

Heroin Maintenance Treatment - Are the Further Investigation Needed?

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Abstract

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The aim of this review is to give new emphasis to key aspects of the proposed treatment of drug addiction. Surveys for so called "second-line" treatment of drug addiction, with heroin (diacetylmorphine) as a pharmaceutical preparation, started since 1990, but this issue is becoming particularly popular in the last period. Drug addiction according to WHO and International Classification of Diseases (ICD10) is chronic, relapsing disease characterized by compulsive drug seeking and use despite harmful consequences as well as neurochemical and molecular changes in the brain. Drugs generate crime, violence and other social problems that are damaging society as a whole. Drug addiction is medical disorder to which contributes more factors and it is necessary to implement the treatment in multi disciplinary manner - from pharmacological, psychiatric, and social aspect. In recent periods studies are carrying out in several countries in the European region, to provide justification, with the scientific medical evidence, for use of heroin as a pharmaceutical dosage form, for treatment of drug addictions for previously unresponsive group. This review paper is focused on maintenance treatment with heroin, retention of the patients into treatment, whether the dose that is expected to be effective at the same time is safe, which organ (systems) are involved in eliminating the drug from the body, whether the injection is the best way for application of the drug.

Purpose of this review paper is not to be supporter or opponent, but to inform, transparently to discuss all aspects and to set conclusions about this type of treatment, within national strategy context.

Introduction

Drug addicts are characterized by persistence in the use of drugs, often combined use of several types of drugs in the same period (F19 – Poly Drug Use), and regardless of the difficulties faced in terms of impaired health, problems related to law, social issues, problems in the family and global functioning in society, criminal behavior and disturbance of the public order, nuisance,

under the influence of drugs [1].

Health problems faced by drug addicts are associated with weakened functioning of major organs liver, renal, pulmonary diseases, cardiovascular diseases, fertility etc. The exchange of non-sterile needles and syringes among drug addicts who inject, gives a possibility for transmission of blood-transmitted diseases such as hepatitis, HIV / AIDS, but also occurrence of

abscesses, infections, damage of veins, thrombosis of the veins, septicemia (generalized bacterial infection of the blood), endocarditic, pulmonary embolism. Many theories explained why individuals with severe mental illnesses are vulnerable to the misuse of substances and how the mental illness-substance misuse relationship co-exists. Does having a psychotic illness lead to substance misuse and in what way? Or is it the case that substance misuse causes psychotic illness? [2].

Opioid dependence is characterized by a range of cognitive, behavioral and psychological disorders [3]. Person needs a drug to function normally. The principles of treatment of drug addiction in accordance with World Health Organization, includes availability and affordability of treatment of disease with pharmacological therapy that has proven effectiveness and efficiency in stabilizing the person with developed drug addiction, based on scientific evidence. The treatment should incorporate psychological and social interventions. Also, the principles of treatment understands reducing of comorbidity, decreasing the risk of mortality associated with use of drugs to a greater extent possible, increasing physical, mental and social capabilities of the person, re-socialization and social integration in society. No single treatment is effective and fits to all individuals. Patients on treatment for opioid dependence have different patterns of use of drugs, different psychological and social problems and diverse risk and protective factors that lead to dependence. That is the reason why treatment should be balanced combination of pharmacotherapy, psychotherapy, psychosocial rehabilitation and reduction of risk factors. Today in global context, there are a number of possibilities for the treatment of people who have developed a drug addiction. Treatment is delivered in outpatient, inpatient, and residential settings. Although specific treatment approaches often are associated with particular treatment settings, a variety of therapeutic interventions or services can be included in any given setting [45]. There are various interventions: detoxification, counseling, maintenance therapy with pharmacological substitution medicine, group work, individual treatment. But all of them have the same goal, to stabilize the patient after some period of abstinence from using narcotic and then maintain this conditions, avoid relapse. Significant therapeutic efforts should be focus on keeping the patient drug-free. National Institute on Drug Abuse of the USA (NIDA) defines addiction as a chronic, relapsing disease characterized by compulsive drug seeking and use despite harmful consequences as well as neurochemical and molecular changes in the brain [46]. Due to developed physical and psychological

