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Frequency and characteristics of drowsiness, somnolence, or daytime sleepiness in patients with advanced cancer

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Abstract

Introduction. Cancer-related drowsiness (CRD) is a distressing symptom in advanced cancer patients (ACP). The aim of this study was to determine the frequency and factors associated with severity of CRD. We also evaluated the screening performance of Edmonton Symptom Assessment Scale-drowsiness (ESAS-D) item against the Epworth Sedation Scale (ESS).

Method. We prospectively assessed 180 consecutive ACP at a tertiary cancer hospital. Patients were surveyed using ESAS, ESS, Pittsburgh Sleep Quality Index, Insomnia Severity Index, and Hospital Anxiety Depression Scale.

Result. Ninety of 150 evaluable patients had clinically significant CRD (ESS); median (interquartile ratio): ESS. 11 (7–14); ESAS-D. 5 (2–6); Pittsburgh Sleep Quality Index. 8 (5–11); Insomnia Severity Index. 13 (5–19); Stop Bang Scoring 3 (2–4), and Hospital Anxiety Depression Scale-D 6 (3–10). ESAS-D was associated with ESAS (r, p) sleep (0.38, <0.0001); pain (0.3, <0.0001); fatigue (0.51, <0.0001); depression (0.39, <0.0001); anxiety (0.44, <0.0001); shortness of breath (0.32, <0.0001); anorexia (0.36, <0.0001), feeling of well-being [(0.41, <0.0001), ESS (0.24, 0.001), and opioid daily dose (0.19, 0.01). Multivariate-analysis showed ESAS-D was associated with fatigue (odds ratio [OR] = 9.08, $p < 0.0001$), anxiety (3.0, $p = 0.009$); feeling of well-being (OR = 2.27, $p = 0.04$), and insomnia (OR = 2.35; $p = 0.036$). Insomnia (OR = 2.35; $p = 0.036$) cutoff score ≥3 (of 10) resulted in a sensitivity of 81% and 32% and specificity of 70% and 44% in the training and validation samples, respectively.

Significance of results. Clinically significant CRD is frequent and seen in 50% of ACP. CRD was associated with severity of insomnia, fatigue, anxiety, and worse feeling of well-being. An ESAS-D score of ≥3 is likely to identify most of the ACP with significant CRD.

Introduction

Cancer-related drowsiness (CRD), somnolence, or excessive daytime sleepiness is common (Davidson et al., 2002) and associated with significant distress in patients with advanced cancer (Degner & Sloan, 1995; Parker et al., 2008). Drowsiness was previously defined in non-cancer settings as "excessive daytime sleepiness and an inability to remain awake which not relieved with sleep" (Atkinson & Davenne, 2007). Drowsiness may be either the result of abnormalities in "sleep drive" resulting from sleep deprivation/loss (Vgontzas, et al., 2007) or sleep propensity (quickness of falling asleep) (Johns, 2010). Drowsiness is associated with significantly decreased physical activity (McClain et al., 2014), resulting in interference in daily activities. Prior studies suggest that drowsiness was associated with increased cardiometabolic risks (Atkinson & Davenne, 2007; Buxton & Marcelli, 2010; Patel & Hu, 2008) and impairment in work-related abilities (Cleeland et al., 2014).

CRD is more common in older patients undergoing treatment (Cleeland et al., 2014; Sanford et al., 2014; Wochna Loerzel, 2015) and its severity increases as the disease progresses (Hui et al., 2015; Mercadante et al., 2000). This type of sleep disorder and its health consequences are often neglected in the advanced cancer patient (ACP) population. CRD is not routinely evaluated in routine cancer care. Routine evaluation of the severity of CRD with a validated tool may be important because it can provide insight into the possible etiologic factors associated with CRD and assist in monitoring the effects of CRD treatments. There are limited published data specifically regarding the frequency and characteristics of CRD in this patient population.

