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Despite the higher level of standardization of heroin addiction treatment, there is a significant mismatch between the scientific ‘gold standard’ and clinical practice. The healing of addiction is not considered to be the ideal goal of a therapeutic process, but as its only acceptable outcome. Moreover, it is not seen as the eventual achievement of gradual improvement, but as the foundation of therapeutic programmes [5]. As a corollary to such a view, relapses by patients and the worsening of their condition are not seen as limitations on the scope of treatment instruments or as treatment failures, but as due to patients’ inadequacy and their lack of will, responsibility or motivation. On the whole, as long as patients are able to control their disease, any interventions may be effective, to the point of thinking that each patient should be targeted with a personalized intervention in order to elicit their individual inner strength. On the other hand, long-term adherence to medical treatment, regardless of the results obtained, is hardly allowed or may even be explicitly discouraged. Instead of applying the gold standard of anti-craving treatment, the world of addiction treatment often gives the impression of dreaming of gold-standard patients, who might be defined as ‘healing the healthy’. In this middle ground, many patients die healing, or after being healed, of apparently ‘new’ and unexpected recurrences of their once-eradicated disease. So it is that what could be called a Malleus Maleficarum (see note 1): a body of beliefs, to date unsupported by any evidence, but also without any standardized definition, is employed instead of scientific observation and intervention [1, 8].

Addictive diseases are a group of clinical pictures described according to a common model of addictive behaviour that implies the chronic, recurrent loss of control over one’s behaviour when that is oriented towards the dominant and exclusive purpose of supplying oneself with a certain kind of stimulation. Any frequent or continuous exposure to certain kinds of stimuli is accompanied by an intrinsic risk of becoming addicted to them, which corresponds to a stable change in the functional array within the brain. The engagement into addictive self-stimulation is, as a rule, linked to increasing individual social impairment, and leads to sociopathic behaviour [4].

A careful reading of current DSM criteria goes to show that psychosocial features are recorded in order to define the presence and severity of addictive impairment, but are regarded as consequences rather than as subtypes of the disease’s core dysfunction.

Some authors [6] have defined a category of ‘reactive’ or ‘self-medicating’ addicts, which, in reality, is not
so much an indication of the psychosocial nature of addiction as a reference to a possible dynamic leading to habitual substance use. In either case, the original motive for drug use is “betrayed” along the transition from free use to pathological use, which displays as maladaptive and mind-weakening. The dynamics of addiction, by definition, do not depend on any further factor, but correspond to a self-perpetuating, counter-intentional instinctual drive towards substance use.

Although psychosocial factors may worsen the life outcome and complication of addiction, no psychosocial advantage has been proved effective in preventing or breaking down the addictive cycle [3, 7].

On the other hand, it is known that opiate addicts display a typical protracted withdrawal syndrome, which itself foreruns relapse in the long term and whose features convey to a picture of impaired psychosocial ability, accounting for the likelihood of association between low-to-high stress (including positive events) and relapse. One could say that addicts can be expected to relapse while just living on after the interruption of substance use, so that the course of their relapses overlaps with the course of their lives, without any need for there to be any specific psychosocial link.

Psychosocial interventions may be divided into at least two categories: interventions that aim to favour rehabilitation by achieving disease remission, and those that aim to influence the course of addiction by means of psychosocial interaction or stimulation. As regards the latter category, reviews appear to show that they are still unsupported by scientific evidence: psychosocial intervention alone is not recommended for opiate addiction, and is thus equivalent to treatment omission or delay [3, 7]. Also, whatever has therapeutic value as part of a combination with other components should not be mentioned as if it was effective as a mono-therapy, as in the case of counseling or motivational treatment. On the other hand, it might be thought that psychosocial interventions are effective in allowing the successful accomplishment of detoxification programmes. However, apart from the intrinsic objectives of detoxification accomplishment, it should be remembered that the successful accomplishment of detoxification has no impact on the likelihood of long-term relapse, and may aggravate the acute complications of unexpected and unprotected relapses (e.g. overdosing) [9].

Helping addicts to manage contingencies may induce them to attend treatment despite obstacles and pending problems. By contrast, it is unjustified to employ the same method in order to reduce relapse rates on the assumption that relapsing, addictive use takes place as a consequence of psychosocial impairment or environmental stress. Thereby, an escalation of psychosocial facilities should be offered: low-weight and short-term psychosocial facilities may encourage a therapeutic relationship and the transition to higher threshold programme, otherwise, higher-weight and long-term psychosocial resources should be hierarchically subordinated to stabilization through specific mainte-

nance treatment. The social assistance policies of several countries seem to run separately, when they do not diverge openly, from the logic of medically assisted rehabilitation, as in the case of most therapeutic communities. The presumption that a community environment will restore addicted people's psychosocial abilities is actually gratuitous, and is often pursued in the absence of any actual maintenance treatment. This paradox accompanies the latency that is often the prelude to a relapse, without conveying residential resources towards the goals of treatment initiation and adherence, in the perspective of releasing the patient in a free environment and in a condition of medical stabilization. At present, drug-free communities cannot be referred to as "therapeutic" places, and may even play a counterproductive role by releasing addicts in a free environment with a high-risk match between "latent craving" and "no tolerance".

In several countries treatments are arranged so that addicts may climb up the pyramid of recovery: medical treatment is prevalent at the bottom and minimized at the top, while psychosocial resources are administered following an inverse trend: on this view, addicts gradually break away from 'chemical' support, and move on to active involvement in psychosocial responsibilities. Unfortunately, the real addiction pyramid is upside down, and addicts end up by being divided into two categories: on one hand, those who can never take advantage of psychosocial resources (usually severely ill), since they are supported by no medical treatment or receive short-term non-specific treatments; on the other, those who improve enough to gain access to psychosocial resources (usually mildly ill), and experience relapse during apparent rehabilitation, or after reaching a satisfactory level of reintegration.

The unsustainable view of psychosocial features as being situated at the core of addictive dynamics generates an inaccurate concept of the patient, by evoking images of "good" and "bad" patients as a direct reflection of disease severity, in the place of the concept of adequacy and inadequacy of treatment to the disease.

The LAR treatment model provided in Bergen is a similar example, whereby “medically assisted treatment should not be the first choice” and, in order to benefit from psychosocial support, patients are required to have attained stable detachment from the drug they are addicted to. In other words, addicts are quite likely not to fit the model, or to be discharged when relapsing, due to the fact that therapeutic measures are discouraged, or actually omitted [2].

All in all, psychosocially centred national policies appear to be like gigantic spaceships sailing towards psychosocial heavens, full of resources but without patients, or like trains that have some passengers at the point of departure but are completely empty when they reach their final destination.

There is no evidence in favour of psychosocial interventions being employed as first-line treatment for any category of opiate addicts. Integrated treatments should be referred to as 'psychosocially enhanced’ rather than 'phar-
macologically assisted’. The psychosocial implications of maintenance treatment should never be ignored, and patients should not be allowed, let alone encouraged, to think that the psychosocial way to recovery as a logical development of the decision to go drug-free. Rehabilitation should, therefore, no longer be seen as a product of a psychosocial intervention, but as the psychosocial outcome of any effective intervention on a socially disruptive condition – more precisely, as the outcome of agonist maintenance, alone or with ancillary psychosocial enhancement.

Note 1

A textbook of diagnosis and treatment of witchery, with special regard to the role of females as hosts of demonic entities and instruments of diabolic goals. Written by Dominican friars at the end of the 15th century, it became famous as one of the fundamentals of inquisition torture and witch-hunts.

References


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A Memorial Gathering

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He will live in our memories
Malleus maleficarum... the superstition of psychosocially centred intervention in addictive diseases. Heroin Addiction as case study

Matteo Pacini 2 and Icro Maremmani 1,2,3

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Summary

The meaning of psychosocial features in drug addiction is often misunderstood. They are often regarded as the core of the disease, or as independent indicators of global severity, instead of being interpreted as possible expressions and consequences of addictive psychopathology. Furthermore, evidence about the psychosocial impairment of drug addicts is treated as if it were directly dependent on the theory and practice of psychosocially based treatment of such patients. Thus, we have become familiar with the paradox according to which psychosocial requirements or engagement are employed as therapeutic instruments in treating a condition characterized by the disruption and neutralization of psychosocial resources. We have tried to analyse the role of psychosocial factors in the diagnosis and treatment of drug addiction, with the aim of distinguishing between the possible frontiers of psychosocially assisted treatment and the counterproductive psychosocial engagement of untreated drug addicts. We have also tried to classify those factors and psychosocial treatments by applying the criterion of consistency with the main aims and known dynamics of drug addiction treatment.

Key Words: addiction treatment philosophy; psychosocially centred interventions; drug addiction; heroin addiction

1. The gold standard for the treatment of heroin addiction

Despite major advances in the field of addiction research and the higher level of standardization of heroin addiction treatment, there is a significant and enduring mismatch between the scientific ‘gold standard’ and clinical practice [5, 8, 10, 11, 13, 39]. In a way different from other fields of medicine, but similar to what is true of most fields of psychiatric practice, the healing of addiction is not considered to be the ideal goal of a therapeutic process, but as its only acceptable outcome. Moreover, it is not seen as the eventual achievement of gradual improvement, but as the foundation of therapeutic programmes. As a result, the healing process runs the risk of being founded on intentions and expectations rather than on scientific knowledge [14]. As a corollary to such a view, relapses by patients and the worsening of their condition are not seen as limitations on the scope of treatment instruments or as treatment failures, but as due to patients’ inadequacy and their lack of will to activate the expected benefits of any kind of intervention. On the whole, as long as patients are able to control their disease, any interventions may be effective, to the point of thinking that each patient should be targeted with a personalized intervention in order to elicit their individual inner strength. On the other hand, long-term adherence to medical treatment, regardless of the results obtained, is hardly allowed or may even be explicitly discouraged. Instead of applying the gold standard of anti-craving treat-
ment, the world of addiction treatment often gives the impression of dreaming of gold-standard patients, who might be defined as ‘healthy people who have to be healed’. In this middle ground, many patients die while being healing, or after being healed, of apparently ‘new’ and unexpected recurrences of their once-eradicated disease. So it is that what could be called the Malleus Maleficarum (Note 1), a body of beliefs, to date unsupported by any evidence, but also without any standardized definition, is employed instead of scientific observation and intervention, setting itself up as an obstacle to the progress of healthcare policies and clinical outcomes, and to the prevention of damage to patients and society [3, 34, 35].

2. Psychosocial feature and addiction diagnosis

Addictive diseases are a group of clinical pictures described according to a common model of addictive behaviour that implies the chronic, recurrent loss of control over one’s behaviour when that is oriented towards the dominant and exclusive purpose of supplying oneself with a certain kind of stimulation. Any frequent or continuous exposure to certain kinds of stimuli is accompanied by an intrinsic risk of becoming addicted to them, which corresponds to a stable change in the functional array within the brain. Later on, chronic exposure to certain kinds of stimuli may cause various pictures of acute and chronic intoxication, together with the possibility of early or late withdrawal [28, 37]. The decision to enter into addictive self-stimulation is, as a rule, linked to increasing individual social and productive impairment [12], and often leads to sociopathic behaviour [4, 9, 19].

