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REVIEW ARTICLE

Effects of the antipsychotic quetiapine on sleep and breathing: a review of clinical findings and potential mechanisms

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Summary

Quetiapine is an antipsychotic medication indicated for schizophrenia and bipolar disorder. However, quetiapine also has hypnotic properties and as such is increasingly being prescribed at low doses 'off-label' in people with insomnia symptoms. Pharmacologically, in addition to its dopaminergic properties, quetiapine also modulates multiple other transmitter systems involved in sleep/wake modulation and potentially breathing. However, very little is known about the impact of quetiapine on obstructive sleep apnoea (OSA), OSA endotypes including chemosensitivity, and control of breathing. Given that many people with insomnia also have undiagnosed OSA, it is important to understand the effects of quetiapine on OSA and its mechanisms. Accordingly, this concise review covers the existing knowledge on the effects of quetiapine on sleep and breathing. Further, we highlight the pharmacodynamics of quetiapine and its potential to alter key OSA endotypes to provide potential mechanistic insight. Finally, an agenda for future research priorities is proposed to fill the current key knowledge gaps.

KEYWORDS
insomnia, lung, off-label prescribing, respiratory physiology, sleep-disordered breathing, upper airway

1 | INTRODUCTION

Quetiapine is an atypical antipsychotic, approved in most countries for the treatment of schizophrenia, bipolar disorder, and in a few

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countries adjunctive therapy with antidepressants for major depressive disorder (AstraZeneca, 2020; FDA, 2020; Pringsheim & Gardner, 2014). However, quetiapine is frequently prescribed 'off-label', most commonly for insomnia, anxiety, and agitation at doses of 100 mg or less (Berge et al., 2022; Carton et al., 2015; Gjerden et al., 2017; McKean & Monasterio, 2012). Daily doses of quetiapine for its approved indications range between 150 and 800 mg/day (AstraZeneca, 2020; FDA, 2020) following a 4–8 day low-dose run-in titration period (Brett, 2015; Drug Utilisation Sub-Committee, 2013; Lee, Pilgrim et al., 2018). Yet, consistent with off-label prescribing, >50% of quetiapine prescriptions are for doses of ≤100 mg (Andrulyte & Bjerrum, 2018; Carton et al., 2015; ClinCalc.com, 2023; Gjerden et al., 2017).

Quetiapine ranks 64th among the most frequently prescribed medications in the United States (ClinCalc.com, 2023). In Norway there was a 10-fold increase in quetiapine prescribing rates from 2004 to 2014, while other antipsychotics have only had a modest increase. Only 2.6% of those prescriptions were for treatment of psychosis (Gjerden et al., 2017). A sampling of prescribing practices in New Zealand found quetiapine was prescribed as much as all other antipsychotics combined. In 2015, the number of prescriptions dispensed annually for quetiapine in Australia with a total population of ~25 million was almost 1 million, of which 41% were for low doses of ≤100 mg (Lee, Pilgrim et al., 2018; Mabbott et al., 2016). While quetiapine is commonly used off-label, it is not recommended in clinical guidelines for the treatment of insomnia (FDA, 2020; Modesto-Lowe et al., 2021; Riemann et al., 2017).

Like other atypical antipsychotics, quetiapine modulates multiple receptor subtypes throughout the central and peripheral nervous systems, as well as cardiac myocytes. Quetiapine and its metabolite *N*-desalkylquetiapine (norquetiapine) are antagonists to histamine H_1 receptors. This may account for its hypnotic effects (Carter & Eckert, 2021; Fang et al., 2016; Jensen et al., 2008; Jones et al., 2001; Sato et al., 2015). Quetiapine and norquetiapine are dopamine, adrenergic, muscarinic (M_1, M_3, and M_5), and serotonin (5-hydroxytryptamine) 5-HT_{2A-C} receptor antagonists. Quetiapine is also a partial serotonin 5-HT_{1A} agonist (Fang et al., 2016; Jensen et al., 2008; Jones et al., 2001; Sato et al., 2015). Quetiapine and norquetiapine have an effect on voltage-gated hERG (the **h**uman **E**ther-à-go-go-**R**elated **G**ene) potassium channels, used by cardiac myocytes, that can lead to prolongation of the cardiac QT interval (Lee, Choi et al., 2018). Quetiapine and norquetiapine block the noradrenaline transporter. This inhibits re-uptake of noradrenaline to increase presynaptic cleft availability (Bortolotto et al., 2021; Cross et al., 2016; Jensen et al., 2008).

2 | HYPNOTIC PRESCRIPTIONS FOR INSOMNIA SYMPTOMS

Primary care complaints of insomnia are very common, and population prevalence estimates of insomnia range from 6% to 22% (Chung et al., 2015; Haycock et al., 2021; Reynolds et al., 2019; Riemann et al., 2017; Sweetman, Melaku et al., 2021). While evidence-based guidelines recommend cognitive behavioural therapy for insomnia (CBT-I), access to trained sleep psychologists who are qualified to deliver CBT-I is limited and are insufficient considering the burden of disease (Haycock et al., 2022).

In the USA, 17% of women and 15% of men report use of a medication for insomnia (Zuo et al., 2022). In Australia, one study found 'pharmacotherapy was used for insomnia in about 90% of management occasions; non-pharmacological advice was given at about 20% of encounters; and onward referral in about 1% of encounters' (Miller et al., 2017). In another Australian study, 96% of primary care clinicians indicated that most of their patients with insomnia symptoms seek pharmaceutical solutions and not lifestyle changes (Sake et al., 2019). A Canadian study found that 5.5% of the adult population reported using a sedative hypnotic agent within the last month (Vozoris & Leung, 2011).

The rate of sedative hypnotic use in people aged >60 years was even higher at >9% and >7% in people who were obese (Vozoris & Leung, 2011), two major risk factors for obstructive sleep apnoea (OSA; Young et al., 2004). Given the increasing awareness of the possible deleterious effects of common hypnotics such as increased risk of falls and serious injury (Thomas et al., 2022) and potential addiction and misuse with benzodiazepine and z-drugs (such as zolpidem), many physicians are reluctant to prescribe these classes of medications. As a result, given the lack of CBT-I options and the need to address insomnia symptoms in their patients, many clinicians have turned to alternate medications with sleep promotion properties. Despite not being supported by insomnia clinical management guidelines, this has led primary care clinicians, sleep specialists, and patients to look for alternatives to manage insomnia with pharmaceutical agents such as the sedating antidepressants mirtazapine and amitriptyline (Bakker et al., 2023; Wong et al., 2017) and atypical antipsychotic medications like quetiapine.

Approximately 30%–40% of people with insomnia also have OSA (Sweetman et al., 2021a), a common sleep disorder characterised by repetitive reductions or obstructions in airflow and consequent periods of hypoxaemia and sleep disruption. Comorbid insomnia and sleep apnea (COMISA) is more difficult to treat than insomnia or OSA alone, and their combination may worsen the severity of each condition (Sweetman et al., 2021a). Difficulty maintaining sleep is the most common insomnia complaint in people with COMISA (Zhang et al., 2019). It is estimated that >80% of people with OSA are currently undiagnosed and untreated (Fleming et al., 2016; Peppard et al., 2013; Swanson et al., 2011; Young et al., 2002). Consequently, a substantial proportion of people who seek assistance from their healthcare providers for insomnia may also have underlying undiagnosed OSA.

