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Undetected Respiratory Depression in People with Opioid Use Disorder.

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Abstract

Background: Opioid-related deaths are increasing globally. Respiratory complications of opioid use and underlying respiratory disease in people with Opioid Use Disorder (OUD) are potential contributory factors. Individual variation in susceptibility to overdose is, however, incompletely understood. This study investigated the prevalence of respiratory depression (RD) in OUD treatment and compared this to patients with chronic obstructive pulmonary disease (COPD) of equivalent severity. We also explored the contribution of opioid agonist treatment (OAT) dosage, and type, to the prevalence of RD.

Methods: There were four groups of participants: 1) OUD plus COPD ('OUD-COPD', n=13); 2) OUD without COPD ('OUD', n=7); 3) opioid-naïve COPD patients ('COPD'n=13); 4) healthy controls ('HC'n=7). Physiological indices, including pulse oximetry (SpO_2%), end-tidal CO_2 ($ETCO_2$), transcutaneous CO_2 ($TcCO_2$), respiratory airflow and second intercostal space parasternal muscle electromyography (EMG_{para}), were recorded continuously over 40 minutes whilst awake at rest during the day. Significant RD was defined as: SpO_2%<90% for >10s, $ETCO_2$ per breath >6.6kPa, $TcCO_2$ overall mean >6kPa, respiratory pauses >10s.

Results: At least one indicator was observed in every participant with OUD (n=20). This compared to RD episode occurrence in only 2/7 HC and 2/13 COPD participants ($p<0.05$,Fisher's exact test). The occurrence of RD was similar in OUD participants prescribed methadone (n=6) compared to those prescribed buprenorphine (n=12).

Conclusions: Undetected RD is common in OUD cohorts receiving OAT and is significantly more severe than in opioid-naïve controls. RD can be assessed using simple objective measures. Further studies are required to determine the association between RD and overdose risk.

Keywords: opioids; opioid substitution treatment; overdose; respiratory depression; lung disease; comorbidity

1 Introduction

Opioid-related deaths have been increasing globally (ONS,2018; UNODC,2018). Opioids impact the control of breathing and cause fatal overdoses, usually by respiratory failure. This action is through a depressant and disruptive effect on the mechanisms that maintain breathing rhythm – 'respiratory drive'. Respiratory complications of inhaled opioid use, coupled with the high prevalence of cigarette smoking in purportedly ageing cohorts of people with opioid use disorder (OUD), are therefore of increasing concern in this population (Bird and Robertson, 2020; Cruz et al., 1998; Jolley et al., 2015; Middleton et al., 2016; Pierce et al., 2018, 2015). Indeed, chronic respiratory disease is recognised to be an important contributor to the increased mortality risk in people with OUD (EMCDDA,2019; PHE,2016; Shook et al., 1990). However, the factors responsible for inter-individual variation in susceptibility to opioid-induced respiratory depression (OIRD) and overdose remain incompletely understood. The contribution of prescribed opioid agonist treatment (OAT), such as methadone and buprenorphine, to respiratory failure in OUD is also an important consideration. It has been proposed that buprenorphine, which has reportedly less of a respiratory depressant effect compared to other OAT due to its partial agonist actions, could be a safer option in OUD with comorbid lung disease (Comer et al., 2008).

Our previous physiological study showed that respiratory depression occurs among people with OUD after administration of their usual prescribed dose of injectable opioid agonist treatment (dose range: 50mg-200mg of diamorphine). Furthermore, in those with OUD and co-morbid chronic obstructive pulmonary disease (COPD), the chronic suppression of respiratory centre output and neural respiratory drive (NRD) may be a risk factor for acute OIRD (Jolley et al.,2015). The aim of the present study was to: i) investigate the prevalence of respiratory depression in people with OUD; ii) compare severity of respiratory depression of people with OUD to an opioid-naïve population, including patients with chronic smoking-related lung disease; iii) investigate the relationship between drug use characteristics, including OAT prescription, and objective physiological indices of respiratory depression.

2 Methods and Materials

The study was conducted in accordance with the principles expressed in the Declaration of Helsinki. Participants were recruited in accordance with local NHS research ethics committee procedures (reference number: 05/Q0703/82) and informed consent was provided in writing by all participants prior to commencing the study.

2.1 Setting

Recruitment and data collection took place over 15 months (March 2016-June 2017). Testing was conducted within the clinical respiratory physiology laboratory at King's College Hospital.

