Title of Research Project

Respiratory risk among heroin/opiate addicts: exploring poor recognition and testing indices of harm

Lead supervisor’s contact details - can be used by potential applicants wishing to discuss the project

Name  Dr Caroline Jolley
Telephone  0207 848 6302
Email  caroline.jolley@kcl.ac.uk

<table>
<thead>
<tr>
<th>Supervisor 1 name</th>
<th>Dr Caroline Jolley</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervisor 1 telephone</td>
<td>0207 848 6302</td>
</tr>
<tr>
<td>Supervisor 1 email</td>
<td><a href="mailto:caroline.jolley@kcl.ac.uk">caroline.jolley@kcl.ac.uk</a></td>
</tr>
<tr>
<td>Supervisor 1 KCL Department/Division</td>
<td>Centre of Human and Aerospace Physiological Sciences (CHAPS)</td>
</tr>
<tr>
<td>Clinical Academic Group &amp;/or Basic Research Group</td>
<td>CHAPS/Human Physiology</td>
</tr>
<tr>
<td>Trust/BRC</td>
<td>KCL/GSTT BRC (also Clinical Respiratory Medicine, King’s College Hospital and GSTT)</td>
</tr>
<tr>
<td>Trust Position</td>
<td>Physiology and KCH/GSTT Honorary Consultant in Respiratory Medicine</td>
</tr>
<tr>
<td>Supervisor 2 name</td>
<td>Professor John Strang</td>
</tr>
<tr>
<td>Supervisor 2 telephone</td>
<td>020 7848 0438</td>
</tr>
<tr>
<td>Supervisor 2 email</td>
<td><a href="mailto:john.strang@kcl.ac.uk">john.strang@kcl.ac.uk</a></td>
</tr>
<tr>
<td>Supervisor 2 KCL Department/Division</td>
<td>Addictions Department, Institute of Psychiatry, Psychology &amp; Neuroscience (IOPPN)</td>
</tr>
<tr>
<td>Clinical Academic Group &amp;/or Basic Research Group</td>
<td>Addictions</td>
</tr>
<tr>
<td>Trust/BRC</td>
<td>SLaM BRC/U-D</td>
</tr>
<tr>
<td>Trust Position</td>
<td>Professor (Addictions) and Head of Department, National Addictions Centre</td>
</tr>
</tbody>
</table>

Any additional supervisors, contact details and organisation

Dr Michael J Kelleher
Consultant Psychiatrist and Clinical Lead for Lambeth Addictions South London and Maudsley NHS Foundation Trust.
Lambeth Addictions Consortium. 12-14 Brighton Terrace, Brixton London SW9 8DG
Telephone: 020 3228 1500
Mobile: 07813 055783
Fax: 020 3228 1585

Name of NIHR GSTT BRC Cluster the project sits under  Cluster 3 - Population Sciences

Name of Cluster at NIHR BRC and Dementia BRU at South London & Maudsley NHS Foundation Trust and King’s College London  Clinical Disorders
Please include a lay summary of the project explaining how the project will address an important aspect of the interface between physical and mental health (max 250 words)

This project addresses under-recognition of the significant physical health burden of chronic respiratory disease in people undergoing treatment for drug and alcohol addiction. A high prevalence of cigarette smoking, coupled with abuse of other inhaled drugs including heroin, crack cocaine and cannabis, puts this population at high risk of developing life-limiting lung disorders, incurring significant NHS costs. Despite this, chronic lung disease in heroin addicts is frequently unrecognised until a late stage, when options for treatment are limited. Opioids are potent respiratory depressants, and it has been suggested that the co-existence of chronic respiratory disease with chronic opioid-induced respiratory depression increases overdose risk in ageing cohorts of opioid addicts. Smoking-related chronic obstructive pulmonary disease/emphysema, and pneumonia, is commonly found post-mortem following opioid overdose. Our experience in the new SLaM Addictions/King’s College Hospital Lung Health Clinic (supported by King’s Improvement Science) suggests that symptoms of lung disease are often under-reported by clients. This could potentially delay diagnosis, impact on adherence to prescribed treatment and reduce awareness of impending respiratory insufficiency, thus contributing to overdose risk.

This 12-month project will investigate whether heroin addicts undergoing treatment with oral opioid substitution regimens are less breathless than matched (non-opioid-using) control subjects during laboratory-based physiological tests. The research findings will inform preparation of applications for Doctoral Fellowships to investigate barriers to equity of access to treatment of lung disease in this population, and the influence of personal characteristics (age, gender, respiratory disease) and medication characteristics (which drug, dose, route, co- medications, alcohol, etc) on overdose risk.

