Published in final edited form as:

Soc Sci Med. 2016 May ; 156: 80–89. doi:10.1016/j.socscimed.2016.03.016.

Cognitive and neurobehavioral symptoms in patients with non-metastatic prostate cancer treated with androgen deprivation therapy or observation: A mixed methods study

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Abstract

BACKGROUND—Few studies have investigated prostate cancer patients' experiences of cognitive functioning or neurobehavioral symptoms (i.e., behavioral changes associated with neurological dysfunction) following androgen deprivation therapy (ADT).

METHODS—Semi-structured interviews conducted from the US by phone and in-person were used to explore and characterize the: 1) experience of cognitive and neurobehavioral functioning in non-metastatic prostate cancer patients undergoing ADT ($n=19$) compared with patients who had not undergone ADT ($n=20$); 2) perceived causes of cognitive and neurobehavioral symptoms; 3) impact of these symptoms on quality of life; and 4) strategies used to cope with or compensate for these symptoms. Neuropsychological performance was assessed to characterize the sample.

RESULTS—Overall, ADT patients experienced marginally more cognitive problems than non-ADT (nADT) patients even though there were no significant differences between groups in neuropsychological performance. ADT patients also experienced more declines in prospective memory and multi-tasking than nADT patients. Significant proportions of participants in *both* groups also experienced retrospective memory, attention and concentration, and information processing difficulties. With respect to neurobehavioral symptoms, more ADT patients

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experienced emotional lability and impulsivity (both aspects of disinhibition) than nADT patients. Among the causes to which participants attributed declines, both groups attributed them primarily to aging. A majority of ADT patients also attributed declines to ADT. For both groups, increased cognitive and neurobehavioral symptoms negatively impacted quality of life, and most participants developed strategies to ameliorate these problems.

CONCLUSION—ADT patients are more vulnerable to experiencing specific cognitive and neurobehavioral symptoms than nADT patients. This study highlights the importance of capturing: a) cognitive symptoms not easily detected using neuropsychological tests; b) neurobehavioral symptoms that can be confused with psychological symptoms, and c) causal beliefs that may affect how people cope with these symptoms. Effective interventions are needed to assist prostate cancer patients in managing these symptoms.

Keywords

prostate cancer; oncology; cognitive functioning; neurobehavioral functioning; androgen deprivation therapy; attributions; quality of life

INTRODUCTION

Androgen deprivation therapy (ADT) is a mainstay treatment for prostate-specific antigen (PSA) recurrence following localized prostate cancer treatment (Han, Partin, Pound, Epstein, & Walsh, 2001; Singh, Trabulsi, & Gomella, 2010). However, ADT has been associated with side-effects, including cognitive impairments. A recent systematic review and meta-analysis of research examining cognitive performance in ADT patients concluded that they performed significantly worse on visual motor tasks than non-cancer control groups, consistent with research highlighting the important role of testosterone on cognition (McGinty et al., 2014). A more recent controlled longitudinal study corroborated these findings (Gonzalez et al., 2015).

Although studies have examined neuropsychological performance in ADT patients, few have investigated ADT patients' experiences of changes in cognitive functioning. Self-reported cognitive functioning tends not to be highly correlated with neuropsychological performance (Joly et al., 2006) but there is evidence that self-reported symptoms: a) provide important complementary information about the lived experience of cognitive impairments (Wu, Diefenbach, Gordon, Cantor, & Cherrier, 2013); b) are an important harbinger of further cognitive decline that may not yet be detectable with neuropsychological tests (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010), and c) are associated with reduced quality of life (Voerman et al., 2006).

The few studies that have examined self-reported cognitive functioning in ADT patients have resulted in mixed findings. One study compared 57 non-metastatic prostate cancer patients undergoing ADT with 51 healthy age-matched controls and found no differences in self-reported cognitive functioning (Joly et al., 2006). However, another study of 238 patients who had been on ADT for more than one year reported worse cognitive functioning than men who received ADT for less than a year (Voerman et al., 2006). In an earlier qualitative pilot study to examine 11 ADT patients' experiences of cognitive impairment

since treatment (Wu et al., 2013), impairments affecting multiple cognitive domains were reported by patients from lower level functions (e.g., concentration) to higher level functions (e.g., executive functioning). Interestingly, neurobehavioral symptoms were also reported. *Neurobehavioral symptoms* are the behavioral signs and symptoms of neurological impairment and include apathy (e.g., loss of initiation, loss of spontaneity) and disinhibition (e.g., impulsivity, emotional lability) (Grace & Malloy, 2001; Larner, 2010). Neurobehavioral symptoms are closely related to cognitive functioning in that they are purported to underlie or are precursors to cognitive alterations in neurologic disorders (Andersson & Bergedalen, 2002; Cummings et al., 1994; Wu et al., 2013). Frontostriatal neuronal circuits of the brain are important for the mediation of both behavior and lower to higher level cognition (Tekin & Cummings, 2002) and are purported to be affected by testosterone loss (Batrinos, 2012).

