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Gender issues in the Pharmacotherapy of Opioid-Addicted Women: Buprenorphine

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Abstract

Gender, a biological determinant of mental health and illness, plays a critical role in determining patients' susceptibility, exposure to mental health risks, and related outcomes. Regarding sex differences in the epidemiology of opioid dependence, one third of the patients are women of childbearing age. Women have an earlier age of initiation of substance use and a more rapid progression to drug involvement and dependence than men. Generally few studies exist which focus on the special needs of women in opioid maintenance therapy. The aim of this paper is to provide an overview of treatment options for opioid-dependent women, with a special focus on buprenorphine, and to look at recent findings related to other factors that should be taken into consideration in optimizing the treatment of opioid-dependent women. Issues addressed include the role of gender in the choice of medication assisted treatment, sex differences in pharmacodynamics and pharmacokinetics of buprenorphine drug interactions, cardiac interactions, induction of buprenorphine in pregnant patients, the neonatal abstinence syndrome and breastfeeding. This paper aims to heighten the awareness for the need to take gender into consideration when making treatment decisions in an effort to optimize services and enhance the quality of life of women suffering from substance abuse.

Keywords

Gender; buprenorphine; opioid dependence; neonatal abstinence syndrome

INTRODUCTION - GENDER DIFFERENCES

In 2002, the World Health Organisation (WHO) passed its first Gender Policy, acknowledging gender as a fundamental human concern. At about the same time, the WHO began using the UN's Millenium Development Goals (MDGs), specifying more particularly that gender equality and the empowerment of women should be main goals worldwide.

Gender, a biological determinant of mental health and illness, intersects with and enlarges the differences associated with other important socioeconomic factors such as income, employment and social position. Gender also differentially affects the power and control men and women have over these socioeconomic factors, their access to resources, as well as their status, roles, options and treatment in society.

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Gender plays a critical role in determining patients' susceptibility, exposure to mental health risks, and related outcomes 1. Gender differences in rates of overall mental health are negligible, but they are highly significant for depression, anxiety and somatic complaints, as well as substance abuse disorders[1]: Lifetime prevalence rates of alcohol dependence are higher for men (20%) than for women (8%)[2], and more generally, in 2003 men were found to be twice as likely to abuse an illicit drug than were women2. Gender differences are also found in patterns of help-seeking for psychological disorders. Men prefer to seek specialized mental health care and more frequently receive inpatient treatment than women, whereas women are more likely to seek help from their primary health care physician. Women are more likely to disclose emotional problems than men, whereas men are more likely to admit having an alcohol problem1.

Regarding gender differences in the epidemiology of opioid dependence, one third of the patients are women of childbearing age[3]. Women have an earlier age of initiation of substance use and a more rapid progression to drug involvement and dependence than men.[4] Women expose themselves to more health risk factors, such as prostitution to secure drugs and sharing syringes, leading to a higher rate of new infections with HIV and other infectious diseases such as hepatitis[5]. Both opioid-dependent men and women show mortality rates 13 to 17 times higher than the general population, with slightly higher rates for men[6].On the other hand, due to a higher vulnerability to the adverse consequences of these disorders, women also show a more rapid progression to treatment entry and consequently a lower number of years of active illicit substance abuse than men, yet, despite of this, women are still underrepresented in addiction treatment.[7]

Several gender-related issues related to the use of maintenance therapy for opioids dependence should be considered. It has been shown that women have a different opioid binding capacity than men, which will influence dosing regimens in opioid pharmacotherapy8. Additionally, specific dose changes have to be considered if the opioid-dependent patient gets pregnant, especially in the last trimester, when hormonal enzyme induction often requires an elevation or splitting of the daily administered opioid dose[9]. In general the more complicated hormonal status in women with individual levels of oestrogen/progesterone in the premenopausal (even considering the changes between pre- and post ovulation) and postmenopausal women needs to be taken into account regarding interaction in the metabolism of medication. Detailed dosing information has been provided so far in the treatment of depression[10], but not in the treatment of opioid dependence. It should also be noted that improved treatment approaches will lead to an aging population being on opioid pharmacotherapy for decades 11.

