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Pharmacotherapy in the Treatment of Addiction: Methadone

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Abstract

Methadone maintenance treatment is the most widely available pharmacotherapy for opioid addiction and has been shown over a period of 40 years to be an effective and safe treatment. While women comprise approximately 40% of clients currently being treated in MMT programs, comparatively little research geared specifically toward this group has been published. This article begins with an overview of neurobiological studies on opioid addiction, including a discussion of gender differences, followed by a review of the pharmacology of methadone The authors then examine the particular needs and differences of women being treated in MMTs, including co-dependence with other substances, women's health issues and psychosocial needs unique to this population. In conclusion, research shows that women have different substance abuse treatment needs in comparison to their male counterparts. One New York City MMT program that has attempted to address these differences is highlighted.

Keywords

women; methadone maintenance; pharmacotherapy; gender differences; addiction; opiate addiction

INTRODUCTION

During the initial development of the first effective pharmacotherapy for an addictive disease, a treatment which remains the most effective and most widely used in the United States and worldwide, methadone maintenance treatment (MMT) for heroin addiction, the initial decision was to study only very severely impaired persons, and only male opiate addicts, because of the special potential complexities of females in reproductive years. Therefore, in the first research done at the Rockefeller Hospital in the then Rockefeller Institute for Medical Research in 1964 (the original work published with the transcription of the discussion at the Association of American Physicians meeting1, and also in the Archives of Internal Medicine2), no women were studied. Similarly in the one-year follow-up of our patients admitted to the Rockefeller Hospital in 1964, along with several new patients admitted and followed for two weeks to three months at Manhattan General Hospital, no women were included3. We set the criteria for admission of subjects for study, criteria that were reviewed by the hospital ethics board at that time: all male subjects; all with a history of short-acting opiate abuse with multiple daily self-administrations for four years or longer; and all with failures at least three times in abstinence-based treatment or in prison with prompt relapse. It was not until 1967, after three years of research had taught us the effectiveness and also the safety of MMT, that the first women were admitted into treatment research.

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Over subsequent years, the numbers of women in MMT sharply rose to the current levels of about 40% females and 60% males in most clinics, reflecting the percentages of opiate addicts in the general population and in all ethnic and cultural groups. Overall, neither we nor other groups have found important biological, pharmacokinetic, or pharmacodynamic differences between females and males in MMT studies. Further, in carefully conducted basic clinical research or applied clinical research studies, very few differences have been reported in terms of the clinical outcome, physiological effects, or pharmacological effects between women versus men in either MMT or in buprenorphine-naloxone treatment.

However, of course, women have special needs, most of which are due to very discrete issues that make women different from men. The most obvious and important, and which we began to address in the early 1970s, was the fact that early on we documented that pulsatile luteinizing hormone (LH) is profoundly blunted by cycles of heroin and other short-acting opiate abuse, and that normalization of this neuroendocrine function occurs within one year of steady-dose MMT[4]. Also, it was quickly ascertained that women who had had hypomenorrhea or secondary amenorrhea during cycles of heroin and other short-acting opiate addiction had a very low fecundity rate at that time, despite the fact that many had derived their income primarily from prostitution and had very frequent sexual exposures without protection. However, with stabilization in MMT, normal menstrual cycles returned and, with the increasing normalization of their lifestyles and social status, many women wished to become pregnant. Therefore, extensive studies were conducted to determine both the impact of MMT on females during pregnancy and on neonates, with minimal neonatal abstinence found in some, but far from all, babies born of mothers maintained on even very high doses of methadone in treatment[5, 6, 7, 8, 9, 10]. The later outcome of the children appears to be normal, but these studies are very complex because of the various social and environmental factors involved. In our laboratory we conducted several sets of studies on the metabolism of methadone during pregnancy, in which we showed an acceleration of biotransformation of methadone during the third trimester, due to progesterone effects with prompt restoration to normal metabolism of methadone in the postpartum period[6]. Further, we conducted two studies of the appearance of methadone in breast milk and found, as predicted, due to the very tight plasma protein binding of methadone, that very small amounts of methadone appear in breast milk, too small to have any negative impact, and also too small to treat any signs and symptoms of opiate withdrawal in this population. These studies are briefly reviewed in this chapter (and also reviewed in the chapter on pregnancy and methadone maintenance treatment)[5, 6, 7, 8, 9, 10].

In all of our extensive basic clinical research addressing the molecular neurobiological aspects of opiate addiction, and further in our human molecular genetic studies of opiate addiction, we have found very few differences between males and females. These will be briefly outlined below. However, the additional obvious needs of women are related to their roles in society, including child bearing, child rearing, and home maintenance, along with the special needs of women brought about by the very different views of the roles and value of women in different theaters of our Western society. Several of these special issues will be discussed below, along with brief presentations of the relative proportion of men and women experiencing the various special concerns commonly encountered during MMT.

