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

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Table of contents

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

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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

Introduction

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 may contribute to altered pain sensitivity and functional decline. This may be more pronounced in the geriatric population who has less functional reserve. This research examines the hypothesis that chronic opioid use causes dysregulation of the neuroendocrine axis, and that older people are vulnerable to the clinical side effects of neuroendocrine dysfunction.

Chronic pain in older persons

Chronic pain is a significant problem amongst elderly or older persons and is therefore an important topic of research in geriatric medicine and gerontology. The definition of 'elderly' or older person is generally accepted as a chronological age of 65 years or older in most developed world countries. In Australia, 65 years corresponds to the current pension age for men and is the age most often used by the Government to define older people(1). Pain increases with age until at least the seventh decade(2, 3). The high prevalence of pain among older persons is due to the burden of multiple comorbidities and age-related painful diseases such as osteoarthritis, degenerative spinal disease, diabetic neuropathy, post-herpetic neuropathic pain and frailty(2, 4). Studies have shown that chronic pain affects 20-50% of community dwelling older persons and up to 85% of older persons in residential care(2, 3, 5, 6).

There is considerable heterogeneity in studies evaluating the prevalence of chronic pain in terms of populations sampled, sampling methods and definitions of chronicity and site of

pain. Blyth and colleagues (3) investigated the prevalence of chronic pain in Australia through telephone interview. They found chronic non-cancer pain affects 17% of males and 20% of females. The peak prevalence of pain in men occurred in the 65-69 year-old age group (27%) and peak prevalence of pain in females occurred between 80-84 years (31%). National statistics from the United Kingdom report 56% of men and 65% of women over the age of 75 suffer from pain or discomfort(7). Statistics from the United States of America indicate 1 in 5 older people take regular analgesics for chronic pain(8).

Chronic painful conditions impact greatly on quality of life and functional capacity. Chronic pain is associated with depression and anxiety, sleep disturbance, decreased socialization, impaired mobility, decreased cognition, and increased dependency for activities of daily living(8-11). Blyth and colleagues showed pain is commonly associated with interference with daily activities, especially in older persons(3, 4). Despite the high prevalence and negative impact of pain in older persons, there is little literature to guide optimum management.

Pain in the older population is already an important public health concern, due to the overall community burden. With the growing ageing population, the prevalence of chronic pain and its cost to society is expected to increase. Chronic pain results in enormous economic costs to society, not only due to its prevalence and the impact on the chronic pain sufferer, but also due to the associated care burden. In Australia, allocated health expenditure associated with chronic pain in 2007 was estimated to be $6.1 billion(12). In addition to health expenditure in 2007, the cost of informal care for people with chronic pain, measured by opportunity, cost was $1.3 billion(12).

Assessment and management of chronic pain in older persons is challenging. There are many reasons for pain being a difficult clinical problem in this population. Assessment is difficult due to under-reporting of pain and barriers to communication such as cognitive decline, hearing impairment and dysphasia(8, 11, 13). Older persons often under-report pain due to stoical attitudes, concerns about being be a burden on health care providers or family, and because many attribute pain to the normal ageing process(8). Deciding on a treatment regimen is complicated in older people due to multi-morbidity, frailty and polypharmacy, which result in increased susceptibility to side effects of analgesics, and adverse drug interactions(11). Adverse drug reactions in older persons occur commonly due to non-steroidal anti-inflammatory drugs (NSAIDs) and tricyclic antidepressant medications (TCAs). Tricyclic antidepressant medications are used with caution due to their anticholinergic side effects and NSAIDs have been implicated in almost one quarter of adverse drug reactions causing hospitalisation in older adults(14). Given the challenges associated with assessment and management of pain in older persons, it is not surprising that many studies have reported pain being under-recognised and under-treated in this group(6, 9-11).

Despite pain in the elderly being a common and often ineffectively managed problem, there is limited literature focusing on pain management in older persons. Older persons have been systematically excluded from trials evaluating analgesics in chronic pain(8). Most national and international guidelines addressing management of chronic pain rely on expert opinion rather than robust literature. The World Health Organisation (WHO) hierarchical analgesic ladder for treatment of pain was initially intended for pain associated with malignancy, however its use has more recently been adapted for non-cancer pain, albeit without strong evidence(11). Guidelines from organisations including the American

Geriatric Society, American Academy of Pain Medicine and the American Pain Society have advocated use of opioids in non-cancer pain(14, 15). Over the past 15-20 years, long-term opioid use has increased in all age groups. Campbell and colleagues (16) studied 4 million individuals on health care plans in the United States of America and found opioid use increased in both men and women between 1997 and 2005. In 1997, 3% of men and 5 % of women aged 65 or older were taking opioid medications whereas in 2005 these figures increased to 5% of men and 8% of women(16). Okie and colleagues report over 3% of the US adult population are currently receiving long-term opioid treatment for chronic non-cancer pain(17). In Australia, opioid prescribing has increased dramatically since 1992. The total number of Pharmaceutical Benefit Scheme opioid prescriptions in Australia increased from 2,397,006 in 1992 to 6,998,556 in 2007(18). Although these figures have not been categorised according to age, it can be assumed from general trends that opioid use in Australia has increased amongst the older population. The increased acceptance and use of opioid medications is due to both the focus on perceived under-treatment of pain as well as aggressive marketing of opioids and opiates over the past 15 years(15, 17). Research examining the use of opioid medications for the treatment of chronic non-cancer pain is of great importance given the increase in prescribing. Currently, there is little literature examining prolonged opioid therapy to guide management of chronic pain non-cancer pain, especially in older persons.

Opioid therapy for chronic non-cancer pain

The increasing utilisation of opioid analgesics in chronic non-cancer pain has prompted concerns about both adverse effects and the effectiveness of this treatment in long-term use. There are few studies evaluating chronic opioid use and there are no efficacy studies beyond 16 weeks(19). More concerning however is evidence of poor pain control, opioid-

induced hyperalgesia and poor outcomes in terms of quality of life (QOL) and function in chronic opioid use. Hyperalgesia is defined as heightened pain sensitivity, due to enhanced nociceptive signal processing(20). In opioid-induced hyperalgesia, this increase in pain sensitivity is thought to occur as a direct result of opioid treatment(20). Well-known adverse effects of chronic opioid use include tolerance, dependence, obstructive sleep apnoea, constipation, diversion, and unintentional deaths(16, 17). Much less well known are opioid-induced hyperalgesia, gonadal dysfunction, and osteoporosis. Results of a recent Danish study that evaluated 1906 chronic pain patients showed that chronic opioid users reported significantly more pain, lower quality of life and inferior self-rated health when compared with non-opioid users. Even after controlling for pain, these associations persisted(21). Studies in former opioid addicts and chronic pain patients suggest opioid exposure increases pain sensitivity. Chu and colleagues (22) performed a pilot study evaluating 6 patients with chronic low back pain. The experimental pain threshold and pain tolerance, using cold pressor test, were significantly decreased after 1 month of oral morphine therapy, indicating the development of opioid-induced hyperalgesia(22). However, since this preliminary study in 2006, there has not been further information published. Poor functional outcomes and opioid-induced hyperalgesia may be related to neuroendocrine effects of opioid analgesics, which have been little explored. This research examines whether chronic opioid use causes neuroendocrine dysfunction and investigates pain and functional outcomes.

Effects of opioids on neuro-endocrine function

The endocrine system is affected by both pain and treatment for pain. These mechanisms are complex and may involve central opiates, noradrenergic and dopaminergic systems. Chronic opioid administration has been shown to inhibit the HPA and HPG axes(23-25).