The diagnosis of any addictive disease requires and implies a certain level of psychosocial impairment, although its definition pertains to what an individual considers as being desirable or harmful to their psychosocial adjustment. Psychosocial features are therefore recorded in order to define the presence and severity of addictive impairment, but are regarded as consequences rather than as subtypes of the disease’s core dysfunction.

A careful reading of current DSM criteria for addiction goes to show that the meaning of psychosocial impairment is always related to subjectivity, so that, if it is rated as a positive diagnostic item by clinicians, that necessarily implies the inability of patients to pursue a desirable level of pleasure [1] (Table 1).

In other words, if a patient does not complain about the psychosocial changes he/she is undergoing in the context of global pleasure deterioration, ‘psychosocial’ criteria should not be rated as positively present. Otherwise, it would be possible to diagnose drug addiction even in the absence of psychosocial impairment, precisely because of the conflicting relationship between the individual and substance-related pleasure (e.g. repeated attempts to cut down substance use, tolerance of substances and their unintentional excessive use).

Some authors [26] have defined a category of ‘reactive’ addicts, which, in reality, is not so much an indication of the psychosocial nature of addiction as a reference to a possible dynamic leading to habitual substance use. Some addicts report starting substance use during a period of psychosocial impairment centring on stressful life events, which, presumably, is also an experience common to a population of non-addicted individuals who would then quit substance use or maintain controlled consumption without reaching the stage of developing addictive behaviours. Thus, the category of reactive addiction implicates the role of psychosocial factors in going back to the stage of initiation to drug use or to the transition to frequent use. The same would go for self-medicating addicts who stick to controlled and instrumental substance use after symptoms of psychic discomfort, but eventually become addicts beyond and against any self-medicating function. The discrepancy between enduring involvement with drug use, usually at an increasing level, and while a patient is subject to increasing damage and risk, and, on the other hand, the absence or the dwindling of potential pleasure or any beneficial function, is the common ground of all possible criteria combinations for the diagnosis of addictive diseases [1].

The dynamics of addiction, by definition, do not depend on any further factor, but correspond to a self-perpetuating, counter-intentional instinctual drive towards substance use [16, 18, 32, 41].

The psychosocial features displayed by drug addicts should allow for the distinction between features which are brought on by the disruptive effects of craving and drug-seeking behaviour (addiction-related), and those which are accounted for by a chronic state of intoxication by substances, or to enduring brain damage following chronic intoxication. We propose a classification (Table 2) according to which we may refer to the former features as “positive”, that is, directly related to the behavioural production of addiction in terms of drug-seeking and drug-consuming urges. We may refer to the latter category as “toxic”, meaning that they are caused by the toxic...
A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:
1. tolerance
2. withdrawal
3. the substance is often taken in larger amounts or over a longer period than was intended
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use
5. a great deal of time is spent in activities necessary to obtain the substance
6. important social, occupational, or recreational activities are given up or reduced
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problems that is likely to have been caused or exacerbated by the substance

A third, more variable category is that of factors belonging to a drug-related lifestyle, which depends on the legal status and social history of the patient previous to drug use and its economic context. Any change in psychosocial conditions during periods of remission will correspond to a change in baseline psychosocial conditions at relapse, and may influence the occurrence and severity of complications, although not in a unique way (e.g. economic well-being may anticipate relapse and be a prelude to latency until treatment is requested). A fourth category is that of non-specific social factors, applying to all conditions of social impairment, whatever their origins, and possibly shared by an age group or ethnic group peers.

Although psychosocial factors may worsen the course and complication of addiction, no psychosocial effects of acute consumption or have the status of residual symptoms during remission, especially in the absence of agonist treatment. In other words, negative psychosocial features correspond to the transient or persistent behavioural and psychological damage caused by exposure to drugs.

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Although psychosocial factors may worsen the course and complication of addiction, no psychosocial effects of acute consumption or have the status of residual symptoms during remission, especially in the absence of agonist treatment. In other words, negative psychosocial features correspond to the transient or persistent behavioural and psychological damage caused by exposure to drugs.

### Table 1. Diagnostic criteria

<table>
<thead>
<tr>
<th>Addiction*</th>
<th>High Discomfort/Effort</th>
<th>Selective social impairment</th>
<th>Global satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crit. 1</td>
<td>Reduced/lost</td>
<td>Increased expense</td>
<td>Reduced</td>
</tr>
<tr>
<td>Crit. 2</td>
<td>Reduced/lost</td>
<td>Increased expense/ Symptoms</td>
<td>Increased</td>
</tr>
<tr>
<td>Crit. 3</td>
<td>Reduced if 1 is satisfied</td>
<td>Increased expense, increased toxicity</td>
<td>Increased</td>
</tr>
<tr>
<td>Crit. 4</td>
<td>Variable</td>
<td>Unwanted expense, excessive involvement</td>
<td>Increased</td>
</tr>
<tr>
<td>Crit. 5</td>
<td>Variable</td>
<td>Variable</td>
<td>Increased</td>
</tr>
<tr>
<td>Crit. 6</td>
<td>Variable</td>
<td>Variable</td>
<td>Increased</td>
</tr>
<tr>
<td>Crit. 7</td>
<td>Variable</td>
<td>Variable</td>
<td>Increased</td>
</tr>
<tr>
<td>Non-addictive use</td>
<td>Present</td>
<td>Expense</td>
<td>Variable</td>
</tr>
</tbody>
</table>

To depend on medication** Absent Treatment rules, expense, logistic factor Decreased Increased

* with respect to the allostatic adjustment related to non-addictive use (pre-addictive) of the same substance
** with respect to the allostatic adjustment related to the addictive use of a substance

Any combination eventually does stick to the “maladaptive pattern of use” (recurrent or chronic) indicated as the leading concept in the diagnosis of drug dependence. The concept of ‘loss of adaptation’ must be understood with respect to the plan to use the substance with positive results or with a positive emotional feedback. Psychosocial changes should therefore be read as follows: in diagnostic terms, psychosocial maladaptation is developed as long as individuals complain about it as a source and sign of one’s global dissatisfaction.

### Table 2. Classification of psychosocial factors from a disease-centred viewpoint.

<table>
<thead>
<tr>
<th>Category</th>
<th>Source</th>
<th>Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction-related / <em>positive</em></td>
<td>Drug-seeking / craving</td>
<td>Patient</td>
</tr>
<tr>
<td>Intoxication-related</td>
<td>Acute and chronic toxicity, including post-withdrawal residual symptoms and persistent functional damage</td>
<td>Patient</td>
</tr>
<tr>
<td>Profile-related</td>
<td>Psychosocial status at index episode and lifetime</td>
<td>Patient</td>
</tr>
<tr>
<td>Environmental</td>
<td>Shared environment, social pressure, acceptance, legal status</td>
<td>Sociocultural context</td>
</tr>
</tbody>
</table>

* as previously defined in the article
advantage has been proved effective in preventing or breaking down the addictive cycle [7, 30].

In clinical studies, psychosocial features may be classified as “passive” (baseline features belonging to the patient) or “active” (belonging to facilities or actual treatment). Especially in short-term observations, either psychosocially passive factors or active ones may show some relation to higher retention and abstinence rates. It should, however, be kept in mind that higher rates of abstinence may sometimes be read as no more than longer latency periods before relapse. Longer-term observations may confirm the relevance of active psychosocial factors in prolonging latency to relapse, without influencing the eventual relapse rate. As far as passive psychosocial factors are concerned, these may simply mirror variations in the potential for spontaneous remission at different grades of disease severity.

When evaluating the dynamics of single relapses, the assessment of psychosocial features is awkward, because of the absence of actual case-control comparisons (how many other addicts do not relapse despite having the same psychosocial features as a given patient?) and because, at any stage, incorrect evaluations may be made of the psychosocial consequences of preliminary triggers.

On the other hand, it is known that opiate addicts display a typical protracted withdrawal syndrome, which itself foreruns relapse in the long term, and consists of a higher susceptibility to stress, a lower pain threshold, higher somatic and mental fatigue, and abnormal interpersonal sensitivity [28, 29, 36]. Taken as whole, these features convey a picture of impaired psychosocial ability, and account for the likelihood of association between events accompanied by low-to-high stress (including positive events) and eventual relapse. One could say that addicts can be expected to relapse while just living on after the interruption of substance use, so that the course of their relapses overlaps with the course of their lives, without any need for there to be any specific psychosocial link.

3. Psychosocial interventions: classification and rationale

Psychosocial interventions may be divided into at least two categories: interventions that aim to favour rehabilitation by achieving disease remission, and those that aim to influence the course of addiction by means of psychosocial interaction or stimulation. As regards the latter category, reviews appear to show that they are still unsupported by scientific evidence, although it is difficult to overview the heterogeneous body of research that is available on the issue. Psychosocial intervention alone is not recommended for opiate addiction, and is thus equivalent to treatment omission or delay, just like non-specific pharmacological treatments [7, 30]. On the other hand, it might be thought that psychosocial interventions are effective in allowing the successful accomplishment of detoxification programmes. However, apart from the intrinsic objectives of detoxification accomplishment, and abstinence lasting until the end of treatment and soon after, it should be remembered that the successful accomplishment of detoxification has no impact on the likelihood of long-term relapse, and may aggravate the acute complications of unexpected and unprotected relapses (e.g. those due to overdosing). Considering relapse and mortality after short-term opioid detoxification, we can state that high mortality mainly occurred in patients who had successfully completed 28-day opiate detoxification; patients who remained longer as ‘in-patients’ in hospitals; patients discharged from prison; patients discharged after successfully completing long-term therapeutic community programmes; patients with severe psychiatric comorbidity. “Only patients who were in long-term detoxification programmes tended to survive (in line with Strang’s principle of ‘4 afters’): i.e. few patients survive for long after short-term detoxification; after hospitalization; after prison; after a period of residence in a therapeutic community)[40].

The rationale of psychosocial intervention is often thought to be a causal one: some authors argue that, since addiction is partly a result of psychosocial factors, and it recurs in response to certain psychosocial dynamics, a belief has arisen that psychosocially based interventions will reverse this mechanism and induce a healing process. That line of reasoning does not actually stand, since the nature of an intervention is not necessarily founded on the intervention having a nature similar to that of the primary cause of the disease. For instance, stress-induced syndromes (e.g. post-traumatic stress disorder) can be effectively treated by chemical means, and psychotherapies can have a major influence of the neurological pathways of certain disorders (e.g. obsessive-compulsive) [2, 38]. Different treatments should therefore be viewed from a unified perspective, as sharing the common biological target of a dysfunctional brain, which acts as the origin of symptoms and discomfort [27].

Addiction essentially develops as a result of a patient who is aware of his/her condition being chronically exposed to certain drugs; it becomes self-per-
petuating, even in the absence of any need or reason for their use; thus any kind of treatment may prove to be effective, regardless of its connection with the basic nature of the disorder. Further ascertainment factors for disease proneness are wide-ranging, as they include genetic traits and environmental factors which share the features of the early, easy availability of substances and their use by relatives of peers.

