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SCIENTIFIC INVESTIGATIONS

Selective serotonin reuptake inhibitor use is associated with worse sleep-related breathing disturbances in individuals with depressive disorders and sleep complaints: a retrospective study

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Study Objectives: The effects of serotonergic agents on respiration neuromodulation may vary according to differences in the serotonin system, such as those linked to depression. This study investigated how sleep-related respiratory disturbances relate to depression and the use of medications commonly prescribed for depression.

Methods: Retrospective polysomnography was collated for all 363 individuals who met selection criteria out of 2,528 consecutive individuals referred to a specialized sleep clinic (Ottawa, Canada) between 2006 and 2016. The apnea-hypopnea index (AHI), oxygen saturation nadir, and oxygen desaturation index during REM and NREM sleep were analyzed using mixed analyses of covariance comparing 3 main groups: (1) medicated individuals with depressive disorders (antidepressant group; subdivided into the selective serotonin reuptake inhibitor and norepinephrine-dopamine reuptake inhibitor subgroups), (2) non-medicated individuals with depressive disorders (non-medicated group), and (3) mentally healthy control patients (control group).

Results: Individuals with depressive disorders (on antidepressants or not) had significantly higher AHIs compared to control patients (both $P \leq .007$). The antidepressant group had a lower NREM sleep oxygen saturation nadir and a higher NREM sleep oxygen desaturation index than the control and non-medicated groups (all $P \leq .009$). Within individuals with depressive disorders, independent of depression severity, the selective serotonin reuptake inhibitor group had a lower oxygen saturation nadir and a higher oxygen desaturation index during NREM sleep than the norepinephrine-dopamine reuptake inhibitor (both $P \leq .045$) and non-medicated groups (both $P < .001$) and a higher NREM sleep AHI than the non-medicated group ($P = .014$).

Conclusions: These findings suggest that the use of selective serotonin reuptake inhibitors may be associated with impaired breathing and worse nocturnal oxygen saturation in individuals with depressive disorders and sleep complaints, but this needs to be confirmed by prospective studies.

Keywords: selective serotonin reuptake inhibitor, antidepressants, depression, sleep-related breathing disturbances, OSA

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Considering alterations in the serotonin system that are linked to depression, and the high comorbidity overlap between depression and sleep-related breathing disorders, there is a need to better understand how selective serotonin reuptake inhibitors may interact with nocturnal respiratory functions in the context of depression.

Study Impact: This retrospective study provides the first empirical preliminary evidence suggesting a link between antidepressant use and sleep-related breathing disturbances in individuals with depression and sleep complaints. If confirmed by future prospective studies, the findings point to an unsuspected adverse effect of the most-prescribed antidepressants, which may have important implications for the clinical management of depression.

INTRODUCTION

Medications commonly prescribed for mood disorders, such as selective serotonin reuptake inhibitors (SSRIs), markedly impact sleep.[1,2] In addition to altering sleep architecture, SSRIs have been shown to modulate breathing patterns during sleep in animal models and in humans with sleep-related breathing disorders (SRBDs).[3–5] Considering the high comorbidity between depression and SRBDs,[6] there is a need to better understand how SSRIs may interact with respiratory functions in the context of depression.

Depression is accompanied by dysfunctions in the serotonin (5-HT) system, both centrally and peripherally. For instance, individuals with depression have low levels of plasma tryptophan (a 5-HT precursor)[7,8] and 5-HT metabolites in the cerebrospinal fluid, low 5-HT1A receptor binding,[9–11] and low availability of 5-HT reuptake sites in the brainstem.[12] These 5-HT abnormalities could interfere with respiration, especially during sleep. Most 5-HT neurons are located in the raphe nuclei, a structure heavily involved in the regulation of respiration and sleep.[13,14] The serotonergic input to motor neurons regulating upper-airway muscles decreases during sleep,[15,16] which is

thought to play a role in upper airway obstruction, the basis of OSA.[17]

