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Original Article

Sleep-related breathing disturbances in adolescents with treatment resistant depression

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ABSTRACT

Objective/background: A considerable subgroup of adolescents does not respond to standard antidepressant treatments. There are some indications that sleep disordered breathing may contribute to refractory depression in adults, but little is known about how it may relate to the course of depressive disorders in adolescents. Focussing on a group of Canadian adolescents with treatment resistant depression (TRD), this study aimed to investigate how the severity of residual depressive symptoms following unsuccessful antidepressant trials relates to breathing disturbances during sleep.
Patients/methods: A retrospective chart review was conducted at a tertiary mental health facility. Polysomnography, the Beck Depression Inventory-II (BDI-II), and the Epworth Sleepiness Scale (ESS) were collated from 18 adolescents (15–18 years old, 44% females) patients with depressive disorders who did not respond to at least two 4-week trials of antidepressant medications.
Results: Of this sample, 39% reported at least mild levels of excessive daytime sleepiness, and 55% had an apnea/hypopnea index ≥ 1. Worse depressive symptoms correlated with higher RDI ($r = 0.53$, $p = 0.022$). This was mainly driven by respiratory effort-related arousals occurring during NREM sleep ($r = 0.52$, $p = 0.029$). No significant correlation was found between depressive symptoms and other respiratory or sleep variables. Higher daytime sleepiness correlated significantly with lower minimum oxygen desaturation ($r = -0.51$, $p = 0.030$).
Conclusions: These results suggest that even subtle respiratory disturbances during sleep may play a role in persistent depressive symptoms and treatment resistance. Early screening for sleep-related breathing disturbances in adolescents with TRD may be relevant, since previous work suggests that treating sleep-related breathing disturbances can attenuate depressive symptoms.

1. Introduction

It is estimated that 21% of people consulting physicians for depression across Canada do not respond to repeated trials of antidepressant medication [1]. In adolescents, the rates of treatment resistant depression (TRD) may be even higher, with up to 30–50% not responding to initial treatment with selective serotonin reuptake inhibitors, cognitive behavioral therapy, or combined pharmacological and psychological treatments [2–4]. There are persisting concerns about the lack of efficacy and adverse effects of antidepressant medications [5–7], as well as about the adverse consequences of lingering untreated depressive symptoms in adolescents. From this perspective, the “trial and error” period during which multiple medications are initiated and stopped may be especially detrimental in this age group. There is thus a need to better understand etiological factors which could be predictive of treatment outcomes and amenable to improved targeted treatment strategies in adolescents. Sleep undergoes major changes during

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adolescence and sleep disturbances have long been proposed to play a role in the emergence and maintenance of depression, notably by reducing the likelihood of successful response to treatment. Of note, sleep disordered breathing (SDB) triggers a complex chain of physiological alterations extending beyond the effects of typical sleep disturbance, many of which have the potential to induce or worsen depressive states via unique pathophysiological mechanisms. While considerable work has been done to understand the role of general sleep disturbances in refractory depression, the potential of SDB as a factor contributing to TRD requires further attention.

SDB ranges from snoring and upper airway resistance syndrome to the more severe central sleep apnea and obstructive sleep apnea (OSA) syndromes. It is increasingly recognised that SDB shares a high comorbidity with depression [8] and, according to a meta-analysis, this is already noticeable during adolescence [9]. Beyond simple associations, there are some reasons to think that SDB may actively contribute to the pathogenesis of depression. For instance, longitudinal studies highlighted a higher risk of depression following the onset or the worsening of OSA [10]. In the long run, untreated SDB can lower mood and increase irritability, interpersonal conflicts, and global fatigue, all factors closely linked to adolescent depression. Also, in addition to the adverse effects of SDB on sleep quality and quantity, and their downstream effects on mood, the chronic periods of hypoxia resulting from SDB are known to impact brain regions involved in emotional regulation, some of which are still undergoing important developmental changes during adolescence. Since SDB is an insidious form of sleep pathology which often goes unnoticed, one could postulate that undetected and untreated chronic SDB could generate a subtype of depression whose specific aetiology, or core maintenance factor, remains unresponsive to standard antidepressant drugs. Accordingly, preliminary evidence suggests a link between SDB and TRD in adults [11], but this remains to be investigated in the context of adolescence.

