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Maintenance Therapy and Sexual Behavior

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1. Introduction

Today, the term "human sexual behavior" sounds familiar and is so widely used that it may be hard to imagine a time when it was unknown (Haeberle, 1981; 1983). However, the realization that people have always done certain things does not necessarily allow us to conclude that they have always thought of them the same way.

Linguists also know that seemingly simple words often have no exact equivalents in other languages and that, as the years go by, they may very well change their meaning (Haeberle, 1981; 1983).

Obviously, the distinction between physical and psychological causes of sexual inadequacy is, to a certain extent, arbitrary, since body and mind are so closely interrelated that a sharp dividing line between them cannot be drawn. Some men and women are restricted in their sexual expression by physical malformations, handicaps, diseases, or injuries.

However, there are also physically healthy individuals who cannot fully enjoy sexual intercourse because their sexual responses have become weakened, inhibited, or even completely blocked for psychological reasons. Today, such a person is usually said to suffer from "sexual inadequacy" or "sexual dysfunction" (Haeberle, 1981; 1983).

Very few people enjoy perfect health throughout their lives. Sooner or later, most of us find ourselves in need of medical attention, if only temporarily. Of course, many of the serious diseases that plague and cripple mankind also have a damaging effect on sexual abilities. Certain illnesses can affect a person's responses or weaken the body to a point where sexual intercourse becomes difficult or impossible.

Usually in such cases, the sexual difficulties are only the by-product of a general infirmity and therefore receive only minor attention (Haeberle, 1981; 1983).

There are, however, certain physical disorders and diseases that affect human sexual activity and procreation directly, such as for example addiction.

Opioid maintenance treatment is the most widespread and well-researched treatment modality for opioid dependence (Giacomuzzi, 2008; 2011; Brown & Zueldorff 2007). Methadone, slow-release oral morphine and buprenorphine are currently the most commonly used pharmacotherapeutic agents.

Maintenance treatment has become a major intervention in the care and treatment of drug dependence in Europe. But still little is known about sexual behavior and sexual dysfunction especially under maintenance treatment.
A greater understanding of sexual behaviour in different maintenance treatment contexts has important consequences for the design and evaluation of substitution programs in opioid therapy.
Sexual dysfunction has been reported as an adverse effect of opioids including methadone and buprenorphine maintenance treatment.
In recognition of this, this chapter also aims to present specific problems and facts regarding this issue. Furthermore, the chapter presents own results regarding sexual behaviour and dysfunction prevalence within maintenance treatment. This chapter therefore provides some basic information about the main physical illnesses and impairments which can interfere with human sexual functioning regarding addiction.

2. Addiction and maintenance treatment

Opioids are commonly prescribed because of their effective analgesic, or pain-relieving, properties. Medications that fall within this class - referred to as prescription narcotics - include morphine, codeine, oxycodone (e.g., OxyContin, Percodan, Percocet), and related drugs.
Morphine, for example, is often used before and after surgical procedures to alleviate severe pain. Codeine, on the other hand, is often prescribed for mild pain.
In addition to their pain-relieving properties, some of these drugs - codeine and diphenoxylate (Lomotil), for example - can be used to relieve coughs and diarrhea (National Institute on Drug Abuse, 2011).
Opioids act on the brain and body by attaching to specific proteins called opioid receptors, which are found in the brain, spinal cord, and gastrointestinal tract.
When these drugs attach to certain opioid receptors, they can block the perception of pain. Opioids can produce drowsiness, nausea, constipation, and, depending upon the amount of drug taken, depress respiration. Opioid drugs also can induce euphoria by affecting the brain regions that mediate what we perceive as pleasure. This feeling is often intensified for those who abuse opioids, when administered by routes other than those recommended. For example, OxyContin is often snorted or injected to enhance its euphoric effects, while at the same time increasing the risk of serious medical consequences, such as opioids overdose.
Many studies have shown that the properly managed, short-term medical use of opioid analgesic drugs is safe and rarely causes addiction - defined as the compulsive and uncontrollable use of drugs despite adverse consequences - or dependence, which occurs when the body adapts to the presence of a drug, and often results in withdrawal symptoms when that drug is reduced or stopped.
Withdrawal symptoms include restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps ("cold turkey"), and involuntary leg movements.
Taking a large single dose of an opioid could cause severe respiratory depression that can lead to death (National Institute on Drug Abuse, 2011).
Long-term use of opioids can lead to physical dependence and addiction.
Addiction continues to be referred to by terms such as drug dependence and psychological dependence (Federation of State Medical Boards of the United States, 1998).

The traditional distinction between addiction and habituation centers on the ability of a drug to produce tolerance and physical dependence. Tolerance is a physiological phenomenon that requires the individual to use more and more of the drug in repeated efforts to achieve the same effect.

Physical dependence manifests itself through the signs and symptoms of abstinence when the drug is withdrawn. A classic feature of physical dependence is the abstinence or withdrawal syndrome. If the addict is abruptly deprived of a drug upon which the body has physical dependence, there will ensue a set of reactions, the intensity of which will depend on the amount and length of time that the drug has been used.

Physical dependence and tolerance are normal physiological consequences of extended opioid therapy for pain and should not be considered addiction (American Academy of Pain Medicine and the American Pain Society, 1997; Commission of Public Records, 2003).