Pharmacological manipulations of the 5-HT system may also impact respiratory functions.[18] Although conflicting effects have also been reported,[5,19] exogenous 5-HT can trigger apneas[20] and increase breathing disruptions during sleep in a dose-dependent manner,[21,22] whereas 5-HT antagonists actively reduce sleep apneas.[23] In humans, small (from 8 to 17 participants) trials attempting to use SSRIs to improve breathing in people with OSA have yielded mixed results; some have reported reduced apnea-hypopnea index (AHI) in a subset of their sample (ie, 33%–65%),[3,24] and some have reported an overall slight (nonsignificant) increase in AHI.[25] These inconsistencies could result from individual differences in the vulnerability to 5-HT agents. The direction of serotonergic effects on respiration may also vary with the expression of 5-HT receptors.[26,27] Agonism at 5-HT3 receptors can have inhibitory effects on upper-airway dilators, thereby reducing patency and airflow,[23,28] and agonism at 5-HT1A receptors can have excitatory effects on respiratory centers.[29,30] From this perspective, the postulated dysregulation of 5-HT receptors in depression may shape the respiratory response to 5-HT agents. For instance, there are some indications of increased 5-HT3 receptor activity in depression,[31] a factor that may potentiate the inhibition of respiratory muscles. In addition, depression-related impairments in 5-HT1A binding may diminish the excitatory effects of 5-HT agents on the respiratory system.

Based on a retrospective cross-sectional chart review in individuals who were referred for a sleep disorder assessment and underwent diagnostic polysomnography (PSG), the present study investigated how sleep-related respiratory disturbances relate to depression and the use of medications commonly prescribed for depression. It was anticipated that people with depression who take antidepressants, more specifically SSRIs, would have a higher AHI and lower blood oxygen saturation compared with those not taking any psychotropic medication and those taking nonserotonergic medication. Supplemental analyses were conducted to explore whether the relationship between antidepressant use and sleep-related respiratory functions is less pronounced in people with a history of depression who are currently asymptomatic for depression compared with those who are currently symptomatic (see supplemental material).

METHODS

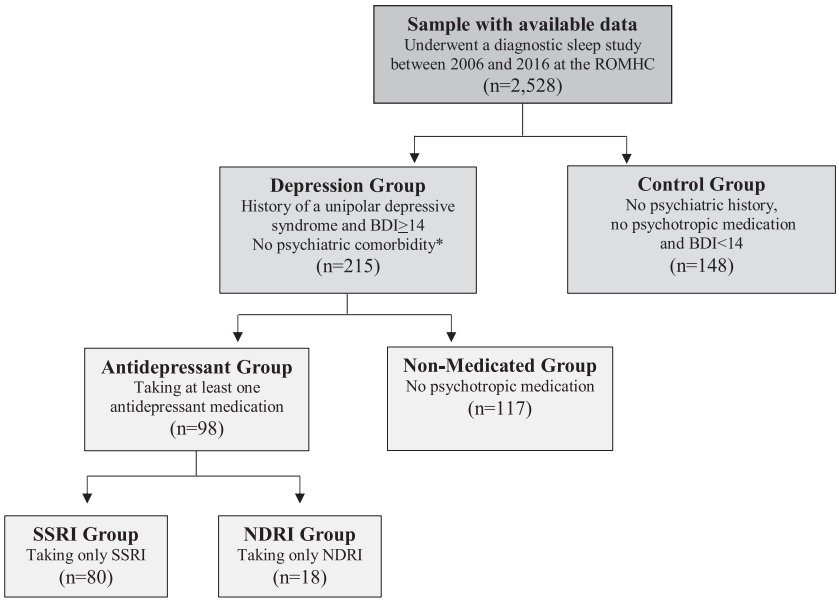
Study design and patients

Data were retrospectively collated from a pool of 2,528 constitutive individuals who underwent diagnostic overnight level 1 PSG at the Sleep Disorders Clinic of the Royal Ottawa Mental Health Centre (Ottawa, Ontario, Canada) between 2006 and 2016 and who met the following selection criteria: (1) individuals with depressive disorders (on antidepressant or not) and (2) mentally healthy control patients (see **Figure 1**). Descriptive information for each group and medication subtypes are reported in **Table 1.** This retrospective study was approved by the Human Research Ethics Board of the Royal Ottawa Health Care Group (REB# 2015028).

Depression group

Individuals included in the depression group (n = 215) had to have documented in their medical chart a history of a unipolar

Figure 1—Study groups for the primary study aim.



Flowchart of cases meeting inclusion and exclusion criteria for each group. *Psychiatric comorbidities included bipolar disorder, psychotic disorder, posttraumatic stress disorder, or neurocognitive disorder. A group of 74 people with a history of a unipolar depressive syndrome who were taking an SSRI but were asymptomatic on the BDI-II (score < 14) was also created (see supplemental material). BDI-II = Beck Depression Inventory-II, ROMHC = Royal Ottawa Mental Health Centre.

Table 1—Sleep architecture and descriptive information across main groups.