Abstract of the research project (max 500 words)

Background
Patients treated for heroin addiction die, on average, 15 years earlier than the general population. Although deaths are frequently attributed to acute drug overdose and the chaotic lifestyle associated with drug addiction, chronic smoking-related respiratory disease is a major factor contributing to excess mortality and morbidity. Recent work suggests that exposure to inhaled/smoked heroin is a risk factor for early-onset emphysema, often first diagnosed at an advanced stage, and that this is an important cause of premature death (Walker et al, Chest 2015). Opioid-induced suppression of neural respiratory drive (NRD), coupled with the progression of lung and systemic disease, could also be important factors contributing to the higher rate of opioid overdose deaths observed with increasing age. Our new SLaM/KCH “Lung Health Clinic”, based in the SLaM Community Drug and Alcohol Service, addresses the need to improve recognition and treatment of chronic lung disease in this population, and parity of access to respiratory healthcare in mental illness in general.

Using physiological measures of respiratory muscle electromyogram activity to quantify NRD, we have shown that significant acute respiratory depression is commonly induced by opioid drugs prescribed to treat opioid addiction. Chronically-suppressed NRD in addicts with comorbid chronic lung disease may be associated with an increased risk of acute opioid-induced respiratory depression (Jolley et al, PLOS ONE 2015). Previously we have demonstrated that breathlessness intensity in patients with chronic respiratory disease is closely related to levels of NRD (e.g. Jolley et al, ERJ 2015). Together these observations suggest that late diagnosis of COPD in opioid addicts, and overdose risk, could be explained, in part, by a “blunted” perception of impending critical respiratory insufficiency, as a consequence of opioid-induced suppression of NRD.

Aims & Hypotheses
This pilot study aims to test the hypothesis that breathlessness during a hypercapnic challenge is lower in heroin addicts established on oral methadone treatment than matched opioid-naïve controls, as a consequence of a blunted NRD response to hypercapnia.

Methods
Patient group: 10-12 heroin addicts established on a stable dose of methadone oral opioid substitution therapy, without significant comorbid cardiorespiratory disease (including moderate-to-severe COPD/emphysema).

Control group: 10-12 opioid-naïve subjects matched for age, cigarette-smoking status and spirometry (FEV1%predicted, VC%predicted and FEV1%VC).
Protocol: All subjects will undergo an incremental steady-state hypercapnic challenge to a maximal inspired CO2 of 5% (Reilly et al, Exp Physiol 2013). NRD will be quantified continuously using surface electromyography of the parasternal intercostal muscles (EMGpara), normalised to peak EMGpara recorded during maximal respiratory manoeuvres and expressed as EMGpara%max (Reilly et al, Exp Physiol 2013). Breathlessness intensity will be recorded each minute using the modified Borg scale.

Analysis
Baseline differences in EMGpara%max between groups will be assessed using Student's unpaired t tests. Respiratory depression in the patient group will be defined by the extent of reductions in the slopes of the ventilatory and NRD responses to hypercapnia, compared to controls. Between-group comparisons of breathlessness and other measured variables during hypercapnic challenge testing will be compared using repeated measures ANOVA, with Bonferroni's post hoc analysis for multiple comparisons.

Please provide ONE key reference relevant to the proposed work

Please include a brief breakdown of estimated project timelines.

Month 0 – 1
Training in essential respiratory physiology techniques, in particular hypercapnic respiratory challenge testing and measurement of parasternal intercostal muscle electromyogram activity.
Introduction to the SLaM/KCH Lung Health clinic at Lorraine Hewitt House, from which potential participants in the patient group will be identified.

Months 1 – 10
Recruitment of patients and control group. Complete data acquisition as per research study protocol. 3-monthly Project Meetings with the Addictions Service User Research Group (our PPI group).
From Month 6 onwards, development of external funding applications to support a PhD.

Months 10 – 12
Final data analysis and preparation of manuscript for submission to peer-reviewed journals. Presentation of findings at national and international conferences.
Feedback of findings to Drug & Alcohol Clinic Service Users and PPI group.

What profession(s) is this project suitable for? (eg. nurse, dietician, physiotherapist, pharmacist etc)
Band 6/7 Specialist Respiratory Nurse Band 6/7 Respiratory Physiotherapist ST3+ Respiratory Registrar

Will fellows be formally supported by any of these professions within the supervisory team? Please provide details.
Yes. The Project Supervisor (Dr Jolley) is an academic respiratory physician with a specialist research interest in the physiological basis of breathlessness, working within CHAPS in affiliation with the KCL Respiratory Muscle Research Group. The KCL Respiratory Muscle Research Group is a multidisciplinary group of doctoral and post-doctoral researchers, which includes research-active respiratory physiotherapists, specialist nurses and respiratory physicians. There is, in addition, support from senior non-clinical physiologists with expertise in the physiological basis of breathlessness and assessment of respiratory control mechanisms. Dr Jolley has direct experience in the physiological and clinical assessment of clients under treatment for opioid addiction, through her ongoing research activity and work in the SLaM/KCH Lung Health in Addictions Clinic.

