Urology : Research And Therapeutics Journal

SCIENTIFIC LITERATURE

Special Issue Article "Hormonal Therapy on Prostate Cancer" Review Article

Evaluating the Effect of Androgen Deprivation Therapy on Sleep Disturbances in Prostate Cancer Patients

Mondal S[1,2], Dimitriou D[2], Edwards SM[3] and Mangar SA[4*]

[1]Rhine Waal University of Applied Sciences, Kleve, Germany

[2]Lifespan Learning And Sleep Lab, Institute of Education UCL, London

[3]Clinical Trials Department, Imperial College Healthcare NHS Trust, London

[4]Department of Clinical Oncology, Imperial College Healthcare NHS Trust, London

ARTICLE INFO

Received Date: March 16, 2020
Accepted Date: April 20, 2020
Published Date: April 24, 2020

KEYWORDS

Actigraphy
Androgen deprivation therapy
Prostate cancer
Insomnia
Sleep questionnaires
Sleep disturbance
Cancer related fatigue

Citation for this article: Mondal S, Dimitriou D, Edwards SM and Mangar SA. Evaluating the Effect of Androgen Deprivation Therapy on Sleep Disturbances in Prostate Cancer Patients. Urology : Research And Therapeutics Journal. 2020; 3(1):130

Corresponding author:
Stephen Mangar,
Dept of Clinical Oncology, Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London, United Kingdom,
Email: s.mangar@imperial.ac.uk

ABSTRACT

Introduction: Androgen Deprivation Therapy (ADT) is used extensively in the management of prostate cancer both in metastatic, locally advanced and localised disease. Whilst the common side effects and toxicities of ADT relating to metabolic, cardiovascular vasomotor, and bone changes have been widely studied, comparatively less is known about how hormone therapy affects sleep disturbance. The purpose of this mini review was to search the literature for assessments of ADT related sleep disturbance and associated fatigue in an attempt to discern how this and general Cancer Related Fatigue (CRF) can impact on quality of life and treatment compliance in prostate cancer patients.

Method: Published literature was searched via Pubmed to identify prospective studies looking at the prevalence of sleep disturbances in patients receiving any form of ADT for prostate cancer. From a total of 176 articles found, 20 were chosen to explore in more detail their methodology of sleep disturbance evaluation, significance of their results, and whether this was influenced by ADT type.

Results: The 20 original studies of which none were case reviews reported on varying forms of sleep disturbance assessment in prostate cancer patients receiving ADT. 5 prospective studies were identified where sleep disturbances were a primary endpoint, and hence the main focus of the study. Causality pathway was not possible to identify due to a lack of baseline assessments of sleep, low number of patients in the studies and confounding effect of other treatments such as radiotherapy used concurrently with ADT. The majority of studies used sleep validated questionnaires, with only 2 studies using objective assessment of sleep patterns with actigraphy. The questionnaires were not sufficiently detailed to account for the effect of nocturia and hot flashes on sleep patterns. The limited actigraphy data suggest that day time napping and sleepiness may also be an important consideration for ADT. It was not possible to determine whether different forms of ADT have a differential effect on sleep disturbances and sleep disorders.

Conclusion: There is a paucity of data to inform us on the effect of ADT on sleep disturbances. Studies utilising a combination of objective assessment of sleep and questionnaires to assess sleep patterns as well as sleep disorders according to current

sleep medicine guidelines are needed. In addition further research is needed to identify whether different forms of ADT may have a differential effect on sleep.

INTRODUCTION

Androgen deprivation therapy (ADT) is widely utilised in the treatment of prostate cancer. It forms the mainstay of management in patients with metastatic disease where it is employed long term, and is also used in the short term to exploit its synergistic effect with external beam radiotherapy to improve the chances of cure for local and locally advanced prostate cancer [1,2].

Whilst much is known about long term side-effects of ADT such as osteoporosis, and metabolic syndrome which result in an increased risk of diabetic and cardiovascular complications, correspondingly less is known about its direct effect on sleep patterns and the development of sleep disorders despite widespread acceptance of its association with fatigue which worsens over time on ADT [3].

