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Comprehensive Systematic Review of long-term opioids in women with chronic non cancer pain and associated reproductive dysfunction (hypothalamic-pituitary-gonadal axis disruption).

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Abstract

A comprehensive systematic literature review of reproductive side effects in women 18-55 years old treated with opioids for one month or longer for chronic non cancer pain. A search of seven databases including EMBASE and Medline was undertaken (October 2014 and a limited re-run April 2016). The search contained key words for opioids (generic and specific drug names) and side effects (generic and specific reproductive). Titles were screened using predefined criteria by a single reviewer and abstracts and full texts by two independent reviewers. 10,684 papers were identified and 12 full texts (cohort (one), case-control (four), cross-sectional (four), case series (one) and case report (two) with a maximum of 41 cases in one paper) were included covering three different modes of administration: oral (six), intrathecal (five) and transdermal (one). Amenorrhoea occurred in 23-71% of those receiving oral or intrathecal opioids. Decreased libido was seen in 61-100%. Out of 10 studies which undertook hormonal assays, only two studies showed a statistically significant decrease in hormone levels. This review supports the view that there is a potential relationship between the use of long-term opioids in women and reproductive side effects. The evidence is however weak and the mode of administration, duration, type and dose of opioid might influence associations. Though hormone levels were statistically significant in only two studies, women exhibited clinically important symptoms (decreased libido and altered menstrual cycle). Further investigation is required with larger cohorts and analysis of different delivery methods.

Key words

Women; Opioids; Chronic non cancer pain; Hypothalamic-pituitary-gonadal axis; Hypogonadism.

Introduction

Chronic Non Cancer Pain (CNCP) has been defined as any painful condition lasting for three months or more and not associated with neoplastic disease (cancer) [12]. CNCP affects many people across the globe; a World Health Organisation (WHO) 15 centre study showed that 22% of those attending primary care suffered from persistent pain, and women were more commonly affected than men [23]. There are many approaches to care of CNCP, including self-care, physical rehabilitation, psychological approaches, medications, surgical intervention and alternative medicine. Patients often need a combination of these, and in CNCP an integrated multidisciplinary approach is commonly required [46]. In 12-13% of patients with CNCP opioids are prescribed [8]. Since the late 1980's there has been a trend towards increased opioid prescribing for CNCP and a recent UK observational database study showed a 38% increase in opioid prescribing from 2002 to 2009, this is despite a Cochrane review showing only weak evidence for their effectiveness [6,32]. Another systematic review did not find any studies that compared opioid use to non-opioid therapy that lasted more than a year with the majority lasting less than 16 weeks [14].

Adverse effects are common among people taking opioids, and 80% of patients will experience at least one, such as constipation, somnolence, nausea, vomiting, dizziness, itching, dependency, tolerance, addiction and opioid induced hyperalgesia [5,22,26,44]. Chronic prescription opioid use in men can lead to hypogonadotrophic hypogonadism and decreased levels of sex hormones, particularly testosterone, leading to reproductive and sexual dysfunction. This is known as opioid induced androgen deficiency (OPIAD), it is increasing in prevalence due to greater recognition and some studies have found up to 92% of those men treated with opioids are affected [1,2,7,16,27,42]. In women, it is recognised that

illegal dependent opioid use (for instance heroin) can be associated with hypogonadism and reproductive dysfunction (low libido, sexual dysfunction and amenorrhoea), with menstrual irregularities affecting over 50% of women using illegal opioids [10,20,39,40].The picture is less clear in women with respect to any association with prescription opioid use. Therefore, in light of the fact that non-prescription opioids can cause symptoms of reproductive dysfunction consistent with hypothalamic-pituitary-gonadal (HPG) axis disruption (hypogonadism) in women, and that there is good evidence of hypogonadism in some men taking long-term prescribed opioids, there is a need to further investigate hypogonadism related to long- term prescription opioids in females [1,2,7,10,16,20,38,40]. This has been highlighted as an area for further research by both the British Society of Pain and in a paper for the American Pain Society and American Academy of Pain Medicine highlighting research gaps [13,44].

The aim of this study is therefore to conduct a comprehensive systematic review of the published literature in relation to long-term opioid use for CNCP and possible reproductive dysfunction in women aged 18-55 years old, with specific focus on endocrine side effects relating to hypogonadism (biochemical or clinical).

