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

**The vision**

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

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<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>City, Country</th>
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</thead>
<tbody>
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When a New Drug Promotes the Integration of Treatment Modalities: Suboxone and Harm Reduction
Icro Maremmani

Pseudo-Addiction: The Illustrative Case of Howard Hughes
Forest Tennant

The Under Treatment of Pain: A Global Problem. An Educational Approach
Ian Buttfield

Finnish Experience With Buprenorphine-Naloxone Combination (Suboxone®): Survey Evaluations With Intravenous Drug Users
Kaarlo Simojoki and Hannu Alho

Fifteen Years of Office-Based Prescribing in Croatia. Attitudes, Obstacles and Outcomes
Ante Ivancic
When a New Drug Promotes the Integration of Treatment Modalities: Suboxone and Harm Reduction

Icro Maremmani

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Summary

In medicine, the introduction of a new drug is often associated with an overall enhanced understanding of the clinical issues that originally stimulated its own development. Sometimes newer drugs must be introduced to counter the improper use of existing drugs. In this paper, we discuss some concepts regarding the pharmacotherapy of heroin addiction (regarding blocking dosages and stabilization dosages), the advantages and disadvantages of opioid agonists in the pharmacotherapy of heroin addiction, the role of motivation for harm reduction strategies, the difficulties of methadone, buprenorphine, naltrexone and naloxone use in harm reduction strategies, and the possible use of buprenorphine-naloxone combination in harm reduction strategies. A buprenorphine-naloxone combination is not only a clinical improvement over pre-existing treatments, but it also represents a good example of a drug designed to limit the misuse of another resulting in the integration of different modalities of intervention, previously believed to be in opposition.

Key Words: Suboxone, Harm Reduction, Heroin Addiction, Pharmacology, Opioid Receptors. Full and Partial Opioid Agonists, Opioid Antagonists

1. Introduction

In medicine, the introduction of a new drug is often associated with an overall enhanced understanding of the clinical issues that originally stimulated its own development. New drugs are generally introduced to improve efficacy and/or reduce or eliminate side effects as compared to existing treatments. When new drugs are introduced for conditions where treatments exist [6], they usually bring an improvement over the existing drugs given essentially the same indications for their usages (perhaps with some expansion of the clinical cohort in which they are used). Newer drugs generally come to be accepted by the public in a way that is not dissimilar to those they replaced. If there was no stigma associated with the older generation drugs, those that replace them also are accepted.

In the treatment of opiate addiction, medications used to treat and stabilize a patient may be perceived by the public has having equal stigma to the drug of abuse. The stigma encountered in the treatment of heroin addicts tends to encompass the abused opioid, the patients, the medications used in the treatment of the abused opioid, and even the doctors involved in addiction medicine. In addition, such medications can be used in a non-legal or non-therapeutic way [15, 17, 18, 38]. Certainly the perversion of a drug used differently than the strict manner in which it was prescribed should not be confused with pseudo-addiction, a phenomenon referred to as a type of self-medication when prescribers...
fail to provide enough relief with their standard dosing strategies [5].

However, as in the case we are about to discuss, sometimes new drugs must be introduced because of the improper use of older medications.

2. Pharmacotherapy of heroin addiction

2.1 The treatment of opiate addiction as de-conditioning from heroin reward with a need to concurrently stabilize and stimulate the opiate system (blocking dosages and opiate stimulation/stabilization)

The main task of pharmacotherapy of heroin addiction is to ensure that the patient interrupts heroin use and resumes a productive and satisfactory life [11, 22, 35, 37, 44]. Many drugs can be helpful for this purpose. In temporal order we can consider opioid agonists (methadone, LAAM, buprenorphine, slow release morphine), opioid antagonists (naloxone, naltrexone) and, the most recently developed, a buprenorphine-naloxone combination.

The pharmacological action of opioid agonists and antagonists may be very different, yet from a clinical point of view there is a commonality. Both classes of substances are, in fact, able to make the opiate receptors insensitive to the effect of heroin by blocking them. The dose at which this phenomenon takes place is called the “blocking dose”. In other words, when a patient takes a blocking dose of any one of the two classes of drugs (agonists or antagonists), he is aware that a further dose of heroin will no longer have an effect on the brain. As a result the patient will tend not to take it, promoting the process of de-conditioning from a sense of pleasure (reward) induced by heroin; eventually this should lead to the cessation of heroin use. The utilization of “blocking dosages” therapy in heroin addiction was initially proposed by Dole and Nyswander. In the sixties, these two researchers discovered that methadone could be used to treat heroin addiction when used at a dose that “blocks” heroin action in the brain [9, 10, 11].

Heroin owes its addictive property to its “rewarding effect”, defined as a sensation of pleasure after assuming a dose superior to an individual’s tolerance [4]. However, tolerance is an adaptive cerebral phenomenon that makes it impossible to have pleasant effects while maintaining stable dosage over a considerable period of time. A heroin addict will increase the heroin dosage over time, in order to continue to experience reward. Heroin addiction is not only characterized by the continuous pursuit of pleasure, but also by the need to avoid suffering once heroin use is abruptly interrupted (a withdrawal syndrome that indicates the subject’s state of dependence). Addiction is characterized by maladaptive behaviours implemented by the patient in order to reach heroin and its reward, and avoid a state of discomfort due to the lack of intake (dependence-withdrawal). Addiction can be better defined, in non-medical terms, as a state of necessity in which the subject is willing to pay a very high price on the physical, psychopathologic and behavioural level while continuing to use its substance of abuse [8].

In the pharmacotherapy of heroin addiction doctors must use, in different times, anti-withdrawal and blocking dosages of medications interfering with opiate function.

One of the main problems of the pharmacotherapy of heroin addiction is that, usually, anti-withdrawal dose (dose that prevents suffering after cessation of use) does not correspond to the blocking dose (therapeutic dose).

For methadone (full agonist) the blocking dose is much higher than anti-withdrawal dose, for buprenorphine (partial agonist) the distance between the two doses is lower, for naltrexone (antagonist) the anti-withdrawal dose does not exist because this class of drugs does not give relief for a withdrawal syndrome.

Specifically, methadone expresses its receptor-blocking action in a progressive manner, when increasing the dose. Above 60 mg, the dose increase causes a progressive increase in number of receptors blocked. Between 80 and 120 mg it causes blockade of receptors in the majority of patients, but higher doses may be necessary because methadone’s kinetics vary depending on subjects’ genetics. To have the same receptor blockade, which depends on blood dose of methadone, oral doses can vary widely, reaching a 1:30 ratio [20, 36, 50]. Buprenorphine explicates blocking activity between 2 mg and 16 mg [3] by 36 - 50% and 79 - 95% respectively [51], after which dose increases do not significantly influence the number of blocked receptors, only increasing the drug’s duration of action. Fifty milligrams of naltrexone permanently block receptors and higher doses are required only for subjects who use a considerable quantity of heroin.

These differences are related to different receptor interaction modes. Methadone is a full agonist and receptor stimulation is proportional to dose, buprenorphine is a partial agonist and, after a certain amount, the stimulation is not directly proportional to dose (ceiling effect) [28, 45, 46], naltrexone does not stimulate opiate receptors and, in some ways, seems to be more of an inverse agonist than an antagonist [21, 23-25, 27, 30].

The heroin addict in his therapeutic process must, therefore, first interrupt heroin intake and then resolve his withdrawal syndrome, either alone or with medical assistance. The latter requires a prescription of withdrawal-suppressing doses of opiate agonists. After this
first step is taken, the patient should gradually increase doses of opiate agonist until the blocking dose is reached in order to prevent the rewarding effect of occasional heroin intake. If a patient is able to interrupt heroin use without opioid agonist medications, then blocking doses of an opioid antagonist can be therapeutic. However, when using opioid antagonists there is a risk that the lack of a sense of well-being (that generally is obtained, in an heroin addict, with an opioid agonist medication), and the post-withdrawal sense of “discomfort” increases the risk of treatment failure. The success of opioid agonist therapy depends on the fact that it blocks heroin’s action but, at the same time, stabilizes subjects’ opiate systems that used to be stimulated by heroin and are unable to immediately resume their function after heroin cessation. It is believed that this lack of receptor stimulation is the main cause of the poor efficacy of opiate antagonist treatments [16, 41].

2.2 Advantages and disadvantages of agonists of opiates used in the pharmacotherapy of heroin addiction

Methadone was the first opiate agonist used in the pharmacotherapy of heroin addiction. It is the best studied drug, but also the most controversial [47].

After oral administration, it is effective for 24 hours, stabilizing opiate addiction and normalizing (neuro-) endocrine systems disrupted by heroin use. Many hundreds of thousands of patients are treated worldwide in primary or secondary settings. Patients, generally, require 1-3 years of treatment, but a minority may need a longer period of time. Among the benefits of methadone are the interruption of the use of heroin, the absence of a euphoric enforcing effect, the reduction of criminal behaviour and recovery of a general state of health by the patient. Among the disadvantages, we have the lack of effect on cocaine and alcohol abuse, a withdrawal syndrome after suspension and a strong stigma that often determines the impossibility of using blocking doses because they are deemed too high.

Buprenorphine is, from the pharmacological point of view, an obvious improvement. Buprenorphine causes less physical dependence and therefore treatment interruption is easier; it has less acute toxicity; it is less attractive for the “grey market”; it has greater effectiveness in reducing the abuse of other substances [13] (especially cocaine [14, 19]); has a longer duration of action and greater acceptance by the patient and public opinion. However buprenorphine is not without flaws. It has a low oral bioavailability and sublingual administration requires protracted observation. Abuse of buprenorphine has been reported in Europe, Australia and New Zealand [18, 29, 31-33, 39, 42, 43]. When buprenorphine was introduced in France, there were no other treatments available for opiate addiction. The overdose mortality was very high and has been reduced since the early years of introduction of the drug [1]. However, the enormous diffusion of the buprenorphine in absence of structured controls also involved i.v. use [12] and a few deaths were reported for intake of buprenorphine i.v. together with alcohol and benzodiazepines.

The buprenorphine-naloxone (Suboxone) combination is currently available in most countries that use buprenorphine for treatment of opiate addiction in order to limit inappropriate use of this drug, and also to try to promote its use by GPs and psychiatrists [2, 7, 49]. This combination, depending on the route of administration of the drug, combines two opposing mechanisms of pharmacological action — partial agonism of buprenorphine for mu receptors and antagonism of naloxone. If the drug is taken properly, with sublingual administration, only buprenorphine will be active. If administration is intravenous, both drugs are active and, in the presence of full opioid agonists, precipitated withdrawal may occur. In this way, the intravenous use of buprenorphine is deterred.

The buprenorphine-naloxone combination partially resolves, therefore, the problem of buprenorphine misuse, and might also introduce new scenarios, once unimaginined.

3. Harm reduction in heroin addiction

There is a certain degree of uncertainty around the role of so-called “harm reduction” in the treatment of heroin addiction [26, 34, 40, 48]. For some, it represents something halfway between the right to continue substance abuse and not harming oneself too much. For others, the task of harm reduction is reaching the maximum number of heroin addicts with minimal medical expenses since high threshold treatments are more expensive and therefore cannot be given for free to all heroin addicts. On the other hand, heroin addicts are usually not able to provide funding for their treatment. Even in the United States, where the vast majority of patients in treatment are able to afford it, the number of patients waiting for therapy is very high. However, in the context of harm reduction, the complete abstention from heroin use is not necessary and therefore nor is the use of blocking doses of agonist opioid medications.

The practice of harm reduction is effective and safe as is exemplified by the provision of education on the sterile use of substances. The same cannot be said of the eventual use of drugs within harm reduction. The majority of heroin addicts contacted on the street by operators of “harm reduction” are, in fact, chaotic, and often lack psychological and social support as well as a conducive mindset for therapy. Introducing pharma-
cotheraphy in these subjects is extremely complicated because of the risks associated with incorrect use of medications. The consequences can go from personal (death by overdose) to social (“grey market”) risk.