Although there is a strong correlation between cancer related fatigue (CRF) and sleep disorders, it is important to make the distinction between these two, as CRF implies persistent tiredness despite 'non problematic' sleep, and confusingly these terms are used interchangeably in the literature [4]. Nevertheless, irrespective of the distinction both can significantly impact quality of life and affect treatment compliance. In general both fatigue and sleep disorders (such as insomnia) have historically been assessed subjectively, and more recently an objective assessment of sleep disturbance using wrist actigraphy has emerged into the clinical arena as a feasible option for different patient groups and endorsed by the American Academy of Sleep Medicine (AASM).

The purpose of this article was to review the recent published prospective data on ADT and its specific effect on sleep disturbances in order to help identify the prevalence of effect, the methodology of data collection, and finally to determine whether there is a differential effect according to the type of ADT. We hope this approach may help identify any unmet needs arising from the potential detrimental effects of hormonal therapy in prostate cancer patients.In the context of this mini-review we are classifying ADT as any hormonal manipulating medication such as anti-androgens and Luteinizing Hormone Releasing Hormone (LHRH) analogues.

SEARCH STRATEGY AND SELECTION CRITERIA

For the purpose of this mini review article we predominantly focused on the prospective data on ADT and sleep disturbance in prostate cancer. To capture the broadest review set, PubMed citations were initially searched using the terms "Androgen deprivation therapy and Sleep". In addition, to improve the capture rate and scope of the review other search term combinations such as "Prostate cancer and Sleep disturbance" and "Prostate Cancer and Actigraphy" were used. This yielded 46 results for 'androgen deprivation and sleep', 141 results for 'prostate cancer and sleep disturbance' and 7 results for the search term 'actigraphy and prostate cancer'. Of the total 194 papers, 18 papers were excluded on account that they were repeated analysis of the same study leading to a final count of 176 articles available for review. The search was restricted to English language and peer-reviewed journals over the last twenty years. The flow diagram in figure 1 shows the various exclusions applied to the 176 articles to refine the cohort down to 5 prospective papers published recording data specifically on ADT for prostate cancer and sleep disturbances (Figure 1).

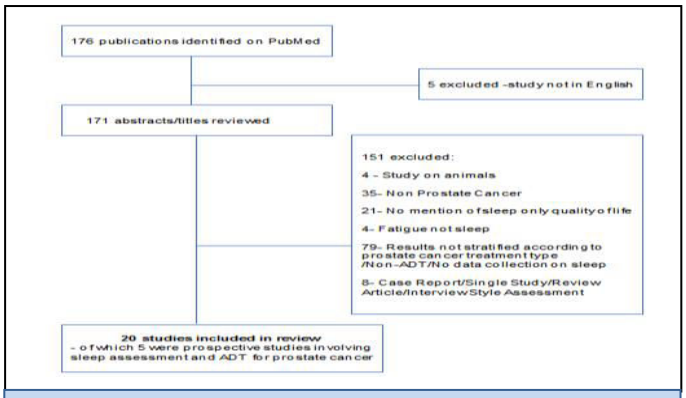

Figure 1: Flow diagram for identification of published data on ADT and sleep disturbance.

RESULTS

Of the 176 studies identified for this review only 20 studies reported data on some form of ADT effect on sleep patterns. This was usually determined as part of a Quality of Life (QoL) assessment, with the full exclusion criteria for the refinement set out in Figure 1. A summary of these 20 studies is shown in Table 1. The date of publication for included studies ranged from 2003 to 2019.

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Table 1: Summary of main studies with regards to ADT and sleep quality.