There has been extensive focus on neuropsychological outcomes in ADT patients at the cost of comprehensive inquiry into patients' self-reported experiences of cognitive and neurobehavioral impairment, their understanding of the causes of impairments, and the impact of symptoms on quality of life. Furthermore, no studies have undertaken an in-depth examination of neurobehavioral symptoms in ADT patients.

To address this gap in the literature, this study was designed to explore and characterize: 1) the experience of cognitive and neurobehavioral functioning in non-metastatic prostate cancer patients undergoing ADT and compare them with those undergoing observation who had not undergone ADT; 2) the perceived causes of cognitive impairments and neurobehavioral symptoms; 3) the impact of cognitive and neurobehavioral changes upon quality of life; and 4) the strategies used to cope with or compensate for cognitive and neurobehavioral impairments. An additional objective was to assess neuropsychological performance in order to characterize the sample. Our inquiry was guided by a self-regulation framework that specifies individual cognitive attributes of a health threat and individual affective responses to a threat (Diefenbach et al., 2008). This framework identifies illness representations of identity, duration, cause, consequence and treatability of health threats and describes affective responses triggered by such representations that are associated with the formation and execution of health behaviors.

METHODS

Recruitment and Procedures

Approval was obtained by Mount Sinai's Program for the Protection of Human Subjects. Prostate cancer patients were recruited: a) from Mount Sinai Hospital in New York; and b) via listservs and advocacy groups housed online (that therefore had international reach) between August 2012 and February 2014. Informed consent was obtained from all participants.

A screening interview established that participants were men who: (1) had completed primary treatment (not ADT) for localized prostate cancer; (2) currently had prostate cancer with no nodal involvement; (3) were able to speak and read English; (4) had no active psychosis; (5) had no evidence of current substance abuse; (6) had no evidence of clinically

significant depressed mood; and (7) were not suicidal. The *ADT group* had been treated with ADT for 3 months or longer. The *Non-ADT (nADT) group* had no history of ADT.

Eligible participants were invited to the medical center to participate in a semi-structured interview, and complete a computerized assessment of cognitive functioning and questionnaires. Those who were unable to come to the hospital were given the option to participate by phone and Internet, which facilitated community recruitment. Participants received a monetary incentive of \$40.

Measures

Sociodemographic and medical information—This information was gathered directly from participants and through medical chart review and included age, race/ethnicity, level of education, cancer diagnosis, date of diagnosis, and cancer treatment.

Medical comorbidities—The self-administered comorbidity questionnaire assessed medical comorbidities (Sangha, Stucki, Liang, Fossel, & Katz, 2003).

Objective cognitive functioning—CNS Vital Signs (Gualtieri, Johnson, & Benedict, 2004), a computer-administered neuropsychological assessment battery, consisting of seven cognitive tests assessed verbal memory, visual memory, psychomotor speed, processing speed, executive functioning/cognitive flexibility, and sustained attention. Although brief (30 minutes), CNS Vital Signs is sensitive to mild cognitive dysfunction and has psychometric characteristics similar to conventional neuropsychological tests (Gualtieri et al., 2004).

Premorbid intellectual functioning—The Wechsler Test of Adult Reading was used to estimate premorbid intellectual ability (Wechsler, 2001).

Semi-Structured Interview

All interviews were undertaken by two of the authors (LW and MT) using an interview guide that mainly consisted of open-ended questions structured around cognitive and neurobehavioral changes since prostate cancer treatment (i.e., ADT for the ADT group and primary treatment for the nADT group). To limit the extent to which participants were primed to the study's aims, the consent form and an introductory question in the interview focused on overall changes to daily functioning:

I want you to think back to life before beginning ADT/before you started treatment for prostate cancer, and compare it to life now. Overall, have you noticed changes in how you function, what you can accomplish at home, at work, or wherever you are active?

A subsequent question was:

I want you to think back to life before beginning ADT/before you started treatment for prostate cancer, and compare it to life now. Overall, have you noticed changes to your concentration, thinking or memory?

Interviewers followed up on reported changes and then asked questions related to specific cognitive and neurobehavioral domains of functioning. If participants reported changes,

follow-up questions addressed how they understood the changes in terms of the time-line of their symptoms (i.e., whether symptoms pre-existed, coincided with, or followed ADT/other prostate cancer treatment); perceived cause(s) of any changes; whether family members or friends had noticed them; the perceived impact of any changes to daily functioning (i.e., work, relationships and home life); and any coping and compensatory strategies used to manage any changes. Interviewers were free to modify the wording and to use probes to elicit further information. All interviews were audio recorded and transcribed for subsequent analysis. The mean length of interview was not statistically different between groups (nADT group mean = 35.0 minutes, $SD = 18.7$; ADT group mean = 42.3 minutes, $SD = 20.7$).

Data processing and analysis

Descriptive statistics were used to characterize demographic, clinical, and neuropsychological variables in each group. Group differences were analyzed with independent *t*-tests, Mann-Whitney U tests, and Fisher's exact tests.

