Heroin Addiction and Related Clinical Problems

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European Opiate Addiction Treatment Association
EUROPEAN OPIATE ADDICTION TREATMENT ASSOCIATION

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

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Necessity of a world federation of health organizations providing opiate agonist therapy for heroin addicts

Mark Parrino

I am grateful to have been invited to be with you this evening and throughout your conference. It is also a great happiness for me to be back in Pietrasanta, where my mother was born some 85 years ago. As some of you know, my grandfather owned a marble studio in Pietrasanta.

I am also grateful for the continued collaboration between our two associations and for the ongoing work with Icro Maremmani, Roberto Nardini and Alessandro Tagliamonte.

Many of you recall that our Association honoured these three extraordinary gentlemen at our national meeting in 1994 in Washington, DC. It represented one of our own proud moments as we were able to acknowledge the great work of all three of these leaders had accomplished. It is remarkable to me that that occurred 12 years ago.

I am also grateful to the Scientific Committee Coordinators and the Scientific Committee Members for creating such an excellent program and to Marilena Guareschi for all of her support and work.

General Remarks

The primary purpose for my presentation this evening is to focus on the necessity and value of a world federation of healthcare professionals, who can actively promote and support the use of medications, such as methadone and buprenorphine to treat opiate addiction for people who need such care.

Methadone treatment has faced many challenges in the United States since its inception, when Drs. Dole and Nyswander formulated their theories about narcotic addiction.
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and treatment in the mid-1960s. enormous progress has been made in expanding access to treatment, but many hurdles remain as younger people are admitted to our treatment programs and as opioid abuse patterns continue to change.

At present, there are 241,000 patients being treated in 1,100 methadone treatment programs throughout the United States.

Clinical Practices and Research

Dr. Maremmani and I convened a meeting during October, 2004 as part of the AATOD conference in Orlando, Florida. A number of international associates from seven countries were present at that meeting, including Dr. Pier Paolo Pani, and Dr. Alexander Kantchelov of Bulgaria, who are both present this evening.

Dr. Maremmani provided the key foundations for the concept of a worldwide federation during these early discussions. It was determined that the world federation would include major regional multi-national associations throughout the world.

One federation would include EUROPAD and the organizing countries within its domain, which are listed on the EUROPAD letterhead.

It was also agreed that AATOD would work with its associates in Mexico and Canada to form another federation, which would include the current AATOD membership of 850 treatment programs throughout the United States and representation within Mexico and Canada. These plans will be further discussed during the approaching AATOD National Conference in Atlanta, Georgia during April, 2006.

It was also agreed that EUROPAD and AATOD would encourage our associates within Asia to form a third regional federation as they increase their experience with methadone maintenance treatment. It is important to point out that methadone treatment programs are rapidly expanding in China and we believe that this represents major progress in responding to the needs of Chinese heroin-addicted individuals. As you know, methadone treatment has been available in Hong Kong and Thailand for many years.

We also agreed to encourage our associates within Australia and New Zealand to form a fourth regional federation, as their organizing activities take shape.

We recognize that few Latin American countries currently provide access to methadone treatment, since the greater problem within the South American nations involve stimulant abuse as opposed to heroin addiction.

It was also critical in our earliest discussions to recognize the need to have these regional federations throughout the world preserve their own independence, following their own policies, procedures and scientifically based medical practices.

It was also understood that these regional federations would continue to communicate with each other through designated representatives within each of the major world regions.

Obviously, Dr. Maremmani and I remain in frequent communication since EUROPAD
and AATOD are the only existing major provider based organizations in the world.

It was also agreed that each of these federations would agree to a set of principles of general governance.

The regional federations would agree to establish some basic best practice clinical standards to treat patients, who gain access to opioid replacement pharmacotherapies. It was also agreed that such regional federations would work to establish best training models so that clinicians, administrators, public health officials and other government representatives in each of the member nations would follow a series of best recommendations and how various individuals would be trained to treat this patients population.

It was recognized that these training vehicles would be culturally sensitive to the unique cultural characteristics of the countries involved.

Finally, the regional federations would be involved in promulgating best government and public policy around the use of medications such as methadone and buprenorphine to treat chronic opiate addiction in their respective countries.

It is with all of these principles in mind that Dr. Maremmani and I have been working with representatives in the Russian Federation to promote the use of such medications to treat hundreds of thousands of untreated intravenous heroin users throughout the Russian Federation.

Dr. Maremmani and I will travel to Moscow following the conclusion of this Conference on Sunday, January 29, 2006 to assist Russian officials in making the final preparations for the first major conference in Moscow involving a number of senior Russian Federation officials with regards to the use of these medications to respond to the needs of their population.

We also understand that there is a very high incidence of HIV infection and Hepatitis-C infection in this untreated patient population.

Dr. Maremmani and Ira Marion, one of my closest associates in the United States and who is with us tonight, already travelled to Moscow during June, 2005 for the first major methadone presentation during a Russian event, which was sponsored by the League of Health of the Nation. This league was established by presidential decree by President Putin and has been chaired by Dr. Leo Bockeria, a leading Russian scientist and physician. While the general mission of the League is to improve the general health of the Russian people, it will also work to provide needed care to heroin addicted people as part of the general mission.

The conference of March 29 – April 1, 2006 in Moscow represents a major initiative, which will lay the foundation for introducing the use of methadone and buprenorphine in the Russian Federation.

Other International Experiences

The value of our international collaboration between EUROPAD and AATOD will lead to the treatment of thousands of individuals in need of care. It will improve the general health of the Russian public and will also decrease the flow of illicit opiates
Through the permeable Russian border between Afghanistan and other areas, it will also have a major impact on decreasing narco-terrorism, which is part of the title of the Russian Conference. This goal certainly attracts the attention of other countries as well since we are affected by such realities.

There have also been favourable reports from the government of Bulgaria extending access to methadone treatment. I also want to take the opportunity to congratulate Dr. Alexander Kantchelov. His own leadership and groundbreaking initiatives have helped to establish methadone treatment in Bulgaria. We are fortunate to have a man of such vision among us.

We also have reports that the government of Croatia is interested in expanding its use of methadone in a formalized clinic-oriented environment. Once again, I will remain in contact with Dr. Maremmani as we provide education to their government leadership and treatment providers.

We have also been informed that the government of Vietnam is interested in providing access to methadone treatment to respond to the needs of its untreated intravenous drug using population.

The Iranian government has also estimated that there are at least two million people using drugs in a nation of 78 million. Their government estimates that 200,000 of these people are intravenous drug-users and 25% of this group are HIV infected.

The point in providing such illustrations is to emphasize the importance of our continued international collaboration.

It is understood that no single nation can truly influence worldwide use of effective treatment techniques. It does require an active collaboration among our various treatment associations, drawing upon proven treatment practices and the best research that is available.

Conclusion

Thank you for being so attentive this evening to my remarks. I am very grateful to be involved in this enormous undertaking, which combines the best efforts of EUROPAD Italia within the structure of EUROPAD and AATOD.

Dr. Maremmani has been an incredible partner in this entire process and I am personally grateful for his leadership and his political wisdom.

We are engaged in a major, strategic and long-term effort to combine our knowledge and our energy to create access to methadone and buprenorphine treatment in other nations and to learn what they need as we form this worldwide federation.

This will allow our various associations to influence the United States and the World Health Organization in ensuring that people gain access to comprehensive and effective treatment to that we can relieve suffering and desperation among so many untreated individuals in so many countries throughout the world. This will affect the lives of the patients, their families, their communities, their cities and nations.
It is an extraordinary and noble undertaking, which will benefit people throughout the world. I am very proud to be associated with this effort, and especially proud to be associated with Italian EUROPA D and our European associates.

Introductory lecture at EUROPAD-Italia 2
January 26, 2006
Pietrasanta (Lucca), Italy, EU
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Heroin dependence in the Russian Federation: the current situation

Alexander A. Kozlov, Vladimir V. Perelygin, Maya L. Rohlina, and Konstantin V. Vyshinsky

Summary

This article reviews the current situation surrounding heroin addiction in the Russian Federation; it describes the epidemic patterns associated with that addiction, including their negative impact and complications (HIV, hepatitis, asocial behaviour, mortality). The need to search further for effective integrated approaches to prevention, treatment and rehabilitation is demonstrated with reference to the attitudes of progressive scientists, to the historical experience of Russian addictive psychiatry and to the recommendations of the WHO. The proposal is made that there should be an ongoing search for a differentiated approach and for appropriate criteria to be adopted in integrated treatments of HIV infection and other socially significant consequences of drug addiction; these will call for discussions on substitution therapy.

Key Words: Epidemiology of drug addiction - Russian Federation - Drug addiction complications - Substitution therapy

Drug dependency has become one of the top priorities in the range of problems faced by modern Russian society. The problem of illicit drugs currently poses a serious health threat to the population, because of the epidemic patterns of their use, the rapid increase in their prevalence among teenagers and women, and the explosive rise now occurring in HIV infection, hepatitis, STIs and tuberculosis among substance abusers. Illicit drugs are becoming more easily available; they comprise a wide variety of substances, and the average age of drug users continues to fall. Overdose-related mortality is rising every year. The scale and tempo of the spread of drug dependency in Russia is so high
that they are affecting the physical and psychological health of Russia’s citizens, and its social stability; this has become an issue of national safety.