	N	ADT +CaP N	ADT Type	Baseline	Questionnaires	Actigraphy	Main parameter assessed	Results
Maguire 2019, Ireland [6]	3348	657	Not specified	No	EORTC QLQC30, QLQPR25, EQ5D-5L	No	QoL including sleep	19% of cancer survivors report some form of sleep disturbance. Does not specify how many of the 19% have had ADT in the past or receiving ADT.
Gonzalez 2018, USA [7]	285	78	Some form of ADT	Yes	ISI, HFRDIS	Yes (worn for 72 hours)	Sleep disturbance	Refer to Table 2.
Reeve 2018, USA [8]	373	22	Not specified	Yes	PROMIS EPIC	No	QoL including sleep	3 out of 22 men fell in the Latent Profile category 3, reporting moderately elevated symptoms including sleep problems and 1 man fell in Latent Profile category 4, reporting severely elevated symptoms (including sleep problems) and overall on average men in Category 3 scored 52 and men in Category 4 scored 56 on the sleep disturbance subscale of PROMIS compared with an average score of 48 for Category 1 men with the best quality of life.
Challapalli, 2018, UK [9]	250	250	LHRH= 223 AA=7 CAB=20	No	Hormone Assessment Sheet	No	Vasomotor Symptoms	20% of patients reported sleep disruption in some form while 40% reported fatigue affecting their daily activities. Questionnaire not specifically designed to discriminate between cancer related fatigue (CRF) and change in sleeping patterns.
Rich, 2017, USA [10]	10	10	Not specified	Yes	EPIC, HFRDIS, HFD, GSDS	No	Hot flushes	Auricular Electroacupuncture (AEA) significantly improved vasomotor symptoms and alleviated sleep disturbance. General Sleep Disturbance Scores (GSDS) went down significantly from 63 (Baseline) to 57 (3 weeks) and finally 37 (6 weeks)
Koskderelioglu2017, Turkey [11]	106	48	Bicalutamide (50mg) + Goserelin or Leuprolide (q 3 months)	No	ESS, FSS, BDI, PSQI	No	Quality of Sleep	Refer to Table 2.
Savard, 2015, Canada [12]	728	25	Tamoxifen (4), Bicalutamide (19), Goserelin (16) and Leuprolide (3)	Yes	ISI, PSQI	No	Insomnia	Refer to Table 2.
Lebret, 2014, France [13]	1276	1276	GnRH antagonists	Yes	EORTC QLQC30, QLQPR25	No	QoL including sleep	**Special Mention**: Patients reported improved sleep at 3 to 6 months after starting GnRH with average sleep scores improving from 22 to 20
Saini, 2013, Italy [14]	103	49	4 weeks of Bicalutamide or Flutamide prior to starting three	No	HADS, PSQI, RLS FACT-P	No	QoL including sleep	**Special Mention:** No statistically significant difference between Global PSQI scores for ADT and Non-ADT groups.