2.2 Study Subjects and Grouping

OUD participants were recruited if they were receiving pharmacological treatment for their opioid addiction (e.g. methadone, buprenorphine), were over 18 years old and were capable of providing voluntary informed consent. They were recruited prospectively from a Lung Health Clinic based in a South London 'Community Drug and Alcohol Treatment Centre' affiliated with South London & Maudsley NHS Foundation Trust.

Two groups of OUD participants were studied: 1) those with chronic obstructive pulmonary disease (COPD) were grouped as 'OUD-COPD' and 2) those with normal spirometry (and subsequently confirmed to have normal lung function as detailed in section 2.5) were grouped as 'OUD'.

Two comparator groups - (1) healthy controls ('HC' group) and 2) patients with COPD and without alcohol or drug addiction ('COPD' group) - were recruited from an existing database within the research laboratory.

Matched (age, sex, body mass index (BMI) and COPD severity (based on GOLD stage (GOLD, 2019)) comparator participants were selected. They were excluded if they had other lung conditions such bronchiectasis or lung cancer or co-diagnoses of cardiac or neurological conditions or drug or alcohol addiction problems. Healthy volunteers were eligible if they had

no history of alcohol or drug addiction, respiratory, cardiac or neurological disease as assessed by patient report and physical examination.

2.3 Study Design

This was an observational study whereby the participant's medication and clinical treatment were not altered. OAT medication can be taken at different times of the day. The study did not interfere with the timing of administration, thus, the study involved testing those who had not yet administered their medication at the time of the study. Participants were asked about whether they had taken their OAT medication or other drugs on the day of testing, and where possible, time of OAT consumption was recorded (Supplementary Table 1).

2.4 Protocol

Urine drug screen ('AllScreen' immunoassay test for seven drugs: cocaine, morphine, benzodiazepine, methamphetamine, THC, methadone and amphetamine) and alcohol breathalyser (BACtrack©) were conducted prior to the testing session for all OUD participants.

2.5 Clinical Assessment of COPD

Lung function tests were conducted in accordance with American Thoracic Society and European Respiratory Society (ATS/ERS) guidance (Miller et al., 2005; Quanjer et al., 2012) for all participants, after which, groups were classified and defined. All OUD and COPD participants also underwent earlobe arterialised capillary blood gas (EBG) analysis to estimate arterial blood pH, bicarbonate, and blood gas (O_2 and CO_2) content (Murphy et al., 2006; Pitkin et al., 1994). EBG analysis was only conducted for those with abnormal (or potentially abnormal) spirometry, thus, healthy volunteers did not undergo EBG analysis. Lung gas transfer for carbon monoxide (TL_{CO}) and transfer coefficient of the lung for carbon monoxide (K_{CO}) tests were performed to investigate for the presence of gas exchange abnormality (Graham et al., 2017).

2.6 Measurements of Respiratory Depression

Indices of respiratory depression were measured continuously in all subjects over a 40 minute period, awake, in a resting seated position. All measures were recorded, and displayed online in real time on LabChart (Version 8, ADInstruments Pty Ltd, Castle Hill, Australia) using a sample speed of 100Hz, unless stated otherwise. Data were stored for offline analysis on an Apple MacBook Air (Apple, MacOSX Yosemite, Apple Inc., California, USA). The measurements were as follows:

- Neural Respiratory Drive (NRD) quantified by measuring parasternal intercostal muscle electromyogram (EMG_{para}) activity recorded transcutaneously over the second intercostal space using surface electrodes (Kendall Arbo1, Tyco Healthcare1, Neustadt, Germany) as previously described (Maarsingh et al.,2000; Murphy et al.,2011; Reilly et al.,2011). EMG_{para} signals were amplified and band-pass filtered between 10Hz and 2kHz (CED 1902, Cambridge Electronic Design Ltd, Cambridge, UK) and sampled at 4kHz. Further details of NRD measurement, and analysis are described in Supplementary Methods.
- Capnography was recorded in two ways: 1) End-tidal carbon dioxide ($ETCO_2$) measured using an adapted nasal cannula in line with a gas analyser (iWorx, New Hampshire, USA). $ETCO_2$ was recorded as the peak CO_2 concentration ($\%CO_2$) measured in each expired breath (breath-by-breath analysis) and converted to kPa: $\%CO_2$ values were converted to mmHg (1:7.5mmHg) and then kPa (1:0.13kPa) (AAST, 2018)); 2) Transcutaneous carbon dioxide ($TcCO_2$, in kPa) measured using an ear clip sensor and TOSCA device (TCM4, Radiometer Medical ApS, Brønshøj, Denmark). The measurement was recorded as mean over the 40-minute testing period, capturing trend over time.
- Oxygen saturation as measured by fingertip pulse oximetry ($SpO_2\%$). This was recorded continuously (Ohmeda Biox 3700) and displayed in real time.