Neuropsychological assessments—Cognitive impairment status for each participant was determined using the International Cognition and Cancer Taskforce (ICCTF) recommendations (Wefel, Vardy, Ahles, & Schagen, 2011). Participants with scores -1.5 standard deviations (SD s) from the normative mean on two different tests and/or scores -2 SD s from the normative mean on one test were categorized as cognitively impaired. Binomial testing was used to examine whether the frequency of cognitive impairment in each group was significantly higher than normative expectations when applying seven tests. Expected frequencies were determined using curves derived from comparable binomial probability distributions (Ingraham & Aiken, 1996) showing that approximately 12.5% of a normative population could be expected to fall within the cognitive impairment category. Correlation analyses were used to explore associations between cognitive impairment and cognitive/neurobehavioral symptoms.

Qualitative interviews—Each interview transcript was compared with the audio recordings and errors corrected. The analysts (LW and MT) coded the text of interviews using NVivo 7 software (Richards, 2005). Due to the need to clarify the timeline of symptoms in relation to different treatments, it was not possible for interviewers (or analysts) to be blinded to ADT status. Thematic analysis was undertaken using a constant comparative method (Glaser & Strauss, 1967), i.e., coding the data into as many categories and subcategories as required, and refining the themes by comparing them across interviews. In general, the themes followed the content of the interview questions. Thematic saturation was determined using the principles described by Francis and colleagues (Francis et al., 2010): at least 10 interviews per group and 3 subsequent consecutive interviews yielding no new themes. Interviews were coded individually, and then the themes were discussed. Differences were reconciled between the two analysts. As new themes were created, the analysts incorporated them into earlier interviews as appropriate. There were 32 themes that fell into 4 major thematic categories and 2 additional miscellaneous themes (Table 1). If a given theme was endorsed by both analysts in a specific interview, or not endorsed by both analysts in a specific interview, this was said to indicate agreement. Based on this criterion there was 88% agreement on average across all themes.

Primary analysis of the interviews consisted of a qualitative descriptive summarization of the major themes. Quantitative analyses of the qualitative data was undertaken to explore differences between groups. The percentage of participants endorsing a given theme was calculated (Table 2). Due to the small sample size for this qualitative study, we interpreted differences of 20% or greater to indicate meaningful differences between groups (de Alba Garcia et al., 2007). Cognitive or neurobehavioral problems that were reported by a substantial proportion of participants in both groups (i.e., 30%) were also examined.

RESULTS

Participant characteristics

Table 3 summarizes the characteristics of the 20 nADT and 19 ADT participants. Two additional participants' interview data were excluded as, during the interview, they revealed histories of cognitive/neurological impairment that had not been endorsed at screening. The groups did not differ significantly in age, race, marital status, educational level, employment status, premorbid intellectual functioning, or medical comorbidities. However, as expected, time since diagnosis was greater for the ADT group (mean=9.5 years) than for the nADT group (5.6 years; $p=.03$).

Neuropsychological outcomes

Table 3 summarizes the neuropsychological outcomes of the participants. Using ICCTF criteria, 32% and 40% of the ADT and nADT patients respectively were cognitively impaired, significantly exceeding normative expectations of 12.5% (binomial test: $p<.01$ and $p=.02$, respectively). There were no between-group differences on cognitive impairment status nor number of impaired cognitive tests, and there was no association between the cognitive impairment status and total number of cognitive problems reported ($r=-.16$, $p=.36$).

Cognitive changes that differed by group

The number of different cognitive problems reported by ADT patients ($Mdn=4$) was marginally greater than in the nADT group ($Mdn=3$) ($U=123.50$, $z=-1.90$, $p=.06$, $r=-0.30$). The ADT group reported problems in prospective memory and multi-tasking more frequently than the nADT group.

Prospective memory—Prospective memory – the ability to remember to execute a planned action in the future (Lezak, Howieson, Bigler, & Tranel, 2012) – was a more prevalent problem in the ADT group (74%) than in the nADT group (50%). One ADT patient stated the following:

I do forget things...I go to do something and then I stop and say, "What am I supposed to be – why am I here? What was I supposed to do?"

A nADT patient said:

Keeping appointments for doctors...if I don't write it down, oh my. Last week I missed two big appointments with friends of mine...because I didn't write it down and I didn't look at the calendar.

Multi-tasking—Multi-tasking – the prioritization, organization and execution of a number of different tasks within a given period (Burgess, Veitch, de Lacy Costello, & Shallice, 2000) – differed between groups. Thirty-two percent of the ADT patients reported declines in multi-tasking compared with 5% in the nADT group. Such reports tended to be mild in nature. An ADT patient said:

I used to be able to juggle four or five things at once and I'm finding if I do, I tend to forget things [now]...I put the garbage bag together, took it out and then got a phone call and forgot to put a new garbage bag in...It's something that is sort of new that's happening more and more.

Cognitive changes shared by ADT and nADT patients

A number of cognitive domains were reported to have declined by both groups in approximately equal proportions.

