Heroin Addiction and Related Clinical Problems

the official journal of

Europad
European Opiate Addiction Treatment Association

ISSN 1592-1638

Vol. 9 • N. 2 • June 2007
EUROPAD
EUROPEAN OPIATE ADDICTION TREATMENT ASSOCIATION

EUROPAD formerly EUMA was founded in Geneva (Switzerland) on September 26, 1994. It shall remain independent of political parties and of any government.

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.

BOARD OF DIRECTORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>City, Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icro Maremmani</td>
<td>President</td>
<td>Pisa, Italy</td>
</tr>
<tr>
<td>Marc Reisinger</td>
<td>Vice-President</td>
<td>Brussels, Belgium</td>
</tr>
<tr>
<td>Alessandro Tagliamonte</td>
<td>General Secretary</td>
<td>Sienne, Italy</td>
</tr>
<tr>
<td>Rainer Schmid</td>
<td></td>
<td>Vienna, Austria</td>
</tr>
<tr>
<td>Gabriele Fischer</td>
<td></td>
<td>Vienna, Austria</td>
</tr>
<tr>
<td>Nermana Mehic-Basara</td>
<td></td>
<td>Sarajevo, Bosnia and Herzegovina</td>
</tr>
<tr>
<td>Alexander Kantchelov</td>
<td></td>
<td>Sofia, Bulgaria</td>
</tr>
<tr>
<td>Ante Ivancic</td>
<td></td>
<td>Porec, Croatia</td>
</tr>
<tr>
<td>Didier Touzeau</td>
<td></td>
<td>Paris, France</td>
</tr>
<tr>
<td>Marc Auriacombe</td>
<td></td>
<td>Bordeaux, France</td>
</tr>
<tr>
<td>Michael Krausz</td>
<td></td>
<td>Hamburg, Germany</td>
</tr>
<tr>
<td>Paul Quigley</td>
<td></td>
<td>Dublin, Ireland</td>
</tr>
<tr>
<td>Matteo Pacini</td>
<td></td>
<td>Pisa, Italy</td>
</tr>
<tr>
<td>Pier Paolo Pani</td>
<td></td>
<td>Cagliari, Italy</td>
</tr>
<tr>
<td>Michael Arieli</td>
<td></td>
<td>Jerusalem, Israel</td>
</tr>
<tr>
<td>Haim Mell</td>
<td></td>
<td>Jerusalem, Israel</td>
</tr>
<tr>
<td>Emilis Subata</td>
<td></td>
<td>Vilnius, Lithuania</td>
</tr>
<tr>
<td>Helge Waal</td>
<td></td>
<td>Oslo, Norway</td>
</tr>
<tr>
<td>Luis Patricio</td>
<td></td>
<td>Lisboa, Portugal</td>
</tr>
<tr>
<td>Wojciech Rudalski</td>
<td></td>
<td>Warszawa, Poland</td>
</tr>
<tr>
<td>Karina Stainbarth-Chmielewska</td>
<td></td>
<td>Warszawa, Poland</td>
</tr>
<tr>
<td>Sergey Koren</td>
<td></td>
<td>Moscow, Russia</td>
</tr>
<tr>
<td>Alexander Kozlov</td>
<td></td>
<td>Moscow, Russia</td>
</tr>
<tr>
<td>Nikola Vuckovic</td>
<td></td>
<td>Novi Sad, Serbia</td>
</tr>
<tr>
<td>Marta Torrens</td>
<td></td>
<td>Barcelona, Spain</td>
</tr>
<tr>
<td>Mercedes Lovrecic</td>
<td></td>
<td>Ljubljana, Slovenia</td>
</tr>
<tr>
<td>Andrej Kastelic</td>
<td></td>
<td>Ljubljana, Slovenia</td>
</tr>
<tr>
<td>Lubomir Okrulhica</td>
<td></td>
<td>Bratislava, Slovak Republic</td>
</tr>
<tr>
<td>Olof Blix</td>
<td></td>
<td>Jonkoping, Sweden</td>
</tr>
<tr>
<td>Jean Jacques Deglon</td>
<td></td>
<td>Geneve, Switzerland</td>
</tr>
<tr>
<td>Peter Vossenberg</td>
<td></td>
<td>Deventer, The Netherlands</td>
</tr>
<tr>
<td>Sergiy Dvoryak</td>
<td></td>
<td>Kiev, Ukraine</td>
</tr>
<tr>
<td>Michael Farrell</td>
<td></td>
<td>London, United Kingdom</td>
</tr>
<tr>
<td>Colin Brewer</td>
<td></td>
<td>London, United Kingdom</td>
</tr>
</tbody>
</table>

www.europad.org
CONTENTS

Can Heroin Maintenance Treatment Be Called a Therapy? 5-10
Gian Paolo Guelfi, Mauro Cibin, Pier Paolo Pani and Icro Maremmani
For the Board of Directors of Italian Society of Addiction Medicine

Buprenorphine for Dual Dependency: Cocaine, Alcohol and Opiates. 11-16
Tracie Gardner and Thomas Kosten

Brain Disintegration in Heroin Addicts: The Natural Course of the Disease and the Effects of Methadone Treatment 17-26
Anna G. Polunina, Dmitry M. Davydov, and Alexander A. Kozlov

Voucher-Based Reinforcement Therapy for Drug-Dependent Pregnant Women 27-38
Sarah H. Heil and Teresa J. Linares Scott

Pharmacokinetic and Pharmacogenetic Factors Influencing Methadone Plasma Levels 39-46
Séverine Crettol and Chin B. Eap

Providing Comprehensive Treatment in Medication Assisted Opioid Treatment: The Development of Needs Based Treatment at a Medical School Sponsored Program 47-54
Ira J. Marion and Dorrie Burke

Dihydrocodeine Treatment of Alcohol Addicts with Previous Opiate Addiction — Case Reports 55-64
Albrecht Ulmer, Marcus Mueller and Bernard Frietsch
Medicina delle Tossicodipendenze
ITALIAN JOURNAL OF THE ADDICTIONS
Organo ufficiale della Società Italiana Tossicodipendenze

Comitato Scientifico:
Vittorio Andreoli
Antonio Angelas
Umberto Anesi
Giovanfio Baggio
Giovanni Battista Camano
Paolo Castrogiovanni
Pietro Corsi
Gianfranco Di Chiara
David S. Fornara
Walter Fratta
Luigi Gallambari
Enzo Gori
Gian Paolo Guadelli
Pier Francesco Manzoni
Ioto Marzumani
Alberto Oliverio
Eugenio Patelli
Zoani Rossetti
Emilio Stresi
Alessandro Tagliamonte
Enrico Tempesia

Società Italiana Tossico Dipendenze

Presidente
Pier Paolo Pati

Segretario
Ioto Marzumani

Tesorere
Augusto Consoli

Consiglieri
Augusto Consoli
Massimo Davoli
Gianfranco Di Chiara
Andrea Negri
Giuseppe Grega
Paolo Forte
Enrico Socera
Luigi Scalchi
Manuela Tegi
Andrea Versmessen
Can Heroin Maintenance Treatment Be Called a Therapy?

Gian Paolo Guelfi, Mauro Cibin, Pier Paolo Pani and Icro Maremmani for the Board of Directors of Italian Society of Addiction Medicine

Summary

Heroin administration may be reasonably accounted for in order to handle the cases of patients who proved refractory to methadone, despite repeated attempts and the employment of enhancement techniques to favour retention and rehabilitative processes. In most countries this is not the case, since standard effective treatments are often neglected or applied with unjustified limitations resulting in hampered effectiveness. As a consequence, effective treatment is far from being actually available to all those who apply for it, let alone those who may benefit from it. The first step to empower the addiction care system is to spread and enhance resources to grant patients with correct and powerful application of effective techniques, methadone/buprenorphine maintenance being regarded as the gold and first-line standard for the average addict. If that will ever be the case, as we hope, we would need to provide patients identified as refractory with a salvage option, along the concept of harm reduction. In any other context, the introduction of heroin administration programs would rather reduce the benefit than the harm.

Key Words: Heroin Maintenance - Heroin Addiction Treatment

Proposals to initiate controlled heroin administration by public services for the emergency management of opiate addiction go back many years, and they become a topic matter of debate from time to time. The Italian Society of Addiction Medicine has now decided to issue an official statement on this question.

As a rule, proposals to employ heroin as means of treatment gather strength on the...
crest of a new wave of hope in some ill-defined healing miracle against the plague of drug addiction. The current line of thought is that legalized, or — to express this idea more correctly — controlled heroin administration may offer a complete solution to the problem of how to take control of accelerating emergencies (such as drug-related crime) or how to prevent the collapse of the system, both in terms of the burden that is being placed on the legal system and in terms of prison overcrowding.

First of all, the issue of the legalization of heroin is a different one from that of its controlled administration, and should be discussed separately and on different grounds. On this basis, the present paper is intended to provide a statement exclusively directed to the second question. As to the former, there would be little point in discussing it here, as it is obvious that, on one hand, making a substance legal raises the probabilities of toxic consequences — a consideration that applies to the widespread phenomenon of alcohol-related driving accidents, and to the frequency of alcohol — and smoke-related illnesses and causes of death. On the other hand, it is predictable that any prohibited substance, as it offers a pleasant experience, will attract the interest of the black market, where its commercial value will be enhanced by prohibition, so that criminal organizations and their affiliates will be made richer by illegal smuggling and selling, and this will develop into a major threat to social stability. The main point to be made is that we cannot believe that anyone aware of heroin’s powerful conditioning properties would knowingly make it available to the whole population as a kind of joyride without placing any restrictions on its use. Also, our aim is not to discuss the establishment of such facilities as shooting rooms or syringe distribution, which proved to reduce drug-related problems without favouring drug consumption, but also without implying controlled heroin administration.

The ISAD/SITD, consistently with its funding aim at supporting the adherence of addiction treatment to scientific knowledge, is committed to promoting enrolment in addiction treatment, to avoiding the consequences of addictive heroin use that are the hardest to treat, to improving the health of addicts and their quality of life, and, whenever possible, to providing addicts with long-term disease control by a specific treatment programme, in answer to their request for help and as a positive response to their motivation and willingness to comply.

Some therapeutic instruments have been shown to be effective in achieving these purposes, when administered alone or in combination with one or more other instruments, either in a single course of treatment or with the resumption of treatment, while choosing between a range of treatment programmes of varying length. Data from the literature make it possible to assess, even if to a limited degree, which category of patients to direct to which treatment options, and what degree of effectiveness is made available by each type of treatment to the average heroin addict.

The most important lesson we have learned so far is that the validity of any new treatment option is conditioned by the likelihood that the addict will comply with it in the longer-term; the technical name of this key criterion is ‘retention in treatment’.

Therapeutic communities appear to fulfil a variety of functions, but in the medium-
term only a minority of participants is retained, while most participants leave the programme earlier than planned, and a substantial number of completers experience relapse after discharge.

Similar objections could be made about antagonist (naltrexone) maintenance, which is safe and effective for those who are currently in treatment, but is only tolerated by a small minority of addicted patients. Moreover, patients need to undergo preliminary detoxification in order to become suitable for naltrexone maintenance, so that dropouts find themselves exposed to a heightened risk of overdose when they relapse into heroin use, due to their loss of tolerance to opiates.

Methadone maintenance, which is often incorrectly described as substitution treatment, is the best known treatment option in countering opiate addiction. Research has demonstrated that methadone maintenance is effective in achieving the following objectives: reduction or extinction of heroin use; sharp reductions in cases of mortality due to overdosing; lower rates of HIV seroconversion and other common infective diseases related to intravenous drug use; the reduction or extinction of drug-related street crime. Patients on methadone maintenance are suitable for any working activity and are able to drive, since no significant neuropsychological abnormality has been reported.

All in, methadone treatment can be expected to normalize behavioural and cerebral parameters and restore subjects’ normal pattern of functioning, so enabling them to survive, to maintain an acceptable state of health, and to sharply improve their quality of life, which may become inversely correlated with their level of tolerance to opiates; this is true even of subjects who would be unsuitable to qualify for detoxification procedures.

The above objectives are achievable, as long as treatment programmes are actually made accessible to local patients, and as long as treatment is provided at an early stage in the history of addiction, while respecting the criteria for effectiveness, with special regard to the three following features.

The first key factor is dosage, which must be sufficient to allow control over the drive towards heroin use and the urge to experience a high by taking heroin. The desire for heroin, when it is overwhelming and irresistible, is technically known as craving. Craving for heroin is suppressed by stable methadone administration at dosages as high as 80-100 mg/day, on average. Lower dosages do at least block or hamper the effects of self-administered heroin doses, but they are usually ineffective in suppressing the craving for heroin. Minimum dosages, even lower, can do no more than provide limited control over withdrawal symptoms. Thus, methadone maintenance can be expected to be effective only at dosages of at least 80-120 mg/day, which can be referred to as the ‘average effective dose’.

The second key feature is the use of a combination of medical treatment with an ensemble of non-medical intervention, which, as a whole, can be referred to as ‘psychosocial intervention’. Controlled studies have shown that if methadone treatment alone is effective, then that effectiveness will be heightened when medical treatment is combined with psychosocial intervention. The increase of effectiveness is proportional
Heroin Addiction and Related Clinical Problems

to the weight of the added intervention.

The third key is treatment chronology: treatment should be undertaken early in the course of the disease, as soon as the patient applies for it; this factor is often neglected, due either to lack of knowledge or a lack of personnel and resources. In this latter case, the delay in providing treatment results in waiting lists, which place an upper limit on the quality of health care for drug addiction. Treatment programmes should be continued for as long as necessary, which typically means some years, since the term ‘addiction’ refers to chronic disorders that are inevitably liable to relapses.

In Italy methadone treatment is far from being widely accessible, despite the fact that the law requires it to be systematically available; in some areas it is just not provided due to local policies, and in others it is not available to all who apply for it. In most areas, the information provided to patients is so poor and incorrect that only a few of them have any precise idea of what benefits methadone treatment could bring to them. This makes it unlikely that the average Italian addict will ever ask for methadone treatment rather than some unspecified, or only vaguely specified, detoxification procedure or a generic type of support. In many cases methadone is administered at ineffective dosages; in fact, inadequate dosage is the most frequent single reason for treatment failure. In some areas, local health authorities aim to set an official, not-to-be-exceed dose threshold corresponding to values far below the effective dose ranges we have mentioned above.

The cultural background underlying this situation is the long-standing body of prejudice against methadone, which is regarded as some absurd “legal narcotic” appealing to drug addicts, or as the reason why addiction becomes chronic, or as a way to surrender to addiction without ever achieving any true cure. Beyond that, there is the denial of the idea of drug addiction as a metabolic disorder with its own core neurobiological dynamic.

On all these grounds, the first priority in the field of drug addiction treatment in Italy is the spread of methadone treatment, in terms of its accessibility and correct application. Increasing the accessibility of methadone treatment also means providing information to potential applicants for treatment who would otherwise be unaware of the expected benefits to their health and social status. We estimate that the addicts who remain without treatment because they are unaware of the therapeutic options or because of mere misinformation are at least as numerous as those who are currently in treatment.