Generally few studies exist which focus on the special needs of women in opioid maintenance therapy. The aim of this paper is to provide an overview of treatment options for opioid-dependent women, with a special focus on buprenorphine, and to look at recent findings related to other factors that should be taken into consideration in optimizing the treatment of opioid-dependent women.

THE ROLE OF GENDER IN THE CHOICE OF MEDICATION ASSISTED TREATMENT

Lack of data may explain why gender has rarely been considered a determinant when considering the choice of medication-assisted treatment for a specific patient. Jones et al. provided data derived from a randomized controlled study of gender differences in response to opioid agonist medications[12]. Opioid-dependent males (n=104) and females (n=61) were assigned to receive either Levomethadyl Acetate(LAAM) (75–115 mg), methadone (60–100 mg) or buprenorphine (16–32 mg) in flexible dosing schedules. Outcome measures included retention in treatment, percentage of positive illicit opioid urine samples, self-reported opioid

use and patient's rating of the current global severity of his or her opioid problem at the last interview before either discontinuation of the study medication or completing the study protocol.

Although no significant disparities were observed in the study population among the three medication groups, some gender differences previously shown in the literature were verified. In former studies, female opioid-dependent patients entering opioid agonist therapy were significantly more likely to be unemployed [13–16], had a shorter duration of opioid addiction before starting treatment and showed more psychiatric and family problems compared to males [15,17,18]. Co-occurring psychiatric problems, such as mood disorders and past and present sexual abuse, were seen more frequently in drug-dependent pregnant women compared to a control female population. Between 56 and 73% of opioid-dependent pregnant women suffer from a major psychiatric disorder according to DSM-IV[19–22]. In the substance-dependent patient the effects of mood disorders are usually detrimental, resulting in patterns of harmful health behaviour during pregnancy, post-partum depression and consequences on mother-child interaction [23, 24]. For women with a history of sexual trauma, key treatment times such as induction or delivery may lead to the occurrence of flashbacks and emotional instability; appropriately trained staff should be present to help patients cope with traumatic memories [25]. The high prevalence of co-occurring psychiatric disorders indicates that opioid-dependent women need to be examined and provided with appropriate and specific medications and other treatments.

Regarding illicit opioid consumption Jones et al.[12] showed that women receiving buprenorphine had significantly fewer opioid-positive urine samples compared to their male counterparts. Females receiving buprenorphine also had significantly fewer illicit opioid-positive urine samples than females receiving methadone. These results support the reported superior effects of buprenorphine in decreasing illicit opioid use[13]. In contrast to this, however, another study conducted by Johnson et al.[26] reported opposite results; women maintained on buprenorphine showed greater rates of illicit opioid use than men. These differences could be partially explained by different study designs, particularly different durations of assessment periods, i.e. Johnson et al.[26] investigated the patients for a short period of fourteen days while Jones et al.[12] and Schottenfeld et al.[13] assessed the participants for seventeen and 24 weeks, respectively.

One explanation for the findings of Jones et al.,[12] who found improved outcomes in women maintained on buprenorphine compared to men in regard to illicit opioid consumption, could be the superior effects of the unique pharmacology of buprenorphine (a partial mu-agonist/kappa-antagonist) combined with basic pharmacodynamic sex differences. Specifically, women of reproductive age may respond better to buprenorphine due to their higher mu- and kappa-opioid receptor concentrations and/or unique differences in signal transduction compared to men[12]. Therefore, women in their reproductive years may predictably be more sensitive to mu- and kappa-opioid medications than men 8,27–29. As levels of estradiol and progesterone both may influence the opioid mechanisms,30–32 factors such as the phase of the menstrual cycle and age (i.e. menopause) may play an important role [27,33].

GENDER DIFFERENCES IN THE PHARMACODYNAMICS AND PHARMACOKINETICS OF BUPRENORPHINE/ DRUG INTERACTIONS

The pharmacokinetics and pharmacodynamics of psychotropic medications show substantial differences between male and female patients 34–37. Many confounding factors (e.g., body weight, fat distribution, gastric absorption and emptying, and colonic transit times) seem to influence the metabolism of these drugs, but a complete understanding of these results remains elusive36. Most studies have shown that cytochrome P-450 (CYP) 3A4 activity is higher in

