



## Antidepressants and anxiolytics treatment lowers serum DHEA-S levels in elderly women

### Tratamento antidepressivo e ansiolítico diminui os níveis séricos de DHEA-S em mulheres idosas

Recebido em 06/12/2011

Aceito em 31/01/2012

Luísa Scheer Ely<sup>1\*</sup>, Paula Engroff<sup>1</sup>, Vanessa Sgnaolin<sup>4</sup>, Guilherme Schroeter<sup>2</sup>, Fernanda Bueno Morrone<sup>2,3</sup>, Geraldo Attilio De Carli<sup>1</sup>

<sup>1</sup> Instituto de Geriatria e Gerontologia, Pontifícia Universidade Católica do Rio Grande do Sul, Rio Grande do Sul, Brasil

<sup>2</sup> Faculdade de Farmácia, Pontifícia Universidade Católica do Rio Grande do Sul, Rio Grande do Sul, Brasil

<sup>3</sup> Programa de Pós-Graduação em Biologia Celular e Molecular, Universidade Católica do Rio Grande do Sul, Rio Grande do Sul, Brasil

<sup>4</sup> Programa de Pós-Graduação em Medicina e Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul, Rio Grande do Sul, Brasil

#### ABSTRACT

In the last decades, the population of older individuals has increased, and this has been accompanied by psychiatric disorders. Recent studies have associated lower levels of DHEA-S with depression. DHEA-S is an androgen that decreases with age and could be a marker for the aging process. The aim of this study was to analyze the serum level of DHEA-S in a group of elderly women in Porto Alegre, Brazil, who were taking antidepressant and anxiolytic drugs. A cross-sectional, observational study was conducted on 512 elderly participants who had been recruited for interview, with regard to medication use, and blood sampling for determination of DHEA-S level. Our results showed that of the 322 of the elderly women tested, 81% did not use antidepressant and/or anxiolytics drugs, as opposed to 19% who did. The benzodiazepines were the most used by elderly women (65%), followed by selective serotonin reuptake inhibitor (51.6%) antidepressants and tricyclic antidepressants (25%). The mean logDHEA-S in the elderly women which used antidepressants and/or anxiolytics was lower than the logDHEA-S of those who were not taking these drugs ( $p < 0.05$ ). We found that DHEA-S levels declined with age ( $p < 0.05$ ). However, further studies are needed for a better understanding of this androgen and its association with drug treatment.

**Keywords:** Aging, drug, depression, DHEA

#### RESUMO

Nas últimas décadas a população idosa tem aumentado e vem acompanhada de disfunções psiquiátrica. Estudos recentes associam baixos níveis de DHEA-S com depressão. O DHEA-S é um hormônio andrógeno que declina com a idade e pode ser considerado um marcador para o processo de envelhecimento. O objetivo desse estudo foi analisar os níveis séricos de DHEA-S em um grupo de mulheres idosas de Porto Alegre, Brasil, que faziam uso de medicamentos antidepressivos e ansiolíticos. Esse estudo faz parte de uma pesquisa transversal e observacional, no qual 512 idosos participantes submeteram-se a entrevistas e coleta de sangue. Os resultados mostraram que das 322 mulheres estudadas, 81% não utilizavam medicamentos antidepressivos e/ou ansiolíticos, enquanto que 19% faziam uso dessas medicações. Os benzodiazepínicos foram os mais utilizados pelas idosas (65%), seguido do uso de antidepressivos inibidores seletivos da recaptação da serotonina (51,6%) e dos antidepressivos tricíclicos (25%). A média do logDHEA-S das mulheres idosas que usavam antidepressivos e/ou ansiolíticos foi menor do que o logDHEA-S daquelas que não utilizavam esses medicamentos ( $p < 0,05$ ) e os níveis de DHEA-S diminuíram de acordo com a idade avançada das idosas ( $p < 0,05$ ). Entretanto, estudos ainda são necessários para o melhor entendimento desse hormônio e a sua associação com o tratamento medicamentoso.

