PROJECT 1

**Supervisor Details**

First Supervisor: **Professor Richard Morriss** (Professor of Psychiatry and Community Mental Health)

Second Supervisor: **Dr Paul Briley** (Academic Clinical Fellow)

Other members of supervisory team:

**Dr Domenica Veniero** (Assistant Professor, School of Psychology)

**Dr Lucy Webster** (Nottingham BRC Research Fellow)

**Project Title**

Developing an approach for boosting the antidepressant effects of transcranial magnetic stimulation (TMS) using synchronised transcranial alternating current stimulation (tACS)

**PhD Aim**

This PhD project will develop an understanding of the mechanisms by which one neuromodulation technique – tACS – can modify or augment the effects of another technique – TMS.

TMS is a NICE-approved treatment for depression. Through a series of studies, in non-patients and in people with depression, measuring changes in brain activity and connectivity using electroencephalography, functional near infrared spectroscopy, and magnetic resonance imaging, the project will build a mechanistic understanding of tACS-TMS. The project will work with people with lived experience of depression to understand experiences of tACS-TMS, how the approach might fit into treatment pathways and barriers to uptake. In doing so, the project will develop tACS-TMS as a means of boosting the efficacy of TMS alone, paving the way for future clinical trials.

**Background/introduction**

Transcranial magnetic stimulation (TMS) is a well-tolerated, NICE-approved, neuromodulation (brain stimulation) treatment for depression. TMS delivers magnetic pulses over the scalp, temporarily altering the excitability of the underlying cortex, leading to changes in and between connected brain regions. Clinical TMS is usually delivered daily over several weeks in an outpatient clinic. Our recently published BRIGHTMIND trial showed that, for those patients that improve with TMS, improvement can be sustained for at least six months (Morriss et al., 2024).

However, outcomes with TMS vary greatly between individuals (Kaster et al., 2019). Some patients improve quickly. For others, improvement takes several weeks, and a substantial number of patients do not improve. Finding ways to augment (boost) the effects of TMS is an important treatment goal.

In a recent non-patient study, we examined a potential approach for boosting the effects of TMS, by delivering TMS in synchrony with another well-tolerated neuromodulation technique that delivers weak electrical currents (Briley et al., 2024). This second technique is called transcranial alternating current stimulation (tACS).

We found participants were more likely to perceive neutral faces as happy after receiving tACS-synchronised TMS than after receiving sham or TMS alone. Positive shift in “emotional bias” has been proposed as an early marker of antidepressant efficacy. This suggests tACS-synchronised TMS may have stronger, or more rapid, antidepressant effects than TMS alone.
We also found that tACS-synchronised TMS boosted a type of brain activity that has previously been associated with clinical response (“frontal theta oscillations”), to a greater extent than TMS alone. Oscillations refer to regularly repeating patterns of brain electrical activity, generated by interactions between groups of neurons. Oscillations control brain excitability and connectivity and are likely fundamental to the effects of TMS.

However, a clear understanding of how tACS modifies the effects of TMS is lacking. Such understanding is needed to refine the technique and develop it as an approach for treating depression in patients for whom TMS alone is insufficient.

**Candidate criteria – essential**
- Undergraduate or Masters' degree in a scientific discipline
- Previous experience of conducting scientific research
- Strong computational abilities (e.g., statistics, mathematics, or computer modelling)

**Candidate criteria – desirable**
- Experience of research related to the field of mental health
- Experience of working with people with mental health difficulties
- Familiarity with conducting or analysing brain imaging or electroencephalography studies
- Proficiency in one or more computer programming languages (can include Matlab)

**Objectives and methodology**

This PhD will build understanding of the mechanisms by which tACS can boost the effects of TMS, and of patient experiences of combined stimulation. This will guide development of tACS-synchronised TMS as a treatment for depression.

As well as the two stimulation techniques, the PhD will use markers of potential antidepressant efficacy (including emotional bias tasks and negative mood induction), measures of brain activity, computational modelling, and focus groups with participants with lived experience of depression.

Brain activity will be measured with electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS) and structural and functional magnetic resonance imaging (MRI). EEG measures brain electrical activity non-invasively using a cap of electrodes on the head – it is excellent for studying brain oscillations. fNIRS detects changes in oxygenated and deoxygenated blood in the brain by measuring light reflectance from the scalp – it is a quick and simple measure of cortical brain activity. MRI provides high resolution images of brain structure and function using a powerful magnet and radio-frequency pulses.