3.1 Difficulties of use of methadone, buprenorphine and naloxone in harm reduction

The use of methadone to achieve the aims of harm reduction is difficult for many reasons. The first is that, generally, an active heroin addict, whose opioid system is dysfunctional, and who has no intention of entering a structured therapeutic program, typically only seeks drugs for the purpose of reducing or eliminating his withdrawal syndrome. Methadone, prescribed by a physician, at withdrawal-suppressing doses, may well meet this need. However, being a full agonist, the dosage should be determined according to the patient’s tolerance. In patients with low tolerance, there is, in fact, a risk of overdose, especially if the patient is ingesting other CNS depressants. In “street” addicts, the patient’s tolerance is often unknown and self report is usually unreliable. If the patient is in full-blown withdrawal, the use of a safe dose of methadone is simplified, but the risk of not completely suppressing his withdrawal symptoms remains. Of course, with clinical observation of the patient there would be no difficulties in effectively determining the proper methadone dosage, but often street contact with drug addicts does not allow refined and precise clinical observations. To complicate the situation further, heroin addicts often do not obviously manifest withdrawal syndromes at treatment initiation. In this case, the drug should ideally be handed over to them for later self-administration at a more clinically appropriate time. This modality elevates the risk of diversion of methadone to the grey market and the risk of inappropriate use increases. Some other patients may be slightly intoxicated. Methadone could be administered in these subjects, without, therefore, handing it over, but this procedure is not free of risk.

In “street junkies” administration of an opioid agonist medication should control the withdrawal syndrome, allowing the formation of a therapeutic relationship — a kind of “enlistment” in order to transfer the patient into more structured programmes that use appropriate doses to block the effects of additional opiate use. Theoretically, therefore, methadone is a drug that can be used in harm reduction, but with the risk of failure in controlling the withdrawal syndrome, and a potential risk of overdose, diversion to the grey market or misuse. If, therefore, it is difficult to use withdrawal-suppressing doses of methadone in street junkies, “blocking doses” certainly cannot be used. It is, in fact, unlikely to be able to have an induction phase lasting at least two or three weeks on the street. Withdrawal-suppressing doses are also much lower than blocking doses. In the absence of structured counselling, however, there is likely to be a cultural resistance among addicts toward transferring from the first to the second.

Buprenorphine has many advantages within harm-reduction oriented treatment. Partial agonism enables it to resolve a full-blown withdrawal crisis without worrying too much about patient’s tolerance. The effect of buprenorphine on respiratory centres makes it unlikely to cause fatal overdose, even in low-tolerant subjects, in the absence of other drugs. The risk increases, however, if the subject has consumed or will consume excessive quantities of alcohol or benzodiazepines. Also entrusting buprenorphine to addicts increases the risk of diversion into the grey market or of misuse. The occurrences of buprenorphine self-administration via the intravenous route rather than sublingual misuse has been well documented. In addition, while buprenorphine can be given to patients showing clear signs of withdrawal, if the patient is still under the effects of heroin or other opioids, it is not possible to administer the drug because of the risk of precipitating a withdrawal syndrome. The distance between the withdrawal-suppressing and blocking doses is minimal and this decreases psychological barriers to transferring from withdrawal-suppressing to blocking doses.

Naltrexone and naloxone are completely ineffective in addressing the symptoms of an opiate withdrawal syndrome. However, naloxone should be considered a life-saving drug for heroin addicts because it can resolve a state of overdose. Unlike methadone and buprenorphine, which have not been utilized in harm reduction, naloxone was distributed for free among drug addicts to enable them to treat companions’ overdoses. This practice has undoubtedly saved many lives, but did not ease the suffering of heroin addicts in withdrawal, nor did it direct them towards more effective forms of therapeutic interventions. Naloxone misuse has been reported as well. This drug should be used, in fact, only in case of acute life-threatening heroin intoxication. Otherwise, naloxone only causes unnecessary withdrawal crisis, potentially deterring heroin addicts from possible future treatment interventions.

3.2 Buprenorphine-naloxone combination in harm reduction

The risks associated with opioid agonist medications in patients that are not part of so-called high threshold treatments have limited, if not made entirely impracticable, their appropriate and safe use in the practice of harm reduction. Consequently alternative, low-threshold therapeutic programs, have not improved overall treatment outcomes. In addition, these programmes, due to restrictions on entrusting opiate
drugs for withdrawal treatment to addicts, were not able to reach a significant number of “street junkies”. The buprenorphine-naloxone combination (Suboxone®) is effective and safe even in harm reduction practices in which the drug is entrusted with the heroin addicts. Suboxone is, in fact, appropriate not only for medical prescription but also for patients’ self-administration. That is, once that diagnosis of heroin addiction is made, Suboxone may also be entrusted to the patient without incurring a particular risk to the patient’s health or of drug diversion. Its efficacy in treating the withdrawal syndrome is due to its partial agonist action on mu receptors. This makes it possible to intervene successfully in the context of a medium-high intensity opiate withdrawal syndrome in the absence of strong opiate stimulation that could create reward in the patient or, worse, overdose. Withdrawal-suppressing doses are themselves “blocking” enough, and therefore “therapeutic”. “Street” drug addicts can readily interrupt their withdrawal crises, therefore controlling a segment of maladjusted behaviour deriving from addiction. After intake of a single dose of around 8-16 mg of buprenorphine contained in Suboxone, moreover, the patient will become relatively insensitive to subsequent heroin intake [3, 51]. Buprenorphine misuse becomes very unlikely since increasing the dose does not increase the pleasurable effect (“ceiling” to reinforcing effects) [46]. The drug can be entrusted even to slightly intoxicated patients since its administration prior to withdrawal onset would only precipitate an immediate withdrawal syndrome. Unlike handing a dose of methadone over to an intoxicated patient to be taken at the beginning of the withdrawal syndrome, it is unlikely that the addict will take buprenorphine while not in withdrawal crisis. Buprenorphine is safe even if subject’s tolerance is not known since the risk of overdose is minimal because of its “ceiling effect”. This is not the case with methadone. Suboxone is safe from the point of view of drug diversion. A patient who has received it in order to ease his/her withdrawal syndrome cannot easily sell a medication whose reinforcing properties are limited by potential antagonism of previously administered full agonists, and that therefore cannot be used to supplement a previously administered insufficient dose of lower affinity opiates. All these advantages can be obtained with the sublingual administration of buprenorphine. Unfortunately, the doses of buprenorphine entrusted to the patient can be injected to increase the opiate action in highly tolerant patients and also for non therapeutic purposes. Adding naloxone, making injection of the combined preparation less attractive, reduces the impact of this limitation. At this point, Suboxone becomes the best option to use in pharmacological harm reduction due to its effectiveness in withdrawal management, ease of transfer to blocking doses, and decreased likelihood of non-therapeutic use.

4. Conclusions

The buprenorphine-naloxone combination (Suboxone) is a clear improvement for pharmacotherapy in opiate addiction. It maintains the effectiveness of buprenorphine and reduces abuse liability in patients seeking treatment. In the various stages of treatment, the greatest risks to patients’ health are during the induction phase; in general we prefer to initiate treatment during this phase in specialized centres. With the introduction of this combination, the pharmacological induction phase will be more simple and safe even if conducted by GPs or psychiatrists who do not work in specialized services for drug addiction. However, the most interesting aspect is, in my opinion, the possibility of proper use of this combination in harm reduction practices. In addition to direct administration, there are few contraindications to entrusting it to patients that do not have a concurrent withdrawal syndrome. The buprenorphine-naloxone combination is not only a technical improvement of pharmaceutical techniques responding to specific clinical needs, it also represents a good example of when a drug designed to limit misuse of another drug promotes the integration of different modes of intervention, once erroneously considered to be in opposition (harm reduction vs comprehensive treatments).

Role of funding source

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Conflict of Interest

No conflict of interest.

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References


<table>
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<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker(s)</th>
</tr>
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<tbody>
<tr>
<td>1:00 PM</td>
<td>Efficacy of Opioid Agonist Therapy on Psychopathological Symptoms: Methadone vs Buprenorphine</td>
<td>Icro Maremmani (Pisa, Italy, EU)</td>
</tr>
<tr>
<td>1:20 PM</td>
<td>Repressive Strategy Against Liberal Strategy in Treating Heroin Addicts in Russia</td>
<td>Vladimir Mendelevich (Kazan, Russia)</td>
</tr>
<tr>
<td>1:40 PM</td>
<td>Economic Evaluation of Interventions To Treat Opiate Dependence: A Review of the Evidence</td>
<td>Christopher M. Doran (Sydney, Australia)</td>
</tr>
<tr>
<td>2:00 PM</td>
<td>The European Experience Delivering Buprenorphine and Methadone. Comparison Between France and Portugal (regulations, clinical experience, practice)</td>
<td>Pascal Courty (Clermont-Ferrand, France, EU), Luis Patricio (Lisbon, Portugal, EU) and Didier Touzeau (Paris, France, EU)</td>
</tr>
<tr>
<td>2:20 PM</td>
<td>Foundamental Principles and Rules in Treating Heroin Addicts at &quot;Fondation Phenix&quot; in Geneve, Switzerland</td>
<td>Michel Bourquin and Jean-Marie Rossier (Geneve, Switzerland)</td>
</tr>
<tr>
<td>2:40 PM</td>
<td>Screening and Treatment of Viral Hepatitis B and C in Inmates With and Without Opioid Agonist Therapy. Results of Four French National Surveys (2000-2005)</td>
<td>Andre-Jean Remy (Perpignan, France, EU)</td>
</tr>
<tr>
<td>3:00 PM</td>
<td>What Treatment is Good Treatment? Clinician's Reflections on Patient Perspectives</td>
<td>Alexander Kantchelov, Tsvetana Stoykova, Orlin Todorov and Alexander Belchev (Sofia, Bulgaria, EU)</td>
</tr>
<tr>
<td>3:20 PM</td>
<td>Heroin Addiction and Mortality</td>
<td>Barbara Lovrecic and Mercedes Lovrecic (Lubiana, Slovenia, EU)</td>
</tr>
<tr>
<td>3:40 PM</td>
<td>Does a Specific Psychopathology of Heroin Addiction Exist?</td>
<td>Pier Paolo Pani (Cagliari, Italy, EU)</td>
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<tr>
<td>4:00 PM</td>
<td>Treating Heroin Addicts in Jail</td>
<td>Andrej Kastelic (Lubiana, Slovenia, EU)</td>
</tr>
<tr>
<td>4:20 PM</td>
<td>Opiates and Alcohol. Important Clinical Connections</td>
<td>Albrecht Ulmer (Stuttgart, Germany, EU)</td>
</tr>
<tr>
<td>4:40 PM</td>
<td>Discussion</td>
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<td>5:00 PM</td>
<td>End of Forum</td>
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In collaboration with EUROPAD-Italia and Italian Society of Addiction Medicine (SITD)
Pseudo-Addiction: The Illustrative Case of Howard Hughes

Forest Tennant

Veract Intractable Pain Centre

Summary

While the need for chronic pain treatment is evident by epidemiologic surveys from many countries, countless persons continue needless suffering due to lack of pain treatment. One is a bias against opioid drugs, and the false belief that persons who take opioids are “addicts”. Modern definitions essentially relegate the term “addict” to persons who take opioids for non-pain purposes. The term “pseudo-addiction” is now the term properly used for those persons who seek pain relief by patronizing a variety of sources to obtain opioids because they lack a regular, medical source of treatment with opioids. Perhaps the most famous “pseudo-addict” was Howard Hughes. He was involved in a plane crash in 1946 and suffered severe chronic pain as a result of facial and neck fractures and third degree burns of the upper torso. His subsequent post-trauma neuropathies are now commonly referred to as Reflex Sympathetic Dystrophy. They were so severe that he often could not brush his teeth, comb his hair, shave, or wear clothes or shoes. He survived 30 years taking about 200 mg equivalent of morphine a day for pain control. At this time the author is treating a cohort of severe, chronic pain patients who have taken high, daily opioid dosages for 20 to 30 years. As did Howard Hughes, these patients lead high quality, productive lives despite high dose opioid treatment. Severe, chronic pain, per se, and unrelated to its underlying cause, has life shortening and debilitating complications that are caused by uncontrolled electrical conduction, excess sympathetic discharge in the autonomic nervous systems, and excess pituitary-adrenal hormone secretions. Pseudo-addicts are easy to clinically differentiate from bona fide opioid addicts and treatment facilities should differentiate between the two. We need a world wide humane movement to provide life-time, opioid, medical management for persons afflicted with severe, chronic pain that can only be controlled by opioid drugs.

