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SPaRC

Scottish Pain Research Community (SPaRC)
10th Annual Scientific Meeting -
Working together post-COVID

04th Dec 2020

via Hopin

Abstracts for Research Presentations and Posters

We would like to encourage all of our delegates to complete the online evaluation form as this helps us improve the event year on year.
The evaluation form can be accessed from the NRS Pain web page or made available on request.
Once completed, CPD certificates will be emailed to the address provided.

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Introduction and Welcome

I am very pleased to welcome you to this 10th Annual Scientific Meeting (ASM) of the Scottish Pain Research Community (SPaRC)! Those who came to the last nine meetings will remember, I am sure, productive and inspiring days, in which we introduced ourselves to each other, shared our work, and learned about some of the exciting Scottish research that is addressing the problem of pain. 2020 will go down as a memorable year, impacted on very significantly by the current COVID19 global pandemic. We had hoped to meet for our usual face to face meeting in March 2020, but lockdown intervened. When we postponed that, there was a hope that things might have settled by autumn, and we could have a F2F meeting. Unfortunately, we are still in the midst of dealing with COVID, so we have opted for a "mini" ASM, as we felt that whole day for an online meeting would be too much. It is still important to remind ourselves of the importance of research, and of working together as a community – perhaps even more so, in this virtual, and sometimes quite isolated world.

The abstracts that were submitted for this year's ASM, again cover the full scientific range, from the laboratory to the community and encompasses important clinical areas such as addiction, cancer, primary care, neuropathic pain and mental health. This year we have seen a significant and welcome increase in the number of research submissions. Not everyone has been able to move to the new date and format, so we will hear from a select. An important aim of SPaRC is to bring together researchers and clinicians from across the board, so that we can learn from each other, informing our research ideas and outputs, and fostering collaborations.

We also aim to promote the aspirations that:

1. clinical practice in managing chronic pain is informed by current research, and
2. current research in chronic pain is relevant to clinical practice

We are extremely grateful to all of our presenters for their time and expertise in submitting and preparing posters and/or talks. I know they have put in lots of practice to try and ensure that things run smoothly today, but please bear with us, if there are any IT glitches. I am looking forward to hearing the results of these and the associated discussions that are stimulated by them, and thank you in advance for your contribution to these discussions. We continue with the popular "Datablitz" session with all posters giving a very short oral presentation, with a session afterwards for you to "visit" posters and ask individual questions.
We are lucky to have Prof Blair Smith, National Lead Clinician for Chronic Pain giving us an update on some of the many initiatives that are being developed. This year we will still have prizes for both oral and poster presentations, which will be awarded in the final session. Oral presentations will be judged by a team from the steering committee, and you, the audience will vote for the best posters. Good luck to all participating.

I would like to thank the conference organizing committee: Professor Blair Smith, Professor Sue Fleetwood-Walker, Dr Mick Serpell, Professor Tim Hales, Dr Kathryn Martin, Dr Rachel Atherton, Professor Gary Macfarlane, Ms Veronica Davey, Dr Paul Cameron, Dr Daniel Govenden and Lorna Semple. It has been a real pleasure and privilege to work with them in preparing for the meeting. Finally, a very big thank you to our conference organizer Jacqui Pearson, who is our NRS Portfolio manager. She has put in an enormous amount of work to ensure that all runs according to plan: the conference today would not be taking place without her input, and I would personally like to extend my thanks to her.
I hope that despite the virtual nature of the meeting you enjoy the varied research being showcased today and get a chance to participate in discussions.

Prof Lesley Colvin
Chair, Scottish Pain Research Community, Lead, NRS Pain Research

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Oral Presentations

Authors' Names: Pamela Andrews, Lorna Paul, Martijn Steultjens

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Title:
Non-pharmacological management of fibromyalgia: A systematic review of systematic reviews

Background:
Despite the number of guidelines and available therapies, many individuals with fibromyalgia (FM) still experience significant pain and a reduced quality of life. Patient heterogeneity and clinical uncertainty leads to delays in selecting management strategies. There are more than 300,000 publications surrounding the management of FM, thus affecting clinicians' ability to make informed decisions.

Objective(s):
To evaluate the quality of the current evidence from SRs on the effects of non-pharmacological interventions for the management of FM.