			monthly 11.25 mg LHRH-A alone					Poor sleep highly correlated with depression rather than ADT use. (r=0.79, p<0.0001)
Savard, 2012, Canada [15]	60	28	4 weeks of Bicalutamide initiated prior to starting three monthly Goserelin or Leuprolide	Yes	ISI, PSQ	No	Insomnia	Refer to Table 2.
Hanisch 2011, USA [16]	60	60	Leuprolide (88%), Bicalutamide 25%, Ketoconazole 12%	No	ESS, FACT	Yes (worn for 7 days)	Sleep and daily functioning	Refer to Table 2.
Garrett, 2011, USA [17]	160	43	Not collected	No	PSQI, GSDS, LFS	Yes (worn for 48 hours)	RT sleep and fatigue	Patients with prostate cancer had a significantly higher percentage of time awake after sleep onset (P=0.03), less total sleep time (P=0.006), and a lower sleep efficiency (P=0.02) compared to breast cancer patients although the sleep data for prostate patients is not separated based on treatment.
Miaskowski, 2011, USA [18]	185	43	Not collected	No	PSQI, GSDS, LFS	Yes (worn for 48 hours)	RT sleep and fatigue	26% of all participants had a global PSQI score above the proposed cut off >8. Over 40% of the patients had a total GSDS score of >= 43. 33.7% and 25.4% patients reported morning and evening fatigue.
Miaskowski 2011, USA [19]	82	42	Not specified	Yes	KPS, PSQI, GSDS CES-D, STAI-S, STAI-T, NRS LFS	No	RT and sleep disturbance	At baseline (Prior to RT) the mean global PSQI score was 5.25 (S.D. 2.93) and the global GSDS was 33.44(16.31)
Beer 2010, USA [20]	22	21	LHRH agonists (15), LHRH+ AA(4), LHRH+ Ketoconazole (1) Orchidectomy + Ketoconazole (1)	Yes	HFRDIS PSQI	No	Hot flushes and acu-puncture	At baseline, 16 patients had a global PSQI score ≥ 5. Of those 20% and 9% saw their PSQI global score improve to less than 5 at 6- and 10-week post acupuncture evaluations.
Van Onselen, 2010, USA [21]	179	43	Not specified	No	KPS, CES-D, STAI-S, STAI-T PSQI	No	Mood disturbance and sleep quality	57% of all patients (with different kinds of cancers) reported some form of sleep disturbance. 53% of prostate cancer patients on ADT.
Dirksen 2009, USA [22]	51	40	Not specified	No	IES, ISI CES-D	No	Insomnia and depression	53% of total men had clinically significant insomnia in a patient cohort where 78% of participants were undergoing hormonal therapy.
Nishimura 2005, Japan [23]	94	64	LHRH - Leuprorelin (42) Goserelin (22)	No	Japanese Questionnaire on Climacteric disorders	No	Climacteric disorders including sleep	Slightly less than 20% had severe issues falling asleep and woke up multiple times at night

Lintz 2003, UK [24]	249	202	LHRH agonists	No	EORTC QLQC30, HADS, Support Care Survey/ Preference	No	Psycho-logical needs	30% of total cohort report some degree of sleep disturbance (81% of participants on hormone therapy)
Fillion 2003, Canada [25]	604	160	Not specified	No	EORTC QLQC30, HADS, ISI	No	Cancer Related Fatigue	Mean ISI score of 6 (49% of total prostate cancer cohort was on hormone therapy)

CAB: Combined Androgen Blockade; CaP: Prostate Cancer; CES-D: Center for Epidemiologic Studies Depression Scale; EPIC: Expanded Prostate Cancer Index Composite; ESS: Epworth Sleepiness Scale; EORTC QLQC30: European Organisation for Research and Treatment of Cancer- Quality of Life Questionnaire; EQ5D-5L: Euro-group 5 Dimension 5 Level questionnaire; FACT-P: Functional Assessment of Cancer Therapy –Prostate; GSDS: General Sleep Disturbance Scale; HADS: Hospital and Anxiety Depression Scale; HFDIS: Hot flash-Related Daily Interference Scale; ISI: Insomnia Severity Index; KPS: Karnofsky Performance Score; LFS: Lee Fatigue Scale; NRS: Numerical Rating Scale (for pain intensity); PSQI: Pittsburgh Sleep Quality Index; PROMIS: Patient Reported Outcomes Measurement Information System; STAI—S: Spielberg-State Trait Anxiety Inventory Scale; (STA-T – anxiety Trait); QoL: Quality of Life; RT: Radiotherapy

Table 2: Summary of 5 prospective studies identified which looked specifically at ADT in prostate cancer and effect on sleep quality employing subjective and objective methods.