Methadone is a chemical compound which is easily available for administration to large populations of patients and it is rapidly effective. Thereafter, all those who wave emergency flags and call for a quick fix solution should consider that the true solution, methadone, has long been available for application — the true being that resorting to heroin is not only unnecessary, but also pointless, because it is generally ineffective.

The proposal to allow controlled heroin administration must immediately raise major objections.

Firstly, evidence provided by double blind controlled trials (the only acceptable
design for determining the superiority of any therapeutic option over any other) is hard to find.

From 1926, heroin administration to heroin addicts has been practised in Great Britain. It first started as the prerogative of any physician, and was restricted after the 1960s to psychiatrists with experience in the treatment of heroin addicts. The debate about its usefulness and ethical acceptability has never stopped. Nowadays, heroin treatment is a neglected option, and some judge it may have played a role in the rising incidence of heroin addiction in Britain during the 1960s, which was the official reason for greater caution afterwards. The Swiss experience is more recent, and, by contrast with the British situation, heroin administration was introduced as an option against addiction in a context where methadone treatment was actually accessible and correctly applied, as it was available to all potential patients. In Switzerland, methadone treatment remained the standard option for heroin addiction treatment, due to its unequalled effectiveness. The Swiss experiment involved about one thousand addicts chosen from those who were not eligible for standard treatment or had failed to improve while on methadone treatment. The one basic reason for providing heroin treatment to addicted patients, as the scientist mainly responsible for that decision stated in his concluding report, was that other effective treatments were widely available to those same patients. In other words, heroin administration can only be scientifically justified in the case of resistant methadone dropouts or untreatable street addicts. Otherwise, it is inadvisable to render heroin administration programmes accessible to patients whose cases have not already been put to the test and challenged by standard or psychosocially enhanced methadone treatment. A new policy of making heroin administration general available in Italy would bring about a shift in the status of potential methadone responders, who are currently able to adopt a scientifically funded rehabilitative perspective, by providing the lure of a kind of treatment which cannot be expected to provide addiction control, and whose best justification is that it might offer a way of reducing harm for untreatable patients.

In a context where methadone treatment faces hostility from the cultural background, just such a waste of therapeutic potential is quite likely to take place.

The Swiss design featured the possibility that patients could receive up to three heroin doses a day, as long as these were self-administered at the centre. However, precautions like these fail to rule out the possibility that patients may have resorted to the black market to purchase further heroin in order to exceed their tolerance level and reproduce the ‘highs’ they desired. In order to prevent such phenomena, most patients had methadone administered to them, too; this fact should act as a reminder of the difference between methadone and heroin in making any form of behavioural control an achievable aim.

The debate about heroin programs turns the spotlight away from the actual limits of the Italian system, where the inadequate provision of treatment and the poor adherence of medical practice to current scientific knowledge are the key problems.

The latest Danish experience has just confirmed the harm-reducing effectiveness of
Heroin Addiction and Related Clinical Problems

controlled heroin administration, but evidence emerged against the hypothesis that it might be made accessible as a side option to already existing methadone programmes. In fact, retention in treatment is undoubtedly greater in methadone maintenance programmes, so that heroin administration, even when controlled, does not seem to allow with behavioural stabilization, of the kind that can be expected from methadone treatment.

Conclusion

Heroin administration may be reasonably taken into account as one way of handling the cases of patients who have proved refractory to methadone treatment, despite repeated attempts and the employment of enhancement techniques to favour retention and rehabilitative processes.

It must be pointed out that in most countries such attempts are simply omitted, since standard effective treatments are often discarded, overlooked, or only applied with unjustified limitations that result in impaired effectiveness. As a consequence, effective treatment is far from being really available to all those who apply for it, let alone all those who may benefit from it. The first step to empower the addiction care system is that of spreading and enhancing resources so as grant patients access to the correct and powerful application of effective techniques, bearing in mind that methadone/buprenorphine maintenance is viewed as the gold standard and the front-line resource for the average addict. If this perspective can ever be implemented, as we wish, we would need to provide patients identified as refractory with a fail-safe salvage option, in accordance with the concept of harm reduction. In any other context, the introduction of heroin administration programmes would have the outcome of reducing the benefits rather than the harm.

Mauro Cibin (Dolo, Venezia), Augusto Consoli (Torino), Marina Davoli (Roma), Gaetano Deruvo (Bari), Gaetano di Chiara (Cagliari), Andrea Flego (Pordenone), Gilberto Gerra (Parma), Gian Paolo Guelfi (Genova), Paolo Jarre (Torino), Icro Maremmani (Pisa), Roberto Mollica (Milano), Enrico Nocera (Bari), Matteo Pacini (Pisa), Pier Paolo Pani (Cagliari), Luigi Stella (Napoli), Manuela Trogu (Cagliari), Andrea Vendramin (Padova).

Received and Accepted March 19, 2007
Buprenorphine for Dual Dependency: Cocaine, Alcohol and Opiates

Tracie Gardner¹ and Thomas Kosten²

Summary

Dual-drug dependency is common in Europe and America and represents a complex management and treatment challenge. Most heroin addicts abuse stimulants or alcohol in addition to opiates. Cocaine pharmacotherapy remains a challenge, but there has been some success with Buprenorphine, Disulfiram, Modafinil and GABA agonists. A promising cocaine vaccine is also under development. Triple-dependency with alcohol or benzodiazepines is also common and can lead to serious dependence requiring detoxification. In addition to regular monitoring following alcohol detoxification, relapse prevention pharmacotherapy is essential. The following review will briefly describe concurrent-drug abuse with cocaine and opiates as well as describe current pharmacotherapies for multi-drug dependence. In addition, we will briefly discuss the implications for combining behavioral therapies with medications to improve treatment efficacy.

Key Words: Dual Dependency - Cocaine - Alcohol - Opiates

Dual-drug dependency is very common throughout Europe and America. Most heroin addicts abuse other drugs besides opiates. Stimulant abuse is common and increasing in European countries with up to 40% of heroin addicts also abusing cocaine and less commonly amphetamine. Alcohol and benzodiazepines are also commonly abused and can lead to serious dependence requiring detoxification. Benzodiazepines are covered separately and the focus of this review will include alcohol pharmacotherapy as well as stimulants. Cannabis abuse is minimally addressed in most opiate treatment programs, and there are no established pharmacotherapies for cannabis at this time.

Address for reprints: Tracie Gardner PhD, Michael E. DeBakey VA Medical Center, Research 151 - BLDG 110, Room 225 - 2002 Holcombe Boulevard, Houston, TX 77030, USA
Email: tgardner@bcm.edu - Phone: 713 794 7170 - FAX: 713 794 7240
Alcohol Abuse and Dependence

The management challenge of dual-drug dependency is complex and often can involve triple dependency on alcohol as well as opiates and stimulants. For alcohol dependent patients detoxification may be required, and that treatment has been well reviewed elsewhere[9]. Prevention of relapse to alcohol abuse after detoxification is the greater challenge and requires regular monitoring by urine drug and breath alcohol levels. Another possible monitoring approach for alcohol uses blood carbohydrate deficient transferrin to assess abstinence[1]. This assay can be used as infrequently as every other week and provide adequate monitoring.

In addition to monitoring for return to alcohol use, relapse prevention pharmacotherapy should be considered. Relapse prevention pharmacotherapy for alcohol includes Acamprosate, Topiramate, and Disulfiram (with monitored ingestion). The other important pharmacotherapy for alcoholism - opiate antagonists such as Naltrexone (and nalmefene) are contra-indicated, since they may precipitate opiate withdrawal. Acamprosate (N-acetylhomotaurine) involves dosing with 2 mg total, given three times daily. The side effects primarily include diarrhea, but it is generally well tolerated. Acamprosate has increased abstinence by 50% in over 3,000 patients across a dozen clinical trials[2, 15, 17, 21, 22]. An illustrative trial enrolled 272 patients and treated them for 48 weeks[19]. Compared to placebo the acamprosate treated alcohol dependent patients had twice the rate of sustained abstinence at 48 weeks (43% vs 21%), and this difference from placebo was sustained at 96 weeks after starting the medication (37% vs 17%). Thus, this appears to be a very effective approach to treating patients who are both opiate and alcohol dependent after detoxification from alcohol in order to maintain alcohol abstinence. Similar success has been described with topiramate vs. placebo, but only in a single study so far[6]. In that topiramate study the patients were actively drinking when started on medication rather than being first detoxified from alcohol and being abstinent. The outcome again was remarkable with an increase from no days abstinent at baseline to 44% of days abstinent by week 12 compared to 18% of days abstinent for the placebo group. Thus, a treatment strategy can be to start on topiramate at a low dose for buprenorphine maintained, alcohol abusing patients who do not need medical detoxification for alcohol. Each week then steadily increase the topiramate dose for up to 8 weeks in order to attain a week of abstinence. If and when abstinence is attained, discontinue the topiramate gradually over several weeks while you start the patient onacamprosate or disulfiram. The choice will depend on your patient’s preference and need for either an anti-craving medication (acamprosate) or a aversive agent (disulfiram).

Cocaine Abuse

The prevalence of cocaine abuse across Europe appears to be growing, which is a particular problem for estimating the current need for treatment capacity since the most recent data are from 2001, and these data indicate substantial variability across Europe. In 2001 the United Kingdom reported that 35% of its population had ever used an illicit drug, and about 5%, or 15% of these illicit drug abusers, reported cocaine use. Italy and Germany each had rates of about 20% for any illicit drug use and about 3%, or again 15% of these illicit drug abusers, had used cocaine. Finally, Spain, like the United Kingdom, reported about 5% abuse rates for cocaine, but no statistics on overall illicit drug use. This cocaine abuse is usually combined with heroin, and only 15% of
cocaine use and 10% of crack cocaine use is primary cocaine use. As an example, England has a large overlap in severe heroin and crack cocaine addicts with almost 50% of heroin addicts also abusing cocaine. There are 120,000 heroin and cocaine users and only 22,000 cocaine users who do not use heroin in England.

Cocaine pharmacotherapy is a continuing challenge, but we are evolving treatments including Buprenorphine, Disulfiram, Modafinil and GABA agonists [11]. We are also developing a cocaine vaccine [12]. Buprenorphine has shown a dose dependent reduction in cocaine abuse with less cocaine use associated with higher doses (e.g. 4 mg vs 16 mg daily) [16,20]. Thus, the first approach to a patient who is abusing cocaine while taking buprenorphine should be to increase the buprenorphine dose to at least 16 mg daily.

Disulfiram is a complex medication that appears to act on the catecholamine system to increase dopamine and decrease norepinephrine production. Disulfiram decreases cocaine craving and cocaine-induced priming, as shown in several human laboratory studies where cocaine has been administered with placebo and active disulfiram. At a cocaine dose of 2 mg/kg intranasally, disulfiram reduced cocaine induced craving (or priming) by more than 50% for peak craving and area under the curve of craving over time [13, 14] as shown in Figure 1. Disulfiram also increased cocaine-free urines in outpatient, placebo controlled clinical trials, and in over 600 outpatients treated across seven studies the disulfiram group had a statistically significant 35% higher rate of cocaine-free urines (P<0.01 in meta-analysis).

Two other promising agents have very different pharmacological actions. Modafinil has shown a significantly increased rate of cocaine-free urines, with rates of 45% for modafinil compared to 20% rates for placebo [3]. Several GABA enhancing agents also are being examined such as tiagabine, gabapentin and recently vigabatrin. While gabapentin has not shown efficacy, both tiagabine and vigabatrin look promising. In a recent clinical trial tiagabine increased cocaine free urines by 80% from baseline, while placebo increased only 20% from baseline [5]. Thus, several medications from different classes of pharmacological actions are showing promise for cocaine.

In order to enhance the efficacy of pharmacotherapy, contingency management designs have proven very effective. The Contingency Management (CM) condition can be to reinforce attendance at treatment sessions, compliance with taking medications and of course, reduction in cocaine abuse. For reducing cocaine use patients are given payment for drug-free urinary toxicology (UTOX) results that are taken at least twice weekly (preferable three times weekly in order to capture all cocaine abuse). For consecutive cocaine-free urines there is an escalating reinforcement schedule. For example, an initial payment of $3 per clean UTOX result will be increased by $1 for each consecutive clean UTOX result to a maximum of $15 per result. Positive or missed UTOX results are penalized by resetting the amount earned for clean UTOX results back to $3.

In a study of bupropion plus contingency management (CM), the proportion of cocaine urines by week steadily decreased for the patients who go CM plus bupropion, while those who got bupropion alone or contingency management (CM) alone or neither bupropion nor CM showed no reduction in cocaine urine results during this 24 week clinical trial [18]. The effect of bupropion on decreasing cocaine urines was easily seen within the patients who also got CM. For both groups, the proportion of cocaine positive urines started at 70% at week 1 then dropped to 35% from weeks 12 to 24 for the bupropion plus CM group, while for the placebo plus CM group the
Heroin Addiction and Related Clinical Problems

Cocaine urines remained between 55% and 60% throughout the 24 weeks. The conclusions are that the contingency management plus bupropion condition made a significant improvement in the proportion of cocaine-positive UTOX results during the first 13 weeks and that these gains were maintained across the 6 month period of study.

Finally, we are developing an anti-cocaine vaccine. This vaccine shows antibody production in animals, and these vaccine generated antibodies bind injected cocaine. This vaccine and the antibodies it produced have decreased cocaine self-administration in rodents \(^\cite{4,7,8}\). This vaccine also produces substantial amounts of antibodies after 3 to 5 vaccinations \(^\cite{10,12}\). As these antibodies accumulate they become effective in patients within 6 to 8 weeks of initial vaccination, and act to keep cocaine out of the brain. Cocaine antibody levels rise as dosing is repeated, even more than antibody levels increase with increasing vaccine dose. For example, peak antibody levels increased more with five vaccinations at 82 µg (410 µg cumulative dose) than four vaccinations at 82 µg (328 µg cumulative dose) (320 vs 200 antibody units). Furthermore, antibody levels increased with four doses at 82 ug (328 ug cumulative dose) to twice the levels attained with three vaccinations at an almost ten times higher dose of 709 µg (2,127 ug cumulative dose) (100 vs 200 antibody units). These higher vaccine doses and more repeated dosing are not only associated with higher antibody levels, but also with less relapse to cocaine use. The percent of patients relapsing in a high vs low dosage group was 30% vs 75% for any cocaine use and no relapse vs 30% relapse for heavy cocaine use.

**Summary**

In summary, heroin addicts are commonly dually dependent on alcohol and cocaine most commonly. Alcohol pharmacotherapies include acamprosate, topiramate, and disulfiram with observed
ingestion needed for disulfiram. The promise of stimulant pharmacotherapies include disulfiram, modafinil and tiagabine or similar GABA enhancing agents, which may be enhanced in opiate dependent patients by using relatively high doses of buprenorphine (e.g. 16 mg daily). Combining contingency management with medications is highly effective for enhancing the efficacy of cocaine therapy. Sustained treatments such as the cocaine vaccine offer great promise to prevent relapse.