- Respiratory airflow measured using a pneumotachograph (AD Instruments, MLT300L) attached to a differential pressure transducer (MP45 Validyne Engineering Northridge, California, USA). Participants were asked to tightly seal their lips around the mouthpiece attached to the pneumotachograph with a noseclip in place. Respiratory airflow was recorded during relaxed, resting breathing over a minimum of 10 minutes with a break after 5 minutes. Tidal volume per breath was calculated as the time integral of airflow rate, and respiratory rate was derived from the airflow signal.

2.7 Respiratory Depression Criteria

Significant respiratory depression was defined using conventional clinical criteria (Dahan et al., 2010; Douglas, 2005):

1. SpO_2 below 90% for longer than 10 seconds; Frequency of dips below 90% for longer than 10 seconds;
2. $ETCO_2$ > 6.6kPa per breath, frequency of breaths above 6.6kPa (equivalent to 6.5%);
3. Mean Transcutaneous carbon dioxide ($TcCO_2$) above 6kPa (across 40-minute testing period);
4. Any absence of EMG_{para} activity or absence of inspiratory airflow of longer than 10 seconds (apnoea/respiratory pause); Frequency of respiratory pauses longer than 10 seconds.

2.8 Personal, Drug Use and Addiction Treatment Characteristics

Characteristics relating to personal drug use or wider behavioural or addiction treatment related factors were obtained through a detailed medical history questionnaire at the start of the study session. These were focussed on age, duration of drug use, number of previous overdose events, dose of OAT, number of times in addiction treatment and length in current treatment.

2.9 Statistical Analysis

Data were tested for normality and analysed using parametric or non-parametric statistical tests as appropriate. Any ordinal data were presented as median (interquartile range) and

non-parametric bivariate testing was used or as mean (standard deviation). Dichotomous 2x2 criteria or categorical data between groups were tested using Fisher's exact test or Pearson's Chi Square. Spearman Rank (Rs) was used to assess frequency data and the relationship between related continuous, scale data and also, Mann Whitney U (U-statistic) were used to test for differences between groups. Data analyses were performed using SPSS software v22 for Mac (SPSS Inc, Chicago, Illinois, USA). Significance was determined at values of $p < 0.05$ level.

3 Results

3.1 Descriptive Data

Twenty participants with OUD and 20 comparator opioid-naïve participants undertook the same protocol (characteristics of both groups in Table 1; flowchart of recruitment for OUD participants in Supplementary Figure 1). Twelve of the 20 OUD participants were prescribed buprenorphine or buprenorphine combined with naloxone (median: 12mg; IQR: 7.5-216mg, per day), six were prescribed methadone (median: 67.5mg; range: 40-105mg, per day; one of which was injectable), one was prescribed injectable diamorphine and one was prescribed oral diamorphine. Three participants were ex-cigarette smokers, and the remaining 17 were current cigarette smokers, with a median 15 (IQR: 10-25) pack-years. Eleven of the 20 participants had taken their OAT on the day of testing.

Fifteen of the 20 participants with OUD self-reported use of other drugs and/or alcohol. Seven participants reported using alcohol at quantities above the UK weekly recommended allowance (14 units per week, equivalent to 10ml or 8g of pure alcohol). More details on other drug use are provided in Supplementary Table 1.

Of the 20 OUD participants, 13/20 had COPD by lung function and clinical criteria. Of these, only five had previously been diagnosed with a chronic lung disease and been prescribed appropriate medication. The remaining seven participants had normal lung function.

Blood gas analysis was conducted for 19/20 OUD participants (1 declined) and for the whole COPD comparator group (Supplementary Table 2).

3.2 Respiratory Depression Frequencies

There were four respiratory depression indicators. Of the OUD participants, at least 1/4 of the respiratory depression indicators was observed for all (20/20 participants), and 2/4 (or more) indicators were observed in over half (11/20 participants) (Table 2). Of the OUD participants, at least 2/4 indicators were observed in 6/7 participants and of the OUD-COPD participants, at least 2/4 indicators were observed in 6/13 participants (Table 2). Between the two OUD

groups, there were no differences in respiratory depression frequencies (X_2 1.7, p=0.19) (Table 2).

Among OUD, episodes of significant SpO_2% desaturation (SpO_2% <90% sustained for >10 seconds) occurred in 5/20 participants, $ETCO_2$ > 6.6kPa in 14/20, mean $TcCO_2$ > 6kPa was in 8/20, and respiratory pauses >10 seconds in 11/20 participants (Supplementary Figure 2).

