapa1, Fulye Argunhan1, Istvan Nagy2, Susan D. Brain1

1Section of Vascular Biology and Inflammation, King's College London, UK. 2Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College London, UK.

Introduction: TRPC5 expression has been found in fibroblast-like synoviocytes and in small-sized dorsal root ganglia neurons (DRG) [1]. On the one hand, TRPC5 blockade enhances synoviocyte secretory activity, on the other hand TRPC4/5 agonist (-)-Englerin-A (EA) induces calcium transients in TRPC5-transfected HEK cells [1]. Hence the overall effect of TRPC5 activity is unclear. Recently, we have found that TRPC5 has a protective role against joint inflammation, in an arthritis model [2]. Here, we studied the effect of EA in the carrageenan model of inflammation and determined its effect on cultured DRG cobalt influx.

Method: Male CD1 mice (~30 g) were lightly restrained and 50 µl of 2% carrageenan (in saline) was injected in the left hindpaw plantar surface. 30 minutes prior to carrageenan treatment, 2, and 4 mg/kg of EA or vehicle (5%EtOh, 10% PEG300, 5% Cremaphor EL in saline) were i.p injected. Animals were tested for paw oedema (callipers) (n=11), at 0, 2 and 4 hours after carrageenan injection and thermal hypersensitivity (Hargreaves test) (n=6) at 0, 1 and 3 hours or mechanical allodynia (manual Von Frey filaments) at 0, 2 and 4 hours (n=8). Animals were sacrificed; paws were severed by the ankle joint and mass will be determined.

WT (n=6) and TRPC5 KO 129S1/SvIm (n=6) mice (20-30g) were euthanised and DRGs (C1–S1) were collected. Primary cultures were prepared as previously described [3]. Coverslips were washed in buffer solution after which, cells were loaded with EA (0.3-100nM) in cobalt chloride solution (CoCl2; 5mM) for 5 minutes at 37°C, followed by incubation with 2.5% β-mercaptoethanol (Sigma). Cells were fixed with 70% ethanol, glycerol-mounted and visualised with a Leica light microscope.

Results: EA inhibited thermal hyperalgesia and mechanical allodynia in a dose dependent matter. Further, EA reduced the volume of carrageenan-induced oedema and the paw weight. In cultured DRG, EA induced a dose-dependent cobalt uptake,

in mainly small-size neurons, which was reduced in cultures from TRPC5-/- mice suggesting that DRG functionally expressed TRPC5 channels.

Conclusions: This study demonstrates an analgesic and anti-inflammatory effect of EA despite its ability to activate nociceptive DRG neurons. Future studies will elucidate the cellular mechanisms behind EA anti-inflammatory and analgesic effects.

Research supported by Versus Arthritis (ARUK 21524).

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#02 Monika Halicka – University of Liverpool

Predictors of pain and functional outcomes following spinal surgery for chronic low back and radicular pain: A systematic review

The success rate of spinal surgeries to treat back pain is highly variable and susceptible to patient heterogeneity. Knowledge of reliable prognostic factors could help identify patients at risk of poor outcomes, and guide preoperative interventions targeting modifiable risk factors. However, evidence synthesis focusing on patients with chronic symptoms, and clear clinical guidelines, are lacking. We aimed to identify and evaluate predictors of pain and disability outcomes of spinal surgery for chronic low back/radicular pain (CLBP).

Searches of electronic databases (01/1984-04/2020) and reference lists returned 2465 unique citations. Studies including adults with CLBP lasting ≥3 months who had first elective lumbar spine surgery, with preoperative prognostic factors, and outcomes defined as change in pain or disability from baseline to ≥3 months follow-up, were eligible.

We included 19 reports (5320 participants), 13 judged to have high and 6 low risk of bias using the Quality in Prognosis Studies tool. Following narrative synthesis of investigated associations, quality of evidence (QoE) was determined using the GRADE framework.

Poor pain outcomes were associated with older age, lower education, and spinal stenosis (low QoE), higher pain, comorbidities, higher pain catastrophising, anxiety, and depression (very low QoE); but not with other demographic and socioeconomic

factors, symptom duration (low QoE), disability, or quantitative sensory testing (very low QoE).

Poor disability outcomes were associated with longer symptom duration in spinal stenosis (moderate QoE), higher job-related resignation, and neuroticism (very low QoE); but not with socioeconomic factors, comorbidities (low QoE), demographic factors, pain, or pain-related psychological factors (very low QoE). The effect of baseline disability was unclear (very low QoE).

Considering low/very low QoE for the identified predictors, we have limited confidence in their true associations with pain and disability outcomes. More confirmatory high-quality evidence is needed to establish reliable predictors of surgery outcomes in patients with CLBP.

Authors: Monika Halicka, Department of Psychological Sciences, University of Liverpool

Rui Duarte, Liverpool Reviews & Implementation Group (LRiG), University of Liverpool

Sharon Catherall, Public Health Policy and Systems / LRiG, University of Liverpool

Michaela Coetsee, Department of Psychological Sciences, University of Liverpool

Martin Wilby, Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool

Christopher Brown, Department of Psychological Sciences, University of Liverpool

#03 Dr Tarnjit Khera – University of Bristol

Specific descriptors of pain in older women with and without spondylolisthesis

Authors: T. Khera, R. Gooberman-Hill, Z. Paskins, T. J. Peters, J. H. Tobias & E. M. Clark

Background: Spondylolisthesis is a spinal condition associated with lower back pain. It is generally agreed that surgical intervention helps any radiating leg pain, but not pain predominately localized to the back. The aim of this analysis was to investigate descriptors of back pain that were used by participants with and without spondylolisthesis.

Methods: 1635 women aged 65+ with back pain in the previous four months were recruited from UK primary care (NRES 18/WS/0061; ISRCTN16550671). Data

included self-reported descriptors of back pain, self-reported frailty measures and basic anthropometry. The outcome was the presence/absence of spondylolisthesis identified from lateral radiographs. Participants with metalwork, malignancies or vertebral fractures were excluded. Logistic regression analyses explored the relationships between each potential pain variable and the presence of spondylolisthesis.

Results: 308/1399 (22.0%) of participants had spondylolisthesis. Compared to participants without spondylolisthesis, participants with spondylolisthesis were slightly older (mean ±SD 74.3years ±5.4 vs 73.4 ±5.6, p=0.007). There were differences in anatomical site of back pain, as those with spondylolisthesis were less likely to have thoracic area pain (OR 0.71, 95% CI 0.51-0.98). Those with spondylolisthesis were less likely to have posterior leg radiation (OR 0.52, 95% CI, 0.32-0.82) but were more likely to have both posterior and anterior leg radiation (OR 1.51, 95% CI 1.15-1.99). In addition, those with spondylolisthesis were more likely to describe their pain as “tiring” (OR 1.30, 95%CI 1.01-1.68), “radiating” (OR 1.46, 95% CI 1.09-1.97), and/or made worse by standing (OR 1.49, 95% CI 1.08-2.07).

Discussion: We believe this is the first in-depth analysis of descriptors of pain in older people with spondylolisthesis and provides proof-of-concept that it may be possible to distinguish between those with and without spondylolisthesis based on their self-reported symptoms. Further studies are required, including qualitative studies to identify additional spondylolisthesis-specific back pain features.

#04 Dr Ian Wilkinson – North Devon Healthcare NHS Trust

Better Out Than in? Genicular Nerve Block Efficacy for Early to Moderate Knee Osteoarthritis

Background and Aims

Knee Osteoarthritis (KOA) is a potentially disabling condition which may affect people of working age, particularly those in manual labour-orientated roles. In this younger age group it is often preferable to delay surgery to prevent the necessity of multiple joint replacement surgeries. To facilitate this, effective treatments are required to ameliorate the pain of the condition and allow sufficient mobility for the individual to adequately perform their activities of daily living. Current treatment modalities have not demonstrated sufficient sustained benefit in pain management of KOA (Bellamy et al 2006).

Method

A retrospective case review was conducted of all patients that were treated with GNB for knee pain at North Devon District hospital pain department over a 7 month

period. Their X-ray images were assessed and selected for review on confirmation of early osteoarthritis in accordance with the Kellgren-Lawrence classification stages 1 to 3. In addition it was stipulated that prior conservative management in the form of physiotherapy and medication had been completed. Ten patients met these criteria and ranged from 48 to 58 years as an all-male cohort. In total of 1ml (40mg) Methylprednisolone and 4ml (5mg/ml) Levobupivacaine was used in each nerve block. All subjects had been evaluated using a numerical pain rating scale (NPRS) and Oxford Knee Score (OKS) to assess function immediately pre-procedure. NPRS had been repeated immediately post-procedure and at 4, 8 and 16 weeks while the OKS was documented at 16 weeks.

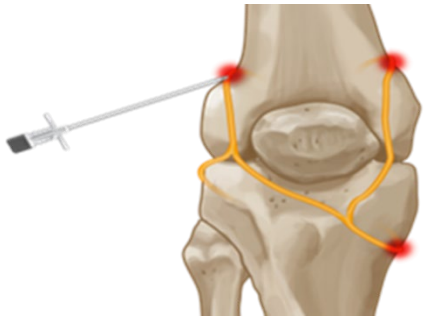

Fig 1: Schematic diagram of a genicular nerve block

Conclusion

Early to moderate KOA resulting in pain and restriction in the younger patient creates a significant burden to the health profession but also Impacts workplace and lifestyle restrictions. The use of GNB in this patient cohort indicated unanimous Improvement in NPRS and OKS over a 16 week time frame. Importantly these patients reported a reduction in occupational restriction and less reliance on medication as secondary outcomes.