To the best of our knowledge, there is only one published report specifically focused on TRD and SDB in youths. This was a case report of an 18-year-old male with severe upper airway resistance syndrome and debilitating functional impairment suggesting that undiagnosed SDB in adolescents may underlie or exacerbate TRD [12]. Based on a retrospective cross-sectional chart review from a Canadian tertiary care facility, the present study investigated how residual depressive symptoms following multiple unsuccessful antidepressant trials relate to breathing disturbances during REM and NREM sleep in a group of adolescents with TRD. Based on the underlying assumption that sleep-related breathing disturbances may actively exacerbate depression, it was predicted that more frequent respiratory dysfunctions during sleep would correlate positively with more severe residual depressive symptoms.

2. Methods

2.1. Patients

The Royal Ottawa Mental Health Centre (ROMHC) is a Canadian tertiary mental health facility providing specialised care to people with complex psychiatric presentations. This is one of few psychiatric settings with a dedicated sleep clinic offering assessments and treatments for sleep disorders by a team of specialists with expertise at the crossroads of mental health and sleep medicine. A systematic review of medical charts was conducted by a psychiatrist to identify ROMHC patients between 15 and 18 years of age who underwent polysomnography between 2010 and 2014, and met criteria for TRD. To be included in this sample, patients had to: have a diagnosis of major depressive disorder by a child psychiatrist certified by the Royal College of Physicians and Surgeons of Canada, have a documented history of two or more trials of antidepressant medication each lasting at least four weeks (ie total of at least eight weeks of antidepressant medication), without clinical remission, and be symptomatic on the Beck Depression Inventory-II (BDI-II score $\geq$ 14) at the time of the sleep assessment. Patients were systematically excluded if they had other psychiatric co-morbidities aside from anxiety disorders, substance-related disorders, and attention deficit/hyperactivity disorder. All had a clinical assessment including physical examination by a Board certified sleep medicine physician. This retrospective study was approved by the Human Research Ethics Board of the Royal Ottawa Health Care Group.

2.2. Procedures

All patients filled out the BDI-II and the Epworth Sleepiness Scale (ESS), underwent height and weight measurement to determine body mass index (BMI), and then underwent level 1 polysomnography at the ROMHC Sleep Clinic. A registered polysomnography sleep technologist placed electrodes according to the 10–20 system with: three electroencephalogram channels (F3, C3 and O1), ground and reference channels, right and left electrooculograms, two chin and leg electromyograms (EMG), and two electrocardiogram channels. Respiration was monitored with an airflow cannula (pressure transducer), nasal-oral thermistor, chest and abdomen plethysmography, and pulse oximetry.

Oximetry data was used to calculate the minimum oxygen saturation percentage reached during sleep (minimum SaO2%). Sleep stages, apneas/hypopneas and arousals were visually scored by registered sleep technologists according to guidelines established by the American Academy of Sleep Medicine. This enabled the quantification of three types of breathing events: apneas ($\geq$10-second pause in breathing with at least a 90% drop in baseline breathing amplitude for 90% of the event), hypopneas (at least 10 s of a reduction in air flow, of at least 30% with a $\geq$4% drop in oxygen saturation from pre event baseline, with 90% of the event's duration meeting the amplitude reduction criteria), and respiratory effort-related arousals (RERAs, sequence of breaths of at least 10 s with a change in respiratory effort or flattening of the nasal pressure waveform associated with an EEG arousal, but not meeting apnea or hypopnea criteria). The respiratory disturbance index (RDI) was calculated as the total number of events (apneas, hypopneas, and RERAs) divided by the hours of sleep. Finer indexes were also calculated: apnea hypopnea index (AHI, total number of apneas and hypopneas occurring during sleep, divided by the number of hours of sleep) and RERAs index (RERAI, total number of RERAs during sleep, divided by the number of hours of sleep). AHI and RERAI were calculated separately for REM and NREM sleep (eg total number of respiratory events during REM sleep divided by the number of minutes of REM sleep). All night AHI is reported for descriptive purposes.