Key Words: Pseudo-addiction, Pain and addiction

1. Introduction

With the emergence of opioid treatment of intractable pain (defined here as incurable, severe, and constant), there is great interest in the long-term survival of patients who require such treatment. At this time, there are no published reports of opioid-treated, intractable pain patients who have survived over a decade.

Because of a combination of fame and wealth the revisiting of the HH case was made possible due to the volume of detailed records available. Underneath the glamour, tilts, sex, money and politics that surround the saga of Howard Hughes (HH), there is a serious and tutorial medical story from which all concerned parties can benefit. HH lived 30 years taking high dosages of codeine in an average daily dosage between 20 and 45 grains a day. He survived a plane crash in 1946, developed intractable pain, and died 30 years later in 1976 due to specific, anti-inflammatory agents that, over-time, produced kidney failure. [1-3]

The author was contacted in 1978 by the US Drug Enforcement Agency to be a consultant on HH. I was given copies of HH’s autopsy report, post-mortem toxicology analysis, birth certificate, death certificate,
1958 memo written by HH involving medication acquisition, and a daily log with medication administration kept his aides dated October 31, 1971 through July 1, 1973. These materials were presented in a public trial and are not confidential documents [3]. This log covering his habits and behaviour, in detail, was in the 25th and 26th year after his plane crash and consumption of opioids. It is very revealing as to how he treated his pain and functioned.

In September 1978 I compiled a written report for the US Government based on the documents given to me. In addition, I appeared as an expert witness in the Federal trial, US versus Thain [3]. At this trial, held in Ogden, Utah, I was able to interview two of HH’s now-deceased, personal physicians about Hughes’ medical history and treatment.

It is cogent to point out that in 1978 I was fully vested in addiction research and treatment and had only begun to research and treat intractable pain patients with opioids. Consequently, my 1978 analysis of this matter including terminology and biologic concepts were archaic given the monumental, historic, and scientific breakthroughs in the understanding of addiction and pain that have occurred since 1977.

Due to the great interest in the long-term survival of pain patients treated with opioids, a re-analysis and report of HH at this time is most informative and instructive for physicians and patients. This re-analysis incorporates many of the current terms, concepts, and scientific advances that have emerged in the past 30 years. To provide perspective on where we have matured from some relevant terms are shown in table 1.

### 2. Precipitating cause of pain and initiation of opioid treatment

Born in 1905, HH was a world-recognized, pioneering entrepreneur engaged in diverse businesses to include chemicals, plastics, moving pictures, entertainment and aircraft design and development. In 1946, at the age of 41, HH solo-tested an experimental reconnaissance plane known as the XF-11. Shortly after take-off from the Santa Monica, California airport he crashed. He miraculously survived the crash and was immediately hospitalized at Good Samaritan Hospital in downtown Los Angeles. His injuries were numerous and included multiple fractures and third degree burns. He required three chest drainings, since he recurrently bled into his left chest cavity. Four skin grafts were required to close a large 3rd degree burn extending from his shoulder to hip. He remained at Good Samaritan Hospital for about 5 weeks between July 7 and August 11, 1946. HH was given morphine while hospitalized and was discharged on codeine. A detailed list of HH’s injuries are listed in Table 2 to emphasize that essentially no one can survive these injuries without developing intractable pain. Modern day pain treatment specifically and clearly recognizes that neck and facial fractures are associated

<table>
<thead>
<tr>
<th>Table 1. Some pain treatment changes in terminology and concepts during the past 30 years</th>
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<tbody>
<tr>
<td><strong>1977</strong></td>
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<tr>
<td>Addict</td>
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<tr>
<td>Psuedo-addiction</td>
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<tr>
<td>Intractable pain</td>
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<td>Breakthrough</td>
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<td>Short and long-acting opioids</td>
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<tr>
<td>Pain characterization</td>
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<tr>
<td>Effect of renal failure on drug serum levels</td>
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<tr>
<td>Morphine Equivalency</td>
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</table>

Usual treatment for severe intractable or persistent pain is a long-acting opioid plus a short-acting one for breakthrough pain

Common classes include neuropathic, myofacial, and reflex sympathetic dystrophy

Poor renal clearance may greatly raise serum levels of therapeutic drugs

Pain potency of all opioids are equated to the effect of 1 mg of morphine
with intractable pain. Third degree burn scars are known to cause pain in peripheral nerves. Pain that radiates from a central nerve injury into the face, arms, legs, or chest wall is now referred to as neuropathic pain. This term was not used during the life of HH. Details of his injuries are given here to eliminate any misconceptions and refute some public reports that he didn’t have pain and require medication.

3. Characterization of HH’s pain

Today’s pain terminology, as confusing and deficient as it may be, helps provide a framework to understand HH and all other pain patients. Acute pain is one of sudden onset and that resolves within days or weeks. A headache is a good example. Chronic pain is an intermittent or constant pain that persists beyond about 90 days. Millions of people suffer from mild or moderate chronic pain due to such causes as arthritis, lumbar sprain, bunions, or carpal tunnel. The severe form of chronic pain is more and more being referred to as “intractable pain”. This form of chronic pain is reserved for those severe chronic pain patients whose pain is severe, incapacitating, constant, incurable, and interferes with biologic functions including sleep, eating, ambulation, and social interaction. Undertreatment results in reclusivity and a home or bed-bound state. Intractable pain patients have a persistent or baseline pain with flares or breakthrough episodes above their baseline pain. Injuries such as those sustained by HH in his 1946 plane crash inevitably produce chronic pain and likely cause intractable pain. Scientific studies now show it is usually possible to separate intractable pain from ordinary chronic pain in that intractable cases demonstrable biologic changes in heart rate, blood pressure, and adrenal hormone production. Analysis of HH’s medical and pain history clearly shows that today he would be characterized as an IP patient.

HH’s pain, according to his physicians, was constant and centred around his neck, shoulders, back, and into his arms. In the 1946 plane crash he suffered fractures of some cervical neck facets. Collapsed vertebrae were noted on x-rays taken at autopsy. His physician in the last years of his life, Dr. Wilbur Thain, described his skin as “extremely sensitive to touch” and any cutting of his finger or toe nails “hurt like hell”. As HH aged, he developed degenerative arthritis in several joints that aggravated his pain. After his fractured left hip was pinned in 1973, he did not walk again and developed a contracture of the left leg. His hip fracture and contracted leg may also have contributed to his pain. Dr. Thain offered Hughes a walker, wheelchair, or even a cute physical therapist to help him walk again. Hughes replied humorously to the latter, “No Wilbur, I’m too old for that”. Thain considered, rightly so, that HH’s resistance to walking after his hip fracture was “the beginning of the end”. Modern day pain specialists ask and demand physical activity and movement from intractable pain patients if they are to escape a bed or couch-bound state. In this regard, Dr. Thain appeared to be a physician well ahead of his time.

HH suffered several neuropathies and had allodynia which is severe pain to the touch. He would possibly today, be given the diagnosis of Reflex Sympathetic Dystrophy or Chronic Regional Pain Syndrome. At times his pain was reported to be so severe that a simple touch or the touching of bedclothes produced pain. His renowned refusal to brush his teeth, cut his toe and finger nails, or wear shoes may have been related to the fact that these actions may have caused increased pain.

<table>
<thead>
<tr>
<th>Table 2. Injuries sustained in 1946 plane crash that produced intractable pain</th>
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<tr>
<td>3rd degree burn of abdomen and chest wall</td>
</tr>
<tr>
<td>Fractures of chin, jaw, left knee, and left elbow</td>
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<tr>
<td>Multiple burns of left ear, left chest, left abdominal wall, little finger left hand, left buttocks</td>
</tr>
<tr>
<td>Third degree burns in some areas. One large one extended from his left shoulder to left hip</td>
</tr>
<tr>
<td>Displacement of 6th cervical vertebrae onto the body of the 7th</td>
</tr>
<tr>
<td>Fracture through lateral articular facets of 5, 6, 7th cervical vertebrae</td>
</tr>
<tr>
<td>Fractures of ribs 1, 2, 3, and 4 on right. Fractures of 1, 2, 3, 4, 5, 6, 7, 8, and 9 on left</td>
</tr>
<tr>
<td>Fracture of left clavicle</td>
</tr>
<tr>
<td>Hemorrhage into left chest cavity with displacement of heart into right chest</td>
</tr>
<tr>
<td>Hemorrhage into mediastinum</td>
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<tr>
<td>Blood loss requiring transfusions</td>
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<tr>
<td>If a person survived the above injuries they would most likely be left in intractable pain.</td>
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His multiple facial fractures probably produced a neuropathy of his jaws and face. At this time, it is not possible to correlate his pain and its treatment to either helping or hurting his renowned, lifelong eccentricity and obsessive-compulsive traits or to his failure to brush teeth, cut nails, or exercise.

4. Pseudo-addiction or addiction?

After HH’s death and the revelation that he had taken high dosages of codeine and diazepam (Valium®) for many years, he was called an addict by all concerned parties including the author. In addition, he was assumed to abuse his medications since reports indicated he became over-sedated with resulting pressure (bed) sores, falls, reclusivity, and obsessive-compulsive traits such as over-washing. To compound this belief a memo was written by HH in 1958 which gave detailed instructions to his aides on how to obtain controlled drugs. This memo was initially believed to be a surreptitious attempt to obtain drugs for purposes of abuse, but later information revealed that it was simply to obtain medications legitimately prescribed by his physicians. His major physician at this time was Dr. Vern Mason, an accomplished internist who cared for HH’s pain in the early years after the plane crash, and prescribed codeine. His physicians instructed him on how to inject codeine.

Today, HH’s drug seeking would be termed pseudo-addiction. There is now a standard set of terms adopted by all major professional, pain treatment organizations and the American Society of Addiction Medicine. New terms and definitions propagated by the National Federation of Medical Boards are critical to the understanding of HH’s pain and medical catastrophe, so they are given here:

Addiction - Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include the following: impaired control over drug use, craving, compulsive use, and continued use despite harm. Physical dependence and tolerance are normal physiological consequences of extended opioid therapy for pain and are not the same as addiction.

Pseudo-addiction - The syndrome resulting from the misinterpretation of relief seeking behaviours as though they are drug-seeking behaviours that are commonly seen with addiction. The relief seeking behaviours resolve upon institution of effective analgesic therapy.

Tolerance - Tolerance is a physiologic state resulting from regular use of a drug in which an increased dosage is needed to produce a specific effect, or a reduced effect is observed with a constant dose over time. Tolerance may or may not be evident during opioid treatment and does not equate with addiction.

Chronic pain - Chronic pain is a state in which pain persists beyond the usual course of an acute disease of healing of an injury, or that may or may not be associated with an acute or chronic pathologic process that causes continuous or intermittent pain over months or years.

Physical dependence - Physical dependence is a state of adaptation that is manifested by drug class-specific signs and symptoms that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Physical dependence, by itself, does not equate with addiction.

There is no more profound example of misinterpretation relative to addiction versus pseudo-addiction than the finding of 5 embedded needles seen on HH’s arm x-rays taken at autopsy. (FIGURE 1) The immediate conclusion by myself and others after seeing these x-rays was that embedded needles must represent addiction and abuse of drugs. Later understanding of the effectiveness of oral versus injectable opioid compounds tells us the true picture. HH self-injected pure codeine phosphate and also took oral compounded codeine (i.e. codeine with phenacetin, aspirin, etc.). In later years HH’s physicians confirmed that his major pain relief was by injectable codeine. It is now clear that codeine would not be potent enough or last long enough in the body to provide much pain relief for HH. For example, codeine’s effective pain relief activity is seldom over about 3 hours, and HH obviously required pain relief...
for 24 hours each day. These simple facts give ample reason for a high daily dosage of codeine. Embedded needles are easy to understand when one realizes that there were no disposable syringes with attached needles in HH’s day. Syringes used today by pain patients are disposable after one use, sanitary, plastic, and have sharp small attached needles to prevent embedding. HH had to use a glass syringe with non-attached needles that easily came loose when injected. The same applied to diabetics in those years who also commonly left needles under the skin. Furthermore, he had to keep his syringes as clean as possible, and he did sustain some periodic skin infections from poorly sterilized needles and syringes.