Molecular Neurobiological Studies: Gender Differences

Over the years, our laboratory has conducted numerous basic clinical research studies in the context of opiate use in which we have probed the function of the brain, as well as integrated neuroendocrine physiology, by conducting a variety of rigorous tests, some of which are standard tests and others of which are provocative tests of various types which we have developed. Many of these tests have been designed to study the stress-responsive hypothalamic-pituitary-adrenal axis (reviewed in 11, 12, 13).

However, in only one of these studies have we found an interesting difference between males and females. This difference occurred in a series of studies in which we used the shortened form of the dynorphin A(1–13) of the natural kappa opioid ligand dynorphin A(1–17), approved for use under an FDA investigator-initiated IND, to probe the tuberoinfundibular dopaminergic system14, 15. In these studies two doses of dynorphin A(1–13) were administered to healthy volunteers and, on a third day, a placebo was administered. In these studies, we used serum prolactin levels as a biological marker for dopaminergic tone in the tuberoinfundibular dopaminergic system, since in humans and non-human primates prolactin release is almost exclusively under tonic inhibition by dopamine. Therefore, when dopaminergic tone is reduced, serum prolactin levels promptly rise. It has been shown that this effect is mediated primarily through the dopamine D2 receptors in the hypothalamus. We found a dose-dependent response to the two doses of dynorphin in healthy human volunteers. However, when we looked at the results in healthy females as opposed to healthy males, even though we had a relatively small number of healthy females, we found significant differences. The females had a greater response to dynorphin administration, as shown through a greater rise, and thus a greater peak, of prolactin levels and area under the plasma concentration time curve. We therefore analyzed those studies in female subjects separately14. In our next set of studies, we looked at dopaminergic tone in long-term successfully maintained MMT subjects, all of whom had a history of short-acting opiate, primarily heroin, dependency15. Again, in these studies, because we had found a significant difference in the two genders in healthy subjects, we began our studies with males in MMT and then added another group of healthy control volunteer males. Again, we found a dose-dependent rise in serum prolactin levels, reflecting a dose-dependent lowering in dopaminergic tone. However, the peak levels in the area under the plasma concentration curve of prolactin were significantly lowered in methadone-maintained former heroin-addicted males than in normal volunteer males15. Currently, we are conducting gender-specific studies in methadone-maintained females as well as cocaine-dependent females. In each case, studies in each gender will be conducted.

Human Molecular Genetics

Since 1994, our laboratory has been studying the human molecular genetics related to each of three different addictive diseases, opiate addiction, and cocaine addiction, without and with codependence with alcohol. To date, we have found association of many specific gene variants with a history of severe heroin dependence, with most studies conducted with long-term methadone-maintained former heroin addicts. In each of these studies, we have analyzed potential differences between males and females and have found none[16]. One of our major focuses has been genetics related to both heroin addiction and alcoholism, considering stress responsivity as a covariable. This work has been extensively reviewed recently[17, 18]. We discovered, in collaboration with Lei Yu, a relatively common variant to the human mu opioid receptor in the coding region, specifically in the N-terminus where opioids and opiates bind[19]. This variant is functionally different from the prototype in molecular and cell biological studies. Later, our group and many others have shown that presence of this variant alters stress responsivity in healthy humans[17, 18, 19]. Further, we have shown that this variant is associated with heroin addiction and also alcoholism in two separate studies conducted in a relatively non-admixed population[20, 21].

In one study, we addressed a question of whether or not baseline levels of the stress-responsive hormones were different in healthy subjects with this variant. We found that male and female healthy control subjects with one or two copies of this A118G variant, which alters mu opioid receptor protein, had higher basal levels of cortisol when studied in a stress-minimized environment, though these levels did not exceed the upper limits of normal[22]. In these studies, we found a small but non-significant difference in females' cortisol levels, compared to healthy males[22]. Specifically, there was a trend, but not a significantly higher level, of basal cortisol

in females with one or two copies of this A118G variant producing a functionally different mu opioid receptor.

The only one of our specific hypothesis-driven studies of the human molecular genetics that has yielded gender differences is in the catechol-*O*-methyl transferase gene (*COMT*)[23]. In this study, we found that a very common and functional variant of the *COMT* gene is significantly associated with heroin addiction, but only in Hispanic subjects[23]. Further, this association was also found in female subjects of Hispanic origin when analyzed separately. Since this is quite an admixed population, further studies are essential to determine whether this finding can be replicated.

Thus, most of the differences in females discussed below are related to their basic reproductive biological differences, as well as differences in their roles in culture and society. However, it is important to continue to address this question, especially related to special needs that might be encountered by women as they enter methadone maintenance or buprenorphine maintenance treatment for short-acting opiate addiction, whether it be heroin addiction or prescription opiate addiction.