Opioid suppression of the neuroendocrine system may lead to hormonal deficiency, which may in turn cause pain, debility and impaired quality of life.

Opioid induced androgen deficiency

Androgen deficiency is a common complication in men taking opioids. Hypogonadism results from mu and delta opioid receptor mediated suppression of gonadotropin secretion and direct reduction in testicular testosterone secretion(23, 26, 27). Studies examining opioid addicts documented hypogonadism over three decades ago(28-32). These studies were intriguing, however were largely forgotten and not thought to impact greatly on clinical practice until more recently. Studies evaluating patients on intrathecal opioids have shown significant hypogonadism(24, 33-35). Table 1 summarises studies evaluating hypogonadism in men on opioid treatment via oral and transdermal or intrathecal routes. None of these studies examined chronic opioid use and hypogonadism in older persons, which is the focus of this research.

More recently, cross-sectional studies have shown hypogonadism affecting both males and females taking oral or transdermal opioid medications for non-cancer pain(36-38). Daniell and colleagues (36) studied 54 men who were consuming sustained-action opioids and found subnormal total testosterone (below 260ng/dL) in 74% of subjects. A majority of subjects (87%) reported developing severe erectile dysfunction or decreased libido after commencing opioid medication(36). Fraser and colleagues (38) studied testosterone and bone mineral density in men and premenopausal women taking oral or transdermal opioid medication for chronic non-cancer pain and found a high prevalence (83%) of men had total testosterone below age-specific normal range. Serum estradiol level was below normal range (120pmol/L) in 36% of women and the prevalence of hypogonadism based

on oligomenorrhea or ammenorrhea was 23%. Osteopenia was reported in 50% of men and 21% of women in this study(38). A testosterone replacement study was performed by Daniell and colleagues (23) in men with opioid induced androgen deficiency. Subjects had markedly subnormal total testosterone at baseline and were treated with a transdermal testosterone patch for 24 weeks. The patch was initiated at 5mg/day for 12 weeks and increased to 7.5mg/day for another 12 weeks. After replacement testosterone patch therapy at a dose of 7.5mg/day, mean total testosterone was within normal range and 88% of subjects had free testosterone levels within normal range. There was no significant change in opioid use, however daily functioning was less restricted by pain and subjects reported increased psychological wellbeing and fewer symptoms of depression and hypogonadism after commencing androgen replacement(23).

Table 1 – Studies assessing gonadal function in men on long-term opioid therapy for non-malignant pain

Author	Type of study	Number of subjects	Age of subjects	Opioid studied	Daily dose of opioid	HPG-axis	Pain	Function	Depression	Symptoms of hypogonadism
Daniell H (36)	Cross-sectional	Active arm - 54 males; Control arm - 27 pain free males.	Mean 49.9 years (range 30-78)	Oral or transdermal opioid ≥ 2 weeks. Oxycodone, morphine sulfate, methadone, tramadol, hydrocodone.	Dose equivalent ≥ 20mg hydrocodone	Active arm: FT subnormal in 56%, and TT subnormal in 74% of subjects. Inappropriately low LH values in active arm.	Not evaluated	Not evaluated	Not evaluated	87% reported erectile dysfunction or decreased libido after initiating opioid therapy.
Daniell et al(23)	Prospective (open-label)	Active arm - 16 males; No control arm.	Range 24-55 years	Oral or transdermal opioid ≥ 1 month. Methadone, oxycodone, morphine sulphate, fentanyl. *Replacement testosterone 5mg/d for 12 weeks then 7.5mg/d for 12 weeks.*	Methadone ≥20mg, oxycodone ≥30mg, morphine sulphate ≥30mg, or transdermal fentanyl ≥ 25mcg/hr.	FT and TT subnormal at baseline; low normal on 5mg/day and mid-normal range on 7.5mg/day. LH decreased with testosterone therapy.	Significantly lower BPI-SF interference scores than baseline. No significant change in opioid dose.	PGWB scores increased after 12 weeks of testosterone replacement at 7.5mg/day.	BDI-II scores decreased in a dose dependent manner.	Symptoms of hypogonadism scores decreased significantly with testosterone replacement.

FT: Free testosterone
TT: Total testosterone
LH: Luteinizing hormone
BPI-SF: Brief Pain Inventory-Short Form. The WHO Collaborating Centre developed the Brief Pain Inventory for Symptom Evaluation in Cancer Care. It measures both intensity of pain and interference of pain with daily functioning. The tool has demonstrated reliability and validity and has been used widely in studies examining the effectiveness of pain treatment(39).
PGWB: Psychological General Well-Being Index. The PGWB is a measure of subjective psychological wellbeing. It is a validated questionnaire that comprises six subscales to evaluate anxiety, depression, vitality, positive well-being, self-control and general health(40).
BDI-II: Beck Depression Inventory, Second Edition. The BDI-II is a commonly employed measure of depressive symptomatology amongst chronic pain sufferers. Studies have shown the BDI-II has validity and internal consistency for assessing depressive symptoms in patients with chronic pain(41).

Table 1 (continued) - Studies assessing gonadal function in men on long-term opioid therapy for non-malignant pain

Author	Type of study	Number of subjects	Age of subjects	Opioid studied	Daily dose of opioid	HPG-axis	Pain	Function	Depression	Symptoms of hypogonadism
Fraser et al(38)	Cross-sectional. Single arm.	Active arm - 12 males; No controls	Mean 45.4 ± 5.5 years	Oral or transdermal opioid ≥ 1 year	Morphine equivalent 679 ± 620mg	Mean TT 6.9 ± 4.2nmol/L. TT below age specific normal range in 83%.	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Finch et al(33)	Cross-sectional	Active arm - 10 males; Control arm - 10 males with chronic pain.	Mean 46.5 ± 3.5 years.	Intrathecal morphine. Mean duration 2.5 years (0.02-8 years)	Mean dose 11.6mg (range 0.5-40mg)	Active arm mean TT 4.9 ± 1.1nmol/L vs. controls mean TT 12.2 ± 1.6nmol/L (p=0.003). LH + FSH lower in active arm.	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Roberts et al(34)	Prospective	Active arm - 10 males. No controls.	Mean 52 years (range 25-64)	Baseline oral opioid (mean 211 ± 60mg morphine equivalent). Commenced intrathecal opioid therapy.	Mean intrathecal dose week 1, 4, 12 (morphine equivalent): 2.6 ± 0.5mg, 3.3 ± 0.6mg, 5.3 ± 1.2mg.	Mean TT at baseline, week 1, 4, 12 (nmol/L): 7.7 ± 1.1, 2.0 ± 0.7, 2.8 ± 0.5, 4.0 ± 0.9. Decrease in FSH. No change in LH, SHBG, prolactin.	Not evaluated	Not evaluated	Not evaluated	Decreased libido and potency

TT: Total testosterone
LH: Luteinizing hormone
FSH: Follicle stimulating hormone
SHBG: Sex hormone binding globulin

Table 1 (continued) - Studies assessing gonadal function in men on long-term opioid therapy for non-malignant pain

Author	Type of study	Number of subjects	Age of subjects	Opioid studied	Daily dose of opioid	HPG-axis	Pain	Function	Depression	Symptoms of hypogonadism
Paice et al(35)	Cross-sectional. Single arm.	Active arm - 6 males; no control arm	Mean 39.8 ± 5.7 years (range 34-50)	Intraspinal morphine or hydromorphone + oral opioids	Intraspinal mean dose 18.65 ± 17.6mg morphine-equivalent + oral opioid 71.8 ± 112.6mg morphine-equivalent.	Mean TT 197.7 ± 119.8ng/dL. 5 of 6 subjects had subnormal TT. No difference in FSH, LH, prolactin and SHBG.	Not evaluated	Not evaluated	Not evaluated	Reduction in libido. 4/6 had erectile dysfunction.
Abs et al(24)	Cross-sectional	Active arm - 29 males; control arm-11 males with chronic pain.	Mean 48.4 ± 11.0 years	Intrathecal morphine or hydromorphone	Mean dose 4.8 ± 3.2mg morphine equivalent (range, 0.6-15.0mg)	Active arm TT and FAI significantly lower. 86.2% active vs. 9.1% controls had subnormal TT. LH significantly lower in opioid group. No difference in FSH.	No difference in NHP- pain scores.	No difference in NHP - total scores.	Not evaluated	95.8% reported decrease libido and potency after initiating intrathecal opioid.