Variable	Antidepressant	Non-medicated	Control	F/χ^2	*P* Value
n	98	117	148	—	—
Sex distribution (% female)	64.3	67.5	45.9	14.8	.001
Age (y)	43.4 ± 15.0	43.7 ± 13.7	52.8 ± 15.2	17.2	< .001
BMI (kg/m^2)	29.6 ± 6.6	28.9 ± 6.5	28.2 ± 5.5	1.2	.310
Sleep architecture ($\bar{x}$ ± SD)					
Sleep efficiency (%)	84.0 ± 11.0	84.0 ± 11.9	79.8 ± 12.2	5.5	.004
TST (min)	357.2 ± 60.8	357.8 ± 75.0	342.9 ± 63.0	2.1	.120
Sleep onset latency (min)	25.2 ± 24.8	17.7 ± 19.1	14.7 ± 15.4	8.1	< .001
REM sleep latency (min)[a]	208.9 ± 103.9	130.2 ± 74.6	136.0 ± 81.5	26.2	<.001
NREM sleep (%)	86.8 ± 7.6	83.2 ± 5.8	85.5 ± 6.0	9.1	<.001
REM sleep (%)	13.2 ± 7.6	16.8 ± 5.8	14.5 ± 6.0	9.1	<.001

[a]There was no REM sleep noted in 1 individual from the non-medicated group and in 8 in from the antidepressant group. F/χ^2 and *P* values reflect global omnibus statistics (statistics for paired comparisons are reported in the text; please see "Main groups analyses" in the Results section). SD = standard deviation, TST = total sleep time.

Table 2—Sleep architecture and descriptive information across depression subgroups.

Variable	Non-medicated	NDRI	SSRI	F/χ^2	*P* Value
n	117	18	80	—	—
Sex distribution (% female)	67.5	55.0	67.5	2.3	.324
Age (y)	43.7 ± 13.7	37.7 ± 16.2	44.7 ± 14.5	1.8	.170
Comorbid anxiety, n (%)	18 (15.4)	5 (27.8)	24 (30.0)	—	—
Substance use disorder, n (%)	5 (4.3)	4 (22.2)	4 (5.0)	—	—
SSRI subtypes, n (%)					
Citalopram (Celexa)	—	—	23 (28.8)	—	—
Escitalopram (Cipralex)	—	—	24 (30.0)	—	—
Fluoxetine (Prozac)	—	—	16 (20.0)	—	—
Sertraline (Zoloft)	—	—	14 (17.5)	—	—
Fluvoxamine (Luvox)	—	—	5 (6.3)	—	—
Paroxetine (Paxil)	—	—	2 (2.5)	—	—
NDRI subtypes, n (%)					
Bupropion (Wellbutrin)	—	18 (100.0)	—	—	—
BMI (kg/m^2)	28.9 ± 6.5	26.1 ± 5.9	30.3 ± 6.5	4.0	.019
BDI-II score	23.1 ± 8.6	26.9 ± 10.0	24.1 ± 7.9	1.7	.177
Sleep architecture ($\bar{x}$ ± SD)					
Sleep efficiency (%)	84.0 ± 11.9	86.2 ± 12.1	83.5 ± 10.8	0.4	.663
TST (min)	357.8 ± 75.0	363.0 ± 64.3	355.9 ± 60.3	0.08	.924
Sleep onset latency (min)	17.7 ± 19.1	20.3 ± 17.4	26.3 ± 26.2	3.6	.030
REM sleep latency (min)[a]	130.2 ± 74.6	112.9 ± 59.7	231.3 ± 99.3	36.6	< .001
NREM sleep (%)	83.2 ± 5.8	83.3 ± 7.9	87.6 ± 7.3	11.3	< .001
REM sleep (%)	16.8 ± 5.8	16.7 ± 7.9	12.4 ± 7.3	11.3	< .001

Numbers in brackets are percentages. [a]There was no REM sleep noted in 1 individual from the non-medicated group, 1 from the NDRI group, and 7 from the SSRI group. F/χ^2 and *P* values reflect global omnibus statistics (statistics for paired comparisons are reported in the text; please see "Depression subgroups analyses" in the Results section). BDI-II = Beck Depression Inventory-II, SD = standard deviation, TST = total sleep time.

depressive syndrome (eg, major depression, dysthymic disorder, depressive disorder not otherwise specified), and current depressive symptoms of at least mild severity (Beck Depression Inventory-II [BDI-II] ≥ 14] around the time of the sleep assessment. Patients were systematically excluded if they had comorbid bipolar disorder, psychotic disorder, posttraumatic stress disorder, or neurocognitive disorder. A psychologist reviewed and classified all diagnostic information.