dependence, it is difficult to achieve abstinence, especially in a short period of time. Therefore as a substitute to drugs taken from the street, with unsure quality, purity, numerous possible side effects of added substance with aim to increase the volume in correlation with decreasing of the concentration of active component, two approaches for treatment, which can be option of choice of the patient, are developed. One is a detoxification and other treatment with maintenance opioid. Pharmacological treatment of drug addicted person can be with: opioid agonist, partial agonist, opioid antagonist, alpha-2-adrenergic agonists. Detoxification is still with limited time efficiency.

Methadone is a full mu-opioid receptor agonist, typically used as a replacement therapy for heroin or other opioid dependence. Methadone's slow start of action when taken orally and long elimination half-life (24–36 hours), allows it to be used as either as a maintenance therapy or detoxification agent [4]. WHO recommendation is that methadone maintenance doses should be in the range of 60–120 mg per day [5].

Methadone maintenance treatment is associated with retention in treatment, and reductions in drug use, criminal activity, and HIV risk behaviors and mortality [6-9]. It is currently the most successful treatment for chronic opioid dependence [10].

Around three-quarters of people who enter methadone substitution treatment respond well [52] [53]. On the other hand, for various reasons, methadone does not go well with all opioid-dependent people. For this group it is important that alternative approaches are available to encourage their retention in treatment. International trials suggest that the supervised use of medicinal heroin can be an effective second-line treatment for this small, and previously unresponsive, group. In practice, most patients who beginning opioid agonist treatment will stop using heroin or use it occasionally, with only 20–30% reporting ongoing regular heroin use [16, 17].

Heroin is semi synthetic derivate. It can be produced with process of acetylating of the natural alkaloid morphine, which is extracted from certain varieties of the plant *Papaver somniferum*. In the past, extraction of morphine and other alkaloids take place by incision of the poppy straw, in a certain time of the year when it reaches the desired maturity of the plant, and thus the accumulation of alkaloids. From the cut parts of the poppy straw, leakage juice which under the influence of external temperature, condense. This juice (latex)

represents the concentration of alkaloids; it is collected and is known as opium. This procedure when alkaloids are obtaining for medical purposes is now prohibited by international legal acts [11], but still admitted to illegal acts, since it provides the highest concentration of active components. For medical purposes, poppy are harvesting in the upper part of the plant and is treated with chemicals to extract alkaloids - the active components, and then evaporating the used chemicals, using known techniques for pharmaceutical synthesis. The largest producer of illicit opium and heroin is Afghanistan in a worldwide scale [13]. According to UNODC it is estimated 12-14 million heroin users in the world, using around 375 mt (metric tons) of heroin [13]. Europe is one of the most important markets for heroin with an estimated 250 kg of heroin used per day [14]. Heroin was first synthesized at St Mary's hospital in London in 1874. In 1898, it was produced as a new drug by pharmaceutical company Bayer. Heroin was initially introduced into the medical world as a respiratory stimulant (particularly for tuberculosis), however later it was found to be a respiratory depressant. It was also widely used as an analgesic. Consequently, it was suggested that it might be an effective cure for morphine addiction but it was soon found itself to have addictive properties. It was found that this product is 2 to 3 times more powerful than morphine, because of its great liposolubility, which allows quickly passing the barriers and entering the central nervous system. That is the reason why it was given the protected trade name "heroin", precisely because of the great, heroic power which is mostly used in the treatment of tuberculosis, for suppression of coughing. But, patients suffering from tuberculosis continued to die, which confirms that this product only stopped the pain and worked to suppress cough but not cure the disease. Heroin was used to combat opium dependence, but soon after introduction into treatment it was confirmed that heroin causes greater dependence than that of morphine [14]. Heroin is a strong analgesic and is highly effective in the treatment of pain. It is mainly injected.