The primary aim of this study was to identify the frequency and factors associated with severity of CRD. The secondary aim was to determine the screening performance of the Edmonton Symptom Assessment Scale-drowsiness (ESAS-D) item using Epworth Sedation Scale (ESS) as a gold standard.

Methods

The University of Texas MD Anderson Cancer Center institutional review board approved this study.

Our current study is a secondary analysis of a previously published prospective survey (Yennurajalingam et al., 2015) conducted from October 2012–June 2013. A total of 180 ACP admitted to MD Anderson Cancer Center inpatient service for at least 24 hours were screened for eligibility and possible enrollment. Eligibility criteria included a diagnosis of advanced cancer, normal cognition, and ability to read, write, and speak English.

After providing signed informed consent, the study participants underwent a single interview with the research coordinator, during which the study was explained. They were then asked to complete the demographic data and study questionnaires independently or with the assistance of the research staff for a single time of 25–30 minutes.

Assessment tools

ESAS is a valid and reliable tool for the assessment of the intensity of symptoms in cancer populations. The symptoms include pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, feelings of well-being, and "other symptom." In this study, we used the sleep item as the "other symptom." The severity of each symptom was rated from 0 to 10 on a numerical scale, with 0 meaning that symptom is absent and 10 meaning that it is of the worst possible severity (Bruera et al., 1991).

ESS measures the general level of daytime sleepiness. It has eight questions and patients rate on a 4-point scale (0–3), their usual chances of falling asleep in eight situations or activities (Johns 1991). ESS has been used in cancer and noncancer patients for the detection of sleep disorders such as narcolepsy, idiopathic hypersomnia, and excessive daytime sleepiness (Johns 2000).

Pittsburgh Sleep Quality Index (PSQI) was used to measure the quality and patterns of sleep disturbance. Each item on a scale is graded 0–3. The sum of the seven component scores are used for the global sleep score (range 0–21). A global sleep score ≥ 5 was used to define *SD* (Buysse et al., 1989). PSQI has internal consistency (Cronbach α) of 0.83 overall.

Insomnia Severity Index (ISI). The ISI is a seven-item questionnaire designed to evaluate insomnia severity (Bastien et al., 2001). Each item was rated using a 5-point scale ranging from 0 (not at all) to 4 (very much), for a total score ranging from 0 to 28.

STOP-Bang Scoring Model: The STOP-Bang test was used as a screening tool for obstructive sleep apnea (OSA; Chung et al., 2008) The questionnaire is short, easy to apply, and has sensitivity for moderate to severe OSA between 92.9% and 100% when compared with the gold standard of polysomnography (Chung et al., 2013).

Restless leg syndrome questionnaire (RLS): This single item-screening questionnaire evaluates restless legs (Ferri et al., 2007). The questions incorporate the clinical component used to make a diagnosis of RLS including characterization of symptoms, timing, and alleviating measures.

Hospital Anxiety and Depression Scale (HADS): The hospital anxiety and depression scale was developed in 1983 for screening of depression in medical patients. It has been studied and validated in cancer patients showing to be a useful screening instrument (Zigmond & Snaith, 1983).

Statistical considerations

We estimated the proportion of patients with CRD, SD, OSA, and RLS. We calculated correlation among CRD, ISI, PSQI, HADS, ESS, and other ESAS symptoms. To assess independent predictors, we initially conducted a univariate logistic regression analysis. Variables that were significant at the 20% level in univariate regressions were included in a multivariate model.

To determine the optimal cutoff score for clinically significant drowsiness as measured by ESAS-D. We used the ESS-D as a gold standard for subjective assessment of drowsiness. The clinically significant cutoff for the ESS is 10. Patients were randomly assigned to either a training dataset or a validation dataset. We used ESS from the training dataset to calculate sensitivity and specificity (along with 95% confidence intervals) for all possible cutoff values of the ESAS-D item, calculate area under the receiver operating characteristic curve, and chose the best clinical cutoff where the best clinical cutoff was defined as the cutoff which maximizes the sum of sensitivity and specificity subject to the constraint that sensitivity is at least 70%.