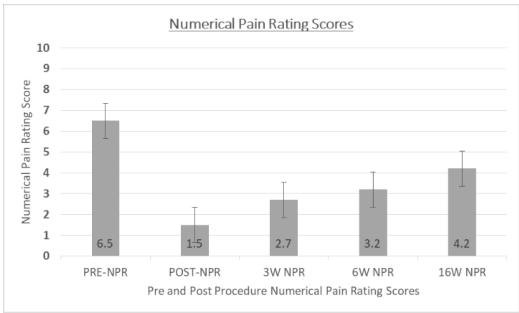

Fig 2 Numerical pain rating score pre- & post-procedure and at 3, 6, & 16 weeks

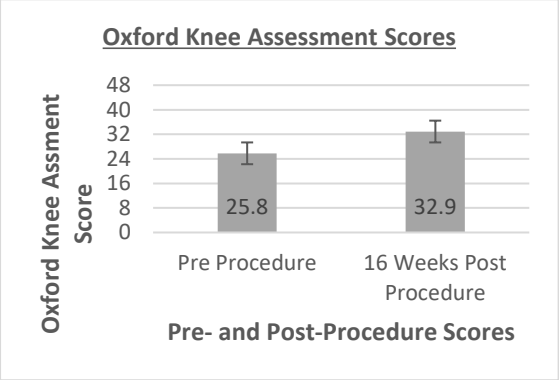

Fig 3 Oxford Knee Score pre- & post-procedure

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#05 Asta Arendt Tranholm - University of Nottingham

Changes to mRNA Expression Localised to Axons of Dorsal Root Ganglion Cells in a Model of Hyperalgesia

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Background and aims

Local translation is a key process underpinning neuronal plasticity, which occurs in sensory nerve terminals. The aim of this study was to explore potential changes in mRNA expression in the axons of dorsal root ganglion (DRG) cells in a model of sensitisation of sensory afferents.

Methods

DRG cells from adult and embryonic mice were treated for 12 or 24 hours, respectively, with 10uM PGE2 to induce sensitisation or saline (control). Stimulation with capsaicin (200nM) evoked intracellular Ca+ transients in the soma of DRG cells which were measured using the Ca+ sensitive dye, fluo-5, and selected mRNAs were quantified using RT-qPCR. Separately, DRG cells were seeded in porous membrane chambers, which allow axons to grow into a compartment separated by a porous membrane. Both compartments were treated with 10uM PGE2 or saline for 12 or 24 hours. RNA was then extracted from the somal and axonal side and prepared for RNA sequencing (RNASeq). Differences in localisation of mRNAs were evaluated by comparing RNA from the axon and the soma using multiple t-tests of upper-quartile normalised transcripts per million (uqTPMs). Effects of PGE2 on mRNA expression in the axon was determined by comparing treated and control samples using DESeq2. Data from embryonic and adult DRGs were compared indirectly.

Results

Capsaicin evoked Ca+ transients were larger in PGE2-treated embryonic DRG cells compared to saline-treated, confirming a functional sensitisation assay. Additionally, there was a significant increase in nerve growth factor (NGF) mRNA in the PGE2-

treated DRG cells, compared to saline-treated. In a separate study using the PGE2 model of functional sensitisation in embryonic and adult DRGs, mRNA expression was compared between the axonal and somal compartment. PGE2-treatment increased NGF mRNA expression in the adult soma, mirroring the qPCR results from embryonic DRGs. There was almost 50% commonality of genes with significantly higher expression in the axon compared to the soma for embryonic (1577 genes with p-value<0.05) and adult mice (2141 genes with p-value<0.05). PGE2-sensitisation was associated with an enrichment of known mediators of nociceptive and inflammatory pathways in the axon, such as chemokine C-X-C motif ligand 4 (Cxcl4), several interleukins (Il6, Il31ra, Il11 and Il1f9) and prostaglandin-endoperoxide synthase 1 (Ptgs1) for either embryonic or adult mice. A significant increase (pval<0.05) in the expression of 23 genes in the axon with PGE2 compared to saline-treated overlapped for embryonic and adult mice. Inflammatory pathways were further highlighted by pathway analysis.

Conclusions

PGE2-sensitised DRGs exhibited localised changes to axonal mRNAs, including increases in known mediators of nociceptive pathways. Novel targets from this functional sensitisation assay may lead to new therapeutic targets for analgesia.

Conflict of Interest

The author has no conflicts of interest to report.

This work was funded by a Versus Arthritis UK Studentship (grant 21586), support from the University of Nottingham International Collaboration fund, support from Arthritis Research United Kingdom (grants 18769, 20777) to the Pain Centre Versus Arthritis, and support from NIH (NS065926) to University of Texas at Dallas.

Ethical Permissions, Mice were housed and bred in accordance with the ethics and animal welfare of the Animal (Scientific Procedures) Act, 1986

Parallel Poster Presentations

(Posters available to view online)

Session 1 & 2: 12.55pm – 13.25pm

Professor Frances Williams, Session 1: Clinical phenotypes and pain mechanisms

Poster Number	Presenter	Organisation	Title
#1	Anne Marshall	University of Liverpool	Diagnosing and determining the contribution of small fibre neuropathy to pain in fibromyalgia syndrome
#2	Cathy Price	University of Southampton	RADICAL trial on radiofrequency lesioning of lumbar vertebra
#3	David Bulmer	University of Cambridge	Modulating visceral nociception to treat visceral pain
#4	Soraya Koushesh	St Georges University of London	Poster title: Development of a novel scoring system for the characterisation of bone marrow lesions in knee osteoarthritis, the osteoarthritis bone score (OABS)
#5	Aidan Nickerson	University of Bristol	An adaptive recall by genotype study for detailed screening of variants within candidate pain genes
#6	Andreea Radulescu	Royal Veterinary College	Investigating pain mechanisms in osteoporotic fractures using an ovariectomised mouse model

Professor David Walsh, Session 2: Signalling

Poster Number	Presenter	Organisation	Title
#7	Martina Morchio	University of Sheffield	The study of miRNAs linked to neuropathic pain with fluorescent in situ hybridisation
#8	Natalie Wong	University of Sheffield	The role of resolvins in chronic pain

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Poster Number	Presenter	Organisation	Title
#9	David Pang	St Thomas Hospital	Interleukin-1 receptor antagonist treatment for refractory complex regional pain syndrome
#10	Oscar Solis Castro	University of Sheffield	The XCL1-XCR1 chemokine axis in pain
#11	Pravallika Manjappa	Royal Veterinary College	Expression of pro-nociceptive factors in joint resident cells and dorsal root ganglia

Session 3 & 4: 15.45pm – 16.15pm

Dr Stephanie Smith, Session 3: Clinical studies

Poster Number	Presenter	Organisation	Title
#12	Maxim Freidin	King's College London	Anthropometric factors modify the risk of chronic back pain in a sex-specific manner
#13	Lidia Sanchez-Riera	Pfizer	Quantifying the healthcare resource utilisation for the management of moderate-to-severe chronic pain among patients with osteoarthritis in England: a retrospective analysis of linked primary and secondary care data
#14	Prof Franklyn Howe	St Georges University of London	MRI and QST measures to predict patient outcome for standard treatments of knee osteoarthritis
#15	Jennifer Todd	Anglia Ruskin University	Using smartphone technology to investigate the associations between internal bodily awareness and pain in fibromyalgia
#16	Janet Deane	Imperial College London	Symptomatic individuals with Lumbar Disc Degeneration use different anticipatory and compensatory kinematic strategies to asymptomatic controls in response to postural perturbation

Dr Sandrine Geranton, Session 4: Neuroscience

Poster Number	Presenter	Organisation	Title
#17	Aerin Thompson	University of Nottingham	The effects of healthy ageing on the number and location of glial cells in the dorsal horn of the spinal cord in rats
#18	Graeme Newton	University of Bristol	Open-Source Solutions for the Investigation of Nociceptor Transduction
#19	Minji Ai	University of Cambridge	Human mesenchymal stem/stromal cells and derived extracellular vesicles reduce pain in DMM mice at 16-weeks
#20	Anna Sales & Jim Dunham	University of Bristol	Recording activity in multiple isolated c-fibres using multisite silicon probes in rat saphenous nerve
#21	Sara Memarpour Hobbi	University of Sheffield	Effect of TNF-alpha antagonist (Etanercept) and interleukin-10 on inflammation, nerve regeneration and neuropathic pain

Workshop Session

The main aim of these workshop sessions is to allow smaller group discussions on specific topics and share and learn from each other's experiences. Sessions will promote discussions and we encourage delegates to interact with the chairs and other delegates.

Workshop No	Workshop Theme	Co-chair	Co-chair	Facilitator
1	Big Data	Emily Jefferson (Dundee)	Tim Hales (Dundee)	Asta Tranholm
2	Pain measurement/ assessment	Cathy Price (Southampton)	Vicky Batchelor (Kennedy Oxford)	Vas Georgopoulos
3	Phenotypes	Frances Williams (KCL)	David Walsh (UoN)	Wendy Chaplin
4	Molecular pain mechanisms	Ewan St John Smith, (Cambridge)	Vicky Chapman (UoN)	Peter Gowler
5	New approaches to treatment	Jennifer Laird, (Lilly)	Nidhi Sofat (St Georges Uni London)	Dan McWilliams

Workshop 1 – Big Data

Chaired by Prof. Emily Jefferson & Prof. Tim Hales

Facilitation – Asta Tranholm

Questions for discussion:

Q1. What are the main barriers to being able to access pain related data?

Q2. What is the most important pain data which is currently unavailable which you would like to see collected?