2.3. Statistical analysis

For descriptive purposes, Mann–Whitney U tests were used to compare age, BDI-II and respiratory variables across males and females. Two-tailed Pearson correlations were used to determine whether age or BMI were associated with BDI-II scores or respiratory variables. Repeated measures t-test were used to compare AHI and RERAI across REM and NREM sleep.

To address the main research question, two-tailed Pearson correlations were conducted to determine whether BDI-II scores and ESS scores were associated with the RDI and minimum SaO2%. To investigate finer subtypes of breathing events occurring in either

REM or NREM sleep, subsequent analyses were performed on the AHI and RERAI for REM and NREM.

3. Results

3.1. Sample descriptive

Eighteen patients met criteria and were included in the final sample (see Table 1 for descriptive statistics). In addition to their diagnosis of major depressive disorder, three patients also had a diagnosis of persistent depressive disorder (dysthymia), seven had a comorbid anxiety disorder, two had substance-related disorders, and four had a diagnosis of attention-deficit/hyperactivity disorder. Only one patient did not take any psychotropic medication at the time of polysomnography. In this sample, there was no significant sex difference in age ($U = 23.0$, $p = 0.112$), BDI-II score ($U = 28.0$, $p > 0.306$) or any respiratory event variables (all $U \leq 37.0$, $p \geq 0.824$). Age and BMI did not correlate significantly with BDI-II scores or respiratory events (both $p \geq 0.260$).

Of these young patients with TRD, 39% ($n = 7$) reported at least mild levels of excessive daytime sleepiness (ESS score $\geq$ 10, Table 1). Sleep architecture and respiratory variables are reported in Table 2. Fifty-five percent ($n = 10$) of the sample had an AHI $\geq$ 1 and 22% ($n = 4$) had an AHI $\geq$ 5. There was no significant difference between REM and NREM AHI ($t(16) = 1.5$, $p = 0.145$), but RERAI tended to be higher during REM than NREM sleep ($t(16) = 1.9$, $p = 0.075$).

3.2. Associations between residual depressive symptoms, sleep and breathing disturbances

A moderate positive correlation was found between BDI-II total scores and RDI ($r = 0.53$, $p = 0.022$; Fig. 1). Subsequent analyses isolating finer subtypes of respiratory events in REM and NREM sleep suggested that this was mainly driven by NREM RERAI ($r = 0.52$, $p = 0.029$). BDI-II total scores were not significantly correlated with REM RERAI, nor with REM or NREM AHI (all $p \geq 0.301$). No significant correlation was found between BDI-II total scores and any of the sleep architecture variables (all $p \geq 0.103$).

Table 1
Demographic characteristics.

	Mean	SD	Range	
			Min	Max
Comorbid Anxious Disorders (n (%))	14 (78%)			
Sex Distribution (n (%) Females)	8 (44%)			
Age (years)	16.8	0.8	15	18
BMI (kg/m^2)	26.7	5.2	19.2	36.1
BDI-II (Total Score)	31.1	8.0	17	47
ESS (Total Score)	8.3	4.1	2	15
Medication Intake (n (%))				
Any Psychotropic Medications	17 (94%)			
Antidepressants	16 (89%)			
Antipsychotics	13 (72%)			
Mood Stabilisers/Anticonvulsants	4 (22%)			
Melatonin	2 (11%)			
Hypnotics	1 (6%)			
Stimulants/modafinil	4 (22%)			

SD: Standard Deviation, Min/Max: minimum and maximum values across the sample, BMI: Body Mass Index, BDI-II: total score on the Beck Depression Inventory-II, ESS: total score on the Epworth Sleepiness Scale. Medications: Antidepressants (Fluoxetine, bupropion, desvenlafaxine, escitalopram, fluoxetine, mirtazapine, sertraline, trazodone, venlafaxine), Antipsychotics (aripiprazole, Olanzapine, Quetiapine, Risperidone), Mood Stabilisers/Anticonvulsants (Gabapentin, Topiramate), Melatonin, Hypnotics (zopiclone), Stimulants (Lisdexamfetamine).

Table 2
Polysomnographic profile.

