


Deterioration in Sleep Quality Affects Cognitive Depression in Prostate Cancer Patients

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Abstract

Men who suffer from prostate cancer (PCa) need to make important decisions regarding their treatment options. There is some evidence that these men may suffer from sleep difficulties due to their cancer or its diagnosis and treatment. Although sleep difficulties have been associated with cognitive depression in other samples of men, they have not been examined in PCa patients, despite the importance of decision-making for these men. This study was designed to investigate the association between sleep difficulties and cognitive depression in PCa patients. A sample of 96 PCa patients completed a background questionnaire, the Zung Self-Rating Depression Scale, and the Insomnia Severity Index. Comparison was made between sleep difficulty scores from before the patients received their diagnosis of PCa to the time of survey, allowing use of a “retrospective pretest” methodology. Just over 61% of the sample reported a deterioration in sleep quality, and this was significantly associated with cognitive depression ($r = .346$, $p = .007$). At the specific symptom level, *having a clear mind* significantly contributed to the variance in *difficulty falling asleep* (R^2 change = .140, F for change = 9.298, $p = .003$). Sleeping difficulties, particularly falling asleep, are common and associated with depression-related to ability to think clearly in PCa patients. This has potentially adverse effects upon the ability of men with PCa to understand their treatment options and make decisions about them.

Keywords

Depression, prostate cancer, sleeping

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Prostate cancer (PCa) is the second-most common cancer among men (after skin cancer), and is forecast to increase during the next 5 years (Kelly et al., 2018). These men are more vulnerable to depression, with a meta-analysis of the prevalence of depression among 4494 PCa patients (Watts et al., 2014), indicating that more than 14% of these men were likely to be clinically depressed at any of these stages. This is almost double the prevalence for depression for same-age males (9%) (Watts et al., 2014). When combined with the finding that PCa patients are 6.5 times more likely to suicide than the general population during the first 6 months following initial diagnosis (Carlsson et al., 2013), it is clear that depression among these men is a major cause for concern. Depression also adversely influences other aspects of PCa treatment efficacy, and is associated with an odds ratio of 4.45 for emergency room visits, 3.22 for hospitalizations, 1.71 for outpatient visits, and increased

costs for health care, compared to other PCa cases without depression (Jayadevappa et al., 2011). The continued investigation of the nature and correlates of, and contributors to, these high rates of depression among PCa patients remains a priority.

Key aspects of the nature of depression include sleeping difficulties, ability to concentrate, and making decisions, which are included in the diagnostic criteria for Major Depressive Disorder (MDD) (APA, 2013). Of

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these, decision-making or comprehension of information is a major challenge for anyone who is under major psychological or physiological stress (Starcke & Brand, 2012), such as receiving a diagnosis of PCa and subsequent treatment. Aspects of the diagnosis and treatment regime for PCa can be cognitively demanding, such as understanding the results of a biopsy (Sharp et al., 2018), having to make decisions about the type of treatment (Smith et al., 2019), or accepting the adverse effects of treatment (Sharpley et al., 2018). Potentially exacerbating these cognitive demands, PCa patients typically exhibit diminished motivation, reduced ability to process information, and elevated distractibility (Boksem et al., 2005). Although there is some evidence that these reductions in cognitive performance may be associated with sleeping difficulties (Royal et al., 2006), at the time of writing, a search (Google Scholar, Pub Med) using the descriptors “prostate cancer, sleeping difficulties, decision making, concentration” failed to identify any studies specifically examining the association between these variables in PCa patients.

In methodological terms, although sleeping difficulties have been reported to correlate with depression in samples of older adults (e.g., Mallon et al., 2000), that may be somewhat due to the overlap between this factor and the diagnostic criteria for MDD, which include the symptom “insomnia or hypersomnia nearly every day” (APA, 2013). Studies of the possible effect of sleeping difficulties on PCa patients’ depressive state need to take that source of confound into consideration. One method of doing that is to focus upon specific “subtypes” of depression as well as total depression scores from a self-report scale. Although several models have been posited for subtypes of depression (Beijers et al., 2019; Fried & Nesse, 2015; Parker, 2005), one model that is based upon neurobiological pathways to select groups of MDD symptoms has identified four depression subtypes—depressed mood, anhedonia, somatic depression, and cognitive depression (Sharpley & Bitsika, 2013)—which have been validated on PCa patients (Sharpley & Bitsika, 2014). One of these (cognitive depression) includes the symptoms of clarity of mind, being able to make decisions, and being able to do things as easily as previously.