Methods

Prior to starting, a systematic review protocol was developed that set out the methods for the search, inclusion/exclusion criteria and data extraction. There was no deviation from this protocol. The age range of 18-55 years old was chosen to include women up to and including those going through the menopause, this was following a preliminary literature search that

revealed menopausal symptoms may be one of the potential reproductive adverse events affecting women associated with long-term opioids [17]. The literature on long-term opioid use in women and associated reproductive dysfunction was retrieved by searching 7 databases Medline (1946-October 2014 via Ovid), EMBASE (1974-October 2014 via Ovid), TOXLINE (1840-October 2014 via TOXNET), PsychINFO (1806-October 2014 via NHS HDAS), CINAHL (1891-October 2014 via NHS HDAS), AMED (1895-October 2014 via NHS HDAS) and Web of Science (1950-October 2014 via Web of Science) in October 2014. A limited update search was performed from October 2014 to April 2016 in Medline (October 2014 – April 2016 via NHS HDAS) and EMBASE (October 2014-April 2016 via NHS HDAS), the update search was performed on a different platform due to change of licensing. The search consisted of 3 search strands. Strand 1 searched for different types of opioid analgesics using generic terms (e.g. exp Analgesics, Opioid/ and exp Narcotics/) and narrow drug name terms (e.g. Alfentanil/ and alfentanil mp). This was adapted from a search used for a Cochrane review on the use of opioids in CNCP and is 178 lines [32]. Strand 2 searched for adverse effects as a generic search term (e.g. safe or safety or side effect*) using a search strategy taken from a paper by Golder et al. which developed adverse effects search filters for Medline (~100% sensitivity) and EMBASE (~83% sensitivity) [21]. This was then adapted for use in the other databases searched. The final search strand looked at specific female reproductive endocrine side effects. These included conditions identified from a preliminary literature search, such as opioid induced hypogonadism, opioid induced androgen deficiency and a wide range of female reproductive health related endocrine disorders, including conditions such as polycystic ovarian syndrome and symptoms such as amenorrhoea, libido, sexual dysfunction, menopause and infertility (e.g. Menopause/, Infertility, Female/, Menorrhagia/) [9,34]. Hypogonadism is also associated with less specific symptoms including fatigue, depression, osteoporosis and weight gain, however for the

systematic review it was decided to focus on reproductive dysfunction specifically [42]. The complete search strategy for Medline can be found in appendix 1. References from relevant papers were tracked, and the papers examined for whether they met the inclusion/exclusion criteria.

The inclusion and exclusion criteria are presented in Table 1. These were applied to the title, abstract and then full text. Due to low numbers of studies identified, we did not reject any papers on the basis of study design. Titles were assessed by a single reviewer (EW) and the abstracts and full texts were reviewed by two independent reviewers (EW, and JB or YC), with a third reviewer arbitrating on any conflicts of opinion (KD).

Data from the identified studies were extracted using a predefined data extraction form which was developed a priori and piloted by EW (available from the author on request). Quality assessment was undertaken using critical appraisal skills programme (CASP) forms to cover the wide variety of papers included. This does not give a grade for the evidence but highlights the limitations and strengths which will be presented with the results [15].

Results

10,694 papers were identified in the initial search, and 22 papers were identified for possible inclusion. The majority of title screening revealed papers that were non-human studies, studied men or had no relevance to the question; there were 324 abstracts for review following title screening. Following abstract review 22 full texts were reviewed and 12 were included (see Figure 1); none were removed following quality assessment. An update identified 241 (253 prior to excluding duplicates) additional papers, of which 225 were excluded based on title; of the 16 abstracts remaining none were included in the review (one

paper men only, one discussed no side effects, one did not mention endocrine side effects, 12 review articles and one conference abstract).

The studies included considered a variety of methods of opioid delivery, including oral (six studies), intrathecal (five studies) and transdermal (one study) opioids. One cohort study, four case-control studies, four cross-sectional studies, one case series and two single case reports were included. The studies all had very small numbers of participants, with a maximum of 41 subjects in the case arm of one of the papers. In total there were only 165 subjects included across all 12 studies (including 35 controls). A summary of the included papers can be seen in Table 2. The outcomes the papers used were either clinical outcomes (irregular menstruation/lack of menstruation or decreased libido) or biochemical (Leutenising hormone (LH), Follicle stimulating hormone (FSH), oestrodiol, progesterone, dehydroepiandrosterone sulphate (DHEAS), free testosterone (fT), total testosterone (TT), prolactin (PRL), sex hormone binding globulin (SHBG) and GnRH stimulation test measuring subsequent levels of LH and FSH) or both clinical and biochemical. The results will be discussed according to the different potential outcomes.

