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Altered Cognitive Function in Men Treated for  
Prostate Cancer with LHRH Analogues and Cyproterone Acetate: A Randomised  
Controlled Trial

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Short Title: COGNITIVE CHANGES WITH HORMONAL MEDICATION

Objective. Luteinising hormone releasing hormone (LHRH) analogues have been associated with memory impairments in women using these drugs for gynaecological conditions. This is the first systematic investigation of the cognitive effects of LHRH analogues in male patients.

Methods. 82 men with non-localised prostate cancer were randomly assigned to receive continuous leuprorelin (LHRH analogue), goserelin (LHRH analogue), cyproterone acetate (steroidal antiandrogen) or close clinical monitoring. These patients underwent cognitive assessments at baseline and before commencement of treatment (77) then 6 months later (65).

Results. Compared with baseline assessments, men administered androgen suppression monotherapy performed worse in 2/12 tests of attention and memory. 24/50 men randomised to active treatment and assessed 6 months later demonstrated clinically significant decline in one or more cognitive tests but not one patient randomised to close monitoring showed a decline in any test performance.

Conclusion. Pharmacological androgen suppression monotherapy for prostate cancer may be associated with impaired memory, attention and executive functions.

KEY WORDS: LHRH, cognition, prostatic cancer, adverse drug reactions, quality of life

## Introduction

Luteinising hormone releasing hormone (LHRH) analogues are used to produce “reversible” chemical castration in both genders. In women, these drugs reduce oestrogen (E) for treatment of gynaecological disorders. In men, the testosterone (T) reducing effect is indicated for management of non-localised prostatic carcinoma. Research regarding how these treatments affect quality of life has the potential to guide clinical decisions such as the timing and nature of treatment.

Accumulating evidence suggests that LHRH drugs can adversely influence cognitive functions such as memory and attention. Research studies have found 6-56% of women treated with an LHRH analogue reported memory problems (1-3). Furthermore, female patients whose verbal memory performance decreased while taking leuprorelin returned to normal performance when E was administered with leuprorelin (4). In contrast, women randomised to receive placebo with leuprorelin continued to show impaired performance (4).

Cognitive effects of these drugs in male patients have not been investigated previously. One anecdotal report described delirium, ataxia, amnesia, fluctuating consciousness, incontinence and impaired concentration in a 68 year-old man treated with goserelin injections. His symptoms improved when goserelin was ceased (5). Other studies have shown that deficits in either T or E are associated with reduced cognitive performance (6-8). Also, T supplementation in hypogonadal men has been found to enhance spatial performance (9) and verbal fluency (10) although null effects on cognitive performance have been reported (11). LHRH injections also improved verbal fluency performances of normal healthy men aged 18-35 (12). Since LHRH analogues initially increase LH and T through the well-known ‘flare-effect’ before downregulating them, this short-term improvement is consistent with the potential for impairment during long-term administration.

The aim of this study was to test whether LHRH analogues were associated with cognitive impairment in men. Men with advanced prostate cancer were randomly assigned to one of 4 arms: a steroidal anti-androgen, two LHRH analogues and close clinical monitoring. Blinded neuropsychological assessment was performed before and during treatment at 6 months. It was hypothesised that men receiving LHRH analogues (leuprorelin or goserelin) would show differential deterioration in cognitive performance compared with men treated with progestogen (cyproterone acetate) or those randomised to close clinical monitoring (Hypothesis 1). Because cognitive impairments were previously found only on verbal memory tasks in women, the greatest cognitive impairment was expected to be with measures of memory (Hypothesis 2).

## Methods

### Participants

Men with non-localised prostate cancer, for whom palliative treatment by hormonal manipulation was considered optional, were eligible to participate. Exclusion criteria were previous hormonal therapy, psychiatric impairment, severe lower tract symptoms (International Prostate Symptom Score > 7), or abnormal serum T. Eighty-two men agreed to participate and gave written consent, 77 were tested at baseline and 65 (56-86 years; mean [M] = 73.3; standard deviation [SD] = 6.4) attended for assessment at 6 months. Demographic characteristics are shown in Table 1. Patients were recruited through collaborating urologists and radiotherapists. All participated voluntarily and received no financial benefit. Local transport costs for session attendance were paid for some participants.