The association between sleeping difficulties and the specific aspects of depression that include ability to make decisions, think clearly, and undertake tasks as well as previously, has not yet been reported for PCa patients. Although cognitive ability can be assessed via particular scales that focus upon problem-solving ability, those indicators do not necessarily link directly to depression. As well as investigating the association between sleeping difficulties and total depression, this study also examined the specific effects that sleeping difficulties had on Cognitive depression, and did so at the

individual symptom level as well as at subscale analysis level in order to better understand the specific pathways between aspects of sleeping difficulties and depression that included decreases in cognitive ability, with the aim of developing a model of the interaction between these factors that might inform clinical practice.

Methods

Participants

From an initial pool of 200 PCa patients identified from hospital records, 96 PCa patients from treatment centers in South East Queensland, Australia, responded to a written invitation to participate in a study “about how you feel.” There were no obvious differences between responders and non-responders in terms of their PCa status, age, or treatment history. To protect non-responders’ privacy, no follow-up was made as to the reasons for their non-participation. All participants had PCa limited to the primary site and regional draining lymph nodes using conventional staging investigations. Treatments included radiotherapy and/or surgery and hormone therapy when required. Other inclusion criteria were: (a) the diagnosis of PCa was proven histologically, and (b) all of the treatment options were properly considered by patients via discussion with their GP, a radiation oncologist, and a urologist. Unwillingness to participate in the study was the only exclusion criterion. Table 1 describes the background data for this sample.

Measures

Background questionnaire: age (in years); living situation (with wife/partner, widowed, separated/divorced, never married); month and year of first diagnosis; past treatments and current treatments (radiotherapy, surgery, hormone therapy, none); present status of their cancer (cancer still present and undergoing initial treatment, no obvious sign of cancer [in remission], cancer reoccurring after previous treatment).

Depression. The Zung Self-Rating Depression Scale (SDS) (Zung, 1965) is a 20-item self-report scale developed on the basis of factor analytic studies of MDD as defined in the DSM series, and includes all of the current DSM-5 (APA, 2013) criteria for MDD. Respondents report the frequency of each of 20 depressive symptoms during the last 2 weeks by indicating 1 (*None or a little of the time*), 2 (*Some of the time*), 3 (*Good part of the time*), and 4 (*All or almost all the time*)—producing raw scores ranging from 20 to 80, with higher scores being indicative of more severe depression. The SDS has demonstrated split-half reliability of .81 (Zung, 1965), .79

Table 1. Background Data for Sample of 96 Prostate Cancer Patients.

Variable	Sample Characteristics
Age	$M = 73.81$ yr ($SD = 7.12$ yr), range = 44–88 yrs
Relationship status	
With wife/partner	75.5%
Widowed	10.2%
Divorced/separated	9.2%
Never married/partnered	5.1%
Time since diagnosis	$M = 58.82$ mo ($SD = 29.72$ mo), range = 1–233 mo.
Treatments received	
Radiotherapy	29.5%
Surgery	8.0%
Hormone therapy	10.2%
Combinations	48.9
Surveillance	3.4
Current treatment	
Radiotherapy	54.4%
Hormone therapy	29.4%
Combinations	10.3%
Surveillance	5.9
Present status	
Cancer still present, undergoing treatment	35.7%
In remission (no signs)	31.6%
Cancer recurring after previous treatment	32.7%
SDS	$M = 35.56$ ($SD = 8.83$), range = 20–57
SDS Cognitive depression	$M = 2.13$ ($SD = 0.89$), range = 1–4
ISI (at diagnosis)	$M = 5.76$ ($SD = 2.52$), range = 0.0–28
ISI (now)	$M = 9.05$ ($SD = 7.43$), range = 0.0–28
ISI change	$M = 3.29$ ($SD = 5.60$), range = -14–21

Note. SDS = Zung Self-Rating Depression Scale; ISI = Insomnia Severity Index.

Table 2. Mean Scores for Cognitive Depression Items From SDS.

SDS Item	<i>M</i>	<i>SD</i>	Range
11. My mind is as clear as it used to be	1.96	1.11	1–4
12. I find it easy to do the things I used to do	2.40	1.01	1–4
16. I find it easy to make decisions	2.02	1.04	1–4

Note. SDS = Zung Self-rating Depression Scale.

