Heroin Addiction and Related Clinical Problems

the official journal of

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European Opiate Addiction Treatment Association
EUROPAD

EUROPEAN OPIATE ADDICTION TREATMENT ASSOCIATION

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The vision
EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The Association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide.

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Addiction and Pregnancy

Loretta P. Finnegan\(^1\), Leslie Amass\(^2\), Hendree Jones\(^3\) and Karol Kaltenbach\(^4\)

Summary

Addiction during pregnancy contributes to maternal and infant morbidity including pre-term deliveries, low birth weight, neonatal withdrawal, lengthy neonatal intensive care and infant mortality. Combined use of pharmacological and behavioral treatment approaches in managing pregnant opioid-dependent women has been shown to be beneficial for improving treatment retention and reducing maternal drug use. Clinicians should understand the complex biopsychosocial factors that make the treatment of opioid-dependent pregnant women a challenge as well as the principles and the differences in using methadone or buprenorphine combined with behavioral treatment. Researchers should consider continued studies on the use of methadone during pregnancy, relationship of maternal dose and neonatal abstinence, the differences between methadone and buprenorphine, and the impact of pharmacological options on patients and treatment providers.

Key Words: Addiction - Pregnancy - Methadone - Buprenorphine

With the chronic relapsing nature of addiction and the chaotic lives of opioid-abusing women, coupled with the frequent lack of consistent prenatal care, many medical problems may arise during pregnancy. Opioid-abusing women are at increased risk for anemia, bacteremia and septicemia, bacterial endocarditis, cellulitis, dental caries, endocrinopathies, hepatitis, nutritional deficiencies, phlebitis, pneumonia, tetanus, tuberculosis, and urinary tract infections\(^{(24)}\). The pregnant opiate addict may have periods of physical well-being but may also feel the extremes of being “high” or “sick” within a relatively brief period of time. Sexually transmitted diseases, particularly...
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HIV, have become inextricably linked to illicit drug use due to direct sex-for-drugs activity, prostitution to purchase drugs, and the sharing of infected needles and drug paraphernalia.

Illicit substance use during pregnancy also places the fetus and newborn infant at increased obstetric risk. Abruptio placenta, amnionitis, early pregnancy loss, intrauterine growth retardation, late intrauterine death, placental insufficiency, postpartum hemorrhage, preeclampsia and eclampsia, premature labor, premature rupture of membranes, and septic thrombophlebitis are amongst the potential complications \(^{(24)}\).

The complexity of medical and psychosocial risk factors which usually characterize substance use during pregnancy dictate that a successful outcome can best be obtained within a comprehensive, supportive, non-judgmental environment which focuses on the multidimensional needs of the woman \(^{(9, 10, 22)}\).

Pregnancies associated with drug abuse should be considered obstetrically “high-risk.” Medical-obstetric management should be carried out by knowledgeable, supportive health care providers in a program that has experience in handling such pregnancies. The existence and interaction of these complex issues make it clear that effective drug treatment must be based on this comprehensive approach to the woman and her addiction. This approach encompasses a continuum of services (residential, outpatient, home-based, and prison-based); multiple counseling modalities (individual, group, and family); counseling on sexual abuse and domestic violence; services for children (day care, play therapy, parental training); concrete services (transportation, housing, food); comprehensive family-based health care (obstetric, pediatric, general medical); educational training (job training, high school equivalency training); appropriate staffing (female staff, supportive, culturally and racially sensitive); advocacy services (legal, child protection, welfare); and aftercare. Provision of these services at a single location will enhance compliance and make accessing the multiple aspects of treatment easier for the pregnant woman.

Treatment for heroin dependency during pregnancy should be tailored to the woman’s individual needs. The pharmacological treatment of choice for heroin-dependent women is methadone maintenance, which offers a unique opportunity for careful supervision of a woman for her addiction, pregnancy, and general medical and psychosocial health \(^{(43)}\). Methadone maintenance has been shown for three decades to reduce both maternal mortality and rates of fetal wastage, fetal morbidity, and pregnancy-associated complications \(^{(6, 20)}\). Although suggested regimens of methadone maintenance vary, provision of an adequate dosage of methadone (60-150 mg/day) is associated with a lower incidence of illicit drug use and higher rates of treatment retention. However, previous studies have shown that 60-90% of the infants exposed to methadone in utero exhibit neonatal abstinence. The onset of symptoms is within 48 to 72 hours after birth. Methadone dose relationship to neonatal abstinence severity has shown inconsistent results. Recently, buprenorphine, an agonist/antagonist pharmacologic agent, has been used in the treatment of opioid dependence.

Neonatal abstinence is a frequent consequence of pharmacological treatment of
pregnant women with methadone. Signs of neonatal abstinence may mimic other serious conditions such as sepsis/meningitis, hypoglycemia, adrenal insufficiency, or cardiorespiratory disease. Since most opioids are short-acting, signs of abstinence will develop shortly (generally within 1-3 days) after delivery, when the cord is clamped and the infant is acutely deprived of circulating maternal medication. Variations in maternal drug use amounts, placental drug transfer, neonatal metabolism and excretion, and gestational age may all potentially affect the time of onset of abstinence. The onset of methadone-associated abstinence, although usually early, is somewhat more unpredictable since methadone establishes a reservoir in fetal tissue and undergoes more variable metabolism and excretion (21).

Signs of neonatal abstinence are usually divided into four groups (2, 11, 21, 43).

(A) Central nervous system signs include irritability, high-pitched crying, tremors, hypertonia, hyperreflexia, and dysrhythmic sucking and swallowing. Seizures may occur in approximately 5% of opioid-exposed infants.

(B) Gastrointestinal signs include vomiting and diarrhea, which when combined with poor intake of nutrients and increased insensible water loss, often results in excessive weight loss and suboptimal weight gain in the first few weeks of life.

(C) Respiratory signs include tachypnea and hyperpnea, which may produce respiratory alkalosis, cyanosis and apnea if untreated.

(D) Autonomic nervous system signs include sweating, sneezing, tearing, and hyperthermia.

Although methadone maintenance has been recommended for the management of opioid dependence during pregnancy since the seventies, there continues to be debate regarding appropriate dose levels and the relationship of maternal dose and severity of neonatal abstinence. With the advent of new medications such as buprenorphine, continued observations and evidence based studies are needed in order to further determine the potential usefulness of this medication for pregnant women and the impact on the fetus and child. Current clinical practice should consider research on the use of methadone during pregnancy, relationship of maternal dose and neonatal abstinence, the differences between methadone and buprenorphine, and the impact of pharmacological options on patients and treatment providers. Clinicians should understand the complex biopsychosocial factors that make the treatment of opioid-dependent pregnant women a challenge and the principles and the differences in using methadone or buprenorphine combined with behavioral treatment for the management of opioid dependence during pregnancy.

The following sections summarize information presented at a symposium on addiction and pregnancy at the 2004 EUROPAD Conference in Paris, France. The areas covered include methadone dose and effects on neonatal abstinence, the role of buprenorphine in the treatment of opioid-dependent pregnant women, benefits of behavioral treatment, and reflections upon interventions for pregnant opiate-dependent women, research dilemmas and choices.
Methadone Treatment for Pregnant Opioid-Dependent Women: Revisiting the Question of Dose and Neonatal Abstinence

In the United States methadone maintenance has been recommended for the treatment of opioid-dependent pregnant women since the early 1970’s (43). With the legalization of methadone maintenance in the 1960’s for the treatment of heroin addiction, methadone was readily adopted as a medication to be used in the management of opioid dependence during pregnancy. A number of projects published findings in the 70’s indicating that methadone was safe and effective for pregnant women. It has been well demonstrated that providing methadone maintenance within a comprehensive program including prenatal care can reduce the incidence of obstetrical and fetal complications and neonatal morbidity and mortality (19, 33, 41). For non-pregnant patients and pregnant patients alike, effective methadone maintenance prevents the onset of withdrawal for 24 hours, reduces or eliminates drug craving, and blocks the effects of other narcotics (47). In addition, for pregnant patients, methadone maintenance prevents erratic maternal opioid levels and protects the fetus from repeated episodes of withdrawal; decreases risks to the fetus of infection from HIV, hepatitis and sexually transmitted disease; and reduces the incidence of obstetrical and fetal complications (42). In 1998 a National Institute of Health Consensus Panel on Effective Medical Treatment of Opiate Addiction recommended methadone as the standard of care for pregnant women (58). (It should be noted that methadone is not officially approved by the US Federal Drug Administration for use during pregnancy but is recommended based on its long history of successful use).

Both historically and contemporarily, however, there has been debate regarding a relationship between maternal dose and Neonatal Abstinence Syndrome (NAS). Initially, when methadone was first used with pregnant women, dosing decisions were made using the same criteria as for non-pregnant patients. Dose was based on achieving the desired therapeutic effect of preventing withdrawal, eliminating craving and blocking euphoric effects. Accordingly, pregnant patients were often maintained on doses of 100 mg or more. In the late 1970’s several studies were published that indicated a relationship between maternal dose and severity of NAS. Recommendations emerged that pregnant women should be maintained on low doses, i.e. ≤20 mg, in order to reduce or eliminate neonatal abstinence (60, 69). While such recommendations may have benefit for the neonate, they are contrary to the benefits of maintenance in that a low non-therapeutic maternal dose may promote supplemental illicit drug use and increase risk to the fetus. Debate has continued over the past 25 years since studies have yielded inconsistent results (39). As indicated in Table 1, nine studies (13, 15, 27, 45, 50, 51, 53, 60, 70), report a relationship between maternal dose and severity of NAS, whereas in Table 2, ten studies (4, 6, 7, 26, 40, 59, 65, 67, 68, 73) do not find a relationship.

Such inconsistent findings are the result in part of considerable variations in outcome measures of withdrawal ranging from the present or absence of any symptoms to the need for pharmacological treatment. Berghella et al. (4) found no difference in
Table 1. Studies showing relationship between maternal methadone dose and NAS

<table>
<thead>
<tr>
<th>Literature report</th>
<th>N° of subjects</th>
<th>Methadone dose (mg)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ostrea et al., 1976</td>
<td>95</td>
<td>15 vs 23</td>
<td></td>
</tr>
<tr>
<td>Madden et al., 1977</td>
<td>110</td>
<td>0-20 vs &gt;20</td>
<td></td>
</tr>
<tr>
<td>Harper et al., 1977</td>
<td>22</td>
<td>Mean = 28</td>
<td>5-60</td>
</tr>
<tr>
<td>Kandall et al., 1983</td>
<td>153</td>
<td>29 vs 50</td>
<td></td>
</tr>
<tr>
<td>Suffet et al., 1984</td>
<td>216</td>
<td>Mean = 29</td>
<td>5-&gt;45</td>
</tr>
<tr>
<td>Doberczak et al., 1991</td>
<td>21</td>
<td>Mean = 47</td>
<td>20-80</td>
</tr>
<tr>
<td>Malpas et al., 1995</td>
<td>70</td>
<td>Mean = 15.4</td>
<td>0-&gt;21</td>
</tr>
<tr>
<td>Mayes et al., 1996</td>
<td>68</td>
<td>Mean = 44</td>
<td>15-80</td>
</tr>
<tr>
<td>Dashe et al., 2002</td>
<td>70</td>
<td>Median = 20</td>
<td>0-150</td>
</tr>
</tbody>
</table>

Table 1. Studies showing no relationship between maternal methadone dose and NAS

<table>
<thead>
<tr>
<th>Literature report</th>
<th>N° of subjects</th>
<th>Methadone dose (mg)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinik et al, 1973</td>
<td>61</td>
<td>&lt;40 vs 40-60 vs 70-90 vs 100 vs &gt;100</td>
<td>80-100</td>
</tr>
<tr>
<td>Newman et al., 1974</td>
<td>313</td>
<td>&lt;50 vs 50 vs &gt;50</td>
<td></td>
</tr>
<tr>
<td>Rosen et al., 1976</td>
<td>29</td>
<td>Mean = 38</td>
<td>10-100</td>
</tr>
<tr>
<td>Stimmel et al., 1982</td>
<td>239</td>
<td>&lt;5 vs 5 vs &gt;50</td>
<td></td>
</tr>
<tr>
<td>Thakur et al., 1990</td>
<td>147</td>
<td>5-40 vs 40-60 vs &gt;60</td>
<td>10-70</td>
</tr>
<tr>
<td>Shaw et al., 1994</td>
<td>32</td>
<td>Median = 35</td>
<td>5-80</td>
</tr>
<tr>
<td>Hagopian et al., 1996</td>
<td>172</td>
<td>Mean = 31</td>
<td>10-60</td>
</tr>
<tr>
<td>Kaltenback et al., 1997</td>
<td>38</td>
<td>&lt;80 vs ≥80</td>
<td>35-135</td>
</tr>
<tr>
<td>Brown et al., 1998</td>
<td>32</td>
<td>50 vs ≥50</td>
<td></td>
</tr>
<tr>
<td>Berghella et al., 2003</td>
<td>100</td>
<td>80 vs ≥80</td>
<td>30-200</td>
</tr>
</tbody>
</table>
birth weight, the percentage of infants who required treatment for NAS, or hospital length of stay for mothers maintained on less than 80 mg or mothers maintained on greater than 80 mg using both mean dose and last dose in the analyses. This is the only study that also looked at the effect of concomitant maternal benzodiazepine abuse on abstinence. They found neonates exposed to benzodiazepine had significantly longer length of hospitalization (p. 1). A recent study by McCarthy (54) which is not included in Table 2, found similar results for women maintained on ≥100 mg and <100 mg. They found no difference in neonates requiring treatment for NAS or length of hospital stay. Additionally they found that women maintained on >100 mg had less concomitant drug use at delivery than the low dose group (p. 5).