Women with OSA often present with non-specific symptoms including sleep disruption consistent with insomnia, mood disturbances, nightmares, and fatigue, rather than the more recognised symptoms of loud snoring, gasping, and daytime sleepiness. Standard questionnaires designed to evaluate the likelihood of OSA are skewed to 'typical' presentations in men, not women (Geer & Hilbert, 2021). Further, after menopause, the risk of OSA increases dramatically

(Heinzer et al., 2015), yet symptoms are often attributed to menopause, not OSA. Women are far less likely to be referred to have objective diagnostic sleep testing then men, even when they present with similar symptoms (Lindberg et al., 2017). Consequently, this may contribute to the observed higher rates of medication use for insomnia in women than men.

Quetiapine is associated with significant weight gain and metabolic syndrome (Barton et al., 2020). Low-dose quetiapine has also been reported to increase the risk of major cardiovascular events compared to z-drugs and serotonin re-uptake inhibitors, particularly for women and the elderly in a Danish nationwide registry study (Højlund et al., 2022). Accordingly, it is essential to establish whether the potential therapeutic benefits of prescribing quetiapine off-label for insomnia in both men and women outweigh any potential adverse effects on sleep and breathing, and important health outcomes more broadly.

One can imagine a common clinical scenario whereby someone approaches their general practitioner to report a sleep problem that may comprise unrefreshed sleep, daytime fatigue, and multiple awakenings during the night. This is likely to be considered by both the patient and the general practitioner as indicative of insomnia, and primarily a problem of sleep maintenance. Thus, a prescription for a hypnotic may seem like a simple solution. However, given the increasing reluctance to prescribe z-drugs and benzodiazepines, and other influential factors, a prescription for off-label use of quetiapine may be considered. Given that OSA is very common in the community and frequently underdiagnosed, a substantial proportion of these individuals may have OSA either instead of, or in addition to, the identified insomnia symptoms.

3 | SEARCH METHOD

To assess the impact of quetiapine in people with OSA, we collected all articles on quetiapine in clinical trial studies that included polysomnography (PSG) and were published in peer-reviewed journals. Both randomised controlled trials (RCTs) and non-randomised studies with objective measurements of sleep were examined. A review of the literature was done independently by two reviewers and then subsequently the completeness of the literature was verified via an additional search to confirm all relevant articles were found.

The first sweep was done using the broad search terms: 'sleep' AND 'quetiapine' OR 'antipsychotic'. The second sweep of the literature used more specific targeted search terms: 'obstructive sleep apnoea', 'OSA', 'sleep apnoea', 'sleep disordered breathing', 'continuous positive pressure', 'CPAP', 'quetiapine', 'seroquel', 'norquetiapine', '*N*-desalkylquetiapine', 'insomnia', 'polysomnography', 'PSG', 'electroencephalography', and 'EEG'.

Databases used: Google Scholar, Medline, Scopus, Web of Science, ProQuest, Cochrane Library Reviews, PsycINFO, and ClinicalTrials.gov. Further, we used the 'Cited by' feature on Google Scholar to review articles that referenced RCTs on quetiapine that used PSG.

This paper incorporated previously established knowledge from secondary sources and prior reviews on topics related to quetiapine or OSA to provide context.

4 | CURRENT KNOWLEDGE ON THE HYPNOTIC EFFECTS OF QUETIAPINE

Even at low doses (25 mg) quetiapine is a strong histamine H_1 receptor antagonist. This is considered the primary reason for its hypnotic and sedative effects (Jensen et al., 2008; Sato et al., 2015). Further, it is an antagonist to several other wake promoting and arousal systems including: dopamine, muscarinic acetylcholine, and 5-$HT2_{A-C}$ receptors (Fang et al., 2016; Jones et al., 2001). PSG studies indicate that quetiapine can improve sleep architecture and increases total sleep time. An increase in N2 sleep has been observed consistently, and some studies report an improvement in sleep efficiency. Duration of light sleep (N1), deep/slow-wave sleep (N3), and rapid-eye-movement (REM) sleep has typically remained largely unaltered by quetiapine (Table 1) (Chakravorty et al., 2014; Cohrs et al., 2004; Fernandez et al., 2009; Gedge et al., 2010; Karsten et al., 2017; Wiegand et al., 2008).

5 | CURRENT UNDERSTANDING OF THE EFFECTS OF QUETIAPINE ON SLEEP-DISORDERED BREATHING

Less is known regarding how quetiapine affects sleep-disordered breathing. In one small study in people with Parkinson's disease, oxygen saturation during respiratory events reached an average of ~81% with quetiapine treatment compared to 93% in the placebo arm. While this was not statistically significant, further investigation as to the possibility of worsening hypoxaemia with quetiapine is required (Fernandez et al., 2009).

In another study, the apnea–hypopnea index (AHI), the standard metric of OSA severity, increased from 11 events/h of sleep at baseline to 43 events/h of sleep with quetiapine. This was both statistically and clinically significant (Khazaie et al., 2018) (Table 2). Another non-RCT noted there was no significant change in respiratory disturbance index between baseline and quetiapine. Unfortunately, however, neither data nor statistical inference were provided (Gedge et al., 2010).

6 | HOW MIGHT QUETIAPINE AFFECT OSA SEVERITY BASED ON ITS PHARMACODYNAMICS AND OSA PATHOPHYSIOLOGY?

As OSA causes fragmented sleep and is characterised by a repeated narrowing with increased resistance (hypopnea) or complete blockage (apnea) of the pharyngeal airway during sleep. Scoring to determine if

TABLE 1 Effects of quetiapine on sleep architecture from polysomnography studies.

Population and Reference	Duration/ design	Quetiapine dose	SE, %	SOL, min	WASO, min	TST, h (min)	N1, min	N2, min	N3, min	REM, min
14 healthy men aged 27 years (Cohrs et al., 2004)	3 nights RCT – crossover	Placebo	90	12	16	7 (13)	28	228	78	99
		25 mg	**94**	7		**7 (30)**	23	258	81	88
		100 mg	**93**	6	16	**7 (28)**	23	275	78	70
18 adults with primary insomnia (Wiegand et al., 2008)	6 weeks	Baseline	83	22		5 (58)			42	
		2 weeks 25–75 mg	**91**	20		**6 (46)**			50	
		6 weeks 25–75 mg	**90**	24		**6 (36)**			44	
16 PD (8 female) patients with visual hallucinations aged 68 years (Fernandez et al., 2009)	1 month (after titration) RCT	Placebo ($n = 8$)	83		63	6 (19)				75
		Up to 150 mg ($n = 8$)	74		96	5 (34)				**40**
11 adults with BD or MDD (Gedge et al., 2010)	28 days	Baseline	70	67		5 (33)	34	190	43	62
		100–200 mg	75	78		5 (53)	37	214	42	61
20 adults treated for alcohol dependency aged 52 years, BMI = 27 kg/m^2 (Chakravorty et al., 2014)	8-week RCT	Placebo arm	83	11	67		26	208	33	88
		400 mg (titrated by week 1)	80	37	**61**		21	251	30	65
19 healthy men without insomnia aged 24 years, BMI = 23 kg/m^2 (Karsten et al., 2017)	2 nights RCT – crossover	Placebo			19	7 (32)	25	200	124	103
		50 mg			**7**	**7 (46)**	**18**	**225**	132	92

Note: not all these studies reported key demographic information. However, where available, these data are included in column 1. **Bold** indicates $p \leq 0.05$ from baseline or placebo.
Abbreviations: BD, bipolar disorder; BMI, body mass index; MDD, major depressive disorder; N1, light stage 1 sleep; N2, stage 2 sleep with spindles; N3, slow wave 'deep sleep'; PD, Parkinson's disease; PLM, periodic leg movement; REM, rapid eye movement (sleep stage); RCT, randomised controlled trial; SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time; VH, visual hallucinations; WASO, wake (wakefulness) after sleep onset.

an individual has OSA continues to evolve with early definitions defining OSA as ≥5 respiratory events/h of sleep (Kapur et al., 2017).

