Impact of obstructive sleep apnea syndrome on cardiac rhythmicity

Impact du syndrome d'apnée obstructive du sommeil sur la rythmicité cardiaque

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Résumé

Le syndrome d'apnée obstructive du sommeil (SAOS) est une pathologie qui affecte près de 2 à 4% des adultes. Le SAOS est connu comme étant un facteur de risque indépendant des maladies cardiovasculaires.

Objectif : Rechercher d'éventuels troubles du rythme cardiaque révélés pendant le sommeil et d'analyser la variabilité sinusale afin de détecter l'impact possible du SAOS sur l'équilibre cardiaque autonome.

Méthodes: Notre étude a inclus 20 patients. Tous ont eu une polygraphie respiratoire et un holter rythmique. Nos patients ont été regroupés en fonction de la valeur de l'indice d'apnée-hypopnée (AHI) en trois groupes: Groupe 1: AHI <5: groupe de patients non apnéiques, groupe 2: AHI ≥ 5 et ≤ 30: groupe de patients avec SAOS d'intensité légère ou modérée et groupe 3: IAH> 30: patients avec SAOS sévère.

Résultats: l'âge moyen était de 48 ans. Des arythmies cardiaques ont été notées dans sept cas. Il n'y avait pas de corrélation statistique entre la présence de ces troubles du rythme cardiaque et la gravité du SAOS L'analyse de la variabilité sinusale était divisé en analyse temporelle et analyse spectrale (dite aussi fréquentielle). Aucune corrélation n'a été trouvée entre la sévérité des apnées et ces paramètres. La confrontation IAH et paramètres fréquentielles a noté une corrélation avec les deux paramètres VLF et LF. Cette corrélation était plus évidente en ne prenant en compte que les valeurs nocturnes.

Conclusions: l'analyse de la variabilité sinusale chez les patients atteints de SAOS peut fournir des arguments en faveur de la gravité du syndrome apnéique. Cela pourrait aider à adapter le traitement des SAOS. Une activation sympathique chez un patient non connu apnéique doit faire rechercher un SAOS. Le traitement de ce dernier permet d'améliorer les arythmies, et surtout d'en diminuer leurs rechutes, si le patient en porte.

Mots-clés

Fibrillation auriculaire, système nerveux autonome, arythmies cardiaques, hypoxémie, syndromes d'apnées du sommeil

Summary

Introduction: Obstructive sleep apnea syndrome (OSAS) is a common pathology affecting nearly 2-4% of adults. It is secondary to repeated collapses of upper airways during sleep, thereby decreasing or even interrupting breathing. Several studies were accumulated in support of the initial hypothesis that OSAS was an independent risk factor for cardiovascular disease.

Aim: We report a prospective cohort study that aims to look for possible heart rhythm disorders revealed during sleep and analyze the sinus variability in order to detect the possible impact of OSAS on autonomic cardiac balance.

Methods: Our study included 20 patients with a mean age of 48 years old. All of them have had a respiratory polygraphy and a rhythmic holter. Ventilatory polygraphy's indication was nocturnal and diurnal symptomatology of sleep apnea with an average Epworth score of 15.Our patients were grouped according to the value of the apnea-hypopnea index (AHI) in three groups: Group 1: AHI <5: group of non-apneic patients, Group 2: AHI ≥ 5 and ≤ 30: group of mildly or moderately apneic patients, Group 3: AHI > 30: severe OSAS.

Results: Cardiac arrhythmias were noted in seven cases. There was no Statistical correlation between the presence of these cardiac rhythm disorders and OSAS severity. The study of cardiac variability's time-domain analysis did not show a statistical difference between our three groups of patients. Similarly, the study of frequency-domain analysis did not show a statistical difference between our three groups of patients. Nevertheless, there was a positive correlation between AHI and the two frequency parameters (VLF and LF). This correlation was more evident by taking into account only the nocturnal values of these parameters of cardiac variability.

Conclusion: Sinus variability analysis in patients with OSAS can provide arguments for the severity of the apneic syndrome. This could help to adapt the treatment of OSAS. Sympathetic activation in an unknown apneic patient should search for OSAS. The treatment of the latter improves arrhythmias and reduces their relapses.