For the time being, we cannot count on any psychosocially based intervention as a mono-therapy for addiction, or any combination of such therapies, if their aim is the direct improvement of treatment goals. The term ‘therapy’ should, in fact, be replaced by ‘methods by which one expects to achieve a direct effect on treatment goals’. Other components may be referred to as ‘interventions’ or ‘treatments’. Also, whatever has therapeutic value as part of a combination with other components should not generally be mentioned as if it was effective as a mono-therapy, as in the case of counselling or motivational treatment [17, 30, 31]

Psychosocial interventions may target intoxication-related psychosocial factors, so providing addicts with resources that may be difficult for socially disabled addicts to reconstruct from the beginning. On the other hand, the effect of psychosocial interventions on addiction-related psychosocial features will, predictably, be temporary and misleading. In fact, the advantage to be gained will typically take place between relapses, and be lost during the subsequent relapse. Moreover, as long as the premises for psychosocial interventions correspond to the omission or interruption of maintenance treatment, such interventions will actually facilitate relapses, and pave the way to, their own failure.

The possible potential of psychosocial interventions may be heightened, inducing an indirect and subordinate effect on treatment goals: combined, ancillary interventions may improve treatment compliance (early and late attrition), insight and secondary poly-abuse, as long as they are administered in a logical sequence with respect to the main therapeutic instrument, and at the right stage of the therapeutic process. Counselling or motivational treatment may be employed continuously throughout the different stages of treatment, while other interventions may be effective in promoting early compliance or shortening the period of latency before psychosocial readjustment. On conceptual grounds, no known psychosocial intervention can promote or correspond to stabilization, which is medically based.

4. Psychosocial features and treatment outcome: the Italian experience

One first large Italian multicentre study had already shown that the outcome of heroin addicts turns out to be equal in comparing full and partial agonists, as long as patients with better psychosocial baseline features and a presumably lower disease severity are prevalent in the partial agonist group [24, 25].

Another retrospective study [33] aimed to examine the relationship between eustress (positive psychosocial events) during the very early phase of treatment and treatment outcome, by comparing a methadone maintenance group with a buprenorphine treatment group. It is known that the best selection of buprenorphine responders can be obtained by rapid treatment induction with fully blocking dosages, and that dosages should be increased until a complete opioid blockade improves the effectiveness of treatment in partial responders [23]. Initially, just after buprenorphine was launched on the Italian market, no standard induction technique was adopted, and effective doses were titrated on a clinical basis, starting from anti-withdrawal dosages that were increased on the basis of the clinical demand raised by the patient’s symptoms of craving, mental discomfort and protracted withdrawal. In that context, dropout did not reach a peak immediately after treatment initiation, but was distributed over the first few months of treatment, with an eventual medium-term dropout rate similar to that expected with high-dose induction regimens. Looking back at the cohort of patients enrolled in those conditions, we were able to examine dropout predictors for buprenorphine treatment – not only predictors related to baseline treatment features, but other predictors linked to possible psychosocial events or conditions occurring during the first few months of treatment. This kind of observation made it possible to distinguish between earlier withdrawal dropout, which was presumably related to withdrawal, and later dropout occurring during the stabilization phase, which was probably related to insufficient control over core symptoms, psychiatric and psychosocial distress.

Patients experiencing immediate psychosocial improvement were more likely to drop out when opiate coverage was limited but opiate demand was rising (partial agonist above 8 mg) but not when the coverage threshold was higher (increasing dosages of a full agonist running parallel to a rising demand). Therefore, while dosage was being increased with the aim of achieving stabilization, after the induc-
tion phase, psychosocial readjustment did not play a productive role, presumably because it heightened the positive stress demand on the brain’s opiate system. Subjects who were able to buffer that demand by increasing the level of agonist opioid being taken stayed in treatment, whereas those who found a ceiling-effect (partial agonist) dropped out just as they were making progress on psychosocial grounds. Obviously, the patients who had been quickly stabilized at lower dosages of either agonist did equally well in terms of treatment retention. Psychosocial improvement, all things considered, did not change the drop-out outcome, but could be viewed as one possible way of accounting for early dropouts in patients treated by a partial agonist during the stabilization phase, after the resolution of withdrawal.

We may conclude that psychosocial stimulation, although constructive, should be regarded as a factor that leads to increased opioid demand, so that the correct response should be dosage adjustment before apparent progress in spontaneous rehabilitation produces unexpected dropout.

5. The launching and crashing of psychosocial spaceships: when treatment results become requirements for admission (or, so to speak, the ‘Bergen park effect’)

Defining the goal of psychosocial interventions is crucial, since the same instrument may be meaningful when applied to the actual node of addictive dynamics, but pointless when applied out of focus, or in a paradoxical way. For instance, helping addicts to manage contingencies may help patients to arrange their daily life and attend treatment despite obstacles and pending problems, so improving compliance and retention. By contrast, it is unjustified to employ the same method in order to reduce relapse rates or substance use on the assumption that relapsing, addictive patterns may represent as a pyramid turned upside down (Figure 1). Treatments are arranged so that addicts may climb up the pyramid of recovery, from its bottom (street life) to its top (social integration). Medical treatment is prevalent at the bottom and minimized at the top, while psychosocial resources are administered and allowed as long as they follow an inverse trend: on this view, addicts gradually break away from ‘chemical’ support, and move on to active involvement in psychosocial responsibilities. Unfortunately, the real addiction pyramid is upside down, and addicts end up by being divided into two categories. One hand, there are those who can never take advantage of psychosocial resources, since they are supported by no medical treatment or receive short-term non-specific treatments. Patients of this type are usually regarded as ‘resistant’ or poorly-motivated, while they are only severely ill and mostly find themselves at a disadvantage on psychosocial grounds. Although psychosocial decay is prominent in their clinical picture, they will never be able to make progress on psychosocial grounds unless they can be enabled psychosocially by agonist anti-craving treatment. On the other hand, some patients improve enough to gain access to psychosocial resources, and experience relapse during apparent rehabilitation, or after reaching a satisfactory level of reintegration. This phenomenon usually takes place with mildly ill patients, who manage to improve in the short-term and are easily detached from medical treatment; or with those who taper their medication in order to gain access to major psychosocial facilities [22].

In any comparison between a programme aiming for harm reduction and a programme based on higher threshold therapy, an escalation of psychosocial facilities should be offered: low-weight and short-term psychosocial facilities may encourage a therapeutic relationship and the transition to higher threshold programme, and may be provided without any basic requirements, in a low-threshold perspective; otherwise, higher-weight and long-term psychosocial resources should be hierarchically subordinated to stabilization through specific maintenance treatment, and not be wasted on a population that offers no treatment-induced behavioural reliability. The social assistance policies of several countries seem to run separately, when they do not diverge openly, from the logic of medically assisted rehabilitation. Needless to say, that kind of incongruity does not apply to all chronic diseases, but to mental disease in general, and addictive disease in particular [19, 21].

In several countries the addiction treatment model is centred upon a misunderstanding of the psychosocial features of drug addiction, which we may represent as a pyramid turned upside down (Figure 1). Treatments are arranged so that addicts may climb up the pyramid of recovery, from its bottom (street life) to its top (social integration). Medical treatment is prevalent at the bottom and minimized at the top, while psychosocial resources are administered and allowed as long as they follow an inverse trend: on this view, addicts gradually break away from ‘chemical’ support, and move on to active involvement in psychosocial responsibilities. Unfortunately, the real addiction pyramid is upside down, and addicts end up by being divided into two categories. One hand, there are those who can never take advantage of psychosocial resources, since they are supported by no medical treatment or receive short-term non-specific treatments. Patients of this type are usually regarded as ‘resistant’ or poorly-motivated, while they are only severely ill and mostly find themselves at a disadvantage on psychosocial grounds. Although psychosocial decay is prominent in their clinical picture, they will never be able to make progress on psychosocial grounds unless they can be enabled psychosocially by agonist anti-craving treatment. On the other hand, some patients improve enough to gain access to psychosocial resources, and experience relapse during apparent rehabilitation, or after reaching a satisfactory level of reintegration. This phenomenon usually takes place with mildly ill patients, who manage to improve in the short-term and are easily detached from medical treatment; or with those who taper their medication in order to gain access to major psychosocial facilities [22].

In any case, patients believe they are at the apex of a regular pyramid while they are only at the apex of an upside down pyramid, and continue to bear the burden of psychosocial expectations and stressors. In fact, the psychosocial misunderstanding of addictive diseases has the effect of damaging patients’ insight and attitude towards treatment. While motivational treatment correctly tries to enhance and orient patients’ personal drives towards recovery and change,
psychosocially centred approaches enhance motivational stress on a brain which is poorly equipped for spontaneous stress adaptation, so producing motivational distress.

In the Italian system, for example, the official classification of treatment distinguishes between “psychosocial treatments”, “pharmacological treatments” and “psychosocial treatment with pharmacological integration”, thus giving the idea that agonist maintenance is an integration to the actual “psychosocial” core of treatment. All patients are, in fact, provided with psychosocial interventions, but most of them are also receiving medical treatment: even so, this majority (two-thirds) is typically regarded as consisting of “incomplete responders” who are waiting to get rid of their pharmacological integration, while psychosocial treatment alone is usually regarded as the gold standard [15].

The unsustainable view of psychosocial features as being situated at the core of addictive dynamics generates an inaccurate concept of the patient, by evoking images of “good” and “bad” patients as a direct reflection of disease severity. To supporters of these views, “good patients” correspond to mildly ill patients, who will eventually turn “bad” after some revolving-door cycles of psychosocial interventions or non-specific medical treatment. “Bad patients” will simply be excluded from psychosocial facilities, according to the distorted rationale that they are still too far from rehabilitation requirements. In reality, they are already in no condition to be reached by any psychosocially centred intervention, and will never benefit from such an approach. In other words, psychosocially centred approaches require the absence of symptoms in order to make treatment accessible and effective – a criterion that flatly contradicts the general principle of applying any therapeutic instrument.

One example in Europe is the LAR treatment model provided in Bergen (N), whereby “medically assisted treatment should not be the first choice” and, in order to benefit from psychosocial support, patients are required to have attained stable detachment from the drug they are addicted to. In other words, addicts are quite likely not to fit the model, or to be discharged when relapsing, due to the fact that therapeutic measures are discouraged, or actually omitted [6].

All in all, psychosocially centred national policies appear to be like gigantic spaceships sailing towards psychosocial heavens, full of resources but without patients, or like trains that have some passengers at the point of departure but are completely empty when they reach their final destination.

6. The placing and handling of psychosocial interventions during the therapeutic process

Since the primary goal (though not the first in chronological order) of opioid agonist maintenance
treatment is behavioural rehabilitation, psychosocial resources should run parallel to the degree and the stability of predictable behavioural balance, which depends on the duration of successful maintenance, stabilization and compliance. The phase of detachment from treatment should also be thought of in psychosocial terms: it is true that psychosocial support should be maintained throughout medically supervised discharge from treatment, but, after successful long-term maintenance, any abrupt interruption of medications or self-administered tapering to a drug-free condition should make the interruption of psychosocial resources imperative. The psychosocial implications of maintenance treatment should never be ignored, and patients should not be allowed, let alone encouraged, to think that the psychosocial way to recovery and well-being could ever take place after treatment termination, or as a logical development of the decision to go drug-free [20].