(DeJonge & Baneke, 1989), and .94 (Gabrys & Peters, 1985), and internal consistency (α) has been reported as .84 with PCa samples (Sharpley et al., 2009). The SDS has greater validity than the MMPI Depression Scale and the Beck Depression Inventory for assessing depression in male psychiatric inpatients (Schaefer et al., 1985). SDS scores of 40 or above indicate the presence of “clinically significant depression” (Zung, 1973, p. 335).

SDS Depression “Subtypes”. SDS items have been allocated to four “depression subtypes” described in the Introduction to delineate depressed mood, anhedonia, cognitive depression, and somatic depression (Sharpley

& Bitsika, 2014) and applied to PCa patients (Sharpley et al., 2017). In this study, only the cognitive depression subtype was investigated separately from the total SDS score, for the reasons given in the Introduction. SDS items that comprise that subtype are presented in Table 2.

Sleeping Difficulties. The Insomnia Severity Index (ISI) (Bastien et al., 2001) consists of seven items measuring difficulty of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleeping difficulties. Respondents use a

five-point Likert scale for each of the seven ISI items, ranging from 0 = *no problem* to 4 = *very severe problem*. Total scores range from 0 to 28, with high scores indicating greater sleep problems, where 0–7 indicates absence of insomnia, 8–14 = sub-threshold insomnia, 15–21 = moderate insomnia, and 22–28 = severe insomnia. Internal consistency has been reported as .74 (Bastien et al., 2001). The ISI has been reported to possess good validity when used with cancer patients in general (Savard et al., 2005) and with PCa patients in particular (Dirksen et al., 2009).

Procedure

During July–December 2020, patients were posted a package including the Participant Information Statement, Background Questionnaire, a copy of the SDS, and two copies of the ISI, plus a stamped and addressed envelope for return of the questionnaire package. Patients were instructed to complete the SDS and one copy of the ISI for how they “felt during the last two weeks” (as per the original instructions for these scales), but they were also asked to complete one copy of the ISI for how they “felt before getting their diagnosis of prostate cancer.” This is sometimes referred to as the “retrospective pretest” procedure (Howard et al, 1979) to determine change in symptomatology over time. The traditional pretest versus posttest design with two administrations of the same questionnaire at different points in time is open to several sources of experimental invalidity, such as history, maturation, and testing artefacts (Campbell & Stanley, 1963). The retrospective pre-test avoids these sources of invalidity via collection of comparative data from the same participants but for how they felt at two different times (“now” and “then”). It is important to note that the then-test is not done according to how participants think that they may have responded to a similar administration of the test in the past (which might have been done as a pre-test) but rather of how they *now think they were* at the specified time in the past using their current perspective. This index allows for “response shift”, or the fact that individuals evaluating themselves on the same self-report instrument at different points in time (e.g., at a pretest and later at a posttest) may not use the same “internalised standard for judging their level of functioning with regard to a given dimension” (Howard et al., 1979, p. 22). This may contribute to spurious results due to changes in the individual’s standard of measurement over that period of time rather than to any real change taking place. The retrospective pretest methodology has previously been applied to Quality of Life and anxiety/depression in studies of PCa patients (Rees et al., 2005; Sharpley & Christie, 2007). Approval for this study was

received from the UnitingCare Health Human Research Ethics Committee (Approval number 2013.32.104) in accordance with the Helsinki Declaration of 1964 and confirmed in 2013. Written informed consent was obtained from all participants.

Statistical Analyses

SPSS 25 was used to analyze these data. Change in ISI score was calculated for each patient by subtracting the “before diagnosis” ISI score from the “last two weeks” ISI score so that a positive score indicated that a patient’s level of sleep problems had increased, a negative score showed that their level of sleep problems had decreased, and a score of zero indicated no change in sleeping problems. SPSS frequencies were applied to describe the sample on relevant aspects of their background and PCa status, and data were checked for normality. Pearson and Spearman correlation coefficients were used to test for significant associations between the demographic variables and the depression and sleep variables, and Pearson correlations also provided information regarding the relationships between the three SDS symptoms of cognitive depression and the seven aspects of sleep problems measured by the ISI, which was the major research foci of this study. A priori power analysis indicated that a sample of 63 participants would be sufficient to detect a moderate effect ($r = .40$) with $\alpha = .05$ and .95 power via Pearson correlational analysis. ANOVA and post hoc tests were used to compare the depression status of patients who reported a deterioration in sleep quality versus those who showed no change and those whose sleep quality improved. Hierarchical regression identified the relative strength of the three cognitive depression items in explaining variance in the ISI item *difficulty falling asleep*.