Keywords

Atrial fibrillation, autonomic nervous system, cardiac arrhythmias, hypoxemia, Sleep apnea syndromes.

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INTRODUCTION

Sleep is associated with physiological cardiovascular changes characterized by decreased activity of the sympathetic nervous system with lowering of blood pressure, heart rate and basal metabolism while parasympathetic activity increases. The role of sleep pathologies in cardiovascular morbidity and mortality begin to be recognized, particularly that of obstructive sleep apnea syndrome (OSAS). In fact, OSAS is a common pathology affecting at least 2-4% of the adult population (1). It is secondary to repeated collapses of the upper airways during sleep, thereby decreasing or even interrupting breathing. Thus, apneas and hypopneas cause repeated hypoxemia and hypercapnia and fragment sleep in the form of a reduction of sleep with a cortical and autonomic awakening, allowing the resumption of breathing. By the early 1980s, several studies were accumulated in support of the initial hypothesis that OSAS was an independent risk factor for cardiovascular disease (1).
The objective of our study was to look for possible heart rhythm disorders revealed during sleep and analyze the sinus variability in order to detect the possible impact of OSAS on autonomic cardiac balance.

METHODS

Study design
This study was a prospective cohort study.

Studied population:
Our study focused on 20 patients admitted to the pneumology department of Tunis Military Hospital for suspicion of OSAS between November 2016 and April 2017. Patients known to have cardiac, renal, hepatic, untreated hypothyroidism or other endocrinopathy were not included in our study. Similarly, patients on treatment that can interact with the autonomic nervous system or known to have a periodic limb movement sleep disorder have been excluded. All our patients had an electrocardiogram (ECG), chest x-ray, blood gasometry, functional respiratory exploration (FRE) and biologic assessment before admission to the service.
A rhythmic holter was performed concomitantly with a respiratory polygraphy as part of a protocol to detect heart rhythm disorders in apneic patients.
At the time of data collection, patients with less than three hours of sleep were excluded. The rest of the patients (20 patients) were grouped according to the value of the apnea-hypopnea index (AHI) in three groups:
- Group 1: AHI <5: group of non-apneic patients.
- Group 2: AHI ≥ 5 and ≤ 30: group of mildly or moderately apneic patients.
- Group 3: AHI > 30: severe OSAS.

Respiratory polygraphy:
The polygraphic record was made with a portable Alice® PDx polygraph. This polygraphy allowed us to measure and record the following parameters:
- Nictemeral Oxygen saturation and heart rate rhythm: by means of a pulse oxymeter and an electrocardiogram.
- Respiration airflow: using a thermal flow and nasal pressure sensors to score apneas and hypopneas successively.
- Qualitative recordings of respiratory efforts (thoracic and abdominal efforts): using thoracic and abdominal straps.
- Body position during sleep: using a position sensor.

Respiratory events were scored as follows:
- Apnea: drop of the airflow signal ≥ 90% from the baseline preceding the event for a duration ≥ 10 seconds.
- Hypopnea: A fall in the airflow signal ≥ 50% or ≥ 30% (relative to the baseline and using a nasal pressure sensor) associated with desaturation greater than 3% and/or to a micro awakeningfor a duration ≥ 10 seconds.
- These events were considered obstructive when associated with high upper airway resistance, if they were accompanied by snoring during the event, if the thoraco-abdominal movements were out of phase or if we noted an inspiratory flattening of the nasal pressure.

As Respiratory polygraphy does not allow specifying sleep stages, "circadian" effect on rhythmic Holter parameters has not been studied. Similarly, the effect of sleep apnea on these parameters has not been studied.

Rhythmic holter and analysis of sinus variability:
Analysis of the rhythmic Holter data was done with the CardioScan software (version 2.0016).
Rhythm disorders were investigated and divided into ventricular arrhythmias, supraventricular arrhythmias and ST segment abnormalities. We, also, looked for heart arrests of more than 2.5 seconds.
Analyzed time-domain variables were: mean RR (mean RR), RMSSD, 24-hour SDNN, SDNN index and pNN50. In frequency domain analysis, the power was calculated for very low frequency (VLF, 0.0033-0.04 Hz), low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.40 Hz). These variables were specified on the rhythmic holter for the 24 hours of recording and for the night period (22pm to 6am).