TT: Total testosterone
LH: Luteinizing hormone
FSH: Follicle stimulating hormone
SHBG: Sex hormone binding globulin
NPH: Nottingham Health Profile. The NHP was designed to give a brief indication of perceived physical, social and emotional health status. Part I contains 38 yes/no items grouped into 6 sections: pain, physical ability, emotional reactions, energy, social isolation and sleep. Part II provides a brief indicator of handicap in terms of activities of daily living(42, 43).

Hypogonadism is not widely recognised as a consequence of opioid therapy in clinical practice. This may be explained by the overlap in clinical consequences of hypogonadism and chronic pain (see Table 2). Poor health in chronic pain treatment may not only be due to opioids and chronic pain, but also due to endocrinopathy associated with treatment. In geriatric medicine many of the symptoms of hypogonadism may be incorrectly attributed to the ageing process, however these symptoms are important to recognise, as they may be amenable to hormone replacement therapy. This research examines both the biochemical and clinical effects of chronic opioid therapy in older persons.

Table 2 – Clinical manifestations of chronic pain (8, 10, 11) and hypogonadism(44-46).

Chronic pain	Hypogonadism
• Depression • Poor functioning • Osteoporosis • Decreased mobility • Decreased muscle strength • Disturbed sleep	• Depression • Poor functioning • Osteoporosis • Decreased muscle strength • Decreased energy • Disturbed sleep • Irritability

Opioid induced adrenal dysfunction

The effects of opioid therapy on the HPA axis are most likely delta and kappa-receptor mediated(26). Evidence suggests that opioids disrupt the normal circadian rhythm of cortisol secretion, suppress basal hormonal levels and suppress the response to acute activation of the system(24, 47). The effects were first observed many years ago in heroin and methadone addicts. Low basal cortisol and decreased diurnal variation of cortisol were reported in 3 studies examining heroin addicts and methadone patients in the 1980s and 1990s(32, 48, 49).

There have been very few studies evaluating adrenal function in pain patients on chronic opioid therapy. Abs and colleagues (24) published a cross-sectional study examining 73 patients on intrathecal opioid treatment. Subjects treated with long-term intrathecal opioids were found to have low basal cortisol and decreased response to acute activation of the HPA axis via insulin-induced hypoglycaemia when compared to controls. Palm and colleagues (50) performed a small prospective study in 8 chronic pain patients and found administration of sustained release morphine lowered both adrenocorticotropic hormone (ACTH) and cortisol levels at 1, 4 and 12 weeks of treatment. A corticotropin-releasing hormone (CRH) stimulation test was performed in 2 of the 8 patients and ACTH and cortisol concentrations increased appropriately suggesting pituitary and adrenal stimulation of the HPA axis remained intact. Apart from these two studies, two case reports have been published demonstrating adrenal insufficiency in patients on chronic transdermal and oral opioid therapy(47, 51). In both of these patients, adrenal function improved with tapering of opioid medication. The mechanisms by which chronic opioid therapy induces hypocortisolism are not known. There is a deficiency of data examining the response of the HPA axis to dynamic testing in chronic opioid therapy. This research looks at the effects of chronic oral or transdermal opioid use on basal functioning of the HPA axis, as well response of the axis to exogenous ACTH and physiological stress.

Patients with primary adrenal insufficiency self-report impaired health-related quality of life, which is thought to be due to an inability of oral therapy to restore physiological hormone levels and biorhythm(52). This theory could be extrapolated to propose that opioid induced disruption to the HPA axis contributes to functional decline and decreased motivation in chronic pain patients. The clinical relevance of opioid induced adrenal insufficiency has

not been studied systematically. This research examines both biochemical and clinical outcomes of chronic opioid treatment.

Pain and endocrine dysfunction

Both androgen deficiency and cortisol modulation have been linked to altered pain response(53). Sex hormones have a modulatory effect in pain sensitivity, and animal models have shown that androgen replacement results in increased pain thresholds(23). However, studies examining pain sensitivity as a function of gonadal status in humans are lacking. Experimental cold pain testing and pain scales are used to examine pain response in this research to determine whether there is a relationship between pain sensitivity and hypogonadism.

The relationship between chronic pain and dysregulation of the HPA axis is an area of great interest given the connection between pain and the stress system. The HPA axis plays a crucial role in the stress system. Basal cortisol secretion is essential to sustain life and increased cortisol secretion is necessary in response to stress or events that threaten homeostasis such as sepsis, trauma or psychological challenge(54). There is substantial evidence that hypocortisolism is associated with the pathogenesis of widespread and regional pain syndromes such as fibromyalgia and chronic pelvic pain(54-59). Price and colleagues showed increased pain responses in patients with fibromyalgia who were exposed to experimental hot or cold pain stimuli, which is suggestive of hyperalgesia(60). Abnormal endocrine function may be responsible for central sensitising events causing hyperalgesia. Pain is a potent stressor and in the short term has been shown to result in stimulation of the HPA axis. It is hypothesised that chronic stress eventually causes dysregulation and hypoactivity of the HPA axis(26, 55, 56). The pathogenesis of

hypocortisolism in chronic pain is unknown, however altered CRF release from the hypothalamus has been postulated(57, 61). Chronic pain sufferers with hypocortisolism have a stressed system that is functioning below normal homeostatic reserve. A hypothesis of this research is that chronic opioid therapy may further decrease functioning of the HPA axis in this group and in turn may contribute to opioid-induced hyperalgesia.

Opioid induced endocrine dysfunction in older persons

Although endocrine dysfunction due to chronic opioid treatment has been recognised for some time, the scale of the problem in older persons is not known. Older persons are likely to be at particular risk of the clinical manifestations of endocrine deficiency as they have reduced endocrine reserve and have less ability to respond to additional stressors. Blyth and colleagues(4) explored the relationship between pain, frailty and comorbid burden and found a significant association between frailty and intrusive pain. Frailty is increasingly being recognised as a distinct entity and can be described as functional and biological decline, accumulating across multiple physiological systems, resulting in a limited capacity to respond to additional stressors(4). Not only is this population more susceptible to pain but likely to be more susceptible to the adverse clinical effects associated with opioid induced endocrine dysfunction. Furthermore, subtle manifestations of gonadotropin and cortisol deficiency such as fatigue, muscle weakness, and poor sense of wellbeing may be attributed inappropriately purely to older age. This study examines both biochemical and clinical effects of opioids and aims to determine whether there is a significant effect of opioid endocrinopathy of pain and functioning.