With 2/7, and 2/13, participants displaying one respiratory depression indicator in the HC and COPD comparator groups, respectively, there were significant differences between the OUD groups and their respecting comparator groups (OUD v HC: p=0.02; OUD-COPD v COPD: p=0.0001, using Fisher's exact test).

Overall, using Fisher's exact test to compare the frequency of significant respiratory depression, there was a greater frequency of significant respiratory depression in all participants with OUD compared to healthy controls (p=0.021, Table 2; for specific criteria, Table 3).

3.3 Respiratory Depression Amongst OUD

Median (IQR) SpO_2 in OUD participants was 95.9% (94-98.5%) and 96.3% (95-98%) in HC, with no significant differences between OUD and HC groups (Table 4). Median (IQR) SpO_2 in OUD-COPD participants was 95.3% (91.8-98.3%) compared to SpO_2 93.8% (89.;4-95.9%) in COPD, with no significant differences between OUD-COPD and COPD groups.

In OUD-COPD participants, median(IQR) $ETCO_2$ per breath was 5.8 (4.6-7.2) kPa, and $TcCO_2$ was 5.7 (4.4-7.4) kPa. Both capnography measures were significantly higher compared to the corresponding COPD group (Median (IQR) $ETCO_2$: 4.6 (3.6-5.5)kPa; Median (IQR) $TcCO_2$: 5 (3.5-6.1)kPa; U-statistic: 19 and 44, p<0.05, respectively). No differences between OUD and HC groups were observed for capnography measures (Table 4).

NRDI was significantly lower in the OUD-COPD group compared to the COPD group (median IQR: 79.9 (35-172.6)min^{-1} and 217 (43.7-504.5)min^{-1}, respectively, with U-statistic 30, p<0.01). There was no significant difference in NRDI between OUD and HC (Table 4).

No significant differences in respiratory rate were observed between OUD groups and their comparators (Table 4).

Overall, no differences between OUD groups and their comparators were observed for SpO_2%. Despite this, $ETCO_2$, $TcCO_2$ were significantly higher in OUD-COPD compared to the COPD group, i.e. respiratory depression was still indicated despite normal levels of SpO_2% (Table 4). Respiratory depression more commonly occurred in OUD participants than in comparator groups (Table 3 and Table 4).

3.4 Individual and Wider Behavioural Features

There were four main significant associations between features of drug use or personal characteristics of OUD participants and physiological markers of respiratory depression: 1) a higher dose of OAT was associated with higher levels of $ETCO_2$ and more frequent number of breaths above $ETCO_2$ 6.6kPa (Rs=0.57 for both, p=0009, p=0.008, respectively) and a number of respiratory pauses (Rs =0.5, p=0.02); 2) age was inversely correlated with NRDI (Rs=-0.43, p=0.04); 3) smoking pack year history was inversely correlated with levels of SpO_2% (Rs=-0.42, p=0.045). 3) a longer duration of drug use was associated with lower levels of NRDI (Rs=-0.44, p=0.05), higher number of respiratory pauses (Rs=0.47, p=0.04) and a higher level of $TcCO_2$ (Rs=0.5, p=0.04). There was no significant relationship between the other features and physiological measures (Table 5).

3.5 Buprenorphine versus Methadone

There were no significant differences in the respiratory depression frequencies between those on buprenorphine and those on methadone (Table 6a, 6b & Supplementary Table 3).

4 Discussion

Among OUD, markers of respiratory compromise as manifest by high levels of carbon dioxide ($ETCO_2$ and $TcCO_2$) were commonly observed, as were pauses in respiration. However, falls in SpO_2% below clinically-acceptable ranges were comparatively less common. This suggests that respiratory depression is frequently present but would not be detected by routine clinical assessments within drug treatment centres, using SpO_2% alone (DOH, 2017). The findings of this study also suggest that respiratory depression is significantly more severe in OUD than in opioid-naïve participants. Importantly, this work demonstrates that detection of respiratory depression is possible using relatively simple measures.

This is the first study to examine respiratory depression in patients with COPD as well as OUD and who are prescribed buprenorphine. Contrary to expectations, we found no differences between markers of respiratory depression frequencies between those on buprenorphine and those on methadone.

4.1 Age, Drug Use Characteristics and Respiratory Depression

Chronic opioid use amongst older people is an issue that has raised much attention in recent years because of links to the increases in drug-related deaths (Bird and Robertson, 2020; Gao et al., 2016; Pierce et al., 2015). This study did not show a strong connection between age and markers of respiratory depression. However, limitations of the dataset denote caution in forming stronger conclusions.