Renewal of use of heroin as a medicine, now for treatment of drug dependence may have benefits, as well as risks. This issue requires looking in depth in the research evidence to determine whether heroin has advantages over other treatment options for some conditions.

Materials and Methods

This review paper was produced after

comprehensive systematic review of international literature on evidence of effectiveness of treatment of drug dependence, search for relevant articles in: *medical Journal*, reports, info facts and literature search in NIDA, SAMSHA, EMCDDA, WHO, UNAIDS, UNODC.

Electronic search for the existing data was carried out in: in databases (Medline/Pub Med, Cochrane Central Register of Controlled Trials (CENTRAL), Elsevier, Google scholar, Medical Subject Headings, DocGuide, , Psycinfo), in publications, monographs, standards and guidelines.

Search terms which were used are: pharmaceutical heroin, diacetylmorphine, maintenance program with heroin, supervised use of heroin, pharmacological profile of heroin.

Results

In this part of the paper are presented description of the reviewed studies, scientific evidence for injectable treatment with heroin, under supervision of health professional, that was accumulate through international trials.

To date, multisite, prospective, open labeled, randomized, control trials were conducted in six countries Switzerland, Germany, Holland, England, Spain, Canada. Target groups were chronic heroin dependent individuals, severe, treatment-resistant heroin addicts, selected by random selection, and were aged 18 to 65. Trials were conducted for treatment with heroin under supervision, reached 1500 patients [18]. The duration of the tests varies between countries from 6 to 12 months. Positive aspects of the conducted tests are that they were applied in the principles of Good Medicine and Good Clinical Practice according to WHO, ICH / EU standards. Also, studies were conducted under the provisions of the Declaration of Helsinki and Medical Ethics Manual regarding the ethical aspects of studies, obtaining consent from patients after their informing in detail about the study, expected outcomes of the study, possible risks and concerning the protection of personal data.

Trials were conducted in accordance with developed protocols [19] in compliance with the international guidelines for Good Clinical Practice. One type of protocol was for the investigation of the effectiveness of intravenously injected heroin and another protocol for the trial involving inhaled heroin [20].

Main goals of the scientific trials were: treatment

Table 1: Design and results of the reviewed studies.

Country	Sample size		Way of application			Time months	Dose of the Heroin group (mean) Heroin + flexible doses of Methadone	Dose Methad. group (mean)	RESULTS						
	Heroin group	Methadone group	Heroin		Methadone		Heroin	Methadone	Retention in treatment		Self reported illicit heroin use		Improvement (Physical, Social, Psychiatric health response to treatment)		Serious Adverse events
			Injection oral	Inhalation		oral			Heroin group	Methadone group	Heroin group	Methadone group	Heroin group	Methadone group	
Switzerland	27	24	X		X	6	509 mg		93% 25 persons	92% 22 persons	22% 6 persons	67% 16 persons			N/A
Netherlands	76	98	X			12	548 mg	60 mg	72% 55 pers.	85% 83 pers.	25 days in the last month		56%	31%	9
	117	139		X	X	12	548 mg (max of 1000 mg per day/400 mg per visit)	60 mg	68% 80 pers.	87% 121 pers.	26 days in the last month		40%		14
	75	23		X	X	6	502 mg Averaged	60 mg	44,5%		25 days in the last month				12
Spain	31	31	X		X	9	275 mg	105 mg	74% 23 pers.	68% 21 pers.	8,3% 3 pers.	16,9% 5 pers.			7
Germany	515	500	X		X	12	442 mg (up to 1000 mg per day)	99 mg	67% 350pers	40% 200 pers	31% 108 pers.	45% 90 pers.	80% 280 pers.	74% 148 pers.	177
Canada	115	111	X		X	12	392 mg (max 1000 mg per day)	96 mg	88% 101pers	54% 60 p pers.	33% 33pers.	52% 31 pers.			51
UK	43	42	X		X	6	399 mg	107 mg	88% 38 pers	69% 29 pers.	34%	81%			7