Over a long period of time alcohol abuse was a more typical phenomenon in Russia. During the last few decades, however, significant changes have been observed in Russia among patients who request treatment for substance dependency. Even if patients with alcohol dependency are still prevalent in terms of absolute numbers, the rising incidence of drug dependency is becoming the dominant issue.

During the years between 1984 and 1996, the incidence of drug addiction rose to 13 times its initial value, and volatile inhalant addiction to 9 times its starting value. Analysis of the dynamics of drug dependency shows a significant deterioration in the situation over the last 10 years. In 1997 there were 88 thousand patients with drug addictions registered at medical institutions; this figure rose to 219,000 in 1999 (154.8 per 100,000 of the population), and to 343,000 in 2004 (223.5 per 100,000).

During the last 10 years, indicators tracking substance dependency, such as the illicit drug dependency syndrome, have increased to 5.5 times their initial level, and the prevalence of heroin dependency (which has been registered separately since 1999), has risen from 133.1 in 1999 to 211.6 per 100,000 of the population in 2003, i.e. to 1.6 times its initial level. In 2004 this indicator stood at 210.9 per 100,000 population (4)(see Table 1).

In the 1980s and early 1990s a majority of drug addicts were using home-made opiates, but a significant increase in heroin abuse was observed in 1994-95. At the present time heroin users make up 87% of patients registered at state-supported treatment facilities. The indicator of the non-narcotic (volatile inhalant) dependence syndrome (known as ‘toxicomania’ in the Russian Federation) was 5.2 per 100,000 population in the 1980s, but since then it has doubled.

According to the Research Institute on Addictions at the Ministry of Health of the Russian Federation, the ‘hidden’ population of those who use illicit drugs regularly was as much as 7 times as high as the number of individuals registered as drug users at state-supported treatment facilities in 1998 (43). If this ratio has remained unchanged, we would expect there to be over 2.5 or even over 3 million individuals with substance abuse in the general population. According to the estimates of some experts, the number of drug users in the Russian Federation is close to 5 million.

It should be mentioned that during the last 15 years the incidence of women registered for drug abuse has risen to 14 times its initial value. In 2000 the Russian health system registered 41,000 women with a diagnosis of drug dependency (53.9 per 100,000 of the female population), which made up 19.5% of all registered patients.

The use of narcotic and non-narcotic psychoactive substances (including illicit drugs, volatile inhalants and both types of substance without physical dependency, which is classified as a separate group) reaches its highest prevalence among younger age groups. The registered prevalence for these conditions is as high as 1,025.6 for 18-19 year olds, and 976.5 for 20-39 year olds per 100,000 within each population.
Table 1. Patients with illicit drug abuse and non-narcotic substance abuse (volatile inhalants) registered at narcological dispensaries in the Russian Federation. Source: official statistical data collected by the end of each reporting year, per 100,000 population.

<table>
<thead>
<tr>
<th>Year</th>
<th>Registered patients with drug dependency (all types)</th>
<th>Registered patients with opiate dependency</th>
<th>Volatile inhalants dependency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>44.0</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>60.2</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>82.6</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>109.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>154.8</td>
<td>133.1</td>
<td>10.1</td>
</tr>
<tr>
<td>2000</td>
<td>198.4</td>
<td>176.0</td>
<td>9.5</td>
</tr>
<tr>
<td>2001</td>
<td>233.2</td>
<td>209.4</td>
<td>9.5</td>
</tr>
<tr>
<td>2002</td>
<td>239.6</td>
<td>213.5</td>
<td>9.9</td>
</tr>
<tr>
<td>2003</td>
<td>222.0</td>
<td>211.67</td>
<td>10.6</td>
</tr>
<tr>
<td>2004</td>
<td>223.5</td>
<td>210.92</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

group. The observed dynamics of incidence parameters for substance abuse now reflects substance use-related conditions in society at an epidemic level, with a tendency for frequencies to rise between 1995 and 2003 (18, 23). In addition, extremely disturbing signals related to drug use are coming from the Armed forces of the Russian Federation. During the last few years almost one out of every 12 army recruits has experimented with drugs; in other words, the problem of drugs is reaching the armed forces as new recruits arrive (26).

Another reason for anxiety is the growing number of complications related to heroin use. The rapid increase in numbers of intravenous drug users (IDUs), mainly due to the increase in heroin use prevalence, has resulted in a rise in cases of B and C hepatitis and in HIV infection within this group. During the last few years the prevalence of these infections has significantly increased as a result of intravenous drug use, turning into a situation of parallel epidemics (3, 42).

IDU-related cases of B and C hepatitis and HIV infection have been registered in all the 89 administrative regions of the Russian Federation. An analysis of HIV prevalence has shown a 310-fold increase from 0.6 per 100,000 of the population in 1995 to 186.4 in 2003, marking an increase in incidence of 276 times. The number of diagnosed cases of HIV infection among intravenous drug users in January 2005 reached 2,081 per 100,000 survey participants (Table 2). Among opiate (mainly heroin) addicts, 80% were HIV-infected.

According to the Central Scientific Research Institute on Epidemiology (2), intravenous drug use was identified as the infection factor in the overwhelming majority of those
Table 2. HIV parameters for the Russian Federation, 1987 - January 31, 2005

<table>
<thead>
<tr>
<th>Year</th>
<th>Newly registered cases</th>
<th>All registered cases</th>
<th>Deaths among HIV positives</th>
<th>Total PLWHA</th>
<th>Prevalence, per 100,000 population</th>
<th>Annual incidence, per 100,000 population</th>
<th>Annual incidence increase ratio</th>
<th>% of all cases of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>726</td>
<td>726</td>
<td>-</td>
<td>726</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1993</td>
<td>163</td>
<td>889</td>
<td>-</td>
<td>889</td>
<td>0.6</td>
<td>0.1</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>1994</td>
<td>201</td>
<td>1,090</td>
<td>169</td>
<td>921</td>
<td>0.6</td>
<td>0.1</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>1995</td>
<td>1,526</td>
<td>2,616</td>
<td>219</td>
<td>2,397</td>
<td>1.6</td>
<td>1.0</td>
<td>7.6</td>
<td>0.6</td>
</tr>
<tr>
<td>1996</td>
<td>4,365</td>
<td>6,981</td>
<td>282</td>
<td>6,699</td>
<td>4.6</td>
<td>3.0</td>
<td>2.9</td>
<td>1.6</td>
</tr>
<tr>
<td>1997</td>
<td>4,058</td>
<td>11,039</td>
<td>370</td>
<td>10,669</td>
<td>7.3</td>
<td>2.8</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>1998</td>
<td>19,953</td>
<td>30,992</td>
<td>549</td>
<td>30,443</td>
<td>20.9</td>
<td>13.7</td>
<td>4.9</td>
<td>7.4</td>
</tr>
<tr>
<td>1999</td>
<td>59,257</td>
<td>90,249</td>
<td>1,092</td>
<td>89,157</td>
<td>61.6</td>
<td>40.8</td>
<td>3.0</td>
<td>21.9</td>
</tr>
<tr>
<td>2000</td>
<td>88,422</td>
<td>178,671</td>
<td>2,750</td>
<td>175,921</td>
<td>121.5</td>
<td>61.3</td>
<td>1.5</td>
<td>32.6</td>
</tr>
<tr>
<td>2001</td>
<td>50,378</td>
<td>229,049</td>
<td>3,164</td>
<td>225,885</td>
<td>157.9</td>
<td>35.1</td>
<td>0.6</td>
<td>18.6</td>
</tr>
<tr>
<td>2002</td>
<td>39,505</td>
<td>270,826</td>
<td>4,152</td>
<td>266,674</td>
<td>186.4</td>
<td>27.6</td>
<td>0.8</td>
<td>14.6</td>
</tr>
<tr>
<td>2003</td>
<td>9,155</td>
<td>279,981</td>
<td>4,177</td>
<td>275,804</td>
<td>192.7</td>
<td>-</td>
<td>-</td>
<td>3.3</td>
</tr>
<tr>
<td>2004</td>
<td>2,081</td>
<td>305,805</td>
<td>5,416</td>
<td>300,389</td>
<td>210.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2005 (Jan.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.3</td>
</tr>
</tbody>
</table>
registered in 2003. 109,673 men and 26,676 women had become infected with HIV via intravenous drug use in Russia by December 31, 2003. The majority of those infected by HIV were in the 20-29 year age group (70,749 men and 16,447 women in 2003). At the present time, the distinctive feature of the HIV epidemic is its active development among women, including women who are intravenous drug users, especially in the 15-25 year age group. The proportion of women among those infected with HIV has reached 33%. Of these, 85% are of reproductive age (with 25% in the 15-20 year group and 50% in the 20-30 year group). Since 1997, the incidence of HIV-infected women has risen to 450 times its initial value. The prevalence of HIV among pregnant women has reached 114.7 per 100,000.