Insert Table 1 about here

### Measurement Instruments

All tests chosen are well-established tools that are used routinely in neurocognitive assessment.

Memory was assessed using Visual and Verbal Memory Indices from the Wechsler Memory Scale – Revised (WMS-R) (13), the sum of words recalled from 5 list-learning trials of the Auditory Verbal Learning Test (AVLT) (14), and 30-minute delayed recall in the Rey-Osterrieth Complex Figure Test (14, 15).

Attention was assessed by the Attention and Concentration Index from WMS-R (13); Digit Symbol, a coding task from the Wechsler Adult Intelligence Scale – Revised (16); time on the Trail Making Test Parts A and B (14); and the sum of three one-minute trials of the Controlled Oral Word Association Test (COWAT) (14).

Executive function was measured with the “Victoria” version of the Stroop Test, in which ink colours are named as quickly as possible for (a) neutral words, and (b) words that are colour names (15); and the copy trial of the Rey-Osterrieth Complex Figure Test (14).

Intelligence Quotient (IQ) was estimated with a four-subtest short form of the Wechsler Adult Intelligence Scale – Revised (17-19).

Mood was assessed by the total score on the Depression Anxiety Stress Scales (DASS-21), in order to rule out an indirect effect on cognition through emotional distress (20).

General health was assessed as the number of illnesses other than prostate cancer. All serious illnesses, injuries and operations reported by participants were recorded at baseline interview (current illnesses) and over the participant’s lifetime (past illnesses).

### Procedure

When patients were referred, a research nurse obtained informed consent and then randomly allocated participants to one of the four management groups using a table generated by computer before study enrolments began. Patient compliance was observed through periodic serum assays of T and prostate specific antigen (PSA). A

clinical psychologist, blinded to the individual patient's management group, conducted cognitive and psychosocial assessments. Assessments took place after randomisation and one week before treatment and 6 months later. Since other pharmaceuticals as well as 'over the counter' preparations have potential to affect cognition, these were comprehensively documented upon entry to the trial and again at 6 months. The research was approved by university and hospital ethics committees.

### Statistical Analysis

To determine whether there were differences in how the groups changed over time, repeated measures Group (4) x Time (2) Analyses of Variance (ANOVAs) were conducted on the serum, cognitive and emotional distress measures. Confidence intervals (95%) were computed for each group for the differences between Time 2 and Time 1 scores. A measure of "clinical significance", the Reliable Change Index, was used to more closely examine individual results and identify clinically significant cognitive changes (21, 22). This measure compares an individual's change in score to the variability that would be expected, calculated from the variance of the sample at baseline and test-retest reliability.

### Results

One-way ANOVA showed that baseline measures of age, years of education, estimated IQ, PSA, T, and number of current or past illnesses did not differ among the 4 groups. Of 77 participants tested at baseline, 12 were unavailable at 6 month follow-up. Reasons for withdrawal were death (2 men assigned to cyproterone), illness associated with treatment (3 cyproterone), worsening of cancer (1 leuprorelin and 3 monitoring), changed treatment decision (1 cyproterone), and refusal (1 cyproterone, 1 monitoring). Deaths occurred in an 81 year-old man with multiple metastases, 4 months after beginning cyproterone, and in a 72 year-old man from liver failure, 2 months after beginning cyproterone. Adverse reactions necessitating treatment withdrawal occurred

in 3 men assigned to cyproterone, each of whom developed fatigue but recovered fully once cyproterone was stopped. One of these men additionally developed depression that improved but did not fully resolve when the medication was stopped.

T-tests showed that participants lost to follow-up did not differ significantly from participants who attended Time 2, in baseline measures of age, education, IQ, PSA, T, and number of current or past illnesses. Therefore, the participants who were lost to follow-up were considered a random sample of baseline participants and their data were not analysed further.

