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Sleep disturbances and restless legs syndrome in postmenopausal women with early breast cancer given adjuvant aromatase inhibitor therapy

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ABSTRACT

Introduction: Whether adjuvant therapy with aromatase inhibitors (AIs) causes sleep disturbances or not in postmenopausal women with early breast cancer (EBC) is still a controversial issue.
Methods: Between March 2014 and November 2017, validated questionnaires for assessing insomnia, anxiety, depression, quality of life (QoL) and restless legs syndrome (RLS) were administered to 160 EBC patients at baseline and after 3, 6, 12, and 24 months of AI therapy.
Results: AI therapy significantly decreased the patients' QoL, but did not influence insomnia, anxiety or depression. However, it significantly increased the frequency and severity of RLS. Patients with RLS at baseline (19%) or who developed RLS during AI therapy (26.3%) reported statistically lower quality of sleep, higher anxiety and depression, and worse QoL compared to patients who never reported RLS (54.7%).
Conclusion: Although AI therapy does not affect sleep quality, it may increase RLS frequency. The presence of RLS could identify a group of EBC patients who may benefit from psychological support.

1. Introduction

Aromatase inhibitors (AIs) are the standard adjuvant treatment for postmenopausal women with hormone receptor (HR)-positive early breast cancer (EBC) [1,2]. The commonly reported side effects of AIs, such as musculoskeletal symptoms and hot flashes, and the accompanying psychological distress can potentially interfere with sleep, causing or worsening insomnia [3–6].

Previous descriptive research revealed that sleep disturbances affect between 30% and 50% of patients with cancer [7,8]: the prevalence seems to be higher in EBC patients treated with chemotherapy and/or radiotherapy in cross-sectional and longitudinal studies [9,10]. Data on sleep disturbances in women taking AIs are somewhat discordant: a cross-sectional study showed a high prevalence of insomnia-related symptoms among AIs users [8], while another longitudinal study did not show any significant change in subjective and objective sleep parameters in this population [9].

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an irresistible urge to move the legs, with typical worsening of symptoms in the evening, night or during periods of inactivity and relief with movement [11,12]. Therefore, RLS interferes with sleep, causes daytime drowsiness and negatively affect patients' quality of life (QoL) [13].

Previous studies which explored insomnia in women receiving AIs did not evaluate RLS, which is diagnosed in a minority of cancer patients [13,14]. Moreover, it is known that insomnia, anxiety, depression, and

Abbreviations: AI, Aromatase inhibitor; EBC, Early breast cancer; FACT-B, Functional Assessment of Cancer Therapy – Breast; HR, Hormone receptor; HADS, Hospital Anxiety and Depression Scale; IRLLSG, International RLS Study Group; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; QoL, Quality of life; RLS, Restless legs syndrome; SE, Sleep efficiency; SOL, Sleep onset latency; TIB, Time in bed; TST, Total sleep time; VAS, Visual analogue scale; WASO, Wake time after sleep onset.

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fatigue tend to cluster together [15], and also a strong association between RLS, depression, and anxiety has been well established in epidemiological and clinical studies [14–19]. Since dopamine agonists are effective in relieving symptoms of patients diagnosed with RLS, a dopaminergic dysfunction is supposed to play a key role in the pathogenesis of this disease [20,21]. However, the pathophysiology of RLS is complex and other biologic system are under investigation, including iron homeostasis and hormones [12,22]: in fact, it is known that RLS is more common in women and that affects up to one in five pregnant women during the third trimester [12,23]. The relationship between hormones and RLS is still uncertain, although preclinical evidence has shown a potential neuroprotective effect of estrogen on dopaminergic neurons [24–26]. Moreover, the risk of developing Parkinson's disease is increased in postmenopausal women [27,28] and recent evidence supports the association between bilateral oophorectomy and risk of developing RLS [29].

We hypothesized that sleep quality is worsened during AI therapy, which might increase the frequency of RLS, potentially due to the profound reduction in circulating estrogen levels: in fact, RLS could be a contributor to the sleep disturbances reported by EBC patients.

The present study aimed to investigate the effect of AI therapy on sleep disturbances and the possible association with RLS, anxiety, depressive symptoms, and QoL.

2. Patients and methods

This is a prospective, single-center trial conducted at the Medical Oncology Department and Breast Unit of Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili of Brescia (Italy), which was approved by the local Ethics Committee and registered in the ClinicalTrials.gov database with the identification number NCT02166281. The study was conducted in collaboration with the Sleep Disorders Center of San Raffaele Hospital in Milan (Italy).

The study's primary endpoint was to evaluate the prevalence of sleep disturbances after 3 months of AI treatment. The secondary endpoints were: 1) to assess the prevalence of sleep disturbances at subsequent timepoints; 2) to assess the longitudinal evolution of RLS, anxiety, depression, and QoL; 3) to investigate the association between sleep disturbances, RLS, anxiety, depression, and QoL.

As post-hoc analyses we evaluated the longitudinal evolution of sleep disturbances, anxiety, depression, and QoL in patients with and without RLS.