Study rational and hypothesis

Most of the literature on opioid-induced endocrine dysfunction is limited to biochemical diagnosis of endocrine deficiency without a clinical assessment of the consequences. Furthermore, literature regarding opioid endocrinopathy is lacking in older persons. Older people may be vulnerable to subtle endocrine effects associated with opioid medications given they have reduced physiological reserve. The study hypothesis is that chronic opioid administration is associated with suppression of gonadal and adrenal function in older people. Previously, endocrine deficiency associated with opioid therapy was documented in opioid use at large doses. We evaluated subjects on smaller doses, more commonly used in clinical practice, to determine whether there is a significant health problem.

Methods

A cross-sectional observational study was performed in older men with chronic non-malignant pain. The study was approved by the Royal Adelaide Hospital Human Research Ethics Committee and all subjects provided written informed consent.

The recruitment goal was 30 subjects in the active arm and 30 controls, which are similar numbers to previous studies in this area that have demonstrated changes to the neuroendocrine axis(24, 36). These numbers would result in the study being powered to detect a 30% difference in the mean values for adrenal and gonadal function assuming a coefficient of variation (CV) of 0.35 or below, given there is a 30% normal variability in endocrine function.

This study included only men given the primary objective of studying hypogonadism in older persons. Older women were excluded from this study given their post-menopausal state. Investigating for androgen deficiency in women was not considered, as there is no well-defined clinical syndrome or normative data in women to define androgen deficiency.

Subjects

The study population included male subjects aged over 65 years who reside in the community and who were chronically consuming oral or transdermal opioids as analgesia for chronic non-malignant pain (defined as pain every day or almost every day for greater than 3 months). Subjects in the active arm must have been receiving continuous opioid treatment for at least 4 weeks at dose equivalence of at least 10mg oral morphine per day. Table 3 shows opioid equianalgesic doses. Patients taking full opioid agonists were included. Patients taking buprenorphine, a partial opioid agonist, were excluded, as

buprenorphine has recently been shown not to lower testosterone levels(27). Control subjects must not have been receiving opioid treatment.

Table 3 – Opioid equianalgesic table

Opioid	Equianalgesic dose
Oral morphine	30mg daily
Oral codeine	200mg daily
Oral oxycodone	20mg daily
Oral methadone	3.6mg daily
Transdermal fentanyl	12.5mcg/hour = 0.3mg daily

Equianalgesic doses adapted from Mercadante and Caraceni (62) and Gordon and colleagues (63).

Exclusion criteria were an active inflammatory condition, glucocorticoid or androgen therapy within 6 months, acute illness or hospital admission within 1 month, severe major organ dysfunction, abnormal sleep wake cycle (that could affect validity of salivary cortisol measurements), a language barrier that would prevent participation in neuropsychology testing, cognitive or visual impairment, impaired dominant hand function, previous neuropsychology testing, and medical conditions in which experimental cold pain testing is contraindicated (unstable angina, Raynaud's disease).

Male subjects were recruited via physician referral, advertisements in local media and fliers placed at the Royal Adelaide Hospital. Advertisements were printed in the Messenger Newspaper, Sunday Mail and The Senior Newspaper. Potential subjects were also identified through the Royal Adelaide Hospital chronic pain database. These men were sent a letter requesting participation from their treating physician. 22 possible subjects were identified from the Royal Adelaide Hospital chronic pain database. Of these men, 4 were included, 10 were not interested, 1 had passed away, 1 was not taking sufficient opioid dose for participation and 6 had illnesses or were taking medications that excluded them from participation.

Telephone screening was performed prior to participation. Patient information sheets were sent to eligible men and written informed consent was obtained from all men prior to their participation.

Study design

Research was conducted at the Pain and Anaesthesia Research Centre (PARC) at the Royal Adelaide Hospital. Each subject was assessed over 2 consecutive days. Initial evaluation included complete medical history, medication profile, and anthropometric measurements. Anthropometric measurements including height, weight, waist and hip circumference and skin-fold testing (biceps, triceps, subscapular and supra-iliac sites), were measured to assess possible physical changes associated with hypogonadism. Percentage body fat was estimated from skin fold testing data using the Durnin and Womersley skin-fold equation for body density and Siri's equation for percentage body fat(64).

Laboratory assessments

Salivary cortisol was collected by subjects in their own home on waking and 30 minutes after waking, using a salivette. There is good correlation between salivary cortisol and free plasma cortisol(65). Salivary cortisol has been validated as a measure of HPA function(65). All other laboratory tests were collected at PARC. These included low dose Synacthen test, androgen studies (dehdroepiandrosterone sulphate (DHEA-S), testosterone, sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH)), serial serum cortisol testing pre and post cold pressor test (samples taken at time=0, 30minutes, 60minutes, 90minutes and 120minutes), thyroid stimulating hormone (TSH), free thyroxine (fT4), free tri-iodothyronine (fT3), insulin-like

growth factor (IGF-1), complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). All hormone analyses were performed by SA Pathology (South Australia, Australia) using validated methods. Endocrine serum and saliva samples were centrifuged and transferred to a freezer at -80 degrees Celsius prior to being sent to SA Pathology in a single batch.

Neuropsychology testing

Subjects underwent initial cognitive screening with Folstein Mini Mental State Examination (MMSE)(66). Neuropsychology testing included Wechsler Test of Adult Reading (WTAR), Repeatable Battery of Adult Neuropsychological Status (RBANS), Depression, Anxiety and Stress Scale – 21 (DASS-21), Letter Cancellation Task (LCT), and Phonemic Fluency.

WTAR combines patient demographics and individual reading and vocabulary ability to give an estimate of premorbid intellect(67).

RBANS measures immediate and delayed memory, visuospatial and constructional skills, language, and attention(68). RBANS was selected because it is a gives a broad measure of neuropsychological performance and has normative data for older persons(69).

Depression Anxiety Stress Scales (DASS) assesses the severity of the core symptoms of depression and anxiety(70). The DASS-21 has been validated in a sample of elderly primary care patients(71). DASS-21 and the Geriatric Depression Scale (GDS) (see appendix 1) were used to assess for depression.

Letter Cancellation Tasks are paper and pencil tests widely used in clinical and research

settings as quick measures of attention and concentration(72).

Verbal fluency FAS test is a commonly used neuropsychology test of phonemic fluency. It requires the subject to list as many words as possible beginning with an F, A and S within 60 seconds(73).

Pain testing

The Likert 10 point pain scale (see appendix 2) is a psychometric scale commonly used in health research studies. This score was used to obtain a baseline pain score for subjects.

Experimental Cold Pain Testing was performed as a measure of pain threshold and pain tolerance. Experimental cold pain testing causes pain that mimics chronic painful conditions without causing tissue damage(74). Experimental cold pain testing has been widely used in the evaluation of psychological and physiological pain treatments(74). Equipment consisted of two temperature-controlled water baths of 34.5-35.5°C and 0.5-1.5°C. Each subject's non-dominant forearm and hand (fingers wide apart) were placed (vertically) into the warm water for exactly 2 minutes. At 1 minute 45 seconds, a blood pressure cuff was inflated to a pressure 20 mmHg below the diastolic blood pressure (to minimise the role of blood flow in determining the reaction to cold). At exactly 2 minutes, the forearm was placed into the cold-water bath. The subject's eyes were covered for the entire procedure to minimise distraction and cues for time. Once the arm was immersed in the cold water bath, subjects were asked to indicate when they first experience pain, and asked to leave their arm submerged until they could no longer tolerate the pain, with a maximum cut-off time of 3 minutes. Endpoints were measured as time (seconds). Measures for determining the resultant pain sensitivity were pain threshold (when the

subject first felt pain), and pain tolerance (when the subject could no longer tolerate the stimulus).