Q3. What can we do to improve the way pain is collected in routinely collected electronic health records?

Q4. How will big data help people living with pain?

Workshop 2 – Pain Measurements and Assessments

Chaired by Dr. Cathy Price & Vicky Batchelor

Facilitation – Vas Georgopoulos

Questions for discussion:

Q1. What are the current constraints on measuring outcomes?

Q2. What are the subtypes of pain that should be phenotyped when considering outcomes?

Q3. How can we better categorise differing pain phenotypes to enable clearer measurement?

Q4. What are the common methods to measure pain like behaviour in animal models?

Q5. What measures are representative of human pain phenotypes that can best represent differing human pain conditions

Workshop 3 – Phenotypes

Chaired by Prof. Frances Williams & Prof. David Walsh

Facilitation – Wendy Chaplin

Questions for discussion:

Q1. What phenotypic characteristics or classifications do you use in your own research?

Q2. What phenotypic characteristics are most likely to advance our understanding and treatment of pain?

Q3. What would be the core phenotypic data that you would want to collect by all researchers in order to combine data from separate research studies/cohorts to answer to big questions for chronic pain?

Q4. What evidence is needed to justify pain phenotyping research?

Workshop 4 – Molecular Pain Mechanisms

How do we identify clinically relevant targets for the treatment of pain?

Chaired by Dr. Ewan Smith & Prof. Vicky Chapman

Facilitation – Peter Gowler

Questions for discussion:

Q1. How do we select appropriate experimental models and experimental endpoints to identify and investigate the mechanisms of novel molecular targets for the treatment of pain?

Q2. How can we maximise the opportunities of recent advances of transcriptomic studies to identify novel targets for treatment?

Q3. How can we best validate targets arising from pre-clinical studies using human tissue?

Workshop 5 – New Approaches to Treatment

Chaired by Dr. Jenny Laird & Prof. Nidhi Sofat

Facilitation – Dan McWilliams

Questions for discussion:

Q1. Measuring pain in the clinic

Q2. Early versus late – how can we detect patients early enough so you can break the cycle? Analogy to Alzheimer's or Rheumatoid Arthritis

Q3. What did the migraine field do well that other pain areas have not?

Q4. What should he approaches be for pain management?

Plenary Lecture

Professor Emily Jefferson, HIC Director & Chair in Health Data Science

Professor Tim Hales, BSc (Hons), PhD, FRCA (Elect)

University of Dundee

Big data for patient benefit: opportunities for pain research

MRC, supported by BBSRC and ESRC, partners with Versus Arthritis, Health Data Research (HDR) UK and Eli Lilly, are investing are investing in a £24m initiative to establish an Advanced Pain Discovery Platform (APDP), supported by the UKRI Strategic Priorities Fund. The APDP will provide new knowledge about the biological, psychological and social mechanisms which maintain and explain the lived experience of pain. It will:

- uncover shared mechanisms
- tackle inconsistencies in diagnosis and treatment
- provide new pain biomarkers
- identify and validate new therapeutic interventions

This talk will cover the new exciting opportunities following the APDP launch and discuss the aims of the **Alleviate**: APDP **hub** for pain research and Consortium Against Pain in Equality (**CAPE**) (one of four multidisciplinary APDP consortia).

Alleviate is one of several HDR UK Hubs. The HDR Hubs are centres of excellence with expertise, tools, knowledge and ways of working to maximise the insights and innovations developed from the health data. The vision of Alleviate is to transform UK pain datasets to be Findable, Accessible, Interoperable and Reusable (**FAIR**) and provide expert data engineering, to enhance responsible, timely and trustworthy analysis by researchers and innovators, with the aim to improve lives. We will discuss how the research and data services provided by Alleviate will support pain research at scale.

CAPE will acquire a range of comprehensive clinical datasets for inclusion in Alleviate, building on preclinical work that links early life adversity to increased vulnerability to long term pain and adverse effects of powerful opioid pain killers. In five related work packages, CAPE will establish whether exposure to adverse childhood experiences (ACEs) contributes to higher levels of chronic pain in the most deprived communities. A secondary hypothesis is that ACE exposure leads to more

frequent prescriptions of opioid analgesics and may contribute to drug misuse and increasing drug associated deaths.

We anticipate that high quality evidence linking ACEs to chronic pain and treatment outcomes, combined with knowledge of mental health and social support, will provide a basis to develop individualised approaches to pain management and enable public health interventions to improve outcomes.

Biography

Professor Emily Jefferson, HIC Director & Chair in Health Data Science

Professor Emily Jefferson is Chair of Health Data Science and Director of the Health Informatics Centre (HIC) at the University of Dundee and also holds a role at the University of Glasgow. She is the Director of the Alleviate APDP Pain Research Data Hub and HDR Imaging Data Co-lead. Emily leads and collaborates on many HDR UK initiatives including Co-PI on CO-CONNECT, work package lead on the HDR UK Phenomics Portal and the HDR UK Multi-omics Project, and PI on the HDR Scottish Data Federation Project and the HDR UK Biorepository Project.

Emily's main research interest is in innovative methods for the provision of sensitive linked data at pace and scale which meets both data governance requirements and those of the research community. She as a wide range of interests in Health Data Science. Emily is PI of the MRC PICTURES programme which is has built software and infrastructure for managing routinely collected clinical radiology data linked to health care records for the whole of the Scottish Population. She is work package lead on the ENS@T-HT EU project developing ML methods for stratifying patients with different types of hypertension.

In her role as Director of HIC, Emily leads a team of c.60 providing services to over 700 different research projects over the past 5 years. HIC provides expertise in health informatics, data science, data management, governance, machine learning and AI. She is responsible for an ISO27001 certified Trusted Research Environment. HIC is a member of the HDR UK Alliance.

Emily has a degree in Biochemistry, a PhD in Bioinformatics and was employed as a post-doctoral researcher in Bioinformatics following her PhD. She then left academia to work in the finance sector. In industry she gained extensive experience of using "Big Data" and leading the delivery of large software and hardware projects. Emily then took a career break to solo cycle from New Zealand to the UK over 1 year.

Professor Tim Hales, BSc (Hons), PhD, FRCA (Elect)

Tim Hales graduated with a BSc (Hons) in Physiology from King's College London in 1986 and a PhD from the University of Dundee in 1990. He completed postdoctoral training in the Department of Anesthesiology, University of California in Los Angeles and in 1997 was appointed Assistant Professor at the George Washington University (GWU) in Washington DC where he gained tenure in 2002. He became Professor in the Departments of Pharmacology and Anesthesiology & Critical Care Medicine and Director of Research in Anesthesiology at GWU in 2006.

Tim returned to Dundee in 2009 as Professor of Anaesthesia and non-clinical head of the Division of Neuroscience. He was elected Fellow of the Royal College of Anaesthetists in 2011 and was appointed Associate Dean in the School of Medicine in 2017. His research group studies the mechanisms of action of anaesthetics and opioid analgesics, drugs that modulate neuronal communication through ion channel modulation. Tim's goal is to improve anaesthesia and analgesia by educating future researchers and anaesthetists and identifying molecular targets responsible for the desirable and detrimental effects of anaesthetics and analgesics. His research has received support from the Wellcome Trust, Tenovus Scotland, the National Science Foundation, the National Institutes of Health (USA), and the National Institute of Academic Anaesthesia (UK).

Recently, Tim established the UKRI/Versus Arthritis funded Advanced Pain Discovery Platform Consortium Against Pain Inequality (CAPE). CAPE is a group of researchers and their patient partners examining the impact of adverse childhood experiences on chronic pain and responses to treatment in later life. Tim is also a co-investigator on Alleviate – The APDP Pain Research Data Hub, led by Professor Emily Jefferson.

Appendices

Poster Presentation Abstracts

POSTER #01

Diagnosing and determining the contribution of small fibre neuropathy to pain in fibromyalgia syndrome

Anne Marshall University of Liverpool

Fibromyalgia is a highly prevalent condition characterised by chronic widespread pain, insomnia, fatigue and cognitive difficulties. Historically fibromyalgia has been considered a central pain syndrome, with evidence from brain imaging studies identifying region-specific changes in volume, activity and connectivity. However, over the past 5 years several studies have demonstrated small nerve fibre pathology in a sub-group of patients with fibromyalgia along with small nerve fibre dysfunction which coincides with sensory phenotypes. These findings suggest a possible non-central neuropathic pain origin in a subset of patients.

Skin biopsy is considered the reference standard for the assessment of small fibre neuropathy and has been advocated for use to diagnose small nerve fibre pathology in patients with fibromyalgia. However, this assessment is invasive and requires specialist diagnostic facilities. Corneal confocal microscopy (CCM) is a non−invasive, time−efficient and a repeatable method of imaging small nerve fibres (in the cornea) which allows for detailed quantification without the need of an invasive procedure.

This study will determine whether in people with fibromyalgia, the presence of small fibre neuropathy can be detected by CCM with similar accuracy to intra-epidermal nerves in skin biopsy. We will also utilise quantitative sensory testing (QST) to determine pain phenotypes and how they are related to small nerve fibre deficits. Additionally, we will also directly measure nerve function through microneurography and determine whether features of nociceptor hyperexcitability associate with distinct neuropathic pain phenotypes. A small subset (n=28) will have a 1-year longitudinal analysis detailing any change in the structure and function of small nerve fibres.

In this study, 77 patients with fibromyalgia and 50 control subjects will undergo anthropometric and biochemical testing, neurology assessment and questionnaires along with CCM, QST, autonomic and skin biopsy assessment, with a sub-group undergoing additional microneurography and longitudinal analysis. We envisage preliminary results in the coming months.

