Effects of Luteinizing Hormone Releasing Hormone Analogs on Cognition

in Women and Men: A Review

H. J. Green¹,², K. I. Pakenham¹, & R. A. Gardiner²

¹School of Psychology and ²Department of Surgery, The University of Queensland, Australia

Running Title: LHRH ANALOGS AND COGNITION


Correspondence should be addressed to: Ms Heather J. Green, Department of Surgery, The University of Queensland, Brisbane, Qld 4072, Australia
Fax: +61 7 3365 5559; Phone: +61 7 3365 5222; Email: heather@psy.uq.edu.au
Effects of Luteinizing Hormone Releasing Hormone Analogs on Cognition in Women and Men: A Review

A group of drugs that causes chemical castration, the luteinizing hormone releasing hormone (LHRH) analogs, has been implicated in cognitive deficits in people using these drugs. Controlled studies in women and case reports from male and female patients support the hypothesis that cognitive changes occur in many patients treated with these pharmaceutical agents. In this paper, actions of LHRH analogs, relationships between sex hormones and cognition, and cognitive effects of LHRH analogs are reviewed. Studies to date have focussed on memory problems. Areas that require further research are the effects of LHRH analogs on cognitive functions other than memory, the effects in men, and cognitive effects of other treatments that affect sex hormone levels such as surgical castration.

KEY WORDS: LHRH, GnRH, cognition, sex differences
Effects of Luteinizing Hormone Releasing Hormone Analogs on Cognition in Women and Men: A Review

Luteinizing hormone releasing hormone (LHRH) analogs are used to produce reversible chemical castration in both women and men, for treatment of certain medical conditions. In women, these drugs are used in treating uterine fibroids, endometriosis, infertility and advanced breast cancer. Uterine fibroids occur in 20% of women and account for 40% of hysterectomies (Shaw & Marshall, 1989). LHRH agonists are the nonsurgical therapy of choice for uterine fibroids (Speroff et al., 1999). LHRH analogs are also one treatment option for endometriosis, which occurs in approximately 10% of women (Newkirk & McGuire, 1998; Shaw & Marshall, 1989; Speroff et al., 1999), infertility, which affects approximately 10-15% of couples (Newkirk & McGuire, 1998; Speroff et al., 1999) and advanced breast cancer (Tobin, 1998). In men, LHRH analogs are the most frequently used treatment for locally advanced or metastatic prostate cancer (Frydenberg et al., 2000; Vaughn, 2000). Prostate cancer is the most frequently diagnosed internal malignancy in men, with a lifetime prevalence of 10% and prevalence of 30% in men aged over 50 (Kunkel et al., 2000). Thus, these drugs are used for several relatively common medical conditions and provide an important alternative to irreversible surgical castration.

Accumulating evidence suggests that LHRH drugs can adversely affect cognitive functions. Cognitive dysfunction appears to have received little emphasis in patient information on LHRH drugs (American Society of Health-System Pharmacists, 1996; MIMS Australia, 1999). However, treatments that cause cognitive dysfunction have the potential to adversely influence patients’ treatment adherence, interpersonal relationships, and daily activities (Boyle et al., 1998; Cull, 1990; Friedman et al., 1993; Zelinski et al., 1998).
Evidence on cognitive effects of LHRH analogs has mainly come from studies of female participants. LHRH is involved in the control of gonadal steroid hormones, which have different concentrations in men and women. Both gonadal hormones and gender have been shown to be associated with certain cognitive functions (Benbow, 1988; Berenbaum, 1998; Fink et al., 1998; McEwen, 1994; Rubinow & Schmidt, 1996). Therefore, cognitive effects of LHRH drugs need to be considered in the context of sex differences. In the first part of this paper, background information on LHRH drugs and sex differences in cognition is discussed. Next, cognitive effects of LHRH drugs and gonadal steroids in women and men are reviewed. Implications for research and clinical practice conclude the paper.

**Actions of Luteinizing Hormone Releasing Hormone Analogs**

LHRH, released by the hypothalamus, acts on the pituitary to stimulate release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH and FSH, collectively called the gonadotropins, are involved in control of the gonadal steroids, estrogens in female organisms and androgens in male organisms. These steroids are also produced extragonadally, such as in the adrenal glands, but extragonadal sites account for relatively little production. It was once thought that there were separate releasing hormones for LH and FSH, but it now appears that there is a single releasing hormone for both gonadotropins (Speroff et al., 1999). Therefore, LHRH is sometimes called gonadotropin releasing hormone (GnRH), to acknowledge that it releases FSH as well as LH (Schaison, 1990). The term, LHRH, is still widely used, particularly in clinical applications, and is the term used in this paper.