Retrospective memory—Retrospective memory – the ability to remember information from the past (Baddeley, Eysenck, & Anderson, 2009) – was a notable area of decline for both ADT (84%) and nADT patients (65%) and trended toward being greater among ADT participants. One ADT patient said:

I forget things more often now, where the car is parked, where I put my keys, where I put my glasses...You could ask me what I had for breakfast today. I'd have to really think to remember.

ADT patients were often made aware of the changes to their memory by family members:

You don't always notice that you're forgetful...my wife reminds me that I said certain things. I say, "I didn't say that" and she says, "Oh yes you did."

A nADT patient said:

I'm just more forgetful I guess. Somebody will say something to me and I'll forget about it.

Attention and concentration—More than half of the participants in both the ADT (58%) and nADT groups (55%) reported declines in attention (i.e., the ability to select target information from an array for enhanced processing) and concentration (i.e., the ability to sustain attention over time) (Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991) in innocent daily activities and in more hazardous activities. One ADT patient said:

I was working when I went on hormone therapy. I've noticed that...I'm a machinist by trade...I'm having trouble keeping my mind on what I was doing...When I was machining a piece of steel I would lose concentration and I lost my plan of what I was going to do with the steel and I had to scrap a couple pieces and that was disconcerting.

nADT patients also reported attention and concentration problems since their primary treatment:

I'll be doing something on the computer and just don't do it. I get distracted, start looking at the TV or just staring off into space at times.

Information processing—Almost half of the participants in both the ADT (47%) and nADT groups (45%) reported declines in information processing (i.e., the brain's ability to interpret sensory information and process it in an integrated way) (Ollendick & Schroeder, 2003). Such problems affected innocent daily life activities and hazardous ones. One nADT patient said:

Things are slower to react to. It takes time to understand listening things or oral things clearly. As a result, I'll react to an email or whatever, quickly but incorrectly, because I haven't really absorbed it.

Visual information processing problems were also reported. An ADT patient said:

We were driving...and my wife and my son and my daughter were all yelling at me because there was a lady in the crosswalk and I did not see her. So my wife says, 'You're getting dangerous!'

Neurobehavioral changes that differed by group

Although the number of different neurobehavioral problems reported by ADT patients ($Mdn=2$) was not significantly different from the nADT group ($Mdn=1$) ($U=140.00$, $z=-1.44$, $p=.17$, $r=-0.23$), two domains differed by group (i.e., emotional lability and impulsivity).

Emotional lability—Emotional lability – one form of disinhibition that includes unpredictable mood changes, low frustration tolerance, irritability, and depressed mood – worsened in more ADT patients (74%) than nADT patients (45%) (Kocka & Gagnon, 2014). Notably, ADT patients commonly attributed this symptom to ADT:

Not only am I crying more often, I feel slightly emotionally unstable and it's only since taking the three pills at once (Casodex)...the instability was like aspects of feeling depressed and it's surprising because I am someone who never really gets depressed...sometimes it's all the time and then all-of-a-sudden it will go away, and then 6 hours later, it will come back. I don't know why.

Such changes were often observed by family members. For example:

I've noticed with [the medication, I'm] more easily down or discouraged. My wife is helpful with that. [She'll say], 'It's the medication. It's not the end of the world. What's our priority? Us.'

Emotional lability manifested similarly among nADT patients, but they tended to attribute it to the life-changing experience of the cancer and its treatment:

I'm probably more emotional [since the treatment]...I cry more easily for sure. I think maybe just the...intrusion into my pelvis makes me very...it's an upsetting thing.

Impulsivity—Impulsivity – another aspect of disinhibition that manifests as acting without preconsideration, or acting too quickly (Kocka & Gagnon, 2014) – increased more frequently in the ADT group (37%) than the nADT group (10%). ADT patients described situations where they were more impatient or swore more than they used to:

I'm very impatient. I mean, I used to be impatient, but now I'm worse. When I'm talking to somebody, I just kind of can't wait to jump in.

I have to catch myself more than I used to in cursing.

Neurobehavioral changes shared by ADT and nADT patients

Apathy—The neurobehavioral form of apathy – a quantitative reduction of self-generated voluntary and purposeful behaviors (Levy & Dubois, 2006) – worsened in both groups in approximately equal numbers (37% of ADT and 40% of nADT patients). One ADT patient said:

I'm not talking about tiredness, but maybe a feeling of not being bothered...you want to do something that's just not happening.

nADT patients also described this phenomenon:

There's no lack of ability. It's just sometimes there's a lack of will to go to the car for no apparent reason.