We anticipate in determining how the structure and function in small nerve fibres relates to pain relieving treatment will promote more targeted medicine.

POSTER #02

The Radical Trial on Radiofrequency Lesioning of Lumbar Facet Joints: Trial Protocol

Vikki Wylde 1 , **Cathy Price 2** , Nadine E Foster 3 , William Hollingworth 1 , Lucy Culliford 1 , Chris Rogers 1 , Kate Ashton 1 , Andrew Moore 1 , Neil Orpen 4 , Ashley Blom 1 , Barnaby Reeves1

1 University of Bristol ; 2 Solent NHS Trust; 3 University of Queensland , 4 Ridgeway Hospital, Swindon

Whilst chronic low back pain is very common and most patients require primary care management only, a subset with localised low back pain are referred for radiofrequency denervation (RFD) of the small nerves to the lumbar facet joints. Whilst there have been many trials either they have been of low numbers or there have been sufficient design flaws to question the conclusions reached. Concerns are regarding entry criteria lack of standardisation of the technique, recruitment and retention of participants and statistical analysis such that NICE recommended a high quality trial in this area (NICE 2016) . RADICAL aims to investigate the clinical and cost effectiveness of RFD for chronic, moderate severe LBP.

The trial protocol was agreed through a consensus process (Price 2020) based upon the National Low Back Pain Pathway and International and National guidance on best practice in the procedure (Eldabe 2020, Cohen 2020) .

The trial design is that of multicentre pragmatic, placebo double-blind controlled trial with an internal pilot to check for recruitment and process issues and a cost effectiveness analysis.

Recruitment will be ahead of the diagnostic Medial Nerve Branch Block (MNBB). The internal pilot will be carried out using recorded interviews investigating recruitment and potential risk of drop out. The entry point is 60% pain relief on a diagnostic block. Participants will be offered to swap to the alternative procedure (either sham or real) after the primary outcome time point on a Numerical Rating Scale (NRS) at three months. Cost effectiveness analysis will estimate the discounted cost per quality adjusted life year and incremental net benefit of RFD over a 2 year follow up period.

It is estimated that recruitment will take 18 months over 20 centres with 25 months follow up and 8 months data analysis/write up.

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POSTER #03

Modulating visceral nociception to treat visceral pain

David Bulmer University of Cambridge

Pain is a leading cause of morbidity for patients with inflammatory bowel disease (IBD). For many, pain persists during remission highlighting a need to further optimise drug therapy for the treatment of pain in addition to inflammation. The activation of pain sensing nerves (nociceptors) by mediators released during inflammation is a principal cause of pain during flare with the subsequent sensitisation of nociceptors promoting visceral hypersensitivity which sustains pain during remission. To identify the mediators key to nociceptor activation in IBD (and other GI diseases), we compared mediator expression in patient biopsy samples, with the ability of supernatants generated from these samples to stimulate nociceptors. Using this system, we identified macrophage metalloelastase (matrix metalloproteinase-12, MMP-12) as a putative mediator of nociception in IBD patients and confirmed the pro-nociceptive effects of MMP-12 on gut nociceptors in mouse and importantly human tissue. Follow-up studies demonstrated an inhibitory effect of MMP blockade on supernatant induced afferent activation and marked increase in intracellular [Ca^{2+}] in DRG neurons to MMP-12. Our data demonstrates for the first time the excitatory effect of MMP-12 on nociceptor signalling and suggests a key role for MMP-12 in visceral nociception during inflammatory bowel disease.

POSTER #04

Development of a novel scoring system for the characterisation of bone marrow lesions in knee osteoarthritis, the osteoarthritis bone score (OABS)

Koushesh S, Shahtaheri SM, McWilliams DF, Walsh DA, Sheppard MN, Westaby J, Haybatollahi SM, Howe FA, Sofat N

Intro Bone marrow lesions are well described by magnetic resonance imaging (MRI) and are associated with pain in osteoarthritis (OA). However, not much is known about their histological changes and how these contribute to pain in OA. We have looked at various histological changes and developed a novel scoring system for the characterisation of BMLs in knee joint, the Osteoarthritis Bone score. Methods Tissue was harvested with full informed consent at total knee replacement (TKR) from 10 participants with knee OA defined by ACR criteria. MRI of the joint identified BML and non-BML tissue which were biopsied in relation to the scan in the TKR group. 10 non-arthritic post mortem (PM) controls were aged and gender matched to the OA TKR group for histological analysis. Additional 163 TKR and 23 PM cases were used to further observe the histological changes. Samples were decalcified and stained by Haematoxylin and Eosin (H&E) and Safranin O/Fast green for tissue morphology. Sections were scored for chondropathy using the Mankin grading system and histological features of BMLs were graded as (0) absent or (1) present and summed to give a total OABS score. OABS was validated by Rasch analysis and sensitivity to distinguish TKR from post mortem samples. Results We identified 7 histological changes associated with BMLs in knee OA including cysts, fibrosis, thickened trabeculae, hypervascularity, loss of tidemark integrity, cartilage island within the bone and infiltration of inflammatory cells. OABS displayed good reliability (Cronbach alpha= 0.676), performed well as a measurement tool, and displayed a 2-factor structure (trabecular/non-trabecular), with moderate correlation between the 2 factors (r=0. 56). OABS scores were higher in TKR than in post-mortem cases (mean difference 1.5, p=0.0026). Conclusion Histopathological changes associated with BMLs in knee OA can now be identified and quantified using the OABS. Histopathological features underlying BMLs might represent 2 inter-related pathological processes affecting trabecular and non-trabecular structures. OABS is a valid tool to assess for OA BML pathology and can be used assess the impact of novel treatments that seek to modify bone structure/function in knee OA.

POSTER #05

An adaptive recall by genotype study for detailed screening of variants within candidate pain genes.

Nickerson et al., University of Bristol

Human genetic studies of pain are essential for clinical understanding and the discovery of novel therapeutic targets. However, genome wide association studies (GWAS) rarely identify allelic association with genes known to have a mechanistic role in nociceptor function, such as Transient Receptor Potential A1 (TPRA1). One explanation is that the large numbers of participants required to detect associations is prohibitive for performing detailed quantification of pain.

In recall by genotype studies, individuals of known genotype are recruited for detailed phenotyping. This allows for testing of specific hypotheses of associations between individual alleles and pain. However, to correctly power the study requires a strong hypothesis of the impact of an individual allele to a specific effect, which is often difficult to estimate. Within clinical drug trials, this challenge is often addressed with adaptive study designs to evaluate the probability of experimental ‘success’ at planned interim assessment. These interim assessments may result in adaptations of the study design such as study termination and altered recruitment. This approach has utility here given the difficulty in estimating potential effect sizes in allele-pain associations

We have developed an adaptive screening paradigm, within the recall by genotype design. We will screen for associations between common alleles within *TRPA1* and pain sensitivity using quantitative sensory testing. At pre-planned interims, a small subset of an individual allele group is compared to a common 'control' allele group to decide whether to recruit the full cohort, or to test an alternative allele group. This design allows hypothesis led screening of alleles coupled with complex traits which is applicable across genetic research.

POSTER #06

Investigating pain mechanisms in a mouse model of osteoporosis

Andreea Radulescu[1], Xiang Li1, Amy Fisher 2, Chantal Chenu1

1 Skeletal Biology Group, Comparative Biomedical Sciences, Royal Veterinary College, London, UK

2 Transpharmation Ltd, London, UK

Osteoporosis affects mainly women over the age of 50, increasing their risk of fragility fractures perpetuated by low bone mass density and bone microarchitecture changes. Commonly occurring in the femoral neck and vertebrae, particularly vertebral fractures are often undiagnosed resulting in prolonged chronic pain. Despite availability of therapeutic interventions for the osteoporotic bone loss, there is an unmet clinical need for better analgesics targeting bone pain.

We aim to study bone pain in postmenopausal osteoporosis before and after fracture. To mimic postmenopausal bone loss, bilateral ovariectomy (OVX) was performed in both young adult (10 weeks) and aged (30 weeks) mice. Nociception was assessed using evoked and naturalistic behaviours. At endpoint, serum oestradiol and the nerve markers brain-derived neurotrophic factor (BDNF) and neurofilament light (NF-L) were measured using ELISA assays.

Mechanical allodynia was significantly decreased in both Sham and OVX when compared to unoperated controls in weeks four and five post - surgery, but while the sham group recovered this sensitivity six weeks post-surgery, the OVX group did not. In both young and old mice, the mechanical withdrawal threshold was significantly decreased from the baseline in the first four weeks post-surgery but there was no statistically significant differences between Sham and OVX groups. Thermal hyperalgesia and naturalistic behaviours (nesting and burrowing), were not affected by OVX regardless the age. The serum levels of BDNF 6 weeks post OVX in young mice were decreased (2.6 times) compared to Sham but this was not statistically significant. In old mice, the serum levels of NF-L were not significantly changed between OVX and Sham groups. Finally, there were no significant decreases in circulating oestrogen levels between OVX and Sham, suggesting that this OVX model may not be adequate to assess the effects of oestrogen deficiency on bone pain, despite reproducing the bone loss observed after menopause.

Our data show limited evidence of pain after OVX suggesting that the bone loss induced by OVX may not be the main mechanism driving this pain. Further work is needed to determine whether oestrogen deficiency contributes to skeletal pain in osteoporosis.