Pharmacological manipulations of this system can involve either agonists or antagonists of LHRH. LHRH agonists cause an immediate increase in LH, FSH and gonadal steroids, followed by downregulation of the pituitary LHRH receptor resulting
in decreased LH, FSH and circulating gonadal steroids (Parmar et al., 1990). LHRH antagonists also decrease LH, FSH and gonadal steroids, but instead of downregulating the LHRH receptor they competitively occupy the receptor (Weinbauer et al., 1990). Most of the LHRH analogs in current clinical use are agonists, such as leuprorelin, goserelin, and nafarelin, but antagonists also show promise for clinical use (Weinbauer et al., 1990). These agents are used clinically to decrease androgens in men or estrogens in women. The next section discusses sex differences in gonadal steroid levels and cognition.

Sex Steroids and Cognition

Androgens and estrogens have different physiological concentrations in men and women. In men, androgens, in particular testosterone and its metabolites, predominate. In women, estrogens predominate. Sex steroids have been shown to affect both brain development (organizational effects) and acute activation of neural systems (activational effects; Berenbaum, 1998). There are a number of structural sex differences in mammal and bird brains (McEwen, 1994). One preoptic hypothalamic nucleus has twice as many neurons in male than female humans, and the planum temporale and anterior Sylvian fissure on the left side are larger in male than female brains (de Courten-Myers, 1999). It has also been reported that male humans have more neurons but fewer neuronal processes than female humans, although these differences balance each other to maintain a similar overall cortical thickness for women and men (de Courten-Myers, 1999).

While many studies have searched for sex differences in cognitive performance in humans, most data have shown an absence of sex differences or a small difference in mean values with much more intrasex than intersex variability (Caplan & Caplan, 1999). Women and men show no difference in mean intelligence, and gender adds no
variance to psychometric evaluations in predicting educational or occupational
achievement (Levy & Heller, 1992). Nevertheless, there are some differences in men’s
and women’s distributions of performance on specific cognitive tasks (Halpern, 1992;
Levy & Heller, 1992). One of the most consistent findings is a higher mean score for
men than women on certain spatial tasks, such as those involving mental rotations
(Halpern, 1992; Janowsky et al., 1998; Levy & Heller, 1992; Moffat & Hampson, 1996;
Tan & Akgün, 1992). It should be noted that some studies have found no sex difference
in spatial performance, and, when sex differences are found, they have been estimated
to account for only 1-5% of variance in spatial performance (Caplan & Caplan, 1999).

Some of the small differences between male and female humans in cognitive
performance appear to be related to prenatal hormone exposure (Reinisch & Sanders,
1992). Clinical endocrine syndromes have been associated with specific patterns of
cognitive performance later in life (Levy & Heller, 1992; Reinisch & Sanders, 1992).
For example, women with Turner syndrome, who have a deficiency in ovarian
hormones associated with ovarian dysgenesis, were reported to have normal verbal
intelligence quotient (IQ) scores but lower than normal performance on many
visuospatial tasks (Levy & Heller, 1992). Girls and women with Congenital Adrenal
Hyperplasia syndrome, in which the fetal adrenals secrete abnormally high levels of
androgens, have shown significantly better spatial performance than girls and women
without this syndrome (Levy & Heller, 1992). These studies, as well as studies with
individuals who had no genetic abnormality but were exposed prenatally to hormonal
preparations intended to prevent miscarriage, suggest that changes in the prenatal
hormonal environment can be associated with changes in brain development and
cognitive performance (Levy & Heller, 1992; Reinisch & Sanders, 1992).
Different socialization of male and female humans is also likely to contribute to cognitive sex differences (reviewed by Benbow, 1988; Caplan & Caplan, 1999; Halpern, 1992). Societal expectations about appropriate behaviour for each gender may affect individuals’ opportunities to acquire and develop specific cognitive skills. Therefore, even if there are biological contributions to sex differences in cognition, these differences are likely to be augmented over time by interaction with the environment, as cultural expectations about appropriate behaviour for each sex are imposed (Reinisch & Sanders, 1992).