Functional assessments

Functional assessments included Instrumental Activities of Daily Living (IADL) questionnaire (see appendix 3), grip strength, and Timed Up and Go.

The Lawton Instrumental Activities of Daily Living Questionnaire is a self-reporting instrument that provides a brief summary of the older person's current functioning(75). This assessment instrument is widely used in both clinical practice and research.

The handgrip strength test was measured with a hand-held dynamometer. Participants were asked to perform the task twice with the dominant hand. The higher of the two measures was used in the analysis. The handgrip test estimates muscle strength and identifies people with functional limitation and disability(76).

Timed Up and Go measures the time it takes a subject to stand up from an armchair, walk a distance of 3 meters, turn, walk back to the chair, and sit down. It was developed as a clinical measure of basic mobility skills for community-dwelling elderly and has been used extensively in research(77, 78).

Clinical features of androgen deficiency

Clinical features of androgen deficiency were assessed using the Androgen Deficiency in Ageing Males Questionnaire (see appendix 4)(46). This screening questionnaire has been validated to detect androgen deficiency in males over 40 years of age(45).

Study flow chart

Procedure	Day 1	Day 2
Informed consent	X	
Inclusion/exclusion criteria	X	
Complete medical history	X	
Salivary cortisol collection	X	
CBE, ESR, CRP	X	
Fasting serum glucose and insulin collection	X	
Thyroid function tests	X	
Gonadal function tests	X	
IGF-1	X	
Prolactin	X	
Cognitive testing	X	
Low Dose Synacthen Test	X	
Androgen Deficiency Questionnaire	X	
Familiarization of cold pain testing	X	
Functional assessments		X
Experimental cold pain tolerance testing		X
Cortisol measurements during cold pain testing		X

Statistical analysis

Statistical analyses initially assumed a normal distribution and results were compared using an independent samples t-test. A Welch-Satterthwaite correction was used where samples had unequal variances. A non-parametric test, the Mann-Whitney U test, was performed where data was non parametric.

Data were also analysed for effect size using Cohen's *d*. Effect size provides a description of the size of an observed effect that is independent of the influences of sample size. When the effects are large but non-significant, further research with greater power is required(79). Cohen's *d* is used to examine the difference between two groups by calculating effect size based on standardized differences between the means(79). In this study, Cohen's *d* quantified the standardized difference in parameter means between the control subjects and opioid subjects normalized at the joint standard deviation, $d=(Mean_{Control} - Mean_{Opioid})/sd_{Combined}$. An absolute value of $d=0.2$ indicates a small effect size, 0.5 indicates a medium one, and 0.8 indicates a large one(80).

Results

26 subjects were enrolled and completed the study. No subjects were found to have active inflammation according to inflammatory markers. Table 4 summarises demographics, pain syndromes, analgesic regimens and MMSE results for the study. In the enrolled study group, the mean age in both groups was 71, and all subjects were Caucasian. The opioid group had a higher Body Mass Index (BMI), however this was not statistically significant (independent samples t-test with Welch-Satterthwaite correction p-value=0.12). There was no statistically significant difference between the two groups in terms of waist and hip circumference and percentage body fat. The majority of subjects in the group receiving opioids had pain syndromes involving the back or spine. There were more subjects with neuropathic pain in the control group and a higher percentage of opioid subjects had back pain. The range of opioid doses in the opioid group was wide, with most being on small doses of opioid. Screening of cognitive function with MMSE showed comparable results with a median MMSE of 29 for opioid subjects and 30 for controls.

Table 4 - Characteristics of Subjects

	Opioid subjects (n=7)	Control subjects (n=19)
Demographics		
Parameter, mean (range)		
Age (yr.)	71 (65-75)	71(65-86)
Anthropometry		
Weight (kg)	94 (77-129)	85 (68-105)
BMI (kg/m^2)	31 (26-33)	27 (22-34)
Level of education (yr.)	11 (10-13)	11 (9-16)
Pain syndrome		
Syndrome, n (%)		
Back/spine pain	5 (71%)	7 (37 %)
Extremity pain	2 (29%)	6 (32%)
Neuropathic pain	0	6 (32%)
Analgesia		
Daily opioid dose (oral morphine equivalent), n (%)		
10-50mg	4 (57%)	0
50-100mg	0 (0%)	0
>100mg	3 (43%)	0
Other analgesia, n (%)		
Paracetamol	2 (29%)	2 (11%)
NSAIDs	1 (14%)	4 (21%)
TCA	0	2 (11%)
Pregabalin	0	2 (11%)
Cognition		
MMSE score, median (range)	29 (28-30)	30 (26-30)

BMI – Body mass index
NSAIDs – non-steroidal anti-inflammatory drugs
TCA – Tricyclic antidepressant

Pain Assessments

Likert Pain Scale scores were higher for opioid subjects compared with the control subjects however this difference was not significant (p-value >0.05). The difference in pain threshold and tolerance between the two groups was not significant (see table 5 below).

Table 5 – Measures of pain

	Opioid subjects (n=7)	Control subjects (n=19)	M-W U test p-value
Parameter, median (range)			
Likert Pain Scale (0-10)	5 (1-9)	3(0-7)	0.50
Parameter, mean (range)			
Experimental pain testing			
Threshold (seconds)	27 (4-137)	14 (3-109)	0.70
Tolerance (seconds)	66 (7-180)	89 (10-180)	0.40

M-W U test – Mann Whitney U test.

Neuro-endocrine function

Salivary cortisol was collected on waking and 30 minutes post waking. Unfortunately many samples did not contain sufficient saliva for testing. Of the waking salivary samples, 5/7 (71%) from subjects receiving opioids and 10/19 (53%) from control subjects were sufficient for analysis. Of the samples collected 30 minutes post waking, (7/7) 100% were sufficient for analysis in the group receiving opioids, and 12/19 (63%) were sufficient for analysis from the control group. Synacthen test was performed in the morning however basal cortisol was taken mid-morning and therefore does not reflect a peak morning cortisol measurement. Synacthen test was performed to determine the adrenal response to HPA activation.

Results of neuroendocrine tests are tabulated below (see table 6). These data were compared using an independent samples t-test. Welch-Satterthwaite correction was used where samples had unequal variances. Mann-Whitney U test was performed where the data were not normally distributed.