Eligibility criteria were the following: HR-positive EBC patients (stage I-III according to American Joint Committee on Cancer staging) receiving adjuvant AI therapy, postmenopausal status, willingness to comply with the study procedures. Exclusion criteria were known cognitive impairment or other major psychiatric disorders, altered sensorium, or regularly taking any of the following medications: anticonvulsants, alpha-2-delta ligands, dopamine agonists or antagonists, histamine antagonists, oral iron tablets, opioids, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors. Written informed consent was obtained from all participants included in the study.

Between March 2014 and November 2017, EBC patients consecutively referring to the Oncology Department and Breast Unit of ASST Spedali Civili Brescia and meeting the eligibility criteria were asked to enter the study. To evaluate the presence and the severity of sleep disturbances, RLS, anxiety, and depression and to assess the overall QoL, the following validated questionnaires were administered:

- International RLS Study Group (IRLSSG) rating scale [30];
- Pittsburgh Sleep Quality Index (PSQI) [31];
- Insomnia Severity Index (ISI) [32];
- Hospital Anxiety and Depression Scale (HADS) [33], composed by the anxiety subscale (HAS) and the depression subscale (HDS);
- Functional Assessment of Cancer Therapy – Breast (FACT-B) [34];

A trained nurse administered the questionnaires longitudinally at the following timepoints: at baseline (before starting AI therapy), and after 3, 6, 12, and 24 months after AI therapy initiation.

A subset of patients was asked to wear an actigraph (Philips® Actiwatch 2) on the non-dominant wrist for seven consecutive nights at the same timeline as the questionnaires' compilation (at baseline, and after 3, 6, 12, and 24 months after AI therapy initiation). The patients were also asked to record a sleep diary during this period to improve actigraphy's specificity [35]. Actigraphic data were analyzed, scored through a validated algorithm and used to extract the following sleep parameters: time in bed (TIB), total sleep time (TST), sleep onset latency (SOL, duration of time from light off to falling asleep), sleep efficiency (SE, ratio between time asleep and time in bed), wake after sleep onset (WASO, wake time after sleep onset), and number of awakenings. Subsequently, these data were manually scored by a single-blinded sleep specialist, who did not know the results of the questionnaires filled by the patients during the same timepoint: every actogram was assigned a score according to a visual analogue scale (VAS), ranging from 0 (good sleep) to 10 (disturbed sleep).

2.1. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 23. Categorical variables were expressed as frequencies and percentages, and the distribution of continuous variables was summarized as mean and 95% confidence interval (CI). After Kolmogorov-Smirnov tests, all variables were treated as non-normal in distribution, hence only nonparametric tests were used.

The sample size was calculated using the *proc power* of SAS Studio, assuming a frequency of insomnia in cancer patients at baseline of 30% (H0) [7,8] and an expected frequency of 50% during treatment (H1) [36]. For an alpha error of 0.05 and a power of 80%, at least 181 patients were needed to be enrolled. Estimating 10% of censored data, 200 patients were planned to be included.

Comparisons at fixed time points between groups (patients with RLS versus patients without RLS) for nonparametric continuous variables were performed by Mann–Whitney *U* test, while comparisons between paired time points (e.g., baseline vs. three months) were performed with Wilcoxon signed-rank test, and the evolution of each factor was assessed in all the time points with Friedman test. We considered a scenario where missing data were random, namely they were unrelated to the study variables: for this reason, we didn't apply any data imputation and patients with missing data were simply excluded from the analyses [37]. In these analyses, we adopted a pairwise method of missing deletions, except for the Friedman test, in which we deleted missing values with the listwise method. Chi-square was used to compare categorized variables. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

3. Results

A total of 200 consecutive EBC patients entered the study, but 40 patients (20%) were not compliant with completing the questionnaires and were excluded from the analysis. All the remaining 160 patients completed the questionnaire after 3 months and 143 patients completed the 6, 12, and 24-month evaluation. The CONSORT diagram is shown in Fig. 1.

The characteristics of the 160 assessable patients are listed in Table 1. The majority of them had pT1 tumors and underwent conservative surgery. Fifty-three patients (33%) had received previous either neoadjuvant or adjuvant chemotherapy.

The prevalence of insomnia, RLS, anxiety, depression and QoL at baseline is reported in Table 2. Noteworthy, sleep disorders were reported with high frequency in these patients, as 96 of them (60%) had a PSQI score above the threshold of insomnia; moreover, 60 patients (37.5%) had a mild insomnia and 20 patients (14.6%) had a moderate or