The depression group was first split into 2 groups based on the use of psychotropic medications at the time of PSG: the antidepressant group (individuals who reported taking at least 1 antidepressant medication and no other psychotropic medication on the night of the sleep study; n = 98), and the non-medicated group (individuals who were free of psychotropic medication on the night of the sleep study; n = 117). The antidepressant group was subsequently split into 2 subgroups based on the class of antidepressant used: the SSRI group (n = 80) and the norepinephrine-dopamine reuptake inhibitor (NDRI) group (n = 18). Individuals taking any other psychotropic drug were systematically excluded. In addition, participants were free of other serotonergic drugs including triptans, 5-HT-3 receptor antagonists such as ondansetron, and muscle relaxants such as cyclobenzaprine.

Control group

Individuals included in the control group (n = 148) had no history of mood disorders, anxiety disorders, psychotic disorders, posttraumatic stress disorder, or neurocognitive disorders documented in their medical records. To be included in the control group, participants additionally had to have a score in the asymptomatic range on the BDI-II (< 14) and be free of psychotropic medication.

Procedures

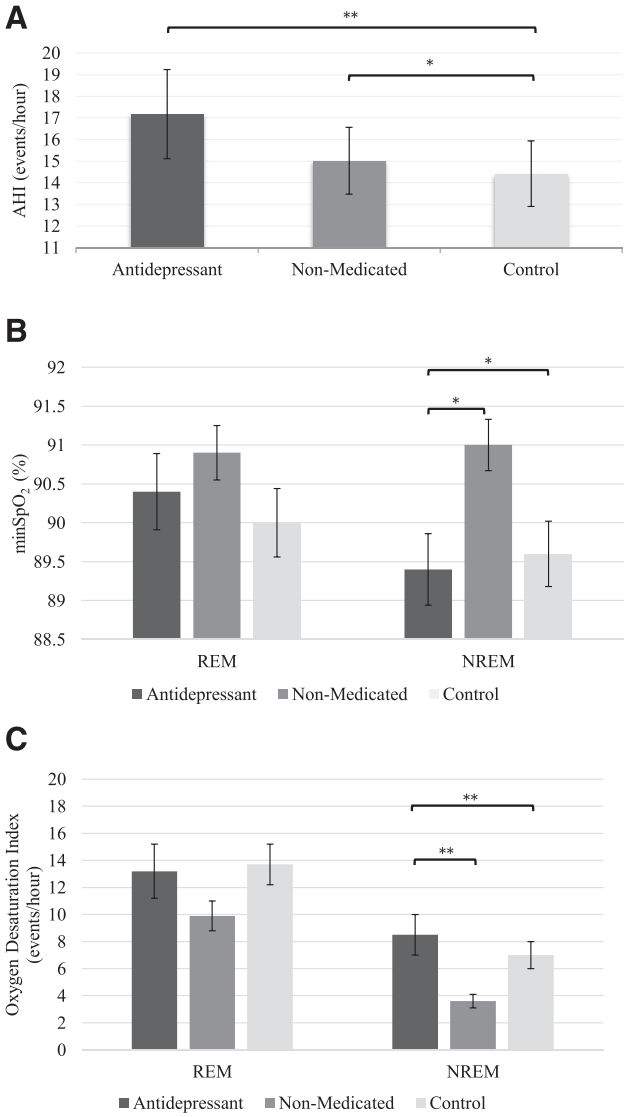
All patients underwent height and weight measurement to determine body mass index (BMI), rated the severity of their depressive symptoms on the BDI-II, and underwent level 1 PSG. PSG was recorded with the Sandman SD32 acquisition software (Sandman 10.1; Natus Medical Incorporated, San Carlos, California) using 3 electroencephalogram channels (F3, C3, and O1), left and right electrooculogram, chin and leg electromyogram (EMG), and 2 electrocardiogram channels. Respiration was monitored with an airflow cannula (pressure transducer) and nasal-oral thermistor plus chest and abdomen plethysmography. Pulse oximetry data were used to calculate the minimum oxygen saturation ($minSpO_2$) percentage reached during sleep.

Sleep stages, apneas/hypopneas, and arousals were visually scored by registered sleep technologists according to guidelines established by the American Academy of Sleep Medicine.[32] Two types of breathing events were defined: apneas (≥ 10-second pause in breathing with at least a 90% drop in baseline breathing amplitude for 90% of the event), and hypopneas (at least 10 seconds of a > 30% reduction in airflow, with a ≥ 3% drop in oxygen saturation from pre-event baseline, with 90% of the event's duration meeting the amplitude reduction criteria). The following indices of respiratory function were computed: AHI (number of apnea and hypopnea events per hour), oxygen desaturation index (ODI; number of blood oxygen desaturations ≥ 3% per hour), and $minSpO_2$ across total sleep time and during REM and NREM sleep.