Results

Background Data

The response rate was 63.2%, which is similar to other postal surveys carried out with this population (Sharpley et al., 2010). The SDS and ISI (both copies) data did not show major evidence of significant non-normality (although the ISI change scores were, as might be expected, widely distributed), and so these data were used without transformation. Internal consistencies (Cronbach α) were: SDS = .839, cognitive depression = .800, ISI at diagnosis = .942, ISI now = .943. There were no significant correlations between any of the background variables and the SDS or ISI total scores (at either time point).

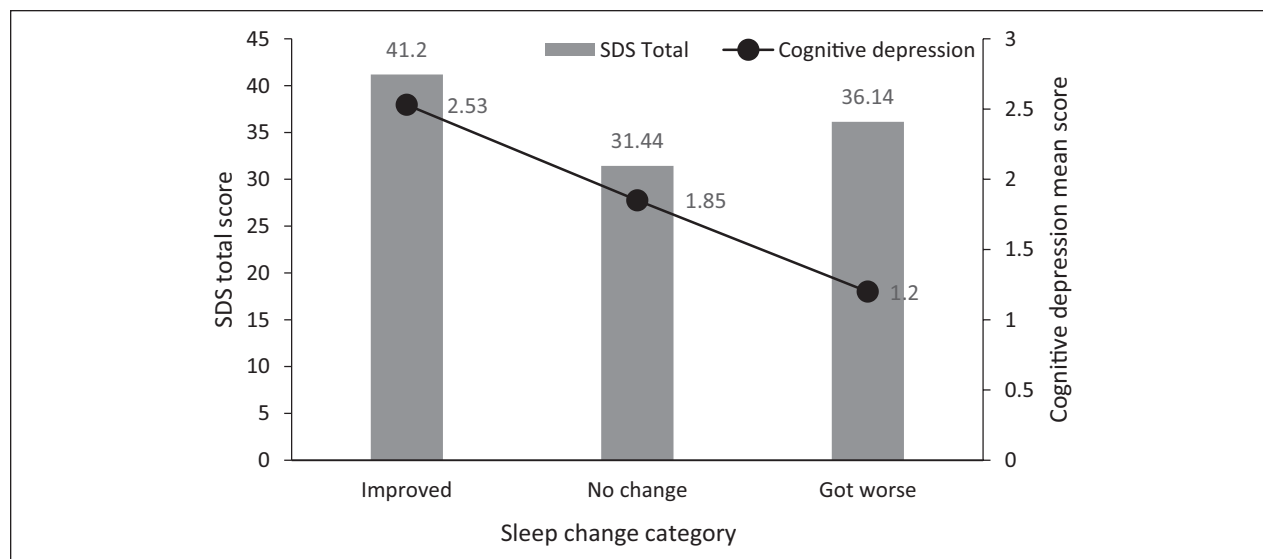


Figure 1. SDS total and Cognitive depression scores across sleep categories. SDS = Zung Self-rating Depression Scale.

Sleep Difficulties and Depression

Of the 96 PCa patients surveyed, 59 (61.4%) reported a deterioration in sleep quality from before their diagnosis to the time of the survey, and 26 (27.1%) reported no change in sleep quality. A small number of patients ($n = 11$; 11.5%) reported an improvement in sleep quality. There were no significant correlations between change in sleep quality or SDS total and Cognitive depression scores and the background variables of: time since diagnosis, status of PCa, marital status, or past or current treatments.

The relative SDS total and Cognitive depression scores for these three subgroups of patients are presented in Figure 1, indicating that, although one subgroup reported that their sleep had improved since diagnosis, that particular subgroup of patients also had the highest SDS total scores. Using ANOVA, there was a significant effect for SDS total score $F(2,89) = 5.318, p = .007$, partial eta squared = .109 (a large effect), power = .826. *Post-hoc* tests (Tukey) identified that the mean difference between the “improved” and “no change” subgroups (9.760, SE = 3.161, 95% CI = 2.22 to 17.29) was significant ($p = .008$), but that the mean difference between the “improved” and “got worse” subgroups (5.050, SE = 2.904) was not significant ($p = .196$), and neither was the mean difference between the “no change” and “got worse” subgroups (4.7055, SE = 2.0374, $p = .060$), although that difference approached the traditional values for significance and could be considered as a trend.