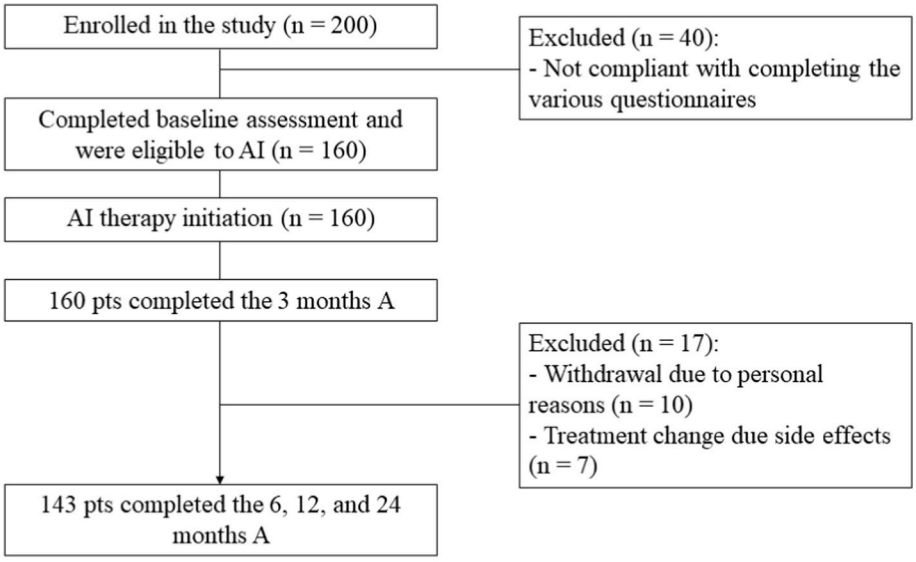

Fig. 1. CONSORT diagram.

Table 1
Characteristics of the patients at baseline.

	N (%)
Number of patients	160
Median age (range)	63.7 (47–83)
Median BMI (range)	25.8 (18.4–39.1)
Surgery	
Conservative	106 (67)
Mastectomy	52 (33)
pT	
1	110 (71)
≥2	45 (29)
pN	
0	93 (64)
≥1	53 (36)
Histological type	
No Special Type (NST)	118 (75)
Others	39 (25)
Grading	
G1 or G2	106 (68)
G3	51 (32)
HER2	
Negative	137 (87)
Positive	21 (13)
Chemotherapy	
No chemotherapy	107 (67)
Adjuvant	46 (29)
Neoadjuvant	7 (4)
Alcohol consumption	
No	106 (79)
Smoke	
No	111 (74)

BMI: body-mass index; pT: pathological tumor stage; pN: pathological nodal stage; G1: well differentiated tumor; G2: moderately differentiated tumor; G3: undifferentiated tumor; HER2: human epidermal growth factor receptor 2.

severe insomnia according to ISI. Thirty-four patients (21%) presented RLS at baseline, which was moderate-to-severe in the vast majority. Mild to moderate anxiety and depression were observed respectively in 47 (28.7%) and 21 (13.2%) patients. The mean FACT-B QoL score was 103.1 (100.4–105.8, 95% CI).

Table 3 shows the variation of insomnia and its severity, anxiety, depression, RLS severity, and QoL at baseline and after 3 months in the 160 fully assessable EBC patients. Mean values of PSQI, ISI, HAS, and HDS did not significantly change, whereas mean RLS scores significantly increased. As regards as QoL, total FACT-B scores significantly decreased, being the physical and the social well-being dimensions more susceptible to deterioration.

Considering the 143 patients who completed the questionnaires at all time points, the same trend of change observed at 3 months for PSQI, ISI, HAS, HDS, and FACT-B was maintained in the following months (Table 1 of Supplementary Materials).

As depicted in Table 4, the presence of RLS significantly correlated with higher PSQI, ISI, HAS, and HDS and lower FACT-B scores both at baseline and after 3 months. On the basis of these results as post-hoc analyses, we subsequently evaluated the longitudinal changes of PSQI, ISI, HAS, HDS and FACT-B scores in the 143 EBC patients, which were stratified in 3 subgroups: 1) RLS-positive patients at baseline, 26 patients (19%); 2) RLS-negative patients at baseline, who became positive during follow-up, 36 patients (26.3%); 3) RLS-negative patients at baseline, who remained negative throughout the whole observation period, 75 patients (54.7%).

Either patients with RLS at baseline or patients who developed RLS afterwards reported lower quality of sleep, higher levels of anxiety and depression at all time points (from baseline to 24 months after starting AI, as showed in Fig. 2) as opposed to their negative counterpart. A statistically significant worsening of QoL was also found in patients with RLS compared to those without RLS: a 10-points mean gap was detected between the two groups according to the FACT-B score.

Forty-six patients agreed to wear an actigraph at least one time for seven consecutive nights: 110 actograms in total were obtained, of which 104 were included in the final analysis due to technical problems and/or actigraph misplacement in six of them. We collected 42 actograms at baseline, 25 at 3 months, 17 at 6 months, 10 at 12 months, and 10 at 24 months after initiation of AI therapy. No statistical differences in the parameters collected by actigraphy were observed among the different time periods. The results are shown in Table 2 of Supplementary Materials.

Patients who did not report RLS symptoms showed better sleep parameters comparing to their counterpart reporting RLS symptoms in a specific timeline. Particularly, TIB and WASO were longer in patients reporting RLS, and SE was significantly worse. Furthermore, the blinded

Table 2
Questionnaires' scores at baseline.