Pharmacology of Methadone

Methadone was approved by the US Food and Drug Administration (FDA) in 1972 as a treatment for opioid addiction. Opioids are all compounds which are related in function to opium, which is derived from poppies (as reviewed in 24). Opiates are those compounds with opioid-like activity and which are directly derived from natural poppy plant thebaine structure compounds, such as morphine and codeine. Methadone is a structurally dissimilar or synthetic opioid, which has two enantiomers found in equal amounts in a racemic mixture; the active *l* (R) enantiomer has a half-life of 36–48 hours and the inactive *d*(S) enantiomer has a half-life of approximately 16 hours25, 26, 27. Methadone is also used very effectively in the treatment of chronic pain. Methadone meets the two important criteria for a maintenance treatment: high systemic bioavailability (>90%)28 when given orally and long half-life with long-term treatment 29. Methadone is rapidly absorbed by the oral route with a delayed onset of action, detectable in plasma at 30 minutes with peak levels at 2–4 hours with sustained levels maintained over 24 hours25, 30, 31, 32, 33. Methadone also has N-methyl-D-aspartate (NMDA) receptor antagonist properties, which affect the development of tolerance[34].

During MMT, methadone levels are relatively constant due to slow release of methadone into the blood from hepatic stores[35, 36]. Methadone is greater than 90% plasma protein bound in the bloodstream and is also redistributed into lipid stores, which are among the reasons that MMT is effective as a once per day, oral treatment for heroin addiction[30]. This is in contrast to heroin and morphine, which have a rapid onset of action and are short-acting[37]. Methadone has both low abuse liability and reward effect due to its slow onset and offset.

Due to the long half-life of methadone, an initial maintenance dose should usually start with 20–40mg/daily; then the dose is gradually increased, since a dose increase greater than the rate of development of tolerance can result in accumulation which can lead to sedation and respiratory depression. Doses must be raised slowly, usually by 10 mg every 4–7 days. Patients in effective MMT receiving appropriate doses (80–150 mg per day) and adequate blood levels (250–400 ng/ml) still may have symptoms of withdrawal toward the end of the dosing interval[38]. These symptoms may be due to drug interactions (e.g., phenytoin, rifampin or alcohol consumption of >4 drinks/day), but in this case lower plasma levels are found at the end of a 24h dosing interval 39, 40, 41, 42. Alternatively early abstinence symptoms may be due to undefined pharmacodynamic factors (those determining response to the drug), or other factors such as medical or psychological comorbidity[38], such as depression, which has been found to be more prevalent in women in MMT43. When relatively high doses of methadone

do not result in apparent therapeutic levels, this may be due in part to individual genetic factors, although these have not been well elucidated, or undefined drug interactions usually due to clandestine use of alcohol[32, 44, 45].

Methadone is metabolized in the liver by the cytochrome P450-related enzyme systems (mostly the CYP3A4 and, to a lesser degree, the CYP2D6, CYP2B6, and CYP1A2 systems) to two biologically inactive metabolites, a pyrroline and a pyrrolidine, which are then further metabolized[27, 46]. Methadone and its metabolites are excreted nearly equally in urine and in feces[47, 48, 49, 50, 51]. The amount of methadone excreted in the urine is modestly affected by urine acidity. In patients with renal impairment, methadone can be metabolized almost completely by the gastrointestinal system[47, 48, 49, 50]. This reduces potential toxicity by avoiding accumulation. In peritoneal dialysis, less than 1% of methadone is cleared, probably because it is extensively protein bound, and also due to the small degree that methadone is actually found in the blood at any given time[49]. Patients with severe chronic liver disease have decreased methadone metabolism, thus slower metabolic clearance of methadone, yet lower than expected plasma methadone levels for a given dose due to lower hepatic reservoirs of methadone because of reduced liver size[52]. Methadone metabolism is relatively normal in the presence of mild to moderate liver dysfunction[36, 50].

Drug-drug interactions with methadone have been well-documented41. The major categories of drugs which may interact with methadone include both inducers and inhibitors of the hepatic cytochrome p450-related enzyme system, mostly CYP3A4, as well as inhibitors of CYP2D6 (reviewed in 27). However, few of these medications (e.g., rifampin, phenytoin)[39, 40, 41, 40] have been shown to have an actual significant drug interaction effect at the therapeutic dose of each second medication, and most medications which have been hypothesized to have an interaction, when studied, have no interaction effect: e.g., disulfiram[53].

Pharmacokinetic interactions occur with methadone and specific antiretroviral medications prescribed in the treatment of human immunodeficiency virus (HIV-1). These interactions are usually via the CYP3A4 system and can have effects on the level of either methadone or the antiretroviral medication, which can then have actual clinical effects (reviewed in 54). Alfa-2b interferon given as treatment for hepatitis C, which is common in intravenous drug users (IVDUs), does not appear to have any clinically significant interaction in terms of subjective or objective effects, as noted in three studies[55, 56, 57]; however, in all patients interferon produces flu-like symptoms which may mimic opioid withdrawal.