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POSTER #07

miRNAs linked to chronic neuropathic pain in humans: a study using fluorescent in situ hybridisation

Martina Morchio, David Collier, Emanuele Sher, Dan Lambert, Fiona Boissonade

University of Sheffield

Chronic neuropathic pain is a debilitating condition affecting up to 8% of the adult population in the UK[3]. It arises following a lesion or disease of the somatosensory nervous system, and may be caused by trauma or conditions such as cancer and diabetes. The pathophysiology is complex and involves a wide range of processes, including alteration of neuronal excitability and synaptic transmission, dysregulated intracellular signalling, and activation of pro-inflammatory immune and glial cells. This can lead to sustained neural activity or loss of inhibitory control, resulting in a persistent sensation of pain[2]. Understanding the molecular mechanisms underlying these processes is crucial to improve the therapeutic options currently available to treat neuropathic pain.

In the past decade, multiple microRNAs (miRNAs) – small non-coding RNA – have emerged as regulators of neuropathic pain development. They act by binding to target mRNAs and preventing the translation into proteins. Due to their short sequence (around 22 nucleotides in length), miRNAs can have hundreds of targets and regulate several pathways[1]. In particular, miR-29a and miR-500a are correlated with symptoms of pain in neuromas from patients affected by lingual nerve injury. Using bioinformatic tools, a list of their potential target genes has been identified, including potassium channels, cytokines and chemokine receptors[4].

The aim of this study is to characterise these miRNAs and validate their potential targets. Fluorescent in situ hybridisation (FISH) allows localisation of miR-29 and miR-500 within the neuroma tissue, facilitating identification of the cell types that express these miRNAs. This will enable us to further investigate the correlation between the expression of miR-29 and miR-500 and the presence and severity of neuropathic pain, leading to a better understanding of the complex mechanisms underlying the establishment of chronic neuropathic pain.

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POSTER #08

The role of resolvins in chronic pain

Natalie Wong, Daniel Lambert, Fiona Boissonade

University of Sheffield

A series of findings suggest that resolvins, a class of molecules derived from omega-3 fatty acids, are instrumental in the active process of terminating inflammation. Recent studies have also shown that resolvins can alleviate pain symptoms in pre-clinical models, demonstrating their therapeutic potential in chronic pain. Since resolvins are naturally occurring molecules and are produced endogenously, they may cause fewer adverse side effects than other therapeutics. Thus, resolvins have potential as pain therapeutics, and may help to address the unmet clinical need for effective and safe pain medications. Therefore, my project aims to explore the role of resolvins in chronic pain, and how they interact to reduce inflammation and pain.

Dental caries can lead to inflammation in the tooth pulp and spontaneous pain, but not all patients with carious teeth report symptoms of pain. By comparing resolvin receptor expression in human tooth pulp tissues from patients with and without pain, we hope to identify resolvin receptors that may be relevant to pain. The first aim of the studies presented in this poster was to validate antibody specificity using human umbilical vein endothelial cells (HUVECs), which have been previously shown to express the resolvin receptors BLT1, GPR32, ChemR23, and ALX/FPR2. The second aim was to explore the correlation between resolvin receptor expression and inflammation and pain in human tooth pulp tissues.

The presence of BLT1, GPR32, and ChemR23 transcripts in HUVECs was confirmed using qPCR, and clear, positive immunocytochemical labelling for these receptors was also present in the cells. BLT1 protein expression was also identified in HUVECs by western blot. Currently, work is being undertaken to knock down BLT1 expression in HUVECS via siRNA transfection to further validate antibody specificity.

To date, expression of BLT1 and GPR32 has been identified in human tooth pulp tissues using immunohistochemistry, with BLT1 expression being examined in detail. BLT1 was found in blood vessels and nerve fibres, and further studies were

conducted to quantify BLT1 expression in different groups of tooth pulp tissues. A significant difference in BLT1 expression was found between carious painful and carious non-painful groups. Ongoing work is examining BLT1 labelling in blood vessels and nerve fibres in human tooth pulp tissues.

POSTER #09

Interleukin-1 receptor antagonist treatment for refractory complex regional pain syndrome (INCA Study)

David Pang, Pain Management Centre St Thomas' Hospital London, Andreas Goebel, Clincial Sciences Centre University Hospital Aintree Liverpool

Background

Complex Regional Pain Syndrome (CRPS) is an uncommon but debilitating cause of chronic limb pain that is associated with inflammation and autonomic features. It is usually preceded by trauma but its pathophysiology is not fully understood. Animal models using immunoglobulin transfer from patients with CRPS show increased nociceptive behaviours and paw oedema compared with immunoglobulin from healthy controls. These features are blocked by an interleukin-1 receptor antagonist but not steroids. This suggests that autoimmune mechanisms and interleukin-1 play a significant role in the pathophysiology of CRPS. Anakinra is an interleukin-1 receptor antagonist that may be a potential treatment in refractory CRPS.

Methods

We propose a prospective multicentre phase II study to test the safety and tolerability of anakinra administration in refractory CRPS. 30 adult patients with refractory CRPS will be recruited between two tertiary UK pain management centres over 18 months. Inclusion criteria include CRPS of 18 months to 10 years and they will be offered a 120-day course of self-administered subcutaneously daily anakinra injections.

Results

Primary outcome will be safety and tolerability measured by the proportion of patients with serious or condition specific adverse events. Secondary outcomes will be changes in pain intensity, retention rate, CRPS severity score, Brief Pain Inventory (BPI), Hospital Anxiety and Depression scale (HADS), Patient Health Questionnaire (PHQ)-9 and EQ5D. Limb sensitivity will be measured by quantitative sensory testing and volume measurement by a figure of eight method.

Conclusions

The INCA study aims to determine if anakinra is safe and tolerated and these results will assist in development of a randomised clinical trial to determine its efficacy in patients with refractory CRPS.

POSTER #10

Modelling nociceptive neurons for pain research through the use of neural crest-derived stem cells from the human dental pulp

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Chronic pain affects more than one third of the UK and world populations and arises from multiple aetiologies including ageing, diabetes, nerve injury, arthritis and chemotherapy. Current treatments are ineffective in up to 40% of patients and often have severe adverse effects. Thus, chronic pain represents a major area of unmet clinical need. The limited effectiveness of treatment can in part be attributed to limited understanding of the neurobiology of pain. In addition, there is also poor translatability of findings from animal research through to the clinic. Hence, more relevant tools for modelling human pain are needed to further understand the pathogenesis of pain. The overall aim of this study is to explore the use of human cells that can provide relevant cellular and molecular information for pain medicine translation. The proposed approach is the use of human cells from the dental pulp that resemble neural crest cells, and in turn differentiate them into nociceptive neurons. We have shown that human dental pulp cells (hDPCs) can be used to derive cells with neural crest characteristics (neural crest-derived stem cells: hDPC-NCSCs), as shown by the expression of neural crest markers. We have also established that hDPC-NCSCs are capable of differentiating into neuron-like cells in vitro and into a sensory-like phenotype in a complex co-culture system. In conclusion, human dental pulp cells can differentiate into a neuronal phenotype with the potential to be used as a tool in pain research. Further work is ongoing to refine the differentiation into a clearly defined nociceptor phenotype.

POSTER #11

Expression of pro-nociceptive factors in joint resident cells and dorsal root ganglia

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Osteoarthritis (OA) is a chronic, progressive, degenerative joint disease, resulting in debilitating pain and affecting older adults significantly (Fayaz, Croft, Langford, Donaldson, & Jones, 2016). There exists a complex interplay between different joint components, which plays a role in disease pathogenesis and pain (Cope, Ourradi, Li, & Sharif, 2019; Findlay & Kuliwaba, 2016). The development of synovitis and abnormal bone modelling in OA is known to be associated with the release of pro-inflammatory cytokines, which aggravate disease progression (Cope et al., 2019). Cytokines such as interleukins (IL-1β, IL-6), Nerve Growth Factor (NGF) and Tumour Necrosis Factor (TNFα) are known to be associated with the development of pain and in its sensitisation (Syx, Tran, Miller, & Malfait, 2018). There have been studies showing upregulation of NGF in chondrocytes (subjected to an inflammatory stimulus with IL-1β) (Pecchi et al., 2014). Our aim was to investigate whether joint resident cells (osteoblasts and synoviocytes) and dorsal root ganglia (DRG) can themselves give rise to nociceptive factors when subjected to an inflammatory insult. Human osteoblasts and synoviocytes (from healthy donors) and mouse DRG neurons were cultured in their respective growth media. They were subjected to a 24-hour treatment with 100ng/ml TNFα (all three cell types) or 100ng/ml NGF (DRG neurons) or a combination of TNFα and NGF (DRG neurons). mRNA gene expression of pro-inflammatory cytokines after stimulation with TNFα and NGF was determined, in comparison to the basal levels. TNFα stimulation induced upregulation of mRNA expression of the pro-nociceptive factors (IL-6, COX-2 and IL-1β) in osteoblasts and DRG neurons, but not in the synoviocytes. NGF stimulation of DRG neurons upregulated P2X3, COX-2 and TRPV1; and the combination (NGF+TNFα) resulted in the upregulation of COX-2 and IL-1β). Future work will aim at examining the upregulated factors and their implication in OA pain, to have a better insight into the mechanisms involved and the potential detection of novel targets.

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POSTER #12

Anthropometric factors modify the risk of chronic back pain in a sex-specific manner.

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Background. Female gender is an established risk factor for chronic back pain (CBP). It is unclear, though, what female-specific factors are responsible. Hypothetically, the differences in body proportions between males and females, such as the relative length of the torso to legs, may contribute: the longer torso results in greater moment force to endure by the lower body muscles and lumbar discs. We set out to test this hypothesis using UK Biobank data.