Statistical analysis

For descriptive purposes, χ^2 and one-way analyses of variance were used to identify significant differences in sex distribution, age, BMI, and sleep architecture across groups. In addition, BDI-II scores were compared across the 3 depression groups.

Figure 2—Respiratory parameters in the main groups.



(A) AHI (REM and NREM sleep combined), **(B)** $minSpO_2$, and **(C)** ODI across REM and NREM sleep. Bars indicate unadjusted mean and error bars indicate the standard errors of the mean. *$P \leq .009$, **$P \leq .001$. There was no REM sleep noted in 8 individuals in the antidepressant group and 1 in the non-medicated group. Analyses were adjusted for age, sex, and BMI.

To address the main study objective, mixed analyses of covariance were used to compare the AHI, ODI, and $minSpO_2$ between groups and assess group and sleep stage interactions. These analyses of covariance had 1 within-subjects factor (sleep stages: REM vs NREM) and 1 between-subjects factor, either (1) the main groups (antidepressant vs nonmedicated vs control groups) or (2) the depression subgroups (SSRI vs NDRI vs non-medicated groups). Age, sex, and BMI were included in these analyses of covariance as covariates because of their potential effects on the relationship between medication use, depression status, and sleep disturbances.[33,34] We used a similar approach for supplemental analysis to explore the potential influence of depressive states (see the supplemental material).

The BMI, sleep onset latency, and ODI were log-transformed, and AHI and BDI-II were square-root-transformed to improve distribution normality. Statistical significance was set at $P < .050$. All statistical analyses were carried out using SPSS (SPSS, version 22.0; IBM Corp, Armonk, NY).

RESULTS

Sample characteristics

Sample characteristics and sleep architecture variables for the main groups and for the SSRI and NDRI subgroups are reported in **Tables 1** and **2**, respectively.

Clinical characteristics

Across the main groups, there were significant differences in age (F [2, 360] = 17.2; $P < .001$) and sex distribution (χ^2[2] = 14.8; $P = .001$), but there was no difference in BMI ($P = .271$). Specifically, the antidepressant and non-medicated groups were significantly younger (both $P < .001$) and had significantly higher proportions of women (both $P \leq .005$) than the control group. Across the depression subgroups, there was a significant difference in BMI (F [2, 212] = 4.0; $P = .019$), wherein the SSRI group had a significantly higher BMI compared with the NDRI group ($P = .007$). There was no significant difference in sex distribution, age, or BDI-II across the depression subgroups (all $P > .050$).

Sleep architecture

In unadjusted analyses, significant differences between the main groups were found for sleep onset latency (F [2, 360] = 8.1; $P = <.001$), sleep efficiency (F [2, 360] = 5.5; $P = .004$), REM sleep latency (F [2, 351] = 26.2; $P < .001$), and the percentages of NREM (F [2, 360] = 9.1; $P < .001$) and REM (F [2, 360] = 9.1; $P < .001$) sleep. The antidepressant group had a slightly, but statistically significant, higher sleep efficiency compared with the control group ($P = .007$) but not compared with the non-medicated group ($P = .974$). The antidepressant group also had significantly longer sleep onset latency and REM sleep onset latency when compared with the non-medicated group ($P = .008$ and $P < .001$, respectively) and the control group (both $P < .001$). The antidepressant group had a lower percentage of REM sleep and a higher percentage of NREM sleep compared with the non-medicated group (both $P < .001$).

Among the depression subgroups, significant differences were found for sleep onset latency (F [2, 212] = 3.6; $P = .030$), REM sleep latency (F [2, 203] = 36.6; $P < .001$), and the percentages of REM (F [2, 212] = 11.3; $P = <.001$) and NREM (F [2, 212] = 11.3; $P < .001$) sleep. The SSRI group had a significantly longer sleep onset latency than the non-medicated group ($P = .011$). Compared with both the non-medicated and NDRI groups, the SSRI group had a significantly longer REM sleep latency, a lower percentage of REM sleep, and a higher percentage of NREM sleep (all $P \leq .014$).

Comparison of respiratory measures across groups and sleep stages

Main groups analyses

Figure 2 depicts respiratory measures for the antidepressant, non-medicated, and control groups. Detailed respiratory data are reported in **Table 3**.