The original work of Dole and Nyswander (16) established that for methadone to be therapeutic, an effective dose is usually in the range of 80-120 mg with blood plasma levels need to be >200ng/ml. A study by Drozdick et al. (8) demonstrated that during pregnancy achieving a therapeutic level is highly variable. For a group of pregnant women (n=20) with therapeutic trough plasma levels of >200ng/ml, the mean methadone dose was 128 mg with a range of 80-190 mg. However, a group of pregnant women (n=25) with sub-therapeutic trough plasma levels of <200 ng/ml, had a mean methadone dose of 98.6 mg with a range of 35-215 mg. These data suggest that an adequate methadone dose during pregnancy is highly idiosyncratic and utilizing arbitrary dose upper limits involves the risk of maintaining a pregnant woman on a sub-therapeutic dose. Moreover, there is no compelling evidence to reduce maternal methadone dose to avoid neonatal abstinence and to do so may promote increased drug use and increase risk to the fetus (39).

Therefore, regardless of the controversies over several decades, methadone maintenance, within the context of recent more valid studies, has been shown to be a therapeutically sound medication for pregnant women. Benefits override the risks with regard to neonatal abstinence. However, with the development, use and further research with regard to other opiate medications, we may be able to reduce the incidence of neonatal abstinence.

Role of Buprenorphine in the Treatment of Pregnant Opioid-Dependent Women

Buprenorphine is approved for the treatment of opioid dependence in men and non-pregnant women in over 34 countries around the world including the United States. For pregnant women, the goals of treatment with this opioid agonist/antagonist are: cessation of opioid use, to stabilize the intrauterine environment, to increase prenatal care compliance, and to enhance pregnancy outcomes. Buprenorphine has unique pharmacological characteristics including a wide safety margin and long duration of action. As a partial mu-opioid agonist (34, 52), the safety profile (e.g., less respiratory depression, less overdose risk) for buprenorphine is greater than that of a full mu-opioid agonist (e.g., morphine, heroin). Additionally, abrupt cessation of buprenorphine
has been reported to have few autonomic associated signs and symptoms of opioid withdrawal (25, 34, 56). It is this mild withdrawal profile that has sparked interest in the use of buprenorphine during pregnancy as the neonate might have a milder neonatal abstinence syndrome (NAS) than that observed with longer acting full mu-opioid agonists like methadone. There are two formulations of buprenorphine: a buprenorphine HCl (alone) tablet (Subutex®) and a 4:1 ratio of buprenorphine HCl to naloxone salt combination tablet (Suboxone®) (57). For the purpose of this review, only Subutex® will be discussed as the safety and efficacy data for Suboxone® administration during pregnancy are lacking.

In 1995, Reisinger and colleagues (64) published the first four cases of maternal and neonatal outcomes following Subutex® exposure. To date, at least 26 published reports of prenatal exposure to Subutex® maintenance can be found in the literature. These reports range from single patient case reports to the largest open-label study of methadone and Subutex® with 153 Subutex®-exposed infants (48). Taken together, the studies represent approximately 419 infants with a median number of 13 infants per report. In general, the literature suggests that Subutex® may be associated with a NAS that differs in quantity and quality from that seen with full mu-opioid agonists (5, 35). Although the body of literature suggests that Subutex® may be a promising medication for the treatment of opioid-dependent pregnant women, data from rigorously controlled randomized trials is lacking. The purpose of the project described below was to compare the neonatal abstinence in infants of mothers stabilized on methadone or Subutex® and to provide preliminary safety and efficacy data for a larger multi-center trial. It was hypothesized that antepartum treatment with Subutex® would result in shorter lengths of neonatal hospitalization and less abstinence compared to antepartum methadone treatment. These results have been accepted for publication in Drug and Alcohol Dependence (Jones H.E., et al. Buprenorphine versus Methadone in the Treatment of Pregnant Opioid-Dependent Patients: Effects on the Neonatal Abstinence Syndrome. Drug Alcohol Depend [In press]).

This study utilized a randomized, double-blind (i.e., neither patients nor staff in contact with patients were aware of medication condition), double-dummy design (i.e., each participant ingested two forms of medications daily). Participants received sublingual tablets followed by oral liquid. One form of medication was active and the other form of medication was a placebo in a flexible dosing and parallel-group design. The study was conducted in a comprehensive drug-treatment facility that included psychiatric, obstetrical, and medical care in residential and ambulatory modalities of treatment. Abstinence was measured repeatedly over ten days using a 19-item modified Finnegan Scale (21). Pharmacotherapy was initiated, maintained and weaned according to a systematic protocol based on the infant’s abstinence score.

One issue of potential concern was the induction onto these randomized study medications. After signing written informed consent, participants were placed onto Immediate Release Morphine (IRM). IRM stabilization was used to determine level of opioid dependence and allow for completion of medical clearance for safe study
participation. Data examining the transfer from IRM and first three days of induction onto methadone or Subutex® showed both medications were associated with similarly mild withdrawal scores (unadjusted means 3.1 vs. 1.5 out of maximum score of 30, respectively). No significant differences between medication groups were observed for individual withdrawal items or measures of fetal and maternal safety (36).

The results of the flexible dosing maintenance study showed that the average medication dose at time of delivery for methadone and Subutex® were 79.1 mg and 18.7 mg, respectively. Low illicit drug use rates during the study in both groups were due in part to the voucher program employed that provided monetary rewards contingent on participants providing biological samples negative for illicit drugs and alcohol. Of the primary outcomes, only the length of hospitalization was significantly different with Subutex®-exposed neonates being released from the hospital an average of 1.3 days before methadone-exposed neonates (p=.021). Two of 10 (20%) Subutex®-exposed and 5 of 11 (45.5%) methadone-exposed neonates received pharmacotherapy (morphine drops) for abstinence symptoms (p=.23). While the total amount of opioid-agonist medication drops administered to treat abstinence in methadone-exposed neonates was three times greater than for Subutex®-exposed neonates (93.1 vs. 23.6, respectively) the difference was not statistically different (p=.13). Results suggest that Subutex® is as safe as methadone on outcome measures assessing neonatal abstinence and maternal and neonatal safety when medication is commenced in the second trimester of pregnancy. These data while limited in sample size, provide strong support for the safety of replicating this study in a randomized multi-center trial.

As reviewed above, pharmacological management with methadone or buprenorphine can greatly reduce obstetrical and neonatal risks for pregnant opioid-dependent women. However, pharmacotherapeutic intervention for opioid dependence is rarely sufficient by itself to manage the multitude of problems faced by pregnant substance abusers. Treatment of this population is often complicated by poor program attendance and serious maternal and fetal health risks resulting from ongoing maternal drug use and underutilization of adequate prenatal care (39, 71). Licit and illicit drug use continues during pregnancy even amongst the general population, with 18.8% and 20.4% of pregnant women surveyed reporting use of alcohol and nicotine and 5.5% reporting use of illicit drugs (74). These rates are higher in substance abusing populations with as many as 23-75% reporting using more than one drug during pregnancy (49,63). The pre- and post-natal impact of continued drug use during pregnancy is well documented and includes problems ranging from low birth weight to Sudden Infant Death Syndrome, neonatal abstinence syndrome and abruptio placentae (23, 39). Given the limited availability of safe and effective pharmacotherapies for managing pregnant substance abusers, additional interventions aimed at eliminating drug and alcohol use and improving program attendance are especially needed.
Compatibility and Benefits of Using Methadone or Buprenorphine Combined with Behavioral Treatment for Managing Pregnant Opioid-Dependent Women

One type of additional, non-pharmacological intervention useful with pregnant substance abusers is behavioral treatment. A robust and reliable form of behavioral treatment called contingency management, in which positive contingency awards are provided for behavior change, is compatible with pharmacotherapy and effective for treating a wide range of substance use disorders and substance-dependent populations, including pregnant opioid-dependent women (29, 31, 37, 38, 61). Because contingency management can also impact a broad array of behaviors other than drug use such as compliance with treatment plans and attending program services (5, 32, 46, 61, 62), applying this behavioral procedure to the treatment of pregnant women makes good sense.

While there have been relatively few systematic studies of contingency management with pregnant substance abusers, there is accumulating evidence that enhanced substance abuse treatment (which includes positive contingency awards for abstinence or attendance) can improve pregnancy outcomes (12, 18, 37, 38, 72). Contingency management incentives that have been tried with pregnant women using licit or illicit substances range from cash (8, 12, 18), to cash or gift certificates (72), to vouchers exchangeable for goods and services (1, 30, 37, 38, 66, 72). With regard to the management of opioid-dependent pregnant women receiving agonist maintenance therapy, treatment issues addressed successfully with contingency management have included continued drug use, treatment attendance, and program retention.

In one of the larger studies of contingency management with 80 methadone-maintained pregnant women, patients were randomized to either standard care (no incentives provided) or a contingency management condition (37). During the inpatient portion of this study, daily treatment attendance was reinforced with vouchers while during the outpatient phase of treatment both daily treatment attendance and cocaine abstinence were reinforced. Interestingly, substantial and significant reductions in both cocaine and illicit opioid use were observed in those patients receiving contingency management relative to those patients receiving standard care. The attendance results are reviewed below. It is noteworthy that contingency management interventions have also been demonstrated to successfully reduce cigarette smoking, a prevalent problem among pregnant substance abusers, in pregnant and post-partum substance abusers receiving intensive outpatient treatment (1) as well as pregnant smokers in a general obstetric practice (30).

Early program retention can also be augmented using contingency management including reducing treatment attrition during transfer from residential to outpatient treatment. A series of randomized controlled studies (37, 38, 72) examined whether brief contingency management interventions could improve patient participation during this transition phase. In methadone-maintained pregnant women, the use of relatively high magnitude voucher incentives increased both residential and outpatient full day treatment attendance (37).

In summary, continued substance abuse during pregnancy and inadequate exposure
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to program services can result in serious negative maternal and fetal consequences. Multidisciplinary treatment approaches are needed to adequately address the needs of pregnant opioid-dependent women. Behavioral interventions such as contingency management are compatible with pharmacotherapy and can serve as strong adjuncts to ongoing care, improving rates of drug abstinence, program attendance and treatment retention in this population.

**Interventions for Pregnant Opioid Dependent Women: Approaches, Research Dilemmas and Choices**

When considering the impact of maternal treatment medications, there are a number of considerations. Intermittent fetal monitoring should be utilized to assess the acute impact of treatment medications as well as chronic use. When assessing the infant for potential abstinence resulting from maternal medications, inter-rater reliability must be assured and objective measures are highly recommended. Neonatal abstinence should be differentiated from other neonatal conditions frequently associated with perinatal drug dependence.

There are a number of clinical observations that can be made when assessing the potential advantages/disadvantages of maternal treatment medications. These include: maternal medical and obstetrical complications, fetal growth, incidence of pre-term birth, health of the baby, neonatal abstinence, and long-term outcome of the infant.

In reviewing the safety of methadone and buprenorphine, one should consider benefits over risks for the pregnant woman, the fetus, the newborn and the child. The issue of maternal comfort and the stabilization of dose to prevent maternal and fetal withdrawal are extremely important factors. Therefore adequate dosing is of prime importance to assure maternal comfort and treatment compliance. Although neonatal abstinence is treatable and not a lethal phenomenon, potential risks and costs associated with the symptoms and their treatment need to be evaluated.

When comparing clinical data looking at methadone verses heroin, methadone shows a better outcome. Maternal and fetal complications are less with methadone, fetal growth is greater, there are more term births, and infant morbidity is less. However, 60-90% of heroin- and methadone-exposed infants have abstinence symptoms.