Methods:
A systematic search of seven databases (1990-2019) was completed to identify SRs reporting the effects of non-pharmacological interventions on the primary outcomes of pain, function and QoL. Data was extracted according to the PICO framework in addition to intervention prescription where appropriate. Methodological quality was assessed using the AMSTAR-2 instrument (Shea et al 2017).

Results:
Thirty-seven SRs with 245 unique primary studies met the inclusion criteria. Reviews were classified into 6 criteria (1) land-based exercise; (2) water-based exercise; (3) mind-body; (4) electrotherapy; (5) manual therapy and (6) CAM. The results of this review support the use of non-pharmacological therapies to manage FM. Quality of the included SRs were variable with many interventions scoring low to critically low. High quality evidence was found to support the use of land-based exercise and mind-body therapies for the improvement of pain, function and QoL.

Conclusions:
The quality of evidence for the non-pharmacological management of FM is poor, with more than half of the included reviews scoring low or critically low on the AMSTAR-2 instrument. Improved reporting of outcome data and stricter methodological quality will allow stronger recommendations in the future.

Relevance for patient care:
The results found support for many non-pharmacological interventions and in agreement with current EULAR guidelines exercise had the largest effect. Despite these findings the results should be reviewed with caution as with poor reporting on long-term effectiveness it is difficult to conclude whether there would be a long-term benefit from these non-pharmacological strategies.

Oral Presentations

Authors' Names: R Ghose, A Veluchamy, F Cowden, L Colvin
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Title:
Non-fatal overdose in patients with substance misuse.

Background:
There are concerns about rising drug related deaths and prescription analgesics. In 2016, opioids and benzodiazepines were the most prevalent combination of drugs, whereas opioid/ gabapentinoid combinations rose from 0%(2009) to 23% in Scotland. There is limited information about drugs in non-fatal overdose (NFOD).

Objective(s):
To identify characteristics of NFOD patients attending Tayside Substance Misuse Services (TSMS).

Methods:
After Caldicott approval, a Scottish Ambulance Service database of NFOD call outs for TSMS patients between 05/12/2017 to 12/05/2019 was studied. Combined with TSMS medical records, basic demographics, NFOD details, Opioid Replacement Therapy (ORT) prescribing, and fatal overdose data were obtained. Analysis used Microsoft Excel and R Studio.

Results:
557 patients (78% male, mean age (38.4), age range ± standard deviation (18-63 ± 7.95), mean SIMD (Scottish Index of Multiple Deprivation) 1.917) took a NFOD: 46.17% at private property; 42.55% in public places. Repeat NFODs were significantly more likely in males (2.1 vs 1.6, $p<0.006$); Methadone (58%), benzodiazepines (50%) and heroin (43%) were most common. Buprenorphine was used in 16% and gabapentinoids in 11%. Patients were more likely to overdose on prescribed methadone (70%) than buprenorphine(33%) ($p=2.816e-18$).The commonest combination was opioids and benzodiazepines (50%), with almost all gabapentinoids taken with opioids (60/61).15/557 (2.7%) had a subsequent fatal OD.

Conclusions:
NFODs are usually with more than one drug, with methadone being the commonest. Where gabapentinoids were involved, almost all patients had also taken an opioid. Males are at higher risk of repeat NFOD.

Relevance for patient care:
Strategies are needed to reduce NFOD and fatal OD. We have shown that polysubstance use with opioids prescribed for ORT are highly likely to be implicated in NFOD. The minority progressing to fatal OD may reflect benefit from the current approach (timely communication between emergency services and TSMS). Future work should focus on reducing all ODs further.

Oral Presentations

Authors' Names: Martin Dunbar, Jennifer Hislop, Helen Moffat, Mairi Albiston, Alan Gillies, & Leeanne Nicklas

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Title:
A systematic review of the cost-effectiveness of psychological therapies in chronic pain

Background:
Psychological approaches to the treatment of chronic pain are increasingly used and have been shown to be effective at reducing pain and improving mood and function (SIGN 136). There is a greater awareness of the need to demonstrate the cost-effectiveness of treatments.

Objective(s):
To systematically identify, and provide a narrative synthesis of, the literature on the cost-effectiveness of psychological therapies in the treatment of chronic pain.