The pathophysiology of OSA is heterogeneous with distinct endotypes, including low arousal threshold, high loop gain, and inadequate upper airway muscle responsiveness during sleep (Figure 1) (Altree & Eckert, 2022; Eckert, 2018; D.J. Eckert et al., 2013). Most individuals with OSA have some impaired anatomy with evidence of increased upper airway crowding and narrowing. Airway crowding and narrowing may be caused by excess adipose tissue, orthostatic fluid shifts during sleep, or muscle hypertrophy (Pépin et al., 2022). Each of these factors, as well as a highly compliant pharyngeal airway, can increase the propensity for upper airway collapse during sleep. Non-anatomical causes of OSA include a low arousal threshold, high loop gain, and inadequate muscle response during sleep (Figure 1) (Eckert, 2018). While most current treatments for OSA target the upper airway crowding, non-anatomical OSA endotypes represent novel targets for emerging pharmaceutical research (Altree & Eckert, 2022; Baillieul et al., 2022; Lim et al., 2021; Osman et al., 2023) (Figure 1). As previously described, quetiapine modulates multiple receptor subtypes with variable antagonist or agonist actions. Accordingly, theoretically, there is potential for both beneficial and detrimental effects on OSA (Table 3).

6.1 | Low arousal threshold

About one third of people with OSA have a low arousal threshold. This manifests as a high propensity for cortical arousal, or 'waking up', to relatively minor respiratory disturbances prior to activation of other compensatory mechanisms. For example, people with a low arousal threshold endotype have fragmented sleep and typically wake up before there is sufficient respiratory stimulus (i.e., negative airway

TABLE 2 Effect of quetiapine on key sleep disordered breathing parameters.

Population	Duration/design	Quetiapine dose	AHI, events/h, mean (SD)		SpO_2 during events, %, mean (SD)
16 PD patients (8 female) with visual hallucinations aged 68 years (Fernandez et al., 2009)	1 month (after titration) RCT	Placebo ($n = 8$)			93 (1)
		Up to 150 mg ($n = 8$)			81 (33)
20 adults treated for alcohol dependency aged 52 years, BMI = 27 kg/m^2 (Chakravorty et al., 2014)	8-week RCT	Placebo arm	Pre-AD Tx	10 (12)	
			Post-AD Tx	4 (5)	
		400 mg (titrated by week 1)	Pre-AD Tx	13 (15)	
			Post-AD Tx	7 (7)	
13 paradoxical insomnia participants (9 female) aged 45 years, BMI = 26 kg/m^2 (Khazaie et al., 2018)	4 ± 1.6 months	100–200 mg (mean 130 mg)	Pre-Tx	11 (10)	
			Post-Tx	43 (21)	

Note: not all these studies reported key demographic information. However, where available, these data are included in column 1.
Abbreviations: AD, alcohol dependency; AHI, apnea–hypopnea index; BMI, body mass index; PD, Parkinson's disease; RCT, randomised controlled trial; SD, standard deviation; SpO_2, oxygen saturation; Tx, treatment.

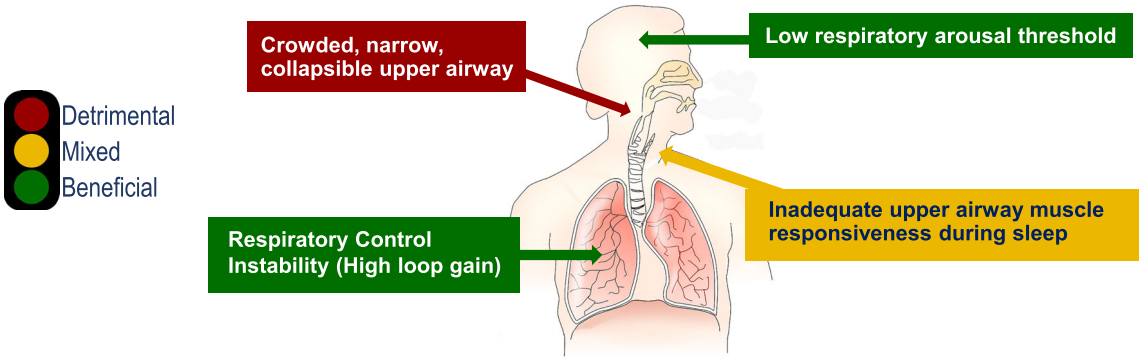

FIGURE 1 Possible effects of quetiapine on obstructive sleep apnoea (OSA). Colour coding indicates how quetiapine may have detrimental (red), mixed (orange) or beneficial (green) effects on the key mechanistic causes (endotypes) that contribute to OSA. Increased weight gain is a common side-effect of quetiapine, which would be anticipated to increase narrowing and crowding; thus, increase upper airway collapsibility. Quetiapine is an antagonist to several receptors, some may increase while others decrease responsiveness of the pharyngeal dilator muscles, also affecting collapsibility. As quetiapine has hypnotic properties, it would be expected to increase respiratory arousal threshold. As a dopamine and serotonin 5-HT_{2A} antagonist quetiapine may decrease carbon dioxide (CO_2) sensitivity and thus decrease loop gain. Refer to the text for further details. Background figure is a modified version of Respiratory System by Theresa Knott and is licensed under CC-BY-SA 3.0.

TABLE 3 Pharmacological properties of quetiapine and potential effects on sleep and breathing.

Receptor	Antagonist or agonist	Effect on sleep and breathing	Possible effect on OSA endotype
Histamine H_1	Antagonist	Sedative Histamine has been found to stimulate the genioglossus muscle	Beneficial for low respiratory arousal threshold endotype? Detrimental to pharyngeal muscle endotype?
Dopamine receptors (all)	Antagonist	Dopamine neurones are involved in regulation of the sleep/wake via ventral tegmental area mediated via GABA receptors Dopamine D_2 receptors inhibit the carotid body chemoreceptors ↓ CO_2 sensitivity	Beneficial for high loop gain endotype?
Muscarinic acetylcholine receptors M_1, M_3 and M_5	Antagonist	Antimuscarinic agents have recently been identified as a target to reduce OSA severity. Antagonist found to increase upper airway muscle hypotonia during sleep	Beneficial for pharyngeal muscle endotype especially in REM?
Serotonin 5-hydroxytryptamine receptor 5-HT_{2A-C}	Antagonist	Activation of the serotonin receptors 5-HT_{2A} are required for hypercapnia (CO_2) arousal from sleep. 5-HT_{2A} receptor provides excitatory input to hypoglossal motor neurones in animal models	Beneficial for high loop gain endotype? Detrimental for pharyngeal muscle endotype?
5-HT_{1A}	Partial agonist	Unknown	
Adrenergic receptor (all)	Antagonist	Adrenergic α_1 antagonist decreases upper airway muscle activity during sleep.	Detrimental for pharyngeal muscle endotype?
Noradrenaline transporter	Blocker	Increase adrenaline at the presynaptic cleft, may reduce OSA severity.	Beneficial for pharyngeal muscle and high loop gain endotypes?