A further 20% of participants were unable or unwilling to complete all cognitive tasks. A combination of missing data replacement procedures was used, to retain as much information as possible about the individual participant (23). When possible, missing data from WMS-R indices were replaced with regression from completed items of the index. If no items were completed but there was a score at the other time point, the score at the other time was used. If the score was unavailable at both time points, a regression procedure (expectation-maximisation from the Statistical Package for the Social Sciences [SPSS]) was used to estimate the score from the participant's scores on other measures at that time point. The small amount of missing data from PSA and testosterone measures was replaced with the group mean at that time point, consistent with accepted practice in such circumstances (23).

Serum measures. Because PSA showed strong positive skew, a logarithmic transformation was used. As expected, there were significant Group x Time interactions for both  $\log_{10}$  of PSA,  $F(3, 61) = 18.21, p < .001$ , and testosterone,  $F(3, 61) = 9.11, p < .001$ . The interaction occurred because each of these measures decreased significantly at Time 2 for the 3 hormonally treated groups,  $p < .001$ , but did not change for the close monitoring participants. Time 1 testosterone values are shown in Table 1; Time 2 means (and standard deviations) were leuprorelin 2.1 (4.9), goserelin 3.7 (5.7),



cyproterone acetate 3.6 (2.5) and close monitoring 15.3 (5.5). Time 2 PSA means and standard deviations were 2.8 (3.9), 6.5 (13.5), 3.8 (4.8) and 34.1 (19.9) respectively.

Cognitive performance within groups. Table 2 shows the performance data for the measures of memory, attention and executive functions. Overall Time 1 means and standard deviations are provided in conjunction with the 95% confidence intervals for the differences in scores between Time 2 and Time 1. Confidence intervals that are symmetric around zero indicate no trend towards increased or decreased performance. For most measures, higher scores indicated better performance. The exceptions were timing scores (Trails A, Trails B, Stroop Neutral Words and Stroop Colour Words) for which a higher score represented a longer time taken (worse performance).

Insert Table 2 about here

The confidence intervals for the close monitoring group, in Table 2, showed that on most tasks this group maintained or increased its mean performance at Time 2 compared with Time 1. This was particularly evident for the WMS-R Verbal Memory measure, for which there was a 95% probability that the true increase in scores in patients in the relevant population was in the range 4.3-16.2. For patients in the hormonally treated groups, some confidence intervals were symmetric around zero, some suggested improved performance, and some suggested decreased performance. In particular, the patients treated with goserelin had confidence intervals that suggested improved performance at Time 2 on the WMS-R Verbal Memory and Visual Memory measures, but decreased performance on the AVLT measure of verbal memory.

Group comparisons were also made using ANOVA. There was a significant Group x Time interaction for the verbal memory task, AVLT,  $F(3, 61) = 4.26$ ,  $p = .008$ . The interaction is shown in Figure 1a. Simple effects showed decreased performance at Time 2 for men assigned to goserelin,  $F(1, 61) = 5.01$ ,  $p = .029$ , and improved performance at Time 2 for men assigned to cyproterone,  $F(1, 61) = 4.92$ ,  $p = .030$ .

Patients assigned to leuprorelin or close monitoring showed no mean change over time on this task. There was also a trend to a Group x Time interaction for Trails B, measuring complex visual scanning and motor performance,  $F(3, 61) = 2.51, p = 0.067$  (see Figure 1b). The leuprorelin group was significantly slower at Time 2 than at baseline,  $F(1, 61) = 6.66, p = .012$ , whereas other groups did not change their scores.

Insert Figure 1 about here

Cognitive performance within individuals. The difference between the Time 2 and Time 1 score on each measure was computed for each individual and compared with the Reliable Change Index. This Index calculates the minimum change in scores that is considered to be clinically significant. The cut-off change scores using the Reliable Change formula (.05, 1-tailed) are shown in Table 2. Table 3 shows the proportion of individuals with clinically significant decreases at Time 2 compared with their own baseline scores. 24/50 men on active treatments showed a reliable decline on at least one cognitive task and 7/50 showed a reliable decline on 2 or more tasks. Decreases were observed only in men on hormonal treatments. The higher frequency of cognitive deterioration in androgen ablation groups was statistically significant,  $\chi^2(3) = 11.70, p < .01$ .