Single-session and multi-session studies will be conducted with non-patients and people with depression. Key questions will include: How does tACS affect propagation of TMS pulses from the cortical target to distal brain areas (including deep brain areas involved in processing emotion)? How do the effects of tACS-TMS depend on the timing relationship between the two techniques? Are effects of tACS-TMS enhanced if stimulation frequencies match the frequencies of spontaneous brain oscillations in each person? Does tACS-TMS lead to greater changes in brain connectivity and in the activity of deeper emotion processing (“limbic”) brain regions than TMS alone?

Focus groups with people with lived experience of depression, and patients included in the candidate’s studies, will examine experiences of tACS-TMS, challenges to uptake or implementation, and perceived benefits.

**Timeline**

In year one, the candidate will develop their knowledge and skills around the two stimulation techniques (TMS and tACS) and two of the measurement techniques (EEG and fNIRS). They will attend external training courses and build hands-on experience through supporting ongoing studies. Guided by focus groups of people with lived experience of depression, they will devise and
implement studies on the effects of modifying the timing relationship between tACS and TMS and of matching stimulation frequencies to those of spontaneous brain oscillations.

In year two, the student will continue to run and analyse the above studies, and develop follow-up studies examining the effects of tACS on the propagation of activity induced by TMS pulses through the brain, and on the effects of tACS-TMS on brain connectivity and the activity of limbic brain regions. This will involve developing knowledge and skills in MRI brain imaging. Focus groups at this stage will examine patient experiences of the stimulation approach, including difficulties or barriers to uptake.

In year three, the student will complete the second group of studies and complete their thesis. They will be encouraged to prepare their findings for submission to peer-reviewed journals during their PhD programme, and will present their findings to lived experience experts, and researchers at national and international conferences.
Supervisor Details

Dr Mairi Houlgreave (Post-doctoral research fellow)
Professor Stephen Jackson (Professor of Cognitive Neuroscience)

Project Title

Exploration of the role of neural noise in tic generation and the effects of rhythmic median nerve stimulation in reducing neural noise

PhD Aim

The aim of this PhD would be to explore whether rhythmic median nerve stimulation (rMNS) is therapeutically beneficial in Tourette syndrome (TS) because it reduces neural noise associated with the generation of tics through plasticity mechanisms.

Background/introduction

Neurotherapeutics Ltd, a University of Nottingham spin-out company co-founded by Prof. Jackson, recently conducted a double-blind, sham-controlled clinical trial which demonstrated a significant reduction in tic frequency and severity following rhythmic 10 Hz MNS in comparison to both sham stimulation and a ‘treatment as usual’ control group (Maiquez et al., 2023). Using electroencephalography (EEG) and magnetoencephalography (MEG) techniques as part of our BRC studies, we have demonstrated a frequency-specific increase in both amplitude and inter trial phase-coherence in the contralateral sensorimotor cortex during rhythmic but not arrhythmic MNS (Houlgreave et al., 2022; Maiquez et al., 2020). These findings suggest that entrainment occurs during rMNS and that entrainment of movement-related brain oscillations contributes to the reduction in tics during rMNS.

However, using magnetic resonance spectroscopy, we found no difference between the neurometabolic effects in the contralateral sensorimotor cortex of rMNS and arrhythmic MNS (Houlgreave et al, in prep). Furthermore, there is evidence that both rMNS and arrhythmic MNS can significantly reduce the frequency of tics in TS (Farr, Houlgreave et al., in prep; Iverson et al., 2023). Thus, the clearly demonstrated beneficial effects of MNS need not be purely related to the entrainment of oscillations in the sensorimotor cortex. Developing a better mechanistic understanding of the clinically beneficial effects of rMNS in tic disorder is of paramount importance in further developing this approach as a potential therapy.

It has been suggested that one potential mechanism for the generation of tics is the presence of ‘sensorimotor noise’ (Ganos et al., 2015). Importantly, results from ongoing research within our group clearly demonstrates increased variability in the magnitude of somatosensory-evoked potentials (SEPs) in response to single MNS pulses, when compared to age- and sex-matched controls (Gialopsou et al., in prep). This increase in variability is constant rather than being specific to a particular SEP component and confirms the proposal that there is increased sensorimotor noise in the TS group.