	N = 160 patients
IRLSSG rating scale	
No RLS (%)	126 (79)
Yes RLS (%)	34 (21)
RLS severity	
No RLS	126 (79)
G1 (%)	4 (3)
G2 (%)	23 (14)
G3 (%)	7 (4)
G4 (%)	0 (0)
IRLSSG rating scale	
Mean value (95% CI)	3.0 (1.9–4.2)
Insomnia (PSQI)	
No (%)	64 (40)
Yes (%)	96 (60)
PSQI	
Mean value (95% CI)	7.5 (6.7–8.2)
Insomnia (ISI)	
No (%)	80 (50)
Mild (%)	60 (37.5)
Moderate (%)	18 (11.3)
Severe (%)	2 (1.3)
ISI	
Mean value (95% CI)	7.9 (7.0–8.8)
Anxiety (HAS)	
No (%)	114 (71.3)
Mild (%)	22 (13.1)
Moderate (%)	25 (15.6)
Severe (%)	0 (0)
HAS	
Mean value (95% CI)	6.1 (5.4–6.8)
Depression (HDS)	
No (%)	139 (86.9)
Mild (%)	10 (6.3)
Moderate (%)	11 (6,9)
Severe (%)	0 (0)
HDS	
Mean value (95% CI)	3.5 (2.9–4.2)
QoL (FACT-B)	
Mean overall (95% CI)	103.1 (100.4–105.8)
Physical well-being (95% CI)	24.7 (24.2–25.3)
Social well-being (95% CI)	17.7 (16.9–18.5)
Emotional well-being (95% CI)	18.5 (17.8–19.1)
Functional well-being (95% CI)	14.8 (14.0–15.6)
Others (95% CI)	27.4 (26.6–28.2)

RLS: restless legs syndrome; IRLSSG: International RLS Study Group; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; HAS: Hospital anxiety subscale; HDS: Hospital depression subscale; QoL: quality of life; FACT-B: Functional Assessment of Cancer Therapy – Breast.

Table 3
Questionnaires' scores variation during AI therapy.

N = 160	Baseline	3 months	p value
IRLSSG rating scale	3.0 (1.9–4.2)	5.7 (4.2–7.3)	**< 0.001**
PSQI	7.5 (6.7–8.2)	7.6 (6.9–8.4)	0.566
ISI	7.9 (7.0–8.8)	8.3 (7.4–9.2)	0.246
HAS	6.1 (5.4–6.8)	5.9 (5.3–6.6)	0.535
HDS	3.5 (2.9–4.2)	3.6 (3.0–4.2)	0.964
FACT-B	103.1 (100.4–105.8)	101.6 (98.6–104.6)	0.199
Physical well-being	24.7 (24.2–25.3)	23.7 (23.0–24.4)	**< 0.001**
Social well-being	17.7 (16.9–18.5)	17.0 (16.2–17.8)	**0.031**
Emotional well-being	18.5 (17.8–19.1)	18.8 (18.2–19.4)	0.114
Functional well-being	14.8 (14.0–15.6)	14.7 (13.8–15.5)	0.947
Others	27.4 (26.6–28.2)	27.4 (26.6–28.3)	0.616

Data are expressed by mean and 95% CI in brackets.
IRLSSG: International RLS Study Group; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; HAS: Hospital anxiety subscale; HDS: Hospital depression subscale; QoL: quality of life; FACT-B: Functional Assessment of Cancer Therapy – Breast.

VAS score was higher in patients reporting RLS symptoms, exhibiting a one-point total difference ($p = 0.012$). These results are shown in Table 3 of Supplementary Materials.

4. Discussion

AIs are the gold standard adjuvant treatment in EBC postmenopausal patients [38]. Nearly 80–90% of women diagnosed with EBC in high-income countries can expect long-term disease-free survival, therefore it is becoming increasingly important to address the potential long-term and late effects of treatments in cancer survivors [39].

The results of this study, whose primary aim was the assessment of insomnia in EBC patients receiving AI therapy in the adjuvant setting, showed a high proportion of patients with sleep disturbances at baseline. This finding is consistent with the literature, confirming the relatively high proportion of breast cancer patients suffering from sleep disorders compared to the general cancer patients' population [3,36,40]. However, there was no worsening of sleep disturbances during the administration of AIs and this finding is similar to the results of a recently published study [41]. As mentioned previously, insomnia often clusters with anxiety and depression and consequently both parameters evaluated by the HADS score did not change after the introduction of AIs in these patients.

To our knowledge, RLS has never been evaluated in EBC patients receiving AIs. This study revealed that RLS frequency is double among EBC patients compared to the general population of healthy women [16]. The higher prevalence of RLS found in the cancer patients' population is consistent with this observation [13,14].