It is worth noting that HH did not have the usual addictive personality witnessed in America. He did not smoke cigarettes and seldom drank alcohol. He did not routinely inject codeine by the intravenous route as an addict will often do but he injected it into the subcutaneous and muscular tissues.

5. Heading under X-Ray

This x-ray taken at autopsy shows 5 needles embedded in HH’s arms. Just as does a diabetic, Hughes had to self-inject codeine intramuscularly with outmoded glass syringes that had detachable needles which frequently came loose under the skin. When this x-ray was first observed, an erroneous conclusion was made that it indicated addiction and abuse of codeine rather than pseudo-addiction. HH’s best pain relief was by injecting codeine, but codeine was probably not nearly potent enough to fully relieve HH’s pain.

6. Complications of intractable pain

It is now known that intractable pain, per se, will produce complications, and HH appeared to suffer some. The most physical demonstration was osteoporosis and teeth erosion. Intractable pain, when uncontrolled, produces hypercortisolemia and loss of bone and teeth composition. Osteoporosis combined with the sedation of diazepam appeared to produce his 1973 fall and hip fracture. Collapsed vertebrae of the neck were seen on x-ray at autopsy. His pain also contributed to his tendency to reclusivity. Today we inquire of intractable pain patients as to whether their baseline pain and flares are causing them to be bed or house-bound. His out-of-control pain likely also caused him to refrain from some types of physical activities or exercise.

Intractable pain is now known to cause profound alterations in hormone production. In addition opioid drugs will decrease testosterone production. Uncontrolled pain seems to decrease the ability of nerves to function. HH had difficulty urinating which is typical of intractable pain patients both due to spinal nerve injury and opioid drugs. According to Michael Drosnin in his excellent book, “Citizen Hughes”, HH quit womanizing about 15 years before his death. [5] He also divorced about this time. Considering the severity of HH’s pain and his necessity for potent medication, this time-point in his 30-year survival appears valid. Today, intractable pain patients are given hormone replacement to help carry on marital life.

The daily log kept by HH’s aides between 1971 and 1973 provide evidence that he was tolerant to codeine and was functioning quite well but he also suffered from complications of intractable pain as well as his medications (Table 3). There is no mention of any female visitors or leaving his quarters to see a female. Evidence for osteoporosis, scoliosis, and collapsed vertebrae is found. Hughes had to sleep in a partial sitting position. He required a “two pillow-pillow”. A very hard pillow was in the pillow case to be next to his back and a regular pillow was on top to be placed against neck and head. The log ends at the time he fell, fractured his hip, and entered a London hospital.

7. Codeine treatment and complications

HH apparently self-administered codeine almost daily after leaving the hospital in 1946 and up until his death 30 years later. Except for a few days just prior to death when HH was unable, he self-administered all his medication and was alert enough to do so. His medication supplies were in his room. The daily log between 1971 and 1973 indicated that aides were often aware of how much and when medication was self-administered, but there is no record that aides routinely administered medication. In the few days prior to death HH’s, when Hughes was incapacitated, his aides apparently administered some codeine, because codeine was in HH’s body at autopsy, although no other drugs were present. There is no medical evidence that HH’s aides or doctors intentionally attempted to over- or under-medicate HH. He self-administered two forms of codeine. One was codeine phosphate which consisted of phenacetin, salicylamide, acetaminophen, aspirin, and caffeine. His

<table>
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<th>Table 3. Likely complications of HH’s intractable pain</th>
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<tr>
<td>Osteoporosis, scoliosis, and vertebrae collapse</td>
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<tr>
<td>Tooth Erosion</td>
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<td>Hormone Alterations</td>
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<tr>
<td>The above may have been partially caused by other factors such as being non-ambulatory and uremic in his last four years of life.</td>
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initial starting dosages of codeine and his split between oral and injectable codeine are uncertain but varied over time. Hughes and his physicians confirmed, however, that he usually consumed an average between 20 to 45 grains (1200 and 2700 mg) a day during most of the 30 years. Some daily dosages may have reached 60 grains (3600 mg) a day. The activity log kept between 1971 and 1973 reveals that he could take 8-10 codeine (480 to 600 mg) at one time indicating considerable tolerance and long-time use of codeine.

It is now clear that codeine is neither potent enough nor lasts long enough in the body to provide adequate pain relief for a case as severe as HH’s. For example, codeine’s pain relief duration is seldom over about 3 hours, and HH obviously required pain relief for 24 hours each day. These simple facts give ample reason for HH’s high daily dosage of codeine. While the number of grains (20 to 45 gr) or equivalent milligrams (1200 to 2700 mg) sound high, codeine is such a weak opioid that HH could not possibly have been able to always control the severe, intractable pain that likely resulted from his plane crash. About 10 mg of codeine are equivalent to 1 mg of morphine, so HH was taking the potency of about 120 to 270 mg of morphine a day. This is a low to moderate dose for many intractable pain patients. Today it is not uncommon for the daily morphine dosage to exceed 1000 mg a day or a daily dosage 4 to 5 times more potent than the opioid dosage taken by HH.

In an effort to achieve some modicum of pain control, HH suffered considerable complications from use of codeine. The phenacetin in the codeine compound produced, over-time, kidney failure and death. He endured severe constipation and haemorrhoids which are well-known complications of codeine. He frequently had to resort to enemas for relief of constipation and he suffered intermittent rectal prolapse. His physicians had to periodically re-insert his rectum.

In summary, HH probably received inadequate pain relief from codeine, and he suffered severe complications from it. In addition, his poorly controlled pain likely interfered with his business and social life. Due to codeine’s weak pain relief and numerous complications it is essentially not used today for intractable pain treatment. Several other opioids are now available which give superior pain relief with fewer complications.

8. Anti-inflammatory treatment

HH constantly self-administered anti-inflammatory agents following his plane crash, because these agents were in the codeine compounds that he took orally. They contained various quantities of phenacetin, aspirin, salicylamide, acetaminophen, and caffeine. In the months just prior to his death he used a simple aspirin and codeine combination.

This author believes that the anti-inflammatory agents used by HH helped enhance his pain relief and promoted his longevity. Despite this likelihood, HH suffered typical complications of excess anti-inflammatory agents. He had multiple bouts of gastrointestinal bleeding and anaemia to the point he required blood transfusions. In the weeks just prior to his death his physicians attempted to increase his aspirin dosage and reduce his codeine dosage. This problem accelerated his chronic renal disease caused by phenacetin. At autopsy there was papillary necrosis of the kidneys which is commonly caused by excess aspirin. A gastric ulcer was present at autopsy which also was likely caused by excess anti-inflammatory agents.

The renal deterioration produced by HH’s anti-inflammatory drugs, principally phenacetin, began several years before his death. Just how long he was uremic is unknown. It is very likely that much of his inactivity, irascible behaviour, and sedation in the decade prior to death was caused by uremic poisoning. Hughes kidneys weighed only about 100 grams each at autopsy, compared to a normal weight of 450 to 600 grams each [7]. Also, HH apparently didn’t need to use codeine on a regular basis in his terminal months as his kidneys progressively failed and couldn’t rapidly eliminate codeine from the body. Two days just prior to death and at autopsy he had blood urine nitrogen levels of 47 and 60 mg/dl while normal range is 8-24 mg/dl. These laboratory findings confirm long-time, progressive, renal failure.

9. Benzodiazepine (Valium®) treatment

In the 1960’s, after diazepam came on the commercial market, HH began using it. It is unknown as to the precise reasons he began this agent, but he continued it until he fractured his hip after a fall in July, 1973. The daily activity log kept by aides between 1971 and 1973 revealed that HH took between 7-15, 10 mg diazepam per day. His aides referred to the blue 10 mg Valium® tablets as “blue bombers” apparently due to their potent sedative effects.

HH was admitted to a London hospital for hip pinning in 1973. Undoubtedly his fall and hip fracture were related to his excessive diazepam use since this occurrence is well known to happen in elderly persons who use benzodiazepines to excess.

In addition to his tragic fall and fractured hip in 1973, HH appeared to suffer from bouts of over-sedation due to his benzodiazepine use. On several occasions HH developed pressure sores on his buttocks and shoulders. He would reportedly sleep for 24 to 48 hours on some occasions [6].

Although HH’s hip was apparently pinned well, HH
refused physical therapy and declined to walk or leave his bed the last four years of his life. This information comes from his doctor’s declaration, since there are no log or medical records about HH after 1973. In my clinical experience, intractable pain patients will refuse to walk, exercise, or leave bed until and unless their pain is well-controlled. HH had scars due to his 3rd degree burns as well as many damaged nerves throughout his body. In my intractable pain practice I find I cannot simply tell patients to exercise or send them for physical therapy. Since exercise or stretching may increase pain, I have to tailor make a stretching and exercise program for each patient often after I’ve reviewed magnetic resonance imaging (MRI’s) x-rays to know what is safe and won’t cause more damage. I suspect HH did not exercise or leave his bed because it caused him additional pain, and his doctors would not have known how to create a special exercise program in those days. After HH had his hip pinned in 1973, I can find no evidence that his physicians continued diazepam. If this were the case, his pain would undoubtedly accelerate, since codeine and anti-inflammatory agents wouldn’t suffice for very good pain control.

HH claimed that diazepam helped him sleep. Diazepam will also suppress opioid withdrawal symptoms which may occur between codeine dosages. Diazepam and other benzodiazepines produce muscle relaxation and some relief for neuropathic pain which HH had. Diazepam is known to enhance opioids’ pain relieving capability. HH undoubtedly took excess diazepam from time-to-time since codeine was not adequately relieving his pain (table 4).

## 10. Autopsy findings

The autopsy of HH is especially of great interest to pain practitioners since none other is available in a 30 year intractable pain patient treated with opioids. Of special note is that the gross and microscopic analysis of his brain, adrenals, testicles, and liver, were reported as normal. Some early studies of uncontrolled pain suggest that brain atrophy may occur. There is also the misconception that opioids and other pain control medications may cause brain damage. Consequently, a detailed description of brain findings from his autopsy done at “The Methodist Hospital” in Houston, Texas is given here for the sake of current and future investigations by researchers. Table 5 provides precise quotes from his autopsy report. To verify the authenticity of the autopsy report given to me by the Federal Government, it is on Methodist Hospital stationary and signed by two physician pathologists. The report additionally contains notes from a 3rd pathologist and a dentist.

The nervous system findings in HH show remarkably normal for his 70-year age and indicates that many things went “right” over the 30-year pain period.

<table>
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<th>4. Drug related complications experienced by HH over 30 years</th>
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<td><strong>Opioid-Codeine</strong></td>
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<tr>
<td>Constipation</td>
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<td>Haemorrhoids</td>
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<tr>
<td>Rectal Prolapse</td>
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<td>Embedded Needles</td>
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<td>Difficult Utrination</td>
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<td>Benzodiazepine-Diazepam</td>
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<tr>
<td>Over Sedation</td>
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<tr>
<td>Falls</td>
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<td>Fractured Hip</td>
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<td>Pressure Sores</td>
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<tr>
<td>Anti-inflammatory Agents - Phenacetin, Aspirin, Acetaminophen, Salicylamide</td>
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<tr>
<td>Gastrointestinal Bleeding</td>
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<td>Peptic Ulcer</td>
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<td>Renal Atrophy/Failure</td>
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HH suffered and endured tremendous complications of the drugs he had to use to control pain and allow physical and social functions during his 30-year survival.