Menstrual Cycle

Ten studies looked for changes in menstrual cycle as a marker for hypogonadism and reproductive dysfunction. They defined this as either amenorrhoea (absent menstruation) or oligomenorrhoea (either an abnormally long period of time (35 days to 6 months) between regular menses, or less than 9 menstrual cycles in a year) [25,33,45].

Daniell [17] undertook a case-control study which was the only paper included in the review that showed a statistically significant difference in the menstrual cycle pattern between those taking oral opioids (52% who developed non-surgical amenorrhoea) and controls (20%, $p<0.05$). The other oral opioid studies that reported data on menstrual cycles were Fraser et

al. [19] which was a cross-sectional study and found 23% (3/13) of women developed oligo/amenorrhoea following commencing opioids, and Rhodin et al. [36] who undertook a case-control study and found amenorrhoea in 81% (13/16) of cases and 0% (0/6) of controls (no statistical analysis given). There were two case studies, both reported amenorrhoea in women whilst taking long-term oral opioids, Mussig et al. [30] then showed resolution of amenorrhoea with decreasing dose of hydromorphone and with conversion to tramadol (a less potent opioid) [30,35].

Four of the papers on intrathecal opioids reported on the menstrual status of their participants showing oligo/amenorrhoea in 67% [1], 71% [18], 31% [31] and 47% [37] of those treated with opioids. In one study, the menstrual cycle irregularities that were present at the start of treatment resolved by 4-8 months of treatment (it was unclear from the paper if abnormal menstruation was an issue preceding treatment or secondary to treatment) [31]. Abs et al. [1] also looked at the menstrual cycle in three control patients and each of these continued to have a regular cycle, but no statistical analysis was made due to the small number of subjects.

One study that examined eight premenopausal women using transdermal buprenorphine found no alteration in menstruation.

The data across the studies suggest that 23% to 81% of women taking oral or intrathecal opioids may be affected by oligo/amenorrhoea [1,17–19,31,36,37]. However, those taking transdermal buprenorphine did not appear to suffer with this particular adverse effect [4].

Libido

Three papers reported on the status of libido for premenopausal women. Wong et al. [48] found no statistical difference between cases and controls attending a chronic pain clinic, with 61% of cases taking oral opioids reporting decreased libido and 70% of controls ($p = 0.62$). Roberts et al. [37] found low libido in 71% of those receiving intrathecal opioids and Finch et al. [18] found low libido in 100% of those commencing intrathecal treatment. Other studies also provided information on libido but this was not stratified for age or gender so could not be included in the review.

Hormone Measurements

All six oral opioid studies reported on hormone levels. Of the three case-control studies (Daniell [17], Rhodin et al. [36] and Wong et al. [48]), two [17,36] found statistically significant decreases in hormone levels in cases compared with controls, but levels were within normal ranges. Daniell [17] found differences in TT, fT, oestrodiol and DHEAS, whereas Rhodin et al. [36] found differences in oestrodiol, FSH, LH, post GnRH stimulation LH and FSH. Wong et al. [48] found a statistically significant decrease in TT when comparing cases and controls complaining of low libido, but otherwise no significant differences in hormone levels were found. Fraser et al. [19] undertook a cross-sectional study and found hormone levels within normal range (LH, FSH, SHBG, oestrodiol and progesterone). The final two oral opioid studies were case studies and found levels that were below normal or within the bottom end of the normal range; Mussig et al. [30] showed a

negative correlation of oestrodiol level with morphine plasma levels ($r = -0.6$, $p = 0.03$) as they withdrew hydromorphone and replaced it with tramadol (a weaker opioid) and reproductive dysfunction resolved [30,35].

Three intrathecal studies looked at hormone levels. Abs et al. [1] undertook a case-control study and found lower levels of hormones (LH, FSH, oestrodiol and progesterone) in cases compared to controls, but this did not reach statistical significance. Finch et al. [18] found low levels of LH, and levels at the low end of normal for oestrodiol and FSH. Kim et al. [28] showed two cases with low levels of TT, fT or DHEAS and the author described these patients as androgen deficient.

Aurilio et al. [4] measured hormones at baseline and throughout treatment of up to 6 months with transdermal buprenorphine. They found no statistically significant change in hormone levels (LH, FSH, TT and fT) during this period.