women than in men38, while the activity of many other systems involved in drug metabolism (e.g., CYP2C19) seem to be higher in men than in women37. Furthermore, other studies have reported higher plasma levels of drugs metabolized by CYP1A2 in women37. In general, buprenorphine appears to have fewer significant drug interactions than methadone because it has low affinity for the 3A4 isoenzyme that is responsible for the metabolism of many drugs by the Cytochrome P-450 system39–41. When drug interactions do occur, they appear to increase the effects of buprenorphine (i.e., decreasing buprenorphine metabolism) and can be alleviated by a buprenorphine dose reduction. Similar to methadone[42], concurrent intravenous or very high-dose use of buprenorphine and benzodiazepines is associated with overdose deaths 43–46. The interaction mechanism does not appear to be pharmacokinetic but is more likely to be pharmacodynamic due to the fact that buprenorphine has a weak ability to inhibit the Cytochrom P-450 3A4 system 47. Since the exact interaction of sublingually taken buprenorphine and orally consumed benzodiazepines is unclear, women put themselves at higher risk for medical complications because they are more likely to misuse benzodiazepines[48].

BUPRENORPHINE AND CARDIAC INTERACTION

Special attention should be given to the recent discussion regarding cardiac complications of opioid medications, particularly taking gender differences into account 49,50. QT Interval Prolongation is a cardiac disorder characterized by abnormalities in cardiac repolarization resulting in prolongation of the QTc interval, T-wave changes, and torsade de pointes ventricular tachycardia (TdP) [50]. TdP poses serious medical risks due to the risks of recurrence and sudden cardiac death. Women have a higher risk of developing a long QT syndrome (LQTS) because of the effect of the reproductive hormones on the electrophysiological structure of the heart 49. While four membrane proteins produce electrical cardiac muscle activity, the KCNH2 channel binds with pharmacological substances to produce QTc interval prolongation 50. Various prescription drugs such as certain antipsychotics, antiarrhythmics, antibiotics, tricyclic antidepressants and antifungals are associated with risk of QTc interval prolongation due to the interference with the rapid component of the delayed rectifier potassium current, IKr 51,52. The human ether-à-go-go related gene (hERG) encodes for the major channel protein underlying IKr, and in vitro studies with hERG cell lines have successfully evaluated drugs suspected of leading to interval prolongation, especially in cardiac repolarization [53]. Methadone, buprenorphine and many structurally diverse drugs can block the hERG 51,54 resulting in a prolonged QTc interval 55. Special caution is required in the prescription of drugs associated with QTc interval prolongation, especially if a combination of several is used.

LQTS can be either congenital or acquired due to medical conditions or drug exposure. Specific to drug-exposure, genetic polymorphisms may play a role in substance-induced LQTS 56. Buprenorphine is less potent in blocking the hERG channel than methadone 51, but nonetheless has been associated with QTc prolongation in electrocardiographic studies 57. To date two published direct comparisons of buprenorphine and methadone on QT interval prolongation exist. None of the 43 buprenorphine-maintained patients had prolonged QTc, while of 407 methadone-maintained patients, 28% of the men and 32% of the women showed QTc prolongation ($p=0.002$) [57]. Similarly, the second study showed that no buprenorphine-treated patients vs. 23% of methadone-maintained patients had a QTc greater than 470ms (men) or 490ms (women); ($p<0.001$). When compared with pre-drug baseline values, fewer buprenorphine (2%) than methadone (12%) participants had increases in QTc of more than 60ms ($p<0.001$) 58. Prolonged QT intervals were also not found in a study of opioid-dependent subjects receiving Suboxone ® 59.

INDUCTION OF BUPRENORPHINE IN PREGNANT PATIENTS

Buprenorphine treatment during pregnancy seems not to be associated with greater risk to the mother or embryo/fetus than treatment with methadone [60,61,62]. However, management of patients with buprenorphine can be more difficult, given the different pharmacology of the two medications. Unlike methadone, buprenorphine has the added complexity of possibly precipitating withdrawal. Methadone and buprenorphine cannot be used interchangeably and patients that are maintained on methadone are usually not good candidates for buprenorphine [63].