This PhD studentship will make use of multimodal brain imaging approaches to test the hypothesis that rMNS leads to a reduction in sensorimotor noise which in turn leads to a reduction in tics as a result of neural (Hebbian) plasticity. Specifically, the student will investigate how neural entrainment during rMNS leads to increased synchronised firing and a more uniform recruitment (i.e., decreased neural noise) of the targeted neuronal population within the sensorimotor cortex. We further hypothesise that when a uniform population of connected neurons are consistently co-activated together then the strength of their connectivity, and their likely future co-activation is increased, through neural (Hebbian) plasticity mechanisms.
References


Objectives and methodology
The PhD studentship would focus on developing an understanding of the mechanisms involved in rMNS and how these mechanisms may lead to therapeutically beneficial effects in common neurodevelopmental conditions highlighted in the BRC Mental Health theme (e.g. Tourette Syndrome, anxiety, OCD, ADHD). A second more specific focus would involve understanding the mechanisms which lead to tics and the urge-to-tic in Tourette Syndrome.

We would investigate whether rMNS leads to a decrease in neural noise and whether this reduction predicts the reduction in tics observed during and following rMNS. The student would be trained particularly in the use of EEG/MEG recording and analysis techniques. The studentship would begin initially with the continuation of the EEG neural noise research described above and would look at the changes in the variability of SEP magnitude in participants with Tourette Syndrome following a period of rMNS.

Timeline

Oct 2024: Start of studentship.

Oct – Dec 2024: Training including EEG recording and analysis, patient questionnaires and video analysis of tics.

Dec 2024: Set up of the study exploring neural noise changes induced by rMNS.

Dec 2024 – May 2025: Data collection and analysis.

May 2025: Discussion between the PhD student and supervisors about future research directions.
PROJECT 3

Supervisor Details

**Dr Michael Craven.** Principal Research Fellow at NIHR MindTech MedTech Co-operative (Institute of Mental Health, FMHS) and Human Factors Research Group (Faculty of Engineering). [https://www.nottingham.ac.uk/engineering/people/michael.craven](https://www.nottingham.ac.uk/engineering/people/michael.craven)  [https://orcid.org/0000-0001-5682-6360](https://orcid.org/0000-0001-5682-6360)

**Dr Jacob Andrews.** ECR in NIHR BRC MH&T, MindTech & AU1: Mental Health and Clinical Neurosciences, School of Medicine. [https://www.mindtech.org.uk/about-us/our-team/dr-jake-andrews](https://www.mindtech.org.uk/about-us/our-team/dr-jake-andrews) [https://orcid.org/0000-0001-8408-5782](https://orcid.org/0000-0001-8408-5782)

**Dr Vicky Booth.** Associate Professor in Centre for Rehabilitation and Ageing, FMHS, NIHR BRC MSK Theme and AU3. Clinical-academic neurological physiotherapist and Associate Chief AHP for Research and Innovation, at Nottingham University Hospitals NHS Trust. [https://www.nottingham.ac.uk/medicine/people/vicky.booth](https://www.nottingham.ac.uk/medicine/people/vicky.booth)  [https://orcid.org/0000-0002-5338-0196](https://orcid.org/0000-0002-5338-0196)

Project Title

Digital tools for visualisation of recovery and rehabilitation

PhD Aim

The PhD will extend the work of Dr Mike Craven in the use of digital tools for visualising wellbeing into the physical rehabilitation space.

Recovery and rehabilitation from neurological injury and trauma typically focus on physical recovery and motor function. However, there is significant potential to augment rehabilitation using visualisation techniques and a mental health/wellbeing focus.

Therefore, this PhD aim is to explore the role of visualisation in recovery and rehabilitation from a person-centred perspective and develop digital techniques to support this.

Background/introduction

Addressing the mental health and social impacts of rehabilitation is very important to ensure successful recovery. However, mental health and social impacts are often given secondary attention. Sub-optimal rehabilitation can lead to life-long impacts on well-being, mental health and capability to maintain or seek employment.

Previous work by Dr Craven highlighted the great potential for digital app/web based or self-authored visualisations using graphics or video. Another untapped area ideal for PGR exploration is the use of generative AI to produce bespoke/personalised representations of recovery for individuals.

The clinical focus, facilitated by Dr Vicky Booth, will come from an augmented physiotherapy perspective and will be linked to the remit of the new National Rehabilitation Centre (NRC; Neuro and Trauma) and Linden Lodge Neuro Rehabilitation Unit at NUH as well as the UoN Centre for Rehabilitation and Ageing.

