# Neuro-endocrine Function in Older Men with Chronic Pain – Effects of Chronic Opioid Usage

**Clare Haylock**

**School of Medical Sciences**

**February 2013**

## Table of contents

**Abstract** 3

**Thesis declaration** 5

**Acknowledgements** 6

**Abbreviations** 7

**Introduction** 8

- Chronic pain in older persons
- Opioid therapy for chronic non-cancer pain
- Effects of opioids on neuro-endocrine function
- Opioid induced androgen deficiency
- Opioid induced adrenal dysfunction
- Pain and endocrine dysfunction
- Opioid induced endocrine dysfunction in older persons
- Study rational and hypothesis

**Methods** 23

- Subjects
- Study design
- Assessments
- Statistical analysis

**Results** 30

- Neuro-endocrine function
- Function
- Pain tolerance
- Cognition
- Depression and Symptoms of androgen deficiency

**Discussion** 39

**Appendices** 46

**References** 50

## Abstract

**Background:** There is increasing concern regarding adverse effects of long-term opioid medication use in non-cancer pain. Chronic opioid use has been shown to affect both the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes. Hormonal deficiency due to chronic opioid use might contribute to altered pain sensitivity and functional decline. This may be more pronounced in the geriatric population who has poor functional reserve.

**Methods:** A cross sectional study was performed looking at men over the age of 65 years, who have chronic non-malignant pain. Active arm subjects were taking continuous opioid treatment (≥ 4 weeks; dose equivalence ≥ 10mg oral morphine/day); control subjects were not receiving opioid treatment. Assessments included androgen studies (dehdroepiandrosterone sulphate (DHEA-S), testosterone, sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH)), waking salivary cortisol, low dose Synacthen test, neuropsychology testing, experimental cold pressor testing, cortisol testing during cold pressor testing, functional assessments (Instrumental Activities of Daily Living (IADL) Questionnaire, grip strength, and Timed Up and Go), Geriatric Depression Scale (GDS), Androgen Deficiency in Ageing Males Questionnaire (ADAM) and anthropometry.

**Results:** Twenty-six subjects were enrolled and completed the study. There were 7 men in the active arm and 19 in the control arm. Opioid subjects had a reduced mean cortisol response 30, 60, 90 and 120 minutes post cold-pain testing compared with controls (p-value = 0.055, 0.003, 0.088, 0.046 respectively), suggesting impaired cortisol release following environmental stress. No statistical difference was seen in waking salivary

cortisol or low dose Synacthen tests. There was no statistical difference between the two groups in measurements of the HPG axis. Opioid subjects performed significantly worse (mean 12 seconds) on Timed Up and Go compared to control subjects (mean 8.6 seconds; p-value = 0.036), however, the difference in grip strength and IADL scores between the two groups was not significant. Experimental pain threshold and tolerance and neuropsychology test results were not significantly different. Opioid subjects scored significantly higher on both ADAM (*median* opioid 8 vs. control 4; p-value = 0.0069) and GDS (*median* opioid 7 vs. control 1; p-value = 0.0024).

**Conclusion**: These results suggest that older patients taking chronic opioid therapy for non-cancer pain have decreased cortisol response to stress. Given that little difference was seen in pain threshold and tolerance between the two groups, the blunted cortisol response is unlikely to be due to the effect of opioids reducing pain. This finding is important in the ageing population as it suggests that those on chronic opioid medication may not adapt well to additional stressors, which is one of the defining features of frailty. Results also suggest patients on chronic opioid therapy have poorer functional levels, and more symptoms of androgen deficiency and depression compared to chronic pain sufferers who are not taking opioid medication.

## Thesis declaration

I, Clare Louise Haylock, certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

**Signature** _____ **Date** 04/02/2013

## Acknowledgements

I would like to acknowledge the following people:

1. My supervisors and research team for guidance and advice regarding this research:
    - Professor Paul Rolan, Professor of Clinical Pharmacology, University of Adelaide and Senior Consultant, Pain Management Unit, Royal Adelaide Hospital.
    - Associate Professor David Torpy, Senior Consultant Endocrinologist, Endocrine and Metabolic Unit, Royal Adelaide Hospital
    - Dr John Maddison, Consultant Geriatrician, Department of Geriatric and Rehabilitation Medicine, Royal Adelaide Hospital
    - Dr Lucia Gagliardi, Consultant Endocrinologist, Endocrine and Metabolic Unit, Royal Adelaide Hospital; The Queen Elizabeth Hospital, Woodville SA

2. Pain and Anaesthesia Research Centre Staff, particularly Ms Melanie Gentgall and Ms Kathy Heyman, who helped with data collection.

3. Ms Amie Foran, Clinical Psychologist, Royal Adelaide Hospital, who gave advice on use of neuropsychology tests and instructed PARC staff how to administer the tests.

4. Ms Nancy Briggs, Statistician, Data Management & Analysis Centre, Discipline of Public Health, The University of Adelaide, who helped with statistical analysis.

5. Consultants and registrars working in the Pain Management Unit at the Royal Adelaide Hospital for helping with recruitment.

## Abbreviations

| Abbreviation | Meaning |
|---|---|
| ACTH | adrenocorticotropic hormone |
| ADAM | Androgen Deficiency in Ageing Males |
| BMI | body mass index |
| DASS-21 | Depression, Anxiety and Stress Scale |
| DHEA-S | dehydro epiandrosterone sulphate |
| CBC | complete blood count |
| CRH | corticotropin releasing hormone |
| CRP | c-reactive protein |
| ESR | erythrocyte sedimentation rate |
| FSH | follicle stimulating hormone |
| fT3 | free triiodothyronine |
| fT4 | free thyroxine |
| GDS | Geriatric Depression Scale |
| HPA | hypothalamic-pituitary-adrenal |
| HPG | hypothalamic-pituitary-gonadal |
| IADL | Instrumental Activities of Daily Living |
| IGF-1 | Insulin-like growth factor (somatomedin C) |
| LCT | Letter Cancellation Task |
| LH | luteinizing hormone |
| MMSE | Mini Mental State Examination |
| NSAIDs | non steroidal anti-inflammatory drugs |
| OPIAD | opioid induced androgen deficiency |
| PARC | Pain and Anaesthesia Research Clinic |
| QOL | quality of life |
| RBANS | Repeatable Battery of Adult Neuropsychological Status |
| SHBG | sex hormone binding globulin |
| TCA | tricyclic antidepressant |
| TSH | thyroid stimulating hormone |
| TT | total testosterone |
| WHO | World Health Organisation |
| WTAR | Wechsler Test of Adult Reading |