A number of studies have reported on maternal methadone dose and how it may affect the frequency and/or severity of neonatal abstinence. Kandall et al. \(^{(44)}\) found that the severity of abstinence did not correlate with late pregnancy maternal methadone dose. In Herslinger’s report \(^{(28)}\), no apparent relationship between maternal methadone dose (10-100 mg/day) and frequency or severity of abstinence-associated seizures was found. Previously noted in this manuscript is the study of Kaltenbach et al. \(^{(40)}\) who studied a dose of methadone >80 mg versus <80 mg and showed that there was no influence on the incidence of neonatal abstinence. Most interesting are the results from studies by Doberczak \(^{(14)}\) and Rosen and Pippenger \(^{(65)}\), who found that the rate of decline of the neonatal plasma methadone level from day 1 to day 4 of life influenced
the severity of withdrawal.

In reviewing the available data on buprenorphine, studies to date have contributed to our understanding of this potentially efficacious medication for perinatal addiction treatment. Therapeutic concentrations of buprenorphine in maternal serum appear to have no in utero adverse effects on placental tissue viability and functional parameters. Transplacental transfer to the fetal circuit is very low. Data suggests that buprenorphine has a favorable outcome with regard to maternal health, fetal growth, birth weight, gestational age, Apgar scores, fetal withdrawal, and biopsychosocial outcomes, but also that neonatal abstinence occurs in a significant percentage of buprenorphine-exposed neonates (20% to 62%). However, duration of neonatal abstinence appears to be less with buprenorphine than with methadone (35). Overall, methadone and buprenorphine appear to have similar outcomes with regard to clinical parameters except for neonatal abstinence where buprenorphine shows less symptomatology. No long-term studies of infant outcomes exist with buprenorphine. Data from buprenorphine studies includes about 400 infants whereas methadone studies include thousands of babies.

The following is known from current studies with regard to breastfeeding in methadone or buprenorphine treated post partum women. Methadone can be detected in breast milk but at very low levels (ratio of milk to plasma concentrations ranged from .05 to 1.2). Maternal doses of 25-180 mg/d gave levels in breast milk from 27-260 ng/ml (mean of 95 ng/ml). Mean daily methadone ingestion for the infant would be 0.05 mg per day. If a mother is compliant with methadone maintenance and is HIV negative, breastfeeding may be recommended (55). Buprenorphine is also detected in breast milk. The plasma to breast milk ratio approximates one. Buprenorphine has poor oral bioavailability so the infant is exposed to 1/5 to 1/10 of the total amount available. Infants are exposed to less buprenorphine through breast milk than with any other opiates (35).

In assessing any data that describes differences in the outcomes of infants who are exposed to methadone or buprenorphine, one must factor in the high incidence of nicotine smoking in drug-dependent pregnant women. Nicotine use in pregnancy has been associated with increased morbidity and mortality, prematurity and its sequelae, Sudden Infant Death Syndrome, lung infections and effects on lung mechanics and Attention Deficit Hyperactivity Disorder. Therefore any treatment that can interrupt the cycle of nicotine addiction is extremely important for the health of the mother and child. Combining traditional therapies with innovative modalities such as contingency management will enhance our success rates for healthy perinatal outcomes.

In summary, in order to have a healthy mother during pregnancy and a physically and developmentally normal baby and child, one needs to provide comprehensive services. Medications and contingency management used in addiction treatment are a small part of the treatment regimen; but if used appropriately, they will be an important adjunct to the overall recovery of the addicted woman. Comparisons regarding methadone and buprenorphine must continue but without the aim to eliminate one or the other until significant harm is shown. No single treatment will be appropriate for all pregnant drug-dependent women. Future studies in perinatal addiction must be rigidly
designed utilizing a multidisciplinary team to carefully evaluate physical, psychological and developmental outcomes and evaluate the efficacy and safety of substitution medications in the mother and child.

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*Received and Accepted May 5, 2005*
Stapleford-Berlin 2006

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**MAIN ISSUES AND CONFIRMED SPEAKERS.**

**Anaesthesia vs light sedation in ROD/RAI (Rapid Opiate Detoxification/Rapid Antagonist Induction)**

H Kleber, New York; Cor de Jong, Nijmegen; Catherine de Jong, Amsterdam; J Currie, P Cox, Sydney; G O’Neil, Perth; N Maksoud, Cairo;

**Update on naltrexone implants and depot injections in alcoholism and opiate dependence.**

D Gastfriend, Alkermes, Cambridge MA; H Kleber, New York; G Hulse, G O’Neill, Perth; A Startosa (for Dr J Volpicelli) Philadelphia; L Partecke, Berlin;

**Clinical experience with rapid benzodiazepine detoxification using flumazenil.**

J. Currie, Sydney; G. O’Neill, Perth;

**Disulfiram vs naltrexone and acamprosate in alcohol abuse.**

H. Alho, Helsinki; (possibly first presentation of the Helsinki randomised trial results.) A de Sousa, Mumbai; M Faiman, Kansas; J Chick, Edinburgh; H Ehrenreich, Gottingen; C Brewer, London.

**Alternatives to methadone for opioid maintenance** - depot buprenorphine (Probuphine) slow-release morphine. – G Fischer, Vienna. (Morphine) Probuphine speaker to be confirmed.

**[Possible additional topics:**

Vaccines and agonist maintenance for cocaine and amphetamine dependence; Bariatric surgery for intractable obesity. Cannabis antagonists.]

Presentations are invited on the above topics or closely related issues and poster facilities will be available. Abstracts should not exceed 250 words and should be received by Jan 13th for the best chance of oral presentation. Poster presentations can be considered up to March 8th. See website for sample layout and typeface.

Dr Linde Partecke and Dr Colin Brewer. November 2005.
Primary care physicians and addiction treatment in Germany. Decentralization and take-home policy

Albrecht Ulmer

Summary

Medical knowledge is not always discovered in universities and laboratories, before finally trickling down to primary care physicians. In some cases, the very opposite is true. Even in Germany, primary care physicians have sometimes been the first to develop new methods of treatment and introduce them in day-to-day medical practice. Unfortunately, the German medical system is unaccustomed to listening to their voice. As a result, new treatment methods introduced by this route meet with specific difficulties. Maintenance therapy for drug addicts was introduced in Germany in the 1980s, mainly by primary care physicians in the face of major resistance from the medical establishment. The need to take action was high, however, and primary care physicians were the professionals who felt this most keenly. Increasing numbers of primary care physicians started putting patients on maintenance therapy. Dihydrocodeine was the agent most frequently chosen, as methadone was prohibited until 1992. Responses were excellent for committed physicians who ensured that the necessary arrangements were in place. However, because of the lack of integration in established medical practice, unstructured prescription was rife, leading to new problems and culminating in a series of deaths. The official reaction was to tighten the regulations, with the consequence that most primary care physicians have given up. Maintenance is now predominantly offered by special maintenance centers, leading to a strong concentration of these specific patients. France and Croatia, but also other countries show us ways out of this dilemma. Decentralized, very liberal maintenance policies in France make maintenance easy and successful. We can learn, that a good support system for the practitioners helps to avoid quality problems, crucially, from the Croatian model.

Key Words: Primary care Physicians - Addiction Treatment - Decentralization - Take Home Policies
Introduction and excursus: decentralized, take-home

Two concepts have crucial implications for the structure and general perception of maintenance therapy: decentralization and a take-home policy. Maintenance therapies in many countries could be substantially improved and their image would be much better if this crucial aspect were given more recognition. This concerns not only many addicts and their families, but also their doctors, the whole treatment system for addicts, and, finally, the whole of society.

The basic question is: Do we want that those who have become outsiders through an illness to become permanently gelled in their identity as outcasts? Or do we want to do all that is possible to enable them to return to a lifestyle that is as normal as possible? To reflect upon guilt is both right and wrong: Of course guilt and feelings of blame play a part in the development of addiction disease. An addict with no feelings of guilt is extremely rare. But to take guilt and blame as a basis for determining our actions is to ignore important principles of pragmatism and solidarity. After all, many other illnesses are partly self-inflicted, but we would not be inclined to blame the sufferers and refuse them treatment possibilities. Examples include heart attacks, diabetes, bronchial cancer, and road traffic injuries caused by hazardous driving.

What is needed is a pragmatic approach. Such an approach requires us to rethink the issue of what we want to achieve. The consensus on drug addicts, the pat answer that comes from the mouths of almost every expert like an article of faith, is: the ultimate and true goal is abstinence. It is important to realize that this is a fundamental principle but not necessarily the best solution from a pragmatic point of view.

Shouldn’t we, in fact, be saying: The ultimate and true goal is to help people with addiction – and those around them - to live their lives as best as possible? After all, these are the goals pursued for every other chronic disease. Partial successes, as opposed to a complete cure, represent significant progress and, in many cases, constitute the best solution that it is possible to achieve. We do the chronically ill an injustice by applying full recovery as the only goal – as will be obvious if you just think of patients with rheumatoid arthritis or diabetes. Naturally, that is not to say that we should not be in permanent pursuit of ever better outcomes. But we have to learn to let go of our illusions. Abstinence and/or full psychiatric recovery are an illusion in many cases, a fatal instance of expecting too much, an injustice to the patients concerned and a flawed therapeutic approach.

The kind of pragmatic aims that are so very necessary are: to help people to live as healthily as possible, with the greatest possible long-term well-being, the greatest possible level of integration in society, and with an acceptance of the role as partly outsider that some have chosen for themselves. Doesn’t every one of us need areas of life where we differ from others, where we are our own person and the odd one out? But to refuse somebody the possibility of integration is terrible and inhumane. If anyone thinks, in relation to “greatest possible well-being”, “Oh sure – at other people’s expense”, then he had got the wrong end of the stick. Every disease and every kind of solidarity is “at other people’s expense”, to a certain extent. The proper correlation between solidarity
and expectation is created on the basis of the fact that most people who feel well will do better in life and give more back. A person treated like a second-class or third-class citizen will learn to behave like one.

If you call upon addicts to go to special centers for treatment – unlike the policy adopted for all other chronic illnesses of similar incidence – then you will create treatment ghettos and help to keep people with addiction disease firmly entrenched in the drug scene.

That is why the concept of DECENTRALIZATION is so important. Only a decentralized treatment system can prevent this extremely negative effect. In many countries and regions, people simply have no idea how extremely negative the impact of a treatment system based on treatment centers is. People have gotten used to the idea that this is what methadone treatment is supposed to be like. People approve of the interdisciplinarity of treatment centers, the quality standards implemented there, and how regulated it all is. The patients, in contrast, have to negotiate long and in some cases unacceptable routes to the treatment centers, must organize a large part of their life around these routes, and have little or no choice in the person to whom they entrust their care. We shouldn’t forget that this is a very sensitive area where earlier and ever present psychological damage (traumata of the soul) is such an important factor. Shouldn’t a primary concern be: Patients must have the widest possible choice in who they receive treatment from? It’s an objective that can only be achieved on the basis of a widespread, decentralized network of treatment venues.

In the case of a decentralized treatment structure, most therapists would have just a few patients. This factor is a crucial prerequisite for a relatively normal treatment setting and a (possible and indeed necessary) way to demand and encourage patients to distance themselves from the drug scene and embrace a “normal”, integrated lifestyle.

A take-home policy is another key element here. A patient who receives a supply of medication for a specific period of time is given the chance to show that he or she can deal with it with the dignity of a “normal patient”. At the same time, the patient’s waking hours and life structure are freed up, allowing the patient to pursue the plans that are normal for a person of his or her age and stage of life.

Of course there will be abuse of this trust, for example in the re-sale of prescribed maintenance drugs. But this kind of abuse spreads in particular in association with treatment structures that aid and abet abuse, through prescriptions without dose specifications and checks, poor therapeutic support, as manifest for example when physicians fail to take into account a patient’s biography, environment, and current options, and, above all, when too little attention is paid to the patient’s well-being and overall development.

Symptomatically, treatment systems based on many regulations and checks tend to be associated with this negative effect, too. A system based on checks usually means that patients have to come for regular tests and hence have to sacrifice more of their time to the process of being tested. Checks in many cases also involve centralization
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with all the negative consequences associated with the creation of a scene. Therapists mostly are powerless in the face of what goes on in front of the door of the treatment facility or in the next market square.

German history and status quo

Physicians in Germany who have provided maintenance therapy for 10 years or more feel these issues particularly keenly due to their experience with both maintenance therapy models.

