



Reversal of central sleep apnoea with change from methadone to buprenorphine-naloxone: a case report

To the Editor:

Preventing prescription opioid poisoning deaths is a major public health priority in Western societies. Deaths from these medications exceed deaths from all illicit drugs combined [1]. Methadone (for pain treatment) is involved in one third of US prescription opioid overdose deaths despite accounting for only 5% of dispensed opioids [2]. There is a dose-dependent increase in the severity of central sleep apnoea (CSA) with methadone [3–5] and sleep disordered breathing is a contributing factor in methadone-related deaths [2]. The partial μ -agonist buprenorphine is putatively safer than methadone with a ceiling effect upon respiratory depression [6]. However, the effect of buprenorphine on breathing during sleep remains unclear. The only relevant report from a cross-sectional observational study suggested that buprenorphine-naloxone therapy may induce significant CSA and hypoxaemia [7].

In contrast, we demonstrate a case of significant CSA reversed following a change from methadone to buprenorphine-naloxone therapy, together with improved hypoxaemia and normalised awake ventilatory control. A 47-year-old man who had been receiving methadone treatment for 3 years and with a 15-year of intravenous heroin use history was referred for overnight polysomnography (PSG). The patient had symptoms of snoring, witnessed sleep apnoeas and daytime sleepiness with an Epworth Sleepiness Scale (ESS) score of 11. During methadone treatment, he described frequent nausea, occasional vomiting, reduced libido and lack of motivation. He had no history of cardiac or neurological disease. His body mass index was $26 \text{ kg}\cdot\text{m}^{-2}$. He reported no recent substance use (confirmed by regular urinalysis over the preceding month) except from smoking $\sim 1 \text{ g}$ cannabis per day. His oral methadone dose was 47.5 mg once daily. Approximate peak plasma (2 h after dosing) [8] level of R-methadone was $184 \text{ ng}\cdot\text{mL}^{-1}$ and S-methadone was $213 \text{ ng}\cdot\text{mL}^{-1}$. Olanzapine 10 mg *nocte* was his only other medication, prescribed for anxiety by his general practitioner. His awake hypercapnic ventilatory response (HCVR) and hypoxic ventilatory response (HVR) was measured using a validated method [9].

After the first sleep study night, he switched from methadone to sublingual buprenorphine-naloxone as an outpatient, stabilising on once-daily $32/8 \text{ mg}$. After 10 weeks of buprenorphine-naloxone treatment, he had a follow-up PSG and ventilatory response test. He did not take other drugs excepting buprenorphine-naloxone, cannabis use (maintained at same quantity and frequency) and olanzapine 10 mg *nocte*. Plasma concentrations 90 min after dosing (expected peak) [10] of buprenorphine was $11.4 \text{ ng}\cdot\text{mL}^{-1}$ and of the metabolite norbuprenorphine was $15.8 \text{ ng}\cdot\text{mL}^{-1}$. Comparison of the two PSGs and ventilatory control data is summarised in table 1. 10 weeks after switching opioids, his CSA index dropped from 29.1 to 0.7 per h while his obstructive sleep apnoea/hypopnea index (OSAHI) remained 41 per h. His overnight oxygenation significantly improved and the change was not due to body supine position or rapid eye movement (REM) sleep (table 1). His HVR dropped by more than half, from 4.57 to $2.21 \text{ L}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$. While on buprenorphine-naloxone, the patient noticed a reduction in witnessed apnoeas. His daytime sleepiness was improved, with an ESS score of 9. Previously reported symptoms of nausea and vomiting, reduced libido, and lack of motivation were also improved. He reported some experiences of constipation while on buprenorphine-naloxone.