Methods:
As part of a broader, PROSPERO registered (CRD42019136922), systematic review, MEDLINE, EMBASE, PsycINFO were searched, as well as reference lists from relevant literature reviews, for RCTs and systematic reviews that had examined the cost-effectiveness of psychological therapies/interventions in chronic pain. Inclusion criteria: set in developed countries published after 2012; exclusion criteria: Education only interventions and studies only considering costs, without utility data. A range of data was extracted and the quality of the studies was rated using SIGN RCT and Economic studies checklists.

Results:
Ten studies were identified; nearly all were rated as high quality. They examined a number of different chronic pain conditions. A range of psychological interventions were examined, including; CBT, ACT, MBSR, relaxation and exposure therapy. Eight of the studies delivered the intervention in a group format, whilst two studies used internet delivery.
Comparisons were made with usual care or other active treatments. Various cost perspectives were presented. The majority of studies computed Incremental Cost-Effectiveness Ratios (ICERS) and concluded that the interventions were cost-effective in that they either were 'dominant' over other treatments or costs were less than the specified willingness to pay threshold for pre-defined benefit.

Conclusions:
Most psychological interventions are cost effective with many producing savings as well as improved outcomes.

Relevance for patient care:
The studies were conducted in a number of different countries with different health care systems. This limits direct comparisons

Oral Presentations

Authors' Names: Cassie Higgins, Tim Hales, Saurab Sharma, Inosha Bimali, Paul Cameron, Blair H Smith and Lesley Colvin

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Title:
Epidemiology of chronic pain in rural Nepal

Background:
Researchers in low- and middle-income countries face numerous challenges compared to affluent nations. Nepal is one of the lowest income countries. New Nepali Government health priorities include musculoskeletal pain. There is an urgent need for an improved evidence base to inform service provision. Current estimates of pain prevalence in Nepal are either anecdotal or based on small samples using non-validated instruments.

Objective(s):
To understand better the burden of chronic pain in rural Nepal.

Methods:
In this cross-sectional study, 530 participants from Baluwa, in rural Nepal, were interviewed, by physiotherapy interns, using a door-to-door survey of all eligible community residents. Data were collected using a range of instruments: a specifically-designed screening questionnaire; the Leeds Assessment of Neuropathic Symptoms and Signs; four PROMIS Domain scales (Pain Intensity, Pain Interference, Sleep Disturbance and Depression); the Connor-Davidson Resilience Scale; and the Pain Catastrophizing Scale. All the validated questionnaires were translated to Nepali using rigorous translation methodology.

Results:
Chronic pain prevalence was 54%%, with a 12% prevalence of neuropathic pain (23% of those with chronic pain). Chronic pain was associated with: older age; being married; Hindus; high caste; poor educational attainment; and active occupations. A surprisingly high prevalence of knee/calf pain (47%) was found, with few associations between this pain locus and a range of sociodemographic and clinical characteristics.

Conclusions:
We have shown that chronic pain is highly prevalent in rural Nepal, with particular impact in specific sociodemographic groups. This study will be rolled out to other rural areas. Whilst the Global Burden of Disease studies found back pain to be the greatest cause of years lived with disability, we found knee/ calf pain to be most prevalent.

Relevance for patient care:
Findings can inform the development of pain services, highlight knowledge gaps and direct future research, in light of newly identified Governmental health priorities in Nepal.

Oral Presentations

Authors' Names: Samuel Singleton, Meriam Nefla, Oualid Abboussi, Simon Arthur, Tim Hales

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Title:
Consequences of chronic morphine use in a mouse model of rheumatoid arthritis

Background:
Opioids are considered unsuitable for treating pain in patients living with rheumatoid arthritis (RA) because of their side effects. Despite this recent studies in the USA report extensive long term opioid prescribing to treat arthritis pain.

Objective(s) – please include the "problem" being addressed in lay terms:
We tested morphine analgesia and its role in influencing disease pathology in mice using the collagen antibody-induced model of RA (CAIA).

Methods:
Three days prior to a lipopolysaccharide challenge, male and female wild type and MOR knockout mice were injected (i.v.) with monoclonal collagen antibody to produce symptoms of RA. Mice were then treated with either morphine (3 mg/kg) or vehicle (s.c.) and tested for hypersensitivity as well as being scored for RA severity. After 12 days, hind limbs were processed for histology to examine pathology.