**Palavras-chave:** Envelhecimento, medicamentos, depressão, DHEA

#### INTRODUCTION

In the last three decades, the older proportion of the in Brazil has increased (Chaimowicz, 1997; WHO, 2011).

This age group demonstrates the fastest growth worldwide, and thus, it is important for older people to be

\* Contato: Luísa Scheer Ely, Instituto de Geriatria e Gerontologia, PUCRS, Av. Ipiranga, 6690, 3º andar Jardim Botânico, CEP: 90610-000, Porto Alegre, RS, e-mail: luisa\_ely@yahoo.com.br

concerned, not only with their longevity, but also happiness, quality of life and personal satisfaction (Joia et al., 2007).

The aging process is accompanied by an increase in psychiatric disorders of which dementia and depression are the most common mental disorders in the elderly (Reys et al., 2006). Studies have reported that the main causes of these disorders are the demographic characteristics old age, female sex, not married (single or widow) and poor health conditions (Borges et al., 2007). The prevalence rates of depression are between 5% and 35% varying with the degree of severity. The rates of depressive symptoms in the worldwide population over 65 years old vary between 10.3% and 13.5%, and in Brazil it is about 14.3% (Borges et al., 2007).

Pharmacotherapy plays an important role in the life of the older population due to psychological changes related with age and concomitant disease (Berra et al., 2007). The most used anxiolytics are the benzodiazepines such as alprazolam, bromazepam and diazepam, and the most used antidepressants are the tricyclics represented by amitriptyline and imipramine, and the selective serotonin reuptake inhibitors represented by paroxetine, sertraline and fluoxetine (Leowattana, 2004).

Recent studies have demonstrated a relationship between depression and the adrenal steroid dehydroepiandrosterone (DHEA) and its sulfated conjugate (DHEA-S). DHEA-S is the major secretory product of the adrenal gland and is produced in a larger quantity than any other circulating steroid hormone (von Mühlen et al., 2007; Wong et al., 2011). Because there are marked declines in circulating DHEA-S with age, investigators suspect that it may be a marker for the aging process and potential longevity (Enemoto et al., 2007; Genazzani et al., 2011). Plasma levels of DHEA and DHEA-S decline by 80% between the ages of 25 and 75 years (Villareal & Holloszy, 2006). This remarkable decrease in DHEA-S with age has led to considerable interest in the possibility that reduced levels of DHEA-S indicate the deterioration of metabolic and physical function with advancing age as well as in the development of aging-related disease processes (Genazzani et al., 2011; Villareal & Holloszy, 2006). The decline in circulating DHEA-S with age has led to considering the intriguing possibility that this change in hormone levels is related to the development of "normal" age-associated changes, as well as diseases such as cancer, atherosclerosis or Alzheimer's disease (Berr, 1996).

There are data that suggest DHEA and DHEA-S may have neuroprotective effects and that the decline in the production of these steroids with healthy aging may contribute to neuronal dysfunction and degeneration, and thus cognitive decline (Davis et al., 2007). Studies have shown that DHEA-S has anti-depressant effects through their modulation of neurotransmitter systems in the brain (Morsink et al., 2007). To correctly interpret studies of DHEA-S in relation to depression disease, it is important to identify significant physiologic and pharmacologic effects on DHEA-S concentrations (Firoozeh et al., 2002).

This study aimed to determine the serum levels of DHEA-S in elderly women in Porto Alegre, Brazil. We

have also investigated the relation between the use antidepressant and anxiolytic drugs and the levels of DHEA-S.

## MATERIALS AND METHODS

### Study Design

This study was part of the "Projeto Idosos de Porto Alegre," PUCRS. This project was developed as a multidisciplinary study with the Instituto de Geriatria e Gerontologia, PUCRS and the City Hall of Porto Alegre. This was a cross-sectional, exploratory, observational study for the most frequent events in the elderly population. Individuals older than 60 years from Porto Alegre, Brazil, participated in this study. The participants were questioned about the use of antidepressant and anxiolytic drugs, blood samples were taken for determination of serum DHEA-S.