Statistical analysis:
Statistical analyzes were performed using version 21 of the Statistical Package for Social Sciences Software (SPSS). Results were expressed as averages for each group. Given the small number of patients in our series,

a Kruskal Wallis test (non-parametric test) was used for bivariate categorical/ continuous (or ordinal) variable correlations.
Bivariate correlations (continuous variables) were estimated with Spearman coefficient.
The correlation between AHI and the indices of sinus variability was done without and then with age and BMI adjustment. This adjustment is called partial correlation.
A value of p<0.05 has been considered significant with 95% confidence intervals.

RESULTS

Our study included 20 patients (four men and 16 women) divided into three groups:

- Patients without OSAS: four patients.
- Patients with mild to moderate OSAS: 10 patients.
- Patients with severe OSAS: six patients.

The mean age of our patients was 48 years old and the BMI was 37 (+/- 10), 37 (+/- 9) and 39 (+/- 5) in the three groups successively. There was no significant difference between the three groups.
There was, also, no statistically significant difference between patients in the different groups in terms of pathological medical history. In fact, no patient was known to have valvulopathy, cardiac arrhythmia, or heart failure. A history of hypertension, diabetes, or myocardial infarction was diagnosed before that of OSAS in patients who are affected (figure 1).

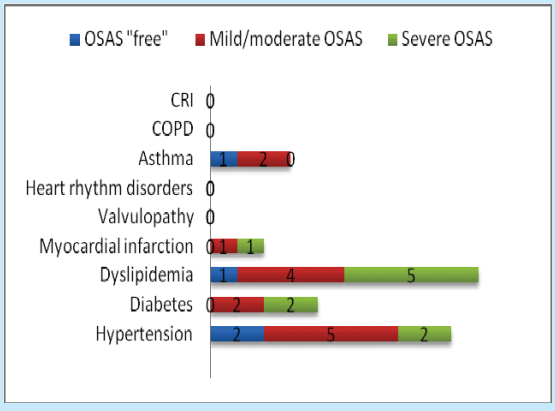

Figure 1 : patients' past medical history.
(CRI: Chronic respiratory insufficiency; COPD: chronic obstructive pulmonary disease).

Ventilatory polygraphy's indication was nocturnal and diurnal symptomatology of sleep apnea with an average Epworth score of 15. The average recording time was 517 minutes (+/- 55 minutes), which was about 8 hours and ½. The average total sleep time or average time in bed was 486 minutes (+/- 68 minutes) or about 8 hours.

The overall AHI was 3.4 (+/- 1), 14.6 (+/- 7) and 40.6 (+/- 12) for the three groups successively.
The rest of polygraphy data was summarized in Table I.

Table 1 : Polygraphy data (comparison between the three groups of patients):
SpO2: Pulsed oxygen saturation; min: minutes; p: patients.

	OSAS "free" (4 p)	Mild/moderate OSAS (10 p)	Severe OSAS (6 p)	(p)
Awakening SpO2 (%)	98 (+/-0.5)	97 (+/-1)	96,6 (+/-1)	0,07
Minimum SpO2 (%)	85 (+/-6)	83 (+/-5)	79,8 (+/-8)	0,01
Sleep time with SpO2<90% (min)	0,05 (+/-0,1)	11,3 (+/-16,8)	118,4 (+/-149)	0,004
Desaturation index	4,4 (+/- 2,9)	19,6 (+/-15,1)	45,1 (+/-11,2)	0,003

An important desaturation was noted in the group of patients with severe OSAS.
Cardiac arrhythmias were noted in seven cases. These were associated supraventricular (SVPC) and ventricular (VPC) premature complexes in four cases, isolated SVPC in two cases and atrial fibrillation (AF) associated with VPC in one case.
Statistically, no correlation was found between the presence of these cardiac rhythm disorders and the OSAS severity (p = 0.87).
We tried to look for potential severe VPCs. Thus the number of these VPCs was on average 0 VPCs, 227 (ranging from 117 to 456) and 20.5 (ranging from 8 to 33) for the three groups of patients successively. The number of repetitive VPCs averaged 0 VPCs, 22 (ranging from 0 to 55) and 0 VPCs for each group. There were no polymorphic VPCs or R/T phenomena. Although these VPCs appear more frequent with an average> 200 in the mild to moderate OSAS group, no statistically difference was found (p = 0.34).
Only two patients with mild-to-moderate OSA had cardiac arrest> 2.5 seconds in holter recording. Thus, no statistical difference was found between our three groups of patients (p = 0.34). In the two patients mentioned above, the number of cardiac arrests was 10 (AHI = 21.7) and 146 (AHI = 5.4).
Concerning cardiac variability's time-domain analysis: Table II summarizes the different values obtained according to the severity of OSAS. Variance study of these parameters did not show a statistical difference between our three groups of patients.
Frequency-domain analysis is a mathematical method for detecting the different rhythm oscillations. Cardiac variability is distributed in a frequency range of 0.04 to 0.50 Hz. This domain can be divided into three components: VLF, LF and HF.