Table 6 – Results of endocrine assays

	Opioid subjects	No. subjects	Control subjects	No. subjects	t-test p-value	M-W U test p-value
Endocrine assay, Mean (SD)						
Waking salivary cortisol (nmol/L)	18 (7.6)	5	21 (8.2)	10	0.47	
Salivary cortisol 30 mins post waking (nmol/L)	20 (17)	7	26 (1)	12		0.30
Synacthen test (nmol/L)						
-Basal cortisol	287 (149)	7	338 (107)	19	0.34	
-30 minute cortisol	630 (91)	7	695 (80)	19		0.83
-60 minute cortisol	521 (111)	7	587(109)	19	0.18	
Testosterone (nmol/L)	13 (5.8)	7	16 (8.6)	19	0.38	
SHBG (10-50nmol/L)	49 (20)	7	46 (23)	19		0.44
FAI	0.29 (0.14)	7	0.36 (0.11)	19	0.21	
Calculated Free testosterone (nmol/L)	0.20 (0.12)	7	0.25 (0.11)	19	0.29	
DHEAS (umol/L)	1.4 (1.1)	7	2.2 (1.6)	19		0.25
FSH (U/L)	10.2 (3.7)	6	7.4 (2.3)	18	0.04	
LH (IU/L)	5.7 (2.1)	6	5.2 (2.6)	19	0.66	
TSH (mIU/L)	1.6 (1.3)	7	1.6 (0.88)	19	0.99	
fT3 (pmol/L)	4.6 (4.0)	7	4.8 (4.0)	19	0.16	
fT4 (pmol/L)	14 (2.4)	7	14.3 (1.6)	19	0.75	
IGF-1 (nmol/L)	15 (5.9)	6	18 (5.3)	18	0.23	
Prolactin (mIU/L)	244 (241)	7	159 (49)	18		0.83

M-W U test – Mann Whitney U test.
t-test – independent samples t-test

Results for endocrine function show numerical trends in the direction of hypogonadism & hypocortisolism, but no statistical significance was seen.

The values presented in table 7 indicate effect sizes were medium (0.5 or larger) or large (0.8 or higher) for the parameters of Synacthen test (30 and 60 minutes), FAI, calculated free testosterone, DHEAS and FSH. This indicates that an effect may be present however there was insufficient power to reach significance.

Table 7 – Effect size for endocrine function

Endocrine assay	Cohen's *d*
Salivary cortisol – waking	0.44
Salivary Cortisol - 30 mins post waking	0.32
Synacthen test – Basal cortisol	0.44
Synacthen test – 30 minutes	0.81
Synacthen test – 60 minutes	0.62
Testosterone	0.41
SHBG	-0.15
Free Androgen Index	0.60
Calculated free testosterone	0.50
DHEAS	0.55
FSH	-1.07
LH	0.21

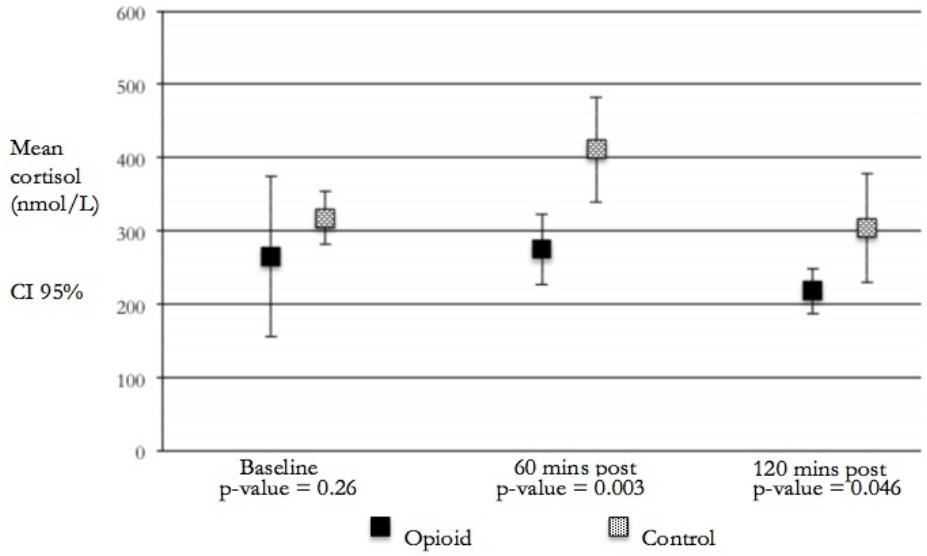
A significant result was observed in cortisol response to cold-pressor testing. Opioid subjects showed a blunted cortisol response at 60 & 120 minutes post cold pain testing (p-value <0.05), suggesting inappropriate response to a moderate environmental stress (see table 8 & figure 1).

Table 8 – Serum cortisol pre and post cold-pressor testing.

	Opioid subjects	No. subjects	Control subjects	No. subjects	t-test p-value
Endocrine assay, Mean (SD)					
Serum cortisol (nmol/L)					
T=0	265 (124)	5	318 (77)	17	0.26
T=30mins	376 (98)	7	522 (180)	18	0.055
T=60mins	275 (48)	7	411 (151)	17	0.0030
T=90mins	244 (75)	7	324 (109)	18	0.088
T=120mins	218 (39)	6	304 (155)	17	0.046

t-test – independent samples t-test

Figure 1 – Cortisol pre and post cold-pressor testing



Function

Measures of function are shown in table 9 below. Opioid subjects took significantly more time to complete Timed Up and Go compared to control subjects (independent samples t-test with Welch-Satterthwaite correction p-value <0.05). The difference in grip strength between the two groups was not significant. There was little difference between IADL scores. Lawton and Brody reported a five-point scale for men where food preparation, laundry, and housekeeping were excluded(75). Using the 5-point scale all men in both groups had normal scores.

Table 9 – Measures of function

	Opioid subjects (n=7)	Control subjects (n=19)	t-test p-value
Parameter, mean (range)			
Timed Up and Go (secs)	12 (8-17)	8.6(6-13)	0.036
Grip strength (kg)	36 (27-42)	40 (26-53)	0.26

	Opioid subjects (n=7)	Control subjects (n=18)	M-W U test p-value
Parameter, median (range)			
IADLs	7(5-8)	8 (5-8)	0.12

M-W U test – Mann Whitney U test.
t-test – independent samples t-test
IADLs – Independent Activities of Daily Living

Cognition

Wechsler Test of Adult Reading (WTAR) was used to give an estimate of premorbid intellect and to ensure our two groups were comparable. There was no significant difference between the group receiving opioids and control groups as shown below in table 10.

Table 10 - Wechsler Test of Adult Reading

	Opioid subjects (n=7)	Control subjects (n=19)	t-test p-value
WTAR, *Mean (SD)*	102 (9.0)	105 (7.5)	0.44

t-test – independent samples t-test

Results of neuropsychology tests were compared using an independent samples t-test. Mann-Whitney U test was performed where the data was nonparametric (see table 11).

Table 11 – Neuropsychology tests

	Opioid subjects (n=7)	Control subjects (n=19)	t-test p-value	M-W U test p-value	Cohen's *d*
Test, Mean (SD)					
Letter Cancellation					
Omission errors	3.4 (3.3)	2.7 (3.2)		0.45	-0.22
Time (seconds)	71 (24)	66 (14)		0.86	-0.31
Phonemic fluency					
FAS (word count)	39 (15)	40 (11)	0.89		0.06
RBANS					
List Learning	22 (5.1)	25 (5.4)	0.36		0.43
Story Memory	12 (3.6)	15 (5.2)	0.27		0.52
Figure Copy	16 (3.5)	14 (4.1)		0.21	-0.62
Line Orientation	18 (1.7)	18 (2.1)		0.98	-0.16
Picture Naming	9.4 (0.79)	9.8 (0.54)		0.18	0.62
Semantic Fluency	19 (5.5)	19 (4.7)	0.94		-0.04
Digit Span	9.3 (3.0)	11 (2.5)	0.28		0.51
Coding	36 (9.8)	40 (10)	0.37		0.42
List Recall	3.0 (1.9)	3.0 (2.4)	1.0		0.00
List Recognition	17 (2.0)	18 (3.1)		0.13	0.34
Story Recall	5.6 (2.2)	7.5 (3.6)	0.19		0.62
Figure Recall	10 (4.0)	9.9 (5.2)		0.94	-0.08

M-W U test – Mann Whitney U test.
t-test – independent samples t-test
Letter Cancellation Task –. A lower score indicates better performance in both speed and omission errors.
FAS – Verbal fluency FAS test. A higher score indicates better performance
RBANS - Repeatable Battery for the Assessment of Neuropsychological Status. Higher scores indicate better performance.