Acknowledgements

Supported by National Institute on Drug Abuse grants K05 DA0454 (TRK), P50-DA18197, and the Veterans Administration (VA) Visn 16 Mental Illness Research, Education and Clinical Center (MIRECC) and VA National Substance Use Disorders Quality Enhancement Research Initiative (QUERI)

References

11. KOSTEN TR. (2005): Advances in pharmacotherapy of stimulant dependence: From alcohol

Received February 13, 2007 - Accepted March 11, 2007
Brain Disintegration in Heroin Addicts: The Natural Course of the Disease and the Effects of Methadone Treatment

Anna G. Polunina 1, Dmitry M. Davydov 1, and Alexander A. Kozlov 2

Summary

The present review aims to clear up the issue of the neurological processes underlying the personality changes induced by chronic opioid use. The effects of methadone treatment on brain functions have been analyzed, too. Brain disintegration becomes evident very soon after an onset of chronic heroin abuse and continues throughout the period of drug consumption. A considerable proportion of opioid addicts are characterized by conspicuous neuropsychological deficits, which preclude the maintenance of complete opioid abstinence in this patient subgroup. At present, there are no data to testify that the effects of methadone maintenance on brain functions exceed the adverse neurological effects of chronic heroin use.

Key Words: Cognitive - EEG - Neuroimaging - Neuropsychological Aspects - Opioid

Introduction

Clinical reality shows that chronic opioid abuse induces progressive neuropsychiatric phenomena, which include acute opioid withdrawal syndrome, protracted opioid abstinence symptoms [33] and unavoidable personality changes. A range of studies has demonstrated that opioid addicts acquire antisocial and criminal life-styles after an onset of chronic heroin use, and these personality changes in opioid addicts exceed...
similar symptoms in alcoholics or cocaine addicts\cite{7, 23, 25, 33}.

Progressive personality changes in opioid addicts are a considerable burden for their families and for the community. Opioid addiction is associated with a high risk of death. Only about 50\% of these patients live longer than 20 years after an onset of opioid use\cite{6}, and about 10\% of them try to commit suicide over a 12-month period\cite{11}. It is also appropriate to stress the contribution of heroin addiction to the prevalence of HIV infection and other morbid conditions. Hence, the progressive personality changes seen in opioid addicts represent the core and most serious complication of chronic opioid use. Unfortunately, all existing treatment approaches, including complete opioid abstinence, do no more than partly alleviate these personality changes in a proportion of addicts.

The present review aims to clear up the issue of neurological processes underlying the personality changes induced by chronic opioid use. The effects of methadone treatment on brain functions in this patient population have been analyzed, too.

**Progressive brain disintegration in heroin abusers**

*Abnormal electric activity in central brain regions in heroin addicts.*

There is growing evidence that electric activity in central brain regions is radically altered in heroin addicts, and that these alterations emerge very soon after an onset of chronic opioid use. In the late '90s heroin addiction spread all over Russia on the scale of an epidemic. In that period, street heroin was relatively pure and in most cases it did not contain contaminants. The duration of daily heroin use ranged from several months to 3.5 years in the addict population of Moscow. Besides this, a considerable proportion of Russian heroin abusers were very young (mean age about 23 years) and otherwise psychiatratically healthy people coming from well-educated and socially integrated families. This gave us the opportunity to evaluate the early effects of daily heroin use on the electric activity of the brain in young patients with a relatively normal psychiatric premorbid history.

We found that the mean frequency of alpha2 band electric activity in heroin addicts was significantly above normal throughout the brain, as assessed by comparison with controls, and that this electroencephalographic (EEG) phenomenon was significantly correlated with the duration of chronic heroin use in our patient cohort\cite{34}. The most important finding in this study referred to relationships between changes in brain electric activity and selective cognitive dysfunctions in the early stages of heroin addiction. Planning deficits (the Tower of London test) was strongly associated with alpha2 mean frequency increases in central derivations (C3, Cz and C4) in our patients\cite{13}. This association was mediated by the length of chronic heroin use in the right hemisphere (C4), whereas it was not related to chronic heroin use at the left central lead (C3). These data gave grounds for hypothesizing that the functioning of central brain structures is affected very soon after an onset of chronic heroin use, and that these alterations first arise in the left hemisphere and a little later spread to the central region of the right hemisphere.
hemisphere in heroin addicts. At least four other research groups similarly recorded electric activity abnormalities in central brain regions in patients with a mean duration of chronic heroin use ranging from 3.5 to 15 years; all of these findings refer to slow wave activity in central structures.

Shufman and colleagues \cite{39} reported an excessive intensity of delta activity at Cz in abstinent patients with a mean length of chronic heroin use of 3.5 years, but in no case did these authors find any similar electric abnormality in current heroin users with a mean duration of opioid use of 4.5 years. Papageorgiou and colleagues \cite{31} also found an abnormal spread of slow wave electric signals from C3 to right hemisphere central and frontal regions during the performance of a cognitive test by heroin addicts who had been abstinent for at least 6 months. The most important findings on electric activity in central brain structures in heroin addicts were reported by Franken and colleagues \cite{16, 17}. This research group found that heroin cues elicited slow wave-evoked potentials with the largest amplitude at central leads (C3, Cz and C4) in heroin addicts who were compared with normal controls, and that the amplitude of these potentials was significantly correlated with the severity of craving for heroin. These authors also reported a significant correlation between craving severity and the coherence of delta activity at central temporal derivations in the same patient cohort.

It should be noted that in our patient cohort we recorded significant correlation between the intensity of delta activity at Cz and C4 and the amounts of heroin which patients used per day before their admission to the in-hospital unit. Following a different line of inquiry, Greenwald & Roehrs \cite{20} found increased delta activity in central derivations in addicts who self-administered fentanyl, in comparison with patients who received the drug passively. Both findings may be interpreted as an indirect confirmation of causal association between delta activity in central brain structures and craving processes.

These contemporary EEG studies go to show that central brain structures are radically altered in heroin addicts at an early stage. This functional brain system is involved in incentive sensitization and craving processes, and is unable to adequately support cognitive operations which do not relate to heroin use in this patient population. The severity of the dysfunction of central brain structures seems to be directly related to the severity of addiction behavior.

All the characteristics of the central brain electric system mentioned above closely resemble the abnormalities of the mesocorticolimbic dopamine system in opioid-abusing subjects. Animal and human studies have shown that the structures of mesocorticolimbic system (dopamine neurons of the ventral tegmental area, the nucleus accumbens and anterior cingulate gyrus) are highly sensitized to opioids and neuroplastically altered in addicts \cite{35, 36}. The baseline activity in these structures is abnormal in abstinent heroin abusers \cite{18}. These structures are involved in incentive sensitization and craving processes \cite{8, 9, 38}, and are unable to adequately support cognitive operations which are not related to drug addiction behavior in opioid addicts \cite{14, 15, 26}. Hence, EEG studies confirm the findings of human neuroimaging and animal experimental studies on the quickly initi-
ated, inevitable long-term reorganization of the dopamine mesocorticolimbic system in heroin abusers.

**Frontal dysfunction in heroin addicts.**

In our study of heroin abusers, a subgroup of patients with a duration of chronic heroin use of under 18 months did not differ from healthy controls in their performance on two cognitive tests evaluating prefrontal functions (Delayed Alternation Test and Wisconsin Card Sorting Test)\(^4\). Even so, individual variations in cognitive performance were significantly associated with the amount of heroin which patients self-administered each day before their admission to the in-patient unit\(^5\). Patients who performed poorly on both prefrontal tests self-administered about 0.7 gram of heroin per day, whereas patients who performed ‘ideally’ on prefrontal tests used only 0.18 gram per day. The subgroup of patients with a selective deficit on Delayed Alteration Test self-administered 0.4 gram per day. Three subgroups did not differ in the duration of chronic heroin use. We concluded that premorbid prefrontal dysfunctions significantly affect patterns of daily heroin use in subjects with a relatively short drug use history.

Four other research groups reported significant clinical effects of prefrontal dysfunctions in opioid addicts. Gerra and colleagues\(^{19}\) observed right prefrontal hypoactivation in heroin addicts with antisocial and/or depressive personality characteristics, i.e. a subgroup of patients with especially severe addictive behavior. Similar findings were reported by Bauer\(^{3}\), who found significant correlation between childhood conduct disorder and amplitude of the P300 component of EEG evoked potential which was recorded during a continuous performance test in adult drug-abusing patients. Besides this, Pezawas and colleagues\(^{32}\) observed a significant effect of the frontal lobe volume on the longest periods of abstinence in methadone-maintained patients, and Lyvers & Yakimoff\(^{29}\) found a correlation between the severity of opioid dependence and the number of perseverative errors made in performing the Wisconsin Card Sorting Test in their similar patient cohort. Hence, prefrontal dysfunction is an individual characteristic of heroin abusers, and it underlies the prominent severity of drug abuse patterns in a proportion of opioid addicts.

Although patients with a short duration of chronic heroin did not differ from normal controls on their performance on the Delayed Alternation Test in our study, patients with a longer heroin abuse history (18 months to 3.5 years) gave a significantly poorer performance on this orbito-frontal neuropsychological task compared with normal subjects (\(p=.04\)). Moreover, we found a significant association between performance on Tower of London test (medial prefrontal cortex) and the duration of chronic heroin use\(^4\). These data gave grounds for concluding that dysfunctions in the orbito-frontal and medial frontal cortex progress in subjects sowing a chronic use of heroin.

Two other research groups reported a similar association between frontal cortex deficits and chronic opioid use history. Liu and colleagues\(^{27}\) found significant and negative correlation between bilateral white matter volume and length of chronic heroin usage in addicts with a drug abuse history of 2 - 15 years. Franken and colleagues\(^{17}\) reported significant negative correlation between frontal interhemispheric coherence and
chronic heroin history duration. It should be noted that, along with neuropsychological deficits, brain electric activity in frontal regions was also significantly correlated with heroin abuse history in our patient cohort [34]. Overall, these findings provide evidence that prefrontal dysfunction progresses in opioid users during their period of drug consumption.

Concomitant brain damage in opioid addicts.

Concomitant brain damage is common in opioid addicts. About 70% of opioid users report non-fatal overdoses and mild to moderate head injuries, which significantly affect cognitive performance in this patient population [10]. Concomitant alcohol and cocaine abuse also significantly contribute to brain damage in chronic opioid users [10, 28].

Ischaemic-hypoxic brain lesions are commonly found in long-term heroin addicts, and these brain alterations develop at significantly earlier age than in non-drug abusing controls [1, 28]. Concomitant adverse factors probably underlie the posterior brain disintegration which was reported in addicts with a long-term heroin history (about 15 - 20 years), but not in patients with a shorter duration of chronic heroin use [2].

The course of brain disintegration in chronic heroin users.

The findings of neuroimaging, EEG and neuropsychological studies cited above may be summarized as follows. Brain disintegration becomes apparent very soon after an onset of chronic heroin abuse. First, opioids inevitably reorganize the dopamine mesocorticolimbic system, which begins to implement addictive behaviour and is ineffective in other domains in chronic heroin users. Second, prefrontal dysfunction progresses in opioid addicts, and its severity is associated with especially prominent patterns of addictive behaviour. Third, concomitant brain damage is another common feature in heroin addicts, and may contribute to cognitive dysfunctions in this patient population.

Effects of methadone treatment and complete opioid abstinence on brain functions

In the second part of this review we make an attempt to summarize the findings of neurological and neuropsychological studies which have compared methadone-maintained patients with completely abstinent former heroin addicts. Few studies have addressed this issue, but we were able to identify six of them.

Physiological correlates of complete opioid abstinence.

Gritz and colleagues [21] registered significant elevation of heart rate with the same trend for arterial blood pressure in opioid addicts who had been completely abstinent for two months. At the same time methadone-maintained patients demonstrated normal haemodynamics, along with a somewhat depressed respiration rate. This study therefore confirmed clinical observations concerning persistent sympathetic hyperactivation in abstinent opioid addicts [33], whereas methadone treatment normalized autonomic
dysfunctions in this patient cohort.

Kouri and colleagues \cite{24} studied cognitive evoked potentials in addicts using heroin and cocaine. On admission day, patients did not differ from normal controls in the EEG parameters that were evaluated, whereas on the 12th day of heroin abstinence two subgroups of patients demonstrated a significant decrease in P300 compared with healthy controls. On the 14th day of treatment, the buprenorphine group showed complete normalization of the EEG-evoked potential, whereas the placebo group still was characterized by a significant decrement in the P300 amplitude.

The two studies just cited provided evidence that complete opioid abstinence is a state in which discomfort is experienced in association with sympathetic hyperactivation and non-specific cognitive dysfunctions. It is obvious from clinical practice that only a proportion of addicts are able to overcome these symptoms of protracted opioid withdrawal and maintain stable sobriety.

**EEG and neuropsychological deficits in abstinent and methadone-maintained addicts.**

Shufman and colleagues \cite{39} demonstrated that both abstinent and methadone-maintained patients were characterized by abnormalities in brain electric activity not found in healthy controls. The two groups demonstrated similar significant deficits of alpha2 band power, but differed in delta and alpha1 power displayed. Delta activity was significantly higher in abstinent subjects, whereas the intensity of alpha1 activity was higher in methadone-maintained patients. Similar data were reported by Gritz and colleagues \cite{21}, who recorded significant slower alpha rhythms in methadone-maintained patients than in normal controls, with intermediate alpha peak frequencies in abstinent subjects.

Cognitive dysfunctions are also commonly reported in both methadone-maintained and abstinent patient populations. Two neuropsychological studies found cognitive deficits to be more frequent and more conspicuous in methadone-maintained patients than in abstinent addicts \cite{12, 21}. However, methadone-maintained subjects were characterized by considerably longer histories of street opioid use compared with abstinent controls in both reports. Bauer \cite{2} too observed significantly more radical changes in visually evoked potentials in methadone-maintained subgroups compared with abstinent ones. Even so, statistical procedures showed that these differences were mediated by the length of chronic heroin use, but not by the effects of methadone treatment.

Methadone-maintained patients and abstinent former addicts with an equal length of chronic heroin use were compared in the study of Mintzer and colleagues \cite{30}. Psychomotor speed was slower in both patient groups than in normal controls, while this deficit was even more marked in former addicts than in the methadone group. However, methadone-maintained patients demonstrated additional cognitive impairment while performing the Gambling Task, which measures orbito-frontal cortex functions. In our opinion, these data provided evidence that the orbito-frontal dysfunction underlies the inability of methadone patients to maintain complete opioid abstinence, whereas addicts showing a normal orbito-frontal performance entered the abstinent subgroup.
Overall, the studies just cited can be summarized as follows. Both methadone-maintained and abstinent addicts display cognitive impairment when compared with healthy controls. At the same time, patients entering methadone maintenance treatment are characterized by more conspicuous cognitive deficits than patients who are able to maintain complete opioid abstinence.