Objectives and methodology

Objectives:

1. Review literature on digital tools for well-being assessment
2. Explore the role of visualisation in recovery and rehabilitation from a person-centred perspective (study 1)
3. Develop digital techniques to support the use of visualisation to recovery and rehabilitation (study 2)

Prior research (visualisation in apps, wellbeing scales, AI etc.) provides a vehicle for a systematic review in the first year which is typical of FMHS PhDs leading to study development. At least 2 original studies will be designed by the candidate applying visualisation techniques and include qualitative and quantitative or mixed methods and digital design.

We expect the candidate to become an expert in wellbeing assessments and gain the skills to work with patients having neurological and/or physical functional injuries to develop suitable tools for visualising their wellbeing. Human Factors methods such as scenario-based designs and personas and focus groups will support visualisation tool development. Study choices include longitudinal (during recovery/rehab) or comparative (physical trauma versus neuro aspects). As is usual, part of the PhD will be to train the candidate in selection of the appropriate study designs and methods to use.

The project will follow guidance on the development and evaluation of complex interventions (4) and the candidate will receive training in this. The candidate will apply for UoN and NHS ethical approval as required. The project will involve practitioners and people with lived experience of physical and mental health recovery with an EDI and RRI (responsible innovation) ethos.

Timeline

Start October 2024 for 3 years (full-time, 2024/27).

- Year 2 (2025/26): Run Study 1 and complete analysis of Study 1. Ethics, set up and begin Study 2.
- Year 3 (2026/27): Completion of Study 2. Thesis write up. Dissemination as appropriate.

References


# PROJECT 4

## Supervisor Details

| Dr Maddie Groom (Associate Professor in Applied Developmental Cognitive Neuroscience) |
| Dr Charlotte Hall (Principal Research Fellow) |
| Professor Chris Hollis (Professor of Child and Adolescent Psychiatry) |

## Project Title

Vibrotactile stimulation (VTS) therapy to support self-management of tics and ADHD in young people: An exploratory investigation and usability study.

## PhD Aim

To explore the potential clinical utility of VTS in supporting symptom management for children with tic disorder and/or ADHD.

## Background/introduction

Behavioural Therapies (BT) for Tourette Syndrome (TS) are recommended as first-line treatments by clinical guidelines and are often preferred to medication by young people with TS and their carers [1, 2]. In general, these therapies require the young person to replace the tic with an alternative action or suppress the tic. The effectiveness of behavioural therapies for tics may therefore be partly due to strengthening of the neural circuitry underpinning cognitive and motoric control [3]. However, not all young people with TS can access BT and some experience no benefit. Barriers include lack of trained therapists and difficulties adhering to such therapies which require significant effort, motivation and time commitment [4]. Alternative therapies that overcome these barriers are needed.

An additional factor which undermines the effectiveness of BT for tics is the co-occurrence of tics with ADHD, a neurodevelopmental condition leading to functionally impairing hyperactivity, inattention and impulsivity. Over 50% of children and young people with tic disorders have ADHD [5] leading to poorer prognosis and treatment response. Brain networks underpinning cognitive control are atypical in ADHD and in those with comorbid ADHD and TS [3] and this may explain the reduced response to BT.

Recently, there has been some success in reducing the symptoms of other movement disorders such as Parkinsons Disease using vibrotactile stimulation applied to the hand [6]. Such stimulation enhances functional brain patterns associated with movement control [7] suggesting this may also be effective for tics. This PhD will further explore the potential application of VTS for reducing tics in young people with TS with and without ADHD.

## Objectives and methodology

Our aim is achieved via the following objectives:

**Objectives:**

1) Explore the current literature, including empirical and theoretical basis for using VTS for TS and ADHD and movement disorders more broadly (e.g. Parkinson’s Disease).
2) Identify potential industry partner/providers of relevant technology to evaluate in a usability study.
3) Evaluate the potential clinical/behavioural mechanisms of action of VTS for tics and ADHD.
4) Assess the usability, safety and short-term early efficacy of VTS for young people with tic disorders and ADHD.
Methods:
The precise specification of work will be further developed by the appointed student.

1. **Literature review**: The student will undertake a systematic review to explore the evidence for using VTS therapy for movement disorders and establish the theoretical evidence for using VTS for tics and ADHD.