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<thead>
<tr>
<th>5. Precise wording from HH’s autopsy done at Methodist Hospital in Houston, Texas in April 1976 regarding his brain</th>
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<tr>
<td><strong>Brain and Spinal Cord:</strong> The dura is intact and no evidence of epidural or subdural hematomas, recent or remote, are found. The brain weighs 1540 grams (Normal range is 1380 to 1590 grams 3 ). The cortical surfaces show no lesions. The basilar cerebral vessels are with usual anatomic distributions with the exception that only one vertebral artery is present, situated on the left. No aneurysms are noted at any of the bifurcations. Athromatous involvement is minimal. No evidences of cingulate, uncal or cerebellar tonsillar herniation is present. Multiple 0.5+ 1.5 cm thick transections of the cerebrum, cerebellum and brain stem show no abnormalities of the cortex, white matter, thalamus, cerebellum, pons or medulla. Modest dilation of the occipital poles of the lateral ventricles is present. The foramina of Monroe are patent. The third ventricle, aquiduct of Silvius and 4th ventricle are not dilated. The spinal cord shows no gross abnormalities.</td>
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<td><strong>Cerebrum:</strong> Slight fibrosis of leptomeninges. Precentral cortical grey matter reveals well preserved motor neurons. There is no evidence of accelerated involutional changes of the cerebral cortex.</td>
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<td><strong>Diencephalon and Brain Stem:</strong> Thalimus and inferior olivary nucleus show hypertrophic astrocytes (Alzheimer type II), consistent with metabolic changes.</td>
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<tr>
<td><strong>Spinal Cord:</strong> Not remarkable.</td>
</tr>
<tr>
<td><strong>Diagnosis:</strong> No diagnosis.</td>
</tr>
<tr>
<td>HH’s brain at autopsy was normal and showed no atrophy or changes due to his pain or medications. These findings support his long-term treatment approach.</td>
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</table>
Certainly his medications did not distort brain anatomy. There was no reported evidence of tertiary syphilis that was widely reported in the press. Late stage syphilis appears in liver and brain, but there was no evidence to show syphilis. Late stage syphilis produces a very distinctive, obvious lesion in brain, liver, and spleen known as “gummas”, because they look like wads of gum. None were present in HH. Even if HH had contracted syphilis in his early life, penicillin became available in the early 1940’s, and only a few dosages will kill syphilis. HH had received antibodies several times over the years, so any syphilis would have been eradicated.

His autopsy clearly showed end-stage renal disease. There were two types of damage. One was generalized atrophy of the type caused by chronic phenacetin use. The other was acute papillary necrosis caused by anti-inflammatory agents and likely related to his physician’s attempt to decrease his codeine use and substitute aspirin in the few months just prior to his death. A gastric ulcer was present which was also likely caused by excess anti-inflammatory agents.

Other cogent findings at autopsy were numerous old scars and fractures related to his plane crash. Severe teeth erosion was present. Roentgenograms showed osteoporosis, collapsed cervical vertebrae, scoliosis, and five embedded needles in his arms. One coronary artery had 60% occlusion (table 6). This finding is typical of a 70-year old person, so it is difficult to relate this finding to either his pain, diet, or drug intake.

A curious finding was the presence of only one vertebral artery rather than two. This intriguing and unusual finding may be a tracer or indicator of unusual vertebral artery rather than two. This intriguing and unusual finding may be a tracer or indicator of unusual.

Toxicologic analysis at autopsy showed only codeine with no benzodiazepines, phenacetin, salicylates, or alcohol. The codeine concentration in blood was .196 mg % (1.96 mg/liter). Much debate as to the meaning of this concentration ensued immediately after his death. There was the belief, as published in some national newspapers that this level meant that HH was given a lethal injection just prior to his death for surreptitious purposes. This reaction is understandable, since there were no studies of opioid blood levels in intractable pain patients in 1976. There was limited data on overdose deaths due to codeine in 1976, and what little was available revealed that HH’s codeine blood level was within ranges observed in codeine overdose deaths. What was not appreciated was that pain patients who chronically consume opioids may have tolerance and maintain very high blood levels and yet function very well [4]. Recent opioid blood studies show that HH’s codeine blood level of 1.96 mg per liter to be quite compatible with his usual intake of codeine. In addition his kidneys were failing and, therefore, blood levels would be artificially high since his kidneys had impaired excretion. HH’s codeine blood level at autopsy does, however, help validate the reports by his physicians relative to HH’s usual codeine intake.

### Table 6. Key autopsy findings

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Brain, Adrenal, Testicle, Liver, Spinal Cord</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>Generalized Osteoporosis</td>
</tr>
<tr>
<td>Renal Atrophy/Papillary Necrosis</td>
</tr>
<tr>
<td>Gastric Ulcer</td>
</tr>
<tr>
<td>Fracture of Left Old Hip with Metallic Pin</td>
</tr>
<tr>
<td>Collapsed Vertebrae and Scoliosis</td>
</tr>
<tr>
<td>The autopsy, x-rays, and toxicologic analysis taken after death confirms the various physician reports about his complications of intractable pain and the drugs he took.</td>
</tr>
</tbody>
</table>

11. Functionality and social contributions while in pain

Even though HH began regular high dose opioid use in 1946 after his plane crash, many of his legendary accomplishments occurred after this time. A partial list includes the development or production of the Spruce Goose, Glomar Explorer, RKO Studios, Hughes Aircraft, Howard Hughes Medical Institute, and Las Vegas Casinos. He eloquently spoke at Senate hearings in 1948. He married Jean Peters in 1958 and essentially normal mental and social function is present. The stereotype of HH as an over-sedated, bumbling, unproductive, germ chasing drug addict is simply false. The logs kept between 1971 and 1973 clearly reveal that HH could function quite well with his high dosages of codeine, anti-inflammatory agents, and diazepam (Valium®). In this two year period, log entries show that he regularly transacted business including stock sales, leases, and tax decisions. On one occasion he left his hotel to fly an airplane. On March 13, 1972 he met with President Somoza of Nicaragua.
The connotation in some of the lay literature about HH’s physicians and the criminal charges brought against some of them give the erroneous impression that his MD’s were second rate. Not so. They had outstanding pedigrees and long-time clinical experience. Additionally, most were older than Hughes. Dr. Thain was totally exonerated at his trial, and he gave, before a jury, a detailed and complete story of HH’s medical condition and treatment based on the latest medical information available at the time. My review of HH indicates that his MD’s were about the only persons he confided in about his true feelings and personal matters. In contrast to the uncaring, ruthless, and purely business person perceived by the public, HH often discussed his life, pain, and fears with his doctors. Dr. Thain related that HH often expressed how he loved his mother and father as well as Jean Peters, his last wife. Despite their divorce, this love must have been reciprocal, because Ms. Peters was essentially the only person to send flowers for HH’s grave after he died. Although more often than not HH rejected his physician’s advice, all accounts that the author can find indicate a close personal, physician-patient relationship between HH and his doctors. His doctors encouraged him to endure and this probably contributed to his 30-year longevity. When asked if Dr. Thain regretted caring for HH he replied, “He had no one else, and I could not have walked away from him”. Indeed, when HH lay in the funeral home waiting to be buried not a single person came to visit and only a handful of family members were at the grave site.

HH had an incredible lust for life and will to live. Within about two hours after HH’s plane crash he was receiving blood transfusions and his long-time physicians, Dr. Verne Mason “internist”, and Dr. Lawrence Chaffin “surgeon” started draining his chest cavity. Hughes asked Dr. Mason, “How am I doing?” Mason replied, “I’m not going to lie to you, Howard, you might not live.” In response HH reportedly stated, “Do what you can, I’m prepared” [1].

Dr. Mason later gave a press statement exclaiming, “My patient is truly “The Man of Steel”, and he is crawling back to health from injuries that would have killed most men. He’s not out of danger yet, but he has a terrific will to live. That alone might save him.”

While it is scientifically impossible to precisely correlate will-to-live and lust-for-life attitudes with intractable pain and longevity, these attitudes must have been enduring and surely have been a foundation for HH’s 30-year survival. Hughes apparently was ready for death but vigorously sought to postpone it. This attitude is a good one for IP patients.

Dr. Mason was the internist who prescribed codeine after his plane crash. In those years (40’s, 50’s, and 60’s) there was no social stigma, “big deal” or con-

### Table 7. Positive longevity factors in HH’s 30 years survival

| 1. | Immediate initiation and continuation of opioids after plane crash |
| 2. | Opioid - High Dose Codeine |
| 3. | Benzodiazepine - Diazepam |
| 4. | Anti-inflammatory Agents - Phenacetin, Aspirin, Salicylamide, |
| 5. | Stimulant - Caffeine |
| 6. | High Protein Diet - Chicken, Milk |
| 7. | Non-smoker, little alcohol |
| 8. | Mind Occupied with Business, Movies |
| 9. | Will-to-Live |
| 10. | Sense of Humour |
| 11. | Excellent physicians |
| 12. | Vitamins and minerals |

Above are the author’s personal opinions as to some of the factors that helped HH survive 30 years against incredible odds.

Several factors likely helped HH survive 30 years. (Table 7) First, he hired and retained excellent personal physicians who provided regular medical attendance and consultation over his 30-year survival period. Despite HH’s reclusivity, geographic mobility and hotel accommodation, his personal physicians had access to him.
troversy about opioids for pain relief as there is today. At one interview Dr. Mason simply said, “I continued prescribing codeine because Mr. Hughes needed it.” The immediate implementation of continuous opioid therapy following the plane crash was probably paramount to HH’s survival. There is an emerging body of scientific evidence that says acute pain from injury or surgery should be aggressively treated early and continuously until the pain is gone lest the injury and pain progressively worsen.

HH remained lean and apparently maintained a normal blood pressure. Hughes did suffer from attacks of high pulse rate as high as 200 to 240 beats per minute. This condition, known as recurrent paroxysmal tachycardia, would respond to carotid pressure. Pain flares are known to precipitate this condition which usually has a genetic basis. The only recorded blood pressure known to the author was in 1973 at the time he had his hip pinned. It was 124/72 mmHg.

Major factors in his survival undoubtedly were that he did not smoke and seldom drank alcohol. On the negative side there is no record of any physical therapy or desire to participate in much physical activity or exercise. He voluntarily chose to remain bed-bound for four years after his hip was pinned in 1973, and he apparently refused his physicians’ advice to exercise or stretch his left leg. Hence he developed contractures and likely increased knee pain. I am unable to explain HH’s apparent aversion to exercise and physical therapy, unless it is related to poor pain control.

HH’s medical regimen was elementary and hazardous, although it contained the major medical components of modern day chronic pain treatment. It consisted of an opioid, anti-inflammatory agents, stimulant, and a benzodiazepine. Codeine, although a weak opioid, was taken in high enough dosages to likely maintain a reasonable serum concentration for pain relief particularly when taken by injection. The high dosages of the anti-inflammatory agents phenacetin, salicylamide, aspirin, and acetaminophen undoubtedly had some therapeutic, longevity, and pain-relieving effects despite their significant complications including renal failure that was HH’s ultimate cause of death.

The role of caffeine is unclear. Although he apparently drank few, if any, caffeinated beverages, he consumed considerable caffeine in his codeine compounds. Caffeine is known to potentiate or enhance codeine’s pain-relieving ability. Caffeine is also a good antidepressant, energizer, and motivator. Today’s modern pain treatment is starting to use a number of stimulant compounds to enhance treatment.

Of great interest is HH’s diet. He liked protein and constantly consumed chicken including chicken-soup. He drank considerable milk. The daily activity log kept by his aides between October 31, 1971 and July 1, 1973 indicates he ate protein in the form of chicken essentially every day. Some notes indicate turkey sandwiches were eaten and he ate steak at times [5]. Protein contains amino acids which are the body’s natural building blocks for tissue, nerves, and various neurotransmitters. This author has observed that intractable pain patients who eat considerable protein and take multiple dietary supplements have far better pain control and function better than patients who do not practice these measures. Although little scientific study can yet back up this statement, it is appropriate to point out that the body’s natural endorphins and opioid receptors are composed of amino acids. He regularly took vitamin and mineral supplements. In fact, he constantly asked his physicians about the contents and affects of his vitamin-mineral supplements. Thiamine and Vitamin B-1 were major components of his vitamin supplements [2].