	Mean	SD	Range	
			Min	Max
Sleep Architecture				
Total Sleep Period (minutes)	424.0	63.7	317.1	539.0
Total Sleep Time (minutes)	382.1	71.7	248.0	533.0
Sleep Onset Latency	22.4	30.1	2.3	126.3
REM Latency (minutes)	190.1	113.7	57.0	473.5
Sleep Efficiency (%)	86.2	14.5	50.8	98.5
Wake After Sleep Onset	41.9	68.2	5.0	226.1
Absolute Sleep Stages Durations (minutes)				
N1	36.3	23.1	7.5	90.0
N2	185.4	60.9	111.0	352.5
N3	97.7	48.3	28.0	222.0
REM	54.1	36.7	0.0	143.0
Respiratory Variables				
AHI (all sleep)	2.2	2.5	0.0	7.5
RDI (all sleep)	14.3	11.4	1.4	37.4
RERAI (REM)	28.3	26.7	0.0	95.2
RERAI (NREM)	18.5	18.0	0.0	59.4
AHI (REM)	11.5	24.1	0.0	102.7
AHI (NREM)	2.9	3.7	0.0	12.5
MIN SaO2%	92.1	2.1	90.0	97.0

SD: Standard Deviation, Min/Max: minimum and maximum values across the sample AHI: apnea hypopnea index, RDI: Respiratory Disturbance Index, RERAI: Respiratory effort-related arousals, MIN SaO_2 %:minimum oxygen saturation percentage reached during sleep.

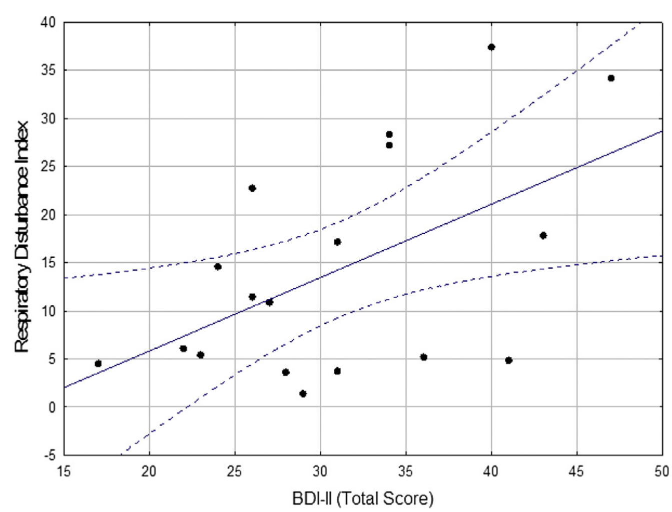

Fig. 1. Significant correlation between depressive symptoms severity rated on the Beck Depression Inventory (BDI-II) and the Respiratory Disturbance Index. The dotted line indicates the 95% confidence interval.

Higher daytime sleepiness on the ESS correlated significantly with lower minimum SaO2% ($r = -0.51$, $p = 0.030$; Fig. 2). Neither the ESS, nor minimum SaO2% were found to be significantly correlated with BDI-II (both $p > 0.524$). ESS scores were not significantly correlated with RDI, REM/NREM AHI or REM/NREM RERAI.

4. Discussion

Adolescents who do not respond to standard antidepressant treatment often have persistent complaints of sleep problems [13]. Based on a clinical sample of Canadian youths, the present findings suggest that subtle respiratory disturbances followed by arousals during NREM sleep could be one of the sleep factors contributing to residual depressive symptoms persisting after multiple antidepressants trials. This sheds some light on a readily identifiable and

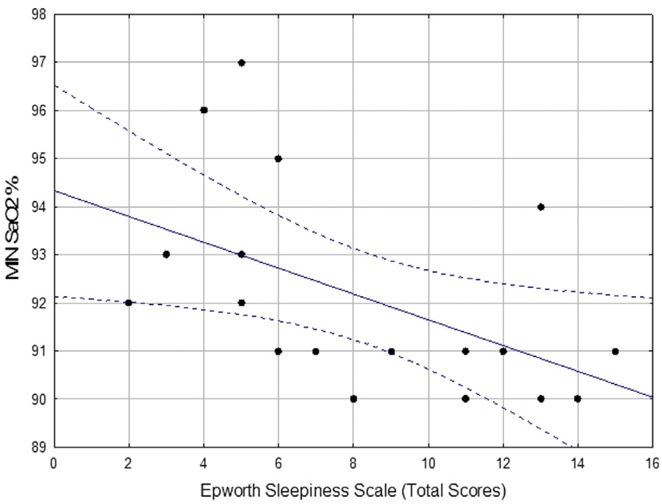

Fig. 2. Significant correlation between subjective daytime sleepiness rated on the Epworth Sleepiness Scale and the minimum oxygen saturation percentage reached during sleep (min SaO2%). The dotted line indicates the 95% confidence interval.