*Outcomes were assessed — using a composite score of measures based on ASI (Addiction Severity Index; McLellan et al., 1992), OTI (Opiate Treatment Index; Darke et al., 1992), SCL-90 (Symptom Checklist-90; Derogatis and Cleary, 1997) and SF-12 (Short Form-12; Gandek et al., 1998). Source: Switzerland trial (Perneger et al., 1998), Netherlands trial (Van den Brink et al., 2003), Spain trial (March et al., 2006), Germany trial (Haasen et al., 2007), Canada trial (Oviedo-Joekes et al., 2009), UK trial (Strang et al., 2010)

of intoxication with narcotics, achieving formal abstinence (considering that they used heroin as drug treatment), prevention of criminal activity (which is expected when there is no need to find ways of ensuring dose of „street“ heroin, when heroin is available, free of charge and more over in the form of injection). Objectives of the studies were also to stabilize the addicted person and to reduce the harm.

The studies assess the efficacy of the prescribed intravenous diacetylmorphine versus oral methadone with medical and psychosocial support, with view of improving physical and mental health as well as social integration among socially excluded, opioid dependant individuals for whom standard treatments have failed [21]. The studies assess also retention in treatment, illicit drug use, HIV risk behavior, criminal activity, social functioning, health and psychological status as measured by self-report, urinalysis and doctor's ratings [19].

In most of the trials for evaluation of the treatment of persons addicted to drugs, as a medication is used

heroin that enters the body by injection, and in addition, treatment with flexible dosage of methadone, but in oral dosage form. These patients are monitored during the study, and as a control (comparison group) were persons to whom were administered only oral form of methadone, without combining it with heroin [18, 20, 21, 51].

A study conducted in Switzerland analyzed and compared the effect of heroin, among persons with developed drug addiction. Heroin was in form of injection. Comparison group were persons selected from the waiting lists for treatment and they used treatment option of their choice, available at that time in Geneva [54].

In the study conducted in the Netherlands, persons with addiction were treated with heroin, but in dosage form: inhalation, complemented with methadone in oral form [20]. As a comparison group of patients were patients to which methadone was given in oral form.

Questionnaires, interviews, and medical examinations done at entry point to assess somatic and

mental health, social integration, and treatment outcomes were used in the trials [22]. Measure of patient response was a reduction in illicit drug use or criminal activity as based on the composite score of the European Addiction Severity Index (EUROP-ASI). Outcomes were assessed at stages in the trial — at baseline and follow-up months with using a complex score of measures of general health, self-reported 'street' heroin use, quality of life, drug addiction-related problems, risk behavior for HIV and hepatitis C virus, psychological functioning, and social and family status as based on ASI (Addiction Severity Index) [47], OTI (Opiate Treatment Index) [48], SCL-90 (Symptom Checklist-90) [49] and SF-12 (Short Form-12) [50].

The primary outcome measures in the trial included a reduction of self-reported drug use, reduction of 'street' heroin use and improved health status and social functioning.

Secondary outcomes across trials included, but were not limited to, safety, criminal activity, other drug use, physical health, and psychological and social functioning. Also the cost-effectiveness was assessed [39].

A measure of reduction of 'street' heroin and/or other drug use, rather than abstinence, was consistently used across the trials. For example main aim of two open-label randomized controlled trials in the Netherlands were to investigate patient characteristics to medical heroin prescription compared to standard methadone maintenance treatment. Analysis showed that treatment with medically prescribed heroin plus methadone was significantly more effective (51.8% response) than standard methadone maintenance treatment (28.7%) Multivariate logistic regression analyses showed that only one of all baseline characteristics was predictive of a differential treatment effect: patients who had previously participated in abstinence-orientated treatment responded significantly better to heroin-assisted treatment than to methadone treatment (61% versus 24%), while patients without experience in abstinence-orientated treatment did equally well in heroin-assisted or methadone maintenance treatment (39% and 38%, respectively) [41].