For safety reasons the use of the combination product (buprenorhpine/naloxone) can not be recommended to pregnant patients. Pre-clinical data suggest that fetal naloxone exposure leads to maternal and subsequently fetal hormonal changes, [64,65] and that when buprenorphine/naloxone is crushed and injected resulting maternal and fetal withdrawal symptoms are unfavourable to neonatal outcome. For patients stabilized on Suboxone®, guidelines recommend transfer to Subutex® following confirmation of pregnancy.[66] Only the combination product buprenorphine/naloxone (Suboxone®) has been available in the US for office-based prescription; the only exception to this has been for treatment of opioids-dependent pregnant women, to whom the mono-product buprenorphine (Subutex®) is administered [67].

Due to the more complex pharmacology (mu partial agonist/kappa antagonist) of buprenorphine, induction may be more challenging than with methadone, especially if the patient is concomitantly consuming illicit drugs at the time of first assessment. A substantial risk of precipitating significant withdrawal exists if the first dose of buprenorphine is too high or if it is administered too soon after the last opioid intake (prior to manifestation of clinical symptoms of opioids withdrawal, which may be many hours if long acting opioids were used). As with methadone, it is important to ensure that the buprenorphine dose is not too low; an inadequate dose will not alleviate or prevent withdrawal symptoms before the next dose is due [63,68].

Transition from slow-release oral morphine (SROM) or methadone to buprenorphine in opioid-dependent pregnant patients has resulted in a “transient dysphoric mood status” which lasted two days [69]. Waiting at least six hours following short-acting opioid cessation to administer buprenorphine (usually some objective signs of opioid withdrawal can be found) has been found to improve the tolerability of induction onto buprenorphine 70.

Finding the right timing for the initial buprenorphine dose is more difficult for patients taking long-acting opioids (e.g., SROM, methadone). Although only a few reports have been published, it is possible (but not recommended) to transition pregnant women from methadone directly to buprenorphine [63]. When women in the second or third trimester were transferred from oral methadone (up to 85 mg) doses to sublingual buprenorphine (up to 12 mg) the most frequent adverse effects reported were dysphoric mood 71,72 and “clear headed” status 73.

Experience with pregnant women has demonstrated that rapid induction onto 12–14 mg of buprenorphine in 2–3 days can be accomplished in pregnant women [60,61]. Administering rapid-release morphine for a period of three days prior to buprenorphine induction seems to be beneficial for patients previously maintained on methadone. An optimal dose should be administered based on the severity of withdrawal symptoms. The fact that buprenorphine is less likely to cause sedation makes it safer for clinical use.

Complementary medications such as certain antihistamines (i.e. hydroxyzin, diphenhydramine) can be administered to ease most symptoms of withdrawal regardless of whether patients are inducted onto methadone or buprenorphine,

BUPRENORPHINE AND PREGNANCY

As the majority of women treated for opioid addiction in maintenance programs are of childbearing age, the use of opioids during pregnancy is continuing to be a clinical challenge. Both methadone and buprenorphine are approved to treat opioid addiction in non-pregnant patients but sufficient data regarding the use of both buprenorphine and methadone during pregnancy are currently lacking. Because of the absence of sufficient randomized clinical trial data in pregnant women to document safety and efficacy, both methadone and buprenorphine are classified as FDA pregnancy category C medications (e.g., well-controlled pregnancy studies are not available; medication should be used during pregnancy only if the potential benefit justifies the potential fetal risk) 74. The benefits of methadone maintenance during pregnancy compared to detoxification have been well established 75. Detoxification is usually associated with relapse and marked fluctuations of serum methadone levels, both of which are unfavourable to fetal outcome. Methadone maintenance treatment (MMT) has been shown to reduce complications of pregnancy, childbirth and infant development in the treatment of pregnant opiate-dependent women, and detoxification is generally not indicated 76. The clinical effectiveness of MMT for opioid dependent non-pregnant adults is conclusive; reductions in HIV risk behaviors, mortality, levels of crime rates as well as positive outcomes on drug use have been demonstrated 77،78. In spite of compelling evidence supporting the use of methadone in pregnancy, methadone treatment during pregnancy is not without side effects. Methadone administration appears to alter fetal activity and heart rate,79، [80]and neonatal abstinence syndrome following methadone exposure is more common than with heroin exposure [81].