Results:
Morphine had no effect on the mechanical hypersensitivity that developed in all mice. Hypersensitivity to cold water (<2°C) was measurable before the onset of clinical swelling in vehicle treated mice only. Morphine initially caused a prolongation in paw withdrawal latencies despite hastening the onset of clinical swelling; however analgesia quickly diminished due to tolerance. Interestingly, the histology revealed that morphine improved synovial hyperplasia and infiltration whilst having no effect on bone or cartilage degradation. Morphine hastened the onset of clinical swelling despite having no analgesic effect in MOR knockout mice.

Conclusions:
Morphine provides short term MOR-mediated analgesia, which rapidly transitions to hyperalgesia. Morphine worsened swelling independently of MORs, but improved synovial hyperplasia and infiltration.

Relevance for patient care:
Understanding the detrimental and beneficial effects of opioids in RA will enable the development of improved analgesic options.

Oral Presentations

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Title:
Adherence with opioid regimes in patients attending a multidisciplinary chronic pain service.

Background:
Chronic non-cancer pain is common and negatively impacts quality of life. Opioid prescribing for chronic pain is increasing, despite limited evidence of efficacy and safety concerns. Under or over-use of opioids may cause harm.

Objective(s):
To determine the prevalence of non-adherence to opioids in patients attending a specialist multidisciplinary chronic pain service, identify factors that may predict non-adherence and identify patients concomitantly prescribed opioids and gabapentinoids.

Methods:
Patients reporting opioid use completed a questionnaire (self-reported opioid use, efficacy, side effects) and the Brief Pain Inventory short-form. Oral swabs were taken to assess medication adherence; non-adherence was defined as mismatch between opioid prescription and self-reported opioid use or oral swab. Underusers and overusers were compared independently to adherent patients, to identify possible non-adherence predictive factors.

Results:
Commonly prescribed opioids included co-codamol, tramadol, morphine, oxycodone. 34.4% (65/202) reported severe pain (>8). 74.3% (150/202) reported opioids relieved their pain. 26.2% (53/202) were non-adherent; overuse (16.3%) was more common than underuse (12.9%). Patient reporting mainly detected overuse. Oral swabs mainly detected underuse. Underusers had a longer pain duration than adherent patients (p=0.048) and reported less pain reduction from opioids (p=0.047). No factor investigated was associated with overuse. 47.0% (94/200) reported concomitant opioid/gabapentinoid use. 9/202 (4.4%) refused an oral swab.

Conclusions:
Despite chronic opioid use, patients had moderate/severe pain. Non-adherence occurs and is difficult to predict; oral swabs can identify non-adherence not detected by patient reporting. Concomitant opioid/gabapentinoid use was prevalent despite reports of increased risk of opioid-related death from co-prescription of these drugs.

Relevance for patient care:
Oral swabs can identify non-adherence not detected by patient self-reporting alone, are acceptable to most patients and feasible to conduct in pain clinic settings. A lack of factors strongly predictive of non-adherence could support routine monitoring of all chronic opioid therapy patients.

Concomitant opioid/gabapentinoid prescribing is prevalent in this population despite evidence of potential harms.

Oral Presentations

Authors' Names:
Harry L. Hébert, Abirami Veluchamy, Georgios Baskozos, Francesca Fardo, Dimitri Van Ryckeghem, Geert Crombez, David L. H. Bennett, Weihua Meng, Colin N. A. Palmer, Blair H. Smith

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Title:
DOLORisk – Development and external validation of a clinical model to predict new cases of neuropathic pain

Background:
Risk factors for neuropathic pain (NP) are poorly understood, but clinical prediction models can help identify patients who are at increased risk of developing NP.

Objective(s) – please include the "problem" being addressed in lay terms:
The aim of this study was to develop and externally validate a clinical model to predict incident cases of NP (iNP) in a Scottish population.

Methods:
A NP questionnaire was sent to 20,400 participants of Generation Scotland: Scottish Family Health Study (GS:SFHS) and 5,242 participants of GoDARTS and consenting respondents were followed-up with a further questionnaire 18 months later. Questionnaire data were linked to routinely collected NHS medical data by electronic record-linkage. The outcome measure was iNP at follow-up (pain duration ≥3months, DN4 ≥3) compared to persistent no-NP (no pain or DN4<3). The GS:SFHS cohort was split into a trainSet (80%) to develop the model using logistic regression with backward elimination based on AIC, and a testSet (20%) for internal validation. GoDARTS was used for external validation. Multiple imputation was used in both cohorts. Model performance was assessed by model discrimination and calibration in both cohorts.