Randomized controlled trial comparing injected diacetylmorphine and oral methadone was carried out in Andalusia, Spain. The subsequent follow-up study evaluated the health and drug use status of participants, 2 years after the completion of the trial. Data collected included information on socio-demographics, drug use,

health and health-related quality of life. Compared data collected before randomization and at 2 years for the following three groups: those currently on heroin-assisted treatment, those who have discontinued. Patients who received on heroin-assisted treatment showed better outcomes compared with those not on heroin-assisted treatments. The results of this study strengthen the evidence showing that on heroin-assisted treatment can improve and stabilize the health of long-term heroin users with severe co morbidities and high mortality [42].

Observational cohort study to describe 4-year treatment retention and treatment response among chronic, treatment-resistant heroin-dependent patients offered long-term heroin-assisted treatment in the Netherlands, showed four-year retention 55.7% [95% confidence interval (CI): 47.6-63.8%]. It was concluded that long-term heroin-assisted treatments is an effective treatment for chronic heroin addicts who have failed to benefit from methadone maintenance treatment. Four years of heroin-assisted treatments is associated with stable physical, mental and social health and with absence of illicit heroin use and substantial reductions in cocaine use [43].

Functioning across several life domains, cross-sectional study with a 6-month follow-up assessed that the Heroin Prescribed group manifested lower levels of psychopathology and showed greater retention in treatment. Although reduced, illicit heroin misuse was not eliminated; the use of other illicit substances was comparable between groups but significantly more of the Heroin Prescribed groups were using illicit cocaine. No differences in current physical health were apparent, criminal activity appeared significantly reduced, but not eliminated, in the Heroin Prescribed group [23].

All these findings support the hypothesis that under the supervised conditions heroin could be safely delivered. In physical health, HIV risk behavior, street heroin use, and days involved in crime, heroin used as a medicine plus methadone was more efficacious than methadone alone [21].

Some argument contra the thesis is that of the estimated 270 000 heroin addicts in the UK, only about 300—400 people are prescribed heroin for their addiction, despite the fact that a subset of people (about 5—10% of all heroin addicts) do not respond to methadone treatment, take methadone but continue to use heroin illegally, and refuse to try existing treatments that might be of benefit. Some experts are skeptical about whether these clinics are really the way forward [44].

This paper review also aims to look at dose of heroin. Research studies in Europe report that the therapeutic dosage of heroin is usually 400-600 mg/day [30]. Researches from Netherlands notify that in heroin maintenance therapy high doses pharmaceutically prepared heroin (up to 1000 mg/day) are prescribed to chronic heroin dependents, who do not respond to conventional interventions such as methadone maintenance treatment [31]. In the Swiss study patients were stabilized on 500 to 600 mg heroin daily [32]. As correlation Methadone maintenance doses is in the range of 60–120 mg per day [5].

As an extremely important segment in terms of assessing the degree of harmfulness of each drug and/or substance that could potentially be used in pharmacological treatment is certainly proper metabolism active component. As an illustration, while Methadone is metabolized primarily in the liver [38], kidneys are primarily involved in the excretion of morphine and morphine glucuronides following heroin administration [33-34]. Liver enzymes are involved in heroin hydrolysis and glucuronidation of the heroin metabolite morphine. The liver is the major organ involved in the glucuronidation of morphine [31]. Morphine-3-glucuronide (M3G) is the major metabolite (M6G/ M3G ratio approximately 0.15) [35]. Morphine-glucuronides are hydrophylic compounds, that are mainly excreted in urine, and in minor quantities in bile.

In order to analyze the situation from all aspects it is useful to mention the existence of heroin injecting centers which are supervised. Medically supervised injecting centers are “legally sanctioned and supervised facilities designed to reduce the health and public order problems associated with illegal injection drug use.” Their purpose is to enable the consumption of pre-obtained drugs under hygienic, low risk conditions [56]. Worldwide, medically supervised injecting centers (also referred to as health rooms, supervised injecting rooms, drug consumption rooms, and safer injecting rooms or facilities) were opened in Sydney, Australia, Germany [58] in the Netherlands, in Switzerland and Spain [59]. They are open from morning to late evening to accommodate drug users who inject up to three times a day [40].