With the increased use of buprenorphine maintenance in women, data supporting its efficacy have now been published. In addition to short retrospective reports, most of the evidence-based studies involve direct comparisons of buprenorphine and methadone, as well as other retrospective reports. The first open-label study with buprenorphine during pregnancy was carried out by Fischer et al. in 2000; fifteen opioid dependent inpatient pregnant women underwent induction with 1–10mg of sublingual buprenorphine followed by outpatient management. Efficacy in terms of maternal and fetal safety, as well as positive results on all birth outcome measures were demonstrated. Neonatal abstinence was not observed in eight of the infants, was mild with no treatment in four infants, and moderate requiring treatment in the remaining three infants. These promising results should be considered in light of study imitations, such as open design, lack of controls, and small patient sample[71]. In a prospective study design, research supporting the safety of buprenorphine during pregnancy was published by Schindler et al, detailing two pregnancies from conception through the postpartum period. Neither of the buprenophine–exposed infants experienced pregnancy-related complications, birth outcomes were considered normal, and neither infant developed NAS[82].

A comparative, multicenter clinical study of high-dose buprenorphine vs. methadone maintenance (259 pregnant women, 101 (39%) methadone and 158 (61%) high dose buprenorphine) by LeJeune et al. found no major difference between the groups in perinatal prognosis. The only differences found were: (1) a higher rate of prematurity in the methadone group which could also be explained by other confounding factors and (2) a mean age at onset of neonatal withdrawal syndrome for the methadone group of 81 hours versus 66 hours (P = 0.066) for the buprenorphine group. [62]

Ebner et al prospectively compared three groups of neonates following intrauterine exposure to either methadone, buprenorphine or slow-release morphine with no concomitant use: thirty-two of fifty-three neonates required treatment for NAS (fifteen of twenty-two in the methadone-maintained group, fourteen of seventeen in the morphine-maintained group, and three of fourteen in the buprenorphine-maintained group). The mean duration from birth to requirement

of NAS treatment was 33 hours for the morphine-exposed group, 34 hours for the buprenorphine-exposed group and 58 hours for the methadone-exposed group. Buprenorphine had a significant lower incidence of NAS appearance compared to the other groups [83].

Buprenorphine has been successfully used in this population over the last decade, and though reports in more than 500 neonates exposed prenatally (0.4 to 24 mg sublingually) have been published showing no increased risk of teratogenic effects and a low rate of prematurity [74], randomized controlled trials (RCT) of buprenorphine in pregnant women with a large enough sample size have not been conducted yet. A summary of 31 published reports of buprenorphine exposure during pregnancy is shown in table 1[74]

These data are limited in their significance, however, by a number of confounding factors. (1) Although 86% of reports noted other maternal drug use, the use of concomitant medication or abuse of other substances was rarely reported in detail, making it difficult to assess the impact of buprenorphine on the neonatal abstinence syndrome. (2) The type of treatment setting and length of fetal drug exposure were not homogeneous, and most reports were retrospective, open-label and had no appropriate control groups. (3) Most important, the lack of details regarding neonatal treatment and the small sample size limit the applicability of any conclusions. Moreover, different scoring systems [e.g., Finnegan 84, Lipsitz 85], were used to assess NAS treatment efficacy87.

With the ultimate goal of establishing international, state of the art, standardized treatment recommendations for pregnant opioid-dependent women, research trials have focused on neonatal outcomes for methadone / buprenorphine-exposed neonates. The two sole previous small sample size RCTs comparing methadone and buprenorphine in a double-blind double-dummy design 60,61 show a shorter intensity and duration of NAS for buprenorphine. As a result of these two RCTs a new multisite study has been designed: The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project, an eight-site randomized, double-blind, double-dummy, flexible dosing and parallel group clinical trial which is currently in progress [74]. Five primary outcome measures were chosen for examination based on the results of the pilot studies; (1) neonatal Abstinence Signs (NAS); (2) number of neonates requiring treatment; (3) amount of medication needed to treat NAS; (4) head circumference; and, (5) length of hospital stay. Based on the pilot studies, the MOTHER study hypothesizes that buprenorphine will produce a superior outcome for all five variables. As the influence of pregnancy on the pharmacokinetics and pharmacodynamics of buprenorphine and methadone is not yet fully understood, detailed research questions such as effects of co-morbid substance abuse, concomitant medications and nicotine on NAS, breastfeeding etc. will be addressed in the MOTHER study.