Addiction is currently also defined as a form of behavior through which an individual has impaired control with harmful consequences. Thus, individuals who recognize that their behavior is harming them or those they care about find themselves unable to stop engaging in the behavior when they try to do so (Giacomuzzi, 2008).

The severity of the medical, psychological and social harm that can be caused by addiction, together with the fact that it violates the individual's freedom of choice, means that it is appropriate to consider it to be a disorder of motivation.

A very commonly used reference text from the American Psychiatric Association – the Diagnostic and Statistical Manual of Mental Disorders – does not use the term addiction at all; rather, it uses substance dependence. And, to be more precise, the particular drug involved is specified: e.g., heroin dependence, alcohol dependence, etc.

Although other forms of treatment for opioid dependence continue to be explored, methadone maintenance treatment remains the most widely used form of treatment for people who are dependent on opioids.

Methadone maintenance treatment is a key component of a comprehensive treatment and prevention strategy to address opioid dependence and its consequences (Giacomuzzi et al., 2003; 2008; 2009).

Methadone was originally developed in Germany as a substitute analgesic for morphine. World War II brought the formula to the attention of North American researchers, who subsequently discovered that methadone could be used to treat heroin withdrawal symptoms in 1964 as a medical response to the post-World War II heroin epidemic in New York City (Giacomuzzi, 2008).

The principal effects of methadone maintenance are to relieve narcotic craving, suppress the abstinence syndrome, and block the euphoric effects associated with heroin. Methadone works by alleviating the symptoms of opioid withdrawal. A stable and sufficient blood level of methadone stems the chronic craving for opioids.

Since methadone is a much longer acting drug than some other opioids, such as heroin, one oral dose daily prevents the onset of opioid withdrawal symptoms - including anxiety, restlessness, runny nose, tearing, nausea and vomiting - for 24 hours or longer. Methadone diminishes the euphoric effects of other opioids (cross tolerance), without necessarily causing euphoria, sedation or analgesia.

This means that self-administered illicit opioids will not lead to euphoria, making it less likely that clients/patients will either use illicit opioids or overdose (Giacomuzzi, 2008).

Methadone maintenance treatment has been demonstrated to be an effective treatment for opioid addiction and curbs the incidence thereof. Although methadone maintenance

treatment has been successful, it is associated with a number of problems. Up to 50% of methadone patients withdraw from treatment in the first 6 months. Daily dosing can be a burden for treatment facilities, some of which provide doses to over 900 patients a day. Patients prefer take-home doses, but they are often associated with diversion. Therefore, nowadays methadone cannot be regarded as the golden standard for all addicted persons.
There are a number of alternatives to methadone as a maintenance agent in the management of opioid dependence.
The most promising of these involve pharmacotherapies which treat patients with a pharmaceutical grade opioid which has a longer duration of action than methadone. These include the opioid partial agonist buprenorphine and the full agonist levo-alpha-acetylmethadol (LAAM) (Giacomuzzi, 2008).

2.1 Buprenorphine maintenance treatment

Buprenorphine is a potent synthetic opioid analgesic initially used for the management of acute pain. Pharmacologically, buprenorphine causes morphine-like subjective effects and produces cross-tolerance to other opioids. Unlike methadone and heroin (which are full agonists), buprenorphine is a partial agonist and exerts weaker opioid effects at opioid receptor sites.
This partial agonist action appears to make buprenorphine safer in overdose. Other benefits of buprenorphine may include an easier withdrawal phase and, because of the longer duration of action, the option of alternate day dosing (Giacomuzzi et al., 2005; 2008).
It was during the initial development of buprenorphine as an analgesic in the 1970s that its potential utility as a substitution agent in the treatment of opioid dependence was recognised. Early work using buprenorphine administered subcutaneously characterised it as an opioid with low physical dependence liability with a minimal withdrawal syndrome.
Subsequently, others provided evidence that buprenorphine does produce a mild to moderate mu-agonist withdrawal syndrome. It was thought that at doses somewhat greater than those used for analgesia, it could be used in the treatment of opioid dependence. Buprenorphine also has also some advantages over methadone. As mentioned earlier, buprenorphine has a ceiling level on agonist activity, limiting adverse reactions at very high doses. Some study results suggest that a twice-weekly dosing regimen may also be possible (Petry et al., 2001).
Evidence on the efficacy of buprenorphine has come from placebo-controlled trials, fixed dosing studies of buprenorphine versus methadone maintenance treatment and variable dosing studies of buprenorphine versus methadone maintenance treatment (Giacomuzzi, 2008). Some of the fixed dose studies showed no difference in efficacy, whereas others showed superiority for methadone and yet others showed the opposite pattern.
The investigators of these fixed dose studies frequently concluded that the doses of buprenorphine or methadone chosen were too low or that poor induction regimes led to poor retention. A series of variable (or flexible) dose studies have been conducted and show essentially equivalent results for the two drugs.
The implication of the results of a meta-analytic review conducted and reported by Mattick et al. (2004) is clear for clinical practice. The authors conclude that buprenorphine is an effective treatment for heroin use in a maintenance therapy approach.
A meta-analysis comparing buprenorphine to methadone for treatment of opioid dependence found that subjects who received 8-12 mg/d buprenorphine had 1.26 times the