Table 2 : Comparison of time-domain (24 h and nocturnal (n)) parameters of sinus variability depending on the severity of OSAS (SD: standard deviation; p: patients).

	OSAS "free" (4 p)	Mild/moderate OSAS (10 p)	Severe OSAS (6 p)	(p)
		Mean (+/- SD)		
Average heart rate	78 (+/-6)	77 (+/-10)	74 (+/-12)	0,55
Mean RR (ms)	801 (+/-83)	806 (+/-83)	843 (+/-105)	0,84
SDNN	110 (+/-29)	120 (+/-38)	111 (+/-34)	0,74
SDNN (n)	80 (+/-27)	90 (+/-37)	94 (+/-36)	0,89
Index SDNN	50 (+/-21)	57 (+/-21)	64 (+/-24)	0,40
RMSSD	30 (+/-23)	36 (+/-17)	38 (+/-16)	0,37
RMSSD (n)	36 (+/-30)	42 (+/-17)	42 (+/-13)	0,41
SDANN	96 (+/-22)	101 (+/-37)	88 (+/-30)	0,63
pNN50	10 (+/-17)	12.5 (+/-15)	14 (+/-12)	0,57
pNN50 (n)	15 (+/-25)	18 (+/-17)	19 (+/-12)	0,55

Table III summarizes the different values obtained depending on the severity of OSAS. Study of these parameters variance did not show a statistical difference between our three groups of patients.

Table 3 : comparison of frequency parameters (24 h and nocturnal (n)) of the sinus variability depending on OSAS severity (SD: standard deviation; p: patients).

	OSAS "free" (4 p)	Mild/moderate OSAS (10 p)	Severe OSAS (6 p)	(p)
VLF		Mean (+/- SD)		
VLF (n)	1754 (+/-1148)	2256 (+/-1900)	3030 (+/-2566)	0,70
LF	1646 (+/-1329)	2476 (+/-2057)	3998 (+/-4088)	0,34
LF (n)	487 (+/-400)	637 (+/-560)	946 (+/-687)	0,34
HF	513 (+/-435)	813 (+/-684)	1182 (+/-996)	0,34
HF (n)	413 (+/-620)	319 (+/-293)	278 (+/-147)	0,58
LF/HF	612 (+/-941)	463 (+/-499)	324 (+/-137)	0,80
LF/HF (n)	2,3 (+/-1,1)	2,3 (+/-1,6)	3,1 (+/-0,8)	0,16
	2 (+/-1,41)	3,1 (+/-3,4)	3,4 (+/-2,2)	0,51

Table IV summarizes the correlation between AHI and sinus variability indices after age and BMI adjustment. There was a positive correlation between AHI and the two frequency parameters (VLF and LF). This correlation was more evident by taking into account only the nocturnal values of these parameters of cardiac variability.

Table 4 : correlation between AHI and sinus variability indices after age and BMI adjustment.

	P' (partial correlation)	P' (nocturnal values)
RR interval (ms)	0,19	-
SDNN	0,49	0,2
Index SDNN	0,11	-
RMSSD	0,45	0,54
SDANN	0,91	-
pNN50	0,46	0,49
VLF	0,05 (r=0,47).	0,01 (r=0,58).
LF	0,06 (r=0,45).	0,02 (r=0,52).
HF	0,92	0,79
LF/HF	0,22	0,64

DISCUSSION

Our study was prospective including 20 patients admitted in pneumology department of Tunis military hospital for suspicion of OSAS between November 2016 and April 2017. Initially designed to watch for disturbances of heart rhythm revealed by sleep in apneic patients, it was extended to look for the impact of OSAS on the cardiac autonomic balance.