Abbreviations: GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine; OSA, obstructive sleep apnoea; REM, rapid-eye-movement sleep.

pressure and carbon dioxide [CO_2]) to activate upper airway muscles to restore airflow (Altree & Eckert, 2022). Dopamine via the ventral tegmental area in the midbrain influences sleep wake regulation (Oishi & Lazarus, 2017). Based on its reported hypnotic properties in the context of insomnia, (Cohrs et al., 2004; Wiegand et al., 2008), similar to other hypnotics (Eckert et al., 2011; Eckert et al., 2013; Eckert et al., 2014), quetiapine would be expected to increase the arousal threshold. This may reduce OSA severity in people with a low respiratory arousal threshold (Carter & Eckert, 2021). Conversely, further suppression of arousal with quetiapine in people who already have blunted arousal responses (i.e., those with a high arousal threshold) may worsen hypoventilation and hypoxaemia (Carter & Eckert, 2021). However, this has not been investigated. Thus, whether quetiapine can reduce OSA severity in people with a low arousal threshold endotype or worsen blood gas disturbances in those with a high arousal threshold remains unknown.

6.2 | High loop gain

During sleep, with the loss of behavioural inputs to breathe, CO_2 provides the main drive to breathe (Eckert, 2021). About one third of people with OSA have 'high loop gain', which is essentially characterised by an excessive response to small changes in CO_2 during sleep that leads to unstable breathing and sleep-disordered breathing pathogenesis (Baillieul et al., 2022; Eckert et al., 2013). Activation of serotonin 5-HT_{2A} receptors is required for hypercapnia (high CO_2) induced arousal from sleep (Buchanan et al., 2015; Smith et al., 2018). The main peripheral sensor for CO_2 and respiratory afferent feedback is via the carotid bodies. Dopamine D_2 receptors inhibit carotid body chemoreceptors (Leonard & Nurse, 2020; Zapata et al., 1983). As quetiapine is an antagonist to both 5-$HT2_A$ and D_2 receptors, its potential effects on respiratory control and breathing stability, including in people with high loop gain, are unclear and require investigation.

6.3 | Inadequate upper airway muscle responsiveness during sleep

During sleep, the genioglossus, the largest pharyngeal dilator, and other upper airway dilator muscles can compensate for an anatomically crowded, collapsible upper airway to maintain airway patency and adequate airflow (Sands et al., 2014). However, approximately one third of people with OSA have inadequate or poorly coordinated upper airway muscle responses to breathing disturbances during sleep (Altree & Eckert, 2022; Eckert et al., 2013). The 5-$HT2_A$ receptors provide excitatory input to hypoglossal motor neurones in animal models (Fenik & Veasey, 2003). Hypoglossal motor neurone

(which provide drive to genioglossus) responses, to chronic intermittent hypoxia are also dependent on 5-$HT2_A$ in animal models (Li et al., 2019). Quetiapine is a 5-$HT2_A$ antagonist. Accordingly, if these mechanisms are important in humans, quetiapine may decrease pharyngeal muscle activity and worsen OSA. Histamine also alters hypoglossal motor neurone excitability to chronic intermittent hypoxia and histamine can activate the genioglossus muscle (Liu et al., 2016; Xie et al., 2021). Quetiapine is a H_1 histamine receptor antagonist, which may therefore reduce upper airway muscle activity and worsen OSA. However, quetiapine also has antimuscarinic properties, as an antagonist to muscarinic acetylcholine receptors M_1, M_3, and M_5 (Fang et al., 2016; Jensen et al., 2008; Jones et al., 2001; Sato et al., 2015). Antimuscarinic agents, in combination with noradrenergic agents, have recently been found to reduce OSA severity via reductions in the AHI and improvements in oxygenation (Aishah et al., 2021; Lim et al., 2021; Perger et al., 2022). Reboxetine alone, a noradrenaline re-uptake inhibitor, reduces OSA severity (Altree et al., 2022). Quetiapine blocks the re-uptake of noradrenaline (Bortolotto et al., 2021; Cross et al., 2016; Jensen et al., 2008). Adrenergic α_1 antagonism decreases upper airway muscle activity during sleep (Taranto-Montemurro et al., 2021). Blockers of the tandem of pore domains in a weak inward rectifying K^+ channel (TWIK)-related acid-sensitive potassium channels, administered topically via intranasal spray reduces airway collapsibility in people with OSA (Osman et al., 2023). While quetiapine blocks voltage-gated hERG potassium channels, even at low doses (100 mg), there are no data on how it affects tandem pore domain potassium channels (Kim et al., 2016; Lee, Choi et al., 2018). Accordingly, given the potentially opposing mechanisms, it is unclear how quetiapine impacts this endotype and the related downstream effects on OSA severity.

7 | WEIGHT GAIN AND METABOLIC SYNDROME

Long-term use of quetiapine causes weight gain (Bernardo et al., 2021; Burin et al., 2022). This would be expected to increase upper airway crowding and narrowing making it more prone to collapse and thus, increasing OSA severity (Peppard et al., 2000; Wang et al., 2020). Quetiapine also increases the risk of metabolic syndrome with reported increases in triglycerides, total cholesterol, and low-density lipoprotein cholesterol (Bernardo et al., 2021; Burin et al., 2022). There is a bidirectional relationship between OSA and metabolic syndrome, compounding the severity of each condition (Gleeson & McNicholas, 2022).

8 | DISCUSSION AND SUMMARY

While quetiapine has an approved indication as an antipsychotic medication, it is now commonly prescribed for the management of insomnia symptoms. This is despite no evidence that this practice is safe in people with OSA, and not being registered or a recommended treatment for this purpose.

Accordingly, a key question remains—what might be the effects of off-label use of quetiapine in people with OSA and sleep maintenance problems? There is evidence that quetiapine improves sleep efficiency and total sleep time. These objective changes are likely accompanied by subjective improvements in sleep quality that further contribute to the continued prescription use of quetiapine in this scenario. However, as highlighted in this review, rigorous RCT data on the effects of quetiapine on sleep and breathing in people with OSA are scarce. Conceptually, quetiapine may have conflicting beneficial and deleterious effects on the key mechanisms, or endotypes, that contribute to OSA. Accordingly, the balance between these opposing mechanisms, and therefore, the effects of quetiapine on OSA severity, may vary widely between individuals depending on inter-individual differences in underlying pathophysiology.

Given that a considerable proportion of the population has undiagnosed OSA with accompanying comorbid symptoms of sleep disturbance/difficulty maintaining sleep, it is crucial to systematically investigate the effects of quetiapine in the appropriate target populations as summarised in the section below.