A longer duration of drug use and higher OAT dose were significantly related to a higher number of respiratory/apnoeic pauses (longer than 10 seconds) and at least one of: a) lower levels of NRDI, or b) a higher level of $ETCO_2$ or $TcCO_2$. Thus, there was an association between duration of drug use and OAT dose with an increase in apnoeic pauses, a more dampened level of respiratory drive and/or a higher level of carbon dioxide, i.e. more episodes of respiratory depression were observed. This is clinically important since an occurrence of these in combination is potentially fatal.

The analysis reported in this paper is based on retrospective data, but introduces the possibility that such physiological measures might serve as predictors of overdose risk.

4.2 Explanation of Findings

SpO_2% was a poor marker of compromised gas exchange in all OUD participants. Generally, decreased SpO_2% is often a late marker of respiratory failure whilst capnography provides an early indicator of respiratory depression and impending respiratory failure (Dahan et al., 2010; Davidson and Hosie, 1993; Jolley et al., 2015; Kopka et al., 2007; Lam et al., 2017; McCarter et al., 2008). In this study, high levels of capnography and respiratory pauses were observed with normal levels of SpO_2%. This suggests that clinical assessments within drug treatment services should incorporate measures of impaired ventilation, such as respiratory rate and pattern, or capnography, in addition to SpO_2% to provide a more reliable measure of respiratory depression.

Levels of NRDI among OUD-COPD were lower than those reported in other studies of COPD patients (Jolley et al., 2009; Murphy et al., 2011). However, these levels were not clinically significant. The levels of NRDI amongst OUD participants actually fell within the ranges seen in healthy adults (MacBean et al., 2016; Reilly et al., 2011), and were consistent with the previous study with a similar cohort (Jolley et al., 2015).

The relationship between drive and measures of respiratory function and respiratory depression is uncertain. A lower NRDI is evidently counterintuitive in the face of chronic use of opioids in combination with a higher likelihood of developing age-related diseases, including COPD where drive is required to increase to maintain adequate levels of blood gases. The data in this study therefore suggest that there may be a chronic suppression of NRD by long-term opioid use, as demonstrated by an inappropriately-low level of NRDI relative to the severity of disease.

4.3 Buprenorphine versus Methadone

There were no observed differences in markers of respiratory depression between those on buprenorphine and those on methadone. This is interesting because buprenorphine is thought to have a lower risk of respiratory depression and lower overdose rates compared to other OAT medication (Dahan, 2006; Strang et al., 2017; Walsh et al., 1994), although it needs to be borne in mind that the latter may be partly due to lower rates of buprenorphine testing at post-mortem (EMCDDA, 2019b) as well as exclusion of patients with lung disease within clinical trials on buprenorphine. Further analysis into buprenorphine participants with or without lung disease shows a more varied picture. Some of the physiological responses among buprenorphine participants with lung disease were significantly different to controls (Table 6b). Comparatively, those on buprenorphine with no lung disease showed no significant differences in physiological measures or indices compared to healthy volunteers. These varied results may be due to the small number of participants in this study but may also represent a difference in the tolerability of buprenorphine in those with lung disease. It is important draw attention to the lack of relative safety data on those on buprenorphine with COPD to date.

4.4 Strengths and Weaknesses of the Study

This study uniquely examines the overlap between chronic respiratory disease, risk factors of overdose and actual measures of respiratory depression. This is an important area and there are very few studies that have been able to conduct such detailed physiological investigations. Nevertheless, it has shown that an investigation into chronic, everyday respiratory depression can be undertaken without disrupting the individual's treatment pattern or using pattern.

The study has a few limitations. Initially, it must be noted that the results described in this paper may well be an underestimate of the true respiratory events as airflow measurement was not continuous. It is well established that instrumentation at the mouth influences and can disturb respiratory pattern (Perez and Tobin, 1985). Studies that we have conducted subsequent to this have resolved the issue by using a different method for obtaining airflow.

Matching age between the OUD-COPD and COPD groups was challenging. The COPD patients were generally older than the OUD-COPD group (median (IQR) age for COPD and OUD-COPD groups, respectively were: 66 (62-72) and 49 (42-55) years). It was difficult to find COPD patients who were matched both for predicted FEV_1% and age. This most likely reflects a high prevalence of severe COPD in relatively young OUD cohorts (Walker et al., 2015) as a result of cigarette smoking (Cookson et al., 2014) and inhaled drug use (Mehta et al., 2020). However, our COPD and OUD-COPD cohorts were well-matched for GOLD disease severity, which is defined with reference to predicted FEV_1%. Mathematical models used to predict normative ranges of lung function parameters such as FEV_1 include age, as well as sex and height, as explanatory variables (Quanjer et al., 2012).