Results:
Longitudinal data were available for 5,292 people in GS:SFHS (of which 236 had iNP and 3,667 had no-NP), and 1,046 people in GoDARTS (of which 61 had iNP and 510 had no-NP). Independent predictors for iNP were sleep disturbance, adverse childhood experiences, a history of smoking, not being open to new experiences, and lower HRQoL. The model had good predictive power in GoDARTS with an AUC of 0.64 and a calibration slope and intercept of 0.62 and -0.51 respectively.

Conclusions:
This is the first externally validated model predicting iNP and demonstrates the role of psychosocial factors. Further analysis will be conducted to incorporate genetic factors into the model.

Relevance for patient care:
This study will help healthcare providers identify patients at risk of developing NP, so that more effective preventive measures can be taken.

Poster and Datablitz Presentations

Authors' Names: Martin Esposito, Tom Archer and Scott Heald

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Title:
Pre-hospital pain management in adults: a service evaluation of the Scottish Ambulance Service

Background:
Oligoanalgesia has been reported in a number of areas of healthcare. Pre-hospital literature highlights that it exists in the pre-hospital environment. Studies have suggested a lack of formal pain assessment as a causal factor. A number of epidemiological factors are suggested as influencing analgesia provision. No pain related audit has ever been completed within the Scottish Ambulance Service (SAS). Therefore, the current situation is unknown.

Objective(s) – please include the "problem" being addressed in lay terms:
The aim was to use service evaluation methodology to evaluate adult pain management within the SAS. This was in order to establish current practice with a view to identifying areas for improvement.

Methods:
One month of anonymised, retrospective data was extracted from the SAS database. Patients were included if they had a positive pain score recorded in the form of a Numeric Rating Scale (NRS) or had received analgesia. Patients in pain were further identified using a key word search. The data extracted related to pain management and epidemiological factors. Basic statistical analysis was used to analyse the data.

Results:
The SAS attended 40,800 emergency incidents in the chosen time frame with 33.3% of patients being identified as in pain. 66.1% received a formal pain assessment in the form of an NRS. The likelihood of presenting with pain increased with age. 26.1% of patients in pain received analgesia with females more likely to receive analgesia than males. Entonox was the most commonly used analgesic being provided to 44.8% of patients who received analgesia.

Conclusions:
Oligoanalgesia appears present within the SAS with significant numbers of patients not having their pain assessed and significant numbers of patients in pain not receiving analgesia.

Relevance for patient care:
The SAS should consider measures that would address the above and promote the understanding of the importance of pain management. This would ultimately improve patient care.

Poster and Datablitz Presentations

Authors' Names: Taalke Sitter, Patrice Forget

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Title:
Persistent postoperative opioid use in Europe: A systematic review

Background:
In the United States, the postoperative opioid prescriptions have been implicated in the so called "opioid epidemic". In Europe overprescribing or misuse of opioids may be less prominent than in the US even if the opioid prescription rates are rising.

Objective(s):
The aim of this systematic review is to summarize the current published data on the proportion of persistent postoperative opioid use of adults (>18 Years) in Europe.

Methods:

We searched the electronic literature databases MEDLINE (Ovid), Embase (Ovid), PubMed/MEDLINE and Scopus for studies describing opioid use of adult patients (>18 years) at least 3 months after surgery. The rate of opioid users after 3 to 6 months was extracted from the studies and categorised into groups, depending on the type of the investigated surgery. These categories were described and compared in terms of quality and results.

Results:
1307 studies were found, and 12 studies were included in the review. Nine studies investigated the opioid use after total hip or total knee arthroplasties (THA and TKA) and reported opioid user rates between 7.9% and 41% after three months. In all included studies a proportion between 2.0% and 41.0% of patients were opioid users three months after surgery. The level of evidence varies from high to very low.

Conclusions:
To give statements about the persistent opioid use about specific countries or surgery types is not possible. Because of the observed ranges, we cannot exclude a public health problem related to persistent postoperative opioid use in Europe.

Relevance for patient care:
There is a need to document the perioperative opioid use in Europe. This will be the objective of the POSE study (observational study on Pain and Opioids after Surgery in Europe).