Perceived causes of cognitive and/or neurobehavioral changes

All participants who experienced increased cognitive or neurobehavioral symptoms were referred back to their reported problems and asked: *What do you make of these changes? What do you think might have caused them?*

More ADT (47%) than nADT patients (17%) cited multiple causes and/or were uncertain about the cause of the changes. Aging was cited most often as a possible cause for the declines in ADT and nADT patients (79% and 78% respectively). A majority of ADT patients (74%) attributed declines to ADT, whereas a small number of nADT patients (17%) attributed declines to their primary cancer treatment. An example of how an ADT patient reported multiple causes is as follows:

I don't know if it's just me getting older and being retired or if it's medication. I don't know if it's the hormone. I don't know if it's the blood pressure medication... I don't know if they're all playing into this or if it's just me.

Close to 50% of ADT patients cited lifestyle changes, particularly retirement, as a reason for cognitive declines. One ADT patient said:

[During] retirement...you don't care about things as much as you used to because you don't have to. Therefore, if you don't have to remember things, you don't.

Illness-related stress was also cited as a possible cause by approximately 40% of both groups. For example, one ADT patient said:

...I'll read a paragraph and have to go back and read it again and read it again...I was pretty preoccupied with [being told of cancer recurrence]..., so that interfered with my ability to concentrate on other things.

Impact on quality of life

Of the participants who reported declines in cognitive or neurobehavioral functioning, 42–47% of ADT and 33–39% of nADT participants reported that the declines impaired daily life functioning and relationships. Both groups phrased their experiences similarly referring to a general inefficiency or slowing down. The ADT patient who had, as told before, lost concentration whilst machining a piece of steel reported that the impact on his work caused him to retire:

I realized I wasn't going to be able to do that type of work for much longer...I wasn't as good of an employee as I was before that, so I figured it was time to retire. It wasn't a traumatic experience – I was ready to retire.

Another ADT patient summed up the broad impact of ADT on his life:

Life was more fluid and easier before...certain things have become much more difficult...from the time it takes me to type, to being able to stay with reading something, to stay[ing] focused on my wife..., to having these emotions coming around all the time, my physical strength is much less...Life is not as easy.

Most nADT patients referred to the negative impact of reduced stamina, fatigue and concentration as impediments to task efficiency. For example:

I'm not as productive. I'm not getting as many things done.

Patients also talked about the impact of changes upon their relationships. An ADT patient described how emotional lability and memory problems affected his interactions:

People get annoyed with me more than they used to... Because of being abrupt or...when people tell you to do something, like the washing machine stops, take the clothes out, put them into the dryer, and you forget to do it, they get annoyed at you.

A nADT patient described how information processing difficulties affected his relationships:

It was very difficult to interact with people. All I could do was get through the workday...Even getting together with people for drinks after work was very difficult...taking in information and interacting normally with people was very difficult for me.

More ADT patients (74%) reported feeling distressed by their cognitive and neurobehavioral changes than nADT patients (44%; $p=.05$). One ADT patient said:

It's upsetting to me...nobody wants to lose their memory. You know it bothers me. Am I eventually going to go into Alzheimer's, or something, you know?

When participants attributed problems to aging, their reactions tended to be mild in nature:

It's frustrating, and I think it can be embarrassing...not being able to maintain a conversation cleanly instead of fits and starts. But again, it just happens because you're getting older and sort of accept it and go on.

Notably, reports of distress regarding these changes were not significantly correlated with the neurobehavioral phenomenon of emotional lability ($r=.24$, $p=.13$).

Coping and compensatory strategies

A majority of participants (72% in the nADT group; 95% in the ADT group) reported using compensatory strategies for reported cognitive or neurobehavioral declines. To ameliorate cognitive problems, most used strategies such as writing things down or recording appointments in a calendar. Other strategies included "going through the alphabet" to help retrieve names; mental exercises such as using online brain training programs or doing Sudoku puzzles; and, in the face of cognitive failures, deferring tasks to a later time point. Cognitive problems were also managed with exercise, rest or sleep/naps, and improved diet. With respect to neurobehavioral problems, participants managed emotional lability by avoiding situational triggers, meditation, mindfulness-based stress reduction, listening to music, and letting others take over stress-inducing tasks.

DISCUSSION

Overall, ADT patients reported marginally more cognitive problems than nADT patients even though there were no significant differences between the groups in their neuropsychological performance. ADT patients reported more declines in prospective memory and multi-tasking than nADT patients. Significant proportions of participants in *both* groups reported retrospective memory, attention and concentration, and information processing declines affecting both benign daily tasks and more hazardous activities, such as driving. With respect to neurobehavioral symptoms, more ADT patients reported emotional lability and impulsivity (both aspects of disinhibition) than nADT patients.

Among the cognitive problems, the greatest difference between groups was in prospective memory, and to a lesser extent in multi-tasking – both domains that are difficult to validly measure using standard neuropsychological tests. For cancer patients who must take medications and keep medical appointments regularly, or who simply need to work effectively, prospective memory impairment can significantly diminish one's ability to accomplish these activities. To the best of our knowledge, there is only one study that assessed prospective memory in ADT patients (Yang, Zhong, Qiu, Cheng, & Wang, 2015). Our findings corroborate their results that showed that ADT patients performed more poorly on a prospective memory task than nADT patients. Multi-tasking is also a skill that can affect daily life tasks, such as talking on the phone whilst cooking or the accomplishment of multiple work tasks that compete for a person's attention. Since both prospective memory and multi-tasking are cognitive areas not easily assessed with standard neuropsychological tests, self-report may be an important method by which impairments to these skills can be detected.