Sex steroids can affect developed as well as developing brains. There are a number of neurons in mammal brains with receptors for gonadal steroids, including areas of the hypothalamus, hippocampus and pineal gland (Berenbaum, 1998; Speroff et al., 1999, p. 191). Neurons containing LHRH have also been found outside the hypothalamic-pituitary axis in mammals, including in the telencephalon cortex, midbrain, limbic brain, main and accessory olfactory bulbs (Daikoku, 1999; Jennes & Stumpf, 1980; Lambert et al., 1992; Oelschlager & Northcutt, 1992). Thus, gonadal steroids and LHRH could potentially affect many different neural mechanisms, including functions not traditionally associated with reproductive behaviour.

Some effects of testosterone on brain function have been suggested to be mediated by local conversion of testosterone to estradiol (aromatization; Berenbaum, 1998; Fink et al., 1998; Fink et al., 1996). The aromatase system that converts testosterone to estradiol has a selective distribution. This helps to explain why, in both male and female rats, the distribution of estrogen in brain when estrogen was infused directly differed from the distribution when estrogen was measured as a metabolite of infused testosterone (McEwen, 1994). The selective distribution of aromatase enzyme, in combination with other differences in male and female brain organization, could
cause the same level of estrogen to affect men and women differently. Thus, the predominant supply of estrogen to brain would be a direct (circulating) supply for women and a metabolite of testosterone for men.

Sex differences in cognitive performance of adults may be associated partly with gonadal hormones (Halpern, 1992; Reinisch & Sanders, 1992). Men have, on average, both higher testosterone and better spatial performance on certain tasks than women. Within sexes, higher testosterone has been found to be associated with better spatial performance in both women (Gouchie & Kimura, 1991) and men (Christiansen & Knussmann, 1987; Tan & Akgün, 1992). Some data suggest that the relationship between testosterone and spatial performance is curvilinear (Halpern, 1992; Moffat & Hampson, 1996; Sternbach, 1998). The curvilinear model posits that there is an optimal level of testosterone, with levels higher or lower than this range resulting in decreased spatial performance. Supporting clinical data have shown that increasing testosterone in hypogonadal men improved spatial cognitive performance (Janowsky et al., 1994), whereas giving extra testosterone to eugonadal men resulted in increased cognitive difficulties including distractibility, forgetfulness and confusion (Rubinow & Schmidt, 1996).

Further support for the theory that testosterone is curvilinearly related to cognitive performance comes from tests in young adults with a normal range of hormone levels. In this population, women with relatively higher testosterone had better spatial cognition performance than women with lower testosterone, whereas men with relatively lower testosterone outperformed higher testosterone men (Gouchie & Kimura, 1991). When hormone levels were not taken into account, men performed better than women on these spatial tasks, but the high-testosterone women had a similar
level of performance to the high-testosterone men, whereas men below the median for
testosterone showed the best performance of any group (Gouchie & Kimura, 1991).

It is unclear whether testosterone or estrogen was the relevant hormone, since
testosterone may be converted to estrogen as stated above and, in studies reported to
date, only some researchers have measured both estrogen and testosterone. In one
cognitive performance study of healthy young men, testosterone and estrogen correlated
positively with each other at 0.80, indicating that within individual men higher
testosterone and higher estrogen frequently occurred together (Kampen & Sherwin,
1996). More studies that examined estrogen and testosterone as well as their ratio
would help clarify the contribution of each hormone to cognitive function (Janowsky et
al., 1998).

The literature on sex steroids and cognition has shown that sex is an important
variable in considering the cognitive effects of drugs that affect sex hormones.
Although women and men show many more similarities than differences in cognitive
performance, there are some sex differences in both cognitive performance and
hormone levels. Even the same level of the same hormone may have different effects
on male and female brains (McEwen, 1994). Thus, cognitive effects of LHRH drugs
need to be considered in the context of sex differences.