Within the last few years the epidemiological situation in Russia has undergone significant changes with respect to viral hepatitis, too. Before, the overwhelming majority of cases with hepatitis B and C were defined as ‘intra-hospital’ infections, but now most are related to drug injections. Currently, the number of cases related to medical procedures does not exceed 20%, while the proportion of those infected via drug injection has risen considerably. According to the World Health Organization, the risk of acquiring viral hepatitis for intravenous drug users is as high as 60-90%, compared with only 5% among the general population. In the Russian Federation intravenous drug use remains the dominant route for the transmission of infection; its structural incidence is now 60% for viral hepatitis B and as high as 90% for viral hepatitis C.

Once communities of drug users in a particular region become affected with HIV, this leads to the process by which the general population becomes infected in its turn via heterosexual contacts, which is the main route for HIV infection worldwide. This is related to a wide prevalence of unsafe sex practices, lack of knowledge about the problem and about methods of reducing health-related risks in the majority of the population. There is an involvement of intravenous drug users in the sex business (selling sex for money or drugs). One of the studies carried out in the Russian Federation has discovered that 80% of those infected with HIV used injected drugs and had had experiences of selling sex for money (16).

The WHO has supplied the following basic parameters relevant to HIV in Russia within the main groups at risk:
- Estimated number of intravenous drug users: 1.5-3.5 million.
- IDUs among PLWHA: 85% (Euro–WHO review, December 2004).
- IDUs on ARV treatment: 50% (Euro–WHO review, December 2004).
- Prevalence of HIV among intravenous drug users in some cities as high as 65%.

Significant numbers of intravenous drug users are involved in commercial sex work; 5-15% of all commercial sex workers (CSWs), and up to 48% of CSWs who use drugs intravenously, are HIV-infected. HIV prevalence among inmates is estimated at 2-4%; 42,000 prisoners are HIV-positive (crf Ministry of Justice of the Russian Federation, November, 2004).

It should be noted that the majority of patients with drug abuse have also got diseases
Heroin Addiction and Related Clinical Problems

of the liver or myocardium, sexually transmitted diseases and even tuberculosis, as well as having a high suicide and mortality risk. According to official statistics, 70,000 (20%) of patients with drug abuse die each year as a result of overdoses or other causes (by comparison, 40,000 patients with alcohol dependency die annually).

Apart from the diseases and complications just mentioned, one result of long-term drug use is the development of a significant level of psychopathization among these patients, in some cases taking the form of a loss of moral and ethical values, the inability to work and antisocial tendencies. It should be stressed that drug use is changing individuals’ social orientation due to social and professional incapacity and increases in numbers of criminal offences.

Drug-taking clearly requires large amounts of money. A long-term heroin user needs up to 1500 roubles (US$50) daily to buy drugs. Naturally, for the overwhelming majority, there is no legal way to earn this money. Accordingly, drug use is an apprenticeship for crime.

The situation is inauspicious not only for drug users themselves, but also for their relatives and their immediate social environment; even the low level of psychological and physical health recorded among a significant proportion of young people has the potential to lead to the destabilization of Russian society in the near future. There are already official reports available about adverse demographic forecasts for Russia; one common linguistic phenomenon has become the many references made to the ‘Russian cross’ of depopulation. In this, a significant role is played by heroin dependency (see Figure 1).

Based on long-term historical experience comprising almost a hundred years of research, it can be stated with confidence that the models and programmes developed in Russian psychiatry and narcology for dependency treatment have been unable to contribute globally to combating addiction-related disorders and their consequences. ‘Recoveries’ do not happen, and remissions do not last long. In today’s situation, using the methods of pharmacological therapy, it is only possible to cope with withdrawal and post-withdrawal conditions, and sometimes to ‘achieve’ more or less durable remission (5–10% lasting over 12 months). According to the results given by the evaluation of treatment effectiveness, the conclusion must be drawn that pharmacotherapy alone is not enough to ensure long or stable remissions.

The low effectiveness of narcological (addiction treatment) services made available to patients with drug abuse can be partly explained by the precedence given to short-term medical interventions. This makes it impossible to dedicate due attention to personality disorders that are developing alongside drug abuse, or to psychological and social rehabilitation, especially prevention.

At the same time, patients with drug dependency do not have an adequate understanding of their disease and therefore have no motivation to free themselves of it. Treatment at narcological facilities is perceived by patients not as a way to achieving recovery, but as a fine to be paid for the pleasures of drug use, and they try to avoid or postpone
such treatment in every way possible. This complicates the work of psychiatrists and narcologists (addiction psychiatrists) even more.

A large number of peer-reviewed publications have been devoted to various aspects of heroin addiction; most of them deal with the use of substitution therapy (methadone programmes), HIV infection, and, especially, social aspects. Almost all the researchers involved emphasize the need to combine medical care directed to combating HIV infection itself with substitution therapy based on methadone in treating HIV-infected drug addicts \(15, 25, 31, 32, 34, 40, 44\). In the authors’ opinion, methadone substitution is a preferential method and, in the view of some researchers \(25\), it is a unique therapeutic method for active heroin users with HIV infection.

At the same time a number of authors \(22\) indicate that, unlike heroin and other opiates, mostly possessing a short period of action, methadone does not suppress the immune system – it actually stimulates it. This important characteristic of methadone has to be taken into account when HIV-infected drug users are included in methadone programmes. However, even supporters of methadone programmes specify a number of contraindications for the use of this approach \(12\).

Methadone treatment is not indicated:

– for individuals not suffering physically from opiate dependency;
– for individuals who used drugs only for a short period of time;
– for young people;
– for individuals who committed a relatively small number of criminal acts.

At the present time, the use of opiates in treating drug dependency is prohibited by the legislation of the Russian Federation (Position 6, Article 31 of the Federal Law, entitled: “On narcotic drugs and psychotropic substances”).

However, the growing AIDS epidemic, which is leading to sharp increases in numbers of HIV-positive patients and those with AIDS among illicit drug users, requires a
change in treatment approach to such patients, and an updating of the existing legisla-
tion. For example, experts in infectious disease units in the city of Kaliningrad who
have faced the problem of treating drug users with AIDS believe that the use of opiates
for substitution therapy should probably be recommended (10). The use of substitution
therapy is particularly urgent in infectious disease inpatient units which treat drug-us-
ing patients with AIDS and with concurrent severe infectious and somatic diseases,
i.e. those in phase C* or in the terminal phase. The use of substitution therapy in these
stages of a disease is primarily needed to improve the patients’ condition and replace
the intravenous route of administration with the oral route. At specialized units that treat
HIV-infected patients suffering from drug dependency, the issue of substitution therapy
is highly topical, as the use of illicit drugs in such units is, in practice, uncontrolled,
and patients share needles, so increasing the possibility of additional infections with
new strains of HIV and further worsening the epidemic.

Thus, substitution therapy for drug dependency (for example, with buprenorphine)
can be recommended to patients with HIV in the final phase of the disease, with seri-
ous infectious and somatic complications, when traditional methods of treatment have
hardly any effect. In oncological practice, prolonged action morphine in tablet form is
now used. This form of morphine can also be recommended for the group of patients
studied (38). Despite the fact that Russian narcology is basically directed towards the
biological, clinical, social and psychological aspects of treatment, research results
show that studies on the issue of integrating methods of substitution therapy (at least
for patients infected with HIV) are insufficient.

At the present moment, discussions about “methadone programmes” are taking
place in the Russian media, accompanied by negative attitudes towards their possible
use in this country, and by positive attitudes towards addressing HIV-infected drug
users (6, 11, 17, 20, 28-30, 35, 36). Perhaps because methadone is considered to be an illicit
drug that is prohibited in the territory of the Russian Federation, a memorandum has
been issued, stating: “Say no to methadone programmes in the Russian Federation
(methadone prescription cannot be considered a treatment)”. Still, the position of the
WHO has not changed, in view of the pandemic situation affecting intravenous drug
users in Russia. According to the WHO, substitution therapy is an effective tool in
programmes of harm reduction, now that the proportion of intravenous drug users
among HIV-infected patients has nearly reached 80%. Substitution therapy will also
lead to a reduction in illicit opiate consumption, criminal activity, and the number of
lethal overdoses. In addition, the WHO considers substitution therapy to be a powerful
tool in achieving ARV therapy compliance by intravenous drug users (which allows
an improvement in general health among HIV-infected intravenous drug users), a
treatment method that is more effective than placebo or detoxification alone, and also
helps patients to resocialize.