9 | RECOMMENDATIONS FOR FUTURE RESEARCH ON QUETIAPINE, INSOMNIA, SLEEP, AND BREATHING

To address the current knowledge gaps on the effects of low-dose quetiapine on sleep breathing, we have identified the following research priorities to investigate. Specifically, appropriately designed studies that include populations relevant to the clinical contexts in which quetiapine is likely to be prescribed are required. Examples include studies to determine the effects of low-dose quetiapine on:

1. The acute impact on OSA severity, including measures such as the hypoxic burden, and PSG parameters in people with a confirmed diagnosis of OSA.
2. The mechanistic effects on OSA endotypes and their potential to explain inter-individual differences in OSA severity (i.e., potential beneficial effects in some versus detrimental effects in others).
3. The effects on next day performance and alertness, with a specific focus on tasks such as driving and vigilance.
4. Potential sex differences.
5. The longer-term effects of drug-related increases on weight gain and the accompanying impact on development of and potential worsening of OSA, and the associated consequences including cardiometabolic risk.

Addressing these research priorities would help establish the required evidence base to inform decisions about the relative harms versus benefits of the use of low-dose quetiapine for sleep complaints, particularly where insomnia overlaps with OSA. This proposed programme of work would also help inform personalised care to help identify potential patient subgroups who may be more likely to experience a net benefit, and vice versa, from quetiapine informed by underlying physiology.

AUTHOR CONTRIBUTIONS

Cricket Fauska: Writing – original draft; conceptualization; writing – review and editing; formal analysis; methodology. **Tarun Bastiampillai:** Conceptualization; writing – review and editing. **Robert Adams:** Supervision; writing – review and editing; conceptualization. **Gary A. Wittert:** Supervision; writing – review and editing. **Danny Eckert:** Conceptualization; writing – review and editing; supervision; funding acquisition; methodology. **Kelly Loffler:** Conceptualization; writing – review and editing; supervision; methodology; formal analysis.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

Aishah, A., Lim, R., Sands, S. A., Taranto-Montemurro, L., Wellman, A., Carberry, J. C., & Eckert, D. J. (2021). Different antimuscarinics when combined with atomoxetine have differential effects on obstructive sleep apnea severity. *Journal of Applied Physiology*, *130*(5), 1373–1382. https://doi.org/10.1152/japplphysiol.01074.2020

Altree, T. J., Aishah, A., Loffler, K. A., Grunstein, R. R., & Eckert, D. J. (2022). The norepinephrine reuptake inhibitor reboxetine alone reduces obstructive sleep apnea severity: A double blind, placebo controlled, randomized, cross-over trial. *Journal of Clinical Sleep Medicine, Jcsm*, *10256*, 85–96. https://doi.org/10.5664/jcsm.10256

Altree, T. J., & Eckert, D. J. (2022). Obstructive sleep apnea endotypes and their postoperative relevance. *International Anesthesiology Clinics*, *60*(2), 1–7. https://doi.org/10.1097/AIA.0000000000000357

Andrulyte, M., & Bjerrum, O. J. (2018). Identifying off-label prescriptions through data Mining in Danish Community Pharmacy Servers: An exploratory study on desmopressin, diclofenac, Fucidin, mirtazapine and quetiapine. *Basic & Clinical Pharmacology & Toxicology*, *123*(2), 155–160. https://doi.org/10.1111/bcpt.13009

AstraZeneca. (2020). Australian Product Information Seroquel. Retrieved from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-02417-1&d=20211103172310101

Baillieul, S., Tamisier, R., Eckert, D. J., & Pépin, J.-L. (2022). Current knowledge and perspectives for pharmacological treatment in OSA. *Archivos De Bronconeumologia.*, *58*, 681–684. https://doi.org/10.1016/j.arbres.2021.12.013

Bakker, M. H., Hugtenburg, J. G., Smits, M. G., Van Der Horst, H. E., & Slottje, P. (2023). Off-label low dose amitriptyline for insomnia disorder: Patient-reported outcomes. *Pharmacoepidemiology and Drug Safety*, *32*(4), 435–445. https://doi.org/10.1002/pds.5561

Barton, B. B., Segger, F., Fischer, K., Obermeier, M., & Musil, R. (2020). Update on weight-gain caused by antipsychotics: A systematic review and meta-analysis. *Expert Opinion on Drug Safety*, *19*(3), 295–314. https://doi.org/10.1080/14740338.2020.1713091

Berge, J., Abri, P., Andell, P., Movahed, P., & Ragazan, D. C. (2022). Associations between off-label low-dose olanzapine or quetiapine and cardiometabolic mortality. *Journal of Psychiatric Research*, *149*, 352–358. https://doi.org/10.1016/j.jpsychires.2021.11.023

Bernardo, M., Rico-Villademoros, F., García-Rizo, C., Rojo, R., & Gómez-Huelgas, R. (2021). Real-world data on the adverse metabolic effects of second-generation antipsychotics and their potential determinants in adult patients: A systematic review of population-based studies. *Advances in Therapy*, *38*(5), 2491–2512. https://doi.org/10.1007/s12325-021-01689-8

Bortolotto, V., Canonico, P. L., & Grilli, M. (2021). β(2) and α(2) adrenergic receptors mediate the proneurogenic in vitro effects of norquetiapine. *Neural Regeneration Research*, *16*(10), 2041–2047. https://doi.org/10.4103/1673-5374.308097

Brett, J. (2015). Concerns about quetiapine. *Australian Prescriber*, *38*(3), 95–97. https://doi.org/10.18773/austprescr.2015.032

Buchanan, G. F., Smith, H. R., MacAskill, A., & Richerson, G. B. (2015). 5-HT2A receptor activation is necessary for CO2-induced arousal. *Journal of Neurophysiology*, *114*(1), 233–243. https://doi.org/10.1152/jn.00213.2015

Burin, L. M., Hahn, M. K., da Rocha, N. S., van Amelsvoort, T., Bartels-Velthuis, A. A., Bruggeman, R., de Haan, L., Schirmbeck, F., Simons, C. J. P., van Os, J., & Cahn, W. (2022). Long-term treatment of antipsychotics and combined therapy with other psychotropic medications inducing weight gain in patients with non-affective psychotic disorder: Evidence from GROUP, a longitudinal study. *Psychiatry Research*, *314*, 114680. https://doi.org/10.1016/j.psychres.2022.114680

Carter, S. G., & Eckert, D. J. (2021). Effects of hypnotics on obstructive sleep apnea endotypes and severity: Novel insights into pathophysiology and treatment. *Sleep Medicine Reviews*, *58*, 101492. https://doi.org/10.1016/j.smrv.2021.101492

Carton, L., Cottencin, O., Lapeyre-Mestre, M., A Geoffroy, P., Favre, J., Simon, N., Bordet, R., & Rolland, B. (2015). Off-label prescribing of antipsychotics in adults, children and elderly individuals: A systematic review of recent prescription trends. *Current Pharmaceutical Design*, *21*(23), 3280–3297. https://doi.org/10.2174/1381612821666150619092903

Chakravorty, S., Hanlon, A. L., Kuna, S. T., Ross, R. J., Kampman, K. M., Witte, L. M., Perlis, M. L., & Oslin, D. W. (2014). The effects of quetiapine on sleep in recovering alcohol-dependent subjects: A pilot study. *Journal of Clinical Psychopharmacology*, *34*(3), 350–354. https://doi.org/10.1097/jcp.0000000000000130