Summary of Results

The results overall found that women taking oral or intrathecal long-term opioids were more likely to have clinical symptoms of hypogonadism and the associated hormones were either low or at the lower end of normal. Three out of four case-control studies found statistically significant differences for hormone levels between cases and controls with the fourth reporting that the lack of statistical significance was likely due to small numbers. However those receiving transdermal buprenorphine did not have symptomatic or physiological changes associated with hypogonadism. All the papers included in the systematic review had very small numbers and the evidence is of low quality.

Discussion

The aim of this review was to identify and describe the current evidence relating to long-term use of opioids in women and associated reproductive side effects, particularly symptoms associated with hypogonadism.

The results of the review show that in women taking long-term oral or intrathecal opioids, there is a potential association with reproductive dysfunction and hypogonadism. Those receiving transdermal buprenorphine did not show symptoms of hypogonadism. However it is difficult to establish whether this could be related to the route of administration, dose or the mode of action of buprenorphine itself. Buprenorphine can be prescribed at much lower doses than morphine as its equipotency ratio is 1:110-1:115 and could potentially explain the lack of reproductive dysfunction. Buprenorphine is pharmacologically different to other opioids as it is a mixed opioid agonist-antagonist and binds strongly to opioid receptors, meaning endogenous opioids will have more difficulty binding to receptors, this could theoretically have an effect on the HPG axis [47]. At clinical doses buprenorphine acts as a full μ-agonist, however compared with other μ-agonists (e.g. morphine and fentanyl) it has a lower risk of several side effects including respiratory depression and withdrawal so this could possibly be reflected for reproductive side effects [29]. It is important to note that only one paper specifically assessed transdermal buprenorphine and numbers included in the study were small.

The review only found a small number of relevant papers and each paper in turn only studied a small sample. Less than 200 cases and only 35 controls were included in the entire review.

This was not likely to be due to omission of relevant studies, as the search was comprehensive and over 10,000 papers were identified and screened according to predefined criteria. The small numbers in the studies did lead to some difficulties with analysis for the authors of the papers. Abs et al. [1] found levels of hormones in cases that were lower than controls but this difference did not reach statistical significance. The authors felt this was probably due to low numbers (21 cases and 3 controls). The original study populations were already initially small, but further restricting this to only women aged 18-55 decreased the numbers even further. Additionally, in the case-control study by Finch et al. [18] there were no controls in this age group and so this had to be considered as a cross-sectional study. Meta-analysis could not be undertaken as numbers were too small and each paper used different hormone assays and measured these in different ways for outcomes, therefore combining them would have been inappropriate.

One issue that could have affected these results is confounding by indication, as chronic pain is associated with low libido and CNCP was the reason for receiving opioids [27]. 73% of patients (both sexes) attending pain clinic report current sexual difficulties associated with their pain due to combinations of reasons including loss of interest or satisfaction, physical difficulty in finding a position that was comfortable and fear of exacerbating the condition [3]. Four case-control studies tried to account for possible confounding factors: three [1,36,48] of the studies controlled for chronic pain whereas the fourth did not [17]. Daniell [17] found statistically significant differences for both hormonal and clinical outcomes. However cases were recruited through public solicitation, with a financial reward and copies of their endocrine blood results for those taking part, which could introduce selection bias. The author acknowledges that controls were not well matched to those taking opioids with statistically significant differences in age (controls older), smoking status (controls smoked less), and BMI (controls weighed less), all of which are potential confounding factors which

could affect menstrual cycle and thereby the reliability of the results. The controls may also have been systematically different from the general population, as the rate of amenorrhoea found in controls (20%) was higher than the rate would be expected for the general population (3-4%) [17,45]. Women receiving intrathecal opioids seem to be the most likely to be affected by reproductive dysfunction, this could be due to confounding by severity (a subtype of confounding by indication). These women are likely to have more severe chronic pain as they have been referred to secondary care for intrathecal opioids and the severity could be related to reproductive dysfunction [8,41].