We are convinced that the development of a differentiated set of approach and
treatment criteria, taking into account the views of progressive Russian scientists and
the recommendations of the WHO, would diminish the negative consequences of drug
addiction. It would also help to improve the effectiveness of preventive and medical interventions that aim to cope not only with affective disorders, cravings for drugs and behavioural disorders among patients with drug dependency (including HIV-positive ones), but also allow the implementation of rehabilitation as their objective. Bearing in mind the WHO strategy and the hundred-year experience of narcology (addiction psychiatry) in Russia, it is important to provide comprehensive, evidence-based research data and to ensure close collaboration with policy-makers, besides achieving greater improvements in the knowledge and expertise of practitioners, and more support for pilot initiatives and research.

According to the WHO information letter (June, 2005), a decision has been made to include methadone and buprenorphine in the additional list of recommended medications (Vladimir Poznyak, Coordinator, Mental Health and Drug Addiction Unit, WHO).

We hope for improvements in the drug use situation in the Russian Federation in the very near future, taking into account the information provided, as well as the implementation of the Federal Programme entitled: “Integral measures to combat illicit drug misuse and trafficking for 2005-2009”, which has now been approved by the Russian Federation Government.

The history of Russian narcology began in October, 1907 when, within the Psychoneurology Institute (set up in June, 1907), an outpatient unit of the Society for the Care and Treatment of Alcoholics was organized. It was temporarily located in the Neurology Clinic of the Imperial Military Medical Academy, headed by V.V. Old-erogge (9). In 1911, an Experimental and Clinical Institute for the Study of Alcoholism (also called “The Anti-Alcohol Institute” and, since the beginning of 1914, sometimes referred to as “The Anti-Narcomanic Institute”) was set up within the Psychoneurology Institute. Still in 1911, at the international exhibition in Turin, the project for this institute was awarded a diploma of honour, and, in 1913, at the International Anti-Alcoholic Congress in Paris, the world scientific community unanimously approved a resolution proposing that the government of Russia should organize an international research centre at the Anti-Alcohol Institute in St. Petersburg. In the years of the First World War, starting in 1914, the Anti-Alcohol Institute was reorganized into a military hospital. In 1919, within the Anti-Alcohol Institute, another institute was organized, called the Institute on Pathological Reflexology, with the primary goal of studying “issues related to mental traumas and the development of substance dependency, as well as resolving scientific and psychiatric problems which have been put forward by military and revolutionary events” (5).

In the 20th century, the development of Russian narcology has always been accompanied by “public storms”, one of which in 1912 once again prevented V.M. Behterev from receiving the Nobel Prize (V.M. Behterev’s and I.P. Pavlova’s polemics on the problem of struggling with alcoholism in Russia) (14, 33). During the next few years, the
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development of narcology was defined by numerous normative documents issued by the supreme authorities of the country. The increase in funding and the creation of additional positions to implement these orders and decisions obviously played a positive role. In 1962 order No. 151 of the MoH of the RSFSR, entitled: “About measures to combat alcoholism and drug addiction” was issued; following this, the V.M. Bekhterev Institute carried out research on alcohol and drug abuse in the North-West of Russia. The “bio-psycho-social” model that had been created by V.M. Bekhterev in the beginning of the 20th century was used as the basis of the struggle against alcohol and drug dependency. It not only stressed the significance of pharmacotherapy, but also suggested a psychotherapeutic solution for substance dependency treatment (the “Bekhterev triad”) and spoke about the unique role of social factors (7).

In this way, the V.M. Bekhterev Institute became the assignee of Russian narcology. Afterwards, following the Decree of the USSR Council of Ministers of May, 16, 1972, No. 362, entitled: “About measures to strengthen the struggle against drunkenness and alcoholism” and corresponding orders issued by the Ministry of Health of the USSR (in the decisions of the Ministry of Health Board taken on July 24, 1975), the narcological service was organized as an independent practical part of psychiatry, a structure without analogues in other countries. At the same time, the Serbskij Central Research Institute of Criminal Psychiatry was given the task of organizing, on the basis of two ‘labour and treatment dispensaries’, an experimental base for the development of new forms and methods of treatment for patients with alcohol and drug dependency, so as to increase the overall effectiveness of these establishments. Ten years later, on June 30, 1985, the National Research Centre on Addictions was organized within the Ministry of Health of the Russian Federation; over the last 20 years, it has become the leading research institution for the study of problems of dependency both in Russia and the countries of the CIS.

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CALL FOR PAPERS

PHYSIOLOGY OF PLEASURE AND REWARD

Based on your interest and research activity in the field of behaviour physiology, psychology, psychiatry, on behalf of The European Opiate Treatment Association (Europad), we would like to extend a cordial invitation for you to submit a paper concerning the physiology of pleasure and reward in humans. One chosen work will be awarded during the next Europad congress (Bratislava October 6-8, 2006).

Requirements
Papers are welcome, which are not under consideration for publication elsewhere, and adhere to following requirements:

- papers must not provide with evidence from clinical populations or subjects displaying altered reward-seeking behaviours, such as drug abusers or drug addicts, or subjects with impulse control disorders of an appetitive kind, or subjects with enhanced or depressed reward-seeking functions, such as depressed or manic patients. In fact, the object of research is intended to be human physiology, in the absence of any impairment of pleasure-related functions.
- Data shall be presented in the form of a statistical elaboration. No case-reports or case-series are considered acceptable.
- Works may consist in a variety of models, including epidemiological studies, observational studies, research designs in which healthy subjects, challenged with stimuli and reward- or pleasure-related parameters are measured.
- Data of interest include social, environmental and demographic features, genetic profiling, direct behavioural measurements, personality features, neurophysiologic measurements, endocrine parameters, brain imaging.
- Papers should include the statement that all ethical requirements (e.g. informed consent) have been fulfilled in accordance with the Declaration of Helsinki.

Procedure
A special committee will select submitted papers and make a check the pertinence of submitted papers to the focus of interest along the above criteria. Authors of selected papers will be invited to provide a poster version of their work to be displayed during the next Europad congress, taking place October 6-8, 2006 in Bratislava. The committee will choose one work, whose authors will be awarded with 1,000,00 Euros

Original papers must be submitted by e-mail to the following address: maremman@med.unipi.it

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No intrauterine growth retardation in babies of mothers stabilized on methadone before conception and throughout their pregnancies

Danica Klempova and Lubomir Okruhlica

Summary

The aim of the present study is to explore the maturity of neonates of women who had conceived while being stabilized on methadone and who remained stabilized throughout their pregnancies. The sample comprised ten women and their neonates. All the neonates were eutrophic and nine of them were full-term. Mean birth weight of the neonates was 3,193 g. None of the measures of maturity differed from the data for the general population. The results obtained do not indicate any negative effect of methadone alone on neonatal maturity.

Key Words: Methadone Maintenance - Methadone Stabilization - Pregnancy - Intrauterine Growth Retardation - Neonatal Maturity

Introduction

Despite the better prognosis, in terms of morbidity and mortality, accorded to the fetuses and neonates of mothers on methadone maintenance treatment (MMT), compared with (1) mothers detoxified during pregnancy, or (2) those who continued to use illicit opiates [2, 7], the results of most observational studies have shown a higher incidence of intrauterine growth retardation and more frequent prematurity than those observed in the general population [1, 4, 5, 8-10, 12]. In the meta-analysis carried out by Hulse et al. [6], the mean reduction in birth weight which could be accounted for by methadone was 279 g (with a range of 229-328 g) in neonates of mothers who did not use heroin...
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during pregnancy.

It is very hard to determine to what extent these problems are caused by the dosing regimen applied, by recourse to other drugs (a very common problem), by other factors related to the lifestyle of an addict, or by methadone alone.

Plenty of studies have documented the benefits brought by the stabilization of a pregnant opioid-dependent woman on methadone, but there are no data, or very few, on the maturity of the neonates of mothers who had conceived them while being stabilized on methadone and who remained stabilized throughout their pregnancy. The present study aims to cover this subpopulation.

Our working hypothesis was that the maturity of neonates born to women who had conceived while being stabilized on methadone and then remained stabilized throughout their pregnancy might not differ from the maturity of neonates in the general population.

Patients and Methods

The treatment approach to pregnant women in MMT programmes in Bratislava is characterized by the following parameters (the first two apply to all MMT patients): (1) no ceiling for methadone doses; (2) methadone doses individually tailored to meet patients’ needs according to their cravings, clinical signs of withdrawal and urinalyses; (3) where it is needed, a gradual increase in methadone dose is applied in the last three months of pregnancy.

We have conducted a retrospective audit among women — some current, some ex-MMT programme patients — at the Centre for Treatment of Drug Dependencies in Bratislava.

An optimal cohort approach was applied. The criteria for inclusion were:

1) if conception occurred after the woman had been on methadone maintenance treatment for at least 8 weeks;
2) if the results of the randomly conducted urinalyses were consistently negative for all the drugs screened (opiates, cocaine, amphetamines, methamphetamines, barbiturates and benzodiazepines) throughout her pregnancy.

One woman was excluded from the study because she was suffering from HIV/AIDS and obstetric complications related to that medical condition.