relative risk of discontinuing treatment than subjects receiving 50-80 mg/d methadone. In this meta-analysis, buprenorphine was more effective than 20-35 mg/d methadone.
These studies also found that the difference in the effectiveness of buprenorphine and methadone may be statistically significant, but the difference was small compared to the wide variance in outcomes achieved in different methadone treatment programmes (Giacomuzzi, 2008; 2009).
Randomized, controlled studies of up to 6 months' duration compared sublingual buprenorphine with methadone in opioid dependent patients. These generally demonstrated comparable efficacy with buprenorphine 8-12mg/d and methadone 30-90mg/d in promoting retention in treatment and reducing illicit opioid.
Nevertheless, it is buprenorphine that has gained more and more importance in addiction treatment because the correlation between dose and therapeutic effects is not linear, indicating a ceiling on the effects in patients due to its opioid agonistic–antagonistic characteristics.
Buprenorphine is therefore a relatively safe substance, and its effectiveness in maintenance therapy has been proved in many studies. It has been used in Austria as a substitution drug since 1999.
Further research is needed to determine whether buprenorphine treatment is more effective than methadone in particular settings or in particular subgroups of patients.
It should be noted that, in an effort to prevent injection of the drug, the Buprenorphine/Naloxone – Sublingual Suboxone® formulation includes naloxone in addition to buprenorphine. Until now, these efforts have turned out to be less fruitful and the acceptance of this new group of preparations (Suboxone®) appears to have decreased in contrast to classical buprenorphine (Subutex®).
However, reasons which lower the acceptance on the part of the clients yet are not fully understood (Giacomuzzi et al., 2011).

2.2 Slow-release oral morphine maintenance treatment

Nowadays, apart from methadone and sublingual buprenorphine, another substitution medication is prescribed for opioid treatment, such as long-acting morphine (retarded or slow-release oral morphine).
Slow-release oral morphine was established in 1998 for substitution, which gives Austria an exceptional position in opioid addiction treatment compared to other European countries (Giacomuzzi, 2008).
Although slow-release oral morphine is used in Austria as an alternative to methadone or buprenorphine for maintenance treatment of opioid dependence, quantitative descriptions of patient outcomes have yet to be reported.
Slow-release oral morphine is an opioid agonist with a 12–24 hour duration of action. It is indicated for use as a maintenance treatment. The slow-release form overcomes many of the disadvantages of the short-acting nature of morphine, so theoretically it should have the same treatment effects as methadone, without some of methadone's disadvantages. Therefore, slow-release oral morphine has been proposed as an alternative maintenance pharmacotherapy to methadone or sublingual buprenorphine for treatment of opioid dependence.
There have been several studies on slow-release oral morphine for maintenance therapy Giacomuzzi, 2008). Morphine is not usually administered at our clinic to children under the

age of 18 years, in respiratory depressions and in the presence of acute alcoholism (Giacomuzzi, 2008). Further research is needed to determine whether slow-release oral morphine treatment is more effective than methadone or buprenorphine in particular settings or in particular subgroups of patients.

3. Effects of opioid maintenance treatment on sexual dysfunctions

Consideration of side effects of opioid pharmacotherapies like cognitive impairment or sexual dysfunction is important. Especially sexual dysfunction, besides creating difficulty in intimate relationships, has the potential to lead to decreased compliance with therapy and to interfere with the known benefits of opioid maintenance treatment.
While the impact of sexual dysfunction upon treatment compliance has scarcely been studied in opioid maintenance treatment-receiving samples, sexual dysfunction has been shown to interfere with therapeutic compliance among subjects with depression, HIV, and hypertension (Brown & Zueldorff, 2007; Giacomuzzi 2008).

3.1 Sexual dysfunction among men and woman

Sexual dysfunction among men on opioid maintenance treatment appears to be related to lower-than-normal serum levels of testosterone. The association between opioids and low serum testosterone levels may occur through a variety of mechanisms (Brown & Zueldorff, 2007). Opioids may also act directly upon testicular tissue to suppress normal testosterone production.
Research regarding sexual dysfunction among females on opioid maintenance treatment is more scant. Sexual dysfunction among women on opioid maintenance treatment appears to be primarily related to interference with the normal cyclic production, possibly due to elevated production of prolactin mechanisms (Brown & Zueldorff, 2007).
This process interferes both with hormones necessary for the maintenance of a normal menstrual cycle (estrogen, progesterone) and for normal libido (androgens). Interference with these sex hormones is thought to lead to the common signs and symptoms of sexual dysfunction and hormonal dysregulation, and among women on opioid maintenance treatment, depressed libido and oligomenorrhea or amenorrhea mechanisms (Brown & Zueldorff, 2007).
Especially literature regarding sexual dysfunction in female subjects on opioid maintenance treatment is also very scant. Studies have indicated that 50% of women switching from heroin to methadone experienced an improvement in sexual function.
Methadone was shown to depress serum testosterone levels in female subjects in one study. This depression of testosterone in women was also associated with increases in serum prolactin (Brown & Zueldorff, 2007).
Nearly 50% of women experience menstrual irregularity while on methadone maintenance. The effect appears to be dose-related, and appears to decline over time, with the potential for resumption of normal menses without alteration of methadone dosing (Brown & Zueldorff, 2007).
While it is clear that impaired androgen production is closely and directly associated with sexual dysfunction in males, the relationship within females is more complicated and less clear (Brown & Zueldorff, 2007; Giacomuzzi, 2009).
The normal mid-cycle rise in serum androgens in women has not been strongly related to sex drive. Transdermal replacement of lower-than-normal serum androgens in female

subjects, however, has been shown to result in improvements in mood and libido. Additionally, when given testosterone supplementation, women with normal levels of serum testosterone have demonstrated an increased sexual response mechanism (Brown & Zueldorff, 2007).