A technical difficultly facing all the studies relates to how and when to measure hormonal levels. Hormone assays present a particular difficulty in women with irregular cycles, as hormone levels fluctuate throughout the menstrual cycle and there are different normal ranges depending on the phase of the cycle. Several of the papers recognised having samples that were unrelated to the menstrual cycle as a limitation [4,9,17,19,30,35,36]. Aurilio et al. [4] did attempt to take the repeat hormonal assays at the same phase of the cycle, but despite this, large variations in oestrodiol levels were found between initial and follow up tests, indicating that this technique did not fully account for natural variations in hormones throughout the cycle. Other studies tried to account for hormone (LH and FSH) variability in different ways, either through serial samples 15 minutes apart, GnRH stimulation tests, or samples taken at specific times of the day [1,36,48]. Fraser et al. [19] did not attempt to time the samples to the menstrual cycle as they were expecting high rates of amenorrhoea due to previous findings. Kim et al. [28] and Finch et al. [18] do not discuss when they sampled hormone levels. As described above various methods were undertaken to try to account for hormonal variation within the cycle but none of these were completely satisfactory and limitations still existed.

A further important consideration is whether the women are receiving other medications that could affect the clinical and biochemical outcomes. The particular medications of interest in

women would be hormonal contraception and hormone replacement therapy (HRT), as well as other steroid based medications. Four papers excluded women who were receiving hormone based medications [4,17,19,48], Rhodin (2010) described hormonal use with three women receiving HRT, one study excluded women receiving steroids [1], three papers did not discuss hormonal medications [18,28,31] and the remaining papers were case studies. These different approaches to hormonal medications do not seem to have had an effect on results, however this would be important to consider in future research.

Generalisability may be limited as the majority of studies were set within secondary care pain clinics (or from cases presenting to secondary care endocrinology clinics). Five of the studies looked at intrathecal opioids, which are only initiated in secondary care [43]. A study within Europe showed that only 23% of patients with chronic pain were seen by a "pain specialist" and the rest were managed in primary care. Additionally, a German study found the median time from pain onset to referral to secondary care pain services of 12 years [8,41]. Consequently these studies represent a small subset of chronic pain patients, and they are likely to include subjects who have had pain for longer than those presenting to general practice.

The review included women aged 18-55 years old and this represents a heterogenous group of women which is a potential limitation, with a median age of menopause in the UK of 52 [24]. This age range was chosen due to a preliminary literature search revealing menopause as a potential adverse outcome and as such we felt it was important to include the peri-menopausal period in the studies. Three papers had a larger age range but stratified for menopausal status [1,37,48], four papers either stratified or only women less than 45 years old [17,18,30,35], with a further five papers using 50 years old as the dividing age [4,19,28,31,36]. The results across the papers were consistent (except for the study examining transdermal buprenorphine), so the inclusion of women who are potentially at all stages of

the menopause did not affect the results and limiting the age range to women less than 45 years old would have limited the included papers significantly.

Clinical Implications

The evidence reviewed appears to indicate that there is a potential relationship between long-term opioid use and hypogonadism and reproductive dysfunction in women. The studies are limited, but show that clinically, women may report amenorrhoea and loss of libido, both of which could possibly be associated with infertility. The implications of the findings from this systematic review are important for shared decision making, in that when discussing long-term opioids with premenopausal women both at initiation and review, these potential adverse effects should be discussed. This may influence decisions about what ongoing analgesia might be used. Patients may also be more likely to report symptoms of reproductive dysfunction if they are aware there is a possible link with their medication.

One study by Aurilio et al. [4] evaluated transdermal opioids and found that measures of hormone levels did not decrease. This was reflected in the clinical findings, with no patients reporting menstrual disorders. This compares with the studies of oral and intrathecal opioids, which showed decreased hormone levels that in some cases were statistically significant. It is important to remember that transdermal buprenorphine is not only different to the other opioids administered due to the route but also in the way buprenorphine works [47]. Another possible reason for this difference in side effects could be the equivalent dose of morphine/day prescribed for which there was no data from the systematic review, but buprenorphine patches typically deliver a much smaller dose than oral opioids.

The link to reproductive dysfunction does appear to be strongest in patients commencing on intrathecal opioids. If use of this route of administration increases in the future, it may be necessary to introduce sequential hormonal assays beginning pre-treatment to detect early changes that may precede clinical symptoms.

Further Research

This area requires further research to generate high quality evidence as the current evidence consists of studies with small numbers of patients. It would be important to ensure that studies had large numbers of women included. Future studies would need to be matched if possible for chronic pain and age. This would be ideally be done either as a secondary outcome in a randomised control trial (RCT) for effectiveness of opioids in CNCP, however RCT's in this area are rare or as a matched cohort study specifically looking at reproductive side effects. It would also be important for future research in this area to conform with recent definitions of long-term opioid use for epidemiological research of 90 days or more opioid supply to provide consistency [11].