**Correlates of cognitive dysfunction in methadone-maintained patients.**

At least 4 neuropsychological studies failed to find any significant association between methadone dosage regimen and cognitive performance \[^{10, 21, 37, 40}\]. Moreover, Gruber and colleagues \[^{22}\] demonstrated an improvement in cognitive functions as little as two months after the beginning of methadone treatment in opioid addicts. At the same time, cognitive deficits in methadone-maintained patients was significantly correlated with the number of non-fatal overdoses, mild to moderate head injuries, severity of alcohol dependency and global health in the study of Darke and colleagues \[^{10}\]. These data all provide evidence that methadone maintenance per se does not seem to radically affect cognitive functions in chronic opioid abusers. However, mildly sedative effects attributable to methadone may not be completely excluded by the data just quoted.

**Conclusion**

From the neurological point of view, populations of opioid addicts are not homogeneous. A considerable proportion of opioid addicts are characterized by conspicuous neuropsychological deficits, which preclude the continuation of complete opioid abstinence by this patient subgroup. So far, no data have been found to testify that the effects of methadone maintenance on brain functions exceed the adverse neurological effects of chronic heroin use.

**References**

117-26


*Received November 20, 2006 - Accepted February 13, 2007*
Voucher-Based Reinforcement Therapy for Drug-Dependent Pregnant Women

Sarah H. Heil and Teresa J. Linares Scott

Summary

Opioid and other drug abuse during pregnancy is a leading preventable cause of fetal and neonatal morbidity and mortality. Given the limited availability of safe and effective pharmacotherapies for this population, additional interventions that address drug use and other behaviors are sorely needed. One of the most robust interventions for increasing drug abstinence is voucher-based reinforcement therapy (VBRT). The present report reviews the growing literature on VBRT interventions to promote opioid and other drug abstinence in pregnant substance abusers. Overall, results suggest that VBRT interventions can foster drug abstinence and other therapeutic behaviors in this special population.

Key Words: Reinforcement therapy - Pregnancy - Drug Dependence

Opioid and other drug abuse by pregnant women is a leading preventable cause of fetal and neonatal morbidity and mortality. While less than 5% of pregnant women self-report recent illicit drug use (41), results from large-scale meconium screening suggest rates at least twice that high in samples in the U.S. (27), as well as abroad (31, 36, 46).

Both licit and illicit substance abuse during pregnancy increase obstetric risk, including early pregnancy loss, placental insufficiency, premature birth, low birth weight, congenital defect, and neonatal death (4, 7, 13, 33, 50). Prenatal substance exposure
may also manifest itself postpartum in the form of poor cognitive skills, mental retardation, and conduct disorders \(^{(33, 45, 50)}\). The adverse consequences of substance abuse during pregnancy are also costly in direct economic terms. It has been estimated that the lifetime cost of caring for a child prenatally exposed to tobacco, alcohol, or other drugs is between $750,000 and $1.4 million \(^{(50)}\).

For opioid-dependent pregnant women, methadone maintenance has long been recommended \(^{(12)}\) and buprenorphine is currently being evaluated as a potentially efficacious medication for perinatal addiction treatment \(^{(22)}\). Though clearly beneficial, pharmacological treatments are not without consequence; infants born to agonist-maintained mothers may exhibit neonatal abstinence syndrome (NAS), a generalized disorder that includes dysfunction of the autonomic and central nervous systems, gastrointestinal and respiratory tracts \(\text{e.g.}^{(14)}\) and often requires treatment with pharmacologic agents. In addition, agonist maintenance therapies for opioid dependence are rarely sufficient by themselves to manage the multitude of problems faced by opioid-dependent pregnant women. Regarding other drugs of abuse, efficacious pharmacological treatments either have not been approved \(\text{e.g.}^{(44)}\), or their safety and efficacy during pregnancy have yet to be determined \(\text{e.g.}^{(8)}\). 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 treatment attendance are sorely needed.

One of the most robust interventions for promoting drug abstinence among non-pregnant drug abusers is a behavioral treatment called contingency management. Contingency management involves systematic delivery of reinforcing or punishing consequences contingent on the occurrence of a target response, and the withholding of those consequences in the absence of the target response \(^{(19)}\). The CM intervention that has garnered the most research attention is voucher-based reinforcement therapy (VBRT) wherein patients receive vouchers or related monetary-based incentives exchangeable for retail items contingent on recent drug abstinence. A recent meta-analysis of 30 controlled studies of VBRT targeting drug abstinence reported that VBRT reliably and significantly improved treatment outcomes compared to control conditions \(^{(28)}\). Across studies, three characteristics of the VBRT interventions were found to moderate the magnitude of the outcome. The first was the number of drugs targeted, meaning studies that targeted abstinence from a single drug \(\text{e.g.}^{(5)}\), opioid abstinence) generally had better outcomes than studies that simultaneously targeted opioid and cocaine abstinence or polydrug abstinence. The second characteristic was voucher magnitude, meaning that studies using vouchers with greater monetary value \(\text{i.e.,}^{(5)}\), values of $5.00 and above per day) generally had better outcomes. The third characteristic was the immediacy of the voucher delivery, such that studies that delivered the voucher immediately after verifying abstinence \(\text{i.e.,}^{(5)}\), same clinic visit) rather than later generally had better outcomes. Overall, this report provided quantitative evidence supporting the efficacy of VBRT for the treatment of substance use disorders as well as practically useful information to those considering the use of VBRT.
While the majority of the studies reviewed in that meta-analysis were performed with non-pregnant substance abusers, a small number focused on pregnant substance abusers and they also reported favorable outcomes. This prompted us to review the extant literature on VBRT interventions to promote drug abstinence in pregnant women with substance abuse disorders. Included in our review are the two reports covered in that meta-analysis, but also nine additional reports that did not meet the various criteria for inclusion in the meta-analysis. The results of our qualitative review were also presented at the 2006 EUROPAD Conference in Bratislava, Slovak Republic as part of a symposium on new approaches in the treatment of opioid dependency during pregnancy. While we certainly include studies targeting opioid-dependent pregnant women in the present report, we did not limit ourselves to this drug class. The meta-analysis described above found that the three moderating characteristics of VBRT interventions (number of targets, reinforcer magnitude, and immediacy of reinforcement) are more critical to the success of this approach than the particular drug(s) targeted. Overall, our review of the growing scientific literature on the efficacy of VBRT with substance-abusing pregnant women suggests likewise that this intervention has equal potential to benefit opioid- and other drug-dependent pregnant women.

**VBRT Interventions Targeting Drug Abstinence in Pregnant Women**

**Cocaine**

The first successful use of VBRT in this population targeted cocaine use by pregnant women. In the early 1990s, the need for cocaine treatment in the general population had increased sharply and there was particular concern about cocaine use by pregnant women and the fate of children who had been exposed to cocaine in utero (32, 34, 35). Our group demonstrated the efficacy of voucher-based incentives combined with psychosocial counseling for treating cocaine dependence in non-pregnant populations (15-17). Following these reports, Elk and colleagues (11) examined the use of incentives to promote cocaine abstinence in pregnant women using a multiple-baseline across participants design. During the baseline phase (average duration = 2 weeks), urine samples were collected thrice weekly and tested for cocaine and all participants were expected to attend weekly prenatal care visits. No explicit contingencies were placed on either behavior. During the intervention phase (average duration = 10 weeks), all participants received $10 each time their urine sample results indicated a significant decrease (≥15%) in cocaine metabolite levels relative to her prior sample or $12 for each sample that was cocaine-negative. A participant could also earn a $15 bonus each week if (1) all three urine samples met the criteria above and (2) she attended her weekly prenatal care visit. Incentives earned at one visit were paid out at the participant’s next visit. On average, participants submitted twice as many cocaine-negative urine samples during the intervention phase compared to the baseline phase (52% vs. 25%). Attendance at prenatal care visits was also increased during the intervention phase. These results provided the first evidence of the efficacy of VBRT in pregnant substance abusers.
**Smoking**

One of the most promising targets of VBRT interventions to date is smoking during pregnancy and postpartum. The majority of trials examining the efficacy of smoking cessation interventions have not resulted in significant differences in end-of-pregnancy quit rates in experimental compared to control conditions, with quit rates often below 20% (2). Three published reports have examined the efficacy of VBRT to promote smoking cessation during pregnancy and postpartum. The seminal study on the use of incentives with pregnant and postpartum smokers examined the efficacy of this approach among pregnant and postpartum women residing in a residential treatment program for other types of substance abuse (26). Carbon monoxide (CO) levels were measured daily for approximately 8 weeks. Each day that a participant’s CO level indicated smoking abstinence, she earned a credit that could be accumulated and redeemed for program privileges (e.g., extra phone or pass time) or prizes donated by community businesses (e.g., jewelry, children’s toys, hair cuts, etc.). Women who received incentives had lower mean daily CO levels compared to participants in another residential substance abuse treatment program for pregnant and postpartum women in the same area who simply provided daily CO samples, but did not receive any incentives (3.07 vs. 12.42, respectively). This study provided compelling evidence that smoking is sensitive to VBRT interventions.

A second report describes a more rigorous randomized trial involving low-income pregnant smokers (9). Women were randomly assigned to VBRT or usual-care control conditions. In the VBRT condition, they received a monthly $50 voucher contingent on biochemically-verified smoking abstinence throughout pregnancy and for two months postpartum. Additionally, women in the VBRT condition included a “Social Supporter” in treatment (i.e., a female non-smoker with whom the subject had a positive association) who also received vouchers when the subject was abstinent (i.e., a $50 voucher in the first and last months and a $25 voucher in each intervening month). Abstinence rates were significantly greater in the VBRT compared to the control condition at the end of pregnancy (34% vs. 9%, respectively) and the end of the voucher program at 2-months postpartum (22% vs. 6%, respectively). These results provided additional evidence that the low quit rates typically observed among low-income, pregnant smokers are not inevitable and that relapse rates postpartum are modifiable.

In our effort to further extend this approach, we conducted a pilot study with low-income women who were still smoking upon entering prenatal care (18). Participants were initially assigned to either contingent or non-contingent voucher conditions as consecutive admissions and later randomly. Vouchers were available antepartum and through 12 weeks postpartum, and earned for biochemically-verified smoking abstinence in the contingent condition and independent of smoking status in the non-contingent condition. Biochemically-verified, 7-day point-prevalence abstinence was significantly greater in the contingent than the non-contingent condition at the end-of-pregnancy (37% vs. 9%, respectively), 12-week postpartum (33% vs. 0%, respectively), and 24-week postpartum (27% vs. 0%, respectively) assessments. Note that the 24-week assessment
occurred 12 weeks after vouchers were discontinued. Total mean voucher earnings across antepartum and postpartum were $397±414 and $313±142 in the contingent and non-contingent conditions. The magnitude of these treatment effects were consistent with those reported by Donatelle et al. (9) and exceeded levels typically observed with low-income pregnant and recently postpartum smokers. Additionally, the maintenance of significant treatment effects through 24-weeks postpartum extended the duration of treatment effects beyond any reported previously in this population. We have recently replicated these results in a fully randomized trial (Heil et al., in preparation).

Overall, these results combined with those of the prior reports suggest that smoking during pregnancy and the early postpartum period is a promising target for VBRT research and dissemination.

**Opioids**

One of the most powerful and innovative demonstrations of the efficacy of VBRT to date is the work of Silverman and colleagues and their Therapeutic Workplace intervention developed for opioid-dependent pregnant and postpartum women. In the Therapeutic Workplace, patients are hired and paid to work in a model work program. Salary is linked to abstinence by requiring patients to provide objective evidence of abstinence (i.e., a drug-free urine) to gain entrance to the workplace. Therefore, patients work and earn salary only when abstinent. In addition, the daily salary increases as the patient’s duration of sustained abstinence and workplace attendance increases. In the Workplace, patients participate in intensive job skills training until they meet strict criteria of sustained abstinence, workplace attendance, job skills and professional demeanor. Once these criteria are achieved, patients can be hired as employees in an income-producing Therapeutic Workplace business, Hopkins Data Services (40). This approach aims to address a fundamental difficulty that many substance-abusing women face; that is, the gap that exists between their occupational interests and their actual academic abilities (37). In addition, because employment can be sustained for years, this approach offers the possible advantage of maintaining high-magnitude salary-based abstinence reinforcement over extended periods of time.

In the first evaluation of this intervention (38), forty women were randomly assigned to either the Therapeutic Workplace group or to a usual care control group. All participants were methadone-maintained pregnant and postpartum women, only 10% of whom reported periods of full-time employment in the three years prior to study entry. Urine samples were collected thrice weekly during the 24-week intervention in both groups and participants were compensated $3.50 for each sample. In the Therapeutic Workplace group, urine samples that were negative for opiates and cocaine allowed the participant to enter the workplace that day. In the workplace, patients participated in basic skills education and job skills training in 3-hour work shifts. On the first day a participant provided a negative urine sample and completed a 3-hour work shift, she earned a $7 voucher. Vouchers increased in value by $.50 for each consecutive successful day, to a maximum of $27. A drug-positive sample or failure to provide a sample reset the voucher value back to $7. After a reset, nine consecutive days of abstinence
and workplace attendance returned the voucher value back to the pre-reset value. The majority of a participant’s earning potential came from these contingencies promoting abstinence and attendance, but modest incentives were also available for productivity, punctuality, and professional behavior.

The results of the initial evaluation of the Therapeutic Workplace’s effects on abstinence and attendance were quite promising. Over the course of the intervention, Therapeutic Workplace participants provided nearly twice as many cocaine- and opiate-negative urine samples compared to the usual care control condition (59% vs. 33%, respectively). On average, 45% of the Therapeutic Workplace participants attended the workplace on a given day. In total, Therapeutic Workplace participants earned an average of $1,013 (range = $0 to $3,126) over the 6-month intervention period.

The Therapeutic Workplace participants were repeatedly offered re-enrollment in 6-month blocks to examine the long-term effects of the intervention. A second article by Silverman and colleagues [39] reported abstinence outcomes based on urine samples collected at monthly assessments between months 18 and 36. Relative to the usual care control group, cocaine and opiate abstinence was significantly higher in Therapeutic Workplace participants (28% vs. 54% and 37% vs. 60%, respectively). In addition, Therapeutic Workplace participants were six times more likely to show evidence of continuous cocaine and opiate abstinence over this extended assessment period than the usual care group (30% vs. 5%, respectively). Across the entire 36-month intervention period, Therapeutic Workplace participants attended the workplace on 43% of the 780 workdays and had earned an average of $10.73 each workday in vouchers. Together, these two reports provide a unique demonstration of the ability of VBRT to produce long-term changes in drug use in an especially recalcitrant population.