Chung, K.-F., Yeung, W.-F., Ho, F. Y.-Y., Yung, K.-P., Yu, Y.-M., & Kwok, C.-W. (2015). Cross-cultural and comparative epidemiology of

insomnia: The diagnostic and statistical manual (DSM), international classification of diseases (ICD) and international classification of sleep disorders (ICSD). *Sleep Medicine*, *16*(4), 477–482. https://doi.org/10.1016/j.sleep.2014.10.018

ClinCalc.com. (2023). Quetiapine Drug Usage Statistics, United States, 2013–2020. Retrieved from https://clincalc.com/DrugStats/Drugs/Quetiapine

Cohrs, S., Rodenbeck, A., Guan, Z., Pohlmann, K., Jordan, W., Meier, A., & Rüther, E. (2004). Sleep-promoting properties of quetiapine in healthy subjects. *Psychopharmacology*, *174*(3), 421–429. https://doi.org/10.1007/s00213-003-1759-5

Cross, A. J., Widzowski, D., Maciag, C., Zacco, A., Hudzik, T., Liu, J., Nyberg, S., & Wood, M. W. (2016). Quetiapine and its metabolite norquetiapine: Translation from in vitro pharmacology to in vivo efficacy in rodent models. *British Journal of Pharmacology*, *173*(1), 155–166. https://doi.org/10.1111/bph.13346

Drug Utilisation Sub-Committee, A. G. D. o. H. (2013). DUSC review on the utilisation of antipsychotics – August 2013. Public Summary Document. Retrieved from https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2013-08/antipsychotics-psd-08-2013.pdf

Eckert, D. J. (2018). Phenotypic approaches to obstructive sleep apnoea – New pathways for targeted therapy. *Sleep Medicine Reviews*, *37*, 45–59. https://doi.org/10.1016/j.smrv.2016.12.003

Eckert, D. J. (2021). Respiratory physiology: Understanding the control of ventilation. In M. H. Kryger, T. Roth, & C. A. Goldstein (Eds.), *Kryger's principles and practice of sleep medicine*. Elsevier Health Sciences.

Eckert, D. J., Malhotra, A., Wellman, A., & White, D. P. (2014). Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold. *Sleep*, *37*(4), 811–819. https://doi.org/10.5665/sleep.3596

Eckert, D. J., Owens, R. L., Kehlmann, G. B., Wellman, A., Rahangdale, S., Yim-Yeh, S., White, D. P., & Malhotra, A. (2011). Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. *Clinical Science*, *120*(12), 505–514. https://doi.org/10.1042/cs20100588

Eckert, D. J., White, D., Jordan, A. S., Malhotra, A., & Wellman, A. (2013). Defining phenotypic causes of obstructive sleep apnea: Identification of novel therapeutic targets. *American Journal of Respiratory and Critical Care Medicine*, *188*(8), 996–1004. https://doi.org/10.1164/rccm.201303-0448oc

Fang, F., Sun, H., Wang, Z., Ren, M., Calabrese, J. R., & Gao, K. (2016). Antipsychotic drug-induced somnolence: Incidence, mechanisms, and management. *CNS Drugs*, *30*(9), 845–867. https://doi.org/10.1007/s40263-016-0352-5

FDA. (2020). Highlights of Prescribing Information Seroquel XR (Quetiapine) extended-release tablets, for oral use. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022047Orig1s042lbl.pdf

Fenik, P., & Veasey, S. C. (2003). Pharmacological characterization of serotonergic receptor activity in the hypoglossal nucleus. *American Journal of Respiratory and Critical Care Medicine*, *167*(4), 563–569. https://doi.org/10.1164/rccm.200202-107OC

Fernandez, H. H., Okun, M. S., Rodriguez, R. L., Malaty, I. A., Romrell, J., Sun, A., Wu, S. S., Pillarisetty, S., Nyathappa, A., & Eisenschenk, S. (2009). Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: Results from a double-blind clinical-polysomnography study. *The International Journal of Neuroscience*, *119*(12), 2196–2205. https://doi.org/10.3109/00207450903222758

Fleming, W. E., Ferouz-Colborn, A., Samoszuk, M. K., Azad, A., Lu, J., Riley, J. S., Cruz, A. B., Podolak, S., Clark, D. J., Bray, K. R., & Southwick, P. C. (2016). Blood biomarkers of endocrine, immune, inflammatory, and metabolic systems in obstructive sleep apnea. *Clinical Biochemistry*, *49*(12), 854–861. https://doi.org/10.1016/j.clinbiochem.2016.05.005

Gedge, L., Lazowski, L., Murray, D., Jokic, R., & Milev, R. (2010). Effects of quetiapine on sleep architecture in patients with unipolar or bipolar depression. *Neuropsychiatric Disease and Treatment*, *6*, 501–508. https://doi.org/10.2147/ndt.s12433

Geer, J. H., & Hilbert, J. (2021). Gender issues in obstructive sleep apnea. *The Yale Journal of Biology and Medicine*, *94*(3), 487–496. http://www.ncbi.nlm.nih.gov/pubmed/34602886

Gjerden, P., Bramness, J. G., Tvete, I. F., & Slørdal, L. (2017). The antipsychotic agent quetiapine is increasingly not used as such: Dispensed prescriptions in Norway 2004–2015. *European Journal of Clinical Pharmacology*, *73*(9), 1173–1179. https://doi.org/10.1007/s00228-017-2281-8

Gleeson, M., & McNicholas, W. T. (2022). Bidirectional relationships of comorbidity with obstructive sleep apnoea. *European Respiratory Review: An Official Journal of the European Respiratory Society*, *31*(164), 210256. https://doi.org/10.1183/16000617.0256-2021

Haycock, J., Grivell, N., Redman, A., Saini, B., Vakulin, A., Lack, L., Lovato, N., Sweetman, A., Zwar, N., Stocks, N., Frank, O., Mukherjee, S., Adams, R., McEvoy, R. D., & Stocks, N. (2021). Primary care management of chronic insomnia: A qualitative analysis of the attitudes and experiences of Australian general practitioners. *BMC Family Practice*, *22*(1), 1–11. https://doi.org/10.1186/s12875-021-01510-z

Haycock, J., Hoon, E., Sweetman, A., Lack, L., & Lovato, N. (2022). The management of insomnia by Australian psychologists: A qualitative study. *Australian Psychologist*, *57*(5), 290–300. https://doi.org/10.1080/00050067.2022.2089544

Heinzer, R., Vat, S., Marques-Vidal, P., Marti-Soler, H., Andries, D., Tobback, N., Mooser, V., Preisig, M., Malhotra, A., Waeber, G., Vollenweider, P., Tafti, M., & Haba-Rubio, J. (2015). Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. *The Lancet Respiratory Medicine*, *3*(4), 310–318. https://doi.org/10.1016/S2213-2600(15)00043-0

Højlund, M., Andersen, K., Ernst, M. T., Correll, C. U., & Hallas, J. (2022). Use of low-dose quetiapine increases the risk of major adverse cardiovascular events: Results from a nationwide active comparator-controlled cohort study. *World Psychiatry*, *21*(3), 444–451. https://doi.org/10.1002/wps.21010

Jensen, N. H., Rodriguiz, R. M., Caron, M. G., Wetsel, W. C., Rothman, R. B., & Roth, B. L. (2008). N-Desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A agonist, as a putative mediator of Quetiapine's antidepressant activity. *Neuropsychopharmacology*, *33*(10), 2303–2312. https://doi.org/10.1038/sj.npp.1301646