This study also showed a worsening of RLS during AI therapy. In our series, the rate of RLS increased consistently after 3 months, either in prevalence (35%) or severity, and remained stable during the next two years of follow-up. This finding was not previously reported and the underlying mechanisms are not clear: a possible explanation might be the profound estrogen depletion caused by AIs, since these hormones possess neuroplastic and neuroprotective effects on dopaminergic neurons [24–26,42]. This concept is further supported by a recent study by Huo et al. who showed an increased risk of developing RLS in women who underwent premenopausal bilateral oophorectomy [29]. However, this result deserves confirmation in larger studies and may comprehend RLS in the variegated spectrum of symptoms reported by EBC patients during AI therapy [5,43].

Similar to other studies conducted in healthy subjects and in patients with a variety of medical conditions, including cancer patients [13,14], RLS was shown to correlate with higher levels of insomnia, anxiety, depression, and with deterioration in QoL. Based on these data, we explored the longitudinal trend of sleep disturbances, anxiety, depression, and QoL, stratifying our patients between those with pre-existing or acquired RLS during AIs and those without RLS. Our results showed that scores referring to insomnia, anxiety, and depression remained persistently high over time in patients with RLS, while QoL consistently decreased. These results are of potential great interest, as they suggest that the RLS questionnaire (whose completion time is only of a few minutes) could identify a group of patients, who may benefit from psychological or social support. Since these findings arise from a post-hoc analysis, they deserve confirmation in a broader case series. In addition, whether RLS is the cause or the effect within a cluster that includes anxiety, depression, and insomnia, still remains an interesting and controversial issue for further research.

The prospective design and the relatively large number of enrolled EBC patients are the main strengths of this study. However, potential limitations should be noted. First, the high proportion (20%) of patients excluded from the analysis due to poor compliance in completing the questionnaires. Other limitations are the absence of blood parameters, the lack of adjusting for potential confounders (e.g., body-mass index, cardiovascular diseases) and the single-center nature of the study.

In conclusion, AI therapy did not statistically worsen sleep

Table 4
Changes in insomnia, anxiety, depression, and quality of life (QoL) according to presence or absence of restless legs syndrome (RLS) at baseline and after 3 months of AI therapy.

	Baseline		p value	3 months		p value
RLS	*No*	*Yes*		*No*	*Yes*	
PSQI	6.8 (6.0–7.5)	10.3 (8.8–11.8)	<0.001	6.6 (5.7–7.4)	7.6 (6.9–8.4)	<0.001
ISI	7.2 (6.3–8.1)	11.4 (9.5–13.2)	<0.001	6.6 (5.7–7.5)	9.8 (8.4–11.1)	<0.001
HAS	5.3 (4.7–6.0)	8.5 (7.1–10.0)	<0.001	4.5 (3.9–5.1)	8.9 (7.7–10.1)	<0.001
HDS	3.0 (2.4–3.5)	5.5 (4.0–7.0)	<0.001	2.4 (1.9–2.9)	5.8 (4.5–7.2)	<0.001
FACT-B	105.3 (102.7–107.9)	93.4 (87.4–99.3)	<0.001	107.5 (104.7–110.4)	89.7 (83.9–95.4)	<0.001
Physical well-being	25.2 (24.8–25.7)	22.4 (21.0–23.7)	<0.001	24.9 (24.3–25.5)	21.2 (19.9–22.6)	<0.001
Social well-being	17.8 (17.0–18.7)	17.4 (15.4–19.3)	0.963	18.0 (17.1–18.8)	15.0 (13.4–16.5)	0.001
Emotional well-being	18.9 (18.3–19.6)	16.6 (15.1–18.0)	0.002	19.9 (19.4–20.5)	16.5 (15.2–17.8)	<0.001
Functional well-being	15.4 (14.6–16.3)	12.1 (10.3–13.8)	<0.001	16.1 (15.2–17.0)	11.8 (10.3–13.3)	<0.001
Others	27.9 (27.1–28.7)	25.0 (23.2–26.8)	0.006	28.6 (27.6–29.6)	25.2 (23.7–26.6)	<0.001

Data are expressed by mean and 95% CI in brackets.
RLS: restless legs syndrome; IRLSSG: International RLS Study Group; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; HAS: Hospital anxiety subscale; HDS: Hospital depression subscale; QoL: quality of life; FACT-B: Functional Assessment of Cancer Therapy – Breast.