	Duration of ADT (Months)	Mean Age (SD)	ADT N	Subjective sleep disturbance				Objective sleep disturbance from Actigraphy data (6 months)	
				Sleep Questionnaire used and criterion	At Baseline	Post ADT		Actigraphic variable	Result
						Time Point 1	Time Point 2		
Gonzalez [7]	6-12	68.49 (8.52)	78	**ISI** scores ≥ 8.	42% (cf 21% for controls)	50% at 6 months (cf 23% for controls)	59% at 12 months (cf 26% for controls)	Wake After Sleep Onset	65.24 mins (SE. 6.15) Controls: 47.28 mins (S.E. 6.08)
								Sleep duration Sleep	417.29 mins (SE.17.66) Controls: 397.42 mins (SE17.47)
								Sleep efficiency	73.22% (S.E. 2.2) Controls: 74.72% (SE. 2.17)
Hanisch, [16]	intermittent	71.4 (9.6)	60	**ESS** ≥10 Note: FACT score- 85.6 suggesting normal wellbeing	Not collected	23% had daytime sleep-iness	Not collected	Wake After Sleep Onset	49.4 (SD. 33.4)
								Total Sleep Time	5.9 hours (S.D. 1.4)
								Sleep Efficiency	74% (S.D 12)
								Total nap time per day	58.8 mins (S.D. 31.7) Results correlated poorly with sleep diary
Koskderelioglu, [11]	6-13	70.79 (6.67)	48	**PSQI** ≥ 5 **ESS** ≥ 11	Not collected	75% had impaired sleep quality (cf 27.5% for non-ADT) 4.1% had daytime sleepiness (cf 5.1% for non-ADT controls)	Not collected	No Actigraphy	
Savard, [12]	6-18 (at least)	61.7 (6.4)	25	**ISI** scores ≥ 8. Note: All underwent RP at baseline and only 10% had ADT.	36.9%,	38.7% at 2 months	29% at 6 months	No Actigraphy	
Savard, [15]	4-16 (at least)	71.0 (6.1)	28	**ISI** scores ≥ 8. Note: Insomnia mediated by sweats, hot flashes and nocturia	22%	41.9% at 4 months	40% thereafter	No Actigraphy	

RP: Radical Prostatectomy; SD: Standard Deviation; SE: Standard Error

Of the 20 studies identified, various methods were employed by the authors to collect sleep data, conducted mainly by subjective questionnaires of various types- see Table 1. Objective sleep assessment by actigraphy was recorded in 4 studies, though 2 of these involved assessment for patients primarily undergoing radiotherapy. In the 2 studies relevant to ADT, using actigraphy recording of 'Wake After Sleep Onset' (WASO) ranged from 49-65 minutes [7,16]. Additionally in the study by Hanisch et al (2011), those patients on ADT took on average greater than 30 minutes to fall asleep and slept for six hours per night with an average sleep efficiency (defined as total sleep time / time spent in bed) of 75% [16]. A similar result for sleep efficiency of 73% was noted in the study by Gonzalez et al (2018) [7]. The authors used different actigraphy equipment and methods to collect sleep data hence direct comparison of the data are somewhat invalid.

Furthermore, of the 20 studies identified, 6 did not specify the type of ADT treatment that was used, with the remaining 14 studies reporting patients being treated with some form of LHRH analogue injection - either as monotherapy or in combination with Bicalutamide for maximum androgen blockade. Only 5 of the 20 studies were designed prospectively to look specifically at prostate cancer patients on ADT therapy and its effect on sleep quality, either subjectively or objectively as an end-point [7,11,12,15,16]. The salient features of these studies are summarised in Table 2 and described in more detail below.

The mean age range of participants in these 5 studies ranged from 61-71 years, and the study sample sizes of subjects receiving ADT for prostate cancer was relatively low ranging from N= 25-78. All 5 studies assessed sleep via subjective tools such the ISI (Insomnia Severity Index), ESS (Epworth Sleepiness Scale), or PSQI (Pittsburgh Sleep Quality Index) scales at one timepoint. The prevalence of sleep disturbances as judged from these scales varied considerably between 23-75% in prostate cancer patients receiving ADT for mainly between 4-6 months, but for some studies the duration of ADT was not specifically recorded in relation to the time of assessment with the questionnaires [11,16]. In addition, in the study by Koskderelioglu et al., the PSQI threshold used for sleep disturbances was lower than in other studies and may in part explain the high observed prevalence of 75% [11].