Ten women with their neonates (N=10) were included in the study. Their mean age at delivery was 23.4 years (SD±1.7, range 21-26). They had been using heroin for an average of 5.9 years, with a range of 2-11 years, before entering into MMT. 70% of the mothers had a history of polydrug use on entry into MMT. Six (60%) of them proved to be positive for HCV antibodies. None were HIV- or HBV- positive. Eight women smoked tobacco during their pregnancy, one did not, and in one case the smoking status was unknown. The mothers’ mean methadone dose on the day before delivery was 106.5 mg (SD±51.9 mg, range 40-190 mg).

All these women were asked to provide a medical report on their babies. Data on
the age of gestation, neonate’s maturity, birth weight, and so on, were analysed.

In assessing the influence of methadone maintenance treatment on the neonates’ condition, we decided on comparison of our sample with national data as being methodologically the most correct procedure in checking the status of all possible local differences and time trends. Descriptive statistics was used to describe the biological maturity of the neonates. Normality of data distribution was tested using both the Kolmogorov-Smirnov and the Shapiro-Wilk Test, while the One-Sample T-Test was applied to compare the data for babies born to mothers stabilized in MMT with the general population data. Pearson product-moment correlation and partial correlation was used to further analyse the data. SPSS software was used.

The study was approved by the Ethical Committee at the Centre for Treatment of Drug Dependencies in Bratislava.

Results

40% of the births were spontaneous. All the neonates were eutrophic (birth weight between 5th and 95th percentile of fetal growth) and nine of them were full-term, with gestational age ranging between 38th and 42nd week. One baby was born in the 37th week (partus inductus). In his mother, lues latens and lymphadenopathia were diagnosed shortly before conception. Mean birth weight of the neonates was 3,193 g, median 3,250 g (SD±329.6 g; ranging between 2,650 and 3,650 g). Their mean gestational age was 39.2 weeks, median 39 (SD±1.3; range 37-41 weeks). The average birth length was 48.8 cm, median 49.5 cm (SD±1.9; from 46 to 51 cm). Median Apgar score was: 9.5/10/9 (the third measurement was only performed in 5 neonates).

Since the data from the studied sample showed a normal distribution, it enabled us to use the One-Sample T-Test to compare the sample data with those for the general population. In 2002 and 2003, the mean birth weight of all live births in Slovakia was 3,255 g and 3,259 g, respectively; mean gestational age was 39 weeks and mean birth length was 50 cm (Ustav zdravotnickych informacii a statistiky, response to request IC-548-2004. Selected Data on Neonates in the Slovak Republic. E-mail dated December 16, 2004.). Results of the comparison are shown in Table 1.

<table>
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<th>Table 1. Comparison of data on babies of the optimal cohorts, who conceived on methadone with the general population data (one-sample T-test)</th>
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Birth weight of the neonates was, to a significant degree, negatively correlated with the length of heroin use history of their mothers before the beginning of methadone maintenance treatment (Pearson $r=-0.717$, $p=0.02$, see Figure 1). This correlation remained significant even after checking for mother’s age (partial $r=-0.708$, $p=0.033$). However, birth weight was not correlated with the length of stay in MMT before delivery. Also, the dose of methadone on the day before delivery failed to show statistically significant correlation with birth weight.

Figure 1. Relationship between baby’s birth weight and mother’s length of heroin use before her enrolment in MMTP

Discussion

Birth weight as well as gestational age of methadone babies born to mothers who were stabilized throughout their pregnancies did not reveal statistically significant differences from the general population data in the present study.

Several studies had analysed this problem and showed similar results, except for the findings on the maturity of newborns whose mothers were in MMT. One study reported the beneficial effects of a longer period of methadone maintenance and a higher methadone dose\[^4\]. Even so, very little research has been done while taking precautions to eliminate all possible interference factors, such as: late beginning of MMT in an already pregnant woman, being in the induction phase into methadone maintenance during pregnancy, incomplete stabilization on MMT, continued drug use, smoking habits and so on. Each of these factors might play an important role in retarding fetus development. A recent study by Sharpe and Kuschel\[^11\], who studied the outcomes of infants born to mothers receiving methadone for pain management during pregnancy.
reported results similar to those of the present study, except for a higher incidence of preterm birth, which could be related to other factors in their sample (the mothers studied by them had multiple health problems).

Another important factor seems to be the length of heroin use before MMT programme enrolment. In our sample, this was negatively correlated with weight of the baby at birth. This could be due to long-term damage to the mother’s body deriving from drug use. As a result, studies carried out on methadone patients with a long history of drug use could yield worse outcomes for their neonates.

It is hard to reach conclusions about the net effect of methadone on the maturity of neonates, because of the possible impact of other factors. It is, however, clear that in the presence of other possible teratogens, the maturity and health condition of the observed neonates were good, which implies that methadone itself had had no clinically significant negative impact.

Despite our encouraging findings, there is still the problem that there is a relatively large proportion of women in methadone maintenance treatment programmes who either use drugs other than methadone or enter methadone treatment very late, at an advanced stage of pregnancy. Either condition could have a negative impact on the maturity and health of their neonates. Further research should be carried out to discover how to successfully eliminate substance use during pregnancy, as well as how to encourage pregnant women to participate in an appropriate substitution programme, comprising prenatal care, as early as possible, preferably before their pregnancy. The results of a contingency management approach to eliminating drug use are promising [3], but further research is needed. Encouraging planned parenthood, with the use of contraception until the mother achieves stabilization, is another option.

**Study Limitations**

The most important limitations on the present study include its small sample size and the lack of checks on other factors which might have an impact on the maturity of the neonates. For instance, eight out of ten women continued to smoke tobacco during their pregnancies, most of the mothers were polydrug users before entering into MMT, and a high proportion had blood samples that tested positive for HCV antibodies. All these noxious factors are much less frequent among pregnant women from the general population in the Slovak Republic.

**Conclusions**

We can conclude that the findings of the present study confirm the good level of maturity of neonates born to women stabilized in methadone maintenance treatment throughout their pregnancy. A clinical priority for the future should be to maximize the proportion of pregnant women with opioid dependence who are treated and stabilized in this way.
References


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Effectiveness of buprenorphine in double diagnosed patients.  
Buprenorphine as psychothropic drug

Icro Maremmani¹,²,³, Matteo Pacini² and Pier Paolo Pani⁴

Summary

Opiate drugs were first proposed for the treatment of dysphoric syndromes, depression and psychoses many years ago. Even so, the usefulness of these compounds in psychiatry is supported by only a small corpus of data. The reasons given for the restrictions placed on opiate use are based on prejudice rather than scientific evidence. Buprenorphine, with its unique pharmacological profile, has proved to possess antidepressant, anti-dysphoric and antipsychotic properties in small groups of psychiatric patients. Moreover, it may turn out to be the opiate of choice in subjects affected by lower severity addiction coupled with dysthymic disorders, anxiety disorders and personality disorders. The best dosages appear to be those that ensure a combination of k-antagonism with high levels of μ-mediated stimulation.

Key Words: Buprenorphine - Treatment of mental disorders

Introduction: opiates and mental disorders

Since the Central Nervous System features opioid-related pathways with their own receptors and their own endogenous metabolic activity, every opiate drug, pure antagonists included, can be expected to possess psychotropic properties. Apart from this, therapeutic properties depend on how each drug interacts with the endogenous opioid system and other opioid-sensitive systems, whether through a fast-acting modality or a slow-acting one: the former corresponds to a major addictive risk and a destabilizing
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effect on endogenous functions, the latter to a potential therapeutic action and a neutral effect on the baseline endogenous metabolism. These categories do not relate to the molecular structure as such, but to its kinetics, so that the same molecule may act as a healing medication or as a drug that is toxic and liable to abuse, depending on how it is prepared (e.g. for quick absorption or by adopting a retard formulation) and how it is administered (e.g. intravenously or orally).

Opium was judged to be useful in treating states of dysphoria \(^{(5)}\) and agitated depression as defined by Kraepelin \(^{(24)}\), and approval of such observations can be found in textbooks of psychiatry until the late fifties \(^{(40)}\). More recently, other classes of drugs have been studied and assessed as useful in treating affective disorders and psychoses, while opiates have been overlooked, except for their use as anticraving agents in disorders induced by drugs belonging to the same class. This attitude is partly due to misunderstandings about the addictive risks associated with opiate drugs and about how to prevent prescription drug abuse.

As a result, little evidence is currently available to support the use of opiates in mental disorders \(^{8-10, 26, 62}\), and most of it derives indirectly from populations of opiate addicts. Higher dosages of methadone are resorted to when symptoms of psychoticism, dysthymia, paranoia and somatic discomfort are a prominent feature or are particularly severe. Other psychopathological dimensions, such as anxiety, phobia, interpersonal sensitivity and obsessive-compulsiveness, seem to depend less on the amount of methadone needed to achieve stabilization \(^{(32)}\). Methadone dosage is higher in dual diagnosis patients, in polyabusers and in aggressive patients who display features of violence, anger, irritability and destructive behaviour \(^{(36)}\).