There was no significant group by sleep-stage interaction or main effect of sleep stages for AHI. A significant main effect of group (F [2, 348] = 6.1; $P = .003$) showed that the antidepressant ($P = .001$) and non-medicated ($P = .007$) groups had a slight but statistically significant higher total AHI compared with the control group. Although the antidepressant group had a marginally higher AHI than the non-medicated group, this difference was not statistically significant ($P = .493$).

Significant interactions between groups and sleep stages were found for minSpO_2 (F [2, 348] = 4.1; $P = .018$) and ODI (F [2, 348] = 3.5; $P = .032$). During NREM sleep, the

Table 3—Respiratory indices across main groups.

	Control $\bar{x}$ ± SD	Non-medicated $\bar{x}$ ± SD	Antidepressant $\bar{x}$ ± SD	Statistics (F)[a]		
				Group	Sleep	Interaction
AHI (events/h)				6.1**	3.7(*)	2.7(*)
NREM sleep	10.9 ± 16.7	9.8 ± 13.0	13.8 ± 16.8			
REM sleep	17.9 ± 20.2	20.2 ± 20.3	20.5 ± 22.3			
MinSpO_2 (%)				2.0	2.4	4.1*
NREM sleep	89.6 ± 5.2	91.0 ± 3.5	89.4 ± 4.3			
REM sleep	90.0 ± 5.3	90.9 ± 3.7	90.4 ± 4.6			
ODI (events/h)				2.9(*)	15.3**	3.5*
NREM sleep	7.0 ± 12.7	3.6 ± 5.6	8.5 ± 14.3			
REM sleep	13.7 ± 17.9	9.9 ± 11.7	13.2 ± 18.8			

[a]Analyses were adjusted for age, sex, and BMI. F values are reported for main group effects (differences between mentally healthy control patients, non-medicated patients with depression, and medicated patients with depression), main effects of sleep stages (NREM and REM sleep), and interactions between main groups and sleep stages. Eight individuals in the antidepressant group and 1 in the non-medicated group had no REM sleep. *$P \leq .032$, **$P \leq .003$, (*)$P \leq .067$ (ie, trends). SD = standard deviation.

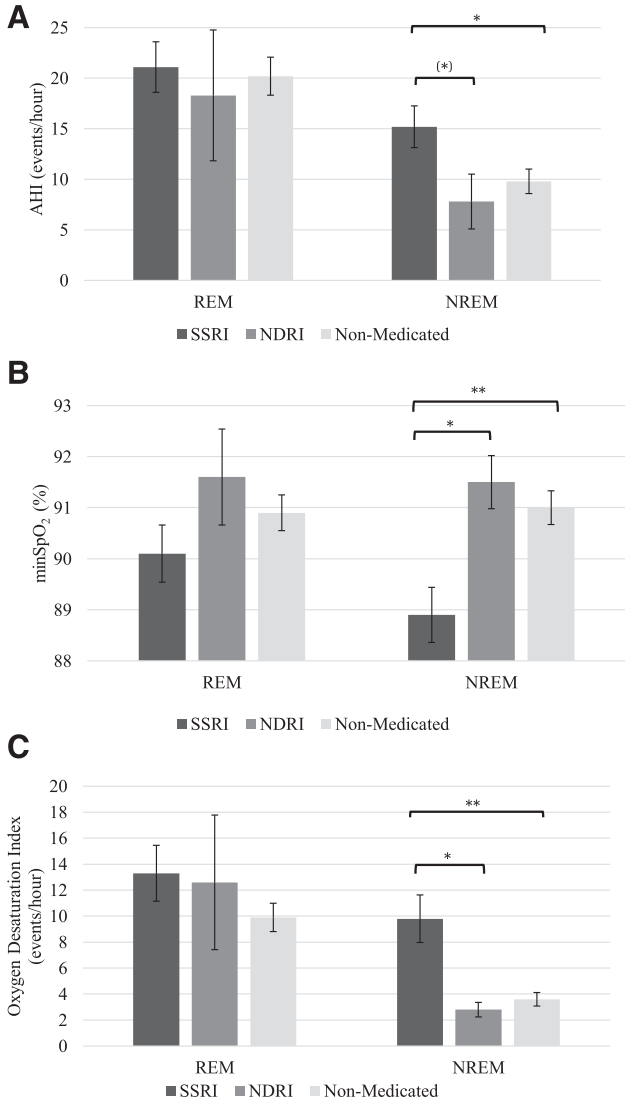
antidepressant group had a significantly lower minSpO$_2$ and a higher ODI than both the control (both $P \leq .009$) and the non-medicated (both $P \leq .007$) groups. The NREM sleep minSpO$_2$, and ODI did not differ significantly between the control and non-medicated groups. There was no significant group difference in these variables during REM sleep.