Insert Table 3 about here

Mood. To check for differential treatment effects on mood, an ANOVA was performed with total DASS score as the dependent variable. All groups had mean DASS scores in the normal range at both baseline and Time 2. There were no significant Group, Time or Group x Time effects on total DASS score. This indicated that cognitive changes were not associated with mood changes.

### Discussion and Conclusions

This is the first published study to investigate cognitive effects of LHRH analogues in male patients. Cognitive changes were demonstrated to differ among

randomly assigned groups. Individuals who showed a reliable decline in cognitive performance came only from hormonally treated groups with approximately 50% of patients having a clinically significant change in one or more parameters assessed at 6 months. Testosterone levels in sera remained the same for patients on close monitoring, but showed the expected decreases for patients on androgen suppressing treatments. One patient received only one leuprorelin injection. The pattern of results was the same with or without this patient included, so his data were retained to maintain analyses on an “intention-to-treat” basis (24).

These findings partially support Hypothesis 1, that there would be differential deficits in cognitive function shown by men randomised to LHRH analogues. Both LHRH treatments were associated with decreased cognitive function. However, cyproterone was also associated with decreased performance. This drug has different mechanisms from LHRH analogues, with progestational and direct antiandrogen actions. Central nervous system effects of progestogens have been reported previously (25, 26).

Evidence was not strong enough to accept or reject Hypothesis 2, that memory deficits would predominate. A verbal memory task showed the strongest interaction in ANOVA, but with the goserelin group declining in performance and the cyproterone group improving in performance. The attention measure Trails B also showed a trend towards an interaction, and significant decreases in individual performances were observed across memory, attention and executive function tasks. Deficits across a range of tasks suggest that the cognitive function affected may be associated with complex information-processing rather than with memory specifically. This interpretation is consistent with the finding of slowing on the more complex Part B of Trailmaking but no change on Part A. Previous studies have found LHRH analogue treatment in women to be associated with memory deficits (1-4). However, these

studies did not comprehensively investigate attention or executive functions. It would be valuable to test whether LHRH analogues affect attention and executive functions in women as well as memory.

Although participants were randomly assigned to treatments, the close observation group appeared to have higher IQ at baseline. This difference was not statistically significant. Also, practice effects are usually greater in people with lower education or lower IQ (27). Thus, apparent group differences at baseline would be expected to lead to greater improvements, not deterioration, in performance for hormonally treated groups and thus increase the differences further between the close observation and treatment groups.

Results were reported above with alpha uncorrected for multiple tests, which increases Type I error rate. A more stringent criterion is to test the 12 univariate ANOVAs at  $\alpha = .05/12$ . With this Bonferroni criterion, the Group x Time interactions were not significant. Although the results indicate small effect sizes and are not statistically significant when corrections for multiple comparisons are used, they are important because this is the first study of its type for male patients. There was no previous data on which to base group numbers. In retrospect, it would have been preferable to have fewer treatment groups to increase the power of analyses.

It is notable that cyproterone acetate, which was the least well tolerated androgen suppressive medication in this study with one patient dying of acute liver failure within 3 months of commencing this treatment, would not be included were the study to be designed today. Recently, the UK Committee on Safety of Medicines recommended that, due to the risk of hepatotoxicity, cyproterone acetate use in prostatic cancer should be restricted to short courses unless patients are unresponsive to, or intolerant of, other treatments. Three patients assigned to cyproterone also withdrew

due to fatigue, whereas there were no deaths or adverse reactions necessitating a change in treatment in patients assigned to leuprorelin or goserelin.