According to his physicians, he maintained mental interests and a sense of humour until the end. He carried on business activities while even in a bed-bound state. Movies were a passion and hobby, and he constantly watched them in his living quarters. Some publications have made fun of HH’s habit of watching movies. His physicians, however, stated that he not only loved movies, but he watched them for technical tips and he even thought about making some movies as he did prior to his plane crash. Daily movie watching as a hobby is a little unusual, but it’s not any more strange than watching an internet screen all day. Whatever the hobby or activity may be, its better than having an idle mind and time on one’s hand, which may depress patients and shorten an intractable pain patient’s life.

13. What we would do medically differently today

There are many therapeutic things we would do differently now, thanks to scientific advances, but HH’s fundamental pain treatment program, however, was basically sound: opioid (codeine), anti-inflammatory agents (aspirin, etc..), muscle relaxants and sleep medication (diazepam), and stimulant (caffeine). No wonder he made it 30 years with intractable pain despite a weak opioid as his major pain reliever. Rather than weak, short-acting codeine, we would today prescribe a long-acting opioid with fewer side-effects for his baseline, persistent pain and a short-acting, opioid for breakthrough pain or pain flares. There are now many anti-inflammatory agents which pose much less risk to the kidneys and rarely cause peptic ulcers or gastrointestinal bleeding. Interestingly, diazepam is still a highly prescribed drug for intractable pain patients. It is one of the few agents available that provide bonafide muscle relaxation, opioid withdrawal suppression, neuropathic blocking effects, and sleep induction. Dosages, however,
are usually below those used by HH, because today’s pain patient is treated with more effective opioids than codeine eliminating the necessity to use so much of a sedative drug, like diazepam.

There are numerous therapeutic measures available today that were not available to HH. Since HH’s day magnetic resonance imaging (MRI’s) has been developed. HH’s spine would be evaluated with MRI’s today to see if any surgery or other new technologies could eliminate his neck and upper back pain. We now have excellent new neuropathic treatment agents such as duloxetine (Cymbalta®) and pregabalin (Lyrica®). Electrical stimulators and implanted intrathecal infusion devices are products of modern science and technology, and HH would have been a candidate for these measures. The new non-opioid pain reliever delivered by intrathecal infusion, called ziconotide (Piralt®) might be considered today.

His severe osteoporosis, dental decay, scoliosis, and collapsed vertebrae indicate that adrenal hormone and testosterone testing and replacement would likely be essential. Poorly controlled intractable pain produces hypercortisolism with resultant osteoporosis, vertebral collapse, and dental erosion.

Apparently, HH did not participate in any type of stretching or physical exercise despite his physician’s recommendations. The scars from his third degree burns, cervical neck degeneration, multiple nerve injuries, and arthritis were all conditions that respond well to the tailored exercise regimens that are prescribed in modern day pain practices. Surely HH would have benefited.

Modern day pain treatment makes great use of topical (applied to skin) medications. The neuropathies that HH had as a result of his third degree burns would likely be near the skin surface and would have responded well to topical creams which contain such medications as morphine, carisoprodol, ketoprofen, or ketamine among others. Countless pain patients benefit today from a lidocaine patch (Lidoderm®) which provides excellent pain relief for shallow neuropathies.

Routine clinical chemical monitoring of intractable pain patients needs to be done every 6 to 12 months. Patients with a high degree of illness, like HH, will require multiple medications and have several concomitant disease processes. For example, routine clinical chemistry would have detected HH’s impending renal failure and possibly tip-off doctors to his osteoporosis, hormone deficiencies, and coronary artery disease. Also, today we can do blood and urine levels of opioids to tell us if the pain reliever is of the right quantity to do the job [4].

14. Lessons learned

As a long-time practising physician, the author has several 20 year patients in intractable pain treatment as this article is being written. It is from this perspective the following lessons learned (or maybe lessons we are slow to “learn”) reflect opinions that may have value to the medical community in general. The major medical lesson for physicians from the HH case is to prescribe more potent, long-acting opioids with a short-acting one for pain flares or breakthrough pain and to minimize anti-inflammatory agents and sedatives. There are some other lessons, however, for IP patients and the major health institutions of today including professional medical societies, medical schools, government, and health insurance plans. The big lesson is that if HH could live 30 years with the poor pain treatment available to him, an army of current IP patients will easily make 30-year survival.

The American medical system is primarily structured and organized for care of emergencies, short-term medical problems, and mental disease. It is not prepared with manpower, facilities, or financing for long-term medical problems such as intractable pain, diabetes, and obesity. Intractable pain can only grow in prevalence, since we have the ability to save people from trauma or disease, and our population is aging.

Another lesson is to quit fighting the use of opioids in whatever dosage is required to treat an individual case. Why? The body’s natural endorphins are simply opioids in action, and only opioids can relieve significant pain. HH was able to obtain opioids because he needed them to survive. So will anyone else in his predicament. Statements that all severe pain can be treated by non-opioid means are fraudulent. The excuses made by medial persons and institutions to prevent or stop opioid prescribing are almost comical. Yes, they may be addiction for street addicts, cause immune or hormone suppression, or hyperalgesia, which means oversensitivity. No question about it. Just as cancer and heart disease medications cause complications so do opioids. But what’s the option? Leave people shut in at home suffering? What intractable pain patients, like HH, need - is a regular MD who specializes in intractable pain and a clinic system that can provide care and medication for the long haul. Like 30 years or more!

15. Summary

HH was a flamboyant person who pushed the envelope in several industries and it is difficult to name a person in the last century who accomplished more. Many of his contributions occurred after he plane-crashed,
developed intractable pain, and required opioids. Even in his death HH is an inspiration and teacher on how to survive with severe pain and injury. His self designed, directed and administered, therapeutic regimen should be studied by pain practitioners and patients. The author has attempted to collect as much information and data about HH as possible and to be as factual as possible. Even if there are flaws in fact or interpretation, it is clear that HH had intractable pain, took opioids, and survived 30 years. The HH case calls for identification and study of intractable pain patients who have lived 20 or more years on opioid therapy.

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**Conflict of Interest**

The authors have no relevant conflict of interest to report in relation to the present study.

**References**


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The Under-Treatment of Pain: A Global Problem. 
An Educational Approach

Ian Buttfield

International Association for Pain and Chemical Dependence

Summary

In order to undertake comprehensive pain treatment, acute and chronic, all prescribers are required to understand opioid medication, and to appreciate the phenomenon of addiction. Throughout the world there is a major concern with under treatment of pain. This paper aims to assist health professionals in their efforts to treat patients’ pain effectively. It also outlines medications available for use, typical patient situations and strategies for intervention to relieve pain. Barriers to pain treatment are reviewed, in both developed and developing nations.

Key Words: Pain, Addiction, Educational Approach. Chemical Dependency, Opioid Dependence

The Pain and Chemical Dependency (PCD) Movement evolved from a shared concern about the inadequate provision of pain relief for people alleged to be or to have been, substance abusers. Subsequently, this focus has widened to incorporate concern for all people who need opioid medication for relief of chronic pain. Pain is experienced in 40 to 60 per cent of methadone clients. A common finding amongst people in methadone programs is inadequate treatment for their pain. A similar finding is noted for many people in the population even though they have no history of drug dependence. This paper will consider factors that affect opioid prescribing and will consider the value of education and accompanying attitude change if we are to achieve more appropriate and compassionate pain management.

1. The problem spreads worldwide.

Under-treatment of pain is a significant problem for all of us but especially for patients and those health care professionals who work with opioid medication (8). The experience in the United States has been widely documented but similar issues are seen across the world. Many millions of people needlessly suffer chronic pain (70). To address this global problem, we need to facilitate practitioner access to information which better informs understanding of both pain management and care of people who are, or have been, drug dependent. Importantly, any discussion of pain management viewed from a global perspective can be of limited value only. Pain is a biopsychosocial problem which crystallises certain meanings unique to each society. It is not simply that certain symptoms are given particular attention in certain cultural and historical settings, but that the meanings of all symptoms are dependent on local knowledge about the body and its pathologies and renders generalisations about pain experience, and its
medical management, problematic. When viewed from the vantage point within a culture, though pain creates undeniable similarities owing to shared problems and though it sharpens recognition of certain uniformities in the condition, is as distinctive as the lived experience of different individuals: because in the end it is the lived experience of different individuals.

The following examples of thyroid treatment drawn from my work in two cultural settings illustrates just how important knowledge of that culture and its peoples’ preference for how that disease is to be managed.

One common intervention strategy in management of iodine deficiency is to supplement the diet with iodised salt. This was initially the preferred method of treatment in Papua and New Guinea (Figure 1). This strategy has proven effective in many settings across the world but is less effective as a means of delivering iodine to the people of rural Thailand. In this setting, a more sensitive and reliable vehicle for the treatment of iodine deficiency is via a water pot located at each house in rural communities (Figure 2).

Figure 2 shows a 20 L clay pot found in most villages in Thailand. This pot sits outside the house and provides water for house dwellers and for travellers passing by. It is a cultural necessity.

The clay water pot method simply requires that the home dwellers place two drops of iodine concentrate into the pot each time the water is replenished. An additional advantage of this approach is that it retains a level of responsibility for this aspect of health care within villagers’ own hands. These examples demonstrate ways in which medical interventions may be tailored to suit cultural characteristics of the target population.

Similarly, when pain relief is the focus of intervention, many factors contribute to successful delivery of adequate pain relief. Attitudes to pain and to local practices in dealing with pain are not simply the availability of medications for pain management. Additional factors apply when opioid medication is involved (1, 2).

The following points summarise common barriers to provision of pain relief.

- Regulation,
- Cost,
- Anxiety amongst people about causing “addiction” (opiophobia).
- The possibility of drug abuse.
- Will this drug harm me?
- Will my peers agree with my using this drug?

2. The problem of pain.

- There is the uncertainty about the nature of chronic pain - What is the diagnosis? How real is this pain?
- Can pain now be classified as an illness and its own right? To what extent is public perception of people’s pain experience used as justification for opioid medication?
- Many people with pain will develop a variety of abnormal “illness behaviours” which may alternatively be more precisely defined as abnormal “treatment behaviours”.

In most cases of non-malignant pain, the diagnosis is uncertain and we all have to do the best we can with this difficult issue.

3. The stigma of pain.

- There is widespread stigma associated with the use of heroin.
- There is probably an even greater stigma associated with the use of methadone irrespective of the reasons for its use, i.e. when methadone is prescribed for people labelled as substance abusers or for people whose chronic pain is treated with methadone, this stigma issue becomes a major problem for both the individual, for significant others and society as a whole.
- The stigma of methadone spills over to all opioid drugs.
- This opioid stigma then spills onto pain.
- And then on to patients whose concern is pain.
- And finally washes over the prescribers of opioid medication in treatment of pain who are often regarded as incompetent, irresponsible or bad doctors largely because of their association with opioids.
This issue of stigma is critical to understanding all we do and the matter needs to be better researched and understood by all persons who work with patients being prescribed opioid medication.

4. The consequences of under treatment or no treatment of pain.

These consequences include:
- Suicide,
- Heroin or other illicit drug use,
- Doctor shopping,
- Over-the-counter medication,
- Abuse of medications such as injecting prescribed oral morphine,
- Suffering,
- Either in silence,
- Or by acting-out.

5. What behaviours are helpful in diagnosis of medication abuse?

- Inappropriate storing of medication.
- Injecting oral medication.
- Using illegal drugs such as heroin.
- Chewing or crushing long acting medication such as morphine or Oxycontin.
- Obtaining extra drugs when the medication has run out earlier than prescribed.
- Over-the-counter medication.
- Doctor shopping.