2. **Horizon scanning**: Using our established links with Health Innovation East Midlands (HIEM), MRC Digital Youth (Lead: Hollis) and NIHR MindTech Health Research Centre (Director: Hollis) the student will seek out potential industry device manufacturers and leading academics in the field of digital mental health technologies to identify potential existing CE marked VTS devises used with movement disorders. They will conduct an options appraisal of potential devices and select the most suitable device and company to evaluate in the PhD.

3. **Develop theoretical hypothesis**: The student will develop a potential theoretical framework to understand the mechanisms of action of VTS for ADHD and tics. This will inform potential outcomes for the usability study.

4. **Pre-post usability study**: Conduct a small-scale usability study in a sample of around 30 young people with tics with and without ADHD to explore the 1) usability 2) acceptability, 3) early indications of potential efficacy, 4) considerations on underpinning mechanisms of action.

The project will be supported by interdisciplinary technical guidance from Dr Michael Craven, an expert in the development and evaluation of digital technology, and clinical guidance from Joe Kilgariff, Clinical Nurse Specialist, a clinical expert in TS and BT.

We will work with our Tech Transfer Office (Jonathon Gibbons) to identify and navigate IP arising throughout this project.

**Patient and public involvement:**

We will engage with Involvement methodology support through the BRC to support this study. This will include forming a PPI panel of parents/carers and young people affected by TS. In addition, through an existing national steering group for TS (led by Groom), we will draw upon clinical, academic and lived experience expertise to inform and guide the project. The student will join this steering group and will benefit from our established links with the national charities Tourettes Action and ADHD Foundation. These charities will support recruitment to the usability study and the PPI panel.

**Timeline**

| Months 1-9: | systematic review and identify potential providers of the technology. |
| Months 6-12: | Hold expert and PPI workshops; develop protocol for usability study; confirm potential provider of the technology. |
| Months 13-30: | Obtain ethical approval for the study, undertake usability study, including analysis. |

The student will be supported to write their thesis as an iterative process, submit papers for publication during the PhD, and present their findings to national and international audiences of academics, healthcare professionals and lived experience groups and charities.

**References**


## PROJECT 5

### Supervisor Details

**Professor Carol Coupland** (Professor of Medical Statistics in Primary Care)  
**Dr Ruth Jack** (Senior Research Fellow)  
**Professor Roger Knaggs** (Clinical Pharmacy Practice)  
**Professor Richard Morriss** (Professor of Psychiatry and Community Mental Health)

### Project Title

Polypharmacy and adverse outcomes in people prescribed antidepressants in primary care

### PhD Aim

This research will determine which adverse health outcomes are associated with multiple medicine prescribing in people taking antidepressants, and which groups of people and drug combinations are at increased risks of these outcomes.

### Background/introduction

Polypharmacy – defined in the simplest terms as taking more than one medicine at the same time – is becoming increasingly common [1,2]. While it is often appropriate for patients to be prescribed multiple medicines, there are risks associated with polypharmacy. These include an increased risk of drug-drug interactions, prescribing cascades (where additional medicines are prescribed to treat drug side-effects), and treatment costs that need to be covered by the patient or healthcare system. Furthermore, the burden of polypharmacy on patients may impact treatment adherence and quality of life [3].

Polypharmacy is an important consideration in the context of antidepressant users. Antidepressants are among the most commonly prescribed medicines in the UK [4,5], and the number of people prescribed antidepressants in England has increased to more than 8.5 million people in 2022/23 [6]. Previous studies have examined the safety of antidepressants and found higher risks of fracture and falls, but no increased risk of cardiovascular outcomes in patients taking antidepressants [7,8]. Antidepressant users are frequently prescribed other medicines [9]. Key adverse outcomes associated with antidepressant interactions with other medicines include serotonin syndrome, gastrointestinal bleeds, and cerebrovascular bleeds [10], but evidence on risks in people taking three or more different drug combinations is limited.

This research will use a large population-based database to investigate whether being prescribed multiple medicines alongside antidepressants affects risk of adverse outcomes, and which combinations are associated with which outcomes. By using population-level real world data, commonly co-prescribed medicines and a range of adverse events can be examined, to identify combinations having the biggest impact on patients’ health. This work will provide information to enable patients, prescribers and policymakers to identify problematic co-prescribing and improve safety. Reducing the number of medicines people are prescribed and the number of adverse events will reduce the burden on patients and costs for the healthcare service.