LHRH Drugs, Gonadal Steroids and Cognition in Women

Case reports of three women treated with LHRH analogs for infertility described
adverse neurological effects including migraine, paresthesia, and hand and face
numbness (Ashkenazi et al., 1990). Symptoms began when hormonal values were at
castrate levels, 8-12 days after injection of the drugs, and subsided gradually over 3-7
days. No neurological pathology was identified. Adverse emotional and cognitive
effects of LHRH analogs in women have also been reported. In one study, 102
premenopausal women treated with monthly injections of leuprolide acetate for leiomyomata uteri completed logs of adverse effects during 12 weeks of treatment (Friedman et al., 1993). Mood lability and depression were reported by 45% and 9% of women respectively. Short-term memory loss was reported by 6% of the women during treatment, even though none of the women had reported memory problems before beginning treatment. Onset of mood lability and depression peaked during the first 4 weeks of treatment, whereas onset of short-term memory difficulties occurred 7-12 weeks after beginning treatment.

Kortepeter, Macmillan and Ferrell (1992) surveyed 16 women aged 21-44 who used the LHRH agonist, naferelin, as a nasal spray treatment for endometriosis. Of these women, 56% reported difficulty remembering things or feeling more forgetful than usual when using naferelin, compared to their usual cognitive function. In a prospective study using a weekly diary of adverse effects and a Memory Observation Questionnaire, Newton and colleagues found that 44% of women treated with LHRH analogs for endometriosis reported moderate to marked impairment in memory compared with community norms by the final week of treatment (Newton et al., 1996). The LHRH group reported memory performance on treatment that was 0.5-1.2 standard deviations below community norms, even though before and after treatment their perceived memory performance was approximately 0.5 standard deviations better than community norms (Newton et al., 1996).

The cognitive studies reported above used subjective measures of memory. Subjective measures often show little correspondence with objective cognitive performance. Instead, subjective cognitive complaints, particularly memory complaints, often indicate emotional distress rather than neurological dysfunction (Lezak, 1995). Subjective cognitive impairment has shown stronger links with depression and anxiety
than with objective cognitive impairment in a number of groups, including people aged under and above 50 years who attended a memory clinic (Derouesne et al., 1999), people who underwent surgery (Moller et al., 1998; Newman et al., 1990) hemodialysis patients (Brickman et al., 1996) and people with cancer (Cull et al., 1996). Newton et al.’s study included comparative subjective data, and demonstrated that the subjective memory complaints were more frequent in women treated with LHRH analogs for endometriosis than in comparable community groups (Newton et al., 1996). Nevertheless, subjective reports of cognitive performance differ from objective impairment.

One objective, randomized repeated measures trial in women has been reported. Women treated with the LHRH analog, leuprolide, for uterine myomas, showed significant decreases in performance on paragraph recall and verbal paired associates (Sherwin & Tulandi, 1996). In a second stage, women continued leuprolide treatment and were also given injections of either estrogen or placebo. Performance of the verbal memory tasks improved to baseline levels in women randomized to estrogen replacement but not in those who received placebo injections (Sherwin & Tulandi, 1996). There was no difference in mood between the estrogen and placebo groups, ruling out an indirect effect of leuprolide on cognition via depressed mood. This study showed that a possible contributing factor to cognitive changes with LHRH analogs in women is reduced estrogen.

A link between estrogen and verbal memory has been found in other groups of women who were not treated with LHRH analogs. Women randomized to receive estrogen injections after hysterectomy and bilateral oophorectomy had significantly higher scores on paired associates and immediate paragraph recall than did women who received placebo injections after surgery (Sherwin & Philips, 1990). Hysterectomy
accompanied by bilateral oophorectomy is surgical castration rather than chemical castration such as that caused by LHRH analogs. Verbal memory scores were also higher in postmenopausal women receiving estrogen replacement therapy, compared with postmenopausal women who did not receive estrogen replacement therapy (Kampen & Sherwin, 1994).

Sherwin and colleagues have consistently found that, in women, estrogen is associated with verbal memory but not with language, attention, spatial memory, or spatial perception (Kampen & Sherwin, 1994; Sherwin, 1994; Sherwin & Philips, 1990; Sherwin & Tulandi, 1996). In contrast, other researchers have found smaller differences or no differences in cognition with different levels of estrogen in women (reviewed by Yaffe et al., 1998b). Estrogen has also been inversely related to cognitive performance, as reported in a study which found that higher levels of endogenous estrogen in women aged 65 or more were associated with worse performance on the attentional tasks, Digit Symbol and Trail Making Part B (Yaffe et al., 1998a). Another finding that contrasts with those of Sherwin and colleagues was that higher estrogen levels within the normal range in healthy young women were associated with better performance on the spatial task, Block Design, but were not associated with verbal memory, spatial memory, or word fluency (Janowsky et al., 1998). Therefore, an association between higher estrogen levels in women and better verbal memory performance has not been universally supported.