Methadone levels are affected by the regular high intake of >4 alcoholic drinks/day. When blood measures of ethanol are acutely elevated (>150mg/dl) increased levels of methadone can be anticipated. However, whenever alcohol is no longer present in the body at these high levels, and there are no longer high doses of alcohol, methadone levels may be lower due to induction of the P450 enzymes (reviewed in 58, 59).

Methadone metabolism is significantly accelerated in the third trimester of pregnancy, and methadone doses often need to be increased at that time to prevent withdrawal symptoms and drug-seeking behavior (e.g., 60). During pregnancy methadone may need to be given twice daily (in divided doses) due to differences in elimination, absorption and clearance61. Methadone crosses the placenta and is metabolized mainly by the placental enzyme aromatase/CYP19, which has large inter-individual variability in its activity. Nanovskaya62 and Hieronymous and colleagues63 suggest that this variability may be a factor related to both the presence and severity of neonatal abstinence syndrome (NAS). Studies have shown a clear relationship to time of dosing of methadone and breast milk levels of methadone, although the levels in breast milk are very low at all times because of the extensive plasma protein binding of methadone[4, 5, 6, 7, 8, 9, 10]. Breast feeding is safe for women in MMT and their babies and

supported by the American Academy of Pediatrics[64]. It is recommended that women who are HIV-1 positive should not breastfeed due to concerns about mother-to-child transmission[65].

No cardiac or significant electrocardiographic abnormalities related to methadone treatments were noted in the early or more recent prospective or cross-sectional studies of medical safety for almost 40 years. In the last six to eight years, and predicted from *in vitro* calcium channel focused studies of opiate effects, issues have been raised regarding possible cardiac effects of methadone. Higher doses of methadone (>200 to around 400 mg/day) in MMT and chronic pain patients have been reported to be potentially associated with prolongation (>500msec) of the QTc interval on electrocardiogram (EKG) and possibly with Torsades de pointes, a potentially life-threatening arrhythmia[66]. Many of these patients had other risk factors67 including taking other medications such as anti-retrovirals68 or antidepressants69, 70, which are known to prolong QTc, or abusing other drugs. The effect may or may not be related to dose or methadone serum concentration[69], and may become clinically significant (generally if >500 ms)[70]. It may be prudent for all patients requiring a chronic methadone dose >150 mg to have a baseline EKG and then to be monitored periodically afterward; also high risk patients with prior QTc prolongation should be monitored71.

Before initiating methadone treatment, it is important to make sure that the patient is in fact opioid dependent, which can be established by history, clinical exam and urine toxicology. Opioids have a number of potential side effects; however when appropriate doses of methadone are used below the level of tolerance developed to each effect, the effects are minimal. If the dose is increased too rapidly, sedation, the major side effect observed in an opioid-tolerant patient, may occur. In an opiate-naïve patient, initial side effects of methadone may include drowsiness, nausea and constipation, while emesis, itching and dizziness are less common[72]. However, in a properly managed long-term MMT patient, the two most significant side effects are constipation, to which tolerance usually occurs over the course of three years, and sweating, which persists in about 50% of patients[73]. Constipation and the other side effects tend to lessen due to the development of tolerance, defined as a loss of an effect over time after repeated use. Tolerance develops at different rates for the side effects of methadone, occurring over days, weeks or years[73]. Dosing must be titrated to the tolerance of the individual patient to avoid somnolence, an early sign of CNS depression. As with all opioids, methadone must be used prudently in patients with compromised respiratory function.

Accidental Methadone Overdose and its Medical Management

Methadone should always be provided in childproof containers. However, in an opioid-naïve child, or when methadone is taken illicitly by an adult who is opioid-naïve or with low tolerance, methadone overdose may occur, characterized by stupor or coma, or respiratory depression, which can lead to death. Decreased response to carbon dioxide in centers of specific areas of the pons and medulla of the brain may lead to CO_2 retention[74]. Depression of the mental status is accompanied by suppressed gag reflex, predisposing the patient to aspiration of gastric contents into the lungs. Constriction of the pupil occurs, which is the result of parasympathetic nerve excitation[75].

A methadone overdose can be effectively treated with an opioid antagonist; however the pharmacokinetic profile of each drug is critical. Naloxone has a half-life of 30 minutes; thus more than one dose will be needed. When overdose occurs due to use of methadone in an opioid-naïve or mildly tolerant person, repeated intravenous doses or a constant infusion of naloxone may be needed for more than 24 hours[75] to prevent relapse into coma[58].