Reports with Negative Outcomes

While the results of the studies described above appear quite promising, there are a similar number of studies with substance-abusing pregnant women where the results indicated no advantage of the VBRT intervention [5, 6, 10, 23, 25]. As described previously, our group’s examination of moderators of the efficacy of VBRT interventions found that studies with single drug targets, relatively larger magnitude reinforcers, and immediate voucher delivery were associated with better outcomes. Consistent with these findings, it appears that many of the studies with negative results simultaneously targeted multiple drugs [5, 6, 23, 25], had relatively low magnitude reinforcers [5, 6] and/or the immediacy of voucher delivery could not be determined, suggesting that it was delayed [5, 6].

Studies Targeting Outcome Measures Other Than Abstinence

In addition to the 11 studies using VBRT to target drug abstinence, our search of the literature also identified six studies targeting other outcomes. Three of the six [23, 24, 43] were a series of studies targeting treatment attendance at the Center for Addiction and Pregnancy in Baltimore, MD [21]. Treatment attendance is related to positive treatment outcome and dropout is associated with relapse and adverse effects on the mother
and the baby (20, 29, 42). Thus, improving treatment attendance is another mechanism by which maternal and fetal/neonatal outcomes may be enhanced. The remaining 3 studies (47-49) targeting other outcomes all took place in the context of the Therapeutic Workplace intervention described above and were efforts to modify other types of behavior relevant to employment settings, such as on-time attendance. Overall, the results of all six studies were favorable and suggest that VBRT can facilitate other therapeutic changes. However, given the small number of reports currently in this literature, additional experimental studies are needed to more fully flesh out this area. Nevertheless, we see no reason to expect that the same variables shown to be significant moderators in interventions targeting drug abstinence would not extend to studies on attendance and other behaviors.

Disseminating Use of VBRT Interventions During Pregnancy

Overall, the results of studies to date on the use of VBRT in the treatment of pregnant and postpartum women with substance use disorders suggest that VBRT significantly improves treatment outcomes in this population. Replications and extensions of the studies reviewed here, including trials by other groups of investigators, are needed to further strengthen this literature. However, the data are sufficiently compelling and the consequences of continued substance abuse during pregnancy sufficiently dire that dissemination of VBRT interventions for pregnant substance abusers appears warranted at this time. One potential challenge facing dissemination of VBRT interventions with this population outside of the research clinic is the cost. However, pregnant women are likely a population where cost is less of an issue for at least two reasons. First, while most people find the idea of a pregnant woman using drugs disturbing and difficult to understand, they are also sympathetic to the fact that the fetus is potentially being harmed. As a result, communities may be more willing to support VBRT interventions targeting substance abuse by a pregnant woman to protect the health of the fetus. One form of support already documented in this literature is donation of goods and services to be used as incentives. In the reports by Ker et al. (26) and Donatelle et al. (9) described above, incentives for their smoking cessation interventions were provided by or purchased with funds donated by community agencies. Amass and Kamein (1) previously reported results from successful donation solicitation programs to supply incentives for VBRT interventions for substance abusing pregnant and parenting women and their methods can serve as a guide for similar campaigns.

A second reason that the cost of VBRT interventions may be less of an issue when those interventions are directed at substance-abusing pregnant women is that cost-benefit analyses are relatively easily calculated and compelling in this population. For example, Svikis et al. (42) calculated the average cost of initial neonatal hospital stays following delivery in women who abused opioids, cocaine, and other drugs during pregnancy, but did not receive substance abuse treatment. The mean cost was $12,183. Assuming a conservative 5% increase (e.g., 3) in health care costs each year since 1992
when these data were collected, that figure has nearly doubled to $24,039. Further, these are conservative cost estimates in that they are limited to only those costs associated with admission to neonatal intensive care units (NICU), suggesting that the true costs are significantly higher. Thus, the economic benefit of reducing or eliminating substance abuse by pregnant women using VBRT interventions would appear to be quite economical and justifiable.

Summary

This review merits several comments and conclusions regarding the use of VBRT interventions to promote opioid and other drug abstinence and other behavior change in pregnant and postpartum women with substance abuse disorders. The overarching point to be noted is that the evidence to date suggests that VBRT significantly improves treatment outcomes in this population. Consistent with research in non-pregnant populations, studies with single drug targets, relatively larger magnitude reinforcement, and/or immediate voucher delivery tended to have positive outcomes. As such, this review provides evidence supporting the efficacy of this approach and suggests that dissemination efforts are warranted. To that end, this review also highlights a number of the innovative settings and funding strategies that researchers in this area have examined, including models such as the Therapeutic Workplace and creative and practical demonstrations of how VBRT programs can be funded outside of the research clinic. Future research replicating and extending these findings will provide additional evidence to further develop the use of this promising intervention in this truly special population.

Acknowledgments

Preparation of this manuscript was supported in part by grant RO1 DA018410 from the National Institute on Drug Abuse.

References


Received October 16, 2006 - Accepted December 20, 2006
Pharmacokinetic and Pharmacogenetic Factors Influencing
Methadone Plasma Levels

Séverine Crettol and Chin B. Eap

Summary

Methadone is widely used as a maintenance treatment for opiate addiction. Methadone plasma levels vary widely for a given dose, so contributing to interindividual variability in response to methadone maintenance treatment. Until recently, the relative in vivo involvement of various cytochrome P450 (CYP) isoforms in methadone pharmacokinetics had been unclear. A recent large-scale pharmacogenetic study with patients in methadone maintenance treatment has now demonstrated that CYP3A4 and CYP2B6 are the major cytochrome P450 isoforms with a major involvement in methadone metabolism, while CYP2D6 only contributes to a minor extent. In addition, P-glycoprotein, a transmembrane efflux protein, is also involved in methadone kinetics.

Key Words: Methadone Treatment - Pharmacokinetics -
Cytochrome P450 Enzymes - P-glycoprotein

Introduction

Methadone, which is widely used as a maintenance treatment for opiate addiction, is a synthetic µ-opioid receptor agonist. It is marketed in almost all countries as a racemic mixture of (R)- and (S)-methadone, although most of the opioid effect is produced by the (R)-enantiomer (26). The metabolism of methadone is mediated by cytochrome P450 (CYP) enzymes, mostly leading to the inactive 2-ethylidene-1,5-dimethyl-3,3-diphe-
nlypyrrolidine (EDDP) by the N-demethylation pathway. Very large interindividual variations in methadone plasma levels after a given dose had already been demonstrated; these variations partly account for the high levels of interindividual variability found in response to treatment. Wide-ranging variations in the relationship between dose and plasma concentration are typical of drugs that are metabolized and/or transported by polymorphic proteins. In addition, many patients in methadone maintenance treatment (MMT) take concomitant medication(s); this may well influence methadone kinetics, so accentuating interindividual variability.

Cytochrome P450 Family

The interindividual variability of the activity of CYP enzymes, along with their potential for inductions and inhibitions, is probably responsible for a large proportion of the variations in methadone kinetics and observed plasma levels. Several in vitro and in vivo studies have demonstrated the involvement of different CYPs in methadone metabolism. For a long time, CYP3A4 was thought to be the main CYP isoform involved in methadone metabolism, together with CYP2D6 and possibly CYP1A2, CYP2C8, CYP2C9 and CYP2C19, but in vivo the involvement of each of these was unclear. More recently, two in vitro studies demonstrated that CYP3A4 and CYP2B6 were the main enzymes involved in the methadone metabolism. Interestingly, in one of these studies, the enantiomers of methadone were evaluated separately and a stereoselectivity was observed for CYP2B6 in favour of the (S)-enantiomer, and for CYP2C19 towards the (R)-enantiomer, whereas CYP3A4 display no stereoselectivity. In a large-scale pharmacogenetic study, we were able to confirm in vivo the impact of CYP2B6 on (S)-methadone plasma levels. The MMT patients carrying a CYP2B6 *6/*6 genotype presented significantly higher trough (S)-methadone plasma levels than the non-carriers of allele *6 (209 and 105 ng/kg/ml*mg, respectively; p=0.0004), whereas the impact on (R)-methadone plasma levels was not significant. As the (S)-enantiomer makes no contribution to the µ-opioid receptor activation, the CYP2B6*6 allele does not influence responses to treatment.

As to CYP3A4, its involvement in the methadone metabolism was most strongly suggested by interaction studies with CYP3A4 inducers and/or inhibitors. It should be noted that one study showed a higher level of CYP3A4 activity measured by the midazolam phenotyping test in 32 MMT patients receiving high methadone doses; this high level of activity may contribute to the need for high doses. On the other hand, based on the lack of specificity of the inducers and/or inhibitors used in these interaction studies, it was concluded that CYP3A4 may play only a minor role in the methadone metabolism in vivo, leading to a predominant role to CYP2B6 and a possible role for intestinal transporters.

The expression and activity of CYP3A4 vary significantly between individuals; most of this variability is thought to be genetically determined. However, the low allelic frequency of the functional polymorphisms of CYP3A4 cannot account for the
variations that have been observed \(^{(10, 34)}\). Therefore, a phenotyping test better reflects its activity than the genotyping of the described alleles. For example, midazolam is a substrate of both CYP3A4 and CYP3A5, and its oral administration makes it possible to measure both intestinal and hepatic CYP3A activity \(^{(9)}\). Midazolam’s metabolic ratio was shown to correlate well with midazolam clearance; this allows it to be used as a marker of CYP3A activity \(^{(9)}\). We recently demonstrated that midazolam’s metabolic ratio correlated with (R)-, (S)-, and (R,S)-methadone plasma levels, so confirming the in vivo involvement of CYP3A in the methadone metabolism \(^{(5)}\). In addition, we found that CYP3A activity failed to display stereoselectivity in favour of any of the enantiomers of methadone \(^{(5)}\), as might have been expected from an enzyme with such a wide range of substrates; this finding confirmed previous in vitro results \(^{(11, 13)}\).

Unlike CYP3A4, the hepatic expression of CYP3A5 is distributed bimodally, indicating the existence of a polymorphism \(^{(34)}\). CYP3A5*3 causes alternative splicing and protein truncation, resulting in an absence of CYP3A5 in most Caucasians \(^{(18)}\). In vitro, CYP3A5 was not shown to be involved in the methadone metabolism \(^{(15, 17)}\), but it can constitute as much as 50% of the total hepatic CYP3A content in people who express it \(^{(18)}\), which makes it likely that it contributes to the interindividual variability of the methadone metabolism. We recently discovered that methadone plasma levels did not differ according to the presence or the absence of CYP3A5, so confirming that CYP3A5 is not involved in the methadone metabolism \(^{(5)}\).

As regards CYP2D6, only a minor involvement in the methadone metabolism was demonstrated in vitro \(^{(13, 15, 17, 21, 32)}\), but observed interactions between methadone and CYP2D6 inhibitors provided an indication of a more important involvement \(^{(1, 6)}\), maybe by another pathway than N-demethylation \(^{(8)}\). A previous in vivo study found a significant difference in methadone concentrations corrected by dose and weight between poor metabolizers (PMs), extensive metabolizers (EMs) and ultrarapid metabolizers (UMs) \(^{(7)}\) of CYP2D6. This influence of the UM genotype on trough methadone plasma levels has recently been confirmed \(^{(5)}\). On the other hand, the PM status of CYP2D6 had no influence on methadone plasma levels, possibly due to a compensatory activity by other CYP isoforms in CYP2D6 PMs \(^{(5)}\).

As to CYP1A2, in vitro it was not shown to be involved in the methadone metabolism \(^{(13, 15, 15)}\) or was shown to have only a minor role \(^{(21, 32)}\). But a previous report on MMT patients who were smokers revealed that the heavy smokers were those most likely to report problems arising from not feeling ‘held’ by their methadone dose \(^{(29)}\). As CYP1A2 is induced by cigarette smoking, these differences may have been caused by the CYP1A2-mediated metabolism, most likely by another metabolic pathway than N-demethylation to EDDP \(^{(8)}\). The CYP1A2*1F allele was proposed as possibly presenting a higher inducibility, on the grounds that a significant difference in CYP1A2 metabolic activity between the genotypes was only observed in smokers \(^{(24)}\). However, we found no influence of the CYP1A2*1F genotype on methadone plasma levels, which suggests that this isozyme does not contribute to the methadone metabolism \(^{(5)}\).

Lastly, certain in vitro studies have shown the involvement of CYP2C9 and CYP2C19
in the methadone metabolism \(^{(11, 13, 17, 21)}\). In particular, one of these studies showed an important involvement of CYP2C19, with a stereoselectivity favouring the active (R)-enantiomer for this isoform \(^{(13)}\). But in vivo, for both isozymes, the PM status was not found to influence methadone plasma levels \(^{(4)}\).

**P-Glycoprotein**

Several in vitro and animal models have been used to demonstrate that methadone is a substrate of P-glycoprotein (PGP) \(^{(3, 22, 23, 30, 33)}\), a transmembrane efflux transporter belonging to the ATP-binding cassette (ABC) family, and encoded by the \(ABCB1\) gene. The expression of PGP in various human tissues, including the intestine, liver, kidneys, testes and blood-brain barrier \(^{(20)}\), demonstrates its protective role against the potentially toxic accumulation of xenobiotics, in enhancing of their elimination and limiting of their distribution in the body \(^{(12)}\). One important function of PGP is its limitation of the access of xenobiotics to the brain, which has been demonstrated in vivo by studies on PGP-deficient mice \(^{(25)}\). The presence of PGP in the blood-brain barrier, intestine and kidneys is therefore of special interest during methadone treatment. In particular, methadone distribution to the brain has been shown to be regulated by PGP in mice and rats \(^{(23, 33)}\). Furthermore, the intestinal absorption or renal elimination of methadone may be related to PGP intestinal or renal content. This probable role of PGP in the intestinal disposition of methadone was suggested in a study on healthy subjects \(^{(16)}\).

Several single nucleotide polymorphisms (SNPs) of the \(ABCB1\) gene have been reported, in particular the synonymous \(3435C>T\) SNP, which has been associated with lower PGP expression \(^{(14)}\). Interestingly, it has recently been demonstrated that the \(3435TT\) genotype is associated with a fall in PGP expression due to a decrease in mRNA stability \(^{(31)}\). In one study in which 51 healthy volunteers took a single methadone dose, no influence of \(ABCB1\ 2677G>T\) and \(3435C>T\) was observed on methadone AUC and peak plasma levels \(^{(19)}\). But in studying steady-state MMT patients, we found that the \(ABCB1\ 3435C>T\) SNP had an influence on trough but not on peak methadone plasma levels \(^{(5)}\). Stereoselectivity in PGP transport was not expected, as PGP can transport a wide range of different chemical substances. Despite this, a study that quantified the enantiomers of methadone to assess stereoselectivity in methadone transport using \(Abcb1a\) knockout mice observed an apparently lower brain access for (S)-methadone than for (R)-methadone, so suggesting stereoselectivity in the activity of mouse PGP \(^{(33)}\). In studying MMT patients, however, we did not find differences in the influence of the \(ABCB1\ 3435C>T\) genotypes on (R)- and (S)-enantiomer plasma levels.