Methods. The sample comprised 222,361 males and 263,602 females of European descend. We applied logistic regression to test the association of CBP with sitting height, standing height, and their ratio while controlling for such covariates as age, BMI, and job involving prolonged standing and heavy lifting. Causality was assessed using mediation analysis and Mendelian randomization (MR). MR-instruments were selected from public GWAS data for sitting-to-standing height ratio, ensuring non-overlap with CBP GWAS.

Results. A weak association between CBP and both sitting and standing height was revealed (OR=1.01, 95% CI 1.01-1.02), while sitting-to-standing height ratio was strongly and positively associated with CBP in males (OR = 14.4 [4.8-42.9]) but negatively in females (OR = 0.14 [0.02-0.38]). Both direct and BMI-mediated risk

effects of the ratio on CBP was found in males; while there was BMI-mediated risk effect and direct protective effect in females. A protective causal impact of sitting-to-standing height ratio on CBP in females was found using MR, but not in males.

Conclusion. The study supports the hypothesis that that different body proportions between men and women are the likely contributory factor to the different risk of CBP between the sexes.

Acknowledgements. The study was carried out under UK Biobank project # 18219.

POSTER #13

Quantifying the healthcare resource utilisation for the management of moderate-to-severe chronic pain among patients with osteoarthritis in England: a retrospective analysis of linked primary and secondary care data

Presenter: Lidia Sanchez-Riera[1]

Authors: Christoph Lohan[1], Hannah Stevenson[1], Greg Coates[1], Robert Wood[2], Stuart Blackburn[2], Theo Tritton[2], Roger Knaggs[3], Alastair Dickson[4,5,6], David Walsh[3]

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Purpose: The healthcare resource burden of osteoarthritis (OA) is driven by appointments with multiple healthcare professionals, surgical procedures, and management of treatment-related complications. Evidence shows increased healthcare economic burden among those with OA compared to those without OA; however, little evidence exists to quantify this burden among those patients with moderate-to-severe chronic pain. This study aims to characterise the healthcare burden of this patient group in the UK compared to general population controls.

Methods: A retrospective, longitudinal cohort design with comparator group was employed using data in England from the Clinical Practice Research Datalink GOLD primary care database linked to secondary care data (inpatient, outpatient, Accident & Emergency [A&E]) from Hospital Episode Statistics. Adult patients (age ≥18 years) with an existing diagnosis of OA of any anatomical site (Read or ICD-10) were indexed between Dec-09 and Nov-17 on a moderate-to-severe pain event (first use of pain-related secondary care services or invasive procedures, or prescriptions [two or more required] indicative of moderate-to-severe pain) occurring within an episode of chronic pain. An episode was defined as a series of pain-related primary and secondary care visits without a 12-month gap. Each case was exact matched to a general population control on age (±1yr), sex, Charlson Comorbidity Index score, general practitioner (GP) practice and linkage eligibility. Healthcare resource

utilisation (HCRU; GP consultations, prescription medications, outpatient appointments, inpatient stays, A&E visits) and associated direct medical costs were observed during 6-, 12- and 24-month follow-up (FU) after and including the index event. A significance level of 0.05 was used for comparisons between cases and controls.

Results: The study cohort consisted of 5,931 patients with OA (57.9% aged ≥65 years, 59.2% female), and an equal number of controls. During the 6-month FU, cases experienced significantly more GP consultations (means: 6.9 vs. 3.0), outpatient appointments (4.1 vs. 0.8), A&E visits (0.2 vs. 0.1) and inpatient stays (0.7 vs. 0.1) compared with matched controls (all p<0.0001). Orthopaedics (cases: 71.3%, controls: 2.6%), physiotherapy (cases: 15.6%, controls: 1.2%) and rheumatology (cases: 8.3%, controls: 1.6%) were the most frequently utilised pain-related outpatient services among cases (all p<0.0001 vs. controls). Cumulative length of stay as an inpatient was significantly longer for cases compared with controls (1.9 vs. 0.4 days; p<0.0001). Similar findings were observed during the FU periods from index event to 12- and 24-months (see Table 1). Total costs incurred by cases during the 6-month FU were significantly higher compared with matched controls (means: £2,576 vs. £371; p<0.0001); by 24 months after index total costs had risen to £6,309 among cases and £1,531 among controls (p<0.0001). Inpatient stay costs accounted for ≈76% (£1,955) of total costs during the first 6 months, of which £1,134 (58.0%) related to inpatient stays for total joint replacements. These observations were largely consistent across the 12- and 24-month FUs (see

Figure *1*).

Conclusions: Patients with OA and moderate-to-severe chronic pain consistently used significantly more healthcare services versus matched controls, making clear the substantial burden to the healthcare system associated with the management of OA pain, both in the primary and secondary care settings. This greater resource use is also reflected in a greater cost burden among cases, predominantly driven by costs of inpatient care.

Table 1. The number of GP appointments, outpatient visits, A&E visits and inpatient stays experienced in the 6, 12 and 24 months following indexing for cases and controls

Mean (SD)	**0-6 months**		**0-12 months**		**0-24 months**	
	Controls (n=5,931)	**Cases (n=5,931)**	**Controls (n=5,931)**	**Cases (n=5,931)**	**Controls (n=4,197)**	**Cases (n=4,197)**
GP appts	3.03 (3.80)	6.86 (5.52)	6.09 (6.85)	12.88 (10.03)	12.22 (12.77)	23.41 (17.90)

Mean (SD)	0-6 months		0-12 months		0-24 months	
	Controls (n=5,931)	Cases (n=5,931)	Controls (n=5,931)	Cases (n=5,931)	Controls (n=4,197)	Cases (n=4,197)
Outpatient visits	0.83 (2.18)	4.10 (3.89)	1.73 (3.96)	7.37 (6.94)	3.50 (8.09)	12.25 (11.89)
A&E visits	0.09 (0.37)	0.22 (0.62)	0.20 (0.63)	0.40 (0.90)	0.38 (0.98)	0.69 (1.40)
Inpatient visits	0.13 (0.55)	0.71 (1.26)	0.26 (0.93)	1.16 (1.76)	0.53 (1.65)	1.80 (2.45)
Cum. LoS (days)	0.35 (4.17)	1.91 (7.56)	0.79 (6.55)	3.15 (10.82)	1.57 (12.95)	4.57 (15.86)

Appts – Appointments; Cum. – Cumulative; LoS – Length of stay; p<0.0001 was observed for the difference in means between cases and controls for each type of healthcare resource use, and across all time periods.

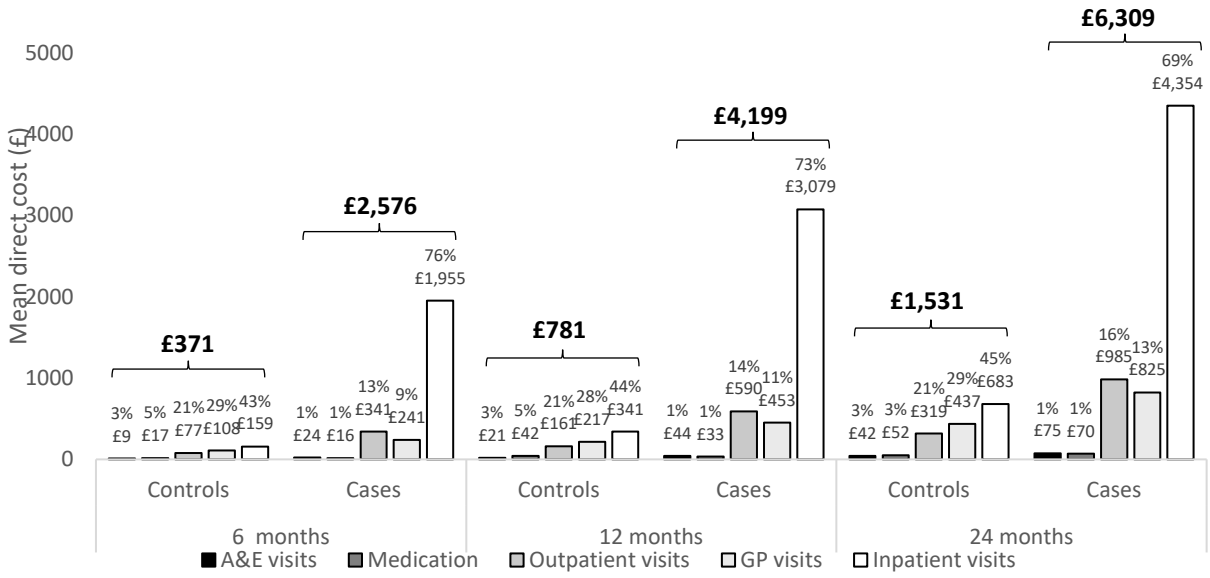

Figure 1. Mean all-cause direct healthcare costs associated with prescription medication, GP consultations, outpatient appointments A&E visits, and inpatient stays, among cases and controls.

p<0.0001 was observed for the difference in mean direct costs between cases and controls across all time periods for each type of healthcare resource use (with the exception of medication) and overall.

(This poster has previously been presented in OARSI Conference, April-May 2021)

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POSTER #14

MRI and QST measures to predict patient outcome for standard treatments of mild and advanced knee osteoarthritis patients

Howe FA, Ejindu V, Heron C, Harrison A, Koushesh S, Sofat N.

Introduction

Structural damage in knee osteoarthritis (OA) is multifactorial, comprising cartilage damage, bone marrow lesions, inflammation and bone-remodelling. Not all patients exhibit a good outcome to current standard treatments. In this study we performed a detailed analysis of knee MRI to assess which pathological factors were associated with a poor response to treatment.