Retention in Methadone Treatment – Women's Issues

A substantial body of research exists, documenting that methadone, when given as maintenance, is the most effective treatment for heroin/opiate addiction. When given in adequate daily doses, methadone will: decrease heroin use[76, 77, 78, 79]; decrease criminal behavior[80, 81, 82]; decrease spread of HIV/sexually transmitted diseases (STDs) and other blood-borne diseases, i.e., hepatitis C[83, 84, 85, 86] decrease mortality[82, 87, 88]; possibly decrease secondary drug use[89, 90, 91]; increase retention in treatment[92, 93]; increase stable family relationships; and increase employment and participation in job training[94].

These benefits can only occur if patients are retained in treatment. Dr. Vincent Dole of The Rockefeller Institute reported that 80–90% of patients discharged or lost to treatment returned to illicit substance abuse and all its inherent risks. The early literature demonstrated that when patients are given adequate doses of methadone, then between 80–120mg, they are more likely to be retained in treatment, and to reduce their illicit opiate use, particularly in the first six months of treatment[92, 95, 96, 97, 98]. Adequate dosing, tailored to the patient's individual need, is the dose that when administered will block superimposed short-acting narcotic euphoria, prevent withdrawal symptoms, and reduce or eliminate drug craving for twenty-four hours or more[99].

In the mid- to late 1960s, during the first six years of MMT clinical trials, the Rockefeller team and their collaborators titrated over 2205 patients to daily doses of methadone equaling 80–120mg100. At that dose level overall retention in treatment was 82%, arrest rates dropped from 20%/year prior to treatment to less than 3%/year after treatment, and employment rates reached 70%, as reported by Gearing and associates101. Nearly twenty years later, in 1983, Hargreaves102 reviewed twenty-two methadone studies and concluded that a 100mg dosage was associated with a more positive outcome than a 50mg dosage in the first five to ten months of MMT. Other studies have shown an inverse relationship between the frequency of heroin use and the dose of methadone. In the 1990s, Strain, Stitzer, Liebson and Bigelow103 followed 247 intravenous opioid-dependent patients for 20 weeks. Patients were assigned to 0mg, 20mg or 50mg methadone groups. The 50mg group had greater retention in MMT (52%, 42% and 21%) as well as less opioid-positive urines (56%, 68%, and 74%). In 2002, Maxwell and Shinderman[104] reported the clinical courses of 245 MMT patients over 152 weeks. Patients on methadone doses greater than 100 mg per day had better retention rates (61.1% vs. 46.3%) and lower rates of opiate-positive urine toxicologies (16% vs. 36.6%) than patients treated with less than 100 mg per day. Peles and colleagues92, in an MMT program in Israel, prospectively studied 492 patients and found that factors predicting retention in treatment were methadone doses of 100mg or greater, negative urine toxicology for opiates, and being a parent.

Other confirmatory studies were conducted in Denver, Colorado, and Ireland. In the former study, Booth and colleagues concluded that higher methadone doses, as well as free treatment, increased retention rates in programs[105]. In the latter study, Kamal and colleagues found that patients enrolled in MMT with higher methadone doses were more likely to be opiate abstinent[106].

Despite this compelling research, by the 1980s more than 40% of MMTP patients were receiving daily methadone doses of less than 40 mg. Even as late as 2005[107], Brady and colleagues found that more than two thirds of methadone patients nationwide were receiving below 60mg/day.

Drug and Alcohol Codependency in Female Methadone-maintained Patients

Cocaine

Beginning in the 1980s and 90s a high prevalence of cocaine abuse among patients entering methadone treatment was reported in the literature[108, 109]. Kosten's study reported a 74% rate of recent cocaine use among a cohort of New York City MMT admissions from 1978 to 1980, and the Drug Abuse Treatment Outcome Studies (DATOS), which tracked MMT admissions during 1990–1995, reported a 42% prevalence. The latter statistic appears steady over the past decade, as 2007 statistics obtained for New York City MMT programs show that 44% of patients self-reported cocaine as the secondary drug of abuse on admission. Interestingly, females in NYC reported a higher frequency (49.4%) than males (41.6%) (New York State Office of Alcoholism and Substance Abuse Services Client Data System)[110]. A higher rate of cocaine-positive urine samples was also observed among females (20%) as compared to males (11.3%) in Israel during the first month of admission to methadone maintenance111, notable in a country where cocaine abuse was not prevalent until a period of time after the clinic opened in 1993. The role of the mu-opioidergic system in cocaine craving and relapse was first elucidated by studies in rodent models demonstrating upregulation of mu-opioid receptors in rats following chronic intermittent "binge" cocaine administration and persisting throughout early withdrawal[112, 113]. These findings were corroborated by PET studies in humans showing an increase in mu-opioid binding immediately following chronic cocaine use, and persisting for up to four weeks during abstinence[114, 115]. Treatment outcome studies have shown that a majority of patients demonstrate significant reductions in cocaine use during long-term MMT[81, 109, 116], and at least two studies have found an association between higher methadone levels and cessation of cocaine use[91, 116, 117].