The use of methadone for maintenance therapy was prohibited in Germany for an inordinately long time. A change did not come about until 1992, and even then a highly restrictive and regulatory system was implemented until 1998. German physicians had long ago identified codeine or dihydrocodeine as an alternative, as codeine did not fall under the Controlled Substances Act. There were no restrictions on the use of codeine for maintenance. Physicians were able to prescribe it like an ordinary medicine. In cases where normal therapeutic structures were applied – dosage schedules, dose monitoring, and the interaction necessary to determine the patient’s well-being, living circumstances and development – the results were excellent on the whole. The percentage of earners was above 80% in some cohorts (13), a figure approximating that of the population at large. The behavior and appearance of most patients was perfectly unobjectionable and likewise corresponded to that of “ordinary patients”. Thus, many patients showed the kind of progress best desired by society and, in particular, by the patients’ families.

My horror was therefore all the greater when I visited one of the first German methadone outpatient clinics designed for the highly regulated treatment of a larger patient population. I was greeted in front of the door by the sight of a group of addicted patients standing around with bottles of beer in their hands, whose general demeanor unmistakably identified them as belonging to the drug scene. This climate had obviously transferred to the staff of the clinic also. The whole place was steeped in the atmosphere of a special model for a class of permanently marginalized patients.

Legislation enacted in 1998 forced German doctors to relinquish codeine maintenance for the most part and to switch their patients to the kind of methadone maintenance described above, with slightly more relaxed regulation but nevertheless subjected to much tighter controls than the former codeine maintenance. Ever since then, drug addicts on a maintenance program are much more caught up in a “meth junkie” role. And wherever methadone treatment is provided, you are likely to see the unlovely trappings of addiction, even in our own specialized practice. Under this system, very many more people with addiction disease have become used to living life as a social misfit than was the case during the earlier era of unregulated codeine maintenance.

How did it come to this? And is there a way out?

There were two main reasons for the lack of sufficient trust in the codeine maintenance system described so positively in this paper:
1. **Lack of trust.** The codeine maintenance era happened at a stage where maintenance as such was mistrusted as a treatment concept. While this form of treatment was mainly pioneered by physicians in the community, and primary care physicians in particular, psychiatric facilities, addiction clinics, and, most importantly, most of the psychiatric universities – in short, the repositories of research and established teaching – maintained a critical distance. In the same measure as the latter required fertilization from the expertise of grass-roots medical practitioners – because community practitioners were evidently quicker to recognize the need for maintenance treatment and more ready to respond – primary care practitioners were unable to establish a necessary new treatment modality on their own without the requisite ties to the research and teaching community. Too few standards were established, not enough scientific data was generated, and maintenance therapy became permanently tarnished with a reputation of representing grubby, unorthodox medical practices that promoted the chronification of addiction. A number of negative terms characterized this approach: gray substitution, replacement-drug, chronifying addiction, dealers in white coats... The mistrust of the expert community and society at large expressed in these terms became part of a vicious circle.

2. **Poor quality.** A lack of standards, no ties to established research, teaching and treatment structures, and a lasting climate of mistrust led to a situation where primary care physicians were left alone in their efforts to treat drug addicts. The climate of mistrust resulted in legal uncertainty and judicial pressure. Jointly developed, robust structures were not developed. Instead, doctors tended to act as lone agents conducting semi-clandestine operations. Treatment quality suffered badly as a result. Prescriptions were made out without the necessary physician-patient consultations and without any structural framework. More and more deaths occurred as a manifestation of these and similar deficits. It was reported for example that addicts would go to 5 doctors one after the other during a single morning, acquiring huge quantities of codeine en route. The mistrust grew.

Something had to be done to implement quality assurance. An approximately 60-hour compulsory course was introduced for physicians involved in maintenance. Codeine and dihydrocodeine intended for maintenance were placed under controlled substance legislation and approved only as a last resort. This made it impossible to conduct maintenance therapy using the same structures as for “normal patients”. Maintenance therapies were now subject to very strict special rules: special prescriptions with special procedures for filling them, strict regulations as regards the frequency of physician contacts, conduct of urinalysis, stringent take-home policies, extensive regulations in the case of travel, significantly more bureaucracy - all of this on pain of criminal prosecution and monitored by quality assurance committees \cite{1,4,9,12}. The series of court actions against maintenance physicians did not abate, and legal prosecution continued to dominate the maintenance therapies.

The medical community soon came to look upon the area of maintenance treatment
as a “minefield”. In contrast to the first phase, it was virtually impossible to recruit new physicians to work in this area. On the contrary: large numbers of doctors gave up their maintenance efforts and many physicians conducting maintenance programs stopped accepting new patients. There are just 11 medical offices offering maintenance treatment in our city of Stuttgart. Basel, Switzerland, has about half the population of Stuttgart and as many as 250 doctors’ offices providing maintenance therapy. Treatment sites are getting thinner on the ground in Germany. The centralization process is increasing, and the cementing of addicts in a circumscribed identity as a maintenance patient dictates these people’s lives.

The role of untrustworthy “alien” is applied not just to patients and their loved ones but also to the doctors who care for them. In addition to hyper-regulation and hyper-bureaucracy, it is this atmosphere that is inimical to the theoretically sound concept of maintenance therapy.

And thus, the approach of assuring quality through regulation, which was possibly well-meant but characterized by fundamental mistrust right from the start, has led to a kind of dead end, resulting in crippling neglect of the crucial principles of DECENTRALIZATION and a lack of adequate provision for TAKE-HOME medication.

What’s the solution? It helps to take a look round Europe. France has a very convincing countermodel at this time. Any physician, practically without any special regulations, can prescribe buprenorphine for maintenance, similarly to the way German physicians were able to prescribe codeine and dihydrocodeine all those years ago. Two basic differences increase the prospects for long-term success: the risk of death by overdose is minimized through the drug’s natural ceiling effect (despite the possibility of fatal toxicity from intravenous combination with benzodiazepines), which helps to significantly reduce the risk of fatalities in association with misuse. Even more importantly perhaps, this system rests on a broad consensus in society and among the expert community and therefore has the best of prerequisites for good scientific evaluation and optimization. The involvement of very many primary care physicians provides a basis for decentralization and take-home policies that is very different to the German experience. Like everywhere if many GPs are involved in the treatment of addicts there is a justified discussion about the quality which surely is not adequate in many cases (5, 7, 11). The extreme decline in heroin overdose deaths since then, the disappearance of overt drug scenes in large cities, and the very positive relaxed approach of our committed French colleagues all point toward a huge success (6, 8). In Germany and perhaps throughout Europe, the French experience must be taken as a stimulus to de-regulate buprenorphine maintenance in a similarly free fashion to the benefit of society.

Reports from Croatia (10) suggest that an uncomplicated decentralized structure can also work for methadone. That country’s secret seems to be the excellent relationship between clinical psychiatry and physicians in the community. The Croatian model is also based on strict decentralization and a good support system for the primary care physicians, possibly the best system in Europe.
Quality problems, such as occurred in Germany in association with the provision of codeine maintenance by primary care physicians alone, are best solved by structural solutions. Active networking of all players – unlike the former situation – and a sufficient support system for the primary care physicians would do away with the necessity of most of the regulations now perceived as oppressive and deterring, and would again motivate very many more primary care physicians to deploy their excellent qualifications in the specific care of addicted patients.

People with addiction disease and all those dedicated to their care need this kind of development. A sense of trust is all it takes.

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Received November 2004 - Accepted March 17, 2005
Psychopathological disorders in heroin addicts and administration of risperidone during rehabilitation

Alexander A. Kozlov¹, Igor V. Dorovskikh², Natalia A. Doljanskaia³, Tatiana S. Buzina³ and Anna G. Polunina⁴

Summary

The topic of the present study is the clinical picture of psychopathological symptoms during post-withdrawal periods in heroin addicts. Craving symptoms can be compared to productive psychopathological symptoms, and their intensity usually corresponds to the severity of depressive disorders in heroin ex-addicts. Risperidone is therefore a preferred choice for craving control when opiate maintenance therapy is unavailable (as it is currently in Russia). This antipsychotic showed its effectiveness and safety during prolonged anti-relapse therapy in the out-patient treatment of heroin addicts.

Key Words: addiction - heroin - risperidone - psychopathological symptoms - treatment

Introduction

The search for the most effective neuroleptic with a low level of toxicity — those which allow administration over a long period during the stabilization of remission — currently constitutes the main task of many Russian researchers, who are working on new methods of treating and rehabilitating drug-addicted patients and on improving already familiar concepts and recommendations pertinent to the use of psychotropic medicines. This is mandatory, partly because drug addicts are difficult to cure, on account of the severity of psychopathological symptoms during abstinence and postabstinence.

¹Medical Department of the Russian Federation State Service of Narcotraffic Control
²Moscow Research Institute of Psychiatry, Russian Federation Ministry of Health
³Department of AIDS Prevention and Other Infectious Diseases of National Research Center of Addictions, Moscow, Russian Federation Ministry of Health
⁴Moscow Practical Research Center of Prevention of Drug Addiction, Russian Federation Ministry of Health

Address for reprints: Alexander A. Kozlov, MD - National Research Center on Addictions (NRCA) - Stavropol'skaya st. 27-7, Moscow, Russia, 109559
periods, and partly because of the absence of durable remissions; in addition, there is a lack of effective clinical programmes in out-of-hospital and rehabilitation practice.

In treating addicts, most researchers consider it necessary to combine general medical care with the administration of naltrexone or maintenance therapy based on methadone, which is of great importance in cases of HIV positivity or in criminal addicts \(^{(11, 12)}\). The spread of HIV epidemics, with rising numbers of HIV-positive and HIV-affected drug addicts, calls for a change in approach towards the treatment and rehabilitation of these patients, as well as changes in current legislation. It should be borne in mind that in the Russian Federation the administration of narcotic substances as maintenance therapy is still prohibited by law \(^{(17)}\).

The craving syndrome is one of the leading syndromes in addiction, including heroin addiction. Craving is such a powerful factor that it regulates and dominates a patient’s behaviour. In focusing on the choice of ways and methods able to set up a craving blockade, our viewpoint is that craving may be equated to a productive psychopathological disorder. In fact, we fully agree with Altshuler \(^{(1)}\), who wrote about the productively psychopathological character of alcohol-craving in alcoholics. A craving for drugs becomes manifest through a variety of different symptoms and syndromes. It may arise periodically, or persist permanently.

Many years of clinical observations have shown that emotional disorders (which include emotional lability, affective and dysphoric reactions) are among the psychopathological disorders most often seen in heroin addiction. During the long periods of withdrawal and remission, these disorders stabilize into a specific psychic deficit \(^{(2, 4, 8, 14-16)}\). Patients become unduly sensitive to even the slightest psychic discomfort. They become more and more inclined to react inadequately to various, even minimally psychotraumatic situations; these aspects heighten the abnormality of behavioural responses, including psychopathia-like ones. These patients are characterized by a bad mood which in its turn contributes to the actualization of craving and often leads to relapses. This so-called “acquired affective lability” is most clearly seen during remission, as described in the literature \(^{(14-16)}\).

Drug abuse, like heroin abuse, induces significant distortions of personality, including the “narcomanic” personality type \(^{(4, 6, 7)}\). The most long-lasting characteristics of the “narcomanic” personality, which tend to persist during the period of treatment, are antisocial behaviour, conflict lability, impaired control of one’s behaviour, apathy, asthenia, mood lability and passivity \(^{(5-7, 18)}\).

Thus psychopathological features in heroin addicts are characterized by emotional disorders involving affective pathology and behavioural deviations, depression and antisocial personality distortions.

This study aims to describe clinical and psychopathological manifestations of heroin craving during the post-abstinence period and during remission, as well as the search for the “safest” and most effective anticraving treatment during the post-withdrawal period.
Material and Methods

28 patients (men) addicted to heroin were included in the study. The age of patients was 18-35 (with an average of 24.65 ± 5.94) and disease duration was between 10 months and 9 years (with an average of 3.81 ± 1.42 years). Over half the patients were under 27 years. The age at which these patients first used narcotics ranged between 13 and 26 years (with an average of 20.97 ± 4.57 years). Almost all the patients had a history including at least one remission from drug abuse history. The average duration of narcotics use after the latest remission was six months. Before using heroin, most patients had smoked cannabis occasionally; a few had used it systematically. Some patients had tried psychostimulants or hallucinogenic substances, though they had no addiction to them. Most patients started to use heroin by snorting, and later, as their tolerance grew, they switched to injections. Patients were treated in hospital for 3 weeks, after which they participated in an out-of-hospital rehabilitation programme lasting at least 6 months. The research methods used were clinico-psychopathological, follow-up, statistical and psychological (Raven’s test, the memorizing of 10 words, and Shulte’s method).