In summary, in vivo and in vitro results converge in identifying CYP3A4 and CYP2B6 as the major CYP isoforms involved in the methadone metabolism, and in indicating that CYP2D6 only contributes to a minor extent. As several CYP proteins contribute simultaneously to methadone kinetics, a decreased function of one of them does not lead to a major effect on methadone plasma levels. The genetic polymor-
phisms of \textit{ABCB1} also contribute to a small extent to the interindividual variability of methadone kinetics.

\textbf{Grant Support:} This work was supported by the Swiss National Research Foundation (project 3200-065427.01) and by the Swiss Federal Office of Public Health (project 02.001382).

\textbf{References}


10. EISLEY R., DOMANSKI T.L., ZIBAT A., MUELLER R., PRESECAN-SIEDEL E., HUSTERT E.,
ZANGER U.M., BROCKMOeller J., KLEINK H.P., MEYER U.A., KHAN K.K., HE Y.A.,
human liver microsomes: lack of stereoselectivity and involvement of CYP3A4.
N-demethylation by cytochrome P4502B6 and 2C19. Chirality 16: 36-44.
14. HOFFMEYER S., BURK O., VON RICHTER O., ARNOLD H.P., BROCKMOeller J., JOHNE
Functional polymorphisms of the human multidrug-resistant gene: multiple
sequence variations and correlation of one allele with P-glycoprotein expression
15. IRIBARNE C., BERTHOU F., BAIRD S., DREANO Y., PICART D., BAIL J.P., BEAUNE P.,
MENEZ J.F. (1996): Involvement of cytochrome P450 3A4 enzyme in the N-
demethylation of methadone in human liver microsomes. Chem Res Toxicol 9:
365-373.
16. KHRASCH E.D., HOFFER C., WHITTINGTON D. (2004): The effect of quinidine, used
as a probe for the involvement of P-glycoprotein, on the intestinal absorption
17. KHRASCH E.D., HOFFER C., WHITTINGTON D., SHEFFELS P. (2004): Role of hepatic
and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and
18. KUEHL P., ZHANG J., LIN Y., LAMBA J., ASSEM M., SCHUETZ J., WATKINS P.B., DALY
A., WRIGHTON S.A., HALL S.D., MAUREL P., RELLING M., BRIMER C., YASUDA K.,
Sequence diversity in CYP3A promoters and characterization of the genetic basis
19. LOTSCH J., SKARKE C., WETING J., OERTEL B.G., SCHMIDT H., BROCKMOeller J.,
by genetic polymorphisms potentially affecting its metabolism, distribution, and
MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol
Ther 75: 13-33.
The involvement of cytochrome P450 3A4 in the N-demethylation of L-a-
acetylmethadol (LAAM), norlaam, and methadone. Drug Metab Dispos 25:


ORDER FORM
Heroin Addiction and Related Clinical Problems

Please enter my subscription:
Heroin Add & Rel Clin Probl = € 70,00
(€ 30,00 for East European Citizens)
Europad annual registration included
( Check if)

Available from:

Not for profit Agency
Pietrasanta -LUCCA
ITALY
"Helping people to understand neuroscientific updates"
AU-CNS
Associazione per l’Utilizzo delle Conoscenze Neuroscientifiche a Fini Sociali
Via XX Settembre, 83 - 55045 Pietrasanta (Lucca) - Italy
Phone: int 39 0584-790073
Fax: int 39 0584-72081
E-mail aucns@libero.it

Family Name ___________________________
First Name ___________________________
Agency ______________________________
Mailing Address:
Street/Road ___________________________
Postcode ________________
City ________________
Country ________________
Phone __________________ Fax ____________
E-mail ________________________________

Payment Enclosed. Check must be payable on an Italian bank
Charge my Credit Card
Master Card  Eurocard  VISA  CartaSi (Italy only)
Card Number ___________________________
Expiration date _________________________
Date _________________________________
Signature ______________________________

Also by Fax
Providing Comprehensive Treatment in Medication Assisted Opioid Treatment: The Development of Needs Based Treatment at a Medical School Sponsored Program

Ira J. Marion and Dorrie Burke

TO THE EDITOR: The Division of Substance Abuse of the Albert Einstein College of Medicine (AECOM) of Yeshiva University is the single largest funded entity at the medical school. Although primarily a clinical program, the Division is fully integrated into medical school teaching, residency training, and research. AECOM has operated a voluntary substance abuse program since 1968 when it began drug abuse treatment as a small in-patient service located at the Bronx Psychiatric Center. Since its inception, the program’s primary focus has been the treatment of opioid dependence through the methadone maintenance modality, reflecting the philosophy and practices of Marie Nyswander, M.D. and Vincent P. Dole, M.D., developers and founders of methadone maintenance treatment through their work at the Rockefeller University, under the leadership of Joyce H. Lowinson, MD, a collaborator with Nyswander and Dole. The program was the first to offer methadone treatment to addicts with multiple addictions, including alcoholism, as well as those with concomitant psychiatric problems. In 1969, the program provided treatment for 350 patients. By late 1970, growing recognition of the need for treatment services for the increasing numbers of narcotic addicts led to the expansion of the Division to nine locations throughout Bronx County, serving over 2100 patients. The Division is now the largest addiction treatment program in Bronx County, second largest public treatment program in New York State, and largest in the world operating under the auspices of a medical school. Serving over 3400 persons, 18 years and older, with primary residence or work site in The Bronx, the Division has developed into a comprehensive opioid addiction treatment at nine (9) community-based outpatient facilities located throughout the borough, as well as ambulatory services for all substances of abuse at the Division’s Chemical Dependency Wellness Services
program located in North and South Bronx facilities. The Division has integrated primary medical and mental health care, evidenced based individual, group and family treatment, HIV and Hepatitis testing, counseling, treatment and partner notification as well as a variety of peer empowerment projects that seeks to engage patients in working as peer leaders, reducing stigma, providing education to patients and their families along with a host of specific peer support efforts.

**Vision and Goals**

The Division started as a small methadone maintenance treatment program in 1969 following the procedures and protocols developed by Drs. Marie E. Nyswander and Vincent P. Dole. Recognizing that our services were integrated into a medical school whose primary goals are and were “teaching” and “research” it became clear almost from inception that we would need to link our treatment goals with those of the medical school and it’s University Hospital, the Montefiore Medical Center in order to establish and maintain a full continuum of the highest quality and culturally relevant addiction treatment, intervention and prevention services that are immediately accessible to the persons and families of the communities we serve. The Division is committed to continuous quality improvement in care of our patients and communities, and provides innovative offerings developed from evidence-based research. The Division is committed to providing a “one-stop shopping” model of care to assure that our enrolled patients are able to access as many services as possible on site at our facilities. We currently offer primary medical care, mental health care, substance abuse treatment, HIV and Hepatitis C treatment as well as vaccinations for Hepatitis A and B, directly observed preventive therapy for tuberculosis and other services at our clinics. To ensure that broad education about substance abuse became a part of our continuum, we educate the public as well as the medical school community about addiction, treatment and prevention. Simultaneously, we work collaboratively with professional and community organizations in efforts to reduce the stigma associated with addicted persons and addiction treatment. Outreach now extends to the harm reduction community as the Division provides treatment education and vaccinations for hepatitis A and B (Twinrix) at two State of New York funded Harm Reduction Centers.

As one of the six major medical schools in New York, in addition to the major affiliate and University Hospital, Montefiore Medical Center, AECOM has clinical affiliations with Bronx Lebanon Hospital Center, Bronx Psychiatric Center, Jacobi Medical Center, Beth Israel Medical Center and Long Island Jewish/North Shore Health Systems. The Division of Substance Abuse considers it a responsibility to educate the public about addiction, treatment and prevention and work collaboratively with professional and community organizations in efforts to reduce the stigma associated with addicted persons and addiction treatment.

Our academic mission as part of the AECOM Department of Psychiatry and Behavioral Sciences includes professional education, training, technology transfer, and research
efforts in addiction treatment and addiction psychiatry. DoSA is an approved training site for continuing medical education (CME), and is certified to provide courses for the alcoholism and substance abuse counselor credential (CASAC) and a major participant in clinical research efforts and in substance abuse and health demonstration and service projects. The Division is also committed to participation in and sponsorship of basic and clinical substance abuse research conducted by faculty of the Albert Einstein College of Medicine that complements the care provided at community-based sites.

Who We Treat

The licensed census capacity for the Division’s opioid treatment program is 3365 patients. The office-based opioid treatment program has no census ceiling and currently provides care for 117 patients. The Division’s Next STEPS chemical dependency wellness services program presently provides services for more than 300 patients and their significant others. During 2005, there were 1390 admission episodes to Division programs.

On February 15, 2006, combined enrollment for all Division programs was 3,722 patients - 61% male and 39% female; 61% of Latino origin, 26% African American, 11% Caucasian and <2% of other ethnicity. The overwhelming majority of patients are between 30 and 59 years of age (91%) - 17% between the ages of 30 and 39 year, 42% between 40 and 49 years old, and 32% between 50 and 59 years. Persons under the age of 29 comprise approximately 4% of the population, and 5% are over age 60. Over 67% of these patients have been in continuous treatment for over two (2) years; 46% for more than five (5) years, and 39% for more than ten years.

Services

The Division provides comprehensive services, almost all on-site, but some by referral to cooperating agencies. These services developed slowly as patient needs were assessed and understood, patient advisory councils established at each clinic and patient satisfaction surveys were conducted on a regular basis. Services that “staff” thought most appropriate, such as individual counseling were not as important to patients as group counseling, peer to peer support and family education. Housing and other scarce services were highly desired. We offer services using validated instruments to determine level of care and placement. Our service system consists of:

**Screening, Assessment and Diagnosis** - Persons referred to the Division are primarily screened and assessed at the Division’s centralized diagnostic and admissions center, Melrose On-Track. At this unique ‘triage’ facility opened in 1992, reliable diagnostic criteria and state-of-the-art assessment techniques are used to identify addiction characteristics and severity, screen and diagnose coexisting medical and mental health conditions, and distinguish the most appropriate treatment path and level of care required. For seriously addicted opioid users entering pharmacotherapy treatment, an
intensive transition program offers individually tailored health and behavior reorientation and treatment planning, followed by relocation to the treatment site and level of care most congruent with the patient’s long-term needs.

**Medication Assisted Opioid Treatment** - At the core of the Division’s treatment options for opioid addiction, medications such as methadone or other approved opioid agonist medications, used either in maintenance or long-term tapering, are medically prescribed to normalize biochemistry, block the effects of abused opioid drugs, and eliminate drug craving. Comprehensive maintenance treatment combines pharmacotherapy with personalized health care, evidenced-based psychosocial supports, relapse prevention and behavioral therapies to manage opioid addiction and substantially improve the patient’s health and quality of life. Methadone Medical Maintenance, a model of office-based opioid pharmacotherapy treatment (OBOT), enables successfully rehabilitated methadone patients who meet specialized criteria to receive pharmacotherapy and health care in a physician office environment on a monthly basis, thus engaging in an advanced treatment regimen. Approved in 2002 by the U.S. Food and Drug Administration, and in 2003 by the State of New York, Buprenorphine is a pharmacotherapy medication now available in the Next STEPS Wellness program in treating opioid addiction. Oral Administration of Suboxone(r), a form of buprenorphine (combined with naloxone for increased safety), is offered along with primary medical care to patients admitted to Next STEPS, whose treatment profile best suits the achievable benefits of the buprenorphine model.

**Primary Medical Care** - Comprehensive and personalized medical care is offered on-site at all of the Division’s addiction treatment sites. Comprehensive medical assessment, diagnosis, and follow-up incorporates: annual physical examination and blood chemistry analyses; medical history; screening for infectious disease, tuberculosis testing and therapy; ongoing on-site medical care for existing and newly identified conditions; gynecological screening, pre-natal assistance, family planning and other specialized women’s health services; and coordinated referrals for disorders requiring specialized evaluation and therapy.

**HIV Testing, Primary Care and Case Management** - Confidential testing for the Human Immunodeficiency Virus (HIV) is performed by State certified and credentialed staff. Patient who are positive for HIV may receive comprehensive on-site HIV primary care, including evaluation, medical monitoring, treatment of HIV-related opportunistic infections, administration of anti-viral medications (including protease inhibitors and other therapies), and HIV counseling, casework and advocacy. Testing, evaluation, and treatment are provided as well for Hepatitis C.

**Hepatitis C (HCV) Integration Project** - A five (5) year project funded by the U.S. Centers for Disease Control (CDC) and conceived by the Division’s Executive Director and former Medical Director, Marc Gourevitch, M.D., this effort is aimed at developing clinical models to achieve effective education, intervention and peer support services to raise awareness about Hepatitis C prevention and treatment in response to the critical emergence of the HCV among persons with a history of substance abuse.
The blueprint for this initiative was developed at the Division’s Hub I opioid treatment clinic, and HCV education and peer support has been extended widely throughout the Division. This work directly spawned several new projects funded by the New York City Department of Health and Mental Hygiene, including a South Bronx Hepatitis C Task Force - a coalition of Bronx-based community organizations, substance abuse treatment providers, harm reduction centers, physicians, liver disease specialists, peer educators and community members living with HCV. This has been instrumental in establishing a South Bronx Hepatitis C Support Group, a South Bronx Peer Education Program and an HCV Referral Directory, benefitting patients beyond our clinics.

**Behavioral and Mental Health Case Management** - Certified social workers at each Division site lead interdisciplinary teams comprised of certified alcoholism and substance abuse counselors (CASAC’s) and trained clinical specialists. Interdisciplinary, culturally sensitive behavioral health treatment supports core medical care, assures effective case management, facilitates patient advocacy and adaptive life skills, and promotes repair of patient living conditions, educational, vocational and family deficits. Physicians and psychiatrists provide specialized mental health interventions as needed. Most importantly all individual, group and family counseling utilize evidenced based practices such as motivational interviewing, positive contingency management and follow standardized curricula throughout our Division.

**Project Grow** - A five (5) year project funded by the New York State Department of Health AIDS Institute, Project GROW (Giving Resources and Options to Women), offers an educational series of group and individual cognitive behavioral interventions focused on women’s health issues, and targeted to HIV-uninfected women, to achieve positive behavioral change in high-risk sexual and drug-using behaviors. Escort services are provided for participants for medical appointments to women’s health clinics, including pre-natal care, gynecology and family planning. Upon completion of the education series, participants may become peer educators trained to co-lead HIV risk-reduction and education group sessions in a variety of settings and to serve as peer escorts.