### Samples

The sample number of this study was in accordance with the number of patients analyzed in a previous study (1995) for each quarter of Porto Alegre and was updated by the Instituto Brasileiro de Geografia e Estatística (IBGE, 2003) according to the estimation of the population variation through 2005.

The patients interviewed were randomly recruited by the social service from different quarters and social conditions. City Hall provided the data on the different quarters where the elderly population was concentrated in Porto Alegre, as well as the names and addresses of these individuals. Contact was made by telephone with the support of Instituto de Geriatria e Gerontologia da PUCRS (Faggiani et al., 2007; Schroeter et al., 2007). The total sample consisted of 512 elderly individuals of both sexes.

The exclusion criteria for this research study were: 1) elderly who did not have results of serum DHEA-S levels because of insufficient blood sample collected; and 2) elderly males, because few used antidepressant and/or anxiolytic drugs. Thus, included in the study were 322 elderly women.

### Determination of Groups

The use of antidepressant and anxiolytic drugs was related to the DHEA-S results. The individuals were classified into groups: elderly women who were taking antidepressant and/or anxiolytic drugs (n=60) and elderly women who were not (n=262).

### Data Collection

The interviews were conducted between January and August of 2008 by trained interviewers (university students, graduate students and professors). The instrument utilized was a previously validated pharmacotherapeutic questionnaire containing the actual therapy and information about the drug utilized (Faggiani et al., 2007; Schroeter et al., 2007). The questions were open-ended and were answered based on the recall of the patient and/or through the use of materials supplied to the patient, such as prescriptions and/or a label.

**Serum DHEA-S Measurements**

Blood samples (5 mL) were collected from each individual and the serum was frozen at -20°C for later determination of DHEA-S. Serum DHEA-S measurements were performed in the Biochemistry and Genetics Laboratory of the Instituto de Geriatria e Gerontologia, PUCRS, using an ELISA method (Biotec ELX 800). The assays were carried out with a DHEA-S ELISA kit (Human Diagnostics Worldwide – Germany). The reference value of DHEA-S for post-menopause women is 0.1 to 0.6 µg/mL.

**Statistical Analysis**

The data were first tabulated and analyzed using Microsoft Excel. A histogram was made with the patients DHEA-S results, but the plot did not show linearity, and therefore, the DHEA-S concentration was log-transformed before statistical analysis.

The results were presented as means and standard error, and 95% confidence intervals (95% CI) were utilized. The statistical analyses were performed using the covariance test (ANCOVA) from the SPSS program, version 11.5. Statistical significance was set at p<0.05. The relationship between logDHEA-S and age of elderly individuals who used or did not use antidepressants and/or anxiolytics was analyzed by linear regression.

**Ethical Considerations**

The Institutional Ethics Committee of PUCRS approved this study (number 0502935), and written informed consent was obtained from all patients.

**RESULTS**

The data collected during the interviews from 322 elderly female participants of this study were analyzed according to the utilization or not of antidepressant and/or anxiolytic drugs. Our result showed that 81% of the elderly women did not use these drugs, as opposed to 19% who did (Figure 1).

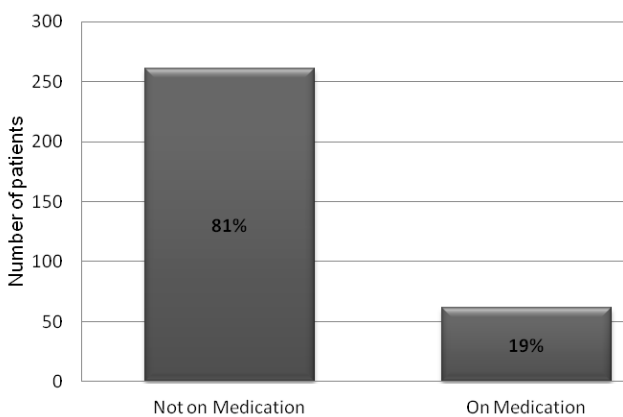


Figure 1. Use of antidepressant and/or anxiolytic drugs in the population studied (n=322).