Conclusions

To our knowledge, this is the first comprehensive systematic review of the literature specifically examining the reproductive side effects of long-term prescription opioids in women of reproductive age. This review supports the view that long-term use of opioids might be associated with a negative effect on women's reproductive function and possibly lead to hypogonadism, however the numbers are small and the evidence is not clear. There is

weak evidence that this may not be a class effect and certain types of opioid or methods of delivery may have a different magnitude of effect or none at all. The evidence found appears to show women treated with opioids have levels of sex hormones that are below or at the bottom end of the normal range, and that there are clinically significant changes including decreased libido and irregular menstrual cycle that might be associated with these low hormone levels. The evidence from the review will help guide discussions with women when considering opioid analgesics and aid in shared decision making. Further work needs to be undertaken to account for the confounding issue of chronic pain, and whether this is a contributing factor to the changes noticed. The route of opioid administration, as well as type of drug and morphine equivalent dose also needs to be investigated with respect to any potential effect of developing hypogonadism. It might be that transdermal buprenorphine is not related to this effect, and therefore might potentially be a safer option for opioid delivery in premenopausal women, this area would be of interest for further research. The key to further research will be larger numbers of patients and controls who are matched for chronic pain and longer follow up periods.

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Table and Figure Legends

Table 1 Inclusion and Exclusion Criteria. CNCP (Chronic Non Cancer Pain)

Figure 1 PRISMA flow chart

Table 2 Summary of included papers – data only described for women less than 55 years old

	Criteria
Inclusion	Females 18-55 years old Opioid use for at least one month CNCP
Exclusion	Non-human studies Methadone use for rehabilitation from illegal drug use with no CNCP Illegal opioid users Cancer pain Full text unavailable after contacting the author (no papers in this category) Systematic review/review papers Editorials Non-English if no translation available (no papers in this category)

Author, Year, Location (ref)	Design	Authors Summary of Findings	Quality Assessment from CASP checklists.
		Intrathecal Opioids	
Abs et al., 2000 Belgium [1]	Case-control study. Setting: Pain Clinic. Duration of treatment: 26.6 +/- 16.3 months. Sample Size: Cases N = 21 and controls N = 3 Opioid: Morphine or Hydromorphone Age: 49.2 (± 11.7), 21 premenopausal women included	Neuroendocrine dysfunction (clinically and biochemically) following opioid use. Obvious difference in hormonal levels between case and control in premenopausal women but did not reach significance due to small numbers within the subgroup.	Positives: matched for chronic pain. Validated questionnaire and hormone levels. Negatives: Selection criteria not described. Larger numbers needed for statistics, no power calculation performed. Missing data reasons not described.
Finch et al., 2000 Australia [17]	Case-control (No controls for women < 45 years old so considered as cross-sectional). Setting: Pain Clinic. Duration of treatment: 0.02-8 years (median 2.5). Sample Size: N = 7 Opioid: Morphine Age: 38.3 (±1.5) (mean ± SEM)	Small doses of intrathecal morphine have a profound effect on the HPG axis so patients should be monitored.	Positives: selection of 30 sequential patients from pain clinic. Negatives: No control for F < 45 years old so no longer case-control. One time hormone measures.
Roberts et al.,2001 Australia [34]	Cross-sectional Study. Setting: Pain Clinic. Duration of treatment: minimum 6 months. Sample Size: N = 15 Opioid: Morphine, hydromorphone, sufentanil Age: 53.4 (±1.4, range 28-88), 15 premenopausal women	HPG axis affected but requires further detailed assessment. This should be discussed with patients.	Positives: 80% response rate. Questionnaire validated. Negatives: Retrospective data collection. Scant data for premenopausal females. Missing data not explained (in reported data for women <50 years old, one reports 14 women included and another 15).