**Chemical Dependency Wellness Services** - Ambulatory treatment of substance abuse is most effective in a frequently occurring regimen. The Division’s chemical dependency wellness services program - Next STEPS - provides intensive outpatient substance abuse treatment, education and prevention services for persons diagnosed with chemical dependency, utilizing effective elements of individualized addiction treatment, day treatment, self-help, peer support, and group therapy. This level of care allows the Division to provide buprenorphine treatment by prescription, along with needed psychosocial group, family or individual services patients may want or need. It provides us with the flexibility to phase in new medications as they become available. For example, our wellness services will soon provide 30 day naltrexone treatment for alcoholism. Most importantly, we provide evidence based medical and behavioral interventions, relapse prevention, family therapies, and interactive group experiences aim at stabilizing emotional health and enhancing self-esteem and interpersonal skills, in individual treatment paths that enable patients to continue work and family life. These
Heroin Addiction and Related Clinical Problems

Interventions are offered by trained, certified counselors utilizing curricula tailored to the patients we treat. Motivational interviewing, contingency management, cognitive behavioral interventions and others are offered to patients in group formats, backed up by individual and family counseling to engage loved ones into the treatment process.

**Vocational Services Initiative** - As part of the Division’s goal to provide comprehensive treatment care, vocational services are offered to all patients through the Vocational Services Initiative Grant funded by the New York State Office of Alcoholism and Substance Abuse Services (OASAS) since 2001. Vocational specialists work as part of the behavioral health treatment team to integrate employment related activities into the overall treatment process, resulting in increased vocational referrals internally and externally for educational, training and employment services. Linkage agreements and collaborative partnerships with State and private vocational service organizations such as the National Association on Drug Abuse Problems (NADAP), an OASAS licensed job placement program, provide on-site employment assessments to increase employment outcomes. Patient vocational deficits, which in many instances are significant, are identified and rehabilitative referrals are facilitated, moving patients towards structured work activities and/or employment whenever possible.

**Management, Continuous Quality Improvement and External Relations** - Centralized management information systems, staff development, marketing and community relations achieve administrative cost-economies and facilitate the quality interface of the Division with patient-consumers, accreditation sponsors, the community-at-large, and other stakeholders. A structured program of continuous quality improvement (CQI) assures a quality driven philosophy of patient care, program development, and operations based upon objective evaluation of performance standards and outcomes.

**Research** - In addition to providing addiction treatment and related health services, the Division is a clinical, research and teaching division of Einstein’s Department of Psychiatry and Behavioral Sciences, committed to participating in and sponsoring basic and clinic substance abuse research that complements the care provided at its community based clinical programs. The Division is an active participant as well in evidence-based research and service demonstration projects that serve to evaluate and bring new technologies and best practices in the treatment of addiction to implementation.

**Teaching, Training and Professional Development** - As part of Einstein, the Division provides basic education and training in substance abuse issues and treatment to students and to other practitioners in the medical and helping professions. The Division had developed and is a major site of the Department of Psychiatry and Behavioral Sciences’ Residency in Addiction Psychiatry.

**Funding** - Funding comes from entitlements such as Medicaid, Medicare, patient insurance and fees as well as financing from the New York State Office of Alcoholism and Substance Abuse Services and other government agencies. The following is a summary of our funding for the fiscal year ending June 30, 2005.

The Division continues to work to bridge gaps in treatment and implement new and
unique services to enhance the continuum of care. For example, recently the Division entered a partnership with a traditional drug free therapeutic community, Palladia, to provide residential treatment services to AECOM patients whose drug abuse problems or co-occurring mental health issues prevented them from succeeding in out patient treatment. Every patient receives the same care regardless of whether they receive methadone or do not and there is no difference in retention or other outcome measures. We continue to try to develop programming that utilizes new medications, like buprenorphine and injectable naltrexone as part of our chemical dependency services in an effort to provide individual treatment based on the needs of the presenting patients.

The program described above article receives funding from the State of New York Office of Alcoholism and Substance Abuse Services and the State of New York Department of Health

Received October 12, 2006 - Accepted January 15, 2007

<table>
<thead>
<tr>
<th>Table 1. Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>OASAS Funded Programs</td>
</tr>
<tr>
<td>AIDS Institute Funded Initiatives</td>
</tr>
<tr>
<td>Revenue Funded Programs</td>
</tr>
<tr>
<td>Grants &amp; Contracts Managed by The Division</td>
</tr>
<tr>
<td>TOTALS</td>
</tr>
</tbody>
</table>
Dihydrocodeine Treatment of Alcohol Addicts with Previous Opiate Addiction — Case Reports

Albrecht Ulmer, Marcus Mueller and Bernhard Frietsch

Summary

Objective: In papers already presented at conferences we were able to report that a successful maintenance therapy for alcohol addicts is possible with Dihydrocodeine (DHC). Here we report the case histories of 9 serious alcohol addicts; eight of these were former opiate addicts and the ninth a former non-addicted heroin user. Methods: We describe here all nine of our former heroin users who have more recently been treated with DHC because of a serious alcohol addiction. They had all distanced themselves for several years from their earlier phases of heroin addiction. All these patients had received professional counselling and, with one exception, had experienced professional addiction treatment. We prescribed DHC very cautiously and normally avoided exceeding the dosage of 320 mg daily, a much lower dosage than would have been needed for opiate substitution; higher dosages were prescribed to only two patients in this group. Results: All these patients substantially reduced their alcohol consumption; this led to a clear general improvement. Two patients stopped drinking altogether, the first over a period of 1.5 years at the time of writing, and the second over a period of nearly 3 years; both report an unrestricted feeling of well-being. One has, meanwhile, also completed his DHC-intake treatment. A third patient showing a similar improvement, who now drinks only very occasionally, does not seem to need absolute alcohol abstinence. In most of the patients the improvement was not sustained or absolutely irreproachable. One patient with a severe phasic depression committed suicide after years of clear improvement. Other patients showed an only transient improvement in their GGT, despite having reported nearly complete alcohol reduction and a drastic improvement in their anxiety and panic attacks, or they experienced a gradual relapse back to their original level of alcohol consumption. Two patients refused to undergo a regular DHC therapy as prescribed by us, and switched back to heroin or alcohol consumption. Conclusions: In 7 out of 9 patients a clear improvement in the situation was achieved by prescribing DHC. These seven patients substantially reduced their alcohol intake; in two cases drinking was completely eliminated. But one suicide, one heroin relapse and two apparently definitive alcohol relapses, in addition to other problems, show that we are unable to present DHC as offering all patients an easily won treatment success.

Key Words: Dihydrocodeine Treatment - Alcoholism - Heroin Addiction

Address for reprints: Albrecht Ulmer, MD, HIV-and Addiction-Disease- Practice, Schwabstr. 26 - D-70197 Stuttgart, Germany, EU
Tel. +49-711-626308; Fax +49-711-610074; E-mail: albrecht.ulmer@gmx.de
Heroin Addiction and Related Clinical Problems

Introduction

Maintenance therapy has become by far the most important treatment for heroin addicts during the last few decades. But society, and even many addiction experts, think that the main reason for this is the illegal status of heroin, and most people tend to classify this therapy as harm reduction. They have not yet recognized that maintenance is a basic principle in the treatment of addiction diseases. What other reason could there be for the fact that dynamic, wide-ranging research into the development of maintenance therapies for alcohol dependants has not yet begun? The need is absolutely evident. Abstinence-based therapies play only a marginal role, as they have almost no statistical relevance, when considered alongside the total number of addicts.

A daunting number of patients have shown us how difficult it is for them to live with or without alcohol. Permanent relapses destroy substantial areas of their lives. In addition, patients who absolutely need alcohol abstinence for their health, but are not able to stay abstinent over long periods of time, bring with them an urgent and often life-challenging indication that they must have some kind of maintenance therapy. But no tests have been carried out, and up till now this approach has never been adopted.

A few German practitioners have experimented by transferring their experience of maintenance therapies for heroin addicts to alcohol-dependent patients. The results have been encouraging and clearly show that this approach should be applied much more widely. Based on the experience that methadone turns out to be accompanied by more problems with alcohol than those that occur when DHC is taken, and that some individual patients reported the disappearance of alcohol craving when using DHC, we started to substitute alcohol systematically with DHC. Since then we have become confident that this can constitute an adequate, in some cases, an optimum treatment, at least for heavily affected drinkers.

For instance, a few of our patients who previously drank continuously or were susceptible to relapses, with countless detoxifications, have now been living as alcohol abstainers for more than 5 years. Their health and quality of life display decisive improvements.

On the basis of our experience, the needed dosage of DHC is around one quarter or one third of what heroin addicts need. As a result, if we proceed in an orderly way, we can avoid any risk of inducing severe opiate addiction. In cases where success is unattainable, it is not normally too difficult to stop this kind of trial.

Our very limited experience is not the outcome of any officially sponsored research, but is a systematic documentation of treatment development in daily practice. Official research is expensive, and often means following a long route from an idea to an official initiation, depending on the priorities of financial sponsors. There are also other handicaps, such as quasi-ideological barriers, especially in the field of addiction treatment.

In daily practice, therefore, a systematic documentation and collection of many individual cases is an essential alternative to, and supplementation of, established research, showing us many phenomena for which we have no established explanations or solutions currently exist. Of course, such learning-by-doing calls for a good degree of integration into professional discussions. That is why I am thankful for this opportunity to publish our first experiences with former opiate addicts here.
In 58 patients we prescribed a low dose of DHC for alcohol addicted patients. We limited the daily dosage to 320 mg (4x 80mg). It is not an easy matter to single out the cases in which this was successful. A DHC prescription was often one in a sequence of steps and only part of an extensive concept, which had to work together with the other parts. Roughly speaking, we can say that one quarter of these patients experienced crucial and sustained benefits from this treatment.

We must take into consideration that the conditions are still being developed. We have no knowledge of the optimal dosage, many fears continue to surround the experimental character of the treatment, and the whole logistical setting is missing. Some of our failures arose from our excessive caution: we explained extensively that this treatment was not an established one and was not accepted by several experts, that the window of DHC is much smaller than that of alcohol; we explained the danger of inducing a new kind of opiate addiction, and in some patients the low dosage reflected too much caution.

Former opiate addicts were not the first category of patients to receive DHC treatment from us because of a condition of alcohol addiction. We first started to treat ex-opiate addicts after years of encouraging experiences with other patients who had no history of opiate addiction. This history is connected with a short list of special questions and problems:

What happens if we lead these patients back to the opiates?

What about their former integration into illegal scenes? Heroin is illegal, alcohol is not. The rules for maintenance therapies pertinent to opiate addicts take the illegal status and the realities of the black market into account (1 - 5). This is a world set apart from the socially integrated world of alcohol addicts.

How about the best dosage?

Patients and methods

What follows is a description of all of our patients who were treated with DHC because of a serious alcohol addiction and who were former heroin users. They had all distanced themselves, over a period of several years, from their phases of heroin addiction. This history had ended many years previously (4 - 25 y) in 8 patients and, when under our care, none of them were opiate addicts. One patient with HIV and hepatitis C was in our maintenance therapy for opiate addiction from January 1989 to April 2004, with no further opiate problems for >10 years, but he had an increasing dependency on alcohol. He therefore underwent a special inpatient treatment in an addiction clinic but relapsed back into alcohol abuse a few weeks later. Another patient was a non-addicted heroin user years ago, but then became seriously alcohol-addicted. He suffered from a gambling addiction, too. All patients received professional counselling and, except one, had experienced in professional addiction treatment. Based on extensive information and a written informed consent, we prescribed DHC very cautiously and normally avoided exceeding a dosage of 320 mg daily (the usual limit was, in fact, 280 mg), a much lower dosage than would have been needed for opiate substitution (800-1000 mg). Higher dosages were only prescribed for two patients.
Case reports

**Patient 1**: A 34-year-old man with hepatitis C (virus type 1) reported that he had stopped using heroin and cocaine over 10 years previously. He then spent 5 years in prison. After leaving prison, he had never relapsed into opiate use. He said that alcohol had always been his leading drug, for over 15 years. This addiction was terrible; he was loud and turbulent, and could not wait. It was very difficult and nearly impossible to help him with any normal treatment. He had many contacts with our problematic patients in opiate maintenance therapy. Three former inpatient detoxifications and one therapy in an addiction clinic had no sustained success. Within 18 months he needed 8 further detoxifications, and he tried one further therapy in an addiction clinic. There was no sustained response.

Because of his hepatitis it was urgent to interrupt his alcohol consumption. Repeated examinations revealed no hint of any further use of illegal drugs. But his GGT figures was 940 U/l. Directly after his 11th detoxification and with his extensively informed consent, we prescribed 160 mg DHC daily. The success obtained was impressive. He immediately reported having no further alcohol craving; he lost his restlessness and distanced himself from the scene of methadone patients. After a few days he suggested reducing the dosage to 120 mg daily, and remained on that dosage for 20 months. Then he completed the maintenance therapy, reducing the dosage within 7 months. Four months after initiating the DHC-therapy, he started a successful therapy for his hepatitis. His liver parameters have now been normal for over 2 years, and he has been living without alcohol or craving for nearly 3 years; in the meantime, he has been living without DHC for 5 months.

**Patient 2**: A 51-years-old man with heroin addiction since 1978, and with HIV (identified in 1985) and hepatitis C (virus type 2b) was in our methadone maintenance therapy for opiate addiction from January 1989 to April 2004, with no further opiate problems for >10 years, but his dependency on alcohol continued to rise. His GGT went up to 1137 U/l. He therefore underwent a special inpatient treatment in an addiction clinic, but relapsed into alcohol abuse a few weeks later. We performed a new detoxification and treated him initially with 160 mg, then with 280, and, since November 2005, with 400 mg DHC daily (exceeding our dosage limit for alcohol addicts because of the short time that had elapsed since our long-term maintenance therapy for his previous opiate addiction ended). Since then he seems to have stayed free of relapses and craving. His liver parameters are normal, despite the still unresolved hepatitis. The HIV-infection remains very stable (his current CD4-count is 900/µl). His quality of life is good — the best he ever had. According to the rules for opiate maintenance therapies (2-5) he has to come for a new prescription and consultation every week.

**Patient 3**: A 32-year-old lady came to us in 1993, because of her HIV infection, which was identified in 1989, (stage B3, OHL, CD4 190/µl) and her chronic hepatitis C (virus type 1). We treated her with antiretrovirals every year, and, unsuccessfully, with interferon in 1996. She had finished her four-year phase of drug-taking in 1987, undergoing an inpatient therapy in a specialized addiction clinic. Since then she has lived a more stable life, working as an office manager in the same factory as her husband. I did not have the impression she had a psychological disorder at any time, apart from a mild depression. But, on her own initiative, she told me she that she was drinking too much alcohol on a daily basis and that she feared
a bad prognosis because of the hepatitis and permanently elevated liver parameters (as high as 164 U/l). “There is always too much strain on me”. Besides this, she reported that her sexual life with her husband was not very satisfying because of the loss of her libido. We tried to stabilize her situation for years with a psychotherapeutic approach, two times with acamprosate, and once with naltrexone, but without success. After 9 years the gravity of her situation escalated, with her GGT rising to 248 U/l.