Depression subgroups analyses

Figure 3 depicts respiratory measures for the SSRI, NDRI, and non-medicated groups. Detailed respiratory data are reported in **Table 4.**

Significant interactions between antidepressant subtypes and sleep stages were found for AHI (F [2, 200] = 4.3; P = .015), minSpO$_2$ (F [2, 200] = 4.8; P = .009), and ODI (F [2, 200] = 7.2; P = .001). During NREM sleep, the SSRI group had a significantly lower minSpO$_2$ and higher ODI compared with both the non-medicated (both $P < .001$) and NDRI (both $P \leq .045$) groups. The SSRI group also had a significantly higher AHI than the non-medicated group (P = .014) and tended to have a higher AHI than the NDRI group (P = .069) during NREM sleep. The NREM sleep AHI, minSpO$_2$, and ODI did not differ significantly between the NDRI and non-medicated groups. There was no significant group difference in these variables during REM sleep. Results from supplemental analyses on the influence of depressive states are presented in the supplemental material.

Figure 3—Respiratory parameters during REM and NREM sleep in the depression subgroups.



(A) AHI, **(B)** minSpO$_2$, and **(C)** ODI. Bars indicate unadjusted mean and error bars indicate the standard errors of the mean. *$P \leq .045$, (*)$P \leq .069$, **$P \leq .001$. There was no REM sleep noted in 1 individual in the non-medicated group, 1 in the NDRI group, and 7 in the SSRI group. Analyses were adjusted for age, sex, and BMI.

DISCUSSION

In this sample of people who were referred for a sleep disorder assessment and underwent a diagnostic sleep study, individuals with depression had significantly more frequent sleep-related breathing disruptions than nondepressed individuals, which echoes previous findings.[35–37] The present study is the first to report that these breathing disruptions, and their effect on nocturnal blood oxygenation, may be worse in individuals with depression who are taking SSRIs, the most commonly prescribed medications for depression.[38–40]

In the current study, individuals using SSRIs had more frequent apneas and hypopneas during NREM sleep than non-medicated individuals with depression, with a similar trend when compared with those taking non-serotonergic antidepressants (ie, NDRIs). The differences in NREM sleep AHI and ODI were clinically meaningful according to established standards.[41] Notably, the overall rates of apneas and hypopneas were 1.6–1.9 times higher in the SSRI group than in the other groups. Supplemental analyses suggest that this effect may be dependent on depressive state, taking place in individuals currently symptomatic for depression but not in those with a history of depression who were no longer symptomatic. Symptomatic individuals using SSRIs also had lower blood oxygen saturation and more frequent desaturations during NREM sleep when compared to non-medicated individuals with depression or to those using non-serotonergic antidepressants. Although these findings need to be further investigated with prospective studies, this is the first empirical evidence in humans suggesting that the use of SSRIs in people with depression and sleep complaints may be associated with worse breathing during sleep. The hypothesis that this condition may operate via alterations in 5-HT-mediated respiratory functions is reinforced by the observation in our study that breathing disturbances were not significantly elevated in people taking non-serotonergic antidepressants.

Previous work indicates that in the central nervous system, the excitatory effects of 5-HT on respiration centers are mostly mediated by 5-HT1A, 5-HT2A, and 5-HT2C receptors.[16] For instance, 5-HT in the brainstem increases the activation of upper-airway dilators,[29,30] which facilitates respiration. Conversely, in the periphery, 5-HT has mostly inhibitory effects on respiration that are mediated by 5-HT2A, 5-HT2C, and 5-HT3

Table 4—Respiratory indices across depression subgroups.