Thus far, there are no published studies reporting actigraphy sleep data at pre-treatment level (baseline) and only three studies had baseline questionnaires [7,12,15]. From these questionnaires it appeared that the prevalence of poor sleep (as defined according to the scoring of the particular questionnaire) prior to starting ADT was in the order 22%, 36.9 % 42% from the studies by Savard et al (2012) , Savard et al (2015), Gonzalez et al (2018) respectively [7,12,15,].

In a correlational study examining subjective and objective data Hanisch et al., (2011) compared actigraphy data with sleep diaries data and reported moderate correlations on night-time sleep and daytime napping [16]. Of the 5 prospective studies reviewed, 4 stipulated the type of hormone treatment given, though no data were stratified according to type of ADT received and its effect on sleep quality.

DISCUSSION

This mini review article shows that whilst general sleep disturbance and ADT is frequently cited in the literature mainly as a component of QoL under the umbrella term of fatigue, there is nonetheless a paucity of prospective data collection on evaluating the effect of ADT on possible changes on sleep patterns during and after treatment. The authors acknowledge that only one search engine was used, and deliberately sought to exclude reporting on fatigue and ADT, as the emphasis of this review was specifically on sleep disturbance reported by patients undergoing ADT for prostate cancer.

Twenty studies were identified from a literature search of 176 articles examining the side-effect of ADT in prostate cancer patients, of which 5 were identified as prospective where sleep patterns were identified as a clear end-point. The methodology of data collection observed in this review was overwhelmingly subjective with a variety of validated questionnaires assessing sleep, fatigue, depression and QoL. There were only 4 studies that made objective assessments with actigraphy [7,16-18], 2 of which concentrated on observing the effects of radiotherapy in addition [17,18]. Interestingly only 3 of the 5 prospective studies had a subjective baseline assessment score which revealed that in general prostate cancer patients generally had poor sleep quality manifesting

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mainly as insomnia before even commencing any form of ADT [7,12,15].

Using a cancer validated score from the ISI, the percentage of patients having clinical levels of insomnia (defined as ISI score ≥8) at baseline ranged from 22-42%. This observation perhaps suggests that sleep onset insomnia associated with a cancer diagnosis is relevant and it is interesting to speculate on what the possible mechanisms may be for this. One explanation might involve the possible effect of prostate cancer tumour cells on mutations of body clock genes which regulate circadian sleep patterns [26], whilst another might involve the direct hormonally mediated effects of cancer on serotonin and melatonin which regulate the sleep/wake cycle [27]. Nevertheless these figures need to be interpreted with caution as for example in the study by Gonzalez et al (2018), completion of the questionnaires were allowed up to one month after starting ADT [7], which might without doubt contaminate the true baseline levels. In addition data presented by Savard et al (2015) were on patients who had previous prostatectomy [12]. This again might skew the results as the cancer diagnosis would have been a significant length of time before the insomnia assessment.

It is also important to note that none of the studies used clinical guidelines for the assessment of insomnia as well as different methodological issues are noted in relation to the use of actigraphy; i.e. sensitivity mode, type of actigraphy and data analysis. In the three studies that had a baseline assessment the prevalence of sleep disturbances increased following the initiation of hormonal therapy ranging from 38.7% at 2 months, 41.9% at 4 months, and 50% at 6 months [7,15,16]. However, these results are clouded by confounding factors, such as the use of radiotherapy commencing shortly after initiation of ADT [7,15]. In addition the overall numbers analysed were low, for example in the study by Savard et al (2015), only 10% of patients with prostate cancer were receiving ADT [12] which might lead to an observation that was highly under-representative of the true insomnia level. In contrast the study by Gonzalez et al (2018), might over-estimate the true insomnia level as 36% of the 78 patients received concurrent radiotherapy [7], which may have its own detrimental effect on sleep patterns.