Results

A total of 1057 consecutive ACP were screened for participation of this study; 483 were not eligible. The reasons were as follows: (1) patients < 18 years ($n = 4$); (2) no advanced cancer ($n = 8$); (3) delirium ($n = 270$); (4) non-English speaking ($n = 114$); and sleep disturbance, 0/10 on ESAS ($n = 72$). Of the 589 patients who were eligible and approached, 180 were enrolled and 409 declined to participate. Reasons for refusal were: (1) symptom distress ($n = 88$) (2) not interested ($n = 277$) (3) clinician refused to allow the patient to be approached ($n = 24$), and (4) missing data ($n = 2$).

Of the180 patients assessed, clinically significant drowsiness was found in 50% ACP, median scores (IQR) were as follows: ESS 11 (7–14); ESAS- drowsiness item 5 (2–6); PSQI 8 (5–11); ISI 13 (5–19); Stop Bang Scoring 3 (2–4); and HADS-D 6 (3–10). Sleep apnea was found in 61% and RLS in 38% (Table 1).

ESAS-D was associated with other ESAS items (r, p) sleep (0.38, <0.0001); pain (0.3, <0.0001); fatigue (0.51, <0.0001); depression (0.39, <0.0001); anxiety (0.44, <0.0001); shortness of breath (0.32, <0.0001); anorexia (0.36, <0.0001), feeling of well-being (0.41, <0.0001), ESS (0.24, 0.001), and opioid daily dose (0.19, 0.01).

Multivariate analysis showed that insomnia ISI (OR = 2.35; 0.036), ESAS Fatigue (OR = 9.08; <0.0001), ESAS Anxiety (OR = 3.0; 0.009), and ESAS feeling of well-being (OR = 2.27; $p = 0.04$) were associated with CRD.

An ESAS-D cutoff score ≥3 (of 10) resulted in a sensitivity and specificity of 78% and 33% and of 75% and 40% in the training and validation samples, respectively (Table 2 and Figure 1).

Discussion

In our study, we found 50% of ACPs had clinically significant drowsiness. The results of our study suggest that CRD was significantly associated with severity of fatigue, anxiety, insomnia, and worse feeling of wellbeing scores. Our preliminary analysis also suggest that a cutoff score of ≥3/10 on ESAS-D item was sensitive (81%) to screen patients with clinically significant drowsiness.

Prior studies suggest the frequency of drowsiness ranges from 25% to 36% (Schwartz et al., 2009) in primary care population. CRD has seldom been studied in cancer patients. In one cross-sectional survey study of 982 mixed-type cancer patients by

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Table 1. Patient demographics

Patient characteristics	*N* (total sample 180)	Result
Age, years (median, IQR)	57	46-65
Female	91	51%
Race		
Caucasian	118	67%
African American	35	20%
Latin American	17	9%
Asian	4	2%
Cancer type		
Head and neck, lung	38	21%
Breast	25	14%
Gynecological	17	9%
Genitourinary	30	17%
Gastrointestinal	34	19%
Other (lymphoma, myeloma, sarcoma)	36	20%
Assessment tools	Mean (*SD*)	Median (IQR)
ESAS-D in past 24 hours	4.1 (2.8)	5 (2-6)
ESS	11.2 (5.8)	7 (5-9)
PSQI Sleep Quality in past 30 days	8 (3.7)	8 (5-11)
PSQI Sleep Quality in past 24 hours	7.3 (3.3)	7 (5-9)
ISI Insomnia in past 30 days	12.3 (7.8)	13 (5-19)
ISI Insomnia in past 24 hours	12 (8)	12 (5-18)
ESAS Sleep item in past 24 hours	5 (2.9)	5 (3-8)
ESAS Sleep item in past 30 days	5.9 (2.2)	6 (5-8)
STOP-BANG Questionnaire	3.1 (1.6)	3 (2-4)

ESAS-D, Edmonton Symptom Assessment System-drowsiness; ISI, Insomnia Severity Index; PSQI, Pittsburg Sleep Quality Index; STOP-Bang Questionnaire, screening tool for obstructive sleep apnea.