In this study, a striking finding was that, unlike those randomised to treatments, not one clinically monitored patient had a clinically significant change in cognitive parameters over 6 months. However, for those receiving treatment, no patient developed cognitive problems severe enough to require withdrawal of treatment. Nevertheless, it is important to be aware that individual patients administered androgen suppression for prostate cancer may represent a susceptible subset and be at risk of developing deficits in attention, memory or executive functions while receiving LHRH analogue or progestogen treatments. There is a need to conduct further research especially in relation to bilateral orchidectomy (currently in progress). Unlike some of the other unwanted effects from LHRH analogues and cyproterone acetate, it is considered that cognitive deficits are likely to be reversible with cessation of pharmacological treatment in men, as in women (3, 5). We consider that the findings from this study have implications for the timing of hormonal therapy and information given to patients facing androgen suppression treatments.

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Table 1.

Baseline Characteristics of 65 Participants Who Attended at 6 Months

	Leuprorelin ( <u>n</u> =19)	Goserelin ( <u>n</u> =20)	Cyproterone ( <u>n</u> =11)	Monitoring ( <u>n</u> =15)
	<u>M</u> <u>SD</u>	<u>M</u> <u>SD</u>	<u>M</u> <u>SD</u>	<u>M</u> <u>SD</u>
Age	72.9 ( 5.7)	72.9 ( 5.9)	74.2 ( 9.2)	73.7 ( 6.2)
Years of Education	8.9 ( 2.8)	8.6 ( 1.6)	9.8 ( 2.6)	9.5 ( 2.4)
Estimated IQ <sup>a</sup>	101.5 ( 15.1)	102.3 (16.3)	107.2 (13.6)	113.3 ( 6.8)
PSA <sup>b</sup>	171.2 (484.3)	48.6 (38.4)	50.2 (41.2)	31.3 (18.9)
Testosterone <sup>c</sup>	11.4 ( 6.4)	11.5 ( 5.5)	8.2 ( 4.2)	14.9 ( 8.1)
Marital Status	<u>n</u> <u>%</u>	<u>n</u> <u>%</u>	<u>n</u> <u>%</u>	<u>n</u> <u>%</u>
Married/de facto	15 (78.9%)	15 (75.0%)	7 (63.6%)	11 (73.3%)
No partner	4 (21.1%)	5 (25.0%)	4 (36.4%)	4 (26.7%)

<sup>a</sup> Missing for 2 men in goserelin, and 1 each in the other 3 groups.

<sup>b</sup> The leuprorelin group included one patient with an outlying PSA value of 2,150 at Time 1. His Time 2 PSA was 1.6. Excluding the outlier, the baseline figures for the leuprorelin group are M = 60.1, SD = 74.1.

<sup>c</sup> Missing for 3 patients assigned to leuprorelin, 6 assigned to goserelin, 4 assigned to cyproterone and 2 assigned to monitoring.

Table 2.

Means and Standard Deviations (Time 1), Confidence Intervals, Reliable Change Index (RCI), and F Values for Group x Time Interactions, for 12 Cognitive Measures