Poster and Datablitz Presentations

Authors' Names: Wu S; Macdonald S; Hanlon P; Mair F; Nicholl B

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Title:
Comorbidity of chronic pain, cardiometabolic diseases and depression: a systematic review

Background:
Chronic pain is commonly co-occurred with heart disease, diabetes, stroke, and depression. Most guidelines for treatments are limited to single diseases. Patients with comorbidity tend to receive multiple prescriptions, which raise concerns over drug safety. The combination of mental and physical diseases could bring more challenges. Yet the prevalence of the comorbidity of the three conditions and their effect remains unclear.

Objective(s):
This work will systematically search the published literature on the measurement and relationship between chronic pain, cardiometabolic diseases and depression, and identify the gaps in the published evidence in the comorbidity (the presence of two or more conditions).

Methods:

Published literature on the three conditions was searched systematically in key medical databases: MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science. Studies were selected based on inclusion/exclusion criteria (epidemiology/qualitative studies with a main focus on the three conditions were included; studies of minors, trials/case/animal/intervention/review studies were excluded). After data extraction and quality assessment by modified instruments, included citations were synthesised and summarised.

Results:
Fifteen publications (thirteen studies) involved the comorbidity of chronic pain, cardiometabolic disease and depression were identified. Eight of the studies reported diabetes as the index condition, three examined patients with stroke, and two examined angina. Chronic pain is poorly defined in the studies. The only study examined the prevalence of this combination shows angina, depression and chronic pain co-occurred in 1.8% of the general population. A higher prevalence of depression among patients with cardiometabolic disease was reported to have a higher risk of chronic pain, or vice versa. No data of the health outcomes or patient experience for people with the comorbidity of this combination. And no information about the sociodemographic and lifestyle factors associated with the combination of the three conditions.

Conclusions:
This study identified key evidence gaps regarding the prevalence, health outcomes and patient experience of the comorbidity of chronic pain, cardiometabolic disease and depression, and potentially direct the further research to understanding the comorbidity pattern of this combination and challenges of the comorbidity.

Relevance for patient care:
This study identified the evidence gap of the combination of both physical and mental diseases and gave a clue of the challenges of the disease management of comorbidity.

Poster and Datablitz Presentations

Authors' Names: Allen C Dickie, Erika Polgár, Maria Gutierrez-Mecinas, Andrew M Bell, Kieran A Boyle, Junichi Hachisuka and Andrew J Todd

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Title:
Characterisation of gastrin-releasing peptide receptor (GRPR) expressing excitatory interneurons in the spinal dorsal horn

Background:
Excitatory interneurons account for the majority of neurons in the superficial dorsal horn, but despite their presumed roles in pain and itch, our knowledge of their organisation and function is limited. Interneurons can be assigned to several distinct populations based on the expression of neurochemical markers. We recently demonstrated that those defined by gastrin-releasing peptide (GRP) or substance P (SP) expression, show major morphological, electrophysiological and pharmacological differences (Dickie;PAIN;2019). Another group of excitatory interneurons are those defined by expression of the GRP receptor (GRPR).

Objective(s) – please include the "problem" being addressed in lay terms:
The aim of this study was to characterise GRPR interneurons, and to determine whether they are functionally distinct from GRP and SP cells.

Methods:
Patch-clamp electrophysiology, immunocytochemistry and in situ hybridisation was used to characterise GRPR interneurons.

Results:
Our findings demonstrated that GRPR cells differed electrophysiologically from GRP and SP cells in several ways, including the action potential firing patterns and responses to pharmacological agents. Recordings performed in the semi-intact *ex vivo* preparation (Hachisuka;eLife;2016) demonstrated that GRPR cells respond to mechanical stimulation of the skin. Morphologically GRPR cells could be classified as vertical cells, which differed from GRP and SP cells that display central and radial morphology, respectively.

Conclusions:
Our findings demonstrate that GRPR cells are vertical cells, and that they differ greatly from GRP and SP excitatory interneurons, both morphologically and electrophysiologically. These findings demonstrate that GRPR cells are functionally distinct, and presumably have a specific role in somatosensory processing.

Relevance for patient care:
Spinal processing is crucial to the perception of pain and itch. Furthering our understanding of the circuitry and function of dorsal horn interneurons underlying this processing could reveal novel targets for analgesic development.