Studies have demonstrated higher rates of sexual dysfunction in methadone-maintained groups than in the general population. Estimates of prevalence, however, vary significantly between 30-100%.

Additionally, the prevalence of specific types of sexual dysfunction (libido, erectile, and orgasm dysfunction) has poorly been examined in detail (Brown & Zueldorff, 2007; Giacomuzzi, 2009).

In one of the first studies to examine particular types of sexual dysfunction in a methadone maintained sample, Teusch et al. (1995) found men maintained on methadone to report reduced libido and orgasm dysfunction more frequently than controls.

Similar to earlier studies, however, the severity of dysfunction and methadone dose were unrelated.

Mendelson et al conducted a prospective study of the effect of acetylmethadol administration on serum testosterone levels in 13 men with opioid dependence which yielded significant results. A statistically and biologically significant decrease in serum testosterone was found 7-9 hours after acetylmethadol administration. Testosterone levels attained normal levels 48 hours after drug administration.

Mendelson also conducted some of the earliest work demonstrating a relationship between methadone dose and serum testosterone concentration. When the sample (n =38) was dichotomized into groups receiving lower dose (10-60 mg) and higher dose (80-150 mg) methadone, the men receiving higher daily doses of methadone were found to be more likely to have abnormally low serum testosterone.

As further evidence of an inverse relationship between methadone dose and serum testosterone levels in this study, reductions in methadone dose were associated with recovery of testosterone levels.

Mendelson et al found similar results in a sample of 10 men administered heroin in a controlled setting for 7 days and then detoxified using methadone at a starting dose of 35 mg. Again, abnormally low serum testosterone levels found during and after the period of heroin administration were found to recover to baseline after methadone detoxification.

3.2 Erectile dysfunctions

Erectile dysfunction (ED) more commonly has an organic or iatrogenic etiology. A variety of systemic illnesses are associated with ED. These include chronic liver disease, renal failure, arteriosclerotic cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and malignancy. Spinal trauma and genitourinary surgery are of potential etiologic importance in ED, as well.

Though rarer, congenital and other anatomic genitourinary anomalies (e.g. Peyronie's Disease, phimosis, post-traumatic aneurysm) should also be considered (Brown & Zueldorff, 2007).

Medications commonly associated with ED include antihypertensives, psychotropic agents, and medications with anticholinergic effects.

Smoking, for example, is strongly associated with ED. The relative risk for ED increases by 1.31 for every 10 pack-years of smoking.

Though organic factors commonly cause ED, mental and emotional health issues may be significant contributors, as well. Depressive symptoms have been most strongly associated with ED, with 90% of men with severe depression reporting ED in one study. Association with anxiety disorders has also been reported (Brown & Zueldorff, 2007).

Several previous studies have demonstrated that erectile dysfunction (ED) is common among heroin users and people undergoing treatment for heroin addiction. Estimates of the prevalence of ED in methadone-maintained patients vary widely: 16% (8 cases/50 subjects), 23%.

Many patients with ED fail to mention ED to clinicians and counsellors and many clinicians and counsellors feel uncomfortable and embarrassed about dealing with sexual problems.

Nevertheless, the assessment of ED in these patients may be quite important. Identification and management of ED problems can improve adherence to treatment, the effectiveness of which, as is well-known, is associated with high doses and long treatment duration.

It is hard to establish the relative importance of possible causes of ED among opioid users.

Many drugs commonly prescribed for co-morbid conditions among drug users (antidepressants, antipsychotics, sedatives, anxiolytics, anticholinergics, etc.) can negatively affect sexual performance (Brown & Zueldorff, 2007).

Low testosterone levels may be a relevant cause of ED among opioid users, although no conclusive results have been reached. Two physiological mechanisms are thought to be responsible for the reported ED associated with opioid use.

The first is the inhibition of the production of gonadotropin-releasing hormone, decreasing the release of the luteinizing hormone (LH) and therefore reducing the production of testosterone.

Opioids can also cause hyperprolactinemia, which produces negative feedback on the release of LH and consequently on the secretion of testosterone.

However, existing studies involve few patients, and no correlation between duration of methadone treatment and testosterone blood levels has been found. Moreover, in the general population, endocrinal causes are responsible only in a small number of cases of ED (Brown & Zueldorff, 2007).

A study by Quaglio et al. (2008) included 201 males; subjects were 18–47 years old (mean = 31, S.D. = 6.0). Eighty-five patients (42%) were on methadone maintenance with a median dose of 40 mg/day (min 10, max 180 mg, 5% above 100 mg/day).

One hundred sixteen patients (58%) were on buprenorphine maintenance with a median dose of 6 mg/day (min 1, max 24, slightly more than 10% had dosages over 12 mg/day). As reported, subjects in methadone and buprenorphine treatment had similar socio-demographic characteristics (the hypothesis of distribution homogeneity was not rejected for almost all study variables).