7. Protected environments as treatment enhancement and implementation

The environment in which treatment takes place is often understood as psychosocial treatment, as in the case of community treatment. When speaking about the treatment of other chronic diseases, the gathering of people with the same illness in a common environment is supposed to simplify treatment delivery and arrange treatment-staff interaction, while having no psychosocial implications. Addicts, and psychiatric patients in general, are the special kinds of patients for whom hospitalization or residence are automatically understood to mean “psychosocial treatment”. The presumption that a community environment will restore addicted people’s psychosocial abilities is actually gratuitous, and is often pursued in the absence of any actual maintenance treatment. This paradox accompanies the latency that is often the prelude to a relapse, without conveying residential resources towards the goals of treatment initiation and adherence, in the perspective of releasing the patient in a free environment and in a condition of medical stabilization.

Communities should therefore be handled as “residential addiction clinics” in which all resources pooled against that specific disease are easily available and directly administered, at least for those who would find it awkward to start maintenance programmes outside or display housing and nutritional needs, or are currently exposed to high environmental risks (e.g. crime-related ones). At present, drug-free communities cannot be referred to as “therapeutic” places, and may even play a counterproductive role by releasing addicts in a free environment with a high-risk match between “latent craving” and “no tolerance”.

Communities may be classified according to their impact on the natural course of addiction. First of all, communities should never embody a cultural attitude towards addictive diseases, which usually means ignoring or actively excluding effective treatments in the name of an ideology. Since no ideology should be mistaken for disease treatment, all communities should simply be viewed as a component of an integrated web of health resources, not as an ideological beacon setting itself up as an alternative to medical treatment.

Secondly, the label of ‘therapeutic’ should always be used only so long as positive effects on the course of addiction can be expected, or actually proved, on a rational basis. Communities may be an opportunity for treatment for those who could not be reached ‘out in the streets’ or are unable to attend treatment programmes or stick to outpatient treatment rules; in that case they could be called ‘pro-therapeutic’. In other cases communities play a positive role with respect to the interruption of intoxication and the prevention of psychosocial disruption, but, as long as they provide no kind of maintenance treatment inside, they miss the opportunity to start the patient on a treatment, or do no more than authorize non-therapeutic intentions proposed by patients (i.e. detoxification followed by good intentions). Such communities should not be referred to as ‘therapeutic’ with regard to addiction, patients should be clearly discouraged from entering them, and they should certainly not be financed by public funds. Some structures of this type may even play an anti-therapeutic role, for two reasons. First, by increasing the risk of fatal events, seroconversion and other accidents due to the unprotected (drug-free) discharge of patients at risk of relapse (as all addicts are). Second, by filling their patients with misconceptions about how to prevent relapses and how to stay on long-term anti-craving treatment.

To sum up, communities should not be seen as psychosocial rearing centres, or gymnasia, but as protected environments providing patients with the best psychosocial conditions to start and maintain treatment, and to improve their patients’ knowledge and awareness about their disease.

8. Conclusions

Experimental studies show a clear effect of
chemical treatment on addictive behaviours, and demonstrate that the improvement in addictive behaviours brings with it a parallel, though delayed, improvement in psychosocial adjustment. Further efforts are necessary for some categories of patients to achieve satisfactory rehabilitation, although no satisfactory outcome can be achieved or planned in the absence of ‘gold standard’ opiate agonist treatment, in a maintenance regimen. On the other hand, there is no evidence in favour of psychosocial interventions being employed as first-line treatment for any category of opiate addicts. As a result, the inclusion of psychosocial intervention within treatment programmes should take place in order to enhance compliance, adherence, and the appeal of programmes, in a medically centred perspective. Integrated treatments should be referred to as ‘psychosocially enhanced’ rather than ‘pharmacologically assisted’. Rehabilitation should, therefore, no longer be seen as a product of a psychosocial intervention, but as the psychosocial outcome of any effective intervention on a socially disruptive condition — more precisely, as the outcome of agonist maintenance, alone or with ancillary psychosocial enhancement.

**Note 1**
A textbook of diagnosis and treatment of witchery, with special regard to the role of females as hosts of demonic entities and instruments of diabolic goals. Written by Dominican friars at the end of the 15th century, it became famous as one of the fundamentals of inquisition torture and witch-hunts.

**References**


Transfer to buprenorphine from daily doses of methadone greater than 30 mg – initial review of transfers

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Summary

Transferring from daily doses of over 30mg methadone to buprenorphine can be challenging due to receptor affinity for buprenorphine, but for many patients reduction to 30mg may be impossible. Other studies have demonstrated the process is possible but have only been conducted as inpatients. This study demonstrates that the transfer from a daily dose of methadone greater than 30mg can effectively be conducted without prior dose reductions in outpatients. It provides data and analysis of the 39 transfers completed to date, examining some biophysical measurements as well as reflecting on the patients’ reasons for transfer and other social factors.

Key Words: methadone to buprenorphine transferring; methadone; buprenorphine-naloxone

1. Background

Methadone has been the Opiate Substitution Treatment (OST) for both maintenance and detoxification since the 1960s, when Dole [2] first published research on the use of methadone as a substitute for heroin users in New York. Since then methadone has been the subject of many reviews and been proven to be an effective treatment as a maintenance therapy, retaining patients in treatment and improving a range of other patient outcome measures, including criminality and illicit consumption [14].

It has been recognised, as with other medicines, that methadone might not be the best suited or most effective treatment for every patient that misuses opiates, and an alternative therapy (or therapies) should be available for use when necessary.

The Scottish Government issued its current strategy for drug misuse in Scotland in 2008 [9]. Entitled “The Road to Recovery”, it sets out a policy of encouraging and enabling patients with substance misuse problems to recover and return to a more socially “normal” role. The strategy, as well as The Scottish National Forum on Drug Related Deaths reports [6, 7], recognised the importance of availability and use of alternative medical treatments.

Buprenorphine was introduced as a treatment option for both maintenance and detoxification in the 1990s, thereby providing an alternative medical treatment to methadone. Buprenorphine continues to be the lesser used treatment alternative to methadone in the UK. In comparison to methadone, buprenorphine...
may offer additional medical benefits to patients [1,10,15], particularly a better safety profile and other social advantages, including reduced stigma, greater patient expectations of treatment and easier to reduce doses [8]. As well as these, there is reported greater “mental clarity” [11], which can facilitate the continuation of the patient’s journey to recovery.

The agonist activities of the treatments differ; methadone is a full opiate agonist while buprenorphine has partial agonist activity on the mu receptor but has antagonist activity on the kappa receptor. As a result of buprenorphine’s partial agonist activity, a “ceiling” effect is noticed on several medication related effects, especially respiratory depression, which therefore in an overdose situation proffers a better safety profile [3]. The high affinity and slow dissociation of buprenorphine displaces and successfully blocks most other opiates from the receptor sites, and prevents the other opiates from re attaching [13].

Initiating treatment with buprenorphine from short acting opiates is common practice and relatively easy as the period of withdrawal from the opiates is short and patients should not experience significant withdrawals; commencing a patient on buprenorphine from long acting opiate agonists (e.g. methadone) is more challenging and complex [5]. Transfer to buprenorphine from methadone doses of up to 30mg is becoming more routinely practiced. At doses at this level, patients report the process as being acceptable, as there are no severe withdrawal effects.

However, from methadone doses greater than 30mg daily, there may be an elevated potential for more severe withdrawal to be experienced, including precipitated withdrawal [13]. The more severe withdrawal experienced following the transfer at a larger methadone dose may be due to buprenorphine’s greater affinity at receptors coupled with a lesser intrinsic activity at the mu receptors. Due to the increased risk of withdrawal effects from doses of methadone over 30mg daily, this has formed the current practice recommendations of transfers only recommended at daily methadone doses up to 30mg.

A few papers have been published examining patients’ methadone to buprenorphine transfers from daily doses greater than 30mg; these tend to have been conducted in inpatient settings [4]. These have illustrated that the transfers can be conducted safely from daily doses in excess of 30mg daily. It should be mentioned that some of these papers also used medications that would have provided some symptomatic relief throughout the transfer e.g. lofexedine [4]. A paper which included both an inpatient and outpatient element has recently been published [12], but it appears to continue to favour the option of the transfer being done as an inpatient.

There has been no formal research conducted into the standardisation of the transfer process and the time frame it should take place over. Some processes mentioned in other articles are gentler and do the transfer over 2-4 days [12], but the article demonstrates that a more rapid titration, within a day, can be conducted with no additional ill effects experienced for the majority of patients.

Addictions Services in NHS Lanarkshire (NHSL) have completed a growing number of transfers from doses over 30mg methadone to buprenorphine. The range of doses stretches from 35mg to 120mg. The patient is seen as an outpatient, with no requirement for admission or symptomatic relief. Dose consumption during the process is witnessed and information recorded as per protocol for the duration of the procedure.

With little published experience and evidence for the safety of transferring patients from doses greater than 30mg methadone daily to buprenorphine, this article aims to:

- Review the process used in NHSL combining the reported experiences with basic bio physical measures to illustrate the effects of the transfer and determine if there is a link between the experiences and the methadone dose.
- Demonstrate that the protocol used in these transfers is a safe process.
- Provide patients maintained on methadone long term with a new treatment option to progress and further embrace their recovery journey.

2. Method

A limited number of articles were identified in an introductory data search, however when looked at more closely none of those in publication at this time had been conducted with the same method as agreed in NHSL. The proposed method in NHSL was to use the outpatient setting and not to routinely utilise any extra medications providing symptomatic relief which may mask the withdrawal.

In NHSL a protocol ratified by the clinical governance group and approved by the clinical leadership group was developed (Appendix A).

Criteria for patients undergoing the transfer process are:

- Methadone dose currently stable
Appendix A – Protocol for transfer

Protocol for Transfer from Methadone to Suboxone at daily doses of Methadone greater than 30mg

The transfers should only be carried out by Dr Conroy, but the process and protocol is to be circulated to staff with in NHS Lanarkshire to ensure correct procedure is followed.

High dose transfer is the term used to describe any transfer of a patients medication from more than 30ml methadone to treatment with Suboxone (at an appropriate level the patient is titrated to)

The patient requires having their liver function checked before the process can occur and a sample should be taken and sent to the lab to ensure recent LFT has been conducted. A copy of the LFT results should be put in the patients notes.

Worker fully discusses transfer with patient, If agreeing to the transfer, the worker contacts Christine Hannaway to arrange the date for the transfer by Dr S Conroy.

The patient will be urine screened at the appointment with the worker prior to transfer and the worker should ensure Dr Conroy has the patient’s medical notes prior to the transfer.

The patient’s last dose of methadone should be more than 36 hours before transfer. i.e. if transfer is arranged for the Monday, the last dose of methadone should be consumed on the Saturday to reduce the possibility of precipitated withdrawal, and ensure the patient attends Dr Conroy in a withdrawal state on the day of transfer. The patient should be reminded they are not to use any other opiates before the appointment for transfer, and that they will need to attend in a state of withdrawal.

The patient should attend Dr Conroy at 9.30am on the day of transfer.

On attending the patient will be examined and assessed using the SOWS withdrawal scale and will sign to agree the score of withdrawal and the information they have given is correct. i.e. consent to the transfer.

The transfer process with then begin.

The initial dose of Suboxone will be 2mg. The patient will be titrated to an appropriate level of suboxone in the clinic. The approximate time scale for the transfer is below.