The studies show a variable effect with regard to ADT treatment and type of sleep disturbances. In the initial study by Savard et al (2012), 11 patients received ADT for less than 9 months and 17 patients were on longer term ADT for greater than 16 months. All received radiotherapy commencing just over three months from starting ADT (mean 104 days). Generally there was a peak in ISI scores at approximately 6 months, likely as a result of the increased nocturia associated with radiotherapy, and this persisted at about 40% thereafter irrespective of duration of hormonal treatment [15]. In a later study by Savard et al (2015), the prevalence of insomnia in prostate cancer patients seemed to peak at 2 months but plateaued after a period of 6 months on hormones increasing from 36.9% at baseline, to 38.7% , 29.0% , 26.4% and 30.9% at 2, 6, 10 and 14 months respectively [12]. Again these results ought to be interpreted with caution given that only 10% of subjects received ADT, and all patients had a prostatectomy.

In the study by Gonzalez et al (2018), sleep disturbance increases significantly with ADT for at least a period of 12 months with frequencies of 42% at baseline to 50% at 6 months and 59% at 12 months, irrespective of whether patients were on ADT for 6 or 12 months [7]. Taken together these results support the notion that ADT over and above a prostate cancer diagnosis is associated with sleep disturbances and can persist even after discontinuing ADT.

There is no doubt that the use of validated sleep questionnaires for cancer patients play an important part of assessments in the studies reviewed with 18 of the 20 initial studies identified using such questionnaires. The most commonly used were the EORTC/QLQC30, ISI and PSQI. While the PSQI is a measure of overall sleep quality, the ISI is used as part of a clinical diagnosis of insomnia. Both questionnaires cover daytime sleepiness in brief, asking participants if sleep “interferes” with their daytime activities, though daytime napping and sleepiness is not fully explored which may limit these questionnaires’ ability to fully capture the extent of sleep disturbances. Interestingly daytime napping which may be a more important component of CRF rather than insomnia or other sleep disorders, was detected in the two actigraphy studies with ADT [7,16], and CRF is covered more comprehensively in the ESS

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questionnaire mentioned earlier. However ESS evaluation was only used in two of the twenty studies [11,16].

The role of sweats and hot flashes which are a common occurrence with ADT [9] and nocturia from potential bladder outflow obstruction from a diseased prostate, including radiotherapy treatment needs to be taken into account when assessing sleep quality. These considerations have been acknowledged and addressed to some extent in the studies by Savard et al (2012), and Gonzalez et al (2018) [7,15]. However, they are rarely fully explored in most of the sleep-related questionnaires available to the researcher. For example, whilst the PSQI briefly addresses these issues, the severity of sweat/flashes or daily frequency of nocturia are not adequately ascertained. Apart from this it was not possible to tease out other important confounding variables that could influence sleep disturbance such as co-morbities, stage of cancer, or analgesia requirments. In the study by Hanisch et al (2010), where just under 50% of subjects were metastatic, no clear patterns for medication use inclusing analgesia were noted except that 78% were taking anti-hypertensives and or cholesterol lowering medication.

An obvious drawback of any self-reported questionnaire is the individual's overall bias of symptom reporting due to the retrospective nature of data collection [28], and there is a notable trend for under-reporting sleep disturbances. For example, in the study by Garret et al (2010), which compared actigraphy with sleep questionnaire data in breast and prostate cancer patients, whilst breast cancer patients had more sleep disturbances based on the questionnaires this was discordant with actigraphy data which showed that prostate cancer patients had in fact worse sleep quality [17]. As such using questionnaires to self-report sleep disturbances in a prostate cancer cohort may not be fully representative as sleep diaries require patients to daily input their sleep data hence compliance and reliability might be reduced. Wrist actigraphy has emerged as a feasible assessment of sleep pattern over extended time periods [29-32]. The data from the device can be downloaded and analysed offline. Various parameters of night- time and day- time sleep can be assessed, with parameters such as actual sleep, sleep efficiency (commonly determined by a percentage of total sleep time/time in bed) being the most important for this patient group.