There was no significant difference between groups for any of the neuropsychology measures. Data were analysed for effect size using Cohen's *d*. Medium effect size was seen for Story Memory, Picture Naming, Digit Span and Story Recall. These tests reflect immediate memory, language, attention and delayed memory. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) measures each cognitive domain with two separate tests; there was no one cognitive domain where both tests had a medium or large effect size.

Depression and Symptoms of androgen deficiency

Opioid subjects scored significantly higher on both ADAM and GDS compared with controls suggesting they have more symptoms of androgen deficiency and depression.

A greater percentage of control subjects had no depressive symptoms on the DASS-21 scale. More than 50% of the opioid subjects, where as only 10% of control subjects, had depressive symptoms on the DASS-21 scale (see table 12 below).

Table 12 – Symptoms of depression and androgen deficiency

	Opioid subjects (n=7)	Control subjects (n=19)	M-W U test p-value
Parameter, median (range)			
ADAM	8 (0-9)	4 (0-7)	0.0069
GDS	7 (0-11)	1 (0-6)	0.0024
Severity, n (%)			
DASS-21 – Depression scores			
Normal	3 (43%)	17 (90%)	
Mild	1 (14%)	1 (5%)	
Moderate	2 (29%)	0 (0%)	
Moderate-Severe	1 (14%)	1 (5%)	
Severe	0 (0%)	0 (0%)	

Discussion

The major finding of this study is a reduced cortisol response to cold pressor testing in subjects on chronic opioid medication. Cold pressor testing acts as a moderate physiological stress that stimulates the HPA axis at the level of the hypothalamus. A blunted cortisol response was seen in opioid subjects despite similar pain responses between the two groups in cold pressor testing. Therefore, the reduced stress response is unlikely to be due to the effect of opioids reducing pain. This suggests that chronic pain patients on chronic opioid medication may not adapt well to stressful situations such as challenging life situations, illness, increased pain or depression. In the context of ageing, this finding is particularly important. It suggests that chronic opioid medication may reduce the capacity to respond to additional stressors, which is one of the hallmarks of frailty and a fundamental threat to wellbeing in older persons.

This research has demonstrated that cold pressor testing is a valuable tool to detect opioid-induced HPA-axis dysfunction. Cold pressor testing is a moderate physiological stress that acts centrally on the HPA axis to stimulate hypothalamic CRH release, and hence ACTH from the pituitary and cortisol from the adrenocortical zona fasiculata. The Synacthen test, presumably due to it being a strong stimulus with adrenal bias, does not seem to detect opioid-induced HPA dysregulation as effectively. Previous studies examining opioid induced endocrine dysfunction have used insulin-induced hypoglycaemia to study the integrity of the HPA axis at a central level (24), however this stimulus is not physiological and varies with response depending on the extent and duration of hypoglycaemia. The cold pressor test is a physiological test and is a much safer test in this research setting. A further benefit of cold pressor testing is the ability to test for pain parameters at the same time as testing the HPA axis. Despite the limitations of this study,

this is potentially a clinically significant discovery that is worthy of further evaluation. Further research is currently in process to examine the effects of opioids on the HPA axis, using cold pressor testing.

Research examining the relationship between opioid receptors and the HPA axis in humans suggests that opioid suppression of ACTH and cortisol release occurs via suppression of hypothalamic CRH release(81-83). The findings of this research and previous studies examining chronic opioid use are consistent with this theory. Abs and colleagues (24) reported blunted response of the HPA axis to stress in the form of insulin-induced hypoglycaemia. Palm and colleagues (50) found low basal cortisol concentrations in subjects on chronic opioid medication, however reported normal pituitary and adrenal response to exogenous CRH. Hypothalamic function may be particularly important in chronic pain as CRH has been shown produce analgesia throughout the central nervous system, particularly in prolonged pain(61). It is not known whether low cortisol, secondary to decreased central stimulation of the HPA axis, has a peripheral effect on pain.

Cortisol deficiency was only found using the physiological relevant test of cold pressor testing. This study does not show significantly low cortisol at baseline or during stimulation of the HPA axis with exogenous ACTH (Synacthen test) in subjects on chronic opioid treatment. However, numerical trends were in the direction of hypocortisolism. This study is the most comprehensive study of oral or transdermal opioid effect on the HPA axis. Previous studies have shown low cortisol levels in patients on chronic opioid therapy (24, 50), however blunted cortisol response to stimulation of the HPA axis with exogenous ACTH has only been reported in a case study(47, 51). Abs and colleagues (24) examined 73 patients on intrathecal opioids and found decrease cortisol response to insulin tolerance

test, however intrathecal opioids are likely to be qualitatively different and be more profound in their effects compared to oral opioids, which are more commonly used in clinical practice. Palm and colleagues (50) examined patients on oral morphine however CRH was administered to assess the HPA-axis and therefore examined the axis at the level of the pituitary rather than the hypothalamus. The findings of this current study have lead to further research examining opioid effects on the HPA axis in an expanded study population.

Low testosterone has been shown to decrease pain tolerance and testosterone replacement has resulted in improved functional status in patients on chronic opioid medication(23). However, subjects on chronic opioid treatment in this study did not have convincing evidence of hypogonadism and had reasonable pain responses. However, numerical values show trends in the direction of relative hypogonadism. These results are a reflection of the small sample size and small doses of opioid in the active arm. Since there is a wide population norm for total testosterone, mean testosterone values relatively to controls rather than absolute deficiency was the focus of this study. Unfortunately there was insufficient power to detect a difference between means in this study. Effect sizes suggest that chronic opioid treatment suppresses the HPG axis; however further research with greater power is required to support this. Previous studies examining gonadal function in people on chronic oral or transdermal opioid therapy have reported frank hypogonadism with subnormal total testosterone in a majority of subjects, however opioid doses used in previous studies were much higher than in this current study(36, 38).

Although there are limitations in comparing the results of this study to previous studies, given the small sample size, our results suggest that older people do not have increased

incidence of opioid related endocrine dysfunction when compared to younger people. It is uncertain whether the lower doses of opioid used in older persons protects them from opioid related endocrine dysfunction. A dose related pattern to testosterone deficiency due to opioid use has been observed in the past(36). The doses of opioid in this study were smaller than in previous studies, although the 3 opioid subjects in our study on large doses of opioid (>100mg oral morphine equivalents) did not have the lowest testosterone levels (all had TT of 13nmol/L). It is difficult, however, to make an assumption about dose related opioid dysfunction from this small sample size given the large normal variation of endocrine function. Older people may not have increased incidence of opioid related endocrine dysfunction when compared to younger persons, however they are most probably at greater risk of the clinical effects of endocrine dysfunction, when it does occur, due to their frailty and inability to cope with added stressors.