Posters and Datablitz Presentations

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Title:
Sex-specific genome-wide association study of multisite chronic pain in UK Biobank

Background:
Multisite Chronic Pain (MCP) prevalence is higher in women than in men. Sex as a biological variable has wide-ranging effects on the functioning of the genome. In the context of genome-wide association studies (GWAS), a "sex-aware" approach to analysis of complex traits is recommended and may provide nuanced insight into sex-specific common genetic variation associated with complex traits.

Objective(s):

1) Carry out a sex-stratified GWAS analysis of MCP in UK Biobank, a general population cohort,
2) Determine similarities and differences between male and female chronic pain.

Methods:
MCP, the number of sites at which a participant experienced pain lasting 3+ months (0-7) was analysed as a quantitative trait using BOLT-LMM in 209,093 female and 178,556 male UK Biobank participants. Male and female MCP GWAS results were meta-analysed using METAL. Genetic correlation analysis was carried out using LD-Score Regression (LDSR) and downstream analyses using FUMA.

Results:
Using genetic correlation analysis, we found that male and female MCP were significantly but not fully genetically correlated with one another, and that there were sex-related differences in genetic correlation with a range of other traits, including sex-specific genetic correlations with psychiatric disorders. Different genes were found to be significantly associated with male and female MCP. More MCP trait-associated SNPs were discovered using the sex-aware GWAS approach than had been previously reported using the unstratified approach.

Conclusions:
The sex-aware GWAS approach proved more powerful than the unstratified approach and identified both new and sex-specific MCP-associated loci and genes.

Relevance for patient care:
The development of chronic pain is not fully understood, and current pharmacological treatments are limited. Fuller understanding of genetic variation contributing to chronic pain has the potential to inform the development of more effective treatments; sex-aware analyses can significantly contribute to this.

Poster and Datablitz Presentations

Authors' Names: Samuel Singleton, **Emily Edelsten**, Kirsty McCaughey, Daniel Baptista-Hon and Tim Hales

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Title:
TRV130 and PZM21 developed as biased opioid analgesics with fewer side effects have incomplete efficacy as mu receptor agonists

Background:
Opioid use in chronic pain is limited by side effects including tolerance, respiratory depression and constipation. These are potentially mediated by β-arrestin2 recruited to active mu-opioid receptors (MOR). Recently, drugs biased towards G-protein activation versus β-arrestin2 recruitment have been developed.

Objective(s) – please include the "problem" being addressed in lay terms:
We examined the efficacies of two of these recently developed biased MOR agonists - TRV130 and PZM21.

Methods:
β-arrestin2 recruitment was measured in PathHunter Chinese hamster ovary cells overexpressing recombinant MORs (DiscoverX). Additionally, the cAMP sensitive pGloSensor-22F plasmid (Promega) was transiently expressed to assay cAMP levels in the same cells. Concentration-response relationships were established for DAMGO, morphine, TRV130 and PZM21 with or without increasing concentrations of the irreversible MOR antagonist βFNA to compare efficacies and potencies as inhibitors of cAMP accumulation and recruiters of β-arrestin2, with full or partial MOR availability.

Results:
Compared to DAMGO, morphine recruited β-arrestin2 in a similar concentration-dependent manner with equal potency but approximately 3-fold lower efficacy (72% ± 6 and 28% ± 4 respectively). By contrast, both TRV130 and PZM21 failed to recruit β-arrestin2 at any concentration tested. All four drugs were maximally efficacious as inhibitors of cAMP accumulation with similar potencies (3.8 ± 1.6 nM, 8.6 ± 1.6 nM, 4.1 ± 2.2 nM and 8.1 ± 1.8 nM respectively). Reducing MOR availability using 30 or 100 nM βFNA reduced the potency of DAMGO by 9- and 57-fold, respectively, without affecting efficacy. The same concentrations of βFNA reduced the potencies of morphine (6- and 23-fold), TRV130 (4- and 58-fold) and PZM21 (6- and 48-fold); however, their efficacies as inhibitors of cAMP accumulation were also greatly reduced.

Conclusions:
TRV130 and PZM21 act as weak partial agonists at MORs potentially giving the false impression of bias and compromising analgesia.

Relevance for patient care:
Despite the possibility of fewer side effects compared to morphine, TRV130 and PZM21 are likely to be weaker analgesics.