Methods

A retrospective analysis was performed on a dataset of 76 knee OA patients for which we had MRI (sagittal T1w and T2w images in 3 planes) of the most affected (target) knee and patient outcome measures at 12 months. WOMAC pain, stiffness and function were evaluated at study entry for mild OA (N=17) treated with standard analgesics and advanced OA (N=59) treated with total knee replacement (TKR). MRI was assessed using MOAKS over 5 individual anatomical sites (Patella (Pa), Trochlea, Tibia, Femur, and sub-spinous regions) for numbers of bone marrow lesions (nBML), number of regions with cartilage damage (nCD), numbers of osteophytes nOst, and also for overall effusion and Hoffa synovitis (Eff_Syn, Hoff_Syn). Pain-pressure thresholds (PPT) were evaluated with an algometer for the patella and as averaged over the whole target knee (PPT_TK, PPT_Pa), and at the radius of the wrist (PPT_R) to assess for central sensitisation. Clinical parameters included Age, BMI and Hospital Anxiety and Depression score (HADS). Patient outcomes were defined as good or poor according to OARSI criteria assessed from changes in the three WOMAC scores from study entry to 12 months post-treatment. Significant differences ($p<0.05$) of parameters between patients with good or poor outcomes were assessed with t-test or Independent-Samples Median test. Linear discriminant analysis (LDA) and Receiver operating characteristic (ROC) analysis was used to determine classification accuracy of potential parameters that could predict outcome.

Results

Of 17 patients receiving analgesics, 5 responded well and 12 had worsened symptoms at 12 months. There were no significant difference in the baseline BMI, Age, HADS or WOMAC, scores, but patients with poor outcome had significantly higher number of BMLs in the patella (nBML_Pa, Median 2, Range 4 v. Median 0, Range 1, $p=0.044$) and by QST they had significantly lower pain pressure thresholds at the wrist (298 ±108 v. 455±167, $p=0.034$). LDA of nBML_Pa and PPT_R to predict

outcome gave a classification accuracy of 82% with a leave-one-out cross-validation accuracy of 71%.

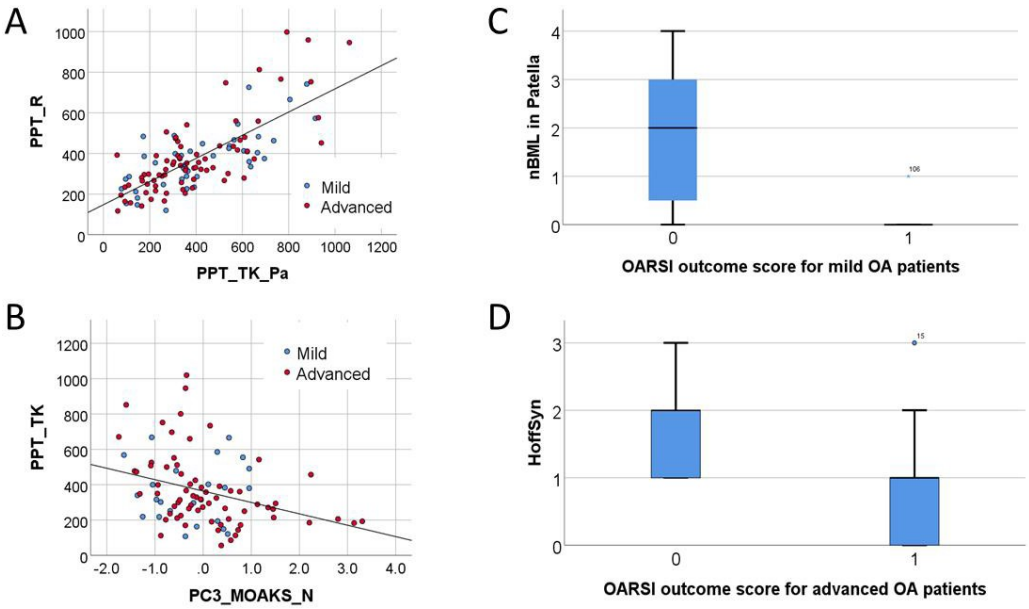
Of 59 patients receiving TKR, 9 patients had a poor outcome. The only significant difference was for greater Hoff_Syn in the poor compared to good outcome group (Median 2, Range 2 v. Median 1, Range 1, p=0.008). ROC analysis of Hoff_Syn gave an AUC = 0.79 for classification. Dividing the patient into groups of Hoff_Syn low (0,1) or high (2,3): 3 of 45 patients (6%) with low Hoff_Syn had apoor outcome, whereas 6 out of 14 patients (43%) with high Hoff_Syn had a poor outcome.

Conclusions

Our data supports the concept of central sensitisation in the mild OA group, who have lower PPTs ata non-affected joint (the wrist) and who do not respond well to standard analgesic treatment. In addition the presence of BMLs in the patella may be indicative of more progressive disease. The patients with the higher nBML_Pa also had lower QST_R scores. For patients undergoing TKR, there were no aspects of MRI observable damage within the regions treated by TKR that related to poor-outcome, whereas high levels of Hoffa synovitis were associated with a worse outcome.

The combination of quantitative sensory testing and detailed assessment of MRI observable damagemay aid patient stratification and understanding treatment response for both mild and advanced OApatients. Further studies with a larger cohort for independent validation is now needed.

FIGURE



POSTER #15

Using smartphone technology to investigate the associations between internal bodily awareness and pain in fibromyalgia

Dr Jennifer Todd.

Dr Michael Lee, Prof Geoffrey Bird, Dr David Plans, Dr Sonya Ponzo, Dr Jane Aspell.

Anglia Ruskin University

Background: *Fibromyalgia* is a disorder characterised by chronic widespread musculoskeletal pain, in addition to fatigue, autonomic disturbances, and hypersensitivity to external stimuli. While the aetiology of fibromyalgia remains unclear, it is increasingly considered a disorder of the central nervous system. *Interoception* refers to the perception of the physiological state of the body. Altered interoceptive processing is thought to be linked to fibromyalgia symptomology, but findings from recent studies have been mixed. Moreover, several interoception tasks are susceptible to physiological and psychological confounds. Accordingly, the associations between interoception and fibromyalgia symptomology require thorough re-examination with new measures. In this study, we are planning to investigate interoception in a sample of adults with fibromyalgia using a recently-developed measure – the Phase Adjustment Task (PAT) – which is administered via smartphone.

Method: In the task, participants' heartrate will be detected using a smartphone camera, and participants will use an on-screen dial to advance or delay auditory tones until they perceive the tones to be synchronous (in-phase) with their heartbeat. We plan to recruit a sample of 300 adults who have been diagnosed with fibromyalgia. Participants will be asked to complete the PAT, the ACR revised fibromyalgia diagnostic criteria, the Revised Fibromyalgia Impact Questionnaire, the Private Body Consciousness Subscale, demographic items, and task-related feedback items.

Implications: Validation of the task will mean that the methodology can be used to examine interoception in adults with fibromyalgia in future studies. This is an important development because the task is more accessible than existing measures (e.g., it can be completed remotely and requires minimal equipment). Future applications include monitoring possible links between internal bodily awareness and fibromyalgia symptoms longitudinally, which could facilitate enhancements in the diagnosing and monitoring of fibromyalgia.

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POSTER #16

Symptomatic individuals with Lumbar Disc Degeneration use different anticipatory and compensatory kinematic strategies to asymptomatic controls in response to postural perturbation

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Introduction: Lumbar Disc Degeneration (LDD) is associated with recurrent low back pain (LBP) (symptomatic). However, in some instances of LDD, people do not experience LBP (asymptomatic). As a step towards understanding why some people with LDD experience LBP and others do not, the primary aim of this study was to examine differences in anticipatory (APA) and compensatory postural adjustments (CPA), between symptomatic LDD patients (LDD pain) and asymptomatic LDD controls (LDD no pain) during postural perturbation. The secondary aim was to determine simultaneous differences in mental health, disability and quality of life status.

Methods: 3T MRI was used to acquire T2 weighted images (L1-S1) from LDD no pain (n=34) and LDD pain groups (n=34). In this observational study, responses to predicted and unpredicted forward perturbations were examined using three dimensional motion capture. A Mann Whitney U-test was conducted to examine group differences in sagittal spine and lower limb kinematics (integrated angular displacements during four established APA and CPA time intervals), anxiety, depression, disability and quality of life.

Results: The LDD pain group exhibited lower hip and knee displacements (p=0.049-0.040) than the LDD no pain group during predicted and unpredicted perturbation. The LDD pain group also exhibited higher compensatory lumbar displacement than the LDD no pain group (p=0.040-0.005) in the predicted condition but there was no difference observed in the unpredicted condition. The LDD pain group experienced higher levels of depression, anxiety and disability (p<0.0001) and lower quality of life (p=0.0001) than LDD controls. Significance: Symptomatic LDD patients are different from LDD controls; they exhibit different kinematic strategies, levels of disability,

anxiety, depression and quality of life. Effective care may benefit from evaluating and targeting these differences.

Acknowledgements: This work was supported by an Allied Health doctoral fellowship grant awarded to JD by **Versus Arthritis** [grant reference 20172].

POSTER #17

The effects of healthy ageing on the number and location of glial cells in the dorsal horn of the spinal cord in rats.