In March 2003 we initiated a very low dose DHC treatment (40 mg daily). Her immediate answer was: “I feel so much better!” She has not needed alcohol to cope with her daily life since then. It also seems that she doesn’t need to be absolutely abstinent; she allows herself a drink at rare intervals, taking a small amount, for instance, at birthday parties. We raised the dosage to 280 mg and then reduced it provisionally to 260 mg. Her GGT didn’t fall into a normal range, but went down to 70 U/l. Our impression is that in the current phase of her life DHC seems to be the ideal answer to her longstanding life problems, the most important of which was her high alcohol consumption. Now, with DHC, the dangerous prognosis for her liver disease has clearly improved.

**Patient 4**: A 26 year-old-lady came to us in 2001, because of her HIV infection, which had been identified in 1998, and her chronic hepatitis C (virus type 1). She was just finishing a follow-up therapy after her third inpatient treatment in an addiction treatment centre. She didn’t like to be questioned about 4 inpatient detoxifications, an unsuccessful Interferon-Ribavirin therapy or about an earlier six-month methadone-maintenance therapy. Her main goal had become that of building up a new, abstinence-based life. But whatever she tried, she didn’t succeed. Recurrent anxiety and panic attacks, and endless trouble with other people destroyed all her attempts to live a normal life. The impression made by her always reminds us of a lack of some addictive substance. She tried several antidepressants, but without success. She reported more and more openly that she had been drinking too much alcohol, starting in 1992. We therefore started to prescribe a low, 80 mg dose of DHC in March 2004. But she felt extremely concerned about contracting a new dependency. This fear was the main reason why she never reported feeling well at any time. She also complained about her DHC-related constipation, and she finished the DHC intake after 10 weeks.

Once again we had to face a very difficult situation. Abstinence was unsuccessful, in July 2006 she needed an alcohol detoxification, and during the last few weeks she has tried to separate from an alcoholic friend. She experienced a lot of trouble with authorities and other people, and it seems that her life will never succeed, or only after a very long period beset with plenty of difficulties. Should we try another approach with buprenorphine? Her desperate parents would support that. But she herself fears the prospect of dependency.

**Patient 5**: A 41-year-old man came to us in 1994 because of his freshly detected HIV infection. It was unclear if he has become infected through his former drug use, years earlier, or, as he believed, through heterosexual contacts. After a short time we had to face a series of severe alcohol intoxications and 12 inpatient detoxifications with him. When asked about the cause of these intoxications he answered: “Because of my desperation”. Several antidepressants didn’t help, and his antiretroviral therapy was seriously endangered. In 1998, we prescribed 150, and, a few months later, 180 mg DHC daily, and for over a year it seemed
perfect: there was no craving, no relapse and no further desperation. But he continued to report a severe relapse into desperation. He urged us to drastically increase the dosage. We raised to 1580 mg, but he needed three inpatient treatments, more because of his desperation than because of slight alcohol relapses. After this phase lasting over six months the rather stable phase returned without any new relapses for the next two years, and he continued to reported a crucial improvement in his life because of the DHC. The dosage was gradually lowered to 360 mg, without encountering any resistance from him. But his depression still failed to respond adequately to treatment. He suddenly committed suicide, by jumping in front of a train.

**Patient 6:** A man, born in 1961, had been addicted to heroin from 1982 to 1989. He came to us in 1992 because of HIV infection (recognized in 1990) and hepatitis C (virus type 1). A treatment with interferon in 1996 was not successful. We have been treating him with antiretrovirals since 1997. He reported increasingly severe alcohol problems. His GGT rose to 136 U/l. In October 1998 we started to prescribe a very low dose of DHC. He was fearful of taking this regularly and started to take it only as needed. This was against our advice, but his use of DHC was very low, and it looked successful for one year, with falling liver parameters. But after this first year, he reported needing more and more, and we switched to our substitution dosages. He took 200, and then 280mg daily for 7 months. His alcohol-craving was drastically reduced, and he was nearly completely alcohol-abstinent. Then he reported relapses into heroin; he preferred to stop the DHC medication and underwent a new inpatient detoxification. He interrupted his HIV-medication too, and didn’t resume until, three years later, his CD4 count fell to 140/µl. Shortly after his detoxification he resorted to alcohol again repeatedly, but he also used more heroin, fearing the alcohol because of his hepatitis and preferring heroin anyway.

Meanwhile, after taking drugs for 26 years, he still fears a “real addiction”, as he calls it, and rejects all offers of substitution. One of the major reasons for this rejection, he says, are the rules for maintenance therapies in our country, which makes him feel under greater pressure than when he buys his drugs on the illegal private market. Last week he underwent a new inpatient detoxification, but “It’s a permanent fight”, as he stated afterwards.

**Patient 7:** A 35-year-old lady came to us in 1996 because of her HIV infection (identified in 1985) and chronic hepatitis C (virus type 3a). In 1991, two inpatient therapies in addiction clinics had stopped her opiate consumption after 10 years. But now she was drinking a lot of alcohol, often smelled of alcohol and always had high liver parameters (with GGT as high as 224 U/l). The major problem was: constant severe anxiety and permanent panic attacks. She was a very difficult patient for us, due to her borderline personality, and was almost nearly untreated, but really suffered from a very poor prognosis. The prescription of a mini-dosage of DHC (50 mg daily) led to an impressive change: her anxiety and panic attacks seemed to have been resolved. Within 20 months, she needed an increase in dosage up to 200 mg. Her general status remained much improved, and she reported that she was not drinking alcohol any more. Her GGT fell to 55 U/l. But during the next few years it oscillated between 22 and at least 338 U/l again. Because of the concomitant hepatitis and the treatment for her HIV infection it was almost impossible to decide whether alcohol or
these diseases were the reason, but she had never again smelled of alcohol. Repeated checks did not show any alcohol in the blood probe. In the meantime the daily DHC dosage has been lowered to 150 mg daily. But we are unsure if this dosage is the optimum one. We think it would be better to treat and stabilize her at a higher dosage. To discuss this in an open manner is difficult because of her borderline disorder and her strong wish to become independent of our treatment in due time.

**Patient 8:** A 36-year-old man reported he had been drinking a lot of alcohol or too much alcohol for 13 years and, that he had finished his sporadic use of heroin, cocaine and fungi, 6 years before. Four inpatient therapies in addiction clinics and 13 detoxifications led to no sustained success. Besides this, he suffered from a gambling addiction. Within 10 months he needed 5 further alcohol detoxifications. Then we prescribed 120 mg DHC daily and raised the dosage to 240 mg within 6 weeks. His alcohol consumption was strictly reduced, but a few weeks later he reduced the DHC dosage by himself, adding the comment: “I don’t like it”. Two weeks later he needed a new treatment for alcohol detoxification. We finished the short DHC treatment together which had, perhaps, been too cautious. But we did not have enough experience to be able to promise him that an improvement would be probable with a higher dosage or a longer treatment. He remained alcohol-dependent, and, up to now, we have not been able to really help him. But since the DHC treatment phase, he has reported a crucial, sustained improvement of his gambling addiction that has been uninterrupted so far.

**Patient 9:** A 45-year-old man came to us, referred to us by an advisory centre, because of his alcohol dependency, together with a simultaneous severe form of Crohn’s disease. He reported that he had been drinking too much alcohol for more than 10 years. 20 years ago, he had used heroin i.v. for two years. After a first outpatient detoxification, we treated him initially with acamprosate. Because of its gastrointestinal side-effects and because there was no immediate positive effect on his craving, he stopped the intake after only 4 weeks. But he obviously remained alcohol-abstinent for a whole year, coming to us every third week. GGT and MCV turned to their normal range. Then he relapsed and interrupted his visits to our practice for nearly two years. When he came back, his situation showed a drastic deterioration. It had become much more difficult to stabilize his addiction disease and his Crohn’s disease. During the next two years, his GGT rose to 250 U/l, and his MCV up 107fl.

After a new outpatient detoxification we started him on 160 mg DHC daily. His alcohol craving disappeared at once, and his GGT fell to 74 U/l. After that, we had several discussions because he had some elevated GGT results, with values as high as 137 U/l and there was sometimes the impression of ongoing alcohol consumption, which, however, he denied. Suddenly, after 10 months, he stopped the DHC intake, complaining that we would not trust him, and interrupted the whole treatment. Then, last week, 11 months later, he came back and asked to resume the DHC treatment. But he remained ambivalent and couldn't bring himself to restart really this treatment.
All these cases go to show that it is possible to treat former heroin addicts with DHC, if they have problems with alcohol addiction. This seemed to be an ideal solution for some of our patients. But the field has not been fully prepared yet. In some cases, the patients, and we ourselves, have been too cautious. Our experience was not broad enough, and the patients showed an extreme fear of the pathway leading back to opiates. They had heard one continually repeated message: that their highest goal should be to get away from opiates. All their counsellors said it, and so did all the experts. There was, in fact, no advisory system in place capable of supporting an alcohol-substituting treatment. We have no secure knowledge of the best dosage or the best substance. We are only able to present preliminary experiences that this principle of treatment method is possible, and that, in a few patients, it gives almost ideal results.

In many cases, however, these results do not come easily. This approach must be founded on systematic research. We need a surrounding system of logistical support, and this requires a complete change in the paradigms being used. Abstinence is not the best solution in all patients, as was true of patient 4. In many patients, too, it is clearly better to keep them on opiates than on alcohol. Thus it is wrong to promote opiate abstinence as the top priority. In this way, too, alcohol proves to be life-devastating and dangerous to our patients, and these constraints on treatment often leave us with a feeling of desperation. A change in attitude is an absolute necessity.

We used DHC because of the experience of two colleagues and because of the report of one of our own first patients that a pain treatment with codeine dissolved his alcohol craving. This patient, who has now been taking DHC for 9 years, has been free of alcohol relapses since then. Before this, all experts and we ourselves were desperate and couldn’t think of any way of helping him with his therapy-resistant craving and permanent relapses.

The history of maintenance therapies in Germany started with DHC. Methadone remained illegal up to 1992, and in the early years, up to 1998, it remained very difficult to prescribe it, because of the Narcotic Act. As we are based in Germany, we were able to gain a lot of experience with DHC, which, up to 1998, could be prescribed freely. But this freedom led to a lot of abuse and inappropriate prescriptions for heroin addicts, and some cases of death were related to these prescriptions. DHC was therefore classified under the Narcotic Act in 1998, and was almost forbidden. Physicians and patients were forced to change over to methadone. This change went almost unnoticed in scientific assessments. But we and other colleagues had the clear impression that many patients went on to develop a severe problem with alcohol dependency thereafter. We therefore came to believe that DHC is a better substitute for alcohol than methadone.

Many heroin addicts report that alcohol was their first gateway drug, but that they stopped drinking it when they became dependent on heroin. Under methadone, many of them started to drink too much alcohol again. This second viewpoint again leads us to conclude that methadone is not as good a substitute for alcohol as DHC, which is pharmacologically closer to heroin.

But we have no knowledge of other opioids. No research and no experience with bu-
prenorphine, for instance, are available. In one single patient, buprenorphine reduced craving, but did so much less effectively than DHC.

Why has there been no research up to now? It is not yet an accepted fact that abstinence is not possible for some patients or that it is not the best option for the patient. A considerable proportion of patients with addiction diseases need substitution therapies for very many years, some of them indefinitely.

Once this is realized, we should follow up by optimizing the structure for this kind of treatment. Subordinating it to many difficult rules has the outcome that very few doctors are able to offer this treatment, and patients have to come to treatment centres regularly. This looks like a dead end. People on maintenance therapies should receive as much support as possible in living a normal, integrated life. For most of them this is made impossible by there being so very few treatment centres. A regular involvement of most of the practitioners is needed, with a minimum of rules and a maximum availability of the best possible support for their efforts.

In any case, systematic research on substitution treatments for alcohol addicts must be the first step.

References

2. Bundesärztekammer und Kassenärztliche Bundesvereinigung: Richtlinien der Bundesärztekammer zur substitutionsgestützten Behandlung Opiatabhängiger vom 22.03.2002

Received October 2, 2006 - Accepted February 19, 2007
International Meeting

EUROPAD
ITALIA 3

Heroin Addiction. The Clinical and Therapeutic Aspects.
7th Italian National Conference

Chairmen and Speakers
Giovanni U. Corsini
(Pisa, Italy, EU)
Loretta Finnegan
(Avalon, NJ, USA)
Gabriele Fischer
(Vienna, Austria, EU)
Mario Guazzelli
(Pisa, Italy, EU)
Guido Intaschi
(Viareggio, LU, Italy, EU)
Iccho Maremmani
(Pisa, Italy, EU)
Milo Meini
(Pisa, Italy, EU)
Roberto Nardini
(Pietrasanta, LU, Italy, EU)
Robert G. Newman
(New York, NY, USA)
Matteo Pacini
(Pisa, Italy, EU)
Pier Paolo Pani
(Cagliari, Italy, EU)
Mark Parrino
(New York, NY, USA)
Marc Reisinger
(Brussels, Belgium, EU)
Francesca Stigini
(Pisa, Italy, EU)
Alessandro Tagliamonte
(Siena, Italy, EU)
Albrecht Ulmer
(Stuttgart, Germany)
Andrea Vendramin
(Padova, Italy, EU)
Giuseppe Zanda
(Lucca, Italy, EU)

Pietrasanta, (Lucca), Italy, EU
"Sala dell'Annunziata"
"Luigi Russo" Cultural Centre
Piazza del Duomo
September 27-29, 2007

For more information: www.europad.org/italia2007.htm
INFORMATION FOR CONTRIBUTORS

The Editor of Heroin Addiction & Related Clinical Problems welcomes contributions of original manuscripts that are not under consideration for publication elsewhere. The Journal publishes research reports, proposals, letters to editor.

Peer Review: All manuscripts, including those written at the invitation of the editor, are subject to peer review by at least two experts to determine the originality, validity, and significance of the submitted material. Authors will usually be advised within eight weeks on the decision on their manuscript. All reviewers will remain anonymous.

Manuscript Specifications: Manuscript must be typed double-spaced with one-inch margins on A4 paper (Max 29.952 characters). The cover page must contain the article title, authors’ names and affiliations, and address for correspondence and telephone number of corresponding author. Please, submit your paper only by E-mail in Rich Text Format Saved File. Please provide figures in .pdf or .tiff, .jpeg format or as Microsoft Power Point Presentation. Each article must include an abstract (100-word maximum) and a reference list.

Bibliography must be ordered by authors’ names alphabetically. Start each reference with bibliography number; use these numbers, in parentheses, for in-text citations. Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in the text.

Please use the following guidelines for arranging references:
Journal article:
Book:
Book Chapter:

Journal names should be abbreviated as they appear in Index Medicus, journals not currently indexed there should not be abbreviated.

Submission Procedure: Submit the files to Icro Maremmani, MD, Editor,<maremman@psico.med.unipi.it> and a Cc copy to <aucns@libero.it>
Submissions should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the journal it is being submitted (Research Reports, Proposals, Letters to Editor);

Ethics of Experimentations: Authors must declare in the cover letter that their studies submitted to Heroin Addiction & Related Clinical Problems have been conducted in accordance with Declaration of Helsinki.