The same conditions that are related to higher stabilization dosages in a methadone maintenance treatment programme \(^{(31)}\) are predictors of dropout from a naltrexone maintenance regimen \(^{(34)}\). The administration of methadone to a group of dual diagnosis psychotic heroin addicts proved to induce remission both of addictive behaviours and psychotic symptoms \(^{(63)}\).

Lastly, we may mention that an 8-year follow-up study of methadone-maintained subjects with a high prevalence of dual diagnosis showed that stabilization is not merely equally likely, but is even more likely for dual diagnosis subjects, as long as higher methadone dosages are attainable and stabilization is pursued as a longer term result. Thus, agonist-maintenance seems to favour a virtuous circle between therapy effectiveness and compliance, which seems to work best in subjects who are most severely impaired, as a result of their dual diagnosis condition \(^{(31, 35)}\).

The restriction of medical opiate drug use to addiction and painful syndromes made them “unadoptable orphans”, to quote Callaway’s verdict on buprenorphine \(^{(4)}\), when it comes to selecting primary psychotropic drugs for the treatment of other mental disorders. The reasons for this restriction are attributable to prejudice, because they have no scientific foundation. Before the opiate addiction epidemic, opiates could be prescribed in cases of persistent opiate-related dysfunction after the gradual withdrawal of opiate replacements (cf. National Conference on Opium, Geneva, Switzerland, 1924). It was
then permissible to restore or maintain somatic dependence on a drug, as long as that condition was judged to be preferable to an opiate-free condition in terms of rehabilitation and psychopathological adjustment. Therapeutic dependence is a feature common to several drugs, including psychotropic (benzodiazepines) and non-psychotropic ones (beta-blockers, thyroid hormone, insulin, cortisones), which can be lawfully prescribed. On the other hand, it is not prohibited to prescribe benzodiazepines to mentally ill people in the long-term, despite the fact that they induce somatic dependence, even if they are certainly liable to abuse, and even if benzodiazepine maintenance is not indicated, and is often counterproductive, in any mental disorder, with only a few exceptions. The view that mental disorders, such as affective ones, are not so severe as to call for maintenance strategies when a relapse-prevention approach is adopted, is open to criticism. Moreover, by contrast with what happens with benzodiazepines, withdrawal from opiates does not bring with it a lethal risk related to seizures. As withdrawal from opiate drugs is gradual, any major discomfort is avoided, whereas the need to abruptly interrupt an ongoing maintenance regimen usually reflects a lack of insight, or a patient’s craving for heroin, in situations where the correct response is to increase dosages. The issue of iatrogenic tolerance to opiates also sounds inconsistent with current views on the nature of addiction as encoded in the DSM-IV\(^{(1)}\): addiction is diagnosed regardless of the state of opiate tolerance/dependence, so it is meaningless to exclude detoxified addicts from maintenance programmes, since agonist maintenance is the first-line treatment for opiate addiction as a relapsing behavioural syndrome, and not for opiate somatic dependence. It should be also remembered that, for addicts who enter treatment programmes in a state of physical dependence, methadone dosages are raised far beyond the current tolerance threshold, since opiate blockade and anticraving effectiveness can only be achieved by dosages higher than what is adequate for anti-withdrawal purposes.

After considering all these factors, we can conclude that buprenorphine, like other opiates, is useful in the treatment of opiate addiction because of its psychotropic properties, beyond withdrawal, so that a distinction between psychotropic properties in addiction and in other mental disorders is groundless and the hypothesis of employing it in non-tolerant individuals does not involve any conceptual leap.

Buprenorphine, with respect to other opiates, is safer, especially in the context of free prescription to psychiatric patients. First, withdrawal from buprenorphine, in cases of ineffectiveness, is quite easy, due to its longer half-life and slower elimination from the body. Its abuse potential may be limited by prescribing the naloxone-buprenorphine combination, in which possible buprenorphine highs are specifically blocked after improper injective use. Lastly, accidental overdosing is self-limiting, due to an early ceiling-effect, so that tolerant subjects do not run that risk\(^{(58, 59, 64)}\).
Buprenorphine and psychopathology

Therapeutic effects on mental disorders can be expected from buprenorphine, in line with its distinctive receptorial profile. Buprenorphine combines μ-agonism, which is closely linked to its anticraving properties and is shared with methadone, with a k-antagonist activity (44). This particular combination makes it easier to assess the psychotropic effects of k-antagonism, since retention rates are higher than those made possible by pure antagonists, such as naltrexone, which are poorly tolerated by heroin addicts, in general, and mentally ill ones, in particular (33, 34).

In a French sample (14), retention in a buprenorphine treatment programme was particularly low for mentally ill addicts, who received no further psychotropic treatment in response to their additional diagnosis. Retention in a buprenorphine treatment programme was predicted by the absence of a family history of affective disorders, and a high level of psychopathological discomfort, as assessed by the Addiction Severity Index (49), while MMPI-rated depression proved to be a negative predictor (49). Depressive and paranoid symptoms rated by the SCL90 negatively affected retention in treatment for buprenorphine-treated subjects compared with a methadone-treated sample, at dosage levels of equal potency (46).

The Italian Multicentric study on quality of life (personal unpublished data) provided interesting evidence on the effects of buprenorphine upon psychopathology dependent on heroin abuse. This study evaluated a subgroup of subjects who had survived 3 months of attrition, i.e. who had stayed in treatment for at least 3 months. The comparison between the buprenorphine-treated group and the methadone-treated group was meaningful, since average dosages corresponded to similar levels of opiate agonism, 8 and 60 mg/day, respectively. After three months, the two groups showed similar levels of improvement, as assessed by the GAF-DSM-IV (1) and a similar reduction in their average SCL90 score (GSI) (7). As treatment proceeded, the scores recorded for all psychopathological dimensions eventually decreased to a similar extent in the two groups. As expected, the gap from baseline to endpoint values during buprenorphine treatment turned out to be widest for opiate-related psychopathology, including anxiety, depression and aggressiveness. On the other hand, baseline psychopathology was more severe for methadone-treated subjects, for all SCL90-rated dimensions. Despite this, the following one-year observation revealed better adjustment for the buprenorphine group: therefore, as μ-agonism is the key factor in achieving psychopathological improvement, a full agonist such as methadone may be optimal in allowing drastic psychopathological improvement in severe cases, whereas buprenorphine may be preferable in the case of mild psychopathological pictures, which are best expressed through an unsatisfactory quality of life.

A higher level of psychopathology does not seem to favour buprenorphine abuse. Buprenorphine mishandlers do not seem to have a higher rate of specific mental impairment and are not concentrated in a high-psychopathology category of drug addicts (48, 61). Although some authors (48) do not mention this while discussing results, the severity of addiction and the intensity of opiate craving seem to be the most likely factors
favouring buprenorphine abuse when no other therapeutic options (e.g. full agonists) are viable.

**Buprenorphine as an antidote to dysphoria**

Evidence of buprenorphine’s psychotropic properties comes from two different kinds of population: the first consists of general drug addicts, whose response and outcome in terms of craving have often been described, so partly accounting for the course of psychopathological features during treatment.

For example, a group of 73 subjects who had survived one month of attrition, out of an original recruitment sample of 115, were made subject to additional observation during the next two months, while receiving buprenorphine at an average dose of 8.5±2.6 mg/day, with the aim of identifying possible outcome predictors. A positive outcome is predicted by a high level of psychopathological discomfort associated with addictive symptoms (psychopathological subscale of the Addiction Severity Index), a low susceptibility to boredom, low disinhibition scores on the Zuckerman scale, an absence of depression as rated by the MMPI but not by the Jouvent scale, the absence of alcoholism, no family history of addictive or affective disorders, and a low duration of addiction (less than 10 years) (49).

Some authors resorted to a pharmacological artefact in order to determine the psychotropic effects of k-antagonism alone (i.e. in the absence of any µ-agonism). In fact, Rothman and colleagues first carried out a three-month observation on a group of 15 subjects who were receiving a buprenorphine-naltrexone combination (4 mg/day of buprenorphine and 50 mg/day of naltrexone). K-antagonism induced by buprenorphine was the only significant effect on those subjects (52). One third of the group were retained in treatment throughout the observation period; these patients were almost completely abstinent from both opiates and cocaine. Responders were male heroin addicts who were not tolerant to opiates at study entrance, with an average age of 41±7 years; these patients had been addicted for an average of 19±8 years. Isolated k-antagonism seems to yield better results than when coupled to µ-antagonism, as it happens with naltrexone. This evidence suggests that buprenorphine may exert an anticraving effect through its k-antagonist property. As an alternative, it could be hypothesized that k-antagonism acts by countering the dysphoric effects of naltrexone, so increasing the likelihood of retention in treatment. In other words, the same kind of dysphoria that can be handled at a later stage by the addition of fluoxetine to a naltrexone-maintenance regimen, with the aim of achieving better retention rates (37), can be prevented from the outset by using a naltrexone-buprenorphine combination.