The study did not exclude participants if they had used other (non-prescribed) drugs as this was an observational study among a population where polydrug use is common. However, it is difficult to state from urinalysis whether the other drugs consumed were recent enough to impact measures obtained on the study day. Future studies should consider saliva testing and/or pharmacokinetic data analysis.

Furthermore, as this was a convenience sample, the study group comprised a smaller number of OUD participants without COPD and a higher number of male participants, although this was seemingly reflective of the general characteristics of opioid treatment population (Palmer et al., 2012; PHE, 2018). The sample size was too small to conduct more detailed statistical tests.

Additionally, whilst participants were discouraged from sleeping during the study and monitored for signs of impending sleep (such as closing of the eyes), we acknowledge that we are not able to provide objective physiological evidence of sleep/wake state, such as polysomonography. However, subjects were communicative throughout the study and so it is unlikely that the respiratory depression observed in the OUD cohort represents sleep disordered breathing. Furthermore, in the current study we were able to distinguish between central apnoeic events and peripheral cessation of respiratory airflow (caused by e.g. upper

airway obstruction) through continuous monitoring of parasternal intercostal muscle electromyogram activity (see Supplementary Figure 2).

It must also be noted that participants with OUD were recruited from a Lung Health service within their drug treatment clinic where they were either self-referred or encouraged to do so by staff. Therefore, generalisability of findings needs to be with caution.

4.5 Implications

Deaths from opioid toxicity could be prevented if more was understood about the mechanisms of respiratory control. These data indicate that patients in an OAT clinic exhibit signs of respiratory compromise and these signs are unobserved in routine care. This might mean that even a slight increase in respiratory challenge – for example, a chest infection - may be enough to produce fatal respiratory depression even if the dose of heroin has not been changed. These data suggest that, in patients with comorbid COPD, buprenorphine has an impact on respiratory function which previous studies have not identified. Importantly, the clinical tool we currently have at our disposal, namely pulse oximetry, will not detect these abnormalities until a comparatively late stage of respiratory depression. Finally, we do not know the prognostic implications of these observed abnormalities. Further research to elucidate the relationship between such abnormalities and both overdose events and episodes of respiratory failure in those with lung disease are now needed so that patients and clinicians can be appropriately informed regarding the benefits and risks of long-term opioid use, including OAT.

Alternative and more convenient measures of respiratory function are also urgently required. This study can inform future research into practical wearable versions of these measures so as to detect overdose onset and trigger an emergency response. Future studies need to concentrate on how to reliably predict vulnerability to a fatal overdose. Determining physiological indices that are most suitable for mobile monitoring is the first step in this journey.

5 Conclusions

Everyday respiratory depression exists in people with OUD, and among those both with and without identified comorbid COPD. Being able to elicit these data by means of a simplified, practical method shows that it can be taken further into a clinical setting and can also inform further technological developments to better improve early detection of opioid overdose and other forms of respiratory compromise.

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Nothing declared

Contributors

BT conducted the research and prepared the manuscript whilst under the supervision of JS and CJJ. ML-G, PSPC were involved in data collection and manuscript preparation. GFR, MK, JM and NJK were involved in manuscription preparation.

All authors have approved the final article.

Conflict of Interest

CJJ, GFR, JM, ML-G declare no conflict of interest.

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All Groups	OUD, n=7 Median (IQR)	Healthy Controls (HC) n=7 Median (IQR)	Between-group comparison, U-statistic (p-value)	OUD-COPD n=13 Median (IQR)	COPDs n=13, Median (IQR)	Between-group comparison, U-statistic (p-value)	Total n=40 Median (IQR)
Age (years)	48 (46 – 52)	50 (45-57)	18.5 (0.44)	49 (42-55)	66 (62-72)	16.5 (0.0001)	**49 (44-55)**
Sex (F:M)	2:5	1:6	21 (0.53)	2:11	3:10	78 (0.63)	**8:32**
BMI (kg/m^2)	30 (27.2–32.1)	26 (23.9-26.6)	11 (0.90)	23 (19.7-28)	27 (24.3-30)	69.5 (0.44)	**26.5 (21.8-30.4)**
FEV_1%pred (%)	96.1 (90.5–96.5)	100 (97.5-110.3)	12 (0.11)	77.1 (66.8-90.1)	60 (52.8-74.5)	51.5 (0.90)	**82.9 (60.1-96.1)**
VC%pred (%)	99.7 (96.9–107.1)	108.1 (99.6-115.1)	16 (0.28)	106.7 (96-114.8)	104.6 (85.4-111.6)	67 (0.37)	**105.5 (93.1-114.6)**
FEV_1/VC%ratio (%)	74.7 (71.9–76.8)	75 (69.7-78.5)	23 (0.85)	60.2 (48.7-64.3)	52 (45-56.6)	62 (0.25)	**62.9 (50.7-74.7)**
COPD Severity	No COPD	No COPD	n/a	Moderate	Moderate	n/a	**n/a**