NEONATAL ABSTINENCE SYNDROME

Intrauterine exposure to opioids or other psychopharmacological medications can produce NAS in the neonate in the first hours and days after delivery. Signs of NAS are usually referable to the central nervous system, autonomic nervous system, gastrointestinal tract, and respiratory system. Intrauterine exposure to buprenorphine during pregnancy also results in NAS in more than 50% of exposed newborns [62]. The onset, nature, and treatment of buprenorphine-associated NAS are comparable but somewhat milder than that associated with methadone[62, 86].

The severity and duration of NAS should be assessed by close clinical observation and monitoring of the newborn using an “abstinence scoring system.” This system assigns points to each abstinence-associated sign and serves as a guide to treatment. Once a predetermined minimum score is reached, treatment, usually with replacement opiate therapy, is begun. Weaning can begin once the neonate is assessed to be clinically stable on a set dosage for at

least 48 hours[60]. Seminal work with regards to perinatal addiction has been published over decades by Finnegan and colleagues with an in-depth focus on the neonatal consequences of intrauterine substance exposure, resulting in the widespread adoption of the „Finnegan-scoring-system“ for neonates[87].

The concomitant use of legal and illegal substances such as opiates, nicotine, cocaine, alcohol and other specific medications such as antidepressants play a key role among the factors influencing NAS appearance, severity and duration.

The onset of buprenorphine-associated NAS is usually observed within the first 12 to 72 hours after delivery, reaching its peak severity within 66 to 96 hours, and lasting approximately 120 to 168 hours. Considerable individual variability in abstinence exists; a reported protracted withdrawal syndrome has been seen in a few infants who exhibited withdrawal signs for 6 to 10 weeks following delivery. This extended withdrawal could be due to both the NAS medication and the regimen used to treat withdrawal rather than a direct effect of buprenorphine [74].

The debate as to whether a correlation exists between the maternal maintenance dosage of opioids and the occurrence and severity of NAS began in the late 1960s, when methadone was first accepted as a method of treatment for opioids-dependent pregnant women. Based on existing data, Ostrea et al. made the recommendation in 1976, that at least one month before delivery mothers should be placed on a low-dose regiment of less than 20mg methadone per day to help prevent serious neonatal withdrawal 88. The controversy continued, and in 2002, Dashe et al. reported that 90% of infants whose mothers had taken more than 40mg/d methadone required treatment for NAS, compared to 44% of infants when mothers had taken 20–39mg/d methadone, and 12% of infants when mothers took less than 20mg/day.[89] However, this finding lacked a clear research design, was retrospective and no standardized urine toxicology was performed to examine the concomitant consumption of illicit drugs. In contrast, Berghella et al. published a report on 100 methadone maintained pregnant women and their neonates, which found no correlation between methadone dosage (doses of more than 80mg/day and less than 80mg/d) and both the need for and duration of NAS treatment[90]. As in many previous studies, however, results should not be considered conclusive since concomitant use of legal and illegal substances was not taken into account.

In a very recent retrospective study of 66 methadone-maintained patients, Lim studied the relationship between maternal dosage at delivery and neonatal abstinence. Dosage groups included (1) < 70 mg in 23 women, (2) 71–139 mg in 26 women, and (3) >140 mg in 17 women. A higher dosage of methadone was associated with a higher incidence and duration of NAS; every increase of 5.5 mg of methadone in the mother was coupled statistically with 1 additional day of NAS treatment for the infant. Studies suggest that the main variable affected by higher dosage may not be appearance of NAS itself, but rather its duration, and that both the occurrence and duration of NAS may be mitigated by a reduction of methadone dosages in motivated mothers.[91] However, conclusions drawn from this study are also limited because it is retrospective and no standardized urine toxicology was collected for assessing concomitant substances consumed.