Neurobehavioral symptoms, though common among individuals with neurological impairment and mild traumatic brain injury (e.g., Mathias & Coats, 1999), have rarely been examined in cancer patients. Only recently has the existence of such symptoms been reported in cancer patients by our team (Wu et al., 2014). In the present study, the neurobehavioral symptoms of emotional lability and impulsivity (both aspects of disinhibition) were reported by significantly more ADT than nADT patients. Emotional lability was the most prominent neurobehavioral symptom for ADT patients (74%). Though there is some overlap between emotional lability and emotional distress, emotional lability was characterized in our data by a) greater emotional amplitude than previously, i.e., patients reported feeling low moods that were lower than before treatment, b) emotionality or irritability that would come out-of-the-blue without any apparent trigger, or c) emotionality that was more pervasive, i.e., triggered by events/things that would not have been triggers in the past. Emotional distress was anxiety or depressed mood that tended to be linked to the individual's illness, quality of life changes, and/or specific life stressors. Impulsivity was another neurobehavioral symptom that was noted to have increased by a greater proportion of ADT patients (37%) than nADT patients (10%). Apathy was a symptom shared by approximately 40% in both groups.

Although the neurobehavioral symptom of emotional lability is already, to some extent, evident in the prostate cancer literature (e.g., Cherrier, Aubin, & Higano, 2009; Donovan, Walker, Wassersug, Thompson, & Robinson, 2015; Gomella, 2007), it has not been described as a symptom with neurological underpinnings, nor distinguished from depressed mood. Instead, it has been referred to as a "psychological effect" (Gomella, 2007) or a change to "social cognition" (Donovan et al., 2015), though it is perhaps more accurately characterized as a neurobehavioral symptom. Indeed, disinhibition in general (emotional lability and impulsivity) may be confused with depression, personality disorder, or hypomania (Butler & Zeman, 2005). Similarly, apathy can be mistaken for depressed mood or fatigue (Lane-Brown & Tate, 2010; Levy et al., 1998). Understanding the unique characteristics and etiology of these neurobehavioral symptoms is important for determining appropriate interventions to treat them should they occur. Our guiding self-regulation framework (Diefenbach et al., 2008) is also helpful in identifying the interplay between cognitive representations of symptoms and negative affect. For example, if a patient perceives that ADT is the cause of his symptoms, this might trigger more distress than if he attributed the symptoms to aging, especially if he does not see cancer treatment as an expected, normal experience in life. Increased distress could, in turn, trigger an increase in health behaviors.

Overall, for all participants, aging was the most common cause to which cognitive or neurobehavioral symptoms were attributed indicating a tendency to normalize these changes. Among ADT patients, ADT was the primary treatment-related cause of their increased cognitive and neurobehavioral symptoms. However, only a small minority of participants in the nADT group attributed symptoms to their primary prostate cancer treatment. Hence, ADT appeared to have a greater perceived impact on symptoms than other prostate cancer treatments, though it is notable that ADT patients were also more uncertain about the primary or exact cause of their symptoms. Lifestyle changes (such as retirement) and illness-related stress were also important causes reported by participants. The diversity of

attributions is not surprising given that they parallel research that points to considerable overlap in the underlying biological risks and pathways for the development of cancer, cancer-related cognitive decline, and aging processes (Mandelblatt et al., 2013).

Between 30% and 47% of participants in both groups who had reported increased cognitive and/or neurobehavioral symptoms experienced problems in daily life functioning and relationships as a result of their symptoms. The negative impacts ranged from decreased efficiency in accomplishing benign tasks to problems with more hazardous tasks such as operating machinery or driving a car. Relationships were also affected; participants reported difficulties interacting with people due to diminished cognitive or neurobehavioral capacities (e.g., difficulty taking in a conversation), and changes in how people reacted to them because of those symptoms (e.g., loved ones getting annoyed with participant's forgetfulness). These results corroborate findings from other studies that have highlighted the deleterious impact of self-reported cognitive impairments on quality of life (e.g., Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Wu et al., 2012).

Although the ADT group tended to report a greater number of cognitive problems than the nADT group, there were no differences between groups on cognitive impairment status measured by neuropsychological tests. The purported association between prostate cancer and cytokine levels (Salman, Ori, Bergman, Djaldetti, & Bessler, 2012), and, between cytokine levels and neuropsychological performance (Ahles & Saykin, 2007) may partly explain this finding. Data suggest that ADT patients do not have elevated levels of pro-inflammatory cytokines compared with age and disease matched controls (Maggio et al., 2006), which may explain why neuropsychological performance did not differ between groups. With respect to the discrepancy between self-report of cognitive problems and neuropsychological test scores, this is consistent with the literature; most studies fail to find an association between objective and self-report measures of cognitive functioning (Hutchinson et al., 2012). Possible reasons for this discrepancy include: i) self-reported cognitive impairment may represent psychological distress more than cognitive functioning (Hutchinson et al., 2012); ii) self-reported symptoms may be an early indicator of later cognitive dysfunction (Kryscio et al., 2014); and iii) neuropsychological tests may not be sufficiently sensitive to detect cognitive impairments that some cancer patients experience (Jansen, Miaskowski, Dodd, & Dowling, 2007). In any case, patients' perceptions of cognitive problems are important due to their significant impact on quality of life.