Table 1: Demographics and lung function results (and between-group comparisons) for all four groups. OUD-COPD participants and their controls (COPDs) were matched in all criteria except age (n=13 in each group), OUD participants without lung disease and their controls (healthy controls) were matched in all criteria (n=7 in each group). FEV_1%pred: % predicted of Forced Expiratory Volume in 1 second; VC%pred: % predicted of Vital Capacity; OUD: Opioid Use Disorder; LD: Lung Disease. COPD severity (GOLD stage of mild, moderate, severe or very severe).

Number	SpO_2 <90% >10s	$ETCO_2$ breaths >6.6kPa	$TcCO_2$ >6kPa mean	Resp Pauses >10s	Number	SpO_2 <90% >10s	$ETCO_2$ breaths >6.6kPa	$TcCO_2$ >6kPa mean	Resp Pauses >10s
OUD:					**Healthy controls:**				
1		✓		✓	**1**		✓		
2[1]		✓	✓	✓	**2**		✓		
5	✓			✓	**3**				
8			✓	✓	**4**				
9		✓	✓		**5**				
16		✓			**6**				
18[1]		✓		✓	**7**				
OUD-COPD:					**COPDs:**				
3[1]			✓		**1**				
4[1]		✓			**2**				
6[1]	✓	✓		✓	**3**				
7[1]			✓		**4**				
10[1]	✓		✓		**5**				
11	✓	✓		✓	**6**				
12		✓			**7**				
13		✓			**8**				
14	✓	✓	✓	✓	**9**		✓		
15[1]				✓	**10**		✓		
17		✓	✓	✓	**11**				
19		✓		✓	**12**				
20		✓			**13**				

Table 2: Table displaying presence of respiratory depression criteria in all participants with OUD and their corresponding controls. Fisher's exact test was used to test for differences between criteria, both groups showed significant differences. OUD and healthy controls p=0.021, and OUD-COPD and COPDs p=0.0001. [1]participants took OAT medication on the day of testing.

Respiratory Depression Indices:	**OUD n=7**	**Healthy Controls n=7**	**Between-group comparison, U-statistic (p value)**	**OUD-COPD n=13**	**COPDs n=13**	**Between-group comparison, U-statistic (p value)**
SpO_2 dips	0.5 (1.2)	None	17.5 (0.28)	1.5 (4.3)	None	58.5 (0.03*)
$ETCO_2$ increases	31.6 (74.4)	0.3 (0.8)	10 (0.04*)	66.1 (94.4)	0.3 (0.9)	30 (0.002**)
Respiratory pauses	1.6 (1.7)	None	7 (0.009**)	2.5 (5.5)	None	45.5 (0.007**)

Table 3: Comparison of severity of respiratory depression indices for all OUD participants and their corresponding controls. The average (standard deviation) number of indices/criteria exhibited by participants across 20 minutes of testing is shown, as well as U-statistic (p value) between the groups. Significant differences (Mann Whitney U test: U-statistic (p value)) between OUD participants and controls were observed in both sets of groups across all respiratory depression criteria except SpO_2. *p<0.05; **p<0.01.

		SpO_2 (%)		$ETCO_2$ (kPa)		$TcCO_2$ (kPa)		NRDI (min^{-1})		Respiratory Rate (breaths/min)	
		Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Groups	**OUD**	95.85	94.20-97.76	5.93	5.32-6.47	5.77	4.81-6.24	87.62	52.56-84.91	13.20	11.58-16.75
	Healthy Controls	96.33	96.10-97.20	5.79	5.69-6.00	5.51	4.65-5.93	76.93	73.74-90.90	13.00	12.30-14.70
	OUD-COPD	95.30	93.20-96.33	**5.80****	5.21-6.65	**5.68***	4.89-6.38	**79.9****	60.00-128.21	13.60	10.45-14.69
	COPD	93.80	91.95-94.93	**4.58****	4.11-5.33	**5.00***	4.75-5.32	**217.02****	159-67-465.52	15.47	13.13-18.92
All	**OUD**	96.22	93.90-98.53	5.84	5.18-6.48	5.68	4.10-6.75	79.69	51.67-164.20	13.60	6.00-18.10
All	**Controls**	94.29	89.44-98.30	5.24	3.56-7.15	5.22	3.46-7.35	158.92	34.99-504.50	13.99	6.60-25.71

Table 4: Physiological measures for all groups. OUD participants (OUD group), their corresponding controls (healthy controls; HC), OUD with COPD (OUD-COPD), with their corresponding controls with Lung Disease (COPD). The bottom rows display all controls and all OUD participants. *Significant difference between medians, *p<0.05; **p<0.01, which was seen only between OUD-COPD and COPD in $ETCO_2$, $TcCO_2$ and NRDI (U-statistic: 19, 44 and 30, respectively).