	Non-medicated $\bar{x}$ ± SD	NDRI $\bar{x}$ ± SD	SSRI $\bar{x}$ ± SD	Statistics (*F*)[a]		
				Group	Sleep	Interaction
AHI (events/h)				0.4	1.8	4.3*
NREM sleep	9.8 ± 13.0	7.8 ± 11.2	15.2 ± 17.6			
REM sleep	20.2 ± 20.3	18.3 ± 26.7	21.1 ± 21.4			
$MinSpO_2$ (%)				3.2*	0.4	4.8**
NREM sleep	91.0 ± 3.5	91.5 ± 2.2	88.9 ± 4.6			
REM sleep	90.9 ± 3.7	91.6 ± 3.9	90.1 ± 4.8			
ODI (events/h)				2.8	9.3**	7.2***
NREM sleep	3.6 ± 5.6	2.8 ± 2.3	9.8 ± 15.6			
REM sleep	9.9 ± 11.7	12.6 ± 21.3	13.3 ± 18.3			

[a]Analyses were adjusted for age, sex, and BMI. *F* values are reported for main group effects (differences between patients with depression taking SSRIs, patients taking NDRIs, and non-medicated patients with depression), main effects of sleep stages (NREM and REM sleep), and interactions between main groups and sleep stages. There was no REM sleep noted in 1 individual in the non-medicated group, 1 in the NDRI group, and 7 in the SSRI group. *$P \leq .041$, **$P \leq .009$, ***$P \leq .001$.

receptors. Hence, although the stimulation of 5-HT2A and 5-HT2C receptors may have opposite effects on respiration in different parts of the nervous system, 5-HT1A and 5-HT3 receptors may induce more consistent excitatory and inhibitory modulation, respectively. Although this remains to be formally investigated, depression-related reduction in 5-HT1A receptor activity[11,42] and potential increases in 5-HT3 receptor activity[31] may worsen individual vulnerability to the suppressing effects of SSRIs on respiration.

In line with the well-known REM sleep–suppressing effects of SSRIs,[1] the SSRI group was found to have significantly reduced amounts of REM sleep and increased REM sleep onset latency compared with the non-medicated and NDRI groups. Considering that there is increased risk for upper-airway collapse during REM sleep, it has previously been suggested that antidepressant medications may reduce sleep apneas by suppressing REM sleep.[43] However, in the present study, significant differences in AHI and blood oxygen desaturation persisted despite the reduction in REM sleep and occurred most prominently during NREM sleep. This result suggests that the effects of SSRIs on nocturnal respiratory function in people with depression may not solely stem from changes in sleep architecture. These findings may have important clinical implications, considering the potential for SRBDs to worsen depression.[44,45] Researchers have suggested that SRBDs negatively impact mood, notably via the effects of chronic hypoxia on the brain.[45,46] If SSRI use in people with depression worsens not only sleep apneas/hypopneas but also oxygen desaturation, then in the long term, their use may induce progressive mood worsening.

This study has several limitations. Because it was based on retrospective data, unmeasured confounders may have resulted in biased exposure effect estimates. For example, we were unable to control for factors such as medication dosage, duration of treatment, central obesity, and smoking status. Because of the cross-sectional nature of this study, causation cannot be inferred. The sample included individuals referred to a sleep clinic, so the findings may not generalize to people with depression without marked sleep problems. Generalizability is further limited by a single-center study design. Only information about medications taken on the night of PSG were available. As such, we were unable to control for other medications that could have been taken around the same period but that may have been skipped on that specific night. Although individuals taking any type of psychotropic medications aside from the ones defining the drug classes under study were systematically excluded, other types of medications (eg, antihypertensives) may have impacted sleep. The sample size of the group taking NDRIs was fairly small. Larger comparative and interventional studies are required to investigate the specificity of the effects of different serotonergic agents as compared with those of non-serotonergic antidepressants on respiratory functions during sleep. There is also a need to assess potential sex differences in these effects.

Although they are limited by the fact that they are based on a retrospective clinical sample, the current study suggests that individuals with depression may have worse SRBDs than mentally healthy individuals. Independent of depression severity, sleep-related respiratory disturbances during NREM sleep may be more prominent in people using SSRIs as opposed to those using NDRIs, possibly because of interactions between depression neuropathophysiology and the effects of exogenous 5-HT manipulation on the respiratory system. Prospective studies are required to determine whether 5-HT agents may actively exacerbate SRBDs in individuals with depression and whether this increase may be modulated by 5-HT receptor expression and/or binding abnormalities linked to depression. Such studies may unveil a new and previously unsuspected adverse effect of one of the most heavily prescribed classes of psychotropic medication. This potential effect would have serious implications for the clinical management of depression because SRBDs can have adverse impacts on physical health and depressive symptoms.

ABBREVIATIONS

5-HT, serotonin
BDI, Beck Depression Inventory
BMI, body mass index
minSpO_2, minimum blood oxygen saturation
NDRI, norepinephrine-dopamine reuptake inhibitor
ODI, oxygen desaturation index
SRBDs, sleep-related breathing disturbances
SSRI, selective serotonin reuptake inhibitor

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