More ADT patients were distressed by increased cognitive and neurobehavioral symptoms than nADT patients, though when patients attributed their problems to aging, their distress tended to be less severe perhaps because aging is a "normal" phenomenon that is easier to accept. This finding highlights the importance of understanding patients' causal attributions of symptoms, as they can influence how well people cope with changes.

Most participants in each group reported using strategies to ameliorate cognitive and/or neurobehavioral declines. The types of strategies patients used to manage cognitive problems included compensatory strategies, restitution strategies, and behavioral/lifestyle changes. A primary strategy for the management of neurobehavioral problems, particularly emotional lability, was building an awareness of when the problem was likely to arise and

then working to remain calm or avoid conversations that might trigger the emotionality. Interestingly, the strategies used by the participants in large part have an evidence base (Cattalani, Zettin, & Zoccolotti, 2010; Chambers, Gullone, & Allen, 2009; Cicerone et al., 2005; Dauncey, 2014; Hillman, Erickson, & Kramer, 2008; Walker, 2009).

This study contributes to the literature in numerous ways. First, unlike many qualitative studies, our case-control design facilitated comparisons between ADT and nADT patients. Second, the mixed methods approach enabled us to quantitatively characterize the cognitive performance of each group and to undertake an in-depth qualitative examination of self-reported cognitive changes. Third, the results corroborate research indicating that ADT impacts neurological and cognitive functioning (Kumar, Barqawi, & Crawford, 2005; McGinty et al., 2014). Fourth, the examination of neurobehavioral symptoms allowed us to uncover emotional lability and impulsivity as key symptoms that distinguished ADT patients' experiences from that of nADT patients'. Fifth, the qualitative approach enabled us to assess the presence of symptoms that are difficult to detect through neuropsychological assessment (i.e., prospective memory and multi-tasking). Sixth, the interviews provided rich information about the specific ways in which cognitive and neurobehavioral symptoms impacted patients' quality of life. Finally, the interviews indicated that the patients evolved a number of strategies to ameliorate cognitive and neurobehavioral symptoms that may also guide treatment recommendations.

Limitations

The findings need to be considered in the context of a few important limitations. First, the expected difference between the two groups on time since diagnosis (which was significantly greater in the ADT group than the nADT group) may be a confounder of the results. For example, the higher frequency of cognitive problems reported in the ADT group may be related to cancer recurrence. Second, most of the sample was Caucasian and highly educated, thus limiting generalization of findings to other groups. Third, since the interviewers/analysts were unable to be blinded to group condition, demand characteristics may have implicitly biased the interviews and ratings. Finally, the ADT group interviews lasted, on average, longer. This difference may have given them an opportunity to verbalize more symptoms; on the other hand, the larger number of symptoms may have necessitated longer interviews.

Conclusion

Understanding the nature of ADT patients' cognitive impairments and neurobehavioral symptoms is important for differential diagnosis from other age-related or disease processes (e.g., mild cognitive impairment, dementia), especially since testosterone loss is also associated with aging (Davidson et al., 1983; Vermeulen, 1991), and low testosterone levels are a risk factor for mild cognitive impairment (Cherrier, Anderson, Shofer, Millard, & Matsumoto, 2015). In addition, knowledge that such problems impair ADT patients' quality of life in substantial ways ought to shape future research into these problems. Further investigation is required, particularly for increasing our understanding of the lesser known cognitive and neurobehavioral problems, such as prospective memory, emotional lability, and personality changes that may be associated with ADT. In addition, the development or

application of appropriate interventions to ameliorate cognitive impairments and neurobehavioral symptoms are warranted. Numerous potential interventions have been examined so far, including cognitive rehabilitation (both compensatory approaches and computerized cognitive training), meditation, exercise, neuromodulation, and pharmacologic agents, but further research is still required as findings continue to be preliminary and limited to few cancer populations, most commonly breast cancer (Von Ah, Jansen, & Allen, 2014; J. S. Wefel, Kesler, Noll, & Schagen, 2015).

Acknowledgments

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Numbers #5R03CA165827-02 and #7K07CA184145-02. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We also thank Krista Herbert, M.A. for her assistance with data management.

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RESEARCH HIGHLIGHTS

- Examined prostate cancer patients on androgen deprivation therapy versus observation.
- Undertook mixed methods study of cognitive impairment and neurobehavioral symptoms.
- Investigated experiences and perceived causes of these symptoms.
- Examined the impact of these symptoms on quality of life.
- ADT patients were more vulnerable than non-ADT patients to these symptoms.