Results and Discussion

After the acute withdrawal symptoms were blocked, the psychopathological disorders began to dominate, and in most cases corresponded to a patient’s strong drive for narcotics. These were affective disorders, which usually included dysphoric depression, responses of psychopathological type, involving irritation, dissatisfaction with surroundings, excitement and inadequate behaviour. At this stage the most important decision to be made was the correct option of an antidepressant with neuroleptic therapy, which was appropriate to the clinical manifestation of the disease.

Depression, irritation, behaviour of psychopathological type and other psychic deviations disguised the actual expressions of the aggravated craving for narcotics, though patients themselves were not always aware of this. They thought that they had already recovered, demanded to be discharged from hospital and misunderstood the fact they were driven by a wish to change their condition. In general, the level of craving for drugs was correlated with the severity of psychopathological symptoms. A certain parallelism could be seen between the severity of depression and the intensity of craving. The intensification of depressive symptoms, with their characteristic dysphoric colouring was almost always evidence for the aggravation of a craving for drugs which needed adequate therapeutic treatment. The use of medication to suppress the craving and eliminate the corresponding physical symptoms was of major importance during the rehabilitation period.

At this stage (during the period of rehabilitation) patients suffered from asthenia, with low levels of intellectual potential and creative activity. Cognitive decline took the form of flat judgments, problems with concentration, and a liking for pointless talk. As early as the Twenties, many researchers working on morphine addiction noted
memory disturbances, a decrease in mental productivity, especially creativeness, intensified fatigue and an inability to plan future activity. These authors (2, 9, 10, 14) noted in her observations that patients with opium addiction were marked out by impairment of psychical functions, and problems with mobilizing and concentrating attention, as well as the inability to make an effort to implement a proposed task. Their quality of thinking, however, remained at a high level, as long as the patient was concentrated enough. Patients’ decline in intellectual activity against a background of asthenia and apathy led them to relapses during the initial period when remission was being set up. These symptoms were compatible with an aggravation of craving, but with a quite different colouring. In this case passiveness, an unwillingness to read, learn or work, to take the initiative in looking for a job or in solving even the simplest everyday problems had led our patients into a state of deadlock. In their view, the only way to resolve this situation was to take up narcotics again.

The anti-relapse, supporting therapeutic treatment during the remission period, did not always give the expected positive effect for a number of reasons. This situation was especially common in patients with a long history of addiction, but was also frequent in those who, by contrast, had just started to use narcotics.

The first reason is that some patients stopped using the recommended medication after discharge; in other words, it was sometimes hard to keep patients in the maintenance medication programme.

The second reason, the long period of taking recommended neuroleptics such as phenothiazine and other medications, often led to side-effects. Because of the lack of fully operative dynamic medical supervision, patients reacted by modifying their own doses and adopting a personal regimen for taking medicines; in this way a negative reaction to such medical treatment (comprising not only neuroleptics, but antidepressants and many other medicines, including nootrops) had been inadvertently created. In such cases psychotherapeutic treatment, too, had little effect.

The use of risperidone in narcology practice has already been reported (3, 13, 19, 20). In any case, the clinical characteristics of heroin-addicted patients noted above, especially during the period when remission is being set up, became the reason why risperidone is included in the out-patient maintenance programme for treating and rehabilitating heroin addicts.

Risperidone (A note) is an atypical antipsychotic from the chemical group of benzosikasals. In the first place it influences the serotonergic and dopaminergic neuromediator systems; its latter effects make it different both from classic neuroleptics and from other atypical antipsychotics. The profile of risperidone’s neurochemical activity is characterized by principal binding with D2-dopaminergic and 5-HT2-serotoninergic receptors, as well as with α1- and α2-noradrenergic ones, while risperidone possesses no tropism with holinergic, istaminergic or D1-dopaminergic receptors.

In our practice the treatment began on the 21-28th day (on average it began on day 25.4 ±3.83) after the most recent use of a narcotic. The problem was to keep patients within the limits of the treatment-rehabilitation (out-of-hospital) maintenance pro-
programme. In this context it was vital to chose the optimum dose of the medication in accordance with the out-of-hospital treatment. In cases of schizophrenia, risperidone in used in pill form in large dosages – as high as 12 mg/24 hours, taking into account its normothymic action; by contrast, in gerontology it is used in dosages as low as 0.5-2 mg/24 hours. As our patients did not show any gross positive psychopathological symptoms, we considered such doses to be too large (or too small) and adopted a dose of 2-6 mg/24 hours. The other available neuroleptics often cause negative reactions among addicts (due to their knowledge of the side-effects of these medicines, including expressions of neurolepsia), so we decided to refrain from administering them. Risperidone was administered daily at a dose of 2-3 mg morning and night during the first 2 months. In the next 2-4 months of rehabilitation patients were given 2-4 mg (depending on the character of their psychopathological symptoms), in most cases once a day (in the morning).

A special registration form comprising 23 questions was drawn up to account for the basic symptoms during the rehabilitation period. It was first filled in before treatment with risperidone, then again on the 3rd, 7th, 14th, 21st, 30th, 45th, 60th and 90th day of risperidone administration, i.e. nine times in all.

This form was used to assess the position of a control group of 12 heroin addicts of about the same age and with the same period of addiction as the risperidone-treated group. It should be noted that we were only able to follow up the patients in the control group, once out of hospital, during the first two months. In most cases they stopped their visits to the rehabilitation programme after two months.

It should be remembered that, on average, up to the 25th day the basic psychopathological symptoms were partly eliminated by “traditional” therapeutic treatment in hospital (without risperidone, as a rule); so, during the next 2-3 weeks many symptoms were only minimally present or actually disappeared as a result of risperidone administration. After one month of out-of-hospital treatment and rehabilitation, most patients had no symptoms to complain of, and the main points discussed at patients’ visits were education, the search for work, and the problem of inactivity. There was a clear need for the administration of risperidone to continue over the whole period of 6 months in 12 patients, i.e. 42.8 % of the patients observed. One patient had to take risperidone for 8 months.

It is important to note that most of the symptoms were not prominent before risperidone administration began. Only 6 positions were close to the mean evaluation corresponding to the description of the symptoms in the postwithdrawal period.

Before risperidone treatment began, the level of dysphoria was recorded as 1 point, and the level of anxiety as 1.57 points; on the 14th day of treatment the level of dysphoria was down to 0.85 and on the 30th day to 0.28. Similarly, the anxiety level fell from 1.57 points to 0.57 on the 14th day and to 0.14 on the 30th. Irritation fell during the first 2 weeks from 1.42 to 0.85 points; there was a less marked fall in lability of affect, from 1.85 to 1.14 points over two weeks and to 0.85 over the first month (Table 1).

Beginning with the first month of treatment, asthenia became considerably less
### Table 1. Dynamics of psychopathological disorders in heroin addicts during the postwithdrawal period when setting up remission, against a background of risperidone administration (in rehabilitation programmes)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Days of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0*</td>
</tr>
<tr>
<td>Poor mood</td>
<td>1.71</td>
</tr>
<tr>
<td>Good mood</td>
<td>0</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.42</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1</td>
</tr>
<tr>
<td>Gloominess–pessimism</td>
<td>1.57</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.57</td>
</tr>
<tr>
<td>Affect lability</td>
<td>1.85</td>
</tr>
<tr>
<td>Motor retardation</td>
<td>1</td>
</tr>
<tr>
<td>Hypochondria</td>
<td>0.71</td>
</tr>
<tr>
<td>Motor restlessness (akathisia)</td>
<td>0.28</td>
</tr>
<tr>
<td>Non-assiduity</td>
<td>0.85</td>
</tr>
<tr>
<td>Agitation, uneasiness</td>
<td>1.85</td>
</tr>
<tr>
<td>Psychomotor excitation</td>
<td>1</td>
</tr>
<tr>
<td>(behaviour of psychopathologi-</td>
<td></td>
</tr>
<tr>
<td>cal type)</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Dynamics of psychopathological disorders in heroin addicts during the postwithdrawal period when setting up remission, against a background of risperidone administration (in rehabilitation programmes)

<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>0*</td>
</tr>
<tr>
<td>Quick exhaustibility</td>
<td>1.71</td>
</tr>
<tr>
<td>Weakness</td>
<td>1.85</td>
</tr>
<tr>
<td>High fatigability</td>
<td>1.57</td>
</tr>
<tr>
<td>Apathy, indifference</td>
<td>1.57</td>
</tr>
<tr>
<td>Absence of desires</td>
<td>1.42</td>
</tr>
<tr>
<td>Passivity</td>
<td>2.14</td>
</tr>
<tr>
<td>Craving for drugs: conscious</td>
<td>2</td>
</tr>
<tr>
<td>unconscious</td>
<td>1.57</td>
</tr>
<tr>
<td>Drug–induced dreams</td>
<td>0.85</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>1.57</td>
</tr>
</tbody>
</table>

* Risperidone was administered after acute withdrawal syndrome had been blocked, i.e. on the 21-28th day after the latest use of a narcotic.

DEGREE TO WHICH A SYMPTOM WAS PRESENT (IN POINTS):
0 – symptom absent
2 - symptom evident
0 – before Risperidone administration
1 – symptom poorly evident
3 - symptom clearly evident
Heroin Addiction and Related Clinical Problems

marked: gradually, by the end of the third week of treatment with risperidone, our patients felt considerably less exhausted (improving from 1.71 points to 0.57), and less weak (improving from 1.85 points to 0.71), while increased fatigue decreased too (from 1.57 points to 0.57). Certainly, up to the 60th day of rehabilitation asthenic disorders decreased even without risperidone, but they did not improve so quickly or markedly.

After only a week of treatment, patients’ mood had already improved a little. Poor mood before treatment was estimated at 1.71 points; on the 14th day it reached 1.28 points, and on the 30th and 45th days it was recorded as 0.85 and 0.57, respectively. It should be noted that during the treatment period we tried to avoid administering antidepressants, or used them in minimum doses. In only two cases did we have to include antidepressants in our therapeutic schedule for a short time, because these patients failed to show better mood while being treated with risperidone monotherapy. In some cases during treatment (at the end of the third week of taking risperidone) some improvement of mood took place (from 0 to 0.42 of a point).

The same is true of apathia and abulia. Patients became more active. Inertia, weakness, apathy and indifference became less marked. Before the initiation of therapy with risperidone, the intensity of these disorders was assessed as 1.57 points, whereas after 14 days it had fallen to 0.85 point, after 30 days to 0.71, after 2 months to 0.57 and after 3 months to 0.14. The 30th day of treatment with risperidone corresponded to the 51-58th day after the latest use of a narcotic. Asthenia and apathetic-abulic disorders showed improvement by this time in patients without risperidone, too, but in most of these patients they persisted and were still evident. Thus, asthenia in the control group was estimated on the 45th day at 1.6 points, and apathy at 1.2 points, i.e. in the control group these disorders were much more severe than in patients treated with risperidone. Passivity before the administration of risperidone was assessed at 2.14 points, but at the end of the second week of risperidone treatment it had already fallen to 1 point and after 2 and 3 months to 0.57 and 0.28 of a point, respectively.

One very important finding was that, with risperidone treatment, the background pathological craving for narcotics was blocked much faster. It was often unconscious and was blocked by risperidone up to the second week without recourse to any other neuroleptics. Before risperidone administration the conscious craving for narcotics was assessed at 2 points, and the unconscious at 1.57; at the end of the third week of risperidone treatment, craving had fallen to 0.57 point. Patients just avoided talking to a doctor about narcotics. However, two patients, though they denied their craving, still admitted to using alcohol (drinking beer) from time to time.

By the 30th day sleep disorders had disappeared completely and narcotic dreams hardly disturbed patients at all.

To sum up, risperidone influenced mostly affective and behavioural disorders and the crucial syndrome of addiction connected with them – pathological craving, together with disorders such as quick exhaustibility, asthenia, and the apathetic-abulic syndrome. Not one of the treated patients demonstrated an exacerbation of craving for narcotics.
One important result is that risperidone has no negative effects on cognitive functions, a great advantage over other neuroleptics. In fact, we noticed an improvement in IQ. Before risperidone treatment, IQ averaged 85.4, but on the 30th day of treatment it was up to 107.5. Patients in the control group who were not taking risperidone also had an IQ over 100, but those treated with risperidone turned out to be quicker and better achievers. In addition, research on the ability to concentrate attention (Schulte’s method) showed a clear tendency towards improvement. There was a clear tendency towards improvement in direct (mechanical) memory, as assessed by the 10-word test. However, the differences in these data compared with those for the control group were not so dramatic.

One must now touch on the very important problem of HIV-infected addicts. In this group one should take into account the aggravations that may be brought about by individual complex therapies relying on immune medicines, vegetostabilizing nootrops or other psychotropic drugs (even those with minimum side-effects). There were no HIV-infected patients in the present study, but, as we have already pointed out in previous studies, we recommend the use of risperidone in addition to the traditional schemes of treatment and rehabilitation of these patients (17).