Despite this success, a percentage of long-term methadone-maintained patients, reported from 15% to 25%, continued chronic cocaine abuse[108, 116, 118]. Treatment strategies employed to reduce cocaine use in these patients vary by program with a majority of MMT programs surveyed by Kolar and colleagues instituting more frequent counseling and urine toxicology submission in response to positive cocaine tests[118]. However, as overall heroin abuse is mitigated and cocaine abuse reduced by MMT, it seems inappropriate to discharge patients due solely to continued cocaine use.

Alcohol

Alcohol abuse at treatment entry and during long-term methadone maintenance is more difficult to assess since data is frequently derived from patient self-report as opposed to breathalyzer or urine testing[119]. Drug Abuse Treatment Outcome Studies (DATOS) showed that 20–50% of all methadone maintenance patients in the United States display alcohol-related problems[109]. Overall, women in methadone maintenance have been shown to abuse alcohol to a lesser extent than men. A recent Swedish study found that 39% of females as compared to 54% of males admitted to MMT had been treated for an alcohol-related diagnosis and/or had positive laboratory tests indicating recent moderate to high alcohol usage119. New York City statistics for 2007 corroborate this; 5.5% of females as compared to 7.7% of men self-reported alcohol as the secondary substance of abuse on admission110.

Early prospective studies performed on 129 long-term methadone-maintained men and women demonstrated that even with 25% of the cohort reporting consumption of four or more alcoholic drinks per day, there were no significant changes in liver enzymes or serum protein values after three years on methadone[30]. Therefore, methadone maintenance does not potentiate alcohol-induced hepatotoxicity. The Swedish study found a significant association between drinking alcohol and relapse to illicit drugs, particularly benzodiazepines and cannabis among females,

but no such association was found in males[119]. Thus, clinicians should make an effort to screen for alcohol abuse in MMT females on admission and plan treatment accordingly.

In contrast to the observation that methadone can reduce illicit drug use, MMT does not appear to affect rates of alcohol use from admission to one year follow-up[120]. Therefore, providers may want to consider treatment of MMT patients for whom heavy alcohol use is a problem. Most studies show limited efficacy of disulfiram, an acetaldehyde dehydrogenase inhibitor which when combined with alcohol induces adverse effects, attributed to poor compliance with self-administration[121]. However, as MMT provides a favorable setting for the supervised dispensing of disulfiram, it may be a helpful adjunct for reducing alcohol intake in certain motivated MMT patients. Disulfiram is metabolized by the liver and prescribing it to patients with abnormal liver tests is not recommended. It is advised that liver enzymes be obtained prior to initiating treatment, and every two weeks thereafter for the first 2–3 mos[121].

Acamprosate, an antiglutaminergic approved by the FDA in 2005, is primarily excreted by the kidneys and therefore may be a better option for patients with compromised liver function[122]. While shown to effect complete abstinence from alcohol in only about a third of patients; female gender was not found to be associated with treatment outcome in a study where potential predictive variables were examined[123].

Benzodiazepines

A study which examined gender-based disparities in benzodiazepine use among those in MMT did not find significant differences between males and females at admission. However, females were less likely than males (18.8% vs. 29.9%) to initiate benzodiazepine use during the first year in MMT than males111. Benzodiazepines share some of the cytochrome P450 metabolic pathway with methadone, and therefore have the potential to cause interactions. While several studies suggested an enhanced subjective effect of methadone when taken concurrently with benzodiazepines, there has been no evidence that benzodiazepines increase serum methadone levels, and the effects are most likely due to increased CNS depression124. Reported interventions for benzodiazepine abuse during MMT include prescribing a single, long-acting benzodiazepine (clonazepam) to replace the patient's total daily illicit dose, which may or may not be administered by the clinic's medical staff125 and/or increasing the daily methadone dose in response to patients' positive toxicology for benzodiazepines124. Higher methadone doses were associated with better outcomes in successful detoxification from benzodiazepines for those patients who declined clonazepam maintenance in one study125.

Cannabis

Information regarding the prevalence of marijuana abuse among MMT patients is less available in the literature as many MMT programs no longer include cannabis in the urine toxicology panel. This may be due in part to the publication of several studies in the 1990s, two of them derived from predominantly male cohorts, which showed no significant association between cannabis use and the use of other illicit drugs[126, 127]. Studies reporting treatment outcomes with methadone maintenance have shown that overall use of cannabis, similar to that of other illicit drugs, declines with long-term methadone treatment[120]. In addition, cannabis use was not found to decrease retention in MMT programs[128].