Specify essential/desirable experience, clinical or academic background

Essential experience/skills:
Clinical experience of diagnosis and management of chronic respiratory disease BSc (or equivalent) in a field related to Physiology or Biomedical Sciences Theoretical and practical knowledge of respiratory physiology
Knowledge of standard adult lung function tests Basic knowledge of word-processing and statistics Excellent written and verbal communication skills Excellent time management and organisational skills Enthusiasm for translational clinical research

Desirable experience/skills:
Previous research experience in respiratory physiology or Addictions
Outline the Department/Divisional research training and in-house research support in relation to this project

The Fellow will be directly supported by a highly experienced, multidisciplinary research team of clinicians, clinical academics and physiologists with expertise in respiratory physiology, Respiratory Medicine and Addictions.

The Centre of Human and Aerospace Physiological Sciences (CHAPS), is a Research Division comprising three interlinking research groupings operating under the overarching strategic theme of Human Physiological Function and Adaptation. This proposal, seeking to better understand the impact of heroin addiction on respiratory physiology and function, is a good strategic fit both to the ongoing work within CHAPS and the research training environment therein. CHAPS is led by Professor Stephen Harridge and comprises a full-time tenured staff: 5 Professors, 5 Senior Lecturers and 5 Lecturers with multidisciplinary backgrounds including medicine, physiology, physiotherapy, cell biology, analytical chemistry and sport/exercise science. There are currently 5 externally funded post-doctoral research assistants and ~15 FTE PhD students are registered at any one time. Each student has a first (lead) and 2nd supervisor, and Fellows’ progress is monitored through regular one-to-one meetings and Divisional presentations. Fellows are encouraged to present work at national and international conferences and prepare manuscripts for publication in peer-reviewed journals. The Fellow’s lead supervisor will be Dr Caroline Jolley, who is both a Senior Lecturer in Human Physiology in CHAPS, and a clinically-active Respiratory Physician. Dr Jolley has a specialist research interest in the physiological basis of breathlessness and respiratory failure, and measurement of neural respiratory drive. Dr Jolley has recently established a “Lung Health Clinic” based in the SLaM Community Drug and Alcohol Service at Lorraine Hewitt House, and has experience of the clinical and physiological assessment of clients undergoing treatment for opioid addiction. The Fellow’s research training will also benefit from Dr Jolley’s role as a Principal Investigator within the London Respiratory Muscle Research Group (LRMRG). The LRMRG is a collaboration between scientists and clinicians working in the field of respiratory physiology and skeletal muscle function in health and disease. Headed by Professor John Moxham, the work of the LRMRG is internationally-renowned. This provides a unique opportunity to be trained in the techniques involved in measuring respiratory muscle function, neural respiratory drive, and physiological respiratory control mechanisms.

Within SLaM/IOPPN, the Fellow will be directly supervised by Professor John Strang, who is Academic Director of the King’s Health Partners Addictions Clinical Academic Group. Dr Mike Kelleher (SLaM Consultant Psychiatrist and Clinical Lead for Lambeth Addictions) will provide clinical supervision and guidance within the SLaM Addictions Service. IOPPN is a leading centre within the CRC UK Centre for Tobacco & Alcohol Studies (a Public Health Centre of Excellence) and has recently been awarded a large NIHR Collaborations for Leadership in Applied Health Research & Care (CLAHRC), which has a large addictions theme. The Fellow will benefit specifically from research training opportunities within the new MRC Addiction Research Clinical Training (MARC) programme, through attendance at MARC Summer schools, MARC events and mentoring.

Summarise the translational and experimental medicine component of the research, as well as the relevance of the project to the BRC Research Cluster(s)

The key translational components of this research are 1) the application of physiological measurements of neural respiratory drive to understanding the clinical impact of opioid-induced respiratory depression on delayed diagnosis of respiratory disease, and 2) the opportunity to better understand mechanisms of heroin overdose through laboratory-based physiological studies. This is of direct relevance to the SLaM BRC/U-D Research Theme “Disorders of affect and addiction, and their interface with medicine” within the Clinical Disorders Cluster. Within the KCL/GSIT BRC Cluster “Population Sciences”, and Research Theme of “Environment, Respiratory Health and Allergy”, this research project addresses health inequalities, seeking to better understand barriers to parity of access to physical (respiratory) healthcare in mental health populations.

Please summarise any patient and public involvement in the proposed research

The supervisory team benefits from a strong relationship with the Addictions Service User Research Group (SURG), hosted by the Aurora Project, which is a peer mentoring service for people who are drug and alcohol users in Lambeth. Since the inception of the KIS-supported Lung Health in Addiction project, SURG contributes on a 2-3 monthly basis to the design, management and evaluation of the Lung Health in Addictions programme, which includes the research proposed here. SURG also advise on the most effective means of dissemination of research findings to Service Users, and contribute to manuscripts, highlighting the value of Service User input to research in this client group.

Name of the School / Department supporting the project:

Faculty of Life Sciences and Medicine