Protocol for Transfer from Methadone to Suboxone at daily doses of Methadone greater than 30mg
Authors: Dr S Conroy and D Hill
Written: August 2012
Approved by Clinical Governance : August 2012
Review: August 2013
Suboxone initiation chart

9.30 Initial dose 2mg Suboxone Requires supervision and observation for first 30 minutes then check every 15 minutes

10.30 2mg Suboxone Continue checks 15 min intervals

11.30 2 x 2mg Suboxone Continue checks at 20-30 min intervals

12.30 8mg Suboxone Continue checks at 20-30 min intervals If patient doing well, can leave for lunch

13.30 if required 8mg Suboxone Continue to check at 30 min intervals

The observation checks should be used to identify the patient’s progress and lack of precipitated withdrawal or withdrawal symptoms.

Patient can be discharged once the appropriate dose of suboxone is reached and there are no further withdrawal symptoms or side effects.

Patient should be provided with a prescription at the appropriate Suboxone dose until the date of their next appointment with the addictions team.

Patient notes should be returned to the addiction team before the next appointment is due with the worker.
were consulted on the need for ethics for this study. Both organisations agreed no ethics was required as patient consent had been given previously and the process used was a retrospective case note review with no further patient contact.

3. Results

39 individuals in total underwent the process of transferring from methadone to buprenorphine, the group consists of 14 females and 25 males, and ages range from 27 to 53 years old. This tends to be an older population that are transferring, but younger people may not be transferring and are more likely to have been commenced on buprenorphine as an initial treatment option.

The range of methadone doses they are transferring from varies considerably, from 35ml daily to 120ml, with 1 person, following the commencement of the transfer, admitting to “topping up” their 100ml of prescribed methadone daily with a further 200ml of illicit methadone daily, taking his daily total to 300ml daily.

The reasons the patients wished to transfer varied, but commonly themes of moving on, moving away from methadone and moving towards recovery and back to work were the most prevalent.

With regards to employment, 8 of 39 (20.0%) patients transferred are currently employed, which is a clear indication that this group appear to be moving towards recovery. A further 2 have recently stopped work due to seasonal employment and a further group have plans in place to return to employment or education, all of which will support the evidence of motivation to change.

Looking at the forensic history of criminal justice, 5 patients are currently on Drug Treatment and Testing Orders (DTTO), 5 have been released from

<table>
<thead>
<tr>
<th>Time</th>
<th>Process</th>
<th>Dose to administer</th>
<th>Total Buprenorphine dose given</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.30</td>
<td>Assessment and commence</td>
<td>1 x 2mg / 0.5mg Suboxone</td>
<td>2mg</td>
</tr>
<tr>
<td>10.30</td>
<td>Assessment</td>
<td>1 x 2mg / 0.5mg Suboxone</td>
<td>4mg</td>
</tr>
<tr>
<td>11.30</td>
<td>Assessment</td>
<td>2 x 2mg / 0.5mg Suboxone</td>
<td>8mg</td>
</tr>
<tr>
<td>12.30</td>
<td>Assessment</td>
<td>1 x 8mg/2mg tablet</td>
<td>16mg</td>
</tr>
<tr>
<td>13.30</td>
<td>Assessment</td>
<td>1 x 8mg/2mg tablet if required</td>
<td>24mg</td>
</tr>
</tbody>
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process successfully within the same day with a single exception, the case mentioned above, completing the transfer on the second day as they experienced some withdrawals. Only 2 failed to complete the transfer, but both admitted consumption of heroin just prior to commencing on buprenorphine and therefore experi-

prison within the last year and 4 have current charges outstanding against them. There is a degree of overlap between these groups. It should be noted that a significant number have no forensic criminal history reported.

The majority of the group completed the transfer process successfully within the same day with a single exception, the case mentioned above, completing the transfer on the second day as they experienced some withdrawals. Only 2 failed to complete the transfer, but both admitted consumption of heroin just prior to commencing on buprenorphine and therefore experi-

Figure 1: SOWS score against dose administered

Figure 2. Systolic Blood Pressure (mmHg) against dose administered
All improved as they continued through the transfer process and felt much fewer symptoms at the end compared with when they commenced the process. Several reported struggling at a point in the transfer, but were glad they persevered with the process, and they were grateful/felt reassured with warnings that there may be a transient increase in feelings of withdrawal.

9 of the 39 (23.0%) reported that the process was too slow and could have been done more rapidly. As can be seen from the analysis of the SOWS assessments (Figure 1), there is an identifiable spike in a worsening of the withdrawal symptoms in many cases. This generally occurs after 4mg to 8mg of buprenorphine administered. There is no rationale or explanation for this currently, and when looking at the simple biometric examination results there is no apparent correlation for all patients.

When reviewing the blood pressures (Figure 2 and 3), there is very little variation for the patients. In most cases there is a reduction from the initial reading after the first dose of buprenorphine is administered but this may be due to reduced anxiety after taking the first tablet, the introduction of the patient to a new prescriber and apprehension about the transfer, as opposed to a direct consequence of the consumption of the medication; subsequent doses fail to demonstrate the same pattern of results.

The final biometric readings taken at the assessment were the pulse rate, (Figure 4). As can be seen from the data collected, there is again very little variation for the patients and there is no identifiable pattern.

4. Discussion

The process and protocol for the transfer of patients consuming over 30mg methadone daily has been demonstrated here to be suitable for outpatient clinics and with no need for additional symptomatic medication.

Patients need to be carefully and fully informed of the process and what they may experience. It is essential that they are experiencing withdrawal as they attend for the first appointment and that they have ceased their methadone dose at least 48 hours previously.

Within this study there are a couple of small anomalies with the demographics of the sample compared to the general population. It is important to be aware that this is the total group of people referred for this process and is not an indication of the process itself but of the group of patients willing to change treatment.

Gender issues are not reflective of gender mix in general population attending addiction services. Approximately 36% were female to 64% male, in comparison to the more traditional ratio of 25% female to 75% male in the general substance misuse

![Figure 3. Diastolic Blood Pressure against dose administered](image-url)
population. A potential explanation for this would be increased motivation for recovery, increased opportunities to return to employment and education or related to a perceived reduction in stigma associated with buprenorphine.

The average age of patients transferring is 36 years and 9 months; this is in an older group than expected and there were no transfers in patients under the age of 26. This can possibly be explained by the treatment options available when the patient first accessed treatment services. Patients newly entering the addictions service in NHS L are now offered a choice as they commence engaging, with the most suitable medication being recommended by the staff. A second possible rationale for the transfer to occur in this group is that they may have decided they are “fed up” taking methadone and the associated life style and now want to recover and return to a more rewarding life.

A possible suggestion relating to the spike in SOWS assessment results of the patients could be related to opioid displacement from receptors. As the quantity of buprenorphine is increased the number of unoccupied opioid receptors will decrease and buprenorphine may start to dissociate some of the remaining residual opioids and attach due to the greater receptor affinity demonstrated by buprenorphine.

The minor fluctuations in blood pressures and pulse do not appear to match any pattern and may be due to individual variation as patients were being assessed.

It is acknowledged that this is a relatively small sample size but 39 patients constitute approximately 9% of the current caseload of people prescribed buprenorphine in NHSL. The process is still being used and the sample size will continue to increase and the recording and data collection of this will continue.

A review of transfers and collation of the further progress these patient have made is planned and will allow the review of the successes, or otherwise, of the patients subsequent to their change in medication and if there have been any related changes in their social circumstances and recoveries.

References


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Safety assessment of low doses of methadone in combination with benzodiazepines in real occasions during methadone maintenance treatment – a pilot study

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Summary

Background. Methadone is a synthetic opioid used for methadone maintenance treatment (MMT) in patients with heroin addiction. However, at therapeutic levels methadone may be related to QT prolongation on the electrocardiogram (ECG), which might induce torsades de pointes. Aim. Our study assessed the safety of low methadone doses in combination with benzodiazepines in opiate addicts in MMT after ascertaining differences in corrected QT (QTc) intervals and side-effects.

Materials and Methods The study included 20 opiate addicts who were referred to the MMT at the Department of Psychiatry, Clinical Centre of Vojvodina, in 2012. Before the beginning of the investigation, all patients underwent an ECG, and data were collected on their sociodemographic status, duration of heroin abuse period, other drugs used in combination with heroin and the presence of ECG disorders. One month after the beginning of MMT, the patients were interviewed about their general condition during the MMT and about the side-effects they had experienced, after which an ECG was performed. Data about the methadone dose applied and the use of other drugs were collected from the medical history of each patient. Results. A significant increase in the length of QTc intervals after one month of MMT compared with those at the baseline was observed. A dose-dependent correlation between the daily dose of diazepam, used in combination with methadone, and QTc was noted. None of the participants experienced any cardiac side-effects. Conclusions. On the basis of our results, it appears to be advisable to perform a pre-treatment ECG and then regular ECG check-ups after one month of MMT, especially in the case of a concomitant use of benzodiazepines.

Key Words: Methadone maintenance treatment; benzodiazepines; corrected QT interval; interactions; safety

1. Introduction

Methadone is a synthetic opioid used for methadone maintenance treatment (MMT) in patients with heroin addiction [24]. MMT is effective at improving outcomes for people with opioid dependence [14]. However, at therapeutic levels methadone may be related to QT prolongation, which might trigger torsades de pointes, a ventricular form of tachycardia that may lead to sudden cardiac death in patients who show no structural evidence of cardiac disease [3, 8, 15]. Methadone has been shown to be a potent inhibitor of the delayed-rectifier potassium ion current (IKr), which is encoded by the human ether-à-gogo related gene (hERG). Blockade of this cardiac ion channel prolongs the terminal portion of the cardiac action potential, and causes delayed repolarization, which manifests as corrected QT (QTc) interval prolongation on the electrocardiogram (ECG) [22].

It must be added that the approaches for implementing the ECG monitoring of time points for patients on MMT vary considerably. The Medicines and Healthcare Products Regulatory Agency in the United Kingdom recommends that patients on a high dose of methadone (>100 mg/day) and/or with other QT interval prolongation risk factors, including heart or liver disease, electrolyte abnormalities, concomitant treatment with CYP3A4 inhibitors, or other drugs...
with the potential to cause QT interval prolongation, should be carefully monitored (by using ECGs) [14]. On the other hand, a group of experts from the United States suggest that all MMT patients should first perform a pre-treatment ECG in order to measure the QTc interval, and then a follow-up ECG within 30 days and annually. According to them, additional ECG should be done if the methadone dosage exceeds 100 mg/day, or if patients have an unexplained syncope or seizures [10].

Moreover, a variety of psychotropic drugs, especially benzodiazepines, are often (ab)used by methadone maintenance patients [7, 25]. Some studies and clinical reports consider the pharmacokinetic mechanisms involved in the interaction of benzodiazepines with opioids [6, 13]. Kuryshev et al., after in vitro studies, suggest pharmacodynamic interaction in cardiac ion channels as a possible mechanism for increased cardiac risk in concomitant methadone and diazepam treatment [11].

Taking into account all that has been said so far, the aim of our study has been to assess the safety of (initially) low doses of methadone in combination with other drugs (especially benzodiazepines) used by opiate addicts in MMT, after ascertaining differences in QTc intervals and the side-effects experienced after one month of MMT.