Benzodiazepines were the drugs most often used by elderly women taking antidepressants and anxiolytics (65%), followed by selective serotonin reuptake inhibitor antidepressants (51.6%) and tricyclic antidepressants (25%). Diazepam was the main representative of benzodi-

azepines, which was used by 20% of the elderly women. Fluoxetine, a representative of selective serotonin reuptake inhibitors was used by 38.3% of the elderly, and amitriptyline, a tricyclic antidepressant, was used by 18.3% (Table 1).

**Table 1.** Central nervous system drugs most often used in the population studied (n=60)

Tricyclic		
Antidepressant	Patients <sup>†</sup>	%
Amitriptyline	11	18.3
Imipramine	3	5.0
Nortriptyline	1	1.7
Total	15	25.0
SSRI		
Antidepressant		
Fluoxetine	23	38.3
Sertraline	6	10.0
Paroxetine	2	3.3
Total	31	51.6
Benzodiazepine		
Diazepam	12	20.0
Alprazolam	10	16.7
Bromazepam	9	15.0
Lorazepam	2	3.3
Others	6	10.0
Total	39	65.0

<sup>†</sup> More than one drug used for patients.

The patients interviewed had an average age of 70 ± 7.6 years. The elderly women who were on anxiolytics and/or antidepressants were 70.3 ± 7.7 years old, while those who did not use these medications had a mean age of 69.2 ± 7.1 years.

A comparison of DHEA-S levels and the age of the patients showed significant differences (p = 0.016) between the groups (Figure 2). The results of this study showed a decreased hormone level in older patients. It is known that DHEA-S declines with age, and it is believed that this constitutes a hormone deficiency that has an important role in altered metabolic states and mental aging, and that may be involved in diseases associated with aging.

Statistical analysis of the data showed a significant difference (p = 0.019) in logDHEA-S between the elderly women who used antidepressant drugs and/or anxiolytics and women who did not take these types of medications. The average logDHEA-S was 3.7 ± 0.049 (0.53 µg / ml) for those taking medication and 3.4 ± 0.102 (0.39 µg / ml)

for those not on medication (Table 2).

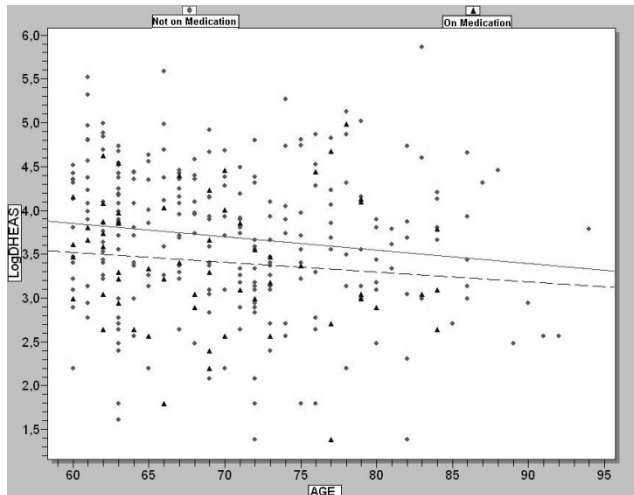


Figure 2. Statistical analysis of the relationship between logDHEA-S and age in elderly women taking or not taking antidepressants and/or anxiolytics (n=262), using linear regression. p<0.05.

Table 2. Mean logDHEA-S in elderly women on medication or not.

	Mean logDHEA-S	Standard error	95% CI
Not on medication (n=262)	3.7	0.049	3.6 – 3.8
On medication (n=60)	3.4*	0.102	3.2 – 3.6

\*p < 0.05

## DISCUSSION

The adrenal androgen dehydroepiandrosterone (DHEA) and its sulfated form DHEA-S have attracted considerable interest in recent years (Genazzani et al., 2011). Serum DHEA and DHEA-S levels differ from those of other major adrenal steroids (cortisol and aldosterone) in displaying a substantial decline with age (Enemoto et al., 2008, Leowattana, 2004). Recently, DHEA-S has been found to be a suitable marker of the aging process (Morrison et al., 2011, von Mühlen et al., 2007; Wolkowitz et al., 2011). Studies have reported that this androgen is associated with depression and that its levels in serum change when using antidepressant and anxiolytic drugs (Deuschle et al., 2004).

