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Letter to the Editor

Anticholinergic Burden and Increased Excessive Daytime Sleepiness in Older Women

Excessive daytime sleepiness (EDS) is characterized by an increased need for sleep throughout the day when an individual needs to be alert and active.[1] EDS is found in 1 in 5 people 60 years and older.[1] Various studies have shown that EDS is associated with decreased functional outcomes, malnutrition, dysphagia, vitamin D deficiency, depressed mood, cognitive impairment, increased frequency of falls, and increased risk of sarcopenia and mortality.[1–4]

Gender differences and neurocognitive disorders and dementia appear to be important for EDS.[5,6] Anticholinergic drug load is the cumulative effect of drugs that can produce anticholinergic side effects.[7] The complications such as falls, delirium, and frequent hospitalization may often be seen due to the effect of anticholinergic drugs used.[7] In a few studies, it has been reported that exposure to anticholinergic drugs may also cause sleep disorders, which may increase side effects.[8] However, to date, there is no study to investigate the relationship between anticholinergic drugs and EDS. Therefore, the aim of this study was to evaluate the relationship between anticholinergic burden and EDS.

A total of 1048 patients who had undergone comprehensive geriatric assessment were retrospectively evaluated and 735 patients were included in the study. EDS was assessed using the Epworth Sleepiness Scale (ESS). A score of $\geq$11 of 24 points indicates EDS.[1] A score of 8 and above for the Insomnia and Severity Index was accepted as insomnia.[1] The anticholinergic load of the drugs was calculated using the anticholinergic cognitive burden (ACB) calculator.[7] We classified patients with a score <2 as ACB (−) and patients with a score $\geq$2 as ACB (+).[7]

A total of 735 people, 71% of whom were women, with a mean age of 80.08 ± 7.38 years (65–98 years) were included. EDS was detected in 26.8% of the patients and 39.3% had ACB (+). Although there was no significant difference in terms of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, previous cerebrovascular disease, or heart failure ($P > .05$), there was a significant difference in terms of age, glomerular filtration rate, hemoglobin, gender, and the presence of insomnia or coronary artery disease, Parkinson disease, dementia, and ACB (+) between the patients with EDS and without EDS ($P < .05$). Logistic regression analysis was performed to clearly reveal the relationship between EDS score and ACB and related parameters; univariate regression analysis is shown in Table 1. However, after multivariable regression analysis and adjustment for all confounding factors, there was no significant association between ACB and EDS in older men [dementia (+), dementia (−)], whereas ACB was still significantly associated with EDS in older women [dementia (+), dementia (−)] ($P < .05$) (Table 1).

It is important to identify possible causes of EDS in older patients, because its prevalence is high (26.8%) and its association with many adverse clinical conditions is known.[1–4] The common causes include insomnia, neurodegenerative diseases, and drugs used (such as antipsychotics, opioid analgesics, antihistamines, benzodiazepines).[9] In this study, which investigated whether these drugs, many of which also have anticholinergic effects, are associated with increased frequency of EDS, the risk of it was found to be 1.6 (1.7 for women with dementia) times in older women with ACB (+) compared with those with ACB (−), but no relationship was found in men. Although it is not a study like ours on this subject, in a study by Kumar et al.[8] in which physical functions and sleep quality were evaluated by the Pittsburgh sleep quality index in patients older than 60 years, a negative correlation was detected between increased ACB score and sleep latency, whereas a positive correlation was found between sleep disturbances. On the other hand, experimental studies showed that acetylcholine is important for both sleep and wakefulness.[9] The results can support the relationship between anticholinergic burden and EDS, albeit indirectly. In addition, our result is remarkable in that it demonstrates that gender difference affects this relationship. Indeed, the factors and consequences associated with EDS may differ between men and women.[10,11] Some hormonal and biological differences between the genders may affect sleep disorders; however, future studies are needed to elucidate the issue.

In conclusion, in our study, although anticholinergic burden was associated with EDS in older women, such a relationship was not found in older men. Therefore, when arranging a drug therapy in older women, it is necessary to regulate the treatment in a way that does not cause EDS and avoid drugs with high ACB. The detailed anticholinergic burden evaluation of older women may be effective in preventing EDS and EDS-related adverse health outcomes. ACB also should be assessed in older female patients with EDS.

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Table 1
The Association of EDS With Anticholinergic Burden and Related Parameters

Unadjusted Logistic Regression	All Patients (n = 735)		Female Dementia (n = 109)		Female Non-Dementia (n = 416)		Male Dementia (n = 66)		Male Non-Dementia (n = 144)	
	OR (95% CI)	*P*	(95% CI)	*P*	(95% CI)	*P*	(95% CI)	*P*	(95% CI)	*P*
ACB	3.2 (2.2–4.5)	<.001	3.2 (1.5–7.3)	<.001*	2.5 (1.5–4.0)	<.001*	2.7 (1.0–7.2)	<.05	1.4 (1.1–1.8)	<.05
Age, y	0.9 (0.9–1.0)	.088	0.9 (0.9–1.2)	.276	1.2 (1.1–1.7)	<.05	0.9 (0.9–1.3)	.744	0.8 (0.9–1.1)	.877
Insomnia	1.0 (0.9–1.0)	.907	0.9 (0.9–1.1)	.314	0.9 (0.9–1.0)	.591	1.0 (0.9–1.1)	.161	1.1 (1.0–1.1)	<.05
eGFR	0.9 (0.9–1.0)	.015	1.0 (0.9–1.0)	.875	0.9 (0.9–1.0)	.468	0.9 (0.9–1.0)	<.05	0.9 (0.9–1.0)	.152
Hb (g/dL)	0.8 (0.8–0.9)	.007	0.1 (0.8–1.5)	.464	0.8 (0.7–1.0)	.059	0.8 (0.6–1.1)	.153	0.7 (0.5–0.9)	<.05
PD	3.2 (1.9–5.4)	<.001	5.3 (1.3–7.4)	.018	1.9 (0.7–4.0)	.167	2.0 (0.5–7.0)	.283	2.5 (0.9–7.1)	.078
CAD	1.3 (0.9–1.7)	.128	1.3 (0.5–4.0)	.563	1.1 (0.8–1.5)	.717	1.6 (0.6–4.3)	.335	1.5 (0.7–3.4)	.299
Dementia	2.8 (1.9–4.1)	<.001	—	—	—	—	—	—	—	—
Gender	0.5 (0.3–0.7)	<.001	—	—	—	—	—	—	—	—
Multivariable logistic regression										
ACB	1.2 (0.8–1.3)*	.134*	1.7 (1.2–2.1)†	<.05†	1.6 (1.1–2.4)†	<.05†	0.9 (0.8–1.2)†	.436†	1.4 (1.1–1.8)†	.556†

CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, hemoglobin level; OR, odds ratio; PD, Parkinson disease.
*Adjusted for age, gender, insomnia, eGFR, Hb, PD, CAD, and dementia.
†Adjusted for age, insomnia, eGFR, Hb, PD, and CAD.

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