Previous studies suggest that as many as 30% of stable methadone patients have CSA [3, 5]. This case demonstrates that methadone-related CSA and oxygen desaturation during sleep can be resolved by changing to buprenorphine-naloxone therapy. The within-subject design suggests the findings are due to the change in prescribed opioid. The clinical effects of sublingual combination buprenorphine-naloxone formulation are generally attributable to buprenorphine alone as there is minimal sublingual naloxone absorption [10]. The patient transferred from 47.5 mg oral methadone, with an oral morphine-equivalent (OME) dose of 223 mg , and stabilised on 32 mg buprenorphine, equivalent to 1200 mg OME [11], such that any changes are unlikely to reflect a lower total opioid dose.

In this case study, overall AHI is higher on methadone than on buprenorphine, while OSAHI is nearly identical. The only difference is the elimination of CSA events. Similar to our previous reported pattern,

TABLE 1 Comparison of key PSG and ventilatory control parameters with methadone and buprenorphine therapy

	Methadone	Buprenorphine
Central apnoea index per h	29.1	0.7
OSAHl per h	41.1	41.2
Overall AHI per h	70.2	41.9
REM-AHI per h	44.7	57.5
Total sleep time min	440	527
Supine sleep %	84	94
Supine REM %	10.4	4.3
Arousal index per h	23.2	9.1
T ₉₀ min	39.9	15.2
ODI per h	60.3	34.0
HCVR L·min ⁻¹ ·mmHg ⁻¹	2.10	1.51
HVR L·min ⁻¹ ·mmHg ⁻¹	4.57	2.21

OSAHl: obstructive sleep apnoea-hypopnoea index; AHI: apnoea-hypopnoea index; REM: rapid eye movement sleep; T₉₀: sleep time with oxygen saturation measured by pulse oximetry <90%; ODI: index of oxygen desaturation >3%; HCVR: hypercapnic ventilatory response; HVR: hypoxic ventilatory response.

these long-term narcotic use-related CSA events are generally continuous, without concurrent sleep fragmentation, and unlikely to be related to REM sleep or supine position (table 1) [3, 5]. Methadone-related CSA rarely occurs in REM sleep, probably because the augmented HVR is naturally depressed during REM sleep [3, 12]. We found only one CSA event during REM sleep on methadone in this case. Therefore, REM-AHI was lower on methadone night, despite a higher overall AHI and % supine REM sleep compared with the buprenorphine night.

It is possible that the elimination of CSA may due to the reduction of the augmented HVR. Our previous study has demonstrated that stable methadone users have significant CSA and a nearly doubled HVR [3, 12]. Similarly, augmented HVR is also a key mechanism of both high altitude-related CSA and heart failure-related CSA/Cheyne-Stokes respiration [13]. Increased loop gain, particularly controller gain (ventilatory chemosensitivity), has been identified to be a key mechanism of forming cyclical CSA events [14, 15]. While acute opioid use is known to depress both HCVR and HVR, the increased HVR in chronic methadone users is probably a compensatory effect of the long-term depressed central respiratory controller/HCVR [12]. Indeed, our previous study showed that chronic methadone users had 29% lower HCVR and 91% higher HVR compared with matched controls [12]. In our case study, with the elimination of the CSA by changing drugs, HVR dropped to half (4.57 to 2.21 L·min⁻¹·mmHg⁻¹) while HCVR also slightly decreased (2.10 to 1.51 L·min⁻¹·mmHg⁻¹). A reasonable explanation for the CSA improvement in our case would be likely through damping the augmented HVR rather than increasing HCVR.

Our findings contrast with a previous observational study, which suggested buprenorphine-naloxone may induce significant CSA and hypoxaemia [7]. PSGs on 70 opioid-dependent inpatients within 2 days of commencing buprenorphine-naloxone treatment found predominant CSA (average CSA index 11.4 per hr). Hypoxaemia, defined as an oxygen saturation measured by pulse oximetry (SpO₂) <90% for >10% of sleep time, was present in 39% of patients [7]. However, PSG pre-initiation of buprenorphine was not measured, and patients may have had significant CSA and hypoxaemia with chronic opioid use pre-buprenorphine. Furthermore, the study was conducted at high altitude (1500 m), where an SpO₂ of 90% during sleep may be considered normal; indeed, the impact of the high altitude on CSA is also unclear [7].