Jones, H. M., Travis, M. J., Mulligan, R., Bressan, R. A., Visvikis, D., Gacinovic, S., Ell, P. J., & Pilowsky, L. S. (2001). In vivo 5-HT2A receptor blockade by quetiapine. *Psychopharmacology*, *157*(1), 60–66. https://doi.org/10.1007/s002130100761

Kapur, V. K., Auckley, D. H., Chowdhuri, S., Kuhlmann, D. C., Mehra, R., Ramar, K., & Harrod, C. G. (2017). Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of sleep medicine clinical practice guideline. *Journal of Clinical Sleep Medicine*, *13*(03), 479–504. https://doi.org/10.5664/jcsm.6506

Karsten, J., Hagenauw, L. A., Kamphuis, J., & Lancel, M. (2017). Low doses of mirtazapine or quetiapine for transient insomnia: A randomised, double-blind, cross-over, placebo-controlled trial. *Journal of Psychopharmacology*, *31*(3), 327–337. https://doi.org/10.1177/0269881116681399

Khazaie, H., Sharafkhaneh, A., Khazaie, S., & Ghadami, M. R. (2018). A weight-independent association between atypical antipsychotic medications and obstructive sleep apnea. *Sleep & Breathing*, *22*(1), 109–114. https://doi.org/10.1007/s11325-017-1537-y

Kim, A., Lim, K. S., Lee, H., Chung, H., Yoon, S. H., Yu, K.-S., Cho, J.-Y., Jang, I.-J., & Chung, J.-Y. (2016). A thorough QT study to evaluate the

QTc prolongation potential of two neuropsychiatric drugs, quetiapine and escitalopram, in healthy volunteers. *International Clinical Psychopharmacology*, *31*(4), 210–217. https://doi.org/10.1097/yic.0000000000000124

Lee, H. J., Choi, J.-S., Choi, B. H., & Hahn, S. J. (2018a). Effects of norquetiapine, the active metabolite of quetiapine, on cloned hERG potassium channels. *Neuroscience Letters*, *664*, 66–73. https://doi.org/10.1016/j.neulet.2017.11.029

Lee, J., Pilgrim, J., Gerostamoulos, D., Robinson, J., & Wong, A. (2018b). Increasing rates of quetiapine overdose, misuse, and mortality in Victoria, Australia. *Drug and Alcohol Dependence*, *187*, 95–99. https://doi.org/10.1016/j.drugalcdep.2018.03.002

Leonard, E. M., & Nurse, C. A. (2020). Expanding role of dopaminergic inhibition in hypercapnic responses of cultured rat carotid body cells: Involvement of type II glial cells. *International Journal of Molecular Sciences*, *21*(15) 5434. https://doi.org/10.3390/ijms21155434

Li, W.-Y., Wang, A., Jin, H., Zou, Y., Wang, Z., Wang, W., & Kang, J. (2019). Transient upregulation of TASK-1 expression in the hypoglossal nucleus during chronic intermittent hypoxia is reduced by serotonin 2A receptor antagonist. *Journal of Cellular Physiology*, *234*(10), 17886–17895. https://doi.org/10.1002/jcp.28419

Lim, R., Messineo, L., Grunstein, R. R., Carberry, J. C., & Eckert, D. J. (2021). The noradrenergic agent reboxetine plus the antimuscarinic hyoscine butylbromide reduces sleep apnoea severity: A double-blind, placebo-controlled, randomised crossover trial. *The Journal of Physiology*, *599*(17), 4183–4195. https://doi.org/10.1113/JP281912

Lindberg, E., Benediktsdottir, B., Franklin, K. A., Holm, M., Johannessen, A., Jögi, R., Gislason, T., Real, F. G., Schlünssen, V., & Janson, C. (2017). Women with symptoms of sleep-disordered breathing are less likely to be diagnosed and treated for sleep apnea than men. *Sleep Medicine*, *35*, 17–22. https://doi.org/10.1016/j.sleep.2017.02.032

Liu, Z.-L., Wu, X., Luo, Y.-J., Wang, L., Qu, W.-M., Li, S.-Q., & Huang, Z.-L. (2016). Signaling mechanism underlying the histamine-modulated action of hypoglossal motoneurons. *Journal of Neurochemistry*, *137*(2), 277–286. https://doi.org/10.1111/jnc.13548

Mabbott, V., Paul Storey, P. B. D., & Commonwealth of Australia. (2016). Australian Statistics on Medicines 2015. Retrieved from https://www.pbs.gov.au/info/statistics/asm/asm-2015

McKean, A., & Monasterio, E. (2012). Off-label use of atypical antipsychotics. *CNS Drugs*, *26*(5), 383–390. https://doi.org/10.2165/11632030-000000000-00000

Miller, C. B., Valenti, L., Harrison, C., Bartlett, D. J., Glozier, N., Cross, N. E., Grunstein, R. R., & Marshall, N. S. (2017). 0319 FAMILY physician management of insomnia in Australia: The beach study (2000–15). *Sleep*, *40*, A118. https://doi.org/10.1093/sleepj/zsx050.318

Modesto-Lowe, V., Harabasz, A. K., & Walker, S. A. (2021). Quetiapine for primary insomnia: Consider the risks. *Cleveland Clinic Journal of Medicine*, *88*(5), 286–294. https://doi.org/10.3949/ccjm.88a.20031

Oishi, Y., & Lazarus, M. (2017). The control of sleep and wakefulness by mesolimbic dopamine systems. *Neuroscience Research*, *118*, 66–73. https://doi.org/10.1016/j.neures.2017.04.008

Osman, A., Mukherjee, S., Altree, T., Delbeck, M., Gehring, D., Hahn, M., Lang, T., Xing, C., Muller, T., Weimann, G., & Eckert, D. J. (2023). Topical K+ channel blockage improves pharyngeal collapsibility: A translational, placebo-controlled trial. *Chest*, *163*(4), 953–965. https://doi.org/10.1016/j.chest.2022.11.024

Pépin, J.-L., Eastwood, P., & Eckert, D. J. (2022). Novel avenues to approach non-CPAP therapy and implement comprehensive obstructive sleep apnoea care. *European Respiratory Journal*, *59*(6), 2101788. https://doi.org/10.1183/13993003.01788-2021

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology*, *177*(9), 1006–1014. https://doi.org/10.1093/aje/kws342

Peppard, P. E., Young, T., Palta, M., Dempsey, J., & Skatrud, J. (2000). Longitudinal study of moderate weight change and sleep-disordered breathing. *Jama*, *284*(23), 3015–3021. https://doi.org/10.1001/jama.284.23.3015

Perger, E., Taranto Montemurro, L., Rosa, D., Vicini, S., Marconi, M., Zanotti, L., Meriggi, P., Azarbarzin, A., Sands, S. A., Wellman, A., Lombardi, C., & Parati, G. (2022). Reboxetine plus oxybutynin for OSA treatment: A 1-week, randomized, placebo-controlled, double-blind crossover trial. *Chest*, *161*(1), 237–247. https://doi.org/10.1016/j.chest.2021.08.080

Pringsheim, T., & Gardner, D. M. (2014). Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: A descriptive study. *CMAJ Open*, *2*(4), E225–E232. https://doi.org/10.9778/cmajo.20140009

Reynolds, A. C., Appleton, S. L., Gill, T. K., Adams, R. J., & Sa, W. (2019). *Chronic insomnia disorder in Australia*. Sleep Health Foundation.

Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J. G., Espie, C. A., Garcia-Borreguero, D., Gjerstad, M., Gonçalves, M., Hertenstein, E., Jansson-Fröjmark, M., Jennum, P. J., Leger, D., Nissen, C., Parrino, L., Paunio, T., Pevernagie, D., Verbraecken, J., … Spiegelhalder, K. (2017). European guideline for the diagnosis and treatment of insomnia. *Journal of Sleep Research*, *26*(6), 675–700. https://doi.org/10.1111/jsr.12594

Sake, F.-T.-N., Wong, K., Bartlett, D. J., & Saini, B. (2019). Insomnia Management in the Australian Primary Care Setting. *Behavioral Sleep Medicine*, *17*(1), 19–30. https://doi.org/10.1080/15402002.2016.1266491

Sands, S. A., Eckert, D. J., Jordan, A. S., Edwards, B. A., Owens, R. L., Butler, J. P., Schwab, R. J., Loring, S. H., Malhotra, A., White, D. P., & Wellman, A. (2014). Enhanced upper-airway muscle responsiveness is a distinct feature of overweight/obese individuals without sleep apnea. *American Journal of Respiratory and Critical Care Medicine*, *190*(8), 930–937. https://doi.org/10.1164/rccm.201404-0783OC

Sato, H., Ito, C., Hiraoka, K., Tashiro, M., Shibuya, K., Funaki, Y., Yoshikawa, T., Iwata, R., Matsuoka, H., & Yanai, K. (2015). Histamine H1 receptor occupancy by the new-generation antipsychotics olanzapine and quetiapine: A positron emission tomography study in healthy volunteers. *Psychopharmacology*, *232*(19), 3497–3505. https://doi.org/10.1007/s00213-015-4002-2

Smith, H. R., Leibold, N. K., Rappoport, D. A., Ginapp, C. M., Purnell, B. S., Bode, N. M., Alberico, S. L., Kim, Y. C., Audero, E., Gross, C. T., & Buchanan, G. F. (2018). Dorsal raphe serotonin neurons mediate CO2-induced arousal from sleep. *The Journal of Neuroscience*, *38*(8), 1915–1925. https://doi.org/10.1523/jneurosci.2182-17.2018

Swanson, L. M., Arnedt, J. T., Rosekind, M. R., Belenky, G., Balkin, T. J., & Drake, C. (2011). Sleep disorders and work performance: Findings from the 2008 National Sleep Foundation sleep in America poll. *Journal of Sleep Research*, *20*(3), 487–494. https://doi.org/10.1111/j.1365-2869.2010.00890.x

Sweetman, A., Lack, L., McEvoy, R. D., Smith, S., Eckert, D. J., Osman, A., Carberry, J. C., Wallace, D., Nguyen, P. D., & Catcheside, P. (2021a). Bi-directional relationships between co-morbid insomnia and sleep apnea (COMISA). *Sleep Medicine Reviews*, *60*, 101519. https://doi.org/10.1016/j.smrv.2021.101519

Sweetman, A., Melaku, Y. A., Lack, L., Reynolds, A., Gill, T. K., Adams, R., & Appleton, S. (2021b). Prevalence and associations of co-morbid insomnia and sleep apnoea in an Australian population-based sample. *Sleep Medicine*, *82*, 9–17. https://doi.org/10.1016/j.sleep.2021.03.023

Taranto-Montemurro, L., Sands, S., Azarbarzin, A., Calianese, N., Vena, D., Hess, L., Kim, S. W., White, D. P., & Wellman, A. (2021). Impact of cold and flu medication on obstructive sleep apnoea and its underlying traits: A pilot randomized controlled trial. *Respirology*, *26*(5), 485–492. https://doi.org/10.1111/resp.14009

Thomas, S. J., Sakhuja, S., Colantonio, L. D., Li, M., Muntner, P., Reynolds, K., & Bowling, C. B. (2022). Insomnia diagnosis, prescribed hypnotic medication use, and risk for serious fall injuries in the reasons

for geographic and racial differences in stroke (REGARDS) study. *Sleep*, *45*(5), zsac063. https://doi.org/10.1093/sleep/zsac063

Vozoris, N. T., & Leung, R. S. (2011). Sedative medication use: Prevalence, risk factors, and associations with body mass index using population-level data. *Sleep*, *34*(7), 869–874. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3119828/pdf/aasm.34.7.869.pdf

Wang, S. H., Keenan, B. T., Wiemken, A., Zang, Y., Staley, B., Sarwer, D. B., Torigian, D. A., Williams, N., Pack, A. I., & Schwab, R. J. (2020). Effect of weight loss on upper airway anatomy and the Apnea–Hypopnea index. The importance of tongue fat. *American Journal of Respiratory and Critical Care Medicine*, *201*(6), 718–727. https://doi.org/10.1164/rccm.201903-0692OC

Wiegand, M. H., Landry, F., Brückner, T., Pohl, C., Veselý, Z., & Jahn, T. (2008). Quetiapine in primary insomnia: A pilot study. *Psychopharmacology*, *196*(2), 337–338. https://doi.org/10.1007/s00213-007-0968-8

Wong, J., Motulsky, A., Abrahamowicz, M., Eguale, T., Buckeridge, D. L., & Tamblyn, R. (2017). Off-label indications for antidepressants in primary care: Descriptive study of prescriptions from an indication based electronic prescribing system. *BMJ*, *j603*, j603. https://doi.org/10.1136/bmj.j603

Xie, L., Wu, Q., Hu, W., Wu, X., Xiang, G., Hao, S., Guo, H., & Li, S. (2021). Impact of histaminergic H3 receptor antagonist on hypoglossal nucleus in chronic intermittent hypoxia conditions. *Psychopharmacology*, *238*(1), 121–131. https://doi.org/10.1007/s00213-020-05663-0

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea: A population health perspective. *American Journal of Respiratory and Critical Care Medicine*, *165*(9), 1217–1239. https://doi.org/10.1164/rccm.2109080

Young, T., Skatrud, J., & Peppard, P. E. (2004). Risk factors for obstructive sleep apnea in adults. *JAMA: The Journal of the American Medical Association*, *291*(16), 2013–2016. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15113821

Zapata, P., Serani, A., & Lavados, M. (1983). Inhibition in carotid body chemoreceptors mediated by D-2 dopaminoceptors: Antagonism by benzamides. *Neuroscience Letters*, *42*(2), 179–184. https://doi.org/10.1016/0304-3940(83)90403-2

Zhang, Y., Ren, R., Lei, F., Zhou, J., Zhang, J., Wing, Y.-K., Sanford, L. D., & Tang, X. (2019). Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *45*, 1–17. https://doi.org/10.1016/j.smrv.2019.01.004

Zuo, L., Chen, X., Liu, M., Dong, S., Chen, L., Li, G., Zhai, Z., Zhou, L., Chen, H., Wei, Y., Shi, L., & Hao, G. (2022). Gender differences in the prevalence of and trends in sleep patterns and prescription medications for insomnia among US adults, 2005 to 2018. *Sleep Health*, *8*, 691–700. https://doi.org/10.1016/j.sleh.2022.07.004

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