In fact, since the early 1980s, the potential cardiovascular consequences of OSAS have been discussed, but have been subject of prolonged controversy.

Let's remind that during Non-REM sleep, sympathetic nervous system activity, blood pressure, heart rate, and basal metabolism decrease, while parasympathetic activity increases. OSAS interrupts this quiescence of the cardiovascular system through a set of acute, hemodynamic, autonomic, biochemical and metabolic changes, with medium and long-term consequences likely to induce or aggravate cardiovascular pathologies. In addition, apneas result in gradual decrease in oxygen blood pressure (PaO2) and an increase in that of carbon dioxide (PaCO2). As consequence, tissue oxygen supply to tissues decreases, especially to the myocardium. Both conjugates contribute to increase the activity of the sympathetic nervous system. Finally, hypoxemia followed by re-oxygenation induces the production of free radicals at the origin of oxidative stress and tissue inflammation, particularly vascular inflammation. These, oxidative stress and inflammation, are the cause of endothelial dysfunction and an increase in sympathetic tone. Furthermore, upper airways reopening contemporary with micro awakening, is accompanied by sympathetic activation that causes an acceleration of the heart rate and an increase in blood pressure. All of these abnormalities contribute to the

increase in cardiovascular risk and cardiovascular morbidity and mortality in patients with OSAS.

Several studies have shown the frequency of cardiac arrhythmias in apneic patients. In a review of the literature published in 2013, Valentina A. Rossi reviewed the pathophysiology of sleep apnea resulting arrhythmia (2). According to the same article, main arrhythmias associated with OSA are atrial and ventricular premature complexes, bradycardias, sinusal pauses and atrial fibrillation tachyarrhythmia (AFT / AF). In the Mehra study, there was no significant difference in the prevalence of nocturnal sinus pauses between patients with severe OSAS (AHI≥30, n = 228) and those without OSAS (AHI <5, n = 338, 11% vs 9%, p = 0.34). Second-degree atrioventricular block was rare and its prevalence did not differ between the groups. In this same article, the prevalence of ventricular premature complexes and complex ventricular ectopia was higher in those with, than in those without, an OSAS (35% vs 21% [p = 0.0003] and 25% vs. 15% [p = 0.02], respectively) (3). Sinus pauses were more common in patients with OSAS (9.1% vs. 0%, p <0.01) in Roche's study (4). In this latest study and that of Mehra, the prevalence of paroxysmal supraventricular tachycardia has not increased in OSAS. The latter author also found a higher prevalence of atrial fibrillation in people with OSAS than in those without (4, 8% vs. 0.9%, p = 0.03) (3).

In other studies, cross-sectional data of 6424 men and women showed an increase of OSA-related heart failure by 2.38 times, regardless of confounding factors (5). Prospective data showed that, 21 days after acute myocardial infarction, the presence of OSA was associated with poor recovery of left ventricular systolic function (6). In patients with OSAS, the relative risk of sudden cardiac death between midnight and 6:00 was 2.57 compared to the general population (10 to 12 years).

In summary, the prevalence of rhythm disorders associated with OSAS reported in the literature was as follows (2):

- Atrial fibrillation: 3% to 39% of OSAS.
- Sinus brady-arrhythmias: 7% to 59% of OSAS.
- Sinus pauses: 11% to 42% of OSAS.
- 2nd-degree atrio-Ventricular blocks: 8% to 13% of OSAS.
- Ventricular premature complexes: 14% to 82% of OSAS.
- Non sustained Ventricular tachycardia: 5%.

Otherwise, several authors have studied sympathetic balance's alteration by referring to a rhythmic holter. Their objective was to detect a possible correlation with the severity of OSAS and to find the parameter (in temporal and spectral analyzes) that could reflect (the most) this severity and that could serve as a screening tool in case of unknown OSAS. Most series were of a small size. Table V summarizes some of published works. The most important series was that of D.-H. Park with 59 patients (7). The spectral power LF and the ratio LF / HF were the two parameters having the most correlation with the AHI. Finding that was rechecked by our study. This reflects, in fact, an autonomic dysregulation with activation of the sympathetic system caused by the OSAS.