2. Methods

This prospective observational pilot study included patients of both genders who had a diagnosis of opioid dependence according to ICD-10, and who had been referred to the MMT, so becoming an MMT outpatient or an inpatient in a single inner-city drug treatment centre (Clinic of Psychiatry, Clinical Centre of Vojvodina, Novi Sad, Serbia), between March and December 2012. The study was approved by the Ethics Committee of the Clinical Centre of Vojvodina and the Ethics Commission of the Faculty of Medicine, University of Novi Sad.

The eligibility criteria included an opioid addiction history of over one year and an age ≥ 18 years and ≤ 65 years, in addition to the absence of illegal substances confirmed by urinalyses that were performed before the initial methadone intake. Patients who reported severe physical disease (a history of clinically significant cardiac, lung, hepatic or renal dysfunctions), mental disorders or polysubstance dependence were not included in the study. The exclusion criterion was the presence of illegal substances confirmed by urinalyses at a regular check-up one month after the beginning of MMT.

A total of 20 patients, 15 males (75%) and 5 females (25%), were enrolled in our pilot study during the observed period. The average age ±SD of recruits was 32.21±5.63 years (30.79±2.97 years for males vs. 36.20±9.34 years for females).

After obtaining their informed consent, all patients were interviewed about their demographic status, duration of heroin misuse time, other drugs used in combination with heroin (e.g. cocaine), as well as the presence of sudden cardiac death or ECG disorders in their first-degree relatives. At their regular check-up (one month after the beginning of MMT) they were interviewed about their general condition during MMT and any side-effects experienced. Data about applied methadone dose and the use of other drugs were collected from the medical history of each patient.

All the patients underwent a 12-lead ECG (Innomed Heart mirror 3D, Hungary) before their initial methadone intake and again one month after the beginning of MMT (one hour after the drug intake). The ECGs were visually inspected by an experienced cardiologist who was blind to the study and the QTc was calculated using Bazett’s formula [23]. QTc prolongation was defined as QTc values above 430 ms in men and above 450 ms in women [18].

The data were statistically evaluated by using the Microsoft Office package (Excel 2010). The evaluated data are given in percentages, mean, standard deviation (SD) and presented in tables. The significance of differences in length of QTc interval before and during the methadone maintenance treatment was calculated by using the t-test for paired samples, where values showing p<0.05 were considered significant. Pearson’s correlation coefficient and multiple linear regression analysis were performed to assess linear relationships between oral methadone and diazepam dose, and the QTc interval.

3. Results

The average heroin misuse time ±SD was 11.95±4.02 years. Men and women patients had the same duration of heroin misuse time (p=0.97): more precisely, 11.93±4.43 years of heroin misuse time in males and 12.00±3.00 years in females. In these patients’ history no cardiovascular diseases were reported, nor were there any cases of sudden cardiac death or of a family history of long QTc in first-degree rela-
Seventy per cent of patients (2 women and 12 men) experienced an increase in QTc compared with baseline. After one month of methadone treatment, the percentage of male and female individuals with QTc exceeding the upper normal limit increased from 20% at the baseline to 46.67% and 40%, respectively. A statistically significant increase (p<0.05) was observed in the length of QTc intervals measured after one month of MMT (QTc1) compared with those at the baseline (QTc0), whether considering all patients, or the group of male patients only (p<0.01). The mean QTc0 as well as the QTc1 intervals showed no significant differences between genders (Table 1). QTc prolongation was longer than 30 ms in 2 men (60 ms and 46 ms) and in 2 women (37 ms in both).

The mean methadone dose ±SD for the two genders was 45.26±15.41 mg, with no significant difference between them (p=0.12); it was 50±12.25 mg for men and 33.33±18.41 mg for women. The drug most frequently used in combination with methadone was diazepam, which was used by 85% of patients. The mean dose ±SD of concomitantly used diazepam was 30.93±10.36 mg. The results obtained from urinalyses verified the absence of illegal substances in the urine of all the participants, both before the initial methadone intake and again one month after the beginning of MMT.

Multiple linear analysis of factors associated with QTc revealed a statistically significant dose-dependent correlation between diazepam daily dose (used concomitantly with methadone) and QTc1 (R²=0.47, p=0.008), but without a statistically significant dose-dependent correlation between methadone and QTc1 (p=0.960). The correlation between diazepam daily dose and QTc1 remained significant in men (p=0.024). In addition to diazepam, midazolam and clonazepam were each used by 25% of patients. Only one patient took 3 different benzodiazepines, while 30% of those recruited took 2 different benzodiazepines at the same time. Analysing all the drugs that were used concomitantly with methadone, 40% of patients used one or more drugs that are well-known inhibitors or that are metabolized by CYP3A4 or CYP2D, while 15% of patients used both a QTc-prolonging drug and a drug metabolized by CYP3A4/CYP2D6 in combination with methadone. None of the participants reported any recent use of cocaine.

The most commonly reported side-effects during the first month of MMT were sweating (65%), obstipation (60%) and itch (55%), while other undesirable effects were reported, but at lower percentages. None of the participants experienced any cardiac side-effects (Table 2).

4. Discussion

MMT is the "gold standard" for the treatment of heroin addiction: the 1997 NIH Consensus Statement reaffirmed that methadone has been shown to be medically safe in many prospective studies for over 30 years; these studies mainly involved methadone doses of up to 120 mg/day [18]. Moreover, MMT contributed to a drop in the mortality of opioid addicts, to termination of or a limitation of heroin use, to reduction or avoidance of relapses and criminal activity, and to a reduction in the risk of HIV and hepatitis virus infections [16].

Despite the fact that QTc interval prolongation may occur over a wide range of methadone doses, it is more likely to occur at higher doses [22]. As the metabolism as well as the cardiac effect of methadone can be altered by other drugs, which are mostly used in combination with methadone, complex interactions between medications may occur [6, 13, 22]. To the best of our knowledge, no safety assessment of low doses of methadone, especially in combination with benzodiazepines in real cases reported during the initiation of MMT, has been carried out to date.

The structure of the groups of participating patients, participants’ age and heroin misuse time reported in our study were in accordance with the previ-
The finding of this pilot study shows that 70% of patients receiving methadone in low doses, whether alone or in combination with diazepam, demonstrate QTc interval prolongation (431.68±16.82 ms) after one month of MMT. Regarding gender differences, the prolongation in QTc remains statistically significant in men, with mean QTc above the defined threshold for men (432.71 ms vs. >430 ms, respectively). Even though 2 of 5 female patients experienced QTc1 equal to 450 ms (the threshold for women), mean measured QTc1 in the women’s group (437.20 ms) was below that value. None of the patients had a QTc1 interval exceeding 500 ms – the threshold level that is considered to be most predictive of the development of drug-induced torsades de pointes [4, 8, 18]. In 4 recruits (20%), however, an increase in QTc greater than 30 ms was observed – a figure that has a high predictive value for the development of drug-induced arrhythmia [1].

Recently published studies regarding patients on methadone or buprenorphine include no cases of QTc prolongation after 1 month of the treatment, and the mean QTc interval was below those in our study (409±19.5 vs. 431.68±16.82) [23]. Conversely, Reddy et al. showed a decrease in the QTc interval between the baseline and after one month of treatment but only in cases of analgesic therapy of advanced cancer patients, and with a methadone dose lower than those in our study [20]. One of the contributing factors for developing prolongation of the QTc interval in our study could be the use of an QTc-prolonging drug in combination with methadone, or else a recent increase in methadone dose [4, 19, 24]. None of our patients reported having used cocaine, which in some cases has been shown to be responsible for QTc prolongation in such patients [4, 12, 18]. Data about tobacco and alcohol use were not taken into account in our study, because we considered them unreliable, whereas other authors have thought that those parameters maintain their importance in predicting the risk of QTc prolongation [9, 24]. It is known that electrolyte depletion can induce QTc prolongation in patients receiving methadone [17, 22], but, in our study, blood sampling and electrolyte analysis were not included in the regular check-up during which we recruit our patients.

Statistically significant correlation between methadone doses and QTc duration has not been shown in our one-month follow-up study, while Chang et al. found that low doses of methadone (<60 mg) correlate in a dose-dependent way with the QTc interval within 6 months of treatment initiation. Men seem to be more susceptible to methadone-associated QTc prolongation than women [2]. On the other hand, other investigators have reported that methadone dose and serum levels did not correlate with QTc within periods ranging between 1 month and 10.7 years [18, 21, 23]. Moreover, diazepam used concomitantly with methadone in our study showed a dose-dependent relationship with QTc duration. According to previously published data, no association between QTc prolongation in patients on MMT and the presence of benzodiazepines in the urine was detected [21]. Krantz et al. found, by using multivariate analysis, that only antidepressant therapy was associated with an increase in QTc dispersion, without there being any correlation with methadone dose or any other

### Table 2. Side effects reported by patients during first month of methadone maintenance treatment

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Total - n (%)</th>
<th>Male - n (%)</th>
<th>Female - n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>13 (65.0)</td>
<td>12 (80.0)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>Obstipation</td>
<td>12 (60.0)</td>
<td>12 (80.0)</td>
<td>/</td>
</tr>
<tr>
<td>Itch</td>
<td>11 (55.0)</td>
<td>9 (60.0)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>6 (30.0)</td>
<td>6 (40.0)</td>
<td>/</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>6 (30.0)</td>
<td>6 (40.0)</td>
<td>/</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4 (20.0)</td>
<td>4 (26.6)</td>
<td>/</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (20.0)</td>
<td>3 (20.0)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (20.0)</td>
<td>2 (13.3)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Difficulty Urinating</td>
<td>4 (20.0)</td>
<td>4 (26.6)</td>
<td>/</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (10.0)</td>
<td>1 (6.6)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>Loss of Libido</td>
<td>2 (10.0)</td>
<td>2 (13.3)</td>
<td>/</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (5.0)</td>
<td>1 (6.6)</td>
<td>/</td>
</tr>
<tr>
<td>Menstrual Disorders</td>
<td>1 (5.0)</td>
<td>/</td>
<td>1 (20.0)</td>
</tr>
</tbody>
</table>
variable [9].

Nevertheless, the findings of QTc prolongation in patients who used methadone concomitantly with diazepam might speak in favour of addictive interaction between methadone and diazepam in cardiomyocytes. It is found that methadone, by inhibiting the hERG K+ channel in cardiomyocytes, can trigger the prolongation of the QTc interval [22]. The latest in vitro findings suggest pharmacodynamic interactions in cardiac ion channels that are supposed to increase cardiac risk in concomitant methadone and diazepam treatment [11]. In addition, methadone is a chiral drug with two enantiomeric forms: r- and s-methadone. R-methadone is primarily associated with the drug’s pharmacological activity as the µ-opioid receptor agonist, while s-methadone has limited pharmacological activity, but possesses a possible cardiotoxic influence with a higher potential for blocking the hERG K+ channel [5]. Recently published data suggest that CYP2B6’s slow metabolizer status (with a *6/6* genotype) is associated with high s- but not r-methadone plasma concentrations which can subsequently lead to QTc interval prolongation [5].

Fortunately, even though the prolongation of the QTc interval was observed in our study, none of the patients experienced any of the cardiac side-effects that it has been recognized to cause (e.g. syncope and palpitations).