The Mental Health & Technology polypharmacy research area project team includes representatives from a wide range of disciplines, including primary care, psychiatry, pharmacy, epidemiology, health data science and statistics. The team also includes two public contributors, one of whom highlighted the burden of polypharmacy among antidepressant users as an area of interest. Supporting GPs and other prescribers to ensure safe prescribing for patients is a core part of the research area’s work, and members of the team, including the National Clinical Director for
Prescribing with NHS England, are well-placed to disseminate and implement any changes suggested by this research.

The project would suit somebody with a Master’s degree or equivalent in medical statistics, data science, epidemiology, health services research, public health, statistics or similar subjects with a strong numeric component.

### Objectives and methodology

The objectives of the research are to:

1. Identify which adverse events are associated with periods of exposure to combinations of antidepressants and other medicines, including multiple antidepressants and the most common medicine combinations prescribed with antidepressants.
2. Determine the associations between adverse events for periods of exposure to the specified drug combinations, compared with periods of exposure to antidepressants only.
3. Identify which patient characteristics, such as demographic and clinical factors, influence risk of adverse events.

Routinely collected electronic health records from primary care linked to secondary care data will be used to assess the adverse effects associated with being prescribed multiple medicines alongside antidepressants, compared with being prescribed antidepressants alone. A study cohort will be selected comprising adults prescribed antidepressants between 2015 and 2024 in England. Periods where people have active prescriptions for multiple medicines will be determined using established algorithms. Adverse events will be determined using existing literature and consulting with healthcare providers and experts by experience. The adverse events will include serotonin syndrome, gastrointestinal bleed, falls and fractures, overdose, mortality, and other conditions identified during the research. Code lists to identify adverse outcomes will be developed and validated to enable the correct data to be extracted.

Statistical models will be used to assess the risk of adverse events, examining the periods while people are co-prescribed multiple medicines compared with periods of antidepressants only. Analyses will account for potential confounding variables including demographic and clinical factors. Further analyses will also determine whether any groups are at greater risks of adverse outcomes when prescribed particular combinations of medicines with their antidepressants.

This research already has a strong patient and public involvement (PPI) component as the original topic was suggested by a public contributor. Two public contributors are already part of the project team and provide support on research focus, interpretation of results, and communication and dissemination of results. Further PPI representation from people with experience of particular co-prescribing or adverse events will be considered.

### Timeline

**Year 1: Set up PPI group.**
- Review literature on antidepressant co-prescribing, including adverse outcomes.
- Define adverse outcomes of interest following discussions with stakeholders (including healthcare professionals, experts by experience) and associated code lists.
- Write protocol to obtain data extract.
- Start to clean and prepare data for analysis.

**Year 2: Regular meetings with PPI group.**
- Complete data cleaning and manipulation.
- Define drug combinations of interest.
- Start to analyse data.

**Year 3: Regular meetings with PPI group.**
- Complete statistical analysis.
Write up and disseminate findings.

References


Supervisor Details

Professor Carol Coupland (Professor of Medical Statistics in Primary Care)
Dr Ruth Jack (Senior Research Fellow)
Professor Roger Knaggs (Clinical Pharmacy Practice)
Professor Richard Morriss (Professor of Psychiatry and Community Mental Health)

Project Title
Investigating the safety of opioid and antidepressant co-prescribing in primary care

PhD Aim
This research will identify the adverse effects associated with being co-prescribed opioids and antidepressants using routinely collected electronic health records from primary care. Trends over time, and variation between groups will be assessed.

Background/introduction
The National Institute for Health and Care Excellence (NICE) has recently recommended the use of some antidepressants to treat chronic pain in adults[1]. This decision was made on the basis of trial evidence on effectiveness, but NICE do not routinely consider drug safety, considering the matter a regulatory issue. There were 85.5 million antidepressant items prescribed in England in 2022/23, to an estimated 8.6 million people, an increase of 46% compared with 2015/16[2]. The new NICE recommendation may further inflate their use.

Although opioids are not recommended by NICE for many types of chronic pain where antidepressants may be used (such as low back pain, neuropathic pain and chronic primary pain), they are also widely prescribed. A Public Health England report found 5.6 million people (12.8% of the population) were prescribed opioid pain medicines (excluding those for treatment of cancer pain) in 2017/18[3].