In summary, research with women treated with LHRH analogs has shown that these drugs adversely affected many of these patients as judged by both subjective reports and objective tests of cognition. LHRH analogs have also been associated with other non-cognitive neurological symptoms. The cognitive decrement related to leuprolide treatment in women was reversed by replacement of estrogen in one study.
The studies by Sherwin and colleagues have suggested that the cognitive deficit associated with LHRH analog use in women is specific to verbal memory and related to an estrogen deficit. These findings require replication by other research groups.

**LHRH Drugs, Gonadal Steroids and Cognition in Men**

There has been little systematic study of cognitive effects of LHRH analogs in men. One case report of an Australian man aged 68, treated with goserelin injections, described adverse effects of delirium, ataxia, amnesia, fluctuating consciousness, incontinence and impaired concentration that ceased when goserelin was stopped (Australian Department of Human Services and Health, 1997). No other published clinical reports of cognitive or neurological effects of LHRH analogs in men were located in searches of Medline and PsycLIT citation databases. Frequent adverse effects of LHRH analogs in men that have been reported are increased fatigue and emotional distress (Herr & O'Sullivan, 2000; van Andel et al., 1997).

One study on acute effects of LHRH injection on cognitive performance in men has been reported. Injection of LHRH in healthy men aged 18-35 was associated with better cognitive performance on a verbal fluency task than the performance of men in the same age group who received placebo injections (Gordon et al., 1986). Performance on other verbal and visuospatial tasks was not affected significantly by LHRH. It is noteworthy that the same researchers using the same methodology found no cognitive effects of testosterone injections in young men (Gordon et al., 1986).

A possibility raised by the findings of Gordon and colleagues is that LHRH or LH may have direct cognitive effects in addition to a “downstream” effect on gonadal steroids that are known to affect cognition. It should also be noted that the initial period after commencement of LHRH agonist therapy would be predicted to have opposite cognitive effects to chronic administration. These drugs are long-acting analogs that
block LHRH receptors, but produce an initial flare of hormones before downregulation. Thus, improvement of cognition with acute doses of LHRH agonists in men could be consistent with subsequent impaired cognition after commencement of these drugs.

Other data relevant to the potential effects of LHRH analogs in men come from studies that have investigated cognitive effects of testosterone or estrogen. Studies that have investigated correlations between endogenous hormones and cognition will be discussed first, followed by studies involving hormonal manipulation in men. When both cognitive performance and physiological (endogenous) testosterone levels have been measured in healthy young men, some researchers have found positive correlations between endogenous testosterone and cognitive performance, for spatial performance (Christiansen & Knussmann, 1987), verbal performance (Alexander et al., 1998) and nonverbal intelligence as measured by Cattell’s Culture Fair Intelligence test (Tan & Akgün, 1992).

In contrast, other researchers have found negative correlations between spatial performance and testosterone in young men (Gouchie & Kimura, 1991; Moffat & Hampson, 1996). Kampen and Sherwin found no relationship between endogenous testosterone and cognitive performance in young men, but did find correlations of estrogen with immediate visual memory in the same participants (Kampen & Sherwin, 1996). Janowsky and colleagues found that men aged 23-34 years had a positive correlation with spatial recall for both testosterone and estrogen, and that testosterone in men also correlated weakly with verbal recall (Janowsky et al., 1998). Thus, within the normal range of testosterone in healthy young men, some studies have reported no correlation between testosterone and cognitive performance; others better cognitive performance with higher testosterone (spatial, verbal, and intelligence measures); and some others worse spatial cognitive performance with higher testosterone. Higher
estrogen levels in young men have been associated with better visual and spatial memory.

Healthy young men are likely to have a restricted range of testosterone. The curvilinear model of the relationship between testosterone and cognitive performance (Halpern, 1992; Moffat & Hampson, 1996; Sternbach, 1998) is consistent with testosterone sometimes correlating positively with performance, sometimes negatively, and sometimes not at all. One way to increase the range of testosterone values is to widen the age range. Morley and colleagues measured bioavailable testosterone and cognitive performance in healthy men aged 20 to 84 years (Morley et al., 1997). Testosterone showed a strong negative correlation with age (-0.70) and positive correlations with performance on the Rey Visual Design Learning Test, the Rey Auditory Verbal Learning Test, and a category fluency task. Each of these tests declined with age, which accounted for 31-50% of variance in performance on these cognitive tasks. Testosterone accounted for 20-28% of variance in performance (Morley et al., 1997). This showed a significant relationship between testosterone and cognitive performance when participants with a wide range of testosterone levels were included.