Results suggest that patients on chronic opioid therapy may have a poorer functional level compared to chronic pain sufferers who are not taking opioid medication. Patients chronically consuming opioids had significantly lower scores on the Timed Up and Go test. Previous literature has shown that chronic opioid therapy does not necessarily improve functional outcomes(21, 84). A Cochrane review in 2010 reported inconclusive findings regarding quality of life and functional status in opioid users due to an insufficient quantity of evidence(85). No difference was found between the two groups in grip strength or IADLs. The IADL questionnaire is a crude measure of function and may not detect subtle functional decline. The sample size was likely to be too small to detect a difference in grip strength. A limitation of this study is the variation in pain syndromes between the two groups, with more neuropathic pain in the control group and a higher percentage of subjects with back pain in the opioid group. These differences may have affected results

in Timed Up and Go given the influence of back pain on transferring from a chair and walking speed.

Previous studies examining hyperalgesia due to chronic opioid treatment have shown decreased pain tolerance in subjects with chronic opioid use(86, 87). However, there was no significant difference between groups for pain threshold or pain tolerance during experimental pain testing in this current study. Likert pain scores were widely variable in both groups. Assessing pain via a Likert scale on a single occasion is not likely to be a reliable measure of chronic pain. In future studies examining the relationship between chronic opioid therapy and pain sensitivity, it would be worthwhile including a measure of both intensity of pain and interference of pain on quality of life, such as the Brief Pain Inventory, in conjunction with cold pressor testing.

Results of this study suggest that most subjects who were taking opioids were not treated with paracetamol (5 of 7 opioid subjects). This is despite all opioid subjects having musculoskeletal pain, for which treatment guidelines recommend initial and ongoing pharmacological treatment with paracetamol(14). Paracetamol has demonstrated effectiveness in musculoskeletal pain and has a good safety profile(14). It is not clear why these subjects were not taking paracetamol; however, this finding is not likely to influence results of this study in terms of neuroendocrine function. Paracetamol can influence the hypothalamic-pituitary-adrenal axis by altering the experience of pain, however, in this study there was no significant difference between groups for pain(88).

There was no significant difference found between the two groups on neuropsychology testing. This is not surprising given that both pain and opioids have been shown to affect

cognition and adequate pain control has been shown to improve cognition(89-91). Weiner and colleagues (89) showed that subjects who suffer from pain had impaired immediate memory, language and delayed memory when compared to subjects without pain. In a cohort study comparing healthy volunteers without pain with chronic pain sufferers who were prescribed opioids, pain subjects had decreased attention, psychomotor speed and working memory(90). Jamison and colleagues (91) examined cognition in 144 patients with chronic pain and found cognition improved in the areas of memory, incidental learning and psychomotor performance once their pain was controlled with chronic opioid treatment for 180 days. These results suggest that long-term opioid use, especially at low doses, does not have a clinically significant affect on cognition in older persons with chronic pain.

Findings suggest that older patients who take long-term opioid analgesia for chronic pain may have more symptoms of depression. However, the cross sectional nature of this study makes cause and effect difficult to determine.

The major limitation of this study is the sample size and lack of power. Endocrine parameters are known to have a wide normal range. A target sample size of 30 subjects in each arm was predicted to give sufficient power to detect a significant difference in endocrine parameters and unfortunately recruitment was only 43% of this target. Recruitment was reasonable for controls however only 30% of target in the opioid group. It is not likely that the incidence of opioid treatment for pain in the older age group is lower than suggested by the literature. It is well known that recruitment of older adults to health research studies presents difficulties(92). Literature examining recruitment of older people to health research studies suggests that strategies involving a face-to-face approach to recruitment are preferable over media advertising(93). Older people may not respond well

to print advertising due to poor vision and due to difficulty using the telephone due to hearing or visual impairment. Older persons are possibly not referred to specialty pain clinics as frequently as younger people. This may be due to pain being accepted as a problem of ageing and older people being less demanding of specialist care for worry of being a burden to their health provider or family. A further limitation is the cross-sectional nature of the study. Although this study found reduced cortisol response to stress in subjects on chronic opioid therapy, the cross-sectional design does not allow conclusions to be drawn on causality.

In conclusion, this study suggests that chronic opioid therapy may disrupt the central regulation of the HPA axis. This is the most thorough study of oral or transdermal opioid effect on cortisol, however it was narrowed to older men. Additional research concentrating on the HPA axis has arisen directly from this current study and will be expanded to include adults of both sexes in all age groups. The objective of further research is to determine whether individuals with low cortisol response to cold pressor testing will benefit from a physiological dose of hydrocortisone replacement in relation to improving wellbeing and analgesic responses.

Appendices

Appendix 1 – Geriatric Depression Scale (short form) (GDS)

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life?	YES / **NO**
2. Have you dropped many of your activities and interests?	**YES** / NO
3. Do you feel that your life is empty?	**YES** / NO
4. Do you often get bored?	**YES** / NO
5. Are you in good spirits most of the time?	YES / **NO**
6. Are you afraid that something bad is going to happen to you?	**YES** / NO
7. Do you feel happy most of the time?	YES / **NO**
8. Do you often feel helpless?	**YES** / NO
9. Do you prefer to stay at home, rather than going out and doing new things?	**YES** / NO
10. Do you feel you have more problems with memory than most?	**YES** / NO
11. Do you think it is wonderful to be alive now?	YES / **NO**
12. Do you feel pretty worthless the way you are now?	**YES** / NO
13. Do you feel full of energy?	YES / **NO**
14. Do you feel that your situation is hopeless?	**YES** / NO
15. Do you think that most people are better off than you are?	**YES** / NO

Answers indicating depression are in bold; score one point for each one selected. A score of 0 to 5 is normal. A score greater than 5 suggests depression.

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Appendix 2 – Likert 10-point pain scale

0 – No pain

1

2

3

4

5

6

7

8

9

10 – Worst possible pain

Appendix 3 - Lawton Instrumental Activities of Daily Living questionnaire (IADL)

A. Ability to use telephone	Score
1. Operates telephone on own initiative; looks up and dials numbers, etc.	1
2. Dials a few well-known numbers.	1
3. Answers telephone but does not dial.	1
4. Does not use telephone at all.	0
B. Shopping	
1. Takes care of all shopping needs independently.	1
2. Shops independently for small purchases.	0
3. Needs to be accompanied on any shopping trip.	0
4. Completely unable to shop.	0
C. Food Preparation	
1. Plans, prepares and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients.	0
3. Prepares meals but does not maintain adequate diet.	0
4. Needs to have meals prepared and served.	0
D. Housekeeping	
1. Maintains house alone or with occasional assistance.	1
2. Performs light daily tasks such as dishwashing, bed making.	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness.	1
4. Needs help with all home maintenance tasks.	1
5. Does not participate in any housekeeping tasks.	0
E. Laundry	
1. Does personal laundry completely	1
2. Launders small items; rinses stockings, etc.	1
3. All laundry must be done by others.	0
F. Mode of Transportation	
1. Travels independently on public transportation or drives own car.	1
2. Arranges own travel via taxi, but does not otherwise use public transportation.	1
3. Travels on public transportation when accompanied by another.	1
4. Travel limited to taxi or automobile with assistance of another.	0
5. Does not travel at all.	0
G. Responsibility for own medications	
1. Is responsible for taking medication in correct dosages at correct time.	1
2. Takes responsibility if medication is prepared in advance in separate dosage.	0
3. Is not capable of dispensing own medication.	0
H. Ability to Handle Finances	
1. Manages financial matters independently, collects and keeps track of income.	1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Incapable if handling money.	0

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Appendix 4 – Androgen Deficiency in Ageing Male (ADAM) questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased ‘‘enjoyment of life’’?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

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