Antidepressant and opioid prescribing rates both vary by patient characteristics, for example people living in more deprived areas are more likely to be prescribed antidepressants and opioids than those living in more affluent areas[4]. While there are safety concerns for both types of medication when taken separately, there is a lack of robust information on risks of adverse health outcomes when they are taken concurrently (co-prescribed). There is potential for drug-drug interactions, which can occur when drugs taken in combination exhibit synergism which can result in toxicity[5]. The risks of these adverse outcomes need to be quantified along with an examination of potential inequalities in adverse outcomes and co-prescribing.

Recent work completed by our team found that 7% of adults in the general population in England were co-prescribed opioids for non-cancer pain and antidepressants between 2010 and 2019. People who were older, female, living in more deprived areas and of White ethnicity were more likely to be co-prescribed these drugs. Public contributors who are part of our research team have expressed concern about the possible adverse effects of being co-prescribed these medicines, particularly if they have long-term prescriptions. The findings of this research will be useful for patients, prescribers and policymakers. The results have potential to inform prescribing policy and could be implemented in clinical prescribing tools. As a result of this work, patient safety will be improved, as riskier drug combinations in more vulnerable patients can be avoided, and better monitoring could be implemented to reduce risks of adverse events happening.

The supervisory team includes clinical, pharmacy and methodology experts, and the wider Mental Health & Technology’s polypharmacy project team this work will be aligned to also includes public
contributors, primary care clinicians and the National Clinical Director for Prescribing with NHS England. This research area is looking more broadly at co-prescribing patterns and adverse outcomes in people prescribed mental health medicines, and results from the PhD would be included in discussions about how to support GPs prescribing these medicines.

The project would suit somebody with a Master’s degree or equivalent in medical statistics, epidemiology, health services research, public health, statistics or similar subjects with a strong numeric component.

**Objectives and methodology**

The objectives of the research are to:

1. Identify which adverse events are associated with being co-prescribed opioids for non-cancer pain and antidepressants.
2. Describe trends over time in adverse events for patients co-prescribed antidepressants and opioids.
3. Determine which specific drug combinations are associated with adverse events and investigate the impact of duration and dose.
4. Identify which patient characteristics influence risk of adverse events, such as demographic and clinical factors.

Routinely collected electronic health records from primary care linked to secondary care data will be used to assess the adverse effects associated with being co-prescribed opioids for non-cancer pain and antidepressants, compared with being prescribed these medications individually. A study cohort will be selected comprising adults prescribed opioids for non-cancer pain or antidepressants between 2015 and 2024 in England. Periods where people have active prescriptions for opioids and antidepressants in combination will be determined using established algorithms. Existing literature will be examined to determine possible adverse events to investigate, as well as consulting with healthcare providers and experts by experience. Code lists to identify adverse outcomes will be developed and validated to enable the correct data to be extracted.

Statistical models will be used to assess the risk of adverse events, examining the periods while people are co-prescribed opioids and antidepressants, as well as short and long term periods after co-prescribing episodes compared with periods of antidepressants or opioids alone. The effect of the length of time someone is co-prescribed for will also be investigated. Analyses will account for potential confounding variables including demographic and clinical factors.

Patient and public involvement (PPI) will be a core element of the project, as public contributors will be part of the wider research team. They will provide guidance on the areas of most concern to them as well as advising on interpretation of results and the most appropriate forms of disseminating the results. Healthcare providers and prescribers will also be consulted to advise on disseminating and implementing the results.

**Timeline**

**Year 1:** Set up PPI group.
- Review literature on antidepressant and opioid co-prescribing adverse outcomes.
- Define outcomes of interest following discussions with stakeholders (including healthcare professionals, experts by experience) and associated code lists.
- Write protocol to obtain data extract.
- Start to clean and prepare data for analysis.