In the two prospective studies that used actigraphy neither conducted a baseline assessment, but sleep efficiency was concordant at approximately 75% at some time point of patients receiving ADT. Both studies collected continuous actigraphy data for at least 72 hours as recommended by Miaskowski et al (2011) [18]; albeit most studies recommend a minimum of 5 continuous days to obtain sleep-wake patterns [33]. Interestingly in the study by Gonzalez et al (2018), little difference in sleep efficiencies between the ADT group treated for six months and corresponding controls were noted (73% vs 74.7%) [7]. These data are important to be replicated using more stringent sleep analyses protocols to assess and determine the prevalence and types of insomnia.

Hanisch et al (2011), showed nocturnal total sleep time as well as daytime napping were similarly reported via actigraphy and sleep diaries. The ESS score was significantly correlated with the actigraphy night-time variable of "total sleep time" indicating that greater hours of nocturnal sleep was associated with lower daytime sleepiness as expected [16]. Similarly, Miaskowsi et al (2011), found a few weak to moderate correlations between subjective and objective sleep data except GSDS score and sleep onset latency, and also between the sub-scale of excessive daytime sleepiness and all of the wake/activity parameters where a strong correlation was seen [18]. This raises the need for better designed questionnaires fully capturing sleep disturbances in this clinical population.

A drawback of actigraphy is that it should be supported with a sleep diary to accurately calculate sleep onset which is often reported to be delayed in prostate cancer patients. Since the use of a sleep diary may not be feasible, future studies ought to utilise a combination of actigraphy and specific sleep questionnaires in order to fully understand sleep patterns in patients who may already be experiencing sleep disturbances prior to the start of ADT.

Finally, it was not possible from the studies reviewed to identify whether the type of ADT was predictive or indicative of poor sleep quality. Whilst many studies used LHRH analogues and some in addition with anti-androgens such as Bicalutamide for maximum androgen blockade, little is published on other hormonal agents such as transdermal oestrogen patches, the second generation anti-androgens i.e. Enzalutamide or

androgen synthesis inhibitors i.e. Abiraterone, all of which are commonly reported to cause fatigue [34,35].

With this in mind, a pilot study has been set up at Imperial College London (The effect of androgen deprivation therapy on sleep disturbance in patients with prostate cancer: DEPRIVED) to examine the differential effect of a variety of hormonal agents on sleep patterns in prostate cancer patients. Sleep patterns will be measured longitudinally using combination of questionnaires with actigraphy at three different time points including a baseline assessment.

CONCLUSION

This mini review article suggests that there are limited data from prospective studies to inform us on the effect of ADT on sleep patterns in prostate cancer patients. The studies mainly utilise subjective questionnaires which are unable to reliably distinguish between sleep disturbances and/or disorders such as insomnia with fatigue, and do not readily account for frequency of nocturia, or severity of hot flashes.

The interpretation of data on the prevalence of sleep disorders such as insomnia or fatigue are hampered by the fact that sleep disturbances may be already prevalent in prostate cancer patients before the start of ADT. Objective assessment of sleep using mixed method design with actigraphy or other new technologies has rarely been used so far. It remains unknown whether different types of ADT may have a differential effect on sleep disturbances. Further research is underway to address these issues.

SUMMARY

-Paucity of robust data assessing particular question of sleep disturbances and ADT in relation to ADT treatment in prostate cancer patients.

-Sleep disturbance prevalence rates difficult to ascertain as compounding effect of radiotherapy and surgery, and also lack of baseline assessment.

-Sleep disturbances are commonly assessed via validated sleep questionnaires but have their limitations (don't take fully into account nocturia and hot flushes).

-Actigraphy can measure objectively sleep- wake cycles/ patterns but not widely utilised in studies. Lack of sleep assessment protocol which should include baseline objective assessment for this clinical population.

-Lack of correlation between questionnaires and actigraphy in this clinical population.

-Lack of data comparing different hormonal treatments and sleep quality.

ACKNOWLEDGEMENTS

This work has been supported by funding from Dr Mangar's Cancer Research Fund.

With support from: P. Abel, H. Ahmed, H. Bhola-Stewart, A. Forde, O. Karim, A. Pope, M. Palmada-Fenes, F. Power, A. Servidad, A Shamshuddin, J. Sethi, M.Winkler.

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