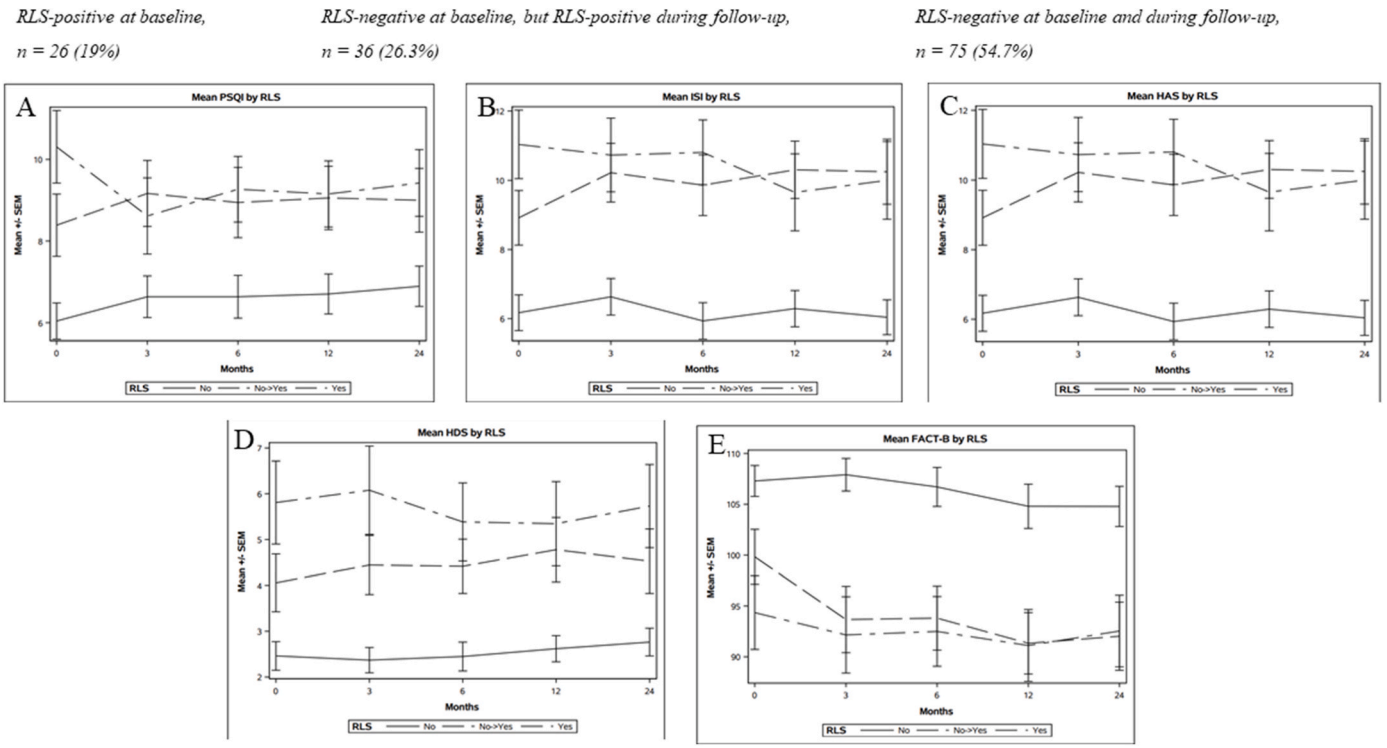

Fig. 2. Longitudinal changes (mean values and standard deviation) in PSQI, ISI, HAS, HDS, and FACT-B scores during AI therapy according to RLS status.

disturbances, anxiety, and depression in EBC patients, but led to a significant increase in RLS. The presence of RLS symptoms allowed us to identify a subgroup of patients characterized by worse anxiety, depression, insomnia, and overall QoL that persisted over time, suggesting that the IRLSSG rating scale questionnaire could be a simple and effective tool to detect EBC patients who may need additional psychological help. The latter aspect deserves to be confirmed in a broader prospective study.

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Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained from all individual participants included in the study.

Contributions

Conceptualization and design: R.P., P.d.M., V·C., L.F·S., A.B. Data Acquisition: R.P., P.d.M., V.A., S·Mo., L.L., G.S., D.C. Data Curation: R. P., P.d.M., V·C., S.Ma. Data analysis: R.P., P.d.M., V·C., M.Z., S.Ma. Interpretation of data: R.P., P.d.M., V.A., V·C., S.G., L.F·S., A.B. Writing - Original draft: R.P., P.d.M., S.Mo. Writing - Review and editing: all Authors. The final version of the manuscript was approved by all authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.10.006.

References

[1] Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, Forbes JF. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 2010;11:1135–41. https://doi.org/10.1016/S1470-2045(10)70257-6.

[2] Mouridsen H, Giobbie-Hurder A, Goldhirsch A, Thürlimann B, Paridaens R, Smith I, Mauriac L, Forbes JF, Price KN, Regan MM, Gelber RD, Coates AS. BIG 1-98 collaborative group, letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009;361:766–76. https://doi.org/10.1056/NEJMoa0810818.

[3] Savard J, Ivers H, Savard M-H, Morin CM. Cancer treatments and their side effects are associated with aggravation of insomnia: results of a longitudinal study. Cancer 2015;121:1703–11. https://doi.org/10.1002/cncr.29244.

[4] Park JY, Lee SK, Bae SY, Kim J, Kim MK, Kil WH, Lee JE, Nam SJ. Aromatase inhibitor-associated musculoskeletal symptoms: incidence and associated factors. J Korean Surg Soc 2013;85:205–11. https://doi.org/10.4174/jkss.2013.85.5.205.

[5] Buijs C, de Vries EGE, Mourits MJE, Willemse PHB. The influence of endocrine treatments for breast cancer on health-related quality of life. Cancer Treat Rev 2008;34:640–55. https://doi.org/10.1016/j.ctrv.2008.04.001.