Author, Year, Location (ref)	Design	Authors Summary of Findings	Quality Assessment from CASP checklists.
Njee et al., 2004 France [28]	Cross-sectional Study. Setting: Pain Clinic. Duration of treatment: 54 +/- 39.8 months (4-144). Sample Size: N = 10 Opioid: Morphine Age: 43.8	No evidence of permanent HPG suppression. Transient amenorrhoea, not accompanied by hormonal assays supportive of HPG suppression.	Negatives: retrospective data collection. Only minor focus on endocrine side effects and collected via a questionnaire which was not described and may not have been validated.
Kim et al., 2014 United States [26]	Case Series. Setting: Pain Clinic. Duration of treatment: 12 months and 24 months.Sample Size: N = 2 Opioid: Morphine Age: 43 and 46	Two female patients < 55 years old were both androgen deficient on hormone assays. Androgen deficiency is common in patients treated with intrathecal opioids for CNCP.	Positives: consecutive patients recruited Negatives: Only two patients included was a cohort study but assessed as a case series. Questionnaire used was not described and may not have been validated.
	Oral Opioids		
Mussig et al., 2007 Germany [27]	Case Report. Setting: Endocrine Clinic. Duration of treatment: 4 months hydromorphone. Sample Size: N = 1 Opioid: hydromorphone Age: 32	Hypogonadism when receiving hydromorphone which resolved when changed onto tramadol	Negative: Single case reported because of positive effect of treatment change.
Daniell, 2008 United States [16]	Case-control study. Setting: Primary Care Duration of treatment: Minimum 1 month. Sample Size: Case N = 21, Control N = 16 Opioid: methadone, morphine sulphate, oxycodone,	Hormonal assays were 48-57% lower in opioid treated women (fT, TT, oestrodiol, LH, FSH, DHEAS) compared to controls. Statistically significant for TT, fT, oestrodiol and DHEAS. Amenorrhoea cases: 52%, controls:20%, p <0.05.	Positives: No drop outs as one time measurement. Negatives: Controls not well matched (chronic pain, statistically different for BMI, smoking status and age). Results not split for oral or transdermal opioid delivery.

Author, Year, Location (ref)	Design	Authors Summary of Findings	Quality Assessment from CASP checklists.
	transdermal fentanyl (in two cases) Age: Cases 39.3 (±4.9 standard deviation) Controls 42.7 (±3.5)		
Fraser et al., 2009 Canada [18]	Cross-sectional Study. Setting: Pain Clinic. Duration of treatment: 5.5 years (+/- 3 years) Sample Size: N = 14 Opioid: daily morphine-equivalent dose 679 ± 620mg Age: 38.6 (± 7.2)	Lower rate of hypogonadism than expected. 21% of women had hypogonadism.	Positives: interviews by a single interviewer with a set method. Negatives: hormone assays not timed to cycle. Single measurement.
Reddy et al., 2010 England [32]	Case Report. Setting: Endocrine Clinic. Duration of treatment: 7 years Sample Size: N = 1 Opioid: Morphine Age: 37	Hypogonadism clinically and biochemically.	Negative: Single case reported because of clinical findings.
Rhodin et al., 2010 Sweden [33]	Case-control. Setting: Pain Clinic. Duration of treatment: at least 1 year. Sample Size: Case N = 16, controls N = 6 Opioid: methadone, morphine, oxycodone Age: 48 (32-63), split into women < 50 but no average age given	HPG axis disruption with sexual disturbance and menstrual irregularities.	Positives: Validated questionnaire. Clinical and biochemical results correlate. Control group had chronic pain. Enough power to show statistical significance. Negatives: small numbers, 3 women receiving opioids on HRT, 0 in control group.
Wong et al.,	Case-control.	A significant decrease in fT in	Positives: Matched for chronic pain

Author, Year, Location (ref)	Design	Authors Summary of Findings	Quality Assessment from CASP checklists.
2011 Canada [44]	Setting: Pain Clinic. Defined chronic pain as pain for > 6months. Duration of treatment : No minimum stated . Sample Size: Cases N = 30, controls N = 10 Opioid: not described Age: 53 (28-83), included 30 premenopausal women	patients with low libido and a non-significant decrease in DHEAS but not correlated with symptoms of hypogonadism.	Negatives: Data only partly stratified for pre-menopausal women. Exact length of time on opiates not reported. Recall bias asked to compare current sexual desire to that before opiates.
		Transdermal Opioids	
Aurilio et al., 2011 Italy [3]	Open prospective cohort study. Setting: pain clinic. Duration of treatment: 6 months Sample Size: N = 8 Opioid: Buprenorphine Premenopausal women. Mean age 39.5 (26-50)	No strong endocrine impairment. No changes in menstrual cycle reported and hormone levels were stable or increasing.	Positives: hormone levels used as outcomes and six month follow up, repeated measures from same patient at four time points. Negatives: small numbers, demographics of group not described. Hormone sampling not timed to cycle.