5. Conclusions

On the basis of this study, the authors are pleased to be able to point out that low-dose methadone therapy is not correlated with QTc interval prolongation during the first month of MMT, but, when methadone is taken in combination with benzodiazepines, a significant relationship with QTc duration can be observed, especially in men. A high number of the latter group of patients experienced prolongation of the QTc interval after one month of treatment, and men seemed to be more susceptible than women. The implication is that both a pre-treatment ECG examination, and regular follow-ups after one month of MMT, should be performed, especially in genetically susceptible patients and in cases where there is the concomitant use of one or more benzodiazepines.

Even though none of the patients involved reported severe cardiac side-effects, practitioners should be aware of possible pharmacokinetic as well as pharmacodynamic interactions between methadone and other concomitantly used drugs.

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Psychosis, trauma, and opioid hypoactivity in the thalamus: a hypothesis

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Summary

There is a considerable overlap between opioid dependence, psychosis and trauma. This review article presents a neurobiological model that links these related clinical issues and centers on the role of the thalamus. Namely, one of the major roles of the thalamus is that of a hub for cortico-cortical interactions. Such interactions enable the recognition of self-initiated actions. Impairments in trans-thalamic cortico-cortical interactions may underpin psychosis by a mechanism whereby self-initiated actions are not recognized as such and are experienced as if they originate from outside of oneself. Impairments in trans-thalamic cortico-cortical communication could occur secondary to deficits in thalamic neuromodulatory mechanisms, including the endogenous opioid system. Indeed, there is evidence that in some individuals with an underlying genetic vulnerability to psychosis, exposure to stress may lead to endogenous opioidergic hypofunction in the thalamus, which could in turn be related to the emergence of psychosis and opioid dependence in such individuals. This scenario could account for reported antipsychotic efficacy of opioid agonist in some individuals with co-occurring psychosis and opioid dependence.

Key Words: Opioids; Psychosis; Trauma; Thalamus

1. Introduction: relationship between opioids and psychosis

Schizophrenia is a mental illness marked by psychosis and a number of other deficits, which together result in severe disability [2]. Opioid dependence is likewise a severe form of mental illness marked by physiological dependence to opioid agonists, withdrawal symptoms if substance is discontinued, as well as addictive behaviors such as spending considerable time and resources trying to obtain the substance, with major detriment to one’s quality of life and relationships [2]. There is considerable overlap between psychosis and pathologic opioid use [1]. Schizophrenia co-occurs with opioid dependence in 4-12% of cases [1, 15, 63], with reported rates of use as high as 22%. The association between psychosis and opioid dependence is likely to be even higher if we include patients with other forms of psychosis, such as psychosis that occurs in the context of certain personality disorders [2], subclinical psychosis [66] and/or psychotic symptoms that occur as a part of the post-traumatic stress disorder (PTSD) [80]. Namely, opioid dependence is associated with personality disorders and PTSD [2, 23, 41, 64]. One third of individuals with opioid dependence have at some point in their lives met criteria for PTSD [41, 64]. In view of these reports, it is not surprising that psychotic symptoms are prevalent in the opioid dependent population with estimates of up to 58% in those with severe dependence [87]. In patients on methadone maintenance treatment for opioid dependence, who are infected
with hepatitis C virus, 11% have been found to have a psychotic disorder and up to 40% were found to meet criteria for Antisocial personality disorder [6].

A number of authors who wrote on the relationship between opioid dependence and psychosis have proposed that opioid agonists, in contrast to some other substances of abuse such as cocaine or cannabis, have antipsychotic properties (for a review see 61, 62), lending some credence to the self medication hypothesis in the case of opioid use with co-occurring psychotic symptoms. Namely, McKenna reviewed, as well as presented, a number of case reports in which individuals with psychotic symptoms used illicit opioid substances such as heroin to alleviate those experiences [62]. The notion that opioids may have some antipsychotic efficacy is further supported by reports that opioid replacement pharmacotherapy, with full mu opioid receptor agonist (methadone) or partial agonist (bupenorphine), has positive impact on the treatment of psychosis co-occurring with opioid dependence [29, 40, 61, 62, 69, 76, 96, 103], with potential benefits for schizophrenic patients without opioid dependence as well [12, 78]. The mechanism of their possible antipsychotic effects is unknown, but was proposed to involve attenuation of the dopaminergic tone (for a review see 61, 62, 69).

The idea that mu opioid receptor agonists decrease dopaminergic tone is in part derived from the finding that these agents (such as methadone) increase blood prolactin levels, which is also observed with dopamine D2 receptor antagonists [54]. However, according to the cited review [54], this is not the only possible explanation for the reported hyperprolactinemia with mu opioid receptor agonists. Namely, Shin et al. found that morphine increased blood prolactin levels even when complete block of dopamine receptors was achieved by pre-treatment with pimozide, leading the authors to the conclusion that opioids stimulate prolactin release by a dopamine-independent mechanism [85]. Therefore, it is also possible that the reported antipsychotic effects of some opioid agonists also occur independently of dopaminergic neurotransmission.

In this context, it is noteworthy that there are case reports of psychosis occurring in the context of methadone withdrawal in patients who were previously not suffering from a psychotic disorder [57] leading the authors to conclude that opioid discontinuation may be a high risk period for the development of psychosis. Also, treatment with mu opioid receptor antagonist naltrexone was reported to result in worsening of psychosis in patients with schizophrenia and co-occurring substance use disorders [8].

The purpose of this theoretical paper is to use a recently presented neurobiological model of psychosis [92, 93, 94, 95] to propose one possible mechanism whereby agents used to manage opioid dependence (methadone and bupenorphine) may exert their reported antipsychotic effects. Namely, in these earlier reports we postulated that those agents that have activity at metabotropic G protein-coupled receptors which increase potassium K+ conductance in neurons of certain thalamic structures, and that thereby enable thalamic neurons to become hyperpolarized in a sustained manner, will tend to have some antipsychotic efficacy [93, 94]. Some of the mentioned concepts will be explained below in detail, but at this point, it should be noted that agonists at the mu opioid receptor fit these criteria: (1) the receptor is highly expressed in the thalamus [25, 50, 60, 70, 74, 86], (2) where it serves a neuromodulatory function by, among other effects, increasing potassium conductance via a G protein-coupled mechanism [13, 14]. Moreover, it has been found that in individuals with genetic predisposition to psychosis, exposure to stress is associated with opioidergic hypofunction in the thalamus [104], which may be related to increased psychosis risk, especially when faced with trauma. The significance of these findings and the mechanism behind the potential antipsychotic efficacy of mu opioid receptor agonists will be addressed in the following sections.

2. The thalamus and psychosis

As already mentioned, a number of authors have argued and reported that there is an intriguing and understudied relationship between psychosis and opioid dependence and treatment. In some cases, opioid use can be a part of an attempt to self-treat psychotic symptoms [62]. Additionally, opioid replacement psychopharmacotherapy with methadone or bupenorphine has been found to have some efficacy in the treatment of psychosis in dually diagnosed patients [29, 40, 61, 62, 69, 76, 96, 103]. In this section, we will review pertinent aspects of thalamic neuroanatomy, neurophysiology as well as function, as it relates to psychosis, which, in our opinion, shed some light on the relationship between psychosis and opioids.

Traditionally, the thalamus has been thought of as a relay of ascending sensory pathways on their way to the cortex. However, the functional role of the thalamus goes beyond this relatively narrow view [81-84]. Namely, the thalamus can be subdivided into at least two classes of nuclei, the first order (FO) and the
higher order (HO) nuclei, which are distinguished based on the origin of their driver inputs. The driver inputs in the thalamus are glutamatergic, utilize ionotropic glutamate receptors (such as the N-methyl-D-aspartate receptor or NMDAR) and represent the main information route. The driver inputs contrast with neuromodulatory inputs, which, in addition to ionotropic receptors, also utilize metabotropic receptors, including the mu opioid receptor (for a more detailed account of driver versus modulator thalamic inputs see 82). The driver inputs to the FO nuclei arrive from ascending sensory pathways (e.g., retinal inputs to the lateral geniculate nuclei), while the driver inputs to the HO nuclei arrive from the cortex and are then relayed to other parts of the cortex (e.g., inputs from the prefrontal cortices to the mediodorsal (MD) nuclei). More specifically, the HO nuclei receive their inputs from the pyramidal neurons in the cortical layer V, which branch and also innervate subcortical motor centers involved in motor control [81-84] (Figure 1). Thus, the HO thalamic nuclei are in the position to inform wider cortical regions about the motor instructions issued by a particular cortical area. In other words, it is likely that the HO nuclei are a neural substrate for internal motor monitoring of self-initiated actions, which may also be important for recognizing oneself as an agent. The other candidate for this function are direct corticocortical connections, which usually parallel transthalamic corticocortical connections [84]. Importantly, the major difference between the two routes for corticocortical interactions is that direct corticocortical links reside entirely in the cortex, while the transthalamic corticocortical pathways originate in the layer V pyramidal cells, which are motor in nature, and therefore, are more likely to be involved in internal motor monitoring mechanisms. Indeed, it has been demonstrated that pharmacologically inactivating the HO thalamic nuclei impairs this brain function [102].

The above concepts are important for our understanding of the pathomechanisms involved in psychosis as it has been convincingly argued by a number of authors that this pathomechanism involves a failure of internal motor monitoring mechanisms [30, 37, 58]. Consistent with this conceptualization of psychosis are the findings that schizophrenia involves so called

![Diagram illustrating cortico-thalamo-cortical circuits.](image-url)

**Figure 1.** Diagram illustrating cortico-thalamo-cortical circuits. The cortical layer V pyramidal neurons provide the major motor output to lower motor centers in the CNS, and some of them branch off and innervate the higher order (HO) thalamic relays, where they act as driver inputs. Therefore, the HO thalamic relays are in the position to inform sensory cortical areas about ongoing motor instructions issued by cortical areas involved in motor control. Direct cortico-cortical are also illustrated. Note that in schizophrenia the HO relays are affected, while the first order relays are relatively spared (see text for references). This is consistent with findings that schizophrenia is associated with source-monitoring deficits, whereby self-initiated actions become misattributed to outside sources, which could have explanatory value in psychosis. The cortical layer VI projections are also illustrated, and they provide neuromodulatory inputs to the thalamus and the thalamic reticular nucleus. Reproduced, with permission, from [84].
source-monitoring deficits [4, 10, 34, 35, 36, 45, 46, 47, 100], whereby individuals with the illness display deficits in recognizing self-initiated actions as such. As a result of impaired internal motor monitoring and related source-monitoring deficits, self-initiated actions become misattributed to outside sources resulting in psychotic experiences such as first rank symptoms. This mechanism has been found to underlie auditory hallucinations [34, 45, 53, 100]. These studies suggest that in schizophrenia, self-generated thoughts and speech are misattributed to an outside agency, which in turn underlies the experience of auditory hallucinations. More specifically, in a functional neuroimaging study of individuals with schizophrenia, Kumari et al. (2010) found that auditory hallucinations and deficits in self-monitoring of speech share a common neurobiological pathomechanism that involves reduced activation of frontotemporal cortices and of the thalamus (medial geniculate nucleus, pulvinar) [53].