Davidson et al. (2002), CRD was reported in 28% of cancer patients. In our study, we found 50% of ACPs had CRD as assessed by the ESS. These findings suggests that its frequency is higher in ACPs than in general population. In our study, we used a more validated questionnaire (ESS) compared with a simple survey used in previous studies. Clinically significant drowsiness is frequently underdiagnosed because of a lack of routine screening. The ESS is a frequently used questionnaire to screen drowsiness. This tool has been validated in previous studies (Johns, 1991); however, it is not always convenient to use ESS in routine clinical practice, especially when assessing other cancer-related symptoms at the same time. Commonly used assessment tools in routine cancer care such as ESAS (Bruera et al., 1991; Chang et al., 2000; Paiva et al., 2015) do assess drowsiness simultaneously with other cancer-related symptoms; however, there are limited data to suggest a cut-off for the diagnosis of clinically significant CRD. In this study, we found the screening performance of ESAS drowsiness item to be ≥3/10; however, receiver operating characteristic analysis suggests low specificity. In view of lack of any literature in regard to screening performance of ESAS-D, the information obtained from our study would be very useful to the practicing clinicians as a

Table 2. Distribution of possible cutoff values of ESAS-D item for clinically significant drowsiness

ESAS	Training (*N* = 120)						Validation (*N* = 60)					
	Sensitivity			Specificity			Sensitivity			Specificity		
≥	Sensitivity	Lower	Upper	Specificity	Lower	Upper	Sensitivity	Lower	Upper	Specificity	Lower	Upper
1	88	77	95	26	16	40	82	63	94	23	10	42
2	83	71	92	28	17	42	79	59	92	27	12	46
3	78	65	88	33	21	47	75	55	89	40	23	59
4	69	56	81	47	34	61	68	48	84	43	25	63
5	63	49	75	60	46	72	61	41	78	57	37	75
6	46	33	59	72	58	83	29	13	49	67	47	83
7	25	15	38	84	72	93	21	8	41	77	58	90
8	10	4	21	93	83	98	14	4	33	87	69	96
9	3	0	12	98	91	100	11	2	28	93	78	99

ESAS, Edmonton Symptom Assessment System.

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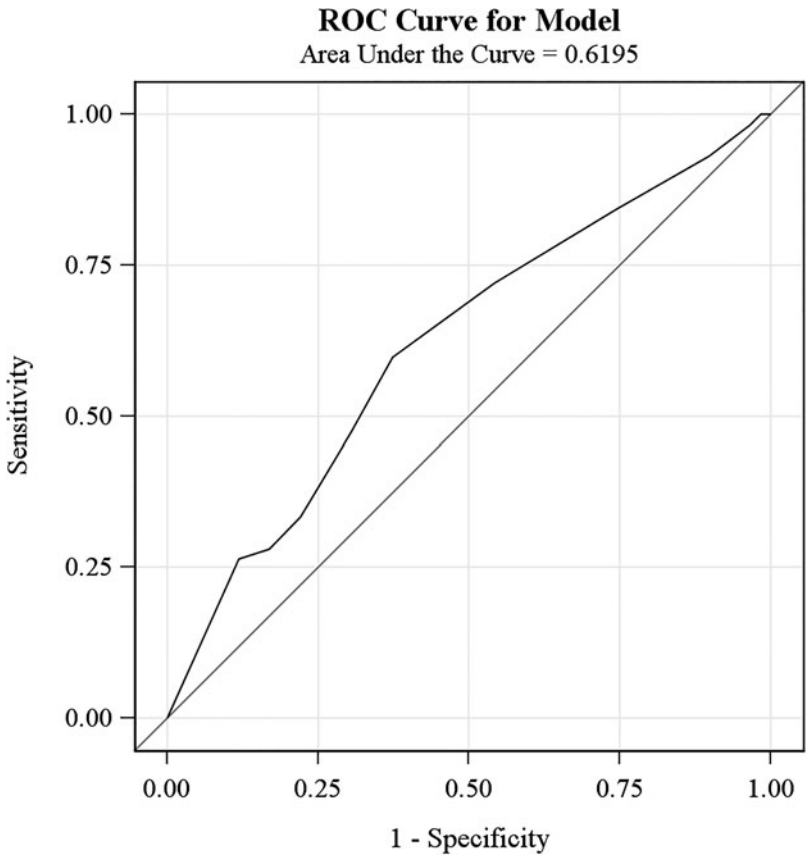