Aerin E Thompson, Stephen G Woodhams, Li Li, Victoria Chapman, Gareth J Hathway, Emma Battell

University of Nottingham

Introduction Glial cells play vital roles in normal and pathological processes, including the induction and maintenance of pain states. Ageing leads to greater susceptibility to pain states, but little is known about changes in the number and activation state of glial cells which contribute to these processes. The aim of this study is to use immunohistochemistry (IHC) to compare markers of astrocytes and microglial cells in young adult and aged rats, determining the effect of healthy ageing on the number and location of glial cells in the dorsal horn (DH) of the spinal cord.
Protocol 40um sections of L5-6 lumbar spinal cord from aged (18-24 months, n=4) and young adult (2-3 months, n=4) male Sprague Dawley rats will be cut on a freezing microtome. 6-8 spinal sections per animal will be immunolabelled for markers of glial cells via established IHC protocols. Non-specific binding will be blocked via incubation in phosphate buffer saline (PBS) containing 5% donkey serum, with 0.3% Triton X-100 for tissue permeabilisation. Sections will be incubated with primary antibody solution of PBS, 5% donkey serum containing GFAP (rabbit, Z0334) to label astrocytes and IBA1 (goat, NB100-1028) to label microglia, both a 1:1000 dilution. Subsequent incubation with donkey anti-rabbit 647 (A-31573) and donkey anti-goat 488 (A11055), both 1:500 dilution. Cell nuclei will be labelled via brief incubation with DAPI (1:500 in PBS) to enable total cell counts and delineation of laminar boundaries. All sections will be mounted onto gelatinised slides and cover-slipped using fluoromount. Slides will be imaged on a Zeiss 200M microscope using DAPI, FITC, and Cy5 filter sets, focusing on the superficial DH. Using ImageJ to analyse immunolabelling. To control for autofluorescence and non-specific labelling, sections from each individual will be processed parallel to primary antibodies omitted. Images from each animal will be collected at 10x and 20x magnification to assess microglial and astrocytic number and morphology. Cell counts/density, laminar distribution, and labelling intensity for each marker will be the primary outcomes. Statistical comparison between groups will be via Mann-Whitney U or T-tests.

POSTER #18

Open-Source Solutions for the Investigation of Nociceptor Transduction.

Authors: Graeme WT Newton (presenting author), Manuel M Perez, Anna C Sales, Gethin Williams, Nathan F Lepora, Anthony E Pickering and James P Dunham (senior author)

All authors from University of Bristol

Nociceptor transduction mechanisms represent an attractive target for novel analgesic development. Functional responses can be measured in heterologous expression systems, dissociated dorsal root ganglion neurons and in nociceptor inhibitory postsynaptic currents. Unfortunately, these model systems cannot recreate the native structure and environment of the nociceptor. Threshold tracking techniques have been developed for the mouse skin-nerve preparation which can detect subtle changes in electrical excitability associated with generator potentials (Sauer *et al.*, 2005).

To build upon this observation, we have developed an open-source solution to single C-nociceptor threshold tracking for the electrophysiology platform, OpenEphys (OE). The RasterTrak OE plugin detects electrically evoked constant latency action potentials and acts upon their presence or absence to modulate the delivered current in a closed loop manner.

We have validated this plugin using the mouse skin-nerve preparation and provide threshold tracking data for multiple C nociceptors. Furthermore, we demonstrate our low-cost custom solution for delivering feedback controlled bidirectional thermal stimulation of nociceptor receptive fields in the skin-nerve preparation. This alpha phase software is built upon the open-source Arduino platform. These developments allow for investigation of natural of nociceptor transducer currents and their pharmacological modulation.

These developments will aid forward and reverse translation in the exploration of pain pathophysiology and analgesic development.

Funding:

This work is funded through a BBSRC-Eli Lilly CTP (GN), an Early Careers Fellowship from VERSUS Arthritis (JD) and a Clinical Lecturers Starter Grant from the Academy of Medical Sciences (JD).

Conflicts of interests

GN is a BBSRC Collaborative Training Partnership Doctoral Student with the University of Bristol and Eli Lilly.

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JPD and AEP have no conflicts of interest to declare.

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Ethical permissions

All animal experimentation was performed in accordance with the Animals (Scientific Procedures) Act 1986.

POSTER #19

Human mesenchymal stem/stromal cells and derived extracellular vesicles reduce pain in DMM mice at 16-weeks

Minji Ai

University of Cambridge

Abstract: Knee osteoarthritis (OA) is a common degenerative joint disease characterized by

joint pain and stiffness. Mesenchymal stem cells (MSCs) treatments have shown promise in improving joint function and OA symptoms in both animal models and human patients. However, it remains unknown if observed pain alleviation effects of MSCs relates to functional changes of pain-sensing neurons. Here, we destabilized medial meniscus (DMM) in mice knee joint to induce knee OA and treated mice with human MSCs. We hypothesized that mouse knee neuron neurons are sensitized 16-weeks following DMM surgery and such sensitization is reduced by MSCs injections at 14-week. To test this hypothesis, we monitored mouse locomotion ability using rotarod test and then performed electrophysiological recordings on retrograde labeled mouse dorsal root ganglion (DRG) neurons in three different mouse groups: sham, DMM and DMM with MSCs injection, and measured their response towards a range of electrical and chemical stimuli. We found that DMM mouse showed a significantly lower locomotion ability at 16-week post-op than sham mice, while such change was not observed in MSCs treated DMM mice. We also observed that DMM knee neurons are more sensitized than sham knee neurons with lower rest membrane potential (RMP), a decreased threshold to fire action potential (AP), and increased acid sensitivity, while MSCs treated DMM knee neurons are less sensitized than untreated DMM knee neurons with higher RMP and AP firing threshold. Thus, we concluded that MSCs improves OA pain through altering sensory neuron activity.

POSTER #20

Recording activity in multiple isolated c-fibres using multisite silicon probes in rat saphenous nerve

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Abstract:

Recordings of activity in intact nerves have provided valuable insights into normal and pathological functioning of the peripheral nervous system. Current high-resolution techniques (e.g. teased fibre recordings) typically utilise electrodes with a single recording site, capturing the activity of a single isolated neurone - and enabling firing patterns to be extracted unequivocally. Such activity may be evoked by electrical or sensory stimulation at receptive fields on the skin, but may also occur spontaneously. In pain research these techniques have enabled a growing understanding of the importance of spontaneous nociceptor activity in generating acute and chronic pain. However, given the low throughput of single electrode approaches, generating group data from specific fibre types is challenging: requiring multiple experimental subjects and recording sessions. This is particularly true when the experimental targets are the small, unmyelinated c-fibres carrying pain information.

To address these challenges we conducted proof-of-principle c-fibre recordings in the intact saphenous nerve of urethane-anaesthetised adult Wistar rats, using multisite electrodes of the type that have become standard in brain recordings. In each experiment, the saphenous nerve was exposed and the epineurium carefully stripped over a ~5mm section. Exposed tissue was then covered in mineral oil. A Neuronexus 32-site silicon probe was inserted at a shallow angle, with the axis of the nerve running close to the probe axis. Data was displayed and recorded using the openEphys recording system. The receptive field of clear units were identified and stimulated using constant current pulses (0.5ms, 0.5mA).

In single, hour long recordings in 5 rats, 34 units with conduction velocities in the range of c-fibres (<1ms^{-1}) were identified via constant latency responses and activity dependent slowing (during either 0.25Hz or 2Hz electrical stimulation). In two animals, 6 c-fibres (5 classified as nociceptors) were well isolated after clustering with the Kilosort 2 algorithm. Recordings were stable with no reduction in action potential amplitude - allowing tracking of spontaneous activity, as well as responses to cinnamaldehyde, von Frey hairs and brush stimuli. The study demonstrates that multisite technology has the potential to greatly increase experimental yields and enhance fibre identification, offering a valuable new tool to researchers studying the peripheral causes of pain conditions.

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POSTER #21

Effect of TNF-alpha antagonist (etanercept) and interleukin-10 on inflammation, nerve regeneration and neuropathic pain.

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Funding: EPSRC

Peripheral nerve injuries are a worldwide problem associated with clinical consequences such as motor and sensory deficits, long-term disability and the development of neuropathic pain. The formation of neuromas and scarring at the site of nerve injury has been associated with neuropathic pain and there is also evidence that pro-inflammatory cytokines at the injury site can stimulate the development of neuropathic pain via a variety of mechanisms.

Previous research in our lab investigated the therapeutic potential of reducing scarring after peripheral nerve repair, via suppression of local inflammation by injection of IL-10 into (epineurial injection) or around the repair site (Atkins et al, 2007). Nerve regeneration was enhanced and scar formation was reduced using IL-10, demonstrating its therapeutic potential for improving nerve regeneration. Studies suggest IL-10 and IL-10 receptor activation may contribute to nerve regeneration through regulation of pro-inflammatory cytokines, or via inhibition of TNF-alpha, respectively.

Subsequent research in our lab has therefore investigated the effects of application of etanercept (TNF-alpha antagonist) at sites of nerve injury and repair. This produced a significant reduction in glial activation in the dorsal horn, indicating reduced potential for development of neuropathic pain, and improved functional recovery (as evaluated by CatWalk gait analysis) by week 3 post-injury. Closer inspection of the regenerated nerves (using a mouse model with axons expressing YFP) revealed moderate improvement in the number of axons crossing the repair site following etanercept application. Our research highlights the potential therapeutic use of etanercept as an anti-inflammatory agent for nerve regeneration and neuropathic pain.

Our further studies have investigated the effects of a combination of IL-10 and etanercept application sites of nerve injury and showed enhanced regeneration, decreased local inflammation at the site of injury, and reduced glial activation in the dorsal horn (vs control group), suggesting a potential synergistic action of IL-10 and etanercept.

Given that our research has only evaluated a limited range of concentrations of IL-10 and etanercept, and that the delivery system (epineurial injection) may be considered clinically challenging, we are currently investigating alternative delivery approaches to provide a more clinically-applicable and controlled local release of IL-10 and etanercept.

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