In our earlier papers (cited above), we have pointed out that the conceptualization of psychosis as a failure of internal motor monitoring mechanisms, which then in turn result in source-monitoring deficits, is consistent with reported thalamic abnormalities in schizophrenia. Namely, schizophrenia is increasingly being recognized as a thalamocortical dysconnectivity syndrome [100]. A better understanding of what constitutes this dysconnectivity, and how it could contribute to the development of psychotic symptomatology, is likely to benefit the search for new pharmacotherapeutic targets. In order to clarify the potential role of the thalamus in psychosis, we have pointed out that a number of studies have found that in schizophrenia, the HO thalamic nuclei are markedly affected relative to the FO nuclei [3, 11, 18, 22, 28, 39, 44], particularly the MD and the pulvinar nuclei, which are anatomically continuous structures [18]. These studies have included neuroimaging and post-mortem data. The deficits involving the MD and the pulvinar nuclei have been found to be present early in the course of the illness [39, 44], and therefore, are unlikely to be due to chronic treatment with antipsychotic agents. Moreover, thalamic volume reductions have been found in non-affected twins of individuals with schizophrenia, with even greater deficits in affected twins [28], which suggests that thalamic volume deficits could be related to genetic risk factors underlying this disorder, and that they confer increased risk of developing psychosis.

Additionally, in a longitudinal study, Welch et al. found that cannabis use by individuals at high familial risk of psychosis is associated with thalamic volume loss as well as with further increased psychosis risk [98]. In summary, psychosis as well as risk factors for psychosis (familial and environmental) are associated with structural abnormalities of the thalamus, with the HO thalamic nuclei affected to a greater extent compared with the FO nuclei. As the HO nuclei are concerned with transthalamic corticocortical interactions [81-84], as well as with the related concept of internal motor monitoring [102], we suggest that thalamic deficits in schizophrenia are related to the genesis of source-monitoring deficits and psychosis.

Also, cerebral vascular accidents (CVAs) affecting the HO thalamic nuclei (MD and pulvinar) have been found to result in impaired internal motor monitoring and source-monitoring deficits [68], as well as psychosis [77], which provides further support for a link between HO thalamic nuclei deficits and psychosis. In the subsequent sections, we will profile the HO nuclei in terms of how they differ from the FO nuclei with respect to their overall neurophysiology and how this may explain the reported antipsychotic efficacy of mu opioid receptor agonists.

4. HO thalamic nuclei and post-inhibitory rebound burst firing

The HO thalamic nuclei have been found to differ neurophysiologically from the FO nuclei. Namely, the HO nuclei display dramatically greater amount of post-inhibitory rebound burst firing in awake, unanesthetized and attentive primates, especially when the animals were presented with novel information [73]. The post-inhibitory rebound burst firing mode is generated by thalamocortical neurons after they have been hyperpolarized for approximately 100 ms [81]. When this occurs, T-type calcium channels become de-inactivated, which results in a large influx of calcium into the cell. Subsequently, the neuron responds to any incoming excitatory signals with a bursts of action potentials. The burst firing mode contrasts with the tonic mode of firing in the thalamus, which occurs when thalamocortical neurons are relatively depolarized. Thus, inhibitory neuromodulatory inputs to the thalamus control the firing mode of thalamocortical cells. More specifically, the shift to the burst firing mode occurs when inhibitory inputs to the thalamus (gamma-aminobutyric acid B receptors or GABAB, adenosine receptors, mu opioid receptors, M2 muscarinic receptors) enable sustained hyperpolarization by increasing potassium K+ conductance, which then in turn leads to the opening of T-type calcium chan-
nels and the subsequent burst firing [48]. Importantly, when in the burst firing mode, thalamocortical neurons respond to sensory signals non-linearly [81] and potently activate and reconfigure larger cortical networks [90]. The finding that the HO nuclei display greater amount of burst firing in wakefulness [73] indicates that this mode of firing in the thalamus has a role in transthalamic corticocortical interactions, as well as internal motor monitoring.

Important for the purposes of this review are the findings reviewed by Krahe and Gabbiani (2004) that burst firing in sensory pathways, including those in the thalamus, occurs under the influence of the cortex, in accordance with ongoing behavioral context, with the effect of amplifying signal detection during a variety of exploratory behaviors [51]. Moreover, burst firing in sensory systems amplifies those features of sensory stimuli that are relevant to ongoing behavior of the animal. Thus, it follows that any disruption in the ability of thalamocortical neurons to display this firing mode would result in reduced ability to adjust sensory responsiveness to ongoing behavior, which could in turn lead to perceptual abnormalities and even psychosis [92, 93, 94, 95].

5. Schizophrenia and thalamic burst firing

There is evidence that schizophrenia involves a reduction in the ability of the thalamus to display the burst firing mode in response to cortical signals. Namely, a number of recent studies reported that this illness is associated with a reduction in sleep spindles [31, 32, 59, 79, 97], and this reduction has not been found to be secondary to antipsychotic medication use [32]. Sleep spindles are an electroencephalographic (EEG) finding and can be described as 11-16 Hz oscillatory bursts of synchronous neuronal firing lasting up to several seconds and involving thalamocortical, cortico-thalamic and intra-thalamic neuronal interactions [16, 17, 88]. They are found in stages 2 and 3 of non-rapid eye movement (NREM) sleep. The reduction in sleep spindles in schizophrenia suggests a reduced ability of the thalamus to display the burst firing mode, which could be secondary to a reduced ability of thalamic neurons to remain hyperpolarized in a sustained manner. Neurobiological factors in schizophrenia that may contribute to this relative inability of thalamocortical neurons to generate sustained hyperpolarization include dopaminergic overactivity, NMDAR hypofunction and potassium K+ channel dysfunction [92, 93, 94, 95]. In this paper, we argue that opioidergic hypofunction in the thalamus is another factor, which will be explained in greater detail below.

In terms of what occurs during wakefulness in psychosis, the proposed deficit in the ability of thalamic neurons to display thalamocortical network-dependent burst firing would be expected to impair adjustment of the thalamocortical firing mode to the overall behavioral context, with a concomitant decrease in signal to noise ratio in sensory processing [81]. Relatedly, this issue may underlie the noted failure of internal motor monitoring resulting in source-monitoring deficits and psychosis [92, 93, 94, 95]. In this context, it is noteworthy that sleep spindle activity in schizophrenia has been found to be inversely related to psychotic symptoms [32, 97], which indirectly supports the idea that the reduced ability to display thalamocortical network-dependent burst firing is related to psychotic symptomatology. Additionally, in rodents, D-amphetamine administration has been found to decrease thalamic burst firing and to concurrently disrupt auditory gating, while haloperidol administration reversed these deficits [52]. As schizophrenia involves dopaminergic overactivity, these results are in agreement with our hypothesis that the illness involves a disruption in thalamocortical firing mode regulation.

Consistent with ideas presented above, we predicted that agents with agonist activity at inhibitory neuromodulatory metabotropic receptors that increase potassium K+ and are present in the thalamus, and particularly in the HO nuclei, will tend to have some antipsychotic efficacy [93, 94]. Examples of such receptors include the M2 muscarinic receptor, the A1 adenosine receptor, the GABAB receptor and the mu opioid receptor.

6. Profiling the HO thalamic nuclei and the implications for schizophrenia

In addition to the fundamental difference between FO and HO nuclei, which concerns the origin of their respective driver inputs (ascending sensory pathways versus cortex), there are a number of other notable differences between the two classes of nuclei [91]. For example, a substantial proportion of thalamocortical neurons within the HO nuclei become hyperpolarized in response to muscarinic stimulation, which is in contrast to the FO nuclei where only a depolarizing effect was observed [65, 91]. This difference was explained by the finding that the HO nuclei contain a higher number of inhibitory M2 muscarinic receptors relative to the excitatory M1 receptors [73].
This is of interest as the cholinergic tone in the thalamus is higher during wakefulness [88] suggesting that, contrary to what one may expect, the awake state is associated with a relative hyperpolarization of some thalamocortical neurons in the HO nuclei. In this context, it is important to note that muscarinic agonists (in particular those at the M2 muscarinic receptor) tend to have antipsychotic efficacy (for a review see 72).

Additionally, the HO thalamic nuclei in the human brain contain markedly higher levels of inhibitory A1 adenosine receptors compared to the FO nuclei [89]. Agonists at the A1 adenosine receptors have also been found have antipsychotic efficacy (for a review see 56). Conversely, adenosine antagonists have been found to be pro-psychotic [42].

The HO nuclei selectively receive substantial GABAergic innervation from the anterior pretectal nucleus [9] and the zona incerta [9, 71]. Zona incerta is a subcortical structure, which is a major source of GABAergic inputs to the thalamus and is itself under strong direct cortical influence [5]. Another important source of the GABAergic innervation in the thalamus is the thalamic reticular nucleus (TRN), which is located adjacent to the rest of thalamus (Figure 2) and itself receives corticothalamic and thalamocortical innervation by the branches of axons that pass through it [83]. It in turn projects to the thalamus. When compared with the FO nuclei, the TRN innervation of the HO nuclei has been found to be complex and diffuse [55]. This finding is of potential significance as schizophrenia has been proposed to involve a dysfunction of the TRN [33]. The function of the TRN is thought to include amplification of corticothalamic signals [20, 27]. Thus, the HO nuclei are a target of multiple sources of GABAergic innervation, which are in turn under direct cortical influence. These hyperpolarizing influences are likely to be stronger when the cortex is in an activated state during wakefulness [26]. This is important for the purposes of current discussion, as it has been reported that enhancing GABAergic neurotransmission is another potential antipsychotic strategy [24], and this may in turn be related to its effects in the thalamus [93, 94]. More specifically, this applies
to agents that act as GABAB agonists such as clozapine and baclofen [24]. In summary, the HO nuclei receive inhibitory inputs from multiple neurotransmitter systems (cholinergic, adenosine, GABAergic, opioidergic), and it appears that potentiating these inputs offers a potential antipsychotic strategy. Next, we will turn to a more detailed discussion of the importance of the opioidergic system within the conceptual framework of psychosis presented in this paper.

7. Psychosis proneness and opioidergic activity in HO thalamic nuclei

As already mentioned, schizophrenia is associated with thalamic abnormalities, particularly in those thalamic nuclei concerned with relay of information from one cortical area to another cortical area (HO nuclei) [3, 11, 18, 22, 28, 39, 44]. We have argued that the thalamic abnormalities in schizophrenia are crucial to our understanding of neural pathomechanisms involved in psychosis. The thalamus is also important for our understanding of the functional role of the opioid system in the human brain. Namely, Raynor et al. (1995) reported that the expression of the mu opioid receptor in the human brain is highest in the diencephalon [74]. More specifically, a number of studies in humans and animals demonstrated that the mu opioid receptor is more highly expressed in the HO thalamic nuclei compared with the FO nuclei [25, 50, 60, 70, 74, 86]. Thus, the opioid system, and particularly the mu opioid receptor, may have a neuromodulatory role in transthalamic cortico-cortical interactions, which are involved in internal motor monitoring of self-initiated actions and recognizing oneself as an agent, and the failure of which may result in psychosis. In this context, it is interesting that opioid dependence itself is also associated with thalamic volume reductions, in particular when there is also significant alcohol use [75].

A failure of the opioidergic system to accomplish this neuromodulatory functional role may contribute to psychosis in some patients who suffer from psychiatric experiences. As already