Project Details	
Project Code	MRCNMH24Ba Bailey
Title	Opioid overdose deaths: Understanding interactions between benzodiazepines and opioids
Research Theme	Neuroscience & Mental Health
Summary	Drug-related deaths are now at the highest ever recorded in the UK. Many of these involved a combination of benzodiazepine and opioid drugs but why this combination is such high risk is unknown. Using a combination of electrophysiology, in vitro and ex vivo assays, and rodent behaviour the student on this project will investigate interactions between benzodiazepine and opioid drugs at the receptor, cellular and systems level.
Description	Drug-related deaths are now at the highest ever recorded in the UK. In 2020 there were nearly 1,200 drug overdose deaths, many of which involved a combination of benzodiazepine and opioid drugs. The reasons why combined use of benzodiazepines and opioids greatly increase the risk of overdose death are unknown and will be investigated in this transdisciplinary project. Opioid drugs, such as heroin and fentanyl, act on mu opioid receptors. Mu opioid receptors (MOPrs) are widely expressed in the brain and, when activated, can cause analgesia, euphoria and respiratory depression. Fatal opioid overdoses are caused by excessive respiratory depression following activation of MOPrs in neurons responsible for controlling breathing. The increased risk of benzodiazepines on opioid overdose could be at the receptor, cellular or system level. All will be investigated in this project. The supervisory group will consist of 3 academics: Chris Bailey (CB), Ana Abdala Sheikh (AAS) and Eamonn Kelly (EK) with complementary expertise in a range of in vitro and in vivo techniques to investigate whether benzodiazepines and opioids interact at a receptor, cellular or system level. To investigate interactions at the receptor level the student will perform cell-based assays including BRET assays to measure G-protein activation and FLIP-R assays to measure potassium efflux (EK) [1]. Further, the student will perform whole-cell patch-clamp electrophysiology recordings from respiratory neurons in brain slices from cre-reporter mice (CB) [2]. Brain slice electrophysiology will also be used to investigate interactions at a neuronal level. Neuronal activation of respiratory neurons will be recorded, and experiments will determine if benzodiazepines and MOPr agonists interact to affect neuronal function (CB) [3]. The in situ heart/brain stem preparation is an ex vivo technique where respiratory parameters can be recorded along with input from respiratory neurons from the brain stem (AAS) [4]. This technique will be used to assess interactions between benzodiazepines and opioids at the system level. Plethysmography will be used to measure respiratory rate and tidal volume and thus determine interactions at the whole animal level (AAS) [5]. In addition to this proposed plan of work there is considerable scope for the student to steer the research into other avenues of their interest. This is part of a wider project aimed at determining not only the molecular mechanisms underlying interactions between benzodiazepines and opioids, but also the motivation for why people co-use benzodiazepines and opioids. As part of this wider project, qualitative research colleagues are

	interviewing people who use drugs to understand their motivations for combined use of benzodiazepines and opioids. Initial findings suggest that one motivation might be that benzodiazepines enhance the euphoric effect of opioids, and another might be that benzodiazepines modulate opioid tolerance. The euphoric effects could be studied using conditioned place preference [6]. Tolerance could be studied using in vitro and ex vivo techniques as outlined above (cellular signalling, brain slice electrophysiology, heart/brain stem preparation), as well as in vivo [7,8]. Additionally, the student could work with our qualitative research colleagues to contribute to the clinical strand of the overall project. References 1. Ramos-Gonzalez N et al (2023) Br J Pharmacol doi: 10.1111/bph.16084. Online ahead of print. 2. Groom S et al (2023) Br J Pharmacol 180:943-57 3. Sun X et al (2019) Elife 8:e50613 4. Paton JFR et al (2022) J Physiol 600:2049-75 5. Kliewer A et al (2020) Br J Pharmacol 177:2923-31 6. Wright VP et al (2019) Addict Biol 24:590-603 7. Llorente J et al (2013) Mol Pharmacol 84:252-60 8. Hill R et al (2018) Br J Pharmacol 175:2653-61
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