Fifty-nine percent reported no depression, 24% reported mild depression, 12% moderate and 4% serious depression.

In all, 67 patients declared they did not have a steady sexual partner: consequently, the characteristics of steady sexual partners are based on data from 134 subjects. These partners were, on average, 3.4 years (S.D. = 6.3) younger than the index subjects, 68% of the partners were employed, 40% had no more than 8 years of education, and 14% of the partners had used heroin.

In the study of Quaglio et al. (2008), very substantial rates of ED were found: 19%of the patients reported severe ED and another 23%reported mild to moderate ED.

The percentage of patients reporting ED is moderately higher than the percentages reporting ED in previous studies of methadone patients (Brown et al., 2004; Hanbury et al., 1977; Teusch et al., 1995; Cushman, 1972).

The majority of previous studies of ED among drug users have used nonvalidated questionnaires, so caution should be exercised when comparing these earlier study findings to the present results.

Nevertheless, all the surveys by Quaglio et al. (2008) indicate high rates of ED among methadone/buprenorphine patients. However, the age of the subjects in this study ranged from 18 to 47, with a mean age of 31 where 42% reported ED, while in a general population study of more than 2000 Italian males, only 2% in the age group 18–39 reported ED.

In a study by Quaglio et al. (2008), the univariate analysis showed a significant association between treatment and ED, with buprenorphine patients reporting less ED than methadone patients, but this was not confirmed by the multivariate analysis.

Quaglio et al. (2008) did not find any significant association between either methadone dose or buprenorphine dose and ED, or with reported duration of either methadone or buprenorphine treatment and ED.

Thus, these data by Quaglio et al. (2008) do not suggest that changing from one medication to the other, or modest changes in the dosage level of either medication, would be effective in reducing ED.

The association between depression and ED is well established in literature and the causal relationship is probably bidirectional, i.e. ED may be a consequence of depression and depression may follow ED. About 1/3 of depressed untreated patients report reduced libido, delayed ejaculation, anorgasm or ED.

Comorbidity of mood disorders and opioid dependence has also been frequently observed. Seventeen per cent of our patients suffered from depression, while only 6% were on anti-depression treatment, and there was no association between receiving or not receiving treatment and ED. The routine assessment of patients in opioid agonist treatment should include a careful evaluation of depression and, when clinically indicated, vigorous treatment.

Three aspects of social/sexual relationships were associated with ED in the study of Quaglio et al. (2008).

Living with a sexual partner (compared to living with parents) was associated with a lower likelihood of ED. Having ED may reduce one's ability to develop and maintain a sufficiently strong sexual relationship to lead to the partners living together. Lack of a steady partner may also contribute to ED.

Quaglio et al. (2008) also found that living with a sexual partner who has a history of heroin use was associated with current ED in these patients.

The association in the study of Quaglio et al. (2008) was very strong, with an adjusted odds ratio of 5.84, which reflects the relevant decrement of the median ED score from 27 in the patients with a non-heroin user partner to 21 in those with a heroin-user partner. Another study observed that when both members of a couple are strongly addicted to heroin, they almost always lose interest in sex.

All the patients in this study, however, had entered drug abuse treatment in order to reduce their heroin use, and it was assumed that interest in sex would return during treatment. There are (at least) two interesting mechanisms in this strong association.

Difficulties in the relationship between two people with histories of heroin abuse may lead to ED, and/or males with a pre-disposition to ED may selectively seek out females who use heroin as sexual partners.

In this study, Quaglio et al. (2008) found a high rate of ED among Italian methadone and buprenorphine patients—18% had severe ED and 24% had mild to moderate ED. Both psychological factors (depression) and social factors (living situation, lack of steady partner, whether partner had a history of heroin use) were associated with ED.
The cross-sectional design of the study precludes determining whether these associations represented mere correlations without causal relationships, whether the factors were causes of ED, or whether ED was the cause of the factors, or some combination of all of these possibilities.
It is also important to note that no data was available on ED among these patients prior to their entry into methadone or buprenorphine treatment, either during periods of intense heroin use or during periods of abstinence from heroin.
There was also no data on the current use of other drugs which might influence the sexual functioning of the patients.
The strengths of the study of Quaglio et al. (2008) include a large sample of patients, its multicentral nature and the identification of predictors for diagnosis.
In addition, their paper presents ED for a large cohort of patients in buprenorphine treatment.
Quaglio et al. (2008) conclude that ED is likely to be an important problem for many males in methadone and buprenorphine treatment, and good addiction treatment will need to address this issue. Androgen replacement and pharmacological treatment may be effective approaches for these patients.
Counselling of couples may also be useful. In our view, taking patients off methadone or buprenorphine, with the high risk of relapse to intensive heroin use, would not be suitable.