Moreover, several interventional studies have investigated the effect of OSAS treatment on OSAS-associated cardiac arrhythmias. For all these studies, an improvement and / or decrease in the rate of relapses of these arrhythmias was noted owing to OSAS treatment by CPAP. These studies were summarized in Table VI.

Table 5 : correlation between AHI and rhythmic holter parameters: review of the literature.
(AHI: apnea-hypopnea index).

Author	Study
Gammoudi N et al(17).	Study of 30 patients with OSAS: Negative correlation between AHI and RR intervals and HF value. Positive correlation between AHI and LF indices and LF / HF ratio. After adjusting for age and BMI, correlation only between AHI and mean RR index.
Zhu et al(18).	Study of 46 patients: 23 control patients and 23 patients with OSAS: Negative correlation between mean RR and AHI.
Reynolds et al (19), Park et al (7), Song MK et al(20).	Positive correlation between LF / HF ratio and AHI.
Guilleminault et al(21).	Study of 20 patients: Positive correlation between LF / HF ratio and respiratory events; negative correlation between these events and HF index.
D.-H. Park et al(7).	Study of 59 patients: 22 patients with mild-to-moderate OSAS and 37 with severe OSAS: In temporal analysis: only HRV TI had a positive correlation with the severity of OSAS. In frequency analysis: three indices had a positive correlation with the severity of OSAS: VLF, LF and LF / HF ratio.
Narkiewicz et al(22).	Study of 49 patients: 15 with severe OSAS, 18 with mild-to-moderate OSAS and a control group of 16 patients: Increased LF / HF ratio, HF power, and normalized LF power in patients with moderate to severe OSAS compared to normal controls. The LF / HF ratio was correlated with the severity of OSAS.
Gula et al(23).	Study of 20 patients with OSAS: LF / HF ratio was higher in patients with moderate/ severe OSAS compared to normal subjects.
Aydin et al(24).	Study of 36 patients: 19 with moderate OSAS and 17 patients with severe OSAS: Total power, VLF, LF and LF / HF spectral power were higher in patients than in controls. LF spectral power and LF / HF ratio were increased in severe OSAS group compared to moderate OSAS group.
Our study	Study of 20 patients: positive correlation between AHI and frequency parameters (VLF and LF).

Table 6 : effect of OSAS treatment on arrhythmias: review of the literature.

Author	Study
Kangala(8)	Study of 39 patients: recurrence of FA 12 months after cardioversion: 82% in OSAS without CPAP treatment, 42% in OSAS treated with CPAP, 53% in control subjects.
Abe (9)	Study of 1394 patients: Treatment with CPAP reduces paroxysmal nocturnal AF and supraventricular ectopias from 14% to 4%. CPAP prevented the occurrence of sinus bradycardias and sinus pauses.
Craig (10)	Study of 83 patients: CPAP does not affect the frequency of atrial arrhythmias or bradyarrhythmias. He also noted less diurnal ventricular tachycardia in the CPAP therapeutic group.
Tilkian(11)	Study of 15 patients with OSAS: Atropine (partially) and tracheotomy (almost completely) prevent bradyarrhythmias during sleep. These same treatments almost completely prevent supraventricular premature complexes during sleep.
Becker (12)	Study of 239 patients with OSAS: 80-90% reduction of heart blocks with CPAP treatment.
Koehler (13)	Study of 16 patients with OSAS: CPAP reduces bradyarrhythmias by 56%.
Simantirakis(14)	Study of 23 patients with OSAS: Treatment with CPAP for 6 months abolished bradyarrhythmias.
Harbison (15)	Study of 45 patients with OSAS: CPAP abolished arrhythmias in 88% of cases.
Ryan (16)	Study of 18 patients: 58% reduction of nocturnal supraventricular premature complexes after 1 month of CPAP treatment.

CONCLUSION

OSAS is a fairly common pathology. It can lead to disturbances of cardiac rhythmicity. For some authors, it constitutes an independent risk factor for cardiovascular diseases. Sinus variability analysis in patients with OSAS can provide arguments for the severity of the apneic syndrome. This could help to adapt the treatment of OSAS. Sympathetic activation in an unknown apneic patient should search for OSAS. The treatment of the latter improves arrhythmias and reduces their relapses.

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