When MANOVA was conducted on all of these SDS items minus those two which are associated with sleep (item 4: *I have trouble sleeping at night*; item 10: *I get*

tired for no reason) across the three sleep subgroups, there was no significant main effect for sleep change subgroups $F(36, 142) = 1.101$, (Pillai’s Trace and Type II sums of squares model were used because of the unequal cell sizes), $p = .338$, partial eta squared = .218, power = .912. At the Bonferroni-corrected p value of $.05/18 = .0027$, the only significant univariate effect was for SDS item 15 (*I am more irritable than usual*) $F(2,89) = 6.651, p = .0020$, partial eta squared = .133, power = .905. *Post hoc* tests revealed that the “improved” subgroup had significantly higher mean scores for SDS item 15 ($M = 1.80, SE = .632$) than the “no change” subgroup ($M = 1.12, SD = .333$): mean difference = .68 (SE = .212), $p = .005$, 95% CI = .17 to 1.19, but not than the “got worse” subgroup ($M = 1.53, SE = .638$), mean difference = .42 (SE = .190), $p = .076$, 95% CI = -.03 to .87.

Deterioration of sleep quality and Cognitive depression

Of the 59 patients who reported a deterioration in sleep quality, there were significant correlations between their ISI-based sleep deterioration from diagnosis to the time of data collection and their total SDS score ($r = .370, p = .005$) and their SDS cognitive depression mean score ($r = .346, p = .007$). Table 3 shows that the strongest correlation between the seven aspects of deterioration in sleep quality and cognitive depression was for the first item on the ISI (i.e., *difficulty falling asleep*) (corrected p value of $.05/7 = .007$). This result was confirmed by linear regression of the four ISI items with correlation coefficients $>.3$ on mean cognitive depression score:

Table 3. Pearson Correlations Between SDS Cognitive Depression and Seven ISI Items.

ISI item	Difficulty Falling Asleep	Difficulty Staying Asleep	Waking Up Too Early	Satisfied With Sleep Quality	Noticeable to Others	Worried/ Distressed About Sleep	Sleep Problems Interfere With Functioning
Correlation with SDS Cognitive depression	.424*	.312	.331	.017	.241	.151	.307

Note. SDS = Zung Self-rating Depression Scale; * $p < .007$.

$R^2 = .225$, $F(4,58) = 3.919$, $p = .007$. ISI item 1 was the only item which reached significance (Standardized $\beta = -.331$, $t = 2.171$, $p = .034$).

To identify which aspect of cognitive depression was most strongly associated with *difficulty falling asleep* in those patients who reported a decrease in sleep quality, Pearson correlation coefficients were calculated between that ISI item and the items from the SDS cognitive depression subscale; all were statistically significant at the adjusted p value of $.05/3 = .0167$. When entered into a hierarchical regression according to the strength of their correlation with *difficulty falling asleep*, the total equation was significant $F(1,58) = 4.184$, $p = .010$, but only the SDS cognitive depression item *my mind is clear* made a significant contribution to the variance in *difficulty falling asleep* (R^2 change = $.140$, F for change = 9.298 , $p = .003$). Addition of the remaining two SDS cognitive depression items did not significantly increase the variance explained in *difficulty falling asleep*.

Discussion

Although both have often been accepted as negative outcomes of cancer, the specific association between difficulties falling asleep and the subtype of depression that is linked to ability to think clearly (i.e., cognitive depression) has not been previously reported for PCa patients. With over 60% of the current sample reporting an increase in sleeping difficulties following their diagnosis of, and treatment for PCa, these results provide further evidence that this process is stressful for these men, and that deterioration in sleeping quality is relatively widespread among them. The fact that the usual "background" factors such as age, time since diagnosis, treatment type, cancer status, and relationship status were not significantly correlated with SDS total or cognitive depression scores suggests another more powerful factor was responsible for these men's depression. That factor may have been their difficulty falling asleep.

The apparently higher score for total depression among those patients who reported that their sleep quality had improved since receiving their diagnosis was resolved when the two SDS items relating to sleep were removed from the analysis. The fact that there was no significant

difference between subgroups for their total non-sleep symptom SDS scores, but that those patients who reported that their sleep quality had improved also said that they were more irritable than patients whose sleep quality remained unchanged, is an unexpected finding.