Everything that has been stated above points to the advantages of including risperidone in therapeutic programmes for treating and rehabilitating patients addicted to opium (especially heroin) not only in hospital, but also when patients are at home. This is the most efficient factor in the long-term anti-relapse treatments that fall within the complex of rehabilitation measures.

**Final Comments**

1. Some distinctive affective disorders were observed in most patients during their out-of-hospital treatment and rehabilitation. Disorders such as affective lability, hypochondria, asthenia, apathy, carelessness, passivity, and inability to work or read persisted over a long period. In this context, behavioural deviations and aggression occupied a special place.

2. At all stages of the disease our patients showed psychic instability, which contributed to an easily provoked craving for narcotics; this was quite often expressed by psychopathological disorders. The intensity of craving corresponded to the severity of psychopathological symptoms and vice versa. Some parallels can be drawn between depressive symptoms and symptoms of craving. In this connection, these patients needed a long rehabilitation programme (lasting as much as 6 months, or more) with administration of neuroleptics involving minimum side-effects.

3. Against the background of the long-term use of risperidone, these patients demonstrated the decline of affective tensions and cruelty, the absence of notable upheavals in emotional background, dysphoric reactions, behaviour of psychopathological type and compulsive craving for narcotics. Levels of asthenia and apathy decreased, and behaviour became better organized. One important outcome was that none of
the treated patients demonstrated an exacerbation of their craving for narcotics.

4. The administration of risperidone did not call for the use of additional neuroleptics or of the correctors used in current therapies. There was no evidence of extrapyramidal symptoms. In cases of severe depression, antidepressants were administered only in one or two cases. Risperidone had no negative effects on cognitive functions, unlike other neuroleptics. Among our patients, interest in everyday life was restored, and communicative functions improved.

5. The results of this study make clear the advantages of including within practical treatment the atypical neuroleptic — risperidone. It is a safe normothymic able to provide maintenance, long-term antirelapse therapy in the out-of-hospital treatment of opiate addiction. In the complex that comprises rehabilitation measures, this approach makes possible a striking improvement in the social adaptation of addicted patients and in their quality of life.

References

2. BORINEVICH V. V. (1963): Narcomanias, Medgiz, Moscow.

A note.

Risperdal Consta – the prolonged action form of Risperidone. During the last 3 months of the study, 6 patients who had been treated earlier with Risperidone per os, were successfully switched to Risperdal Consta. They were given 25 mg of Risperdal Consta every 2 weeks. The use of Risperdal Consta in treating drug addiction needs to be analysed further.

Received January 15, 2005 - Accepted June 21, 2005
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Also by Fax
Methadone reduces the need for antipsychotic and antimanic agents in heroin addicts hospitalized for manic and/or acute psychotic episodes

Matteo Pacini 1,2 and Icro Maremmani 1,2,3

Summary

Clinicians are in agreement about the primary psychotropic properties of opiate drugs, but the issue of opioid abuse liability and physical dependence has hampered research. Despite this, the psychotropic properties of therapeutic opiates can be investigated indirectly in populations of dual diagnosis heroin abusers. We retrospectively evaluated the clinical files of 114 consecutive heroin addicts admitted for in-patient treatment of manic and/or acute psychotic episodes, in order to assess the relationship between methadone treatment during hospitalization and prescriptions at discharge. Regardless of the reasons for their hospitalization, subjects receiving increasing dosages of methadone were judged to be less in need of antimanic and antipsychotic drugs at discharge. These results support the idea that methadone has quick-acting anti-dysphoric and anti-impulsive properties which apply to a wide range of psychiatric disorders.

Key Words: Methadone - Anti-manic Drugs
Antipsychotic Drugs - Dual Diagnosis

It has long been documented that opiate drugs possess psychotropic properties that go beyond their narcotic effects. In recent years, slow-acting opiate agonists have shown potentially useful effects on mental illness or disturbances, such as anxiety, aggressiveness and dysphoric mood (1,3,9,10,12,13,23,24,26,27). Unfortunately, concerns about the abuse liability of certain street opiates have been extended to include therapeutic opiates, so limiting opportunities to put them to the test as primary psychotropics. A small, not easily interpretable body of knowledge comes from the use of opiate drugs
on morphine and heroin addicts, especially those suffering from autonomous mental diseases. Some findings have been reported about possible antidepressant and mood-stabilizing effects. In addition, indirect evidence has shown that opioids should have antipsychotic and anxiolytic properties. Symmetrically, naltrexone may have primary psychoactive properties in opiate-naive individuals. However, in dual diagnosis addicts, higher methadone dosages provide equivalent stabilization, though only over a longer term. The retention of mentally ill addicts seems to be more soundly based: their stronger therapeutic dependence may be due to a stable medicating effect on mental illness beyond the resolution of addictive symptoms. Severely ill addicts tend to concentrate within agonist treatment programmes, and higher levels of psychopathology correspond to higher dosages, as long as stabilization is the goal. On the other hand, psychotics and subjects suffering from affective disorders have a poor outcome in opiate antagonist programmes, and the rate of suicidal thoughts also tends to be higher among naltrexone-maintained subjects. In treatment programmes targeting dual diagnosis, the general strategy is that of providing patients with addiction treatment and with psychotropics, at the same time. Regrettably, drug addicts are, as a category, poorly compliant; so, even if it is true that a complex therapeutic regimen may provide better results, a dual diagnosis makes it quite unlikely that patients will keep to even a simple one. Addiction treatment is the first step to take in stabilizing dual diagnosis, so the possible psychotropic properties of agonist or antagonist drugs may be resorted to, to allow the level of compliance required to be minimized, while maximizing the product of the number of prescriptions and their therapeutic effectiveness.

The aim of this study has been to verify whether heroin addict inpatients treated with methadone during an acute episode with prominent psychotic, manic or aggressive features had longer periods of hospitalization and more complex therapeutic regimens at discharge, as might logically be expected. The fact of being judged to be in need of agonist drugs should mean impairment on grounds of opiate addiction, too, the outcome being a higher grade of current global severity. Therefore, in manic or psychotic heroin addict inpatients, whether receiving methadone or not, we compared their therapeutic regimens used during the hospitalization period. We also tested their discharge rates.

Material and methods

Sample

The sample consisted of 114 heroin addicts consecutively admitted to two Public Mental Health Inpatient Services (Pisa and Livorno, Tuscany, Italy) at any time during 2002 due to emergency pictures (psychotic, manic or violent episodes). Their clinical files were retrospectively examined in order to gather data about prescriptions and the duration of hospitalization. Mean age was 32.2±6 (range 17-49); 96 (84.2%) were male.

Thirty-six patients (31.58%) were on methadone at the time of admission, at an
average dosage of 57 mg/die (median 30, mode 30, range 6-600).

According to the status of their methadone treatment while hospitalized, heroin addicts were divided into three groups. The first, known as the M0 Group, comprised 62 (54.4%) patients, 53 (85.5%) of them males, with an average age of 31±8 years; these had not been on methadone treatment either at admission or at discharge. The second, M1 Group, included 22 patients (19.3%), 18 (81.8%) of them males, with an average age of 34±6 years; these had had their methadone dosage increased while they were hospitalized. The increase in methadone was as high as 52±32 mg/day (median 45, mode 30). The third, M2 Group, included 30 (26.3%) patients, 25 (83.3%) males, with a mean age of 32±5 years, who continued to receive exactly the same dosage they were on at the time of admission, with no variations throughout the hospitalization period. In no case was methadone tapered during hospitalization.

**Statistical analyses**

The χ2 test was used to compare categorical variables. The ANOVA one-way analysis with a post-hoc Scheffé test was used to compare continuous variables between the three groups. Analyses were performed according to the SPSS statistical routines.

**Results**

Pharmacological prescriptions at discharge are reported in table 1. The duration of hospitalization does not differ between the groups. M1 subjects were less often given a prescription of antipsychotics (p <.03) and anti-manic agents p < .02) at discharge, but no differences were found for the other drug classes.

**Discussion**

Anti-manic agents and antipsychotics were less needed in M1 patients, although these showed the same probability of being agitated, psychotic or manic at the time of hospitalization. The hypothesis of our study does not seem to be supported by these data. Addicts who are given a prescription of methadone do not receive that as a further prescription, in addition to general psychotropics: the number of prescribed drugs is similar and they belong to a similar number of pharmacological classes. Methadone treatment is, in fact, inversely related to the prescription of other commonly used psychotropics (anti-manic and antipsychotic agents); the duration of hospitalization is similar in the two cases. Heroin addicts, who receive higher methadone dosages during the treatment of psychiatric emergencies, are judged to be less in need of antipsychotics and anti-manic agents as a means of post-discharge stabilization.

One might object that the findings are not justified by the handling of methadone treatment during hospitalization. In others words, the presence or absence of methadone at admission may be responsible for our results. Otherwise, the number and typology of prescriptions at discharge does not vary according to methadone presence at admission. It must also be pointed out that average methadone dosage at admission was slightly
lower than the lowest recommended dose (60 mg/day), sharply below the range of effectiveness (80-120 mg/die), and definitely far lower than what can be indicated as useful in treating dual diagnosis heroin addicts (22).

In other words, the psychopathological symptoms displayed by heroin addicts may be challenged either by traditional psychotropics or by methadone, with a similar degree of effectiveness (rated according to the duration of hospitalization), but a different impact on addiction. In fact, patients whose condition is responded to by initiating methadone treatment are discharged with specific treatment for their addictive disease, and are likely to be discharged with their other psychiatric symptoms under control, too. By contrast, addicts receiving standard psychiatric medications are returned to their environment without any protection against craving. The data gathered point to the need for further evaluation of the psychotropic effects of agonist drugs in mentally ill addicts, and also support the indication of higher methadone dosages for dual diagnosis patients from the point of view of cost-effectiveness. The short-term effectiveness already verified may also apply in the long term, by ensuring a degree of prevention of relapses for dual diagnosis addicts, who are usually regarded as being simply mentally ill, and are, therefore, less likely to receive addiction treatment. Our data support the idea that methadone is useful in providing short-term treatment for the psychiatric emergencies of heroin addicts, regardless of longitudinal dual diagnosis. Raising the methadone dosages of heroin addicts hospitalized for psychiatric emergencies seems to reduce their need for anti-manic and antipsychotic drugs, suggesting an anti-dysphoric effect covering a variety of autonomous psychiatric conditions.

Table 1. Days of hospitalization and prescriptions of 114 heroin addicts consecutively hospitalized in a psychiatric ward according to methadone treatment during hospitalization

<table>
<thead>
<tr>
<th></th>
<th>M0 (N=62)</th>
<th>M1 (N=22)</th>
<th>M2 (N=30)</th>
<th>(\chi^2/F)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>40 (64.5)</td>
<td>11 (50.0)</td>
<td>21 (70.0)</td>
<td>2.29</td>
<td>.318</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>37 (59.7)</td>
<td>6 (27.3)</td>
<td>13 (43.3)</td>
<td>7.36</td>
<td>.025</td>
</tr>
<tr>
<td>Anti-manic agents</td>
<td>18 (29.0)</td>
<td>0 (0.0)</td>
<td>8 (26.7)</td>
<td>8.11</td>
<td>.017</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>36 (58.1)</td>
<td>13 (59.1)</td>
<td>21 (70.0)</td>
<td>1.27</td>
<td>.528</td>
</tr>
<tr>
<td>Antihistaminic drugs</td>
<td>16 (25.8)</td>
<td>9 (40.9)</td>
<td>11 (36.7)</td>
<td>2.20</td>
<td>.332</td>
</tr>
<tr>
<td>Anticholinergic drugs</td>
<td>4 (6.5)</td>
<td>0 (0.0)</td>
<td>2 (6.7)</td>
<td>1.51</td>
<td>.468</td>
</tr>
<tr>
<td>N° classes</td>
<td>1.83±1.15</td>
<td>1.52±1.16</td>
<td>2.15±.97</td>
<td>3.12</td>
<td>.800</td>
</tr>
<tr>
<td>N° drugs</td>
<td>2.65±1.37</td>
<td>2.09±1.67</td>
<td>2.46±1.17</td>
<td>1.95</td>
<td>.164</td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>10.08±7.6</td>
<td>14.13±21.8</td>
<td>16.77±28.5</td>
<td>.015</td>
<td>.901</td>
</tr>
</tbody>
</table>

(M0 = methadone-free, no methadone treatment; M1 = increase in methadone dosage, or initiation of methadone; M2 = no change in ongoing methadone dosage).
M. Pacini and I. Maremmani: Methadone reduces the need for antipsychotic and antimanic agents in heroin addicts hospitalized for manic and/or acute psychotic episodes

References


Received November 3, 2004 - Accepted February 8, 2005
Methadone serum concentration  
and its relationship to methadone dose revisited

Lubomir Okruhlica, Jindra Valentova, Ferdinand Devinsky, 
Sona Formakova and Danica Klempova

Summary

The study sample included 64 patients, who were divided into two subgroups on the basis of their daily methadone dose: 'Group 1': 29 patients with doses up to 80 mg; 'Group 2': 35 patients with doses above 80 mg. The overall correlation in the whole group was: $r = 0.570$. A strong correlation was found between dose and serum concentration in 'Group 1': $r = 0.799$. Non-significant correlation close to zero was found in 'Group 2'. Our findings suggest that the linear relationship between methadone dose and its serum concentration in lower doses cannot be extrapolated to higher doses.