Table 1

Major themes from the qualitative analyses

Cognitive changes	Neurobehavioral changes
<ul style="list-style-type: none"> • Attention/concentration • Taking in information • Expressive language • Remembering things • Prospective memory • Getting the main idea of something • Problem-solving • Decision-making • Multi-tasking • Organizing/planning activities • Other Cognitive 	<ul style="list-style-type: none"> • Neurofatigue • Initiation • Task completion • Impulsivity • Emotionality • Interpersonal style • Personality change • Other neurobehavioral
<i>Attribution of changes</i>	<i>Impact on well-being</i>
<ul style="list-style-type: none"> • External stress • Physical symptoms • Aging • Illness-related stress • ADT • Other PC treatment • Lifestyle change • Uncertainty about attribution • Other attribution 	<ul style="list-style-type: none"> • Impact on functioning/quality of life • Impact on relationships • Distress about cognitive/neurobehavioral changes • Distress about illness
	<i>Miscellaneous codes</i>
	<ul style="list-style-type: none"> • Feedback from others • Strategies

Table 2

Differences between nADT and ADT patients

	nADT(%)	ADT(%)	Difference 20% between groups
<i>Cognitive decline</i>			
Attention and concentration	55	58	
Information processing	45	47	
Verbal fluency	15	26	
Memory (general)	65	84	
Memory (prospective)	50	74	Yes
Main idea	5	21	
Problem solving	10	21	
Decision making	10	16	
Multi-tasking	5	32	Yes
Organizing and planning	5	16	
Other cognitive decline	5	21	
<i>Neurobehavioral decline</i>			
Neurofatigue	30	16	
Apathy	40	37	
Task completion	15	16	
Emotional lability	45	74	Yes
Impulsivity	10	37	Yes
Interpersonal style/personality change	20	37	
<i>Perceived cause(s)</i>			
External stress	17	16	
Physical symptoms	28	11	
Aging	78	79	
Illness-related stress	39	42	
ADT	n/a	74	
Non-ADT prostate cancer treatment	17	11	
Most recent PC treatment (i.e., ADT or primary treatment)	17	74	Yes
Lifestyle change	28	47	
Uncertain/multiple causes	17	47	Yes
Other cause	22	26	
<i>Use of strategies</i>	72	95	Yes
<i>Impact on well-being</i>			
Daily life functioning	33	47	
Relationships	39	42	
Distress about cognitive/neurobehavioral decline	44	74	Yes

Table 3

Demographic, clinical and neuropsychological characteristics of participant groups.

Characteristic	Non-ADT group (n=20)		ADT group (n=19)		p value
	M(SD)	n(%)	M	n(%)	
Demographics					
Age (years)	67.5(7.1)		70.0(7.2)		.29
Race					
Caucasian		16(80.0)		19(100.0)	.11
Non-Caucasian		4(20.0)		0(0.0)	
Marital status					
Married or cohabitating		15(75.0)		17(89.5)	.41
Not married		5(25.0)		2(10.5)	
Educational level					
Less than a college degree		5(25.0)		5(26.3)	1.00
College degree or higher		15(75.0)		14(73.7)	
Employment status					
Employed		11(55.0)		7(36.8)	.34
Retired or semi-retired		9(45.0)		12(63.2)	
Clinical characteristics					
Time since diagnosis (years)	5.6(4.3)		9.5(6.2)		.03*
Prostate cancer treatment(s) ^a					
Surgery only		12(60.0)		3(15.8)	}
Surgery followed by radiation		0(0.0)		11(57.9)	
Brachytherapy		6(30.0)		1(5.3)	
External beam radiation therapy (EBRT)		1(5.0)		4(21.1)	
EBRT and brachytherapy		1(5.0)		0(0.0)	
ADT medications					
Leuprorelin and bicalutamide				7(36.8)	
Leuprorelin				6(31.6)	
Bicalutamide				2(10.5)	

Characteristic	Non-ADT group (n=20)		ADT group (n=19)		p value
	M(SD)	n(%)	M	n(%)	
Other combinations				4(21.1)	
Medical comorbidities ^b	4.7(4.1)		4.6(4.8)		.93
Neuropsychological outcomes					
Premorbid intellectual functioning ^c	113(15.7)		115(11.2)		.63
Cognitively impaired ^d		8(40.0)		6(31.6)	.74
Number of impaired tests (-1.5 SD below mean)	0.8(1.2)		0.6(.96)		

^aIn order to test whether there was an observed difference in the frequency of specific prostate cancer treatments between groups, the prostate cancer treatment variable was dichotomized into those who had surgery vs. those who had not;

^bSelf-administered Comorbidity Questionnaire scores;

^cWechsler Test of Adult Reading standard score;

^dbased on neuropsychological assessment using International Cognition and Cancer Taskforce criteria for cognitive impairment;

* significance level $p<.05$.