Medical Issues Specific to Women in MMTP

Women entering into methadone maintenance treatment present with a wide range of medical issues throughout their life spans. A recent study in Israel has shown that females are more likely to enter MMT at a younger age than males, with more than double the percentage of total female admissions occurring in the 18–30 age group as compared to males[129]. Statistics

obtained for admissions in 2007 to New York City MMT programs indicated that 62% of all female admissions were women between 18–34 years as compared to 56% of the total male admissions in this age range.

Because of the relatively young age of entry into treatment, MMT programs have an opportunity to address contraception and pregnancy planning with women during intake and throughout treatment. Few studies have examined sexual activity and contraceptive practices in methadone-maintained females. Those that specifically addressed this topic reported the number of sexually active women in MMT ranged from 61% at a rural MMTP to 84.5% at an urban clinic; however birth control rates were similar in both MMT programs, with at least a third of sexually active women reporting no use of contraception[130, 131]. In one study, Harding and colleagues interviewed a subset of seven women who did not use contraception, and cited a perceived low risk of pregnancy due to a variety of reasons: infrequent sex, a history of infertility, difficulties with male erection due to partner drug use and falsely assuming breastfeeding afforded protection against pregnancy. Altered menstrual cycles during drug use, and in early methadone maintenance were also mentioned by several women as a significant reason why they were not using contraception[131].

Effects of illicit opiates on the menstrual cycle are well-documented, with early studies reporting that 30–54% of heroin-using women to have secondary amenorrhea[59, 132]. In comparison, the prevalence of amenorrhea in a population of healthy, adult women has been estimated to be 2–4%[133, 134]. Few researchers have examined the effects of methadone maintenance on menstrual regulation. Early data from our laboratory demonstrated that in a cohort of methadone-maintained females, 54% had reported amenorrhea on admission, while 83% of the subjects were reporting normal menses after an average methadone stabilization time of 2.7 years[59]. More recently, Schmittner and colleagues found that 59% of women reporting pre-study secondary amenorrhea had resumed menses during a six-month period of methadone maintenance[135]. No studies have found a correlation between methadone dose and menstrual dysfunction[132, 135].

Intravenous drug use (IVDU) forms the route of acquisition of up to half the cases of HIV infection among women in the U.S., while having had sex with a male IVDU accounts for almost 25% of new HIV cases[136]. This risk of HIV acquisition underscores the need to assess sexual history in determining appropriate contraception with female methadone patients. The World Health Organization (WHO) reported that barrier methods differ in rates of pregnancy prevention for women in general, with condoms highest at 86–97%, diaphragms with contraceptive gel (84–94%) and cervical caps (68–91%), with the lower number representing typical use and the higher number corresponding to perfect (correct and consistent) use137. While condoms are the only method to effectively prevent HIV transmission, diaphragms and cervical caps have been found to confer low level protection against chlamydia and gonorrhea. Pregnancy prevention rates with oral hormones range from 92–99%, injectable hormone preparations are 97–99.5%, and intrauterine devices 99.5%, but none of these methods offer protection against STDs. While there are no reports of medication interactions between the hormonal methods and methadone, the use of some medications prescribed for methadone-maintained females, such as anti-retrovirals and certain anticonvulsants, may reduce the effectiveness of hormonal preparations. In addition, certain co-morbid conditions, such as active viral hepatitis, may be a contraindication to prescribing hormonal preparations. Clinicians may access the WHO Medical Eligibility Criteria for Contraceptive Use138 online at www.who.int/reproductive-health/publications/mec for guidance.

The substance abuse treatment population as a whole is aging, and an increasing percentage of women remain in treatment into middle age. As of 2000, 60% of all women in New York City MMT programs were between the ages of 35 and 54[110]. To date, only one researcher has

specifically examined menopausal symptoms in methadone-maintained females. Tuchman reported a similar prevalence of vasomotor symptoms (i.e. hot flashes and night sweats) among methadone-maintained women vs. other study populations, while a much larger percentage in the methadone-maintained group complained of insomnia. In a report by Tuchman and colleagues, ethnic differences were also noted as Hispanic methadone-maintained women had a higher degree of symptom reporting than African American or Caucasian women[139]. Thus, it is important for clinicians to differentiate menopausal symptoms from opiate withdrawal and/or inadequate methadone dose in mid-life women.

Treatment Addressing Specific Needs of Women

A consensus exists in the addiction treatment literature that women have different substance abuse treatment needs than do their male counterparts and that lack of gender-specific services is a barrier to care. A strong positive correlation exists between troubled relationships, family violence, sexual abuse and poor self esteem as integral factors in substance abuse among women[140, 141]. Also, a large percentage (25% to 57%) of women in drug treatment programs reported a history of intimate partner violence (IPV)[142, 143, 144, 145], compared to rates of 1.5% to 16% in community based samples[146, 147].