Key Words: methadone maintenance - serum methadone concentration - methadone dose - linear relationship

Introduction

By now it is generally agreed that methadone concentration in serum may be significantly correlated with the amount of a drug available at the receptor level. That still leaves open the question whether it is possible to predict the proper daily dose of methadone required to ensure the serum concentration appropriate to a particular patient by utilizing the relationship between a methadone dose and its serum concentration\(^{[17]}\).

A wide variety of researchers have studied the relationship between methadone dose and methadone plasma/serum concentration\(^{[1, 2, 3, 5, 7, 9, 10, 11, 12, 14, 17, 19, 20, 21, 22, 23, 24, 25]}\).
Heroin Addiction and Related Clinical Problems

Some of the studies also provided calculations of correlation coefficients between methadone doses and methadone plasma/serum concentrations, which ranged between weak and strong: Charlier et al. [3]: r = 0.20, (p < 0.05); Nicolaou et al. [15]: r = 0.41; De Vos et al. [4]: r = 0.50; Eap et al. [7]: r = 0.55, (p < 0.01); Wolff et al. [24]: r = 0.82, (p < 0.001). A strong linear correlation was reported by Wolff [24]. Many variables affect the kinetics of methadone. Some of the most pertinent include: compliance with treatment regimen, different pharmacogenetic dispositions of patients, phase of methadone treatment, induction period or steady state, and drug interactions with others. Variability, which may be attributable to the out-patient treatment environment, was eliminated in the studies performed in closed metabolic wards [4]. Still, the correlation coefficient was only slightly above 0.5, so the dose could not explain much more than 25% of the methadone concentration in plasma.

The visual exploration of findings in our previous work [17] and the findings of the others on their scatter plots [2], where relationships between methadone dose and plasma/serum concentration were illustrated, suggested the relationships are different at higher and lower doses of methadone. The hypothesis was that the linear relationship between methadone doses and their serum concentrations differ significantly between the group of patients with lower methadone doses and that with the patients receiving higher doses of methadone.

Patients and Methods

Sample description

The study group consisted of 64 patients who had been stabilized in the methadone maintenance treatment programme (MMTP) for 614.8 days on average (SD ± 192.2, median 592, range 393-1,327) at the Centre for Treatment of Drug Dependencies in Bratislava. There were 52 males (81%) and 12 females (19%). Their average age was 25.8 years (SD ± 5.9; range 19-50). All of them were HIV negative and 46% were positive for HCV antibodies. There was no upper dose limit to their methadone maintenance. None of the patients had a recent history of positive urine screen for morphine. Prior to study entry, the number of days of their take-homes, which were granted on the basis of a past drug-free history of urinalyses, ranged from a minimum of one day at the end of the week to a maximum of 5 days of take-homes per week. In that case, take-homes were divided into two supervised provisions at the out-patient clinic, comprising one group of 2 and a second of 3 consecutive days per week.

Fieldwork Procedures

Subjects were asked to participate in a prospective study, in which they took methadone under supervision at the out-patient clinic every day for 14 consecutive days. Oral racemic methadone was dispensed in orange juice mixture once a day. After 14 days of supervised methadone intake, samples of venous blood were taken from the patients, approximately 24 hours after the previous intake of methadone dose for trough metha-
done serum concentration testing. All subjects had negative urinalyses for morphine at that time. Take-home privileges were renewed at a later stage.

**Serum Sample Analysis**

A quantitative analysis of blood samples using GC/MS methodology was performed in a toxicological laboratory in order to detect trough serum methadone levels.

**Sample preparation for analysis**

To a 0.5ml-aliquot of serum, 0.5 µl of proadifen (internal standard), 1ml of 0.2 M carbonate buffer, pH 10, and 5 ml of n-hexane were added. The extraction was performed in a shaker and lasted 20 min. After centrifugation (10 min, 2800 rpm), the organic layer was transferred into a separate tube and evaporated under a gentle stream of nitrogen at 40°C. The residue was reconstituted in 200µL of methanol. A sample of 1µl was analysed by GC.

**Conditions of GC analysis**

GC analysis was performed on a HP 5890 gas chromatograph with a nitrogen-phosphorus detector, equipped with an HP ULTRA 2 capillary column (12 x 0.2mm I.D., 0.33 µm film thickness of crosslinked 5% phenyl methyl silicone). The injection port (splitless) was set to 220°C. The column temperature had been initially held at 100°C for 1 min; later it was increased to 250°C (18°C/min), then held at 250°C for 2 min, then increased to 300°C at 30°C/min. The carrier gas was helium at 0.6 ml/min.

**Statistical Analyses**

Descriptive statistics (including variance), covariance and Pearson correlation (SPSS statistical software) have been applied in describing the relationship between methadone dose and methadone serum concentration. Data were then analysed with the use of AMOS statistical software. A model for testing variances and covariances equality simultaneously in the two groups allowed us to obtain more precise estimates (see Picture 1).

**Ethical Issues**

Approval was obtained from the Ethical Committee at the Centre for Treatment of Drug Dependencies in Bratislava before the study was started.

![Picture 1. Model for testing variances and covariances equality simultaneously](image-url)
Results

Daily Dose of Methadone and its Concentration in Serum

The average daily dose of methadone was 93.1 mg (SD ± 48.1; median 90 mg; range 10-190 mg). The mean concentration of methadone detected in serum was 338.2 ng/ml (SD ± 211.8); median 295.0 ng/ml; range 41.0 – 1058.0 ng/ml in the sample of all 64 patients.

After visual exploration of the scatter plot (see Figure 1), the sample of 64 patients was divided into two subgroups on the basis of their daily methadone dose: Group 1 — a subgroup of 29 patients who received daily methadone doses up to 80 mg (mean 48.8 mg, SD ± 23.1; median 50 mg; range 10-80 mg); and Group 2 — a subgroup of 35 patients with daily methadone doses above 80 mg (mean 129.7, SD ± 28.1; median 130 mg; range 90-190 mg).

![Graph 1](attachment:image.png)

Figure 1. Relationship between methadone dose and serum concentration
Variance and covariances

The variance of methadone dose was $s^2 = 533.3$ in Group 1, and $s^2 = 788.2$ in Group 2. The methadone serum concentration variance was $s^2 = 9,609.8$ in Group 1, and $s^2 = 47,239.1$ in Group 2. The analysis of the relationship between methadone dose and methadone serum concentration revealed a covariance of 1,809.23 in Group 1, and a covariance of 27.1 in Group 2.

Correlations

The overall Pearson correlation found in the whole group was $r = 0.570$, $p = 0.000$. A very strong and statistically significant correlation was found between methadone dose and methadone serum concentration in Group 1, with $r = 0.799$, $p = 0.000$. In this case, methadone dose was able to account for 64% of its serum levels. On the other hand, the correlation in Group 2 was close to zero and not significant, $r = 0.004$, $p = 0.980$.

Statistical Model

A statistical model was proposed for the simultaneous testing in the present study of all relationships suggested by previous exploratory analysis. It has been supposed that the variance of methadone dose remains the same regardless of dose magnitude. The model assumed that while dose variance remains unchanged, methadone serum level variance might differ in the two groups. As the covariance between methadone dose and its level in serum was, statistically, not significantly different from zero in Group 2 — implying that it could be considered noise — it was set to zero.

Estimates: The model-induced estimate of variance of methadone dose for both groups was 652.030. For Group 1, the covariance between methadone dose and its level in serum was estimated at 2211.970 (S.E = 485.426, C.R = 4.557, $p<0.001$) and the estimated correlation was 0.831. In Group 2, covariance was set to 0, so the correlation was estimated at 0.000. The model had a good fit: Chi-Square = 1.187, df = 2, $p = 0.552$.

Discussion

Several authors [1, 2, 5, 9, 10, 11, 12, 14, 18, 23, 25] have suggested the use of serum levels in optimizing methadone doses for patients in a methadone maintenance treatment. A strong linear relationship between methadone dose and its plasma concentration was suggested by Wolff [24] in the early Nineties. However, Leavitt et al. [13] stated that, even if a strong correlation between methadone dose and concentration in serum has been found, the relationship may not be linear.

When reviewing the literature on the relationship between methadone doses and methadone concentrations in serum or plasma, one should be aware of many interfering and, probably, very important differences between the studies based on different sample characteristics, such as ceilings for a maximum daily dose of methadone in different MMTPs, inclusion of non-stabilized patients in studies, different take-home regimens, and so on. These are only some of the external or environmental factors that may influ-
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ence the methadone dose - serum relationship. Other variables which could play a role, such as intake of some medications during MMTP, or eating habits. The importance of these factors has been exemplified by Nicolaou’s study \[^{15}\], where correlation was poor at the beginning: $r = 0.37$, but improved when non-compliers were excluded: $r = 0.41$, and was even stronger after the exclusion of outliers: $r = 0.66$.

The present study has attempted to minimize external interfering influences caused by possible behavioural irregularities and possibly incomplete compliance of patients with the treatment regimen, as far as possible in the out-patient conditions of the MMTP. The detected overall correlation of racemic methadone dose and its serum concentration was similar to those found by some other authors \[^{4,7,15}\]. Despite strictly supervised methadone dispensing under experimental conditions, the correlation coefficient found in the whole sample in the present study was lower than those found by Loimer \[^{14}\] or Wolff \[^{24}\].

One hypothetical explanation for this is that it could be due to different frequency distributions of daily methadone doses of the subjects in the studies. While previous studies were based on data from MMTPs with more conservative dosing policies, the daily dose ceiling usually being around 100 mg and, therefore, with lower average doses than those used in more recent studies, where the upper dose limit was left open, and maximum doses ranged up to 200 mg of methadone and above, with higher average daily doses of methadone in the samples.

It is probably no coincidence that, against the background of the wide variability of the findings reported in the literature, our overall correlation ($r = 0.57$) was practically identical with the correlation ($r = 0.55$) for racemic methadone found by Eap \[^{7}\] for racemic methadone in his study under similar MMTP conditions and sample characteristics (sample size, age and gender of the patients, average dose, dose range).

The small covariance of data distribution is evident on the right side of the scatter-plot (Figure 1), which shows the relationship between higher methadone doses and their serum concentrations. This can also be seen on the scatter-plots presented by some other authors \[^{2}\]. The resulting correlation coefficients in the sub-samples of patients (Group 1: $r = 0.799$; Group 2: $r = 0.004$) are in accordance with the hypothesis of the present study. The underlying cause of the phenomenon of heteroschedasticity should be a topic of future research.

Our study has not been concerned with other internal biological variables, such as body weight. A determination of phenotypes and/or genotypes of proteins such as cytochromes P450s, offers another valuable route to an understanding of methadone pharmacokinetics. What is more, the excretion of methadone via kidneys is pH-dependent \[^{16}\] and methadone clearance was positively associated with haematocrit in Plummer’s study \[^{19}\]. We did not, however, carry out checks on these variables in our study.

Due to the fact that racemic (R,S)-methadone consists of two enantiomers with different pharmacokinetic characteristics, of which (R)-methadone alone accounts for the majority, if not all of the opioid effects of racemic (R,S)-methadone \[^{8}\]. This must be taken into account when looking at the correlation between methadone doses and its
plasma concentrations. In Eap’s study [7], a correlation coefficient of \( r = 0.55 \) was found for racemic (R,S)-methadone, but only \( r = 0.34 \) for (S)-methadone; the correlation was as high as \( r = 0.69 \) for (R)-methadone. As there is marked interindividual variability in the R/S ratios of methadone in blood [6], further research could be oriented in this direction, too. One possible factor determining a weak correlation of methadone dose with serum concentration at higher doses may be differences in the pharmacokinetic action and elimination of (R)- and (S)-methadone enantiomers.