**Year 2:** Regular meetings with PPI group.
- Complete data cleaning and manipulation.
- Start to analyse data.

**Year 3:** Regular meetings with PPI group.
- Complete statistical analysis.
- Write up and disseminate findings.

References


**PROJECT 7**

**Supervisor Details**

*Professor Elvira Perez Vallejos (Professor of Digital Technology for Mental Health)*

*Transitional Assistant Professor Aislinn Gomez Bergin*

*Dr Camilla Babbage (Post-doctoral research fellow)*

*Dr Sachiyo Ito-Jaeger (Post-doctoral research fellow)*

**Project Title**

Anticipating the impact of AI therapists

**PhD Aim**

This PhD aims to anticipate the impact of embodiment of AI therapists (e.g., chatbots) and other emerging technologies in the provision of digital mental health treatment. With a landscape rapidly changing, this PhD will focus on impact that innovative applications that embed AI-driven therapeutic innovations could have on clinical practice and the therapeutic outcomes of patients. For example, there are already novel approaches that apply generative AI and large language models (LLMs) to create new virtual spaces in real time for exposure therapy or relaxation, or virtual therapist and conversational agents. However, some of these novel approaches do not apply methods to apply Responsible Research and Innovation frameworks and therefore, there is no anticipatory work that could assess the impact of such technologies.

Emerging technologies such as technology-as-advocate offer people with mental health issues with an always-on, personalised, assistant that can anticipate their every need. What is the potential in digital mental health services? For example, what do personal-human assistants for those with mental health conditions currently do and could this be supported or replaced by technology? Could technology offer people with mental health conditions advocacy?

**Background/introduction**

In recent years, the application of artificial intelligence (AI) in healthcare has witnessed unprecedented growth, with one notable domain being AI therapists. These digital entities represent a groundbreaking intersection of technology and mental health, offering a novel approach to addressing the ever-growing global demand for mental health support.

The surge in the prevalence of mental health disorders and the shortage of human therapists has created a pressing need for innovative solutions. AI therapists, equipped with advanced natural language processing (NLP) and machine learning (ML) capabilities, have emerged as a promising alternative. These intelligent systems are designed to engage in empathetic conversations, analyse speech patterns, and discern emotional cues, enabling them to comprehend and respond to a wide array of human emotions.

One of the key advantages of AI therapists lies in their accessibility. As standalone applications or integrated platforms, they provide users with on-demand mental health support, eliminating geographical barriers and reducing the stigma associated with seeking help. This accessibility proves invaluable, especially in regions where mental health services are scarce or in high demand.

The development of AI therapists also underscores the potential to alleviate the burden on human therapists. By handling routine interactions, these digital counterparts free up human professionals to focus on more complex cases, fostering a more efficient and scalable mental health ecosystem. Moreover, AI therapists can operate around the clock, ensuring continuous support for individuals in need.
However, the integration of AI in mental health services raises ethical considerations and concerns regarding privacy, data security, responsibility and the risk of overreliance on technology. Striking a balance between the benefits of AI therapists and safeguarding the well-being of users remains a critical challenge.

As the field of AI therapy evolves, ongoing research, ethical frameworks, and collaborations between technologists and mental health experts will play pivotal roles in shaping the future of this transformative technology. The journey towards a harmonious coexistence between artificial intelligence and human well-being is marked by both promise and responsibility.

Game engines are now embedding conversational AI into Non-Playable Characters (NPCs) and it is only a matter of time before we begin doing this for mental health chatbots. But what does that mean for important elements like the therapeutic alliance? Can we trust the therapists we meet to be real/not real? Does it make therapy better when you can personalise your therapist or does it have the potential to reinforce bias?

The lack of responsible innovation in the area of AI, especially when applied to mental health, is worrying and a potential problem that requires careful consideration.

Objectives and methodology

Objective 1.: Conduct a scoping review to identify the latest therapeutic applications applying AI techniques (e.g., ML and NLP), including chatbots and virtual therapists.

Objective 2.: Apply Responsible Research and Innovation (RRI) frameworks [1] to anticipate the impact of embodied AI therapists on therapeutic outputs. Use the RRI Prompt and Practice Cards [2] to facilitate discussion among stakeholders about potential issues.

Objective 3: Understand how can we apply RRI within development, evaluation, and implementation of emerging technologies – what are the challenges and opportunities? Can we truly ‘anticipate’? Who needs to be involved?

The methodology will include mixed methods including large scale quantitative survey triangulated with qualitative data emerging from interviews and focus groups.

Timeline

Y1 Sept 24: Induction, training on research methods, scoping review, PhD planning, ethics clearance, PPIE engagement, stakeholder involvement
Y2 Sept 25: Study design, recruitment, data collection and analysis and interpretation
Y3 Sept 26: PPIE input on results, writing up, conference attendance, paper publications.
Y4 Sept 27: PhD submission

References