The debate over maternal methadone treatment may be considered in one major context: which has the greater impact on NAS, high dosages of maternal maintenance opioids or the often-seen concomitant illicit use of other substances when women are treated with an inadequate dose of methadone to achieve clinical stability? In one study, McCarthy et al[92] reported that pregnant patients receiving mean daily methadone doses of 132 mg had less illicit drug use at delivery and their neonates had no more severe NAS than expectant mothers receiving mean doses of 62 mg of methadone. Higher incidences of illicit drug abuse occurred in women who

were receiving less than 80mg/day than in women receiving more than 80mg/day. It is generally felt that concomitant use of illicit drugs increases the severity of NAS, one factor cited in promoting the use of higher maintenance dosages for pregnant women.

Fewer reports exist on the correlation between maternal buprenophine dosages and the incidence, severity, and duration of NAS in exposed neonates. In a recent population-based comparison of 47 consecutive, prospectively followed buprenorphine-exposed pregnancies to 35 retrospectively analyzed consecutive methadone-exposed pregnancies, Kakko et al. reported significant advantages with buprenorphine treatment in terms of birth weight and incidence of NAS requiring pharmacological treatment compared to methadone. The average maternal dosage was 15.4mg +/− 6.4mg buprenorphine and 71.3 +/− 27.3mg methadone and 14.9% of the buprenorphine-exposed group vs. 52.8% of the methadone maintained group developed NAS requiring pharmacological treatment. Kakko argues that the key to lowering NAS rates is the successful clinical management of substance use, which usually involves higher maintenance dosage. [93] Further supporting this viewpoint, a Finnish study (Kahila et al, 2007) of 67 women maintained on buprenorphine where tapering doses or even abstinence from buprenorpine was encouraged (mean dose of buprenorphine at time of birth 4.3 mg), resulted in a NAS incidence of 76%, with 57% requiring treatment. [94] This low maintenance dosage was linked to a low retention rate and higher rates of illicit use, both of which are unfavourable to NAS occurrence. To date, only one report has found a positive correlation between maternal buprenorphine dose and the severity of the NAS 95; this finding pertained only to the maximum Lipsitz score. Other more recent reports 60›61 and one that included a large sample size [62] have reported no such correlation.

In summary, all of these results strongly suggest that pregnant women should be treated with dosages of methadone or buprenorphine that adequately treat their addiction. Concerns regarding the impact of higher therapeutic dosages on NAS do not seem to be warranted, based on available clinical data. The variability of NAS, however, mandates that close clinical surveillance of the neonate and infant should be maintained. It is hoped that the MOTHER study comparing methadone and buprenorphine in pregnant women, will shed further light on this subject.

BUPRENORPHINE AND BREAST FEEDING

An issue naturally related to opioid treatment during pregnancy is that of breast feeding. The plasma to milk ratio for buprenorphine is approximately 1 as it is excreted in breast milk and levels are similar or higher than levels found in the blood [96]. Given this information the total daily amount of buprenorphine consumed by the infant can be estimated. Due to the low oral bioavailability of buprenorphine, the actual infant exposure is only 1/5 to 1/10 of the total amount of buprenorphine ingested. The low oral bioavailability of buprenorphine also explains why levels in breast milk may have little effects on NAS [97]. For methadone, recent reports have confirmed earlier findings that breastfeeding could serve as a means of diminishing duration of methadone associated NAS, [98,99] both from comfort obtained through mother/child bonding, [91] and from the oral bioavailability of methadone. If methadone-maintained women wish to breastfeed and no specific contraindication, such as certain infectious diseases and illicit drug use, exist, physicians should support their decision [100]. For buprenorphine, although similar recommendations might be valid, these guidelines are based on shorter periods of observation and smaller numbers of investigated cases. [61,71]

CONCLUSION

Since data governing the use of buprenorphine are limited, significant gender-related differences in the epidemiology of opioid dependence and maintenance treatment, the

pharmacodynamics and pharmacokinetics of buprenorphine and its effects on cardiac physiology require future investigation. Promising evidence has suggested that neonatal abstinence following intrauterine exposure to buprenorphine may be less severe than that associated with methadone, and that breastfeeding may be safely accomplished with buprenorphine maintenance, but more evidence is required to support these findings. Data obtained from the international MOTHER study will soon be available to shed light on whether methadone or buprenorphine should be the preferred treatment of choice for pregnant opioid-dependent women.