The Australian government reports that doctor shopping is a common practice amongst pain patients. Our health system subsidises medication use for certain prescribed conditions. As a consequence, government records allow close analysis of patients suspected of doctor shopping. The definition of a doctor shopper is a person who obtains more medication than is considered as being necessary for a given illness. Initially this label was attached to patients who made 15 or more visits to separate physicians in the course of the year. However, many in this group visited one or more doctors on many occasions. Some patients, in addition, were found to have sought 30 or more consultations in the year, and obtained 30 or more prescriptions in that year. This group was also defined as doctor shoppers. One person was found to have visited 360 separate physicians in one year. The record does not indicate the number of times any one physician was consulted during that year! Clearly, such conduct would allow little time for the patient to undertake employment.

Today we now know that 70% of patients who doctor shop have another significant illness, commonly pain but it may also be a psychiatric disorder, or combination of the two. Many such patients had been inadequately treated so that they felt that doctor shopping was their only recourse to obtain adequate pain relief. Drugs sought by patients were largely a combination of opioid medication and benzodiazepines. The vast majority of patients were diagnosed as having a psychological

Figure 2. A 20 L clay pot found in most villages in Thailand.
disorder (“Psyche Ache”) or a physical pain and were so distressed by their symptoms that they self-medicated by means of doctor shopping (2, 6, 8.).


Pseudo-abuse frequently presents as apparent abuse of medication. The behaviour is triggered by under treatment of pain which leads to patients ‘hitting out’, to be verbally abusive, or appear to be inappropriately seeking extra medication. Such people may well be diagnosed as having a drug abuse problem, because they may also inject oral medication, bite tablets prescribed to give long-term pain relief thereby undermining their beneficial long-term effect, or seek extra medication by doctor shopping. One way in which physicians could assess the presence of pseudo-abuse is to listen to patients’ stories of pain, rather than acting on the assumption of abuse. By seeking understanding of a patient’s reality, a more appropriate treatment response may be called for. If pseudo-abuse is present, there is a cessation of behaviours once adequate pain relief is achieved.

7. Pain Classification and medication available.

7.1 Acute pain.

Acute pain occurs after an injury or illness where expectations are that the pain will last for a short period: a few minutes to some hours. In time-limited circumstances, the patient is unlikely to require ongoing opioid medication. Thus, it is generally concluded that it is safe to prescribe opioid medication appropriate to the level of pain experienced, for example, injectable morphine. Such medications may be associated with abuse if the medication is unnecessarily continued. A general rule of thumb when prescribing for patients requiring analgesia for acute conditions is drugs offering short-term relief and consistent with the level of pain expected from the illness or injury. For example, injectable morphine may be the most appropriate drug in the treatment of acute myocardial infarction, but is less suitable when administered in treatment of chronic illness.

The table below lists the major parameters for treating acute pain.

- May use short acting opioid drugs.
- Do not use Meperidine!
- Avoid parenteral where possible.
- Note pseudo-addiction.
- Check that the pain is acute!

The following chart highlights medications available for use in acute pain.

- Tramadol
- Oxycodone
- Endone
- Oxynorm
- Proladone Suppositories
- Morphine
  - Oral - long acting medication
  - Dilauidid (Hydro-morphone)
  * Parenteral
  * Liquid
  * Tablet
  * (Meperidine)
- Parenteral

Please note, Tramadol is an excellent medication for the treatment of many types of acute pain.

Tramadol is:
- Non-addictive.
- Can be long-acting.
- Side effects are:
  - Infrequent.
  - Not severe.
- Schedule 4 (Non-addictive) poison.

8. Chronic non-malignant pain

Chronic pain is not time limited and may continue for some time (months to years), for example, cancer pain or chronic lower back pain. Cancer pain has generally been accepted as warranting medication for its relief. What is much less acknowledged is the rapid increase in numbers of people whose pain experience is both chronic and non-malignant. This group of patients pose considerable concern to health professionals responsible for their management. A number of factors coalesce to complicate treatment (1, 8). On the one hand there is the fear of accusation of causing “addiction” in patients as well as the heavy hand of the drug regulation authorities, while on the other, the patient’s need for pain relief. People in severe pain, who are unable to function adequately because of their pain levels, will be most anxious to obtain relief. If analgesia in not offered it will almost certainly be obtained by other, less appropriate means.

It is widely believed that the most common cause of non-malignant pain is lower back pain, and although this is indeed common, non-malignant pain in chronic osteoarthritis of the knees is the most common pain source. One consequence of under-treatment of osteoarthritis, particularly amongst elderly people, is that they become less and less mobile, have considerably reduced quality of life, and risk development of the complications of reduced mobility such as muscle weakness, immobility, and even pressure sores.

The list below summarises some principles in treatment of chronic non-malignant pain.

- Use long acting drugs.
- Treat break-through pain.
• Check for abuse.
• Check adequacy of dosage!

The principle of treating chronic non-malignant pain is relatively simple. If pain is long-term, then drugs which are long-acting must be prescribed. The provision of short-acting medication, particularly injectable medication, may well lead to abuse and even to ‘addiction’.

Chronic non-malignant pain patients may require breakthrough pain relief at specific times, for example, during periods of exercise in people with back pain. Such patients may require a small quantity of short-acting medication to deal with breakthrough pain. Although abuse is uncommon in patients with chronic malignant pain, it does occur, and the health professional must be vigilant in checking for abnormal use, as for example, when doses are increased without approval, or when the patient has a history of injecting oral medication. Unfortunately these behaviours may occur also in situations where pain is under treated. It may take prescribers some time to differentiate the ‘true’ cause.

Indications for opioid prescription in chronic pain management are set out below:
• Pain present.
  – Occasionally in Somatoform Disorder
• Less powerful analgesics tried unsuccessfully.
• Other treatments unsuccessful.
• To assist quality of life.

There is now a wide variety of medications available for the treatment of chronic pain which allows the prescriber to draw from an extensive selection. When a patient experiences side effects from one drug, alternative medications can be trialled. Trial and error is important as there is no way to be certain which patient will do well on any particular drug.

9. Getting the dose right.

Physicians who have prescribed opioid medication for pain patients are no doubt quite familiar with the air of disapproval of colleagues. The table below shows three common approaches to opioid prescribing throughout the health care community.

- Types of prescribing (Tenin).
  - Instrumental — objective analysis and dosages.
  - Command — fear of penalties.
  - Customary — what peers will agree to.
- Failure in system or system failure?

Many prescribers are comfortable to prescribe the customary or so termed ‘standard’ dosage. However, this measure may well be far too low for the needs of some patients. Many prescribers operate within climate of fear and accompanying concern about the potential for penalties to be imposed by medical boards or the imposition of legal sanctions. Legal sanctions are commonly imposed, or threatened on opioid prescribers in most countries. The current IAPCD organisation has evolved in order to educate health professionals in optimal practice and prescribing techniques for opioid medication. Perhaps the best way to proceed is via the instrumental approach. This strategy is grounded in careful analysis of the patient’s condition, the dose calculated to obtain relief for the particular patient, and the dose titrated until pain relief is achieved. If the initial dose is inadequate to relieve the pain, medication can be increased until the pain is relieved or it is established that opioid medication does not alleviate this patient’s pain.

So, what needs to be recognised and underscored in this approach to pain management? What is salient to this approach is the understanding that: dosage is a far less significant criterion for prescribing than improvement of patient function. Some patients do require very large doses. This action may be a cause for concern to some colleagues.

10. What then are the barriers to opioid prescription?

These are:
- Cost and availability
  • Some countries have little finance for medication among their priorities.
  • Some have limited availability of medication for:
    • Political reasons
    • Or, fear of “addiction”
- Fear
  • Fear of regulators
  • Fear of peer pressure
  • Anxiety about what is best for the patient!
  • Cost is an issue which distorts prescribing
    — especially, but not only, in developing countries
    — It may be necessary to prescribe a less effective drug than offer none.

In every country in the world, many significant barriers can be identified. In countries such as the United States, cost of the newer drugs is less problematic but fear of regulation is much more significant. The concerns in the USA have been well documented but similar issues are found in many, if not most countries (7).

In many developing countries cost is a huge issue. For example in India, Dr. Rajagopal (a palliative care doctor) is obliged to prescribe the less effective drug dextro-propoxyphene even though morphine is produced in India. Most patients are simply unable to afford it. This drug can be very helpful in many clinical situations and we must acknowledge the fact that a second
order drug is preferable to no analgesia. We therefore need to recognize that inadequate pain relief for both non-malignant and malignant pain is almost a normal way of life in many parts of the globe. As clinicians, we need to acknowledge the extent of this international issue and to support one another in seeking to obtain better access to pain relief.

11. Is it possible to treat pain in people with a history of drug abuse?

This group of patients poses considerable challenge to health professionals charged with responsible for their care. Time and space does not permit a detailed description of possible strategies, except to say that it is possible to match the drug prescribed to the drug abuse (4, 5, 6, and 9).

12. Matching prescribing to the abused drug.

When persons with a history of drug misuse are treated in an appropriate clinical situation, there is a need to ensure that the drug prescribed for pain will allow flexibility in follow up. A good example of the problem is the use of Morphine (usually long-acting) in persons with a history of heroin abuse. In this situation, heroin and morphine both show up in a similar fashion in urine tests, making it difficult or even impossible to understand if heroin abuse continues.

In many, if not most cases, methadone is the analgesic drug of choice for active drug abusers.

Summarising techniques for this group:
* Use methadone syrup in many cases.
* Methadone - often needed at least twice daily to give around the clock analgesia, and occasionally methadone does not give adequate analgesia.
* May use long acting morphine - note this will return a positive for opioids.
* Fentanyl patches.
* Oxycontin has a place here but care is needed.

There are a number of studies which show significant numbers of patients in methadone programs have chronic pain. Depending on the study, the incidence is between 40 and 60 percent of persons in such programs. What is certain that methadone program patients can be treated but they require care and special techniques.

- Pain in methadone program patients:
  - Can be treated.
  - Require special techniques.
  - Under-treatment of pain leads to abuse of medications as described above. Past drug abusers will be more effective in obtaining improper medications than those who had no experience with obtaining illicit medications.

- Pain in other pain patients:
  - Need adequate dosage.
  - Monitor for abuse.
  - Still need care.

12. Conclusion.

There is a worldwide epidemic of chronic non-malignant pain and the incidence is rising. This reality is due to people’s increased longevity, improved survival rates following major illness and/or trauma, who now succumb to degenerative diseases which may necessitate long-term pain management. This paper has addressed many of the issues confronted in first world settings which obstruct people’s access to opioid medication. Significant challenges surround both access to and payment for opioid medication. It has considered the part played by drug-regulating bodies, medical boards, litigation fear and impact of collegial attitude as constraints upon those who prescribe opioid medication for relief of pain. It has identified an additional concern for physicians who treat chronic pain the challenge of finding ways to overcome the educational and emotional issues which bedevil the field. In attempting to tackle this concern, the paper offers for consideration a series of typifications of characteristic patient situations and associated strategies for intervening in those circumstances. The typifications offer practitioners various ways of conceptualising and intervening in these common problematic situations when faced with the responsibility for the treatment of those who suffer chronic pain.

Under-treatment of pain is not restricted to industrialised countries. Many less industrialised nations experience significant problems in addressing most medical problems in their populations. Pain management, particularly when opioid medication is involved, may be well beyond the reach of their budget. The additional barrier of insufficient financial resources adds to the burden of the lack of access to opioid medication throughout worldwide.

Chronic pain sufferers will go to significant lengths to obtain relief. This leads many pain patients to being unfairly labelled as “drug addicts”. People who are, or have been substance abusers, also require humane pain relief. Treatment approaches need to be individualised to suit particular circumstances. Chronic pain is common amongst clients engaged in methadone programs and appropriate pain treatment is possible and indeed essential if drug misuse is to be minimised.