modifiable risk factor for refractory depression in adolescents, stressing the need to investigate the prophylactic value of screening and treating sleep-related breathing disturbances to prevent TRD early in the course of illness. This is one of the areas where pediatric sleep care is likely to bring impactful contributions for the management of depression in youth.

The general prevalence of SDB in children and adolescents is estimated to range from 1 to 7% [14]. In our sample of otherwise healthy adolescents with TRD, this was considerably higher, with 55% having an AHI suggestive of sleep apnea based on standard pediatric criteria. Yet, across the overall sample (ie even in those without frank sleep apnea), RERAs, a subtler form of respiratory disturbances, were found to correlate with the severity of residual depressive symptoms. Since residual depressive symptoms were not significantly correlated with AHI or oxygen desaturation, this suggests that refractory depression can be linked to subtle sleep fragmentation associated with repeated respiratory arousals, even in the absence of hypoxia. This is somewhat in line with previous observations that depression relapses in children and adolescents are predicted by poorer sleep consolidation [15]. In our sample of adolescents with TRD, residual depressive symptoms were not significantly associated with overall sleep consolidation or spontaneous arousals, but more specifically to those arousals following respiratory disturbances. From a physiological perspective, this subtype of arousals differs from those linked to spontaneous arousals, but the mechanisms via which RERAs may more specifically relate to depression pathophysiology remains to be investigated.

In adults, SDB-driven sleep fragmentation is often accompanied by reductions in both REM and slow wave sleep [16–18]. Children with OSA have been found to have minimal abnormalities in overall sleep architecture, but have high rates of breathing disruptions and worse desaturation during REM as compared to NREM sleep [19,20]. Similarly, in our sample of adolescents with TRD the RERAs were most prominent during REM sleep. However, it was the respiratory-related arousals occurring during NREM which were more closely linked to residual depressive symptoms.

While no direct correlation between oxygen desaturation and overall BDI-II total scores was found, oxygen desaturation was significantly associated with excessive daytime sleepiness, a phenomenon likely to worsen more specific depressive symptoms like those pertaining to global energy levels. However, the physiological and functional impacts of oxygen desaturation could possibly vary based on the severity and length of exposure to SDB. Hence, further work is required in people with longer courses of untreated SDB, to determine if extended exposure to chronic hypoxia may have more prominent effects on depressive symptomatology.

There is some evidence that successful treatment of sleep-related breathing disturbances with mandibular advancement or positive airway pressure therapies can lead to significant mood improvements (eg Refs. [21–25]), but this still has to be investigated in clinically depressed adolescents. Considering that early age at onset is one of the key factors contributing to depression chronicity and TRD [26], adolescence may be a critical window for targeted interventions with high impact on the subsequent course of illness.

Several limitations inherent to this study should be acknowledged. Firstly, this was based on a retrospective dataset. Also, the relatively small sample size limits the formal investigation of potential modulating factors such as sex differences. Although patients had at least eight weeks of cumulative antidepressant trials with at least two different types of medication (ie at least four weeks on each type of antidepressant), it may be possible that some patients may have been responsive to one of these antidepressant medication if it was maintained for more than four weeks. Since most patients included in this sample were medicated, it is possible that some psychotropic medications actively interacted with sleep and respiratory functions. Hence, further work is required to decipher the effects of refractory depression from that of various types of medications.

In conclusion, while half of our sample of adolescents with TRD had signs of significant sleep apnea as reflected by their global AHI, subtler sleep-related breathing disruptions accompanied by arousals from sleep were linked to more severe refractory depression across the wider sample. Prospective interventional studies are required to determine whether treating even mild respiratory disturbances could have positive impacts on depressive symptoms. The present findings add to growing evidence stressing the need to address sleep disruptions in the management of adolescent major depression.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.12.010.

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