Administration of exogenous testosterone to men has been trialled for two main clinical indications: hypogonadalism due to aging or other causes (Bhasin & Tenover, 1997), and male hormonal contraception (Alexander et al., 1998). Testosterone supplementation in older hypogonadal men was found to enhance spatial cognition as measured by the block design subtest of the Wechsler Adult Intelligence Scale - Revised, but had no effect on verbal or visual memory, mood, or fine motor speed (Janowsky et al., 1994). Another study found that hypogonadal men aged 20-59 initially had lower verbal fluency scores than eugonadal men, but after testosterone
replacement therapy their verbal fluency scores improved to be no different from those of eugonadal men (Alexander et al., 1998). Estrogen has also shown promise in cognitive remediation of hypogonadalism, in that it improved spatial memory performance of aged male rats compared to rats given placebo (Luine, 1994).

In contrast to the above findings, no cognitive effect of testosterone replacement was found in a 12-month randomized trial in which men aged 50 years or more with bioavailable testosterone less than 60 ng/dL received biweekly injections of either testosterone or placebo (Sih et al., 1997). The normal range of bioavailable testosterone in young adult men is 72-250 ng/dL (Sih et al., 1997). Testosterone was found to increase muscle strength and hemoglobin, but it had no effect on cognitive performance as measured by the Rey Auditory Verbal Learning Test, Rey Visual Design Learning Test and verbal fluency.

Eugonadal men aged 21-44 who received exogenous testosterone as part of a male contraceptive trial showed no effect of additional testosterone on performance of verbal, visuospatial or speeded tasks (Alexander et al., 1998). However, other researchers have found that treatment of eugonadal men with testosterone or anabolic-androgenic steroids led to increased cognitive symptoms such as distractibility, forgetfulness and confusion (Rubinow & Schmidt, 1996). Also, the pattern of hormonal responses to anabolic-androgenic steroids differed significantly between individuals who did and individuals who did not show cognitive deficits in association with these agents (Rubinow & Schmidt, 1996). This implied that the individuals studied had different biological susceptibilities to cognitive disruption with drugs affecting gonadal hormones.

In summary, there is a paucity of evidence on the effect of LHRH analogs on cognition in men. Within physiological ranges, testosterone has been associated with
improvements, decrements, or no change in cognitive performance. However, it is studies of abnormally low levels of testosterone that relate most directly to predicting effects with chronic administration of LHRH. Although there are some null findings (Sih et al., 1997) a number of studies have reported decrements in cognition associated with hypogonadalism and improvement in cognitive performance of hypogonadal men who receive testosterone replacement (Alexander et al., 1998; Janowsky et al., 1994; Luine, 1994). These findings imply that LHRH analogs may be associated with cognitive dysfunction in some men who receive them. Similar to the studies that have been done in women, it would be helpful to test whether replacing testosterone would reverse cognitive effects of LHRH drugs in men.

Future Directions for Research

Information on the prevalence of cognitive dysfunction associated with use of LHRH analogs shows a discrepancy between formal information provided to patients and clinicians and data from research studies. Data from adverse effect reports suggested that memory problems occurred in less than 5% of patients using the LHRH analog, leuprolide (American Society of Health-System Pharmacists, 1996; MIMS Australia, 1999). In comparison, research studies found 6-56% of women treated with an LHRH analog reported subjective memory problems (Friedman et al., 1993; Kortepeter et al., 1992; Newton et al., 1996). Objective testing also showed a significant group decrease in verbal memory scores of women treated with leuprolide (Sherwin & Tulandi, 1996). Adverse effect reports appear to have underestimated the prevalence of cognitive dysfunction with these drugs. Additional research using objective measures of cognition or systematic information on subjective cognitive function would help to establish more accurately the prevalence of cognitive dysfunction in these patient groups.
Cognition is best measured by objective, psychometrically sound measures. Significant cognitive dysfunction can be detected by screening instruments such as the Mini Mental-Status Examination (Folstein et al., 1975). More detailed assessments of cognition can be performed by neuropsychologists, psychologists, or neurologists. Different cognitive functions may need to be measured, especially in light of the assertion that verbal memory is most affected by LHRH analogs, at least in women. The time scale of cognitive changes should also be identified. It would be valuable to track both onset of and recovery from cognitive dysfunction associated with LHRH analogs. Of men with advanced prostate cancer who were withdrawn from LHRH agonists after at least 2 years of treatment, patients continued to show significantly suppressed levels of luteinizing hormone and testosterone for up to 12 months (Hall et al., 1999). This slow recovery of hormonal levels suggests that cognitive functions compromised by LHRH analogs may also show prolonged recovery over time.