The same experiment was replicated by Gerra and colleagues in a small group of addicts (N=6) who had dropped out of a naltrexone maintenance programme after only days or weeks. The same subjects, in this study, were treated by a combination of buprenorphine (4mg/day) and naltrexone (50 mg/day), in line with Rothman and coll.’s study. Retention in treatment was as high as 83% in facing immediate attrition, and as long as 5.5±1.1 months on average. Retained patients reported better psychopathological adjustment (dysphoria, depression, irritability, depression, anxiety, asthenia,
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nausea, sickness or stomach ache) than they had experienced before dropping out of naltrexone maintenance (15).

Other authors investigated buprenorphine’s beneficial effects on heterogeneous groups of psychiatric patients who shared what is generically referred to as dysphoria. Resnick and Falk (50) studied two groups of patients with a high prevalence of DSM-III-rated borderline personality disorder (60%): the first group did not include heroin addicts, while the second consisted of abstinent heroin addicts. Among non-addicts, borderline patients only showed improvement after receiving buprenorphine stably for the first month of treatment (with a 30-50% reduction along the HAMD scale and a 43-50% fall in overall psychopathology). This short-term effect was placebo-controlled along a Pl-B-Pl 9-14 day schedule, or a Pl-B / B-Pl reverse switching schedule. Some limitations should, however, be recognized in this study. The second group was not suitable for an evaluation of the primary psychotropic properties of an opiate drug, because it consisted of former heroin abusers, whose current state of abstinence was not enough to qualify them as possessing a normal opiate metabolism. Moreover, the first group was suitable for evaluation, but the conclusive observation that symptoms re-emerged after the withdrawal of medication fails to provide any new evidence.

Morgan and Callaway (42) evaluated the effects of buprenorphine on a group of adult males treated with repeated buprenorphine 0.15 mg doses in a single session, until the effects became measurable. The sample comprised 8 subjects who were evaluated in a double-blind schedule, and 4 in an open-label fashion; it also included 11 mentally ill subjects, most of them diagnosed as depressed, but with a high rate of comorbidity, plus one non-mentally ill “control” subject. Six subjects suffered from some kind of chronic pain, and substance abuse was common in the history of the 11 mentally ill patients. All things considered, the data authorize the conclusion that buprenorphine exerts acute beneficial effects on patients with affective disturbances. On an anecdotal level, the only adverse reaction to buprenorphine (nausea and dysphoria) was reported by the “control” subject.

In addition, we can consider the maladjustment of heroin addicts as a residual state during stable abstinence or as a relapse precursor. Addicts who respond to anticraving treatment programmes benefit from a gradual improvement in, and broadening of, their environmental chances; this is commonly referred to as spontaneous rehabilitative potential. If rehabilitation is to succeed, it must be able to count on an increasing availability of resources, but it also means that an individual will be challenged by new duties and will have to enter into stressful experiences with no certainty of success. While normal individuals tolerate such stress and react by increasing their involvement in their duties, subjects with a history of opiate abuse are likely to feel distressed. Thus, a lower pain threshold, a lower tolerance of effort, and a blunted reactivity to outer stimuli may forerun relapse, signalling persistent opiate damage which will later find expression in an overshoot of craving (30, 38, 45).

In the case of agonist maintenance, the maintenance phase is meant to favour rehabilitation, since the level of opiate coverage can be adjusted to help patients stick to
their rehabilitative goals. Beyond its basic anticraving goals (abstinence), maintenance is meant to allow rehabilitative recovery, counteracting its burden of distress with an increase in opiate coverage which will allow detachment from abuse substances to continue.

**Buprenorphine and Mental Disorders**

**Depression**

Some data have suggested a link between depressive states and endogenous opioid dysfunction \(^{(13, 51, 65)}\), whereas other studies have failed to support this theory \(^{(43)}\).

Both opiate agonists with a prevalently μ-mediated action (morphine, methadone) and k-agonists (cyclazocine, pentazocine) have revealed antidepressant properties \(^{(12, 18)}\), although psychotic effects were one possible outcome with the latter, so suggesting a manic effect rather than a specifically antidepressant one.

Buprenorphine combines the properties of partial μ-agonism, with an early plateau due to its high affinity, and k-antagonism, which curtails the risk of psychotomimetic effects. Some clinicians have issued warnings about possible manic effects, as in the case of other opiates \(^{(39)}\), but those effects may be transient or may develop only in risk-prone subjects \(^{(20)}\).

On the basis of the positive effects recorded in drug addicts, and the background body of evidence about the primary psychotropic properties of other opiates, buprenorphine has been administered to small groups of depressed patients without any history of drug abuse.

Emrich and colleagues performed a controlled double-blind study on a small group of patients with double depression, in most cases resistant to standard therapies, and reported rapid and major beneficial effects \(^{(9)}\).

Bodkin and colleagues examined 10 patients with a depressive syndrome that had proved refractory to at least two classes of traditional antidepressant drugs (TCAs, SSRIs, MAO-Is). Six out of the seven patients who completed the study with no adverse reaction showed significant improvement by six weeks at an average dosage of 1.3 mg/day (which corresponds to a 60% response with an ITT correction). Depression was atypical in 9/10 cases, and the only subject with a typical picture was one of the responders \(^{(3)}\).

Resnick and Falk reported a reduction in psychopathological symptoms in 9 out of 15 patients, and were able to identify borderline personality disorder rated according to the DSM-IIIIR as a predictor of response. In borderline patients, the HAMD score fell by 30-50% during the first month of treatment, at dosages ranging from 0.3 to 12.3 mg/day, while other subjects performed the same as when on placebo \(^{(50)}\).

Morgan and Callaway reported a 73% response in a small group of 11 male non-addicted psychiatric patients, with a variety of conditions, 8 of whom displayed an axis I depressive disorder \(^{(42)}\).

In the multicenter Italian study, depression, anxiety and aggressiveness were the psychopathological dimensions which, as expected, benefited most from buprenorphine treatment. Buprenorphine’s antidepressant action was preferentially expressed on
Heroin addicts, who were depressed at treatment entrance (46). This effect is achieved at dosages ranging from 2 to 8 mg/day, by the end of the first month of treatment (23).

In a randomized controlled comparison with methadone, Dean and coll. reported an equivalent level of improvement along the BDI (Beck Depression Inventory) (6). One hundred and fifty-four heroin addicts were assigned to two equal-sized treatment groups by Gerra and colleagues; methadone was administered at an average dosage of 81,5±36,4 mg/day vs. buprenorphine at 9,2±3,4 mg/day (16). By the end of the third month, retention was similar, but after an intention-to-treat correction, depressive symptoms turned out to predict retention selectively for the buprenorphine group. Although no randomization was performed, depressive symptoms were linked both with longer retention and with lower rates of opiate use at the end of the observation period, so suggesting a buprenorphine-mediated effect.

Anxiety disorders seem to be sensitive to opiates even at low dosages. Anxious subjects require lower methadone dosages for stabilization, suggesting there may be a favourable interaction between opiate agonists, anxiety and retention in treatment (35).

Seifert and colleagues (56) compared two treatment regimens for opiate withdrawal, combining carbamazepine with either methadone or buprenorphine over a two-week period. Results indicate the superiority of the carbamazepine-buprenorphine regimen, even if one major limitation must be pointed out. Carbamazepine is, in fact, known to increase methadone metabolism by induction of the CYP3A4 enzyme system, an effect that develops in a period as short as 1-2 weeks (11), whereas no clear knowledge is available as regards its interactions with buprenorphine. It could be that the fall in methadone availability due to its increased metabolism is the real reason for the difference that was observed on clinical grounds. Despite this problem, the main features of the study design could be replicated, with the improvement of introducing a neutral combination.

Kosten and colleagues (23) assessed the antidepressant effects of buprenorphine in a group of 40 patients, of whom 35% were recruited from ongoing methadone programmes in which the average dosage was as low as 55 mg/day. After a preliminary methadone tapering phase, methadone dosage was kept stable at 25 mg/day for as long as two weeks before a switch to buprenorphine, simultaneously with that of the other 65% of probands, who had been recruited while in a drug-free condition. Interpretation of the results is awkward: no comparison with methadone is possible, since the mean buprenorphine dosages used were not equipotent with the methadone dosage (3.2 mg/day of buprenorphine is, indeed, comparable with 25 mg as far as withdrawal is concerned, but not to 55 mg, which was the latest known stabilization dose). Moreover, the recent tapering of methadone dosages does not justify ruling out possible late withdrawal as the cause of depressive symptoms which lasted no longer than a couple of weeks.