Of those men who reported that their sleep quality had deteriorated, the severity of that deterioration was significantly correlated with their cognitive depression. Further, that association appeared to be based upon their difficulties in falling asleep rather than staying asleep, waking too early, and the ways that sleep difficulties interfered with their daily functioning or caused distress to them.

There is already an established relationship between depression and adverse treatment outcomes in PCa patients, and these results add to that literature by suggesting a more detailed association between one aspect of those adverse outcomes (i.e., sleep deterioration) and a particular subtype of depression that may hinder these men's ability to consider the diagnostic results and treatment options that they receive, and about which they are required to make decisions that can bring long-lasting sequelae. For example, the prevalence of urinary incontinence (Tienza et al., 2018) and erectile dysfunction (Emanu et al., 2016) are not trivial after treatment for PCa, and there is some discussion in the literature regarding the relative likelihood of these side effects from the major PCa treatments such as surgery and radiotherapy (Barocas et al., 2017). This information is often provided to PCa patients before they make treatment decisions, and it is perhaps not surprising that they report that making decisions about treatment, or understanding how treatment might affect them, are the "worst aspects" of the PCa experience (Sharpley et al., 2018).

Study Limitations

The sample size was satisfactory for the analyses undertaken, but larger and more comprehensive samples would enhance the generalizability of these results. The validity of the patient group was confirmed by clinical assessment relevant to determine the presence of PCa. The instruments used to assess total depression and cognitive depression and sleep quality are valid and reliable for PCa patients, but clinician interviews may offer greater

validity. The sample was restricted to one geographical region of Australia, and no attempt was made to test the generalizability of these results to other cultural and social settings. Although background factors such as age, cancer status, treatments, and relationship status were examined via correlational analyses, no direct comparison of these factors' effects upon sleep quality was undertaken. In particular, changes in sleeping habits due to age deserve further exploration. A single measure of sleep quality change was taken via the retrospective pretest procedure which, although validated in several samples (including PCa patients), remains a cross-sectional methodology. Longitudinal data collection is always valuable in teasing out variability over time, and this is a recommended avenue for further research.

Clinical Implications

These results underscore the need to examine the specific effects of sleep-related MDD symptoms when assessing the associations between sleep quality and depression and raise the issue of confounding of symptoms in clinical settings where multiple self-report scales such as the ISI and SDS may be used to assess PCa patient well-being and mental health. In terms of treatment options, medication might be considered as a "first-line" therapy to assist PCa patients who have experienced an increase in difficulty falling asleep. Although not a feasible long-term solution, the assistance of this line of treatment might relieve the anxiety and stress experienced by PCa patients who find that they are no longer able to fall asleep easily since receiving their diagnosis of PCa. One systematic review of 13 studies of behavioral interventions for sleep quality in 1154 hospital patients reported that relaxation techniques were effective for between zero and 38% of patients, sleep hygiene was effective in 5% of patients, and between 7% and 18% of patients improved under daytime bright light exposure (Tamrat et al., 2014). Those authors concluded that there was little evidence that non-pharmacological treatments were effective in hospitalized patients. PCa patients are hospitalized only briefly during treatment and occasionally for subsequent procedures if necessary. The results of another review of 112 papers of "Mind-Body Interventions" (MBI) for non-hospitalized participants may be more relevant. That review reported that 60% of studies reported beneficial effects on sleep quality; medication, movement-based MBI, and relaxation showed at least some improvements in sleep quality according to at least one sleep outcome measure. Of the most common interventions, 13/23 studies using meditation, 21/30 using movement MBI, and 14/25 using relaxation reported at least some improvements in sleep (Neuendorf et al., 2015). These results suggest that some behavioral treatments such as stimulus control therapy,

relaxation training, cognitive behavior therapy, sleep restriction therapy, biofeedback, and paradoxical intention that have been reported to be efficacious in treating sleep problems (Medicine, 2006) might be useful following short-term pharmacological interventions, which may provide PCa patients with some initial relief from their sleep difficulties.

In conclusion, sleep-related cognitive depression was relatively common among this sample of men with PCa and had a significant inverse correlation with the severity of patients' sleeping difficulties. Treatment aimed at assisting these men to sleep more effectively represents a major target for clinical practice. The high rate of irritability in patients whose sleep patterns were not adversely affected raises an issue for further research, but it is worthwhile noting that irritability is a key aspect of "male depression" (Rutz et al., 1995), which has previously been reported in PCa patients (Sharpley et al., 2014) and which may require specific treatment approaches.

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