The United Nations International Narcotics Control Board views the centers as violating international drug conventions [60].

Discussion

The main objective of the conducted studies is to define treatment maintenance of adult chronic drug addicts in order to eliminate the use of illegal drugs, “street drugs” and risky behavior in terms of criminal activities to provide the drug, the occurrence of possible blood-transmitted diseases and functioning within the family and society as a whole. Also these studies aimed to verify the effectiveness, safety of maintenance treatment, retention of the patient into treatment, to define the daily dose of substitution therapy and with counseling therapy to reduce as much as possible, the degree of parallel use of other substances, alcohol, benzodiazepines etc. Regarding the first group of targets of the studies, it can be concluded that there has been a significant step forward. Mainly all studies confirmed the following benefits of the treatment: reducing of illegal drug use [24], avoiding illness and death as a result of overdose by ensuring access to a drug of known quality and strength [25], retention in medical care [25] reducing the risk of HIV and hepatitis follow-on unsafe injection practices [26], reducing crime related to drugs, promoting social integration, including employment, accommodation and family life [27].

What is perceived is that all performed studies do not used heroin as a treatment of addiction in the same category. There are substantial differences in methodology. Namely, some studies have used heroin in the form of an injection alone, sometimes in combination therapy with methadone who is in oral form and diluted, in other studies heroin and methadone are applied in the form of injection, while in some studies, (the Netherlands) heroin in the form of inhalation. The method of application is extremely important in the context of its pharmacokinetics and pharmacodynamics, and consequently to the effect achieved. This different methodology further puts into question the results especially in the context of the small (limited) total number of persons in the studies to whom heroin as a treatment was applied. As a parallel: The average prevalence of problem opioid use in the European Union and Norway is estimated to be between 3.6 and 4.4 cases per 1 000 population aged 15–64. This corresponds to some 1.35 million (1.2–1.5 million) problem opioid users in the EU and Norway in 2008 [28].

Methadone is usually administered orally and as such is rapidly absorbed, diacetylmorphine (heroin) is usually administered intravenously. In the trials heroin was supervised but self-administrated [39]. Two issues should be taken into consideration: what in cases and

that is not uncommon among drug addicts, when person has a collapse of the veins, sclerosis and/or thrombosis of the veins? If treatment takes place in specialized institutions and under the supervision of medical staff, including nurses, why in the studies as a main option is self administration of intravenous heroin?

Medically supervised injecting centers was set up, open from morning to late evening to accommodate drug users who inject up to three times a day[40]. All efforts of the new therapies are patient to return to "normal" way of life and integrate into society. Is it rational such a patient to come to medical facility 3 times a day for therapy, including time about 30 mins, after each administration of heroin needed for observation of the patient? As well, there are additional financial costs of transport 3 times a day. Is this arrangements will be attractive enough for the patient to retain on the treatment from one side and from the the other, how he can efficiently perform normal work activities during the day.

Lastly but not least, whether such therapy will be keep only for groups that do not respond to other kind of therapy. Availability of heroin in the form of injection can be attractive to other drug addicts, as well. Consequently, there is a risk of possible increase in the number of heroin addicts, if and when pharmaceutical preparations of heroin will have a marketing authorization.

Considering the higher rate of serious adverse events, the eventual risk-benefit balance of heroin prescription should be carefully evaluated before its implementation in clinical practice [55].

In conclusion, main aim of something new is to get more, to get closer to the goal. The main goal of therapy is abstinence. New forms of therapy with heroin, rapidly increase the treatment dose of opioids. But considering that there are a limited number of subjects, different and combined approach, may be it should be noted that the evidence database of records is relatively weak and it is necessary to perform further tests, taking into account more of the medical aspects of the action of the new therapy, no just improvement of social performance and to set up conclusion whether the introduction of heroin as a treatment, reduce harm from drug use, or increase it.

From human aspect, new treatment will protect patients from criminal activities, but will it contribute to improvement of health as well or not?

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