The data presented here show that only 19% of the elderly women studied used antidepressant and/or anxiolytic medications. This percentage is within the incident rates already reported by Giron and co-workers (Giron et al., 2005). It is believed that women are more common users of these drugs than men, because women undergo changes in their androgen levels after middle age (Haren et al., 2007).

Based on our results, a significant difference in logDHEA-S was found among ages in the elderly women. With the aging process, the serum concentration of this hormone declines gradually (Genazzani et al., 2011). Studies have shown that adrenal production of DHEA-S begins during puberty and peaks at 20 years old.

Beginning at the age of 25, serum DHEA-S begins to decline markedly and rapidly, so that, by age 75 years old, the serum DHEA-S level is 80% lower than at 24 years old (Mazat et al., 2001; Wolkowitz et al., 2011). Hormone replacement, sometimes used in postmenopausal women, changes DHEA-S levels (Sherwin, 1994). The participants of this study did not use any hormone replacement, because they were more than one decade past menopause. Studies have reported an association of low or undetectable DHEA-S levels with depressive symptoms in post-menopausal women who are not on hormone replacement (von Mühlen et al., 2007).

With regard to the use of antidepressant and anxiolytics drugs, DHEA-S levels were lower in the group of elderly women who did not take these drugs. However, these values, as well as those of the elderly women taking these medications, are within the reference range for post-menopausal women.

Other studies have shown that women with depression have low DHEA-S levels (von Morsink et al., 2007; Mühlen et al., 2007; Wolkowitz et al., 2011). However, the DHEA-S values observed in the present study were in the normal reference range for elderly women using antidepressants and/or anxiolytics, but significantly different from that of healthy women not suffering from depression and anxiety (Michael et al., 2000; Morrison et al., 2011).

Psychotropic drugs are the most prescribed drugs for the elderly (Forlenza, 1999). In this population, the choice of medication is very important. In our study group, benzodiazepines were the most used for the elderly women (65%), and although they cause more adverse reactions, they are very therapeutically effective (Alvarenga et al., 2008; Souza et al., 2003). Many reviews consider the selective serotonin reuptake inhibitor (SSRI) antidepressants the first-line treatment for depression in the elderly, because they have fewer side effects. This preference was observed in our study in 51.6% of the individuals. The use of tricyclic antidepressants was observed in 25% of the elderly women, and they are given to the elderly for depression. The efficacy of these antidepressants is well established, and in patients over 80 years old as well (Scalco, 2002).

The choice of antidepressant treatment in the elderly is influenced by medical and social conditions. The use of tricyclic antidepressants, SSRI and benzodiazepines requires more frequent office visits to monitor the treatment and often for laboratory tests (Forlenza, 1999).

The biological function of DHEA-S in humans is not completely defined. The abundance of this hormone and its decline with age, chronic disease and physiologic disabilities has led to the hypothesis that there is a correlation between DHEA-S and the aging process. Thus, the measurement of DHEA-S in the elderly is very important to have a better understanding about this hormone's role in aging and its involvement with the use of antidepressant and anxiolytic drugs.

Research on DHEA-S is intriguing and sometimes contradictory. Thus, further studies are necessary to elucidate fully the function of DHEA-S and how it relates to health and disease, as well as its physiologic and thera-

peutic roles.

#### ACKNOWLEDGMENTS

This study was supported financially by Conselho Nacional Desenvolvimento Científico e Tecnológico (CNPq) nº 475137/2009-4. Our thanks to Irênio Gomes Filho and Angelo José Gonçalves Bós for statistical advice. We would like to express our appreciation to Carla Helena Augustin Schwanke and Rodolfo Schneider for their helpful advice. Also received logistic support from the Pharmacy College, Hospital São Lucas da PUCRS and Instituto de Geriatria e Gerontologia, PUCRS.

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