Fig. 1. Receiver operating characteristic (ROC) curve to determine the cutoff values for the Edmonton Symptom Assessment Scale-drowsiness item using Epworth Sedation Scale as a gold standard.

benchmark to identify and monitor clinically significant CRD in routine cancer care.

In our study, we found a significant association between CRD and fatigue. Prior studies also show a strong positive correlation between fatigue and various sleep parameters, including CRD (Roscoe et al., 2007). Using a multidimensional model, Hwang et al. (2003) showed a significant correlation between drowsiness and fatigue. CRD usually clusters with other symptoms such as fatigue, anxiety, nausea, decreased appetite, dyspnea, and poor sense of well-being (Cheung et al., 2009; Fan et al., 2007); therefore, targeted interventions of associated symptoms, such as fatigue, may positively affect the CRD (Roscoe et al., 2007). Similarly, management of CRD could potentially improve fatigue, anxiety, nausea, decreased appetite, dyspnea, poor sense of well-being, and overall quality of life (Baldwin et al., 2001).

The management of CRD is complex because of its multifactorial nature in ACP patients. CRD may be attributed to the cancer itself, effects of cancer-related symptoms such as pain, cancer-related treatments such as chemotherapy, opioid analgesics (Ripamonti & Bruera, 1997), or antiemetic agents (Glare et al., 2011; Rao & Faso, 2012). The most effective initial step in management is therefore to identify the causative mechanism. If the "primary" cause cannot be treated, a trial of pharmacological and nonpharmacological approaches should be explored. Management of drowsiness therefore may include treatment of CRD using psychostimulants drugs such as methylphenidate (Bruera et al., 1987; Wilwerding et al., 1995) modafinil, or armodafinil (Ballon & Feifel, 2006; Valentino & Foldvary-Schaefer, 2007). Nonpharmacological management includes eliminating polypharmacy and using behavioral therapy such as counseling focused on sleep hygiene. This management strategy may not only alleviate CRD but also improve fatigue and sleep disturbance. Further randomized controlled studies are needed to determine the best strategy to manage CRD in ACPs.

Inflammation has been associated with common symptoms and clinical correlates of cancer including CRD. Prior studies suggested significant association between inflammatory cytokines and CRD (Vgontzas et al., 1997). Exogenous administration of interleukin-6 (IL-6) in patients with cancer (Mastorakos et al., 1993) and increased production of endogenous IL-6 (Papanicolaou et al., 1996) were associated with increased CRD and fatigue, suggesting that IL-6 may be associated with CRD. High IL-6 levels also correlate with high cancer symptom burden in stem cell transplant patients. Further studies are needed to understand the mediating role of inflammatory cytokines, specifically IL-6, in the causation of drowsiness and its associated symptom clusters.

Future studies should focus on the operational definition of CRD; moreover, important future studies are required to determine the causation, subtypes, and objective measures that can be used in routine clinical care to develop personalized management strategies.

Conclusion

CRD is frequent and often neglected in ACP. Our study confirms the association of CRD with severity of fatigue, anxiety, insomnia, and worse feeling of well-being. An ESAS-D score ≥3 has moderate sensitivity and low specificity. Because of a lack of adequate literature regarding ESAS-D screening performance, this information is likely to screen most of the ACP with significant CRD. There is a need for future studies to confirm the finding of this study .This may help in creating personalized management

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strategies to reduce CRD in ACP by addressing underlying causative mechanisms.

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