Women who use substances are more likely to report a history of emotional, sexual or physical abuse than men who use substances; this may impede or prevent the process of recovery. Unlike women with psychiatric problems, men in treatment who have a history of abuse appear to recover at rates similar to men without a history of abuse[148]. The prevalence of diagnosed post-traumatic stress disorder (PTSD) ranges from 20% to 60% among women in substance abuse treatment[149, 150]. Research has found an association between women experiencing IPV and heroin use145. Female methadone patients report more depression and anxiety than males as well as more suicidal thoughts and attempts[140, 141].

In a study which examined the different perceptions of causal factors related to their substance abuse between men and women, women substance users indicated that domestic violence or incest had a greater impact on their substance use than men[140]. Retention rates appear to be similar for males and females. Older female patients are more likely to remain in treatment longer; heroin users are less likely to be retained in a program[92, 93, 129]; having children and less frequent use of benzodiazepines were also associated with long term retention[92, 129].

As a result of research showing that women have different substance abuse treatment needs than males, a women-only MMT program was established in 2000 within the Beth Israel Medical Center (BIMC). This program is named Billie's Place in memory of Billie Holiday. Billie Holiday, an African American female, has been described as the most influential singer of the 20th century and is still considered the most famous of jazz singers. "Lady Day" was also a heroin addict and alcoholic, and died in 1959 at the age of 44 in a New York City hospital of complications of her addictions.

The BIMC-MMT program is the largest methadone maintenance program in the nation. It operates 18 clinics in two boroughs of NYC, with a patient census of 6,500. BIMC, the sponsor of the methadone maintenance program, is a full service acute care teaching hospital in Manhattan. It is accredited by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), as is its network of methadone clinics. The methadone clinics comply with, and are overseen by, government agencies, Substance Abuse and Mental Health Services Administration (SAMHSA), the Drug Enforcement Agency (DEA), the New York State Department of Health, and the New York State Office of Substance Abuse Services (OASAS). All 18 clinics are in good standing with these agencies. All of BIMC's methadone clinics serve both men and women; however Billie's Place is the only gender-specific clinic.

The overall plan for Billie's Place was to establish a positive therapeutic relationship with the female patients, and quickly stabilize each patient's methadone dose, with the aims of decreasing or eliminating heroin use and promoting program retention and improvement in overall health status. At time of inception, and during a period of three years of its existence, Billie's Place provided an intensive day treatment program for predominantly African American and Hispanic/Latina women who were already in MMT, as well as new admissions who were HIV-1- positive or at high risk for HIV and other infectious diseases. Female IVDUs who were HIV-1-positive, or at high risk for HIV, had more complex medical and social problems than their male counterparts. Women's health is often complicated by obstetrical, gynecological, and family issues; women often choose to attend to their children's and partner's health care needs before their own. For women of color in particular, lay therapeutic practices combined with ethnic and/or cultural beliefs and attitudes may complicate their acceptance of mainstream healthcare. Also, for women with limited resources, lack of health insurance, transportation difficulties, and childcare are additional barriers to accessing substance abuse treatment and as well as other health care.

Billie's Place was originally established through a SAMHSA grant 5H79TI12162 awarded in 1999 and opened in 2000, with an initial capacity for fifty women. Formal services provided on site included MMT, co-dependency drug treatment and counseling, counseling and testing for HIV, complete gynecological examinations with initial testing for sexually-transmitted diseases, i.e., chlamydia and gonorrhea, HIV risk reduction counseling, tuberculosis screening and group counseling in the areas of sexual abuse, domestic violence and negotiating safer sex. Workshops in parenting, employment skills, and life skills training were provided. All services were sensitive to cultural backgrounds of patients and were offered in English and Spanish. Referrals were made to primary medical care and primary HIV medical care in clinics located in the community, or to BIMC services. Patients were screened for other STDs (syphilis) and hepatitis B and C, prenatal and postpartum care; family planning services, were also available through referral. Vocational services and educational programs were provided on site and through referrals.

The program focused on informal social activities as well. These included providing a social space where health education materials, as well as light reading, were available. A computer with internet access was available for patients' use. In addition, the women could use this space to socialize, eat light refreshments, and participate in structured weekly events.

The original staffing consisted of one program director, one case manager, two substance abuse counselors, one neighborhood outreach worker, one nurse practitioner, one registered nurse, and one administrative assistant.

Billie's Place successfully provided intensive partial day treatment, individualized case management, an inclusive and non-judgmental support network, and comprehensive, direct links to health care treatment and rehabilitation services. Although the grant from SAMSHA ended, Billie's Place continues to exist, as a separate women-only clinic (with markedly reduced staffing), within the BIMC MMT program. Direct inquiries for additional information regarding Billie's Place to Dr. Randi Seewald, Medical Director, BIMC MMTP, 160 Water Street, 24th floor, New York, NY 10038 rseewald@chpnet.org

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