[6] Savard J, Davidson JR, Ivers H, Quesnel C, Rioux D, Dupéré V, Lasnier M, Simard S, Morin CM. The association between nocturnal hot flashes and sleep in breast cancer survivors. J Pain Symptom Manag 2004;27:513–22. https://doi.org/10.1016/j.jpainsymman.2003.10.013.

[7] Savard J, Morin CM. Insomnia in the context of cancer: a Review of a neglected problem. J Clin Oncol 2001;19:895–908. https://doi.org/10.1200/JCO.2001.19.3.895.

[8] Ancoli-Israel S. Sleep disturbances in cancer: a Review. Sleep Med Res 2015;6. https://doi.org/10.17241/smr.2015.6.2.45.

[9] Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. J Clin Oncol 2011;29:3580–6. https://doi.org/10.1200/JCO.2010.33.2247.

[10] Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep 2001;24:583–90. https://doi.org/10.1093/sleep/24.5.583.

[11] Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB. Restless legs syndrome/Willis–Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria – history, rationale, description, and significance. Sleep Med 2014;15:860–73. https://doi.org/10.1016/j.sleep.2014.03.025.

[12] Manconi M, Garcia-Borreguero D, Schormair B, Videnovic A, Berger K, Ferri R, Dauvilliers Y. Restless legs syndrome. Nat Rev Dis Prim 2021;7:80. https://doi.org/10.1038/s41572-021-00311-z.

[13] Saini A, Berruti A, Ferini-Strambi L, Castronovo V, Rametti E, Giuliano PL, Ramassotto B, Picci RL, Negro M, Campagna S, Furlan PM, Ostacoli L. Restless legs syndrome as a cause of sleep disturbances in cancer patients receiving chemotherapy. J Pain Symptom Manag 2013;46:56–64. https://doi.org/10.1016/j.jpainsymman.2012.06.018.

[14] Ostacoli L, Saini A, Ferini-Strambi L, Castronovo V, Sguazzotti E, Picci RL, Toje M, Gorzegno G, Capogna S, Dongiovanni V, Dogliotti L, Furlan PM, Berruti A. Restless legs syndrome and its relationship with anxiety, depression, and quality of life in cancer patients undergoing chemotherapy. Qual Life Res 2010;19:531–7. https://doi.org/10.1007/s11136-010-9614-8.

[15] Sevim S, Dogu O, Kaleagasi H, Aral M, Metin O, Çamdeviren H. Correlation of anxiety and depression symptoms in patients with restless legs syndrome: a population based survey. J Neurol Neurosurg Psychiatry 2004;75:226. https://doi.org/10.1136/jnnp.2003.017467.

[16] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286–92. https://doi.org/10.1001/archinte.165.11.1286.

[17] Dikici S, Bahadir A, Baltaci D, Ankarali H, Eroglu M, Ercan N, Sav T. Association of anxiety, sleepiness, and sexual dysfunction with restless legs syndrome in hemodialysis patients. Hemodial Int 2014;18:809–18. https://doi.org/10.1111/hdi.12175.

[18] Ozder A, Eker HH. Anxiety levels among Turkish public transportation drivers: a relation to restless legs syndrome? Int J Clin Exp Med 2014;7.

[19] Winkelmann J, Prager M, Lieb R, Pfister H, Spiegel B, Wittchen HU, Holsboer F, Trenkwalder C, Ströhle A. Anxietas tibiarum". Depression and anxiety disorders in patients with restless legs syndrome. J Neurol 2005;252:67–71. https://doi.org/10.1007/S00415-005-0604-7.

[20] Comella CL. Restless legs syndrome: treatment with dopaminergic agents. Neurology 2002;58. https://doi.org/10.1212/WNL.58.SUPPL_1.S87.

[21] Gossard TR, Trotti LM, Videnovic A, St Louis EK. Restless legs syndrome: contemporary diagnosis and treatment. Neurotherapeutics 2021;18:140–55. https://doi.org/10.1007/s13311-021-01019-4.

[22] Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. J Neurol 2017;264:1634–41. https://doi.org/10.1007/s00415-017-8431-1.

[23] Tuna Oran N, Yuksel E, Ruzgar S. Prevalence of restless leg syndrome and effects on quality of life during pregnancy. Sleep Breath 2021;25:2127–34. https://doi.org/10.1007/s11325-021-02311-5.

[24] Azcoitia I, Santos-Galindo M, Arevalo MA, Garcia-Segura LM. Role of astroglia in the neuroplastic and neuroprotective actions of estradiol. Eur J Neurosci 2010;32:1995–2002. https://doi.org/10.1111/j.1460-9568.2010.07516.x.

[25] Bourque M, Dluzen DE, di Paolo T. Signaling pathways mediating the neuroprotective effects of sex steroids and SERMs in Parkinson's disease. Front Neuroendocrinol 2012;33:169–78. https://doi.org/10.1016/j.yfrne.2012.02.003.