Characteristic	$ETCO_2$ (kPa)	$ETCO_2$ >6.6kPa freq.	NRDI (min^{-1})	Respiratory pauses >10s freq.	$TcCO_2$ (kPa)	SpO_2 (%)	SpO_2 < 90% >10s freq.
Age	-0.30	-0.32	**-0.43***	-0.08	0.28	-0.28	0.17
BMI	0.28	0.12	-0.10	0.22	-0.08	-0.30	0.37
Smoking pack history	-0.36	-0.30	0.17	0.03	0.17	**-0.41***	0.28
Duration of Drug Use	0.15	-0.14	**-0.44***	**0.51***	**0.47***	-0.04	0.06
No. previous overdose events	**0.42***	0.17	-0.16	0.23	0.14	0.13	-0.04
OAT dose	**0.57****	**0.57****	-0.13	**0.47***	-0.09	0.07	-0.03
No. opioid addiction treatment episodes	0.02	0.05	-0.26	-0.28	0.05	-0.07	0.17
No. months on current dose	-0.07	0.03	0.002	-0.007	-0.05	0.19	-0.32

Table 5: Results of bivariate correlation (Rs) for personal and wider behaviour, drug use and opioid addiction treatment factors underlying risk of opioid overdose for all OUD participants. OAT dose for each OUD provided in Supplementary Table 1 (average dose of methadone for OUD=77.5mg and for OUD-COPD=64mg; average dose of buprenorphine for OUD=12mg and for OUD-COPD=13mg. Physiological markers shown are: end-tidal carbon dioxide ($ETCO_2$) both level in kPa and frequency of breaths above 6.6kPa ($ETCO_2$>6.6kPa freq.; neural respiratory drive index (NRDI); number of respiratory pauses longer than 10seconds (Respiratory pauses >10s freq.); Transcutaneous carbon dioxide (T_cCO_2 (kPa)); pulse oximetry (SpO_2(%)) as well as number of dips below 90% for longer than 10 seconds (SpO_2 <90%>10s freq.). Freq. = frequency *p<0.05, **p<0.01

		SpO_2 (%)		$ETCO_2$ (kPa)		$TcCO_2$ (kPa)		Respiratory Rate (breaths/min)		NRDI (min^{-1})	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
OAT	Methadone (n=6)	95.05	93.55-97.23	6.46	5.03-6.92	6.07	5.50-6.68	13.30	10.43-16.00	84.68	48.02-108.71
	Buprenorphine (n=12)	95.60	94.00-96.10	5.78	5.30-5.82	5.68	4.70-6.31	13.60	11.40-14.88	78.71	65.50-93.50

Table 6a. Median and ranges of physiological responses of participants on methadone and buprenorphine. There were no significant differences between the two groups (Mann-Whitney U test).

		SpO_2 (%)		$ETCO_2$ (kPa)		$TcCO_2$ (kPa)		Respiratory Rate (breaths/min)		NRDI (min^{-1})	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Group	Buprenorphine with lung disease (n=8)	95.45*	93.55-96.55	5.68*	5.17-5.82	5.62	4.68-6.15	13.60	9.98-14.69	78.75*	54.50-168.94
	Buprenorphine without lung disease (n=4)	95.60	94.30-n/a	5.90	5.37-n/a	5.89	4.86-n/a	13.40	12.60-n/a	78.71	52.85-115.30
	Controls with lung disease (n=13)	93.80*	91.95-94.93	4.58*	4.11-5.33	5.00	4.75-5.32	15.47	13.13-18.92	217.02*	159-67-465.52
	Healthy controls (n=7)	96.33	96.10-97.20	5.79	5.69-5.99	5.51	4.65-5.93	13.00	12.30-14.70	76.93	73.74-90.90

Table 6b. Median and ranges of physiological responses of participants on buprenorphine with or without lung disease and their relevant control groups. *There were significant differences in SpO_2%, $ETCO_2$ and NRDI between those with lung disease and relevant controls (U-statistic: 23, 1 and 14, respectively, all $p<0.05$).