Our report is limited by its single-case-study nature. We cannot easily explain the improvement in clinical symptoms from our findings. Nevertheless, our case study suggests that at least some methadone patients with CSA and/or hypoxia will have their symptoms resolved by switching to buprenorphine-naloxone. Given the alarming excess deaths with opioid use [16], there are significant clinical and public health benefits to confirming our observations and exploring relevant clinical outcomes in larger populations, preferably using randomised-controlled or within-subject designs.



@ERSpublications

Methadone-using patients with central sleep apnoea may reverse symptoms with switch to buprenorphine-naloxone therapy <http://ow.ly/NilUq>

David Wang^{1,2,3,4}, Nicholas Lintzeris^{4,5}, Stefanie Leung^{4,5}, Paul S. Haber^{4,5}, Brendon J. Yee^{1,2,3,4} and Ronald R. Grunstein^{1,2,3,4}

¹Sleep and Circadian Group, Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia.

²Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Sydney Local Health District, Sydney, Australia. ³Centre for Integrated Research and Understanding of Sleep (CIRUS), University of Sydney, Sydney, Australia.

⁴Sydney Medical School, The University of Sydney, Sydney, Australia. ⁵Drug and Alcohol Services, South East Sydney Local Health District, Sydney, Australia.

Correspondence: David Wang, Woolcock Institute of Medical Research, 431 Glebe Point Road, Glebe NSW 2037, Australia. E-mail: david.wang@sydney.edu.au

Received: March 30 2015 | Accepted after revision: April 29 2015

Support statement: D. Wang is supported by an Australian National Health and Medical Research Council (NHMRC) Project Grant (1043633). R.R. Grunstein is supported by an NHMRC Practitioner Fellowship (1022730). Funding information for this article has been deposited with FundRef.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

References

- Centers for Disease Control and Prevention. Addressing prescription drug abuse in the United States: current activities and future opportunities. www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf Date last updated: September 2013.
- Webster LR, Cochella S, Dasgupta N, *et al.* An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med* 2011; 12: Suppl. 2, S26–S35.
- Wang D, Teichtahl H, Drummer OH, *et al.* Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005; 128: 1348–1356.
- Walker JM, Farney RJ, Rhondeau SM, *et al.* Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med* 2007; 3: 455–461.
- Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. *Sleep Med Rev* 2007; 11: 35–46.
- Dahan A, Yassen A, Romberg R, *et al.* Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* 2006; 96: 627–632.
- Farney RJ, McDonald AM, Boyle KM, *et al.* Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone. *Eur Respir J* 2013; 42: 394–403.
- Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet* 2002; 41: 1153–1193.
- Wang D, Marshall NS, Duffin J, *et al.* Phenotyping interindividual variability in obstructive sleep apnoea response to temazepam using ventilatory chemoreflexes during wakefulness. *J Sleep Res* 2011; 20: 526–532.
- Chiang CN, Hawks RL. Pharmacokinetics of the combination tablet of buprenorphine and naloxone. *Drug Alcohol Depend* 2003; 70: Suppl., S39–S47.
- Nielsen S, Degenhardt L, Hoban B, *et al.* Comparing opioids: A guide to estimating oral morphine equivalents (OME) in research. Technical Report No. 329. Sydney, University of New South Wales, 2014.
- Teichtahl H, Wang D, Cunningham D, *et al.* Ventilatory response to hypoxia and hypercapnia in stable methadone maintenance treatment patients. *Chest* 2005; 128: 1339–1347.
- Dempsey JA, Veasey SC, Morgan BJ, *et al.* Pathophysiology of sleep apnea. *Physiol Rev* 2010; 90: 47–112.
- Dempsey JA, Xie A, Patz DS, *et al.* Physiology in medicine: obstructive sleep apnea pathogenesis and treatment – considerations beyond airway anatomy. *J Appl Physiol (1985)* 2014; 116: 3–12.
- White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 1363–1370.
- Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med* 2010; 363: 1981–1985.