[26] al Sweidi S, Sánchez MG, Bourque M, Morissette M, Dluzen D, di Paolo T. Oestrogen receptors and signalling pathways: implications for neuroprotective effects of sex steroids in Parkinson's disease. J Neuroendocrinol 2012;24:48–61. https://doi.org/10.1111/j.1365-2826.2011.02193.x.

[27] Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, Melton LJ. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology 2008;70:200. https://doi.org/10.1212/01.wnl.0000280573.30975.6a.

[28] Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric 2015;18:483–91. https://doi.org/10.3109/13697137.2015.1020484.

[29] Huo N, Smith CY, Gazzuola Rocca L, Rocca WA, Mielke MM. Association of premenopausal bilateral oophorectomy with restless legs syndrome. JAMA Netw Open 2021;4. https://doi.org/10.1001/jamanetworkopen.2020.36058. e2036058–e2036058.

[30] Horiguchi J, Hornyak M, Voderholzer U, Kryger M, Skomrow R, Lipinski JF, Masood A, Phillips B, Oertel WH, Stiasny K, O'Keeffe S, Oldani A, Zucconi M, Ondo WG, Picchietti D, Poceta JS, Rich GB, Scrima L, Shafor R, Sharon D, Silber M, Smith R, Trenkwalder C, Wetter TC, Winkelmann J, Vanek Z, Wagner M, Walters AS. Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32. https://doi.org/10.1016/S1389-9457(02)00258-7.

[31] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28:193–213. https://doi.org/10.1016/0165-1781(89)90047-4.

[32] Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34:601–8. https://doi.org/10.1093/sleep/34.5.601.

[33] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.

[34] Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, Deasy S, Cobleigh M, Shiomoto G. Reliability and validity of the functional assessment of cancer therapy-breast quality-of-life instrument. J Clin Oncol 1997;15:974–86. https://doi.org/10.1200/JCO.1997.15.3.974.

[35] Walia HK, Mehra R. Practical aspects of actigraphy and approaches in clinical and research domains. In: Handb clin neurol; 2019. p. 371–9. https://doi.org/10.1016/B978-0-444-64032-1.00024-2.

[36] Desai K, Mao JJ, Su I, DeMichele A, Li Q, Xie SX, Gehrman PR. Prevalence and risk factors for insomnia among breast cancer patients on aromatase inhibitors. Support Care Cancer 2013;21:43–51. https://doi.org/10.1007/s00520-012-1490-z.

[37] Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP, Stern H. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;367:1355–60. https://doi.org/10.1056/NEJMsr1203730.

[38] Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, Colleoni M, Regan MM, Piccart-Gebhart M, Senn H-J, Thürlimann B, André F, Baselga J, Bergh J, Bonnefoi H, Brucker SY, Cardoso F, Carey L, Ciruelos E, Cuzick J, Denkert C, di Leo A, Ejlertsen B, Francis P, Galimberti V, Garber J, Gulluoglu B, Goodwin P, Harbeck N, Hayes DF, Huang C-S, Huober J, Khaled H, Jassem J, Jiang Z, Karlsson P, Morrow M, Orecchia R, Osborne KC, Pagani O, Partridge AH, Pritchard K, Ro J, Rutgers EJT, Sedlmayer F, Semiglazov V, Shao Z, Smith I, Toi M, Tutt A, Viale G, Watanabe T, Whelan TJ, Xu B. De-escalating and escalating treatments for early-stage breast cancer: the st. Gallen international expert consensus conference on the primary therapy of early breast cancer 2017. Ann Oncol 2017;28:1700–12. https://doi.org/10.1093/annonc/mdx308.

[39] Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, Jemal A. Cancer treatment and survivorship statistics. Ca - Cancer J Clin 2016;66:271–89. https://doi.org/10.3322/caac.21349. 2016.

[40] Savard J, Liu L, Natarajan L, Rissling MB, Neikrug AB, He F, Dimsdale JE, Mills PJ, Parker BA, Sadler GR, Ancoli-Israel S. Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. Sleep 2009;32:1155–60. https://doi.org/10.1093/sleep/32.9.1155.

[41] Bhave MA, Speth KA, Kidwell KM, Lyden A, Alsamarraie C, Murphy SL, Henry NL. Effect of aromatase inhibitor therapy on sleep and activity patterns in early-stage

breast cancer. Clin Breast Cancer 2018;18:168–74. https://doi.org/10.1016/j.clbc.2017.12.012. e2.
[42] Siani F, Greco R, Levandis G, Ghezzi C, Daviddi F, Demartini C, Vegeto E, Fuzzati-Armentero M-T, Blandini F. Influence of estrogen modulation on glia activation in a murine model of Parkinson's disease. Front Neurosci 2017;11. https://www.frontiersin.org/article/10.3389/fnins.2017.00306.
[43] Tobias L, Thapa S, Won CHJ. Impact of sex on sleep disorders across the lifespan. Clin Chest Med 2021;42:427–42. https://doi.org/10.1016/j.ccm.2021.04.005.