This adverse effect may occur in only a proportion of individuals treated with LHRH analogs. Individual factors that contribute to susceptibility to or protection from cognitive difficulties should be investigated. For example, Rubinow and Schmidt (1996) noted that hormonal responses to androgenic-anabolic steroids differed between individuals who did and did not develop cognitive dysfunction. Biological or other parameters may also differ between individuals who show greater or lesser susceptibility to cognitive dysfunction with LHRH analogs. Different patient populations should also be investigated. Under researched populations include adult men, and male and female children treated for precocious puberty.

Identification of causal mechanisms linking hormonal changes to cognitive changes would be valuable. The finding that estrogen replacement reversed verbal memory deficits associated with LHRH agonists in women (Sherwin & Tulandi, 1996)
should be replicated. Investigation of whether there are cognitive effects in men that could be reversed, possibly by testosterone replacement, is needed. However, given that the main clinical indication for LHRH analogs in men is advanced prostate cancer, which may be exacerbated by testosterone, testosterone replacement may be difficult to study in this patient group. Other research that will continue to inform understanding of causal mechanisms is research on extra-pituitary actions of LHRH analogs, such as recent reports of the presence of LHRH receptors in some gynecologic and prostatic tumours (Halmos et al., 2000).

Studies showing effects of sex steroids on cognition imply that, not only LHRH analogs, but also other treatments that alter sex steroids, may affect cognitive function. For example, surgical castration or direct antagonists to sex steroids might be predicted to have similar effects on cognition to LHRH drugs. However, if cognitive function were affected more by the specific action of LHRH than by its downregulation of gonadal steroids, these other treatments would not be expected to have the same effects as LHRH analogs on cognition. Cognitive effects of these other hormonal treatments should be investigated.

**Implications for Clinical Practice**

Clinicians may consider alerting patients to this potential adverse effect of treatment with LHRH analogs. Timing of treatment may take into consideration the patient’s lifestyle and possible consequences of cognitive disruption. For example, occupational functioning, parenting, driving, planning and interpersonal functioning could potentially be affected by cognitive dysfunction. Friedman and colleagues (1993) noted that four women who developed depression or short-term memory problems while being treated with leuprolide had significant personal consequences involving loss of their job or disturbances in their personal relationships. Studies need to examine
everyday activities as well as laboratory tasks to elucidate the prevalence and
significance of cognitive changes with these drugs.

Another consideration is that LHRH analogs are expensive drugs. In longer-
term administration such as treatment of prostate cancer, there is increasing advocacy
for intermittent LHRH treatment (Barradell & Faulds, 1994). Intermittent treatment
may help to reduce adverse effects including cognitive dysfunction, and would also
decrease the expense to the healthcare system and the patient (Hall et al., 1999). It
would be helpful for trials of intermittent LHRH agonist administration to track
beneficial and adverse effects of treatment, including cognitive effects.

Conclusions

Cognitive performance is associated with sex hormones. LHRH analogs, which
greatly reduce sex hormones when administered chronically, would be expected to
affect cognition. This appears to be the case, in controlled studies in women (Newton et
al., 1996; Sherwin & Tulandi, 1996) and in case reports from women (Friedman et al.,
1993; Kortepeter et al., 1992) and men (Australian Department of Human Services and
Health, 1997). Further cognitive research with this group of drugs would inform
clinical practice and improve understanding of the effects of sex steroids and sex
differences on cognition and behaviour. Studies reviewed in this article also serve as a
reminder that it is crucial to consider sex differences when studying cognitive effects of
drugs, particularly in systems that involve sex hormones.
References