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Finnish Experience With Buprenorphine-Naloxone Combination (Suboxone®): Survey Evaluations With Intravenous Drug Users

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Summary

Finland, with a population of around 5.5 million, has four years of prescribing a buprenorphine-naloxone combination product (bup/nx) under its belt, and it already has the most bup/nx experience within Europe. Our data show that the decision to transfer patients from buprenorphine to bup/nx more than halved the street value of an 8 mg tablet, in a country where buprenorphine had previously been the most widely intravenously-abused drug. Patients are now maintained on an average daily dose of 16 mg bup/nx and, reassuringly, buprenorphine misuse is decreasing. Most importantly, the pre-buprenorphine heroin mortality figures have all but vanished: from 63 deaths in 2000, in the last few years Finland has seen heroin claim just 0 - 4 lives per annum.

Key Words: Suboxone, Finnish Experience, Survey

1. Introduction

Buprenorphine is a mu-opioid receptor partial agonist and kappa-opioid receptor antagonist. The high dose sublingual tablet formulation (Subutex) has proved to be an effective treatment for opioid dependence \([5]\) and is in use in over 40 countries worldwide. The buprenorphine plus naloxone (Suboxone) combination tablet was developed with the objective of having the same sublingual effectiveness and safety profile as buprenorphine alone (Subutex) but with a lower intravenous (IV) misuse potential \([2]\). Naloxone, when taken sublingually, is poorly absorbed and should have few or no pharmacological effects \([4]\). When Suboxone is injected intravenously, naloxone is intended to precipitate withdrawal effects in opioid-dependent users, to attenuate feelings of 'drug-liking', and to provide a generally unpleasant experience \([4]\). Suboxone is currently approved for use in the United States, Australia, New Zealand, Malaysia, and has recently been approved in the European Union.

In Finland, the most misused IV opioid during the last few years has been buprenorphine \([1]\), mainly originating from other countries, notably France. As a consequence of abuse, access to and monitoring of the treatment has been very strictly controlled, so creating a need for significant resources. At the initiation of this study approximately 200 patients were receiving treatment with Subutex in Finland. When Suboxone became available under special license in Finland towards the end of 2003, several treatment centers switched their patients rapidly from Subutex to Suboxone as a strategy to curb the misuse of buprenorphine.

2. Methods

A questionnaire consisting of six multiple-choice and ten fill-in-the-blank questions was distributed...
to all attendees at a needle exchange programme in the Helsinki area over two weeks in April, in 2005, in 2006, and again in 2007. Survey completion was voluntary and anonymous; the return or non-return of the survey in no way influenced the services provided by the programme. In 2005 a total of 589 surveys were distributed and 176 were returned; in the other years the distribution and return rates were very similar. The actual return rate, however, is probably higher than 30%, because the same person may have been present at more than one meeting and thus received two or more copies, but they respected instructions to return only one copy.

All surveys had an informed consent attached to the survey, explaining why the information was being collected. Needle exchange personnel did not receive completed surveys, but directed participants to place surveys in a box accessible only to the investigators. No identifying information was obtained.

3. Results

In this paper we present data on the illicit use of buprenorphine in 176 IDUs. With buprenorphine, unlike other misused drugs, 78% of patients reported that they misused it to help treat their addiction: only 10% said they did so for pleasure (Figure 2). Indeed, over half of all patients interviewed were willing to enter treatment. Our data indicate that the decision to transfer patients from buprenorphine to bup/nx more than halved the street value of an 8 mg tablet (Figure 1). Nevertheless, it was imperative to address these drug misuse problems. Less than a third of patients abusing buprenorphine were using it on its own and 8% were misusing benzodiazepines, too. As a result, many treatment centres transferred their buprenorphine patients onto the bup/nx combination tablet. If patients try to inject this combination, the naloxone component can induce severe precipitated withdrawal in the presence of full agonists - an ideal deterrent.

Compared to the earlier estimates of opiate use in Finland (EMDCC report), our data indicate that buprenorphine has become the main opiate (73% of all IV drugs) in Finland, instead of heroin. The decrease in heroin supply has resulted in an increase in the demand for other drugs, particularly buprenorphine, as evidenced by the sharp fall in death rates from heroin overdose in 2000-2004 and the sharper rise in death rates due to buprenorphine misuse. Data from this report and data from 2004 are presented here in Table 1, which clearly demonstrates the `switch' from heroin to buprenorphine as the primary opiate of abuse resulting in death for the abuser.

4. Discussion

Our recent data [1] and EMCDDA data [3] indicate that buprenorphine has replaced heroin as the main injected opioid (73% of all IV drugs). The rise in the use of buprenorphine and deaths associated with its use in the period from 2000 to 2004 has been accompanied by a sharp fall in death rates from heroin [6]. The reduction in heroin use was probably not caused by reduced availability because the street price for heroin in Finland in 2000 - 2004 did not increase; in fact, it reached its lowest level (United Nations Office on Drugs and Crime, World Drug Report, 2005), averaging only US$ 181 per gram in contrast to an estimate of US$ 800 per gram in 1990. One reason for the reduction in heroin use may be that these addicts were successfully treating their heroin addiction and/or withdrawal by substituting buprenorphine. Support for this conclusion comes also from the finding that our respondents had used other IV opioids over significantly longer periods.

**Figure 1. Street value for buprenorphine and bup/nx in Finland, 2007**
than IV buprenorphine). This is in agreement with other findings indicating that buprenorphine-related deaths are mostly linked to polydrug abuse. However, the death rate statistics make it clear that, even with the rigid controls designed in Finland to reduce diversion of buprenorphine for illicit use, the number of deaths due to buprenorphine misuse are still on the rise, and further reforms will probably be required to significantly impact the diversion, importation and mortality rate for buprenorphine abuse in Finland. These findings are of particular importance when examining the death rates associated with opiate abuse in Finland. It is possible that the provision of education and treatment for this population is paramount, given the rising rate of deaths associated with the use of buprenorphine in Finland.

The buprenorphine+naloxone combination was introduced to help eliminate the diversion and IV use of buprenorphine. This combination is supposed to have a lower IV abuse potential than buprenorphine alone. 68% of the respondents had tried IV buprenorphine+naloxone; 66% of those who tried it went on to take it again or, even, began taking it regularly [4]. This may indicate that combining naloxone with buprenorphine does not block all agonist effects when used IV. However, the continued usage of the combination product might reflect the fact that the study population originated from a needle exchange programme, so these patients were accustomed to using drugs IV, and the habit may not have been extinguished by a few non-reinforced attempts. The latter conclusion is supported by the finding that 80% reported that they had a ‘bad’ experience with the combination product, while fewer than 20% reported that it produced experiences ‘similar’ to those with IV buprenorphine. Consistently with this finding, respondents were willing to pay a significantly higher street price for buprenorphine than for the combination product.

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 Contributors

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Conflict of Interest

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TO THE EDITOR: Like many other European countries, Croatia had to face a heroin addiction epidemic in the early 1990s. However, unlike many of those countries, Croatia gave a prompt medical response to its new public health problem. Methadone for outpatient treatment was introduced in 1991, and by 1995 there were over 1500 patients on methadone. Currently, more than 50% of 2400 GPs in Croatia have patients on maintenance treatment [1]; buprenorphine was introduced in 2004, and by now about 25% of all maintenance patients take buprenorphine.

There are certainly many reasons for this unusually fast and ‘painless’ introduction of addiction treatment in Croatia, but two have certainly played a key role:
- Historical background (tradition of social psychiatry)
- Health policy background.

The capital of Croatia, Zagreb, was one of the chief centres of psychiatry in the Austrian empire at the beginning of the 20th century. In the 1950s Prof. Hudolin had established a model for the outpatient treatment of alcoholism; it soon became the leading model for treating alcoholism throughout this part of Europe. In 1971 the Department for Drug Addiction Treatment was founded at the ‘Sestara Milosrdnica’ University Hospital; it was the first such department in former Yugoslavia.

There is also a deeply rooted tradition of social medicine in general practice in Croatia. Prof Andrija Stampar, one of the founders of WHO, was also one of the leading promoters of social sensitivity in general practice and of the idea that public health threats should be given priority status in the work of GPs.

The health policy of the Croatian Government has the following characteristics:
- Easy access to health insurance. If a heavy addict is not otherwise insured, which most of them are, he/she is provided with health insurance to cover the problem.
- A patient who needs methadone or buprenorphine treatment does not usually need to find a doctor who will provide it. Virtually all patients have their ‘own’ doctor, and every GP has an obligation to provide Opioid Treatment (OT).
- GPs act as ‘gate keepers’ in the Croatian health care system. There is a referral system to see specialists, and only GPs are authorized to prescribe medicine to be paid for by the national health institute.

The basic idea for addiction treatment in Croatia is cooperation: between GPs and Centres for Addiction Treatment.

This model allows a wide availability of treatment, while guaranteeing professional quality.

a) Availability: a heroin addict can get OT in ‘every village’ in Croatia. More than half of all GPs have addicts in OT. (The others simply have no heroin addicts among their patients.) [1]

b) Professional quality: quality is ensured through the advisory role of experts from Centres for Addiction Treatment. A family physician who provides OT
The results showed that 51 GPs (26%) are afraid of addicts. The role of Centres for Outpatient Treatment is the clinical assessment, decision to give OT, the individualization of starting dose, the dose adjustment, psychosocial counselling, urine testing and collecting epidemiological data. The role of GPs in OTP is to prescribe methadone-buprenorphine, to supervise consumption, to prepare take-home doses, and to treat all other health problems.

The key accomplishments of the model are: a) the wide availability of treatment, b) no waiting lists for those who wish to enter treatment. OT for a new patient sometimes starts on his/her very first day of attendance at the Centre or a GP's office, or, more often, the next day; c) high retention rates. It is estimated that retention in treatment is generally as high as 70-80% [4]; d) a high level of coverage. It has been estimated that more than 50% of all heroin addicts are involved in some kind of treatment [2,3].

The major problems in providing OT are the following:
- Some doctors do not follow the procedure (no cooperation!). There is inadequate control over the procedures for administering addiction treatment. This leads to the public opinion that “things are out of control” (whereas only some doctors are).
- In some places it is hard to find a GP.
- Preparing take-homes in GPs offices. Since there are no medical products that are suitable for “taking home”, medical nurses in GPs' offices have to prepare one themselves by crushing the tablets and mixing them with orange powder! It is the most boring and time-consuming work that is done in a GP’s office.
- Lack of payment of GPs who provide OT. The whole procedure, including supervised consumption and the preparation of take-home doses, does not qualify for an extra pay! This leads to major disappointment and dissatisfaction among GPs.

In terms of outcomes the model seems to work very well.

In this letter we report the acceptance of the cooperation provided by GPs. In 2004 - 2005 a survey was carried out on the attitude and convictions of GPs in Croatia towards drug addictions and drug addicts. It included 193 GPs in Croatia (8% of all GPs) [1].

Since GPs have an obligation to provide MT, we asked them about their possible fear of addicts. The results showed that 51 GPs (26%) are afraid of addicts.

There is no significant difference in “fear of addicts” between doctors who have addicts in treatment and those who do not! It is almost unbelievable that the attribution of such a specific population leads to no change in the attitude of the therapist.

Again, on the question whether drug addicts are ‘more difficult’ patients, there were no significant difference between doctors who have drug addicts in treatment and those who don't. Prejudice seems to be the most plausible explanation for this result.

In Croatia, treatment in therapeutic communities is generally seen as the “only treatment that works”. On the question: “TC or MMT?”, there were no significant differences between two groups of GPs. 18% of general practitioners in Croatia have an addict as a member of their family [1]. Those in the group of GPs who have a heroin addict in family are significantly less likely to believe that there is a “cure for addiction” and they paid greater attention to methadone as a good treatment option. It seems that personal experience rather than professional one has a strong influence on the convictions and attitudes of the general practitioners in Croatia!

The results of this survey offer support to the idea that the key premise of the Croatian approach to heroin addiction treatment is that heroin addiction does not differ from the treatment of any other chronic disease, and opioid agonists do not act very differently from any other medicine. As a result, addiction is treated on the primary health level, with GPs as key providers. Research on the attitudes of GPs to drug addiction and drug addiction treatment gives some unexpected results, which should be taken into considerations. In any case, the results obtained during 15 years of experience give no reason for changing the key points of the model.

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Conflict of Interest

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