Specific study findings on buprenorphine

Studies comparing buprenorphine to the more commonly used methadone have found that rates of success in treatment are similar and that buprenorphine may result in fewer adverse effects. However, only a few studies to date have examined the prevalence of sexual dysfunction in particular among patients treated with buprenorphine and it is important that the influence of buprenorphine on ED be investigated further in the near future (Brown & Zueldorff, 2007; Giacomuzzi 2008; 2009).
One previous study found that buprenorphine has fewer negative effects on male sexual performance than methadone (Bliesener et al., 2005). This study, however, included only a small number of subjects, 17 patients in buprenorphine and 37 in methadone treatment.
In 2005, Bliesener and colleagues examined 17 male patients maintained on buprenorphine and 37 male patients maintained on methadone. Patients self-reported effects on libido and potency, and total and free testosterone, estradiol, and prolactin were assayed. Blood samples from 51 male volunteers were used as a control group for the hormone analyses. Twenty-three percent of patients in the buprenorphine group reported a decrease in libido, compared to 83% in the methadone group. Twelve percent reported reduced potency, compared to 72% in the methadone group.
Other forms of sexual dysfunction, such as orgasm dysfunction, were not examined in this study.
The Bliesener study also found that patients treated with buprenorphine had significantly higher mean levels of total (5.1 ± 1.2 ng/mL) and free (17.1 ± 4.8 pg/mL) testosterone than patients treated with methadone (2.8 ± 1.2 ng/mL and 7.8 ± 2.9 pg/mL, respectively), and

that in fact mean total testosterone levels of those patients being treated with buprenorphine did not significantly differ from levels in the healthy control group sample (4.9 ± 1.3 ng/mL).
Mean levels of prolactin were significantly higher in the methadone group (8.7 ± 8.3 ng/mL) than in the buprenorphine group (5.0 ± 2.0 ng/mL), though all groups were in the normal range. There were no other significant differences found in the hormonal analysis.
In an examination of BDI scores collected in the same study, mean scores of the opioid therapy groups were not found to differ significantly from one another.
This lack of difference, as well as a lack of significant difference in age, medical status, length of addiction, concurrent medications, or frequency of illicit opioid use led the authors to conclude that it was most likely the treatment drug rather than other variables that contributed to the differences between therapy groups in hormone levels and reports of sexual dysfunction.
The aim of our own examination was to determine which substitution agent seemed most suitable as a substitution drug for narcotic-addicted men and women in relation to both sexuality and relationship quality. In particular, the examination of female sexuality amongst women administered substitutes presented a considerable challenge, both in psychological and medical terms.
As part of sex research by Büsing, Hoppe und Liedtke in 2000, an examination of 'Sexual satisfaction amongst women – survey development and results' was carried out. The subject of this study focussed on the conception, creation and execution of a survey to determine the sexual satisfaction of women. As basic data, the survey considered the frequency and duration of sexual activity, satisfaction with the frequency and duration of the activity and desired sexual behavior. In the first study, 112 heterosexual women between the ages of 20-48 were interviewed. On the one hand, the results reveal the importance of the orgasm experience, which is emphasised through the high rate of desire concerning coital orgasm. On the other hand, half of the women who participated in the study did not state orgasm as their favourite part of sex. 37% of the women state that the emotional and physical closeness to their partner is more important than climaxing. In between-group comparison, sexual satisfaction above all correlates with the degree of autonomy within the relationship, satisfaction of communicative desires within the relationship and the need for affection. (Büsing et al. 2000)
This study shows that assessing sexual satisfaction amongst heterosexual women without addiction represents a significant hurdle within research. There are several reasons for this: women have different sexual requirements, and their sexual behavior cannot be compared to that of men. Given that this subject area deals largely with 'virgin territory', the focus now turns to general studies of sexual behavior in order to better address the questions posed by this thesis.
Our own study aimed therefore to evaluate patterns of sexual behavior and dysfunction prevalence within buprenorphine and methadone maintenance treatment (Giacomuzzi, 2009). Two questionnaires, in addition to socio-demographic data sets, adapted Relationship Quality Test System (Qualität der Partnerschaftsbeziehung) and EQ-5D (EuroQol), were randomly administered in person by a researcher. A response rate of 100% was obtained. 60 patients (30 buprenorphine; 30 methadone), mean age 30.2 years (IQR 22.5–43.3), were enrolled in the study (Giacomuzzi, 2009).

The study assumed that, in comparison to methadone, the effect of buprenorphine would reduce the additional use of substances. However, this hypothesis could not be established. Neither the substances specified by the various groups in relation to additional use, nor the frequency of consumption were statistically significant.

As a result of this, the study results of Fischer et al. (1999) concerning additional consumption were confirmed. Another assumption of our study was that individuals who take buprenorphine enjoy certain advantages concerning sexual behavior in comparison to those who are administered methadone.

Significant differences were noted between the substitution groups in relation to the question of whether their current sexual life was satisfying. In specific, it is significant that more participants from the buprenorphine group (90%) were satisfied with their current sexual life than participants in the methadone group (63.3%). AT p = 0.030, this difference was of considerable statistic significance.

Men on methadone maintenance treatment, but not buprenorphine maintenance treatment, had a high prevalence of sexual excitation disturbances and ability to orgasm in this study.

Significant differences between both groups could be observed regarding sexual excitation disturbances and ability to orgasm. 33.3% of the methadone-maintained group showed significantly higher sexual excitation disturbances (p = 0.006) and problems reaching orgasm (40%) (p = 0.015) compared with 3.3% respectively 10% within the buprenorphine-maintained group. These results were not affected by sex, since both groups exhibited the same sex distribution (30 men; 30 women).