Our findings suggest that a linear model for the relationship between racemic methadone dose and methadone serum concentration can probably not be extrapolated to daily doses of methadone above 80 mg.

**Conclusions**

A linear relationship between methadone dose and its serum concentration was only found among patients taking lower methadone doses (up to 80 mg, in our study). Zero correlation was demonstrated for those with higher daily doses of the medication. A dose of racemic methadone is a good predictor of its serum blood levels at lower doses, but this does not hold with higher doses of methadone. The reason for this lies beyond the scope of this study and calls for further research.

**Acknowledgements**

We wish to acknowledge the support of the Protidrogovy Fund, which awarded us a grant, so allowing this research to be carried out. This project was also supported by the Ministry of Education of the Slovak Republic, via grant No. VEGA 1/1198/04.

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Received December 8, 2004 - Accepted August 25, 2005
Medical and social factors determining early poly-drug dependence

Tamara V. Chernobrovkina 1,2 and Igor A. Nikiforov 1

Summary

Adolescent narcotism has grown into an epidemic in Russia. Younger drug experimenters seem to run a higher risk of habitual involvement in drug use as a lifestyle, which also makes them liable to develop addictive diseases through enduring exposure to drugs. Moreover, polyabuse seems to be the rule among younger addicts, which increases the likelihood that physicians will have to deal with multiple addictive pictures, destined to a poor outcome and pervasive disruption. Upbringing, environmental ties and opportunities, economic status and family-related lifestyle may play a crucial role in supporting or discouraging a sensation-seeking lifestyle, although personality factors come first in establishing a risk disposition. In any case, on preventive grounds, the identification of stereotypes in drug user populations may offer a helpful means of impeding or reversing the transition from experimental drug use to habitual drug use and then addiction. The administration of a 20-item psychosocial questionnaire to a sample of 150 subjects aged between 7 and 18 helped us to ascertain the prevalence of social problems and drug use trends in a younger risk population. The handling of pleasure-seeking drives and needs by environmental facilities may reduce youngsters’ interest in substance use and provide them with other kinds of practical, spiritual and pleasurable habits.

Key Words: Narcotic abuse - Polyabuse - Adolescents psychosocial factors

Abuse of drugs with a narcotic effect (DNA) is a serious problem with an impact on the morals and health of the nation. Adolescents’ drug dependence is a special cause for concern. Every year sees a growing number of research studies on the problem, but the combination of DNA use with poly-drug dependence in children and adolescents has not yet become the subject of thorough scientific investigation. Even so, the everyday routine of medical centres in Russia dealing with young drug addicts shows that the combined abuse of DNAs is becoming frequent in adolescents as a result of a cluster of social and economic factors.

Address for reprints: Dr. I.A. Nikiforov Institute of Post-Graduate Education, "Medbioextrem" Federal Board of the Russian Health Ministry, Moscow. E-mail: nikiforov@3psy.com
In order to study the social and economic factors contributing to the development of a polydrug dependence early in life, a questionnaire has been drawn up comprising 20 questions. Its aim is to investigate the cultural, environmental, family and living conditions of young addicts abusing various DNAs, and evaluate the impact of hereditary mental-somatic disorders on the frequency of adolescents’ deviant behaviour and on their sphere of interests.

The questionnaires were filled in by 150 males aged between 7 and 18 (average 15.7 years). Of these 150 questionnaires, one hundred, filled in by males aged between 9 and 17 and dated 1994-1998, were selected using the total sampling method. Anamnestic, psychopathological and laboratory data were attached to the filled in questionnaires. The statistical treatment and medico-sociological analysis of the material obtained revealed interesting regularities.

For example, less than half of the group (43%) grew up in full families. The parents’ position, in terms of education, occupation, and financial and social status, appeared to be rather unfavourable; as a rule they had only a secondary education and were employed as factory or office workers. These families could be called inharmonious and destructogenic (1).

More than a half of the group (57%) grew up in incomplete families (with only one parent), incomplete-extended families containing direct or indirect relatives (including families which substituted the parents), and deformed (with stepfather or stepmother), or extended-deformed (with stepfather and direct or indirect relatives) families. A majority of these cases (39% of the total sample) were brought up in incomplete families, where the mother or grandmother was the only breadwinner and mentor. Very often the children in these families grew up under hypoprotection, which took the form of a lack of supervision. Still more often the children grew up with a lack of care and control; their problems and interests received little attention. In their inner life the adolescents appeared to be left to themselves; they were given no opportunities to develop their abilities or satisfy their spiritual needs.

Some of the adolescents were brought up under latent hypoprotection (1); in these cases control over the child’s life and behaviour seemed to be exercised, but it bore the marks of extreme formalism and was often combined with a concealed emotional rejection. These subjects learned quite quickly how to avoid control and lead their own life; they often joined asocial groups, and found it easy to adopt an idle way of life full of amusement and adventure.

In 7% of the group, the adolescents lived in deformed families with a mother and stepfather, where they experienced tough relationships, often including emotional rejection.

In incomplete families where the father was the only parent (5%), the upbringing combined hypoprotection and increased moral responsibility (“You are a grown-up now and must take care of yourself”).

Some of the adolescents (5%) lived in incomplete-extended families where grandparents or elder sisters took the role of the parents. In some cases the upbringing in
these families combined indulgent hyperprotection and a discrepancy over views on education (in those with grandfathers and grandmothers), while in other cases it was characterized by hypocare (in those with elder sisters, who, due to the absence of the parents, were supposed to assume full responsibility for their younger brothers, a condition they were not prepared to accept).

Lastly, 1% of the group grew up in extended-deformed families, where conflicting methods of education prevailed.

All grown-ups in these families stuck to different educational rules; for example the stepfather exercised a dominating hyperprotection, while the mother or grandmother remained indulgently hyperprotective. As a rule, the living conditions in these families were inadequate. They lived in small or communal flats where the children didn’t have a room of their own, sometimes not even a table. Their early childhood was embittered by numerous frustrations caused by poverty and by refusals to satisfy their needs in terms of the toys, books, clothes and shoes which they wanted. Those frustrations were the outcomes of poor nutrition and lack of pocket money.

The investigation also disclosed a high degree of genetic loading in most of the subjects: various diseases totalling 89.3% affected them (see figure 1).

![Figure 1. Genetic loading](image)

An inheritance of alcoholism was revealed in 70% subjects. Its types are shown in Figure 2.

As can be seen from the diagram, of the adolescents examined who have a burdensome inheritance, those whose anamnesis includes their father’s alcoholism are predominant (69.3%). Second place is taken by those with other relatives’ alcoholism (16.3%), this being alcoholism of grandfathers, elder brothers and sisters. Alcoholism in both parents was found in 10.4% of all cases. Mother’s alcoholism was the least frequent (4%).

Most of these adolescents (84.5%) had an incomplete secondary education. Of these, just 55% continued schooling: 36% at secondary schools, 14% at vocational schools,
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and 4% at boarding schools. 16% of these subjects, generally belonging to the group that had had a complete secondary education, had a job; in some cases the jobs were regular, but in most cases they were temporary. Almost a third of the subjects (29%) left school without getting a diploma; they had neither worked nor studied during the previous 1-3 years.

Due to their deviant behaviour, such as drinking alcoholic beverages in public or secretly (for example, in basements of houses), leaving home, group abuse of DNAs, fights, and committing crimes, 60% of these subjects appeared in police files and 32% had taken part in criminal acts.

An absolute majority of these subjects (95.7%), irrespective of their age, were aware of DNAs, various psychoactive substances (PAS) and psychotropic drugs. Older adolescents wrote in the questionnaires that they “knew all narcotic drugs”.

Combined DNA abuse appears to be a distinctive characteristic of these subjects, simultaneous abuse of two or more PASes being very rare. PASes were mostly taken in order to intensify the effect of the “main drug”; for example, hallucinogenic drugs intensify the effect of alcohol, while alcohol boosts the effects of cannabinoids. In most cases the adolescents took various DNAs separately, though it was typical of this group to systematically take more than one DNA. At the same time they occasionally experimented with other types of PAS, both to experience a new psychedelic effect and to heighten the activity of the “main” DNA.

Only 53% of these subjects admitted DNA dependence and expressed a wish to undergo treatment; 38% denied any drug dependence and 9% expressed doubts. A large number of those who were planning to take treatment used volatile solvents; some of them wanted to be treated for “tobacco only”. The rest either denied any dependence or said “I’ll manage by myself”.

The clinical-dynamic and psychopathological analyses revealed similar personality alterations in the subjects with DNA abuse combined with poly-drug dependence:

1. Egoism, indifference and cruelty towards their relatives, with a tendency to live at the expense of other people, to manipulate them in order to get as much
money from them as possible;
2. Light-mindedness, capriciousness, variability of intentions, inconsistency of thoughts and actions, irresponsibility, undue familiarity, idleness, absence of self-criticism and self-control, inability to keep a personal distance while communicating with other people, untidiness, low stress resistance;
3. Highly pronounced affective instability and quick polarization of affect, fits of anger mixed with hatred and hostility towards his/her associates and relatives, vanity, demonstrative self-confidence, recusancy, inclination to hysterical-like reactions;
4. Diffidence, anxiety, fear for the future, a keen feeling of dependence on his/her relatives, fear of suicide.

In summarizing the results of the investigation, we can distinguish a number of medico-social factors contributing to the problems of adolescents who combined poly-drug and substance abuse. These factors can be taken as basic distinctive features of the “risk group” who have a high probability of developing an early poly-drug and substance dependence. These factors are:
1. Upbringing in an incomplete, disharmonious, deformed, malfunctioning family;
2. Inadequate upbringing methods in the family: hypocare, indulgent hyperprotection, emotional rejection, severe relationships in the family, discrepant approaches;
3. Unfavourable and adverse domestic conditions, such as living in a small flat, without a personal room, corner or table, low financial and social status of the family, insufficient nutrition;
4. A high degree of alcoholic inheritance, most often due to alcoholism in the father;
5. An incomplete secondary education, shirking school, poor progress at school, early broken contacts with pedagogues;
6. Connection with antisocial adolescent groups of the same or older age, where deviant and delinquent behaviour “blossoms” and PAS abuse is widely spread, which results in rapid social decompensation;
7. Awareness in early age about PASes or DNAs and their psychedelic effects;
8. Taking alcohol in intoxicant doses at an age under 14 years;
9. An early (under the age of 14) start of occasional abuse of PASes, mostly cannabinoids, volatile solvents, sedative and somnolent drugs and their combination with alcohol, and also the combined use of cannabinoids and opiates;
10. An early (under the age of 14) start of systematic tobacco smoking in doses of more than 10 cigarettes a day;
11. Anosognosia about developing PAS dependence;
12. Mental organic disorders such as residual-organic cerebral deficiency of a traumatic or toxic origin, retarded mental development and mental deficiency.
of various degrees;
13. Early manifestation of somatic disorders caused by combined PAS and drug abuse, such as dysfunctioning liver, pancreas, urinary tracts, adrenal glands and cardiomyopathy, immune deficiency and allergic reactions;
14. Non-involvement in group leisure pastimes, especially sports activities.

Taking into consideration the biological and social role of the younger generations, it is easy to foresee the adverse medico-social consequences of adolescents’ poly-drug dependence. That is why it is extremely important to take preventive steps against it and organize effective treatment for drug dependent adolescents. On one hand, we should consider the above-mentioned medico-social factors that cause the early development of poly-drug and substance dependence, and, on the other, work out an adequate medico-social rehabilitation system for young addicts.

Young addicts’ rehabilitation can be defined (2) as a set of pedagogical, psychological, educational, medical, social, juridical, training and other measures directed at preventing them from using psychoactive drugs and substances, developing their personalities and convincing them to reject drugs, together with their resocialization and reintegration in society.

From our point of view, the main rehabilitation principles for adolescents with early poly-drug and substance dependence should be the following:
* voluntary, intentional and active participation in rehabilitation programmes;
* motivation to entirely reject all PASes;
* anonymity and strict confidence;
* a complex approach towards patients and their treatment through the joint efforts of various specialists (psychologists and psychiatrists, pedagogues, lawyers, priest, and soon);
* a stage by stage rehabilitation process: for example, arranging for an initial stage (adaptation to the programme), a full-scale and a final stage;
* encouragement and approval of spiritual growth together with moral support;
* promotion of taking responsibility for decision-making and a planned course of action, removal of hyperprotection;
* involvement in the rehabilitation process of all those concerned (the family and the microsocial environment);
* formation of a new, positive, healthy way of life and adoption of socially acceptable forms of behaviour;
* long-term supervision after release from the rehabilitation centre, with the purpose of prolonging the therapeutic remission and preventing relapses.

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Received March 14, 2005 - Accepted February 14, 2005
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