Measure	M	SD	95% confidence interval for T2-T1				RCI	F
			Leuprorelin	Goserelin	Cyproterone	Monitoring		
<u>Memory</u>								
Verbal	46.4 (13.5)		-1.9– 8.3	<b>2.6– 9.5</b>	-0.1– 13.2	<b>4.3– 16.2</b>	17.4	1.50
Visual	43.2 ( 8.3)		-0.1– 5.5	<b>1.1– 5.9</b>	-0.9– 8.1	-0.5– 6.6	11.0	0.08
AVLT	30.6 ( 8.3)		-0.9– 5.0	<b>-5.9– -0.5</b>	-1.2– 9.7	-5.1– 1.8	12.7	4.26**
Rey Delay	12.1 ( 5.9)		-1.2– 3.1	-2.0– 2.0	-2.4– 3.9	-2.1– 2.0	6.8	0.22
<u>Attention</u>								
Att/Con	58.3 ( 9.7)		-2.7– 4.0	-3.2– 3.2	-6.3– 0.9	-4.1– 4.2	11.2	0.63
Digit Symbol	32.1 (10.8)		-2.3– 1.8	-3.1– 0.8	-5.3– 0.6	-1.1– 2.8	6.7	1.49
Trails A	54.7 (26.9)		-15.2– 3.2	-7.5– 8.2	-15.2– 13.2	-7.9– 5.5	37.2	0.48
Trails B	134.9 (66.6)		-6.1– 49.9	-22.0– 2.3	-13.4– 13.1	-11.0– 11.8	58.1	2.51
COWAT	28.0 (13.0)		-3.8– 3.7	-2.8– 2.7	-7.0– 2.4	-1.8– 7.0	11.4	1.03
<u>Executive Functions</u>								
Rey Copy	30.5 ( 3.8)		-1.3– 1.6	-2.8– 0.3	-2.4– 2.9	-1.8– 1.3	5.1	0.98
Stroop Words	23.3 ( 6.5)		-2.6– 3.3	-1.4– 1.2	0.0– 3.6	-2.8– 0.9	7.9	1.32
Stroop Colour	41.4 (13.2)		-4.7– 8.6	-9.6– 1.4	-2.8– 8.6	-4.6– 4.7	18.3	0.77

\*\*  $p < .01$

Note. Confidence intervals in bold are those that do not overlap with zero. RCI = Size of difference between Time 2 and Time 1 score that is clinically significant for an individual, AVLT = Auditory Verbal Learning Test, Att/Con = Attention and Concentration Index, COWAT = Controlled Oral Word Association Test

Table 3.

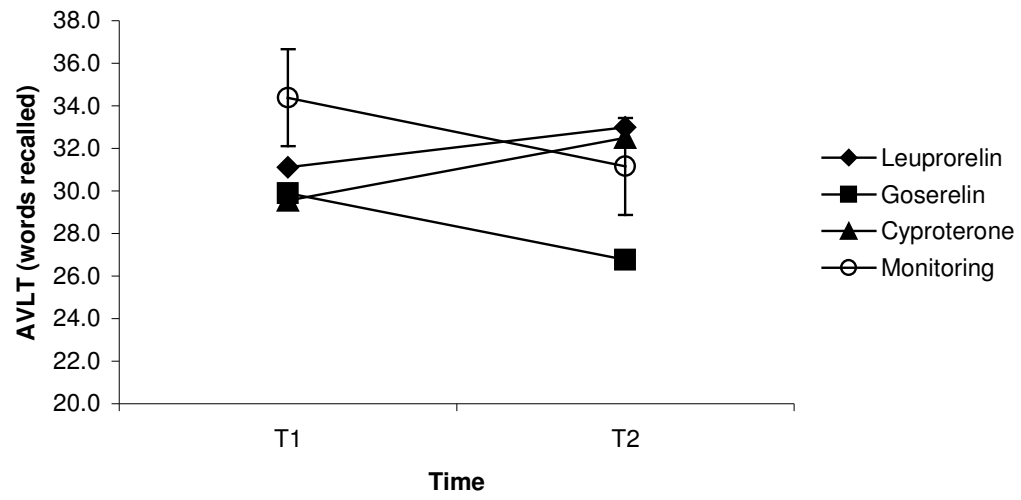
Proportion of Individuals Showing Clinically Significant Decreases in Cognitive Performance as Measured by the Reliable Change Index

Group	Decrease on 1 or more		Decrease on 2 or more	
	tasks		tasks	
	Count	Percent	Count	Percent
Leuprorelin	9	47.4	4	21.1
Goserelin	9	45.0	1	5.0
Cyproterone	6	54.5	2	18.2
Monitoring	0	0.0	0	0.0

Figure Caption

Figure 1. Graphs of means representing Group x Time interactions for pre-treatment and 6 month performance on (a) a verbal memory task (AVLT Sum of Trials 1-5) and (b) an attention task (Trails B). Solid symbols represent patients assigned to active treatments; open circles represent patients assigned to close monitoring. Standard errors are shown for patients assigned to close monitoring; other groups had similar size standard errors.

(a)



(b)