The study by Bliesener et al. (2004) was confirmed by these results. It should, however, be added that only male participants were represented in the study carried out in 2004. Nevertheless, Bliesener et al. did identify significant results between the methadone and buprenorphine group in relation to libido and virility. In the study presented here, one might assume that these results are influenced by the confounding variable of 'sex', although in light of the identical sex distribution, this was not possible.

	Medication						
	Methadone			Buprenorphine			
	N	Md	IQR	N	Md	IQR	p-value[a]
EQ5D-Index[b]	30	0.752	0.5–0.9	30	0.843	0.7–0.9	0.112
Actual health status in comparison with 12 months ago[c]	30	2.0	1.0–2.0	30	2.0	1.0–2.0	0.725
Self rating regarding acutal health status[d]	30	62.5	43.8–75.0	30	72.5	60.0–80.0	0.032*

[a] * p < 0.050; ** p < 0.001 (2 sided)
[b] range from -0.3841 to 0.9599 regarding german norm values (the higher the score, the better QOL)
[c] range from 1–3 (1 = better, 2 = equal, 3 = worse)
[d] range from 0–100 (0 = low QOL vs. 100 = high QOL)

Table 1. Quality of Life EQ-5D

A significant correlation between treatment mode and ejaculation praecox, erectile dysfunction, vaginal cramps and sexual aversion could not be observed.
Sexual life satisfaction was scored significantly higher by the buprenorphine-maintained group (90%) compared with the methadone-maintained (63.3%) group ($p = 0.030$).
The question as to whether climax is experienced during sex was answered with 'mostly' by the median of participants in both substitution groups. The question of how often participants had sex with their partner was answered by participants from the methadone group with a median of 'once a week', and by participants in the buprenorphine group with a median of 'two to three times a week'. However, on average, both groups would like to have sex with their partner 'two to three times a week'. No significant group differences were identified in relation to these three questions concerning sexual behaviour.
In relation to questions concerning the degree of satisfaction with how participants or their partners reacted sexually, consistently high levels of satisfaction (80 to 90%) were recorded. Significant group differences were not identified in relation to these two questions.
Furthermore, sexual partnership was scored significantly higher by women within the buprenorphine-maintained group ($p = 0.020$).
Further significant differences between the substitution groups were noticed amongst women concerning the question of affection, which was dealt with in the 'Relationship Quality' survey. It was interesting to note that women using methadone as a substitute rated affection higher than women administered the substitute substance Subutex.

		Medication				
		Methadone		Buprenorphine		
		N	[%]	N	[%]	p-value[a]
Is your actual sexual life satisfaying with your partner?	no	11	36.7	3	10.0	
	yes	19	63.3	27	90.0	0.030*
Do you feel comfortable with your sexual reactions?	no	6	20.0	4	13.3	
	yes	24	80.0	26	86.7	0.731
I feel comfortable with my partners sexual reactions.	no	5	16.7	3	10.0	
	yes	25	83.3	27	90.0	0.706

[a] * $p < 0.050$; ** $p < 0.001$

Table 2. Sexual satisfaction

Significante differences between the groups were also identified in the area of quality of life. Patients receiving Subutex as a substitute agent gave considerably higher values concerning their self-rated physical health condition than methadone patients.
The self-rated physical health score was significantly higher in the buprenorphine-maintained group compared with the methadone group (p = 0.032). A significant correlation could be found between physical health and substitution mode (p =0.039).

		Substitution substance		
		Methadone	Buprenorphine	
		[%]	[%]	p-value
Is your current sex life with your partner satisfying?	No	36.7	10.0	
	Yes	63.3	90.0	0.030*
I am satisfied with the way in which I react sexually.	No	20.0	13.3	
	Yes	80.0	86.7	0.731
I am satisfied with the way in which my partner reacts sexually.	No	16.7	10.0	
	Yes	83.3	90.0	0.706

* p < 0.050; ** p < 0.001

Table 3. Frequency comparison of sexual satisfaction according to substitution substance

Concerning the self-rated physical health condition on a scale of 0 to 100, participants from the Subutex group achieved a median of 72.5, which was significantly higher than the median value of 62.5 recorded in the methadone group.
In relation to the EQ-5D index, both groups achieved a relatively high index value. The figure for the methadone group was 0.752, whilst the Subutex group even achieved 0.843. Nevertheless, this difference did not reveal any statistical significance. If we consider the answers to 'Current physical health compared with the last 12 months', the median of both groups stated 'Approximately the same'.
In a further step, the connection between the life quality index and the four scales of the relationship survey was calculated. Here, the highest scores on the affection scale amongst men, and the raw scores amongst the female participants, revealed significant results.
In order to verify the results obtained, a covariance test was carried out to explain whether the significant results could be irrefutably attributed to the substitution substance or the intervening covariates. The conclusion of this analysis was that the differences identified were indeed attributable to the different substances.

		Substitution substance		
		Methadone	Buprenorphine	
		[%]	[%]	p-value
Do you masturbate regularly?	No	76.7	60.0	
	Yes	23.3	40.0	0.267
Do you climax (orgasm) when masturbating?	No	30.0	16.7	
	Yes	70.0	83.3	0.360
Do you have arousal disorders?	No	66.7	96.7	
	Yes	33.3	3.3	0.006*
Do you have difficulty reaching orgasm?	No	60.0	90.0	
	Yes	40.0	10.0	0.015*
Do you suffer from premature ejaculation?	No	86.7	100.0	
	Yes	13.3	0.0	0.483
Do you suffer from erectile dysfunction?	No	93.3	100.0	
	Yes	6.7	0.0	1.000
Do you have vaginal cramps during sex?	No	93.3	100.0	
	Yes	6.7	0.0	1.000
Do you have cramp-like pain during sex?	No	93.3	100.0	
	Yes	6.7	0.0	1.000
Do you have sexual aversion?	No	73.3	93.3	
	Yes	26.7	6.7	0.330

* $p < 0.050$; ** $p < 0.001$

Table 4. Frequency comparison concerning questions on sexuality according to substitution substance

4. Conclusions

Substitution therapy has become the main form of post-acute treatment of opiate addicts. Despite this, the most suitable substitution substance remains a topic of controversial debate today. Alongside methadone, which is by far the most researched substance, buprenorphine is now increasingly used.

On the one hand, methadone substitution has become established as suitable treatment worldwide, given that it not only has a stabilising and health-maintaining effect, but also leads to an improvement in social rehabilitation (Giacomuzzi, 2009). A central argument put forward by those in favour of methadone against buprenorphine is the danger of intravenous consumption of this substance, through which the 'rush' is achieved, which is missing with oral administration. In contrast, methadone opposers contend that precisely the low euphoric effect of methadone causes problems with the acceptance of the substitute and leads to increased parallel consumption behavior.

On the other hand, in light of the diverse side effects of methadone, new substances like buprenorphine are becoming increasingly popular. Proponents affirm that when compared

directly with methadone, buprenorphine presents more advantages. A wide range of studies have shown that even in high doses, buprenorphine causes fewer side effects than methadone, presents a lower dependence potential, increases drive and has anti-depressive properties.

The standard substitution therapy continues to be methadone. All new drugs or substances used must be able to compete with the success or failure experiences of traditional methadone substitution (Giacomuzzi, 2009).

The clarification of the individual needs of different groups of drug addicts seems particularly important for the future (Giacomuzzi, 2009). Therapy studies have proven that psychosocial measures, coupled with substitution, achieve significantly better effects than psychopharmacotherapy alone. The current offer of drug clinics, private associations, etc. is not sufficient to meet patients' needs.

Opioid maintenance treatment, primarily methadone, appears to be associated with alteration of serum levels of hormones related to normal sexual function.

In males, opioids may act via: (1) interference with the normal production of hypothalamic and pituitary regulatory hormones, (2) elevation of serum prolactin, (3) direct action on the testes to suppress testosterone production (Brown & Zueldorff, 2007).

While elimination of other common medical and psychiatric etiologies for sexual dysfunction is warranted, replacement of abnormally low serum testosterone may effectively treat libido or erectile dysfunction, and potentially delayed orgasm or anorgasmia. Replacement of abnormally low androgens in women on opioid maintenance treatment may also improve libido as well as mood.

Abnormalities in the menstrual cycle are thought to be transient and may not require alteration of opioid maintenance treatment dosing. Patients with refractory sexual dysfunction and a stable course in terms of their opioid use disorder may correspond to reduction in the dose of their opioid maintenance treatment agent, with methadone likely being of greater significance here than buprenorphine (Brown & Zueldorff, 2007).

Sexual behavior is not only of basic biological importance, but also of central social importance. Not only does it perpetuate the human species, but it is the central behavior around which families are formed and defined, a vital aspect of the psychological well-being of individuals, and a component of a variety of social problems.

There has been very little research on ED among buprenorphine patients. Men on methadone maintenance treatment, but not buprenorphine maintenance treatment, had a high prevalence of sexual excitation disturbances and ability to orgasm. Orgasm dysfunction seems to be a special case and may respond to methadone dose (Giacomuzzi, 2009).

In light of the paucity of studies in the area of sexual dysfunction as an adverse effect of buprenorphine, more research is needed, utilizing larger patient populations and examining more thoroughly specific types of dysfunction in both male and female populations.

Future studies of sexual dysfunction in opioid-treated persons should examine the potential benefits of dose reduction, androgen replacement, and choice of opioid (Giacomuzzi, 2009).

Practitioners should screen for sexual dysfunction in men receiving opioid replacement treatment. Orgasm dysfunction seems to be a special case and may correspond more to methadone dose. Future studies of sexual dysfunction in opioidtreated persons should examine the potential benefits of dose reduction, androgen replacement, and choice of opioid (Giacomuzzi, 2009).

Therapy and patient care should be structured in a more flexible manner.

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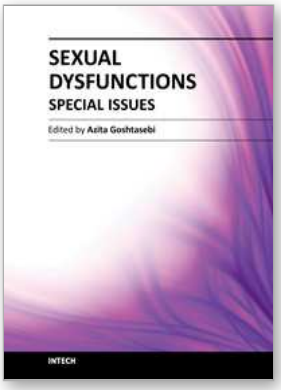

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Sexual dysfunctions have recently recognized as one of the major public health problems. This book enhances our scientific understanding of sexual function and dysfunction from different perspectives. It presents evidence-based interventions for sexual dysfunctions in difficult medical situations such as cancer, and gives a valuable overview of recent experimental researches on the topic. Published in collaboration with InTech - Open Access Publisher, this imperative work will be a practical resource for health care providers and researchers who are involved in the study of sexual health.

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