Buprenorphine is gaining recognition as an effective treatment for opioid dependence. The drug is well tolerated, and due to its partial agonist properties, appears to be a safe therapeutic option, especially since the severe side effects, such as respiratory depression seen with other opioids, develop only with severe overdosing with buprenorphine [101]. Individuals who have been well stabilized on buprenorphine face the risk of clinical destabilization if that medication is changed during pregnancy. The same concern applies to the fetus, which is totally dependent on maternal medications for intrauterine homeostasis.

The fact that relatively few gender studies exist in the field of drug dependence may be partially explained by the fact that men have had a higher rate of substance abuse than women, although the gap has been closing in recent years. [102] In addition, women are more expensive and difficult to study due to the added complexity of hormonal interactions in the reproductive years, the special requirements of postmenopausal medication response, and the unique condition of pregnancy.

The understanding of gender issues is important in the treatment of opioid dependence for several reasons. Optimizing treatment outcomes in terms of retention and completion requires consideration of barriers to treatment access and entry such as lack of child care, lack of services for pregnant women, fear of losing custody when the baby is born, fear of prosecution, voyeurism and sexual harassment that are specific to women. [103] In addition, treatment settings that are designed for a predominantly male population may not adequately deal with gender-specific social factors such as intimate partner violence (IPV) by a co-dependent partner, unplanned pregnancy and higher rates of sex-related risk behaviour with a consequence of infectious disease. [104–106] Significant psychiatric co-morbidity, such as affective disorders, eating disorders and post traumatic stress disorders following sexual trauma, adds to the complex challenge of attaining treatment success in women with substance abuse problems. [103,107–109]

Critical assessment of the current regimens of pharmacological treatment of opioids dependence is needed since gender and age considerations have often been neglected in treatment decision-making. Public-funded studies as well as pharmaceutical supported drug trials are urgently needed to provide a better understanding of the gender related differences in response to psychopharmacological medication. Women constitute a unique study group, especially under circumstances of pregnancy and child care. Optimizing treatment effectiveness for opioid-dependent women across the life cycle of teenage, child bearing age, midlife and old age should be a goal for the international community of opioid maintenance treatment researchers, improving services and enhancing the quality of life for women suffering from substance abuse.

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Table 1

Summary of Studies of Buprenorphine Exposure during Pregnancy (Multiple publications of the same neonates combined as one report) (Jones et al.)

Author, Year	Type of Study	Number of buprenorphine-exposed neonates reported	Number treated for NAS	Other Drug Use (e.g., self-reported or verified by urine toxicology)
Fischer et al, 2000	Prospective	15	3	Yes
Johnson et al, 2001	Prospective	3	0	No
Rohrmeister et al., 2001	Prospective	16	3	Not reported
Gourarier et al, 2001	Prospective	159	83	Yes
Lejeune et al, 2001				
Lejeune et al, 2002				
Lejeune et al, 2005				
Schindler et al, 2003	Prospective	2	0	No
Lacroix et al, 2004	Prospective	31	8	Yes
Jones et al, 2005	Prospective	10	2	Yes
Gordon et al., 2005	Prospective	32	18	Yes
Fischer et al., 2006	Prospective	8	5	Yes
Reisinger 1995	Case Reports	4	0	No
Mazurier et al, 1996	Case Reports	6	6	Yes
Marquet et al, 1997	Case Reports	6	2	Yes
Marquet et al, 1998				
Dos Santos et al, 1998	Case Reports	12	11	Yes
Regini et al, 1998	Case Reports	1	1	Yes
Herve & Quernum 1998	Case Reports	1	1	Yes
Jernite et al, 1998	Case Reports	24	16	Yes
Jernite et al, 1999				
Burlet et al, 1999	Case Reports	14	8	Yes
Auriacombe et al, 1999	Case Reports	16	5	Yes
Loustauneau et al,2000				
Auriacombe et al, 2001				
Marquet et al, 2002	Case Reports	21^	10	Yes
Kayemba-Kay's 2003	Case Reports	13	10	Yes
Siedentopf, 2004	Case Reports	33	20	Yes

Author, Year	Type of Study	Number of buprenorphine-exposed neonates reported	Number treated for NAS	Other Drug Use (e.g., self-reported or verified by urine toxicology)
Noblet 2000	Case Reports	27	?	Not reported
Ross, 2004	Case Reports	1	?	Not reported
TOTAL		**455**	**212 of 427 (50%)**	