In conclusion, it appears to be difficult to provide a coherent interpretation of this corpus of data, since some studies indicate antidepressant properties for buprenorphine, whereas others identify depression as a dropout predictor in buprenorphine programmes.
The heterogeneity of depressive syndromes is the most likely explanation: depressive symptoms are featured in depressive episodes of varying severity, in chronic minor pictures (dysthymia), in states of intoxication due to a variety of substances, in depressive or mixed phases of bipolar syndromes and, frequently, during anxiety disorders. On one hand, therefore, major melancholic depression may be refractory to buprenorphine treatment, in either unipolar or bipolar pictures. On the other, dysthymia, anxiety disorders with secondary depression and personality-based chronic dysphoria (cluster B personality disorders) may show quick-acting and powerful sensitivity to buprenorphine. Moreover, buprenorphine may be able to improve the outcome of naltrexone-maintained subjects, who become depressed during successful treatment (55). In opposition to the view that drug-free or agonist-free regimens should be the final objective of addiction treatment, we consider it to be preferable, mainly on ethical grounds, to switch from a badly tolerated, even if successful antagonist, to a better tolerated and, presumably, equally successful agonist. This sounds reasonable, especially considering that naltrexone-responders do, in any case, often require supplementary antidepressants. For those not receiving any specific treatment, buprenorphine alone should be preferred to any psychotropic treatment which fails to act on the opioid system, while possessing its own side-effects, in any case.

**Psychosis**

During the induction phase of opiate maintenance, μ-agonist drugs may induce hormonal variations resembling those elicited by classic neuroleptic agents (22); these feature the suppression of hypophysis-controlled adrenal cortisol secretion (41) and hyperprolactinemia (22, 47). Likewise, sedation and depressive symptoms may develop as a result of central nervous dopaminergic antagonism.

In mania (22), 10 mg of methadone, acting as a full μ and k-agonist, proved effective against symptoms of excitement. It should also be borne in mind that the abrupt withdrawal of methadone in tolerant individuals may be followed by psychotic outbursts (27, 57).

K-agonist opiates do possess psychotomimetic properties, especially when, as in the case of cyclazocine or pentazocine, k-antagonism is not linked to any μ-agonism (12, 18, 19). Levels of the endogenous k-agonist dynorphin are related to psychopathological conditions in schizophrenic patients (17, 66).

It is reasonable to conclude that buprenorphine probably possesses antipsychotic properties deriving from its k-antagonist activity. Shmauss and coll. report some evidence of this kind in a small open-label study on 10 patients suffering from schizophrenic spectrum disorders, who were not receiving any antipsychotic treatment at the outset. The frequency of remission of psychotic symptoms was as high as 70% after single buprenorphine doses and lasted an average of about 4 hours (53).
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Dosages and psychotropic effects

Buprenorphine’s psychotropic profile varies with dosage. At lower (< 16 mg/day) dosages, μ-agonism is dose-related, showing a linear progression; k-antagonism is also exerted, and μ-blockade is incomplete. At over 16 mg/day, μ-agonism reaches its plateau (44, 59, 64), providing the same level of stimulation as 65 mg of methadone (21, 28, 60); at this point μ-blockade becomes complete (2).

In subjects who are not tolerant to opiates, antidepressant effects were recorded at very low dosages (0.4 mg) (8, 9). In heroin addicts, higher dosages are likely to be needed, since the baseline tolerance threshold is above zero, and dosages must therefore be raised to achieve the remission of addictive behaviour, independently of depression. Even those dosages, however, are lower than the standard recommended for the treatment of heroin addiction (2-32 mg/day). Also, the effects of buprenorphine on psychopathology, especially of a depressive kind, do not appear to be dose-related: in fact, mean effective dosage is 8.5 mg/die over a wide 3-16 mg/day range (25, 49).

Data discussed by Schottenfeld and colleagues (54) suggest that buprenorphine’s effects on depression may be biphasic, with lower dosages (around 4 mg/day) corresponding to a sharply favourable effect, and higher, blocking dosages corresponding to a less favourable or even an adverse effect. Two types of depression may, in fact, be distinguished: one is usually associated with severe addiction and sensation-seeking traits; it tends to have a poor outcome and is refractory to low potency opiates. The other is milder (dysthymia), is often associated with anxiety disorders and is highly sensitive to buprenorphine. The course of substance use during depression may address towards the best treatment option as suggested by data from Gerra and colleagues (16): their depressed patients do better on buprenorphine; these are cases in which depression is associated with lower rates of positive urinalysis. Conversely, depressed peers in the methadone group are not characterized by a higher retention rate, or by a lower abuse rate as evaluated/tested by urinalyses. It may just be that the two groups correspond to two different longitudinal diagnostic clusters, according to the distinction previously hypothesized.

Patient-treatment matching.

The assignment of patients to buprenorphine programmes should take into account two different factors: the severity of addiction and the severity of psychopathology, on grounds of behavioural stability and reliability. Less severe psychopathology can be taken to include non-bipolar anxiety disorders, dysthymia, obsessive-compulsive disorder and personality disorder in the absence of major affective disorders. As for addiction, severity can be understood to comprise intense cravings, shorter-term relapsing behaviour, habitual polyabuse and multiple concurrent addictions.

The position of buprenorphine with respect to other better-known options (opioid agonists and antagonists), should first be thought of in terms of retention in treatment. In this connection, widely effective options should be chosen first. Patients who are re-
sponders to other agonist treatments can be switched later to buprenorphine programmes, depending on the degree to which a switch is thought to be feasible and preferable.

Let us first consider the case of naltrexone maintenance; short-term naltrexone treatment is out of the question, since it is non-specific towards addiction. Some responders to naltrexone need supplementary medication due to affective disturbance (SSRIs) or resort to non-opiate substances (benzodiazepines, alcohol) in order to keep a balance, while others simply fail to respond and continue to use opiates, or actually drop out. Non-responders or dropouts, as well as dysphoric responders or non-opiate abusing responders could be switched to buprenorphine treatment. On the other hand, full responders, ex juvantibus, may satisfactorily be kept on naltrexone.

To the extent to which the minimization of dropout rates is a goal, buprenorphine could be chosen for those who would fit the criteria for enrolment into naltrexone programmes: in other words, naltrexone treatment may be abandoned in favour of buprenorphine maintenance, which allows the average heroin addict a higher retention rate and a better psychopathological balance.

As to the role to be assigned to methadone, it is useful to classify addicts by applying two criteria: severity of their addictive symptoms, and the severity of other types of psychopathology:

- averagely-to-severely ill addicts (expected to be responders to high dosages of methadone and to be refractory to naltrexone) who are also affected by mental disorders of average severity.
- mildly-to-averagely ill subjects (expected to respond to lower dosages of methadone, with unpredictable reactions to naltrexone), who are also affected by mental disorders of low severity.
- mildly-to-averagely ill subjects (expected to respond to lower dosages of methadone, with unpredictable reactions to naltrexone), who are also affected by mental disorders of high severity.

The first category should be treated by methadone maintenance, with a perspective of complete or partial response. Those who are actually resistant to higher dose, long-term methadone maintenance may thus be labelled as treatment-resistant.

The second group may be started on buprenorphine or, if already on methadone, switched to μ-equipotent buprenorphine dosages, with a perspective of achieving an improved quality of life, fewer and milder side-effects, and a better endocrine function. The transition should only be chosen with stabilized patients, who are almost balanced on psychopathological grounds.

The third group may be preferentially assigned to buprenorphine, as a first-line option. In other words, buprenorphine may be preferable for them, not merely equivalent, in terms of their cost/benefit ratio.

The higher the ratio between psychopathology and addiction, the lower the expected level of effectiveness of buprenorphine on the clinical course will be. In other words, buprenorphine is expected to work best in forms of addiction that are mild-severe and have a short duration. It should be added that buprenorphine may also be effective in
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**Legend:**
- **Add** = Addicted patients
- **av.** = average
- **Bup** = Buprenorphine
- **CBZ** = Carbamazepine
- **db** = Double-Blind
- **DEP** = Depression
- **ITT** = Intention-to-treat
- **Meth** = Methadone
- **mos** = months
- **Pl** = Placebo
- **Psych** = General psychiatric patients
- **Rc** = Randomized-controlled
- **SCL-90** = Somatic Symptom Scale
- **vs.** = versus
- **wk, wks** = week, weeks
- **Open** = Open-label study
- **ITT** = Intention-to-treat
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treating severe psychopathology, as long as comorbid addiction is approached very early and is not accompanied by intense cravings.

Conclusions

Opiate drugs were first proposed for the treatment of dysphoric syndromes, depression and psychoses many years ago. Even so, the usefulness of these compounds in psychiatry is supported by only a small corpus of data. The reasons given for the restrictions placed on opiate use are based on prejudice rather than scientific evidence. Buprenorphine, with its unique pharmacological profile, has proved to possess antidepressant, anti-dysphoric and antipsychotic properties in psychiatric patients. Moreover, it may turn out to be the opiate of choice in subjects affected by lower severity addiction coupled with dysthymic disorders, anxiety disorders and personality disorders. The best dosages appear to be those that ensure a combination of k-antagonism with high levels of μ-mediated stimulation.

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Buprenorphine attenuates the effects of cocaine on adrenocorticotropic (ACTH) secretion and mood states in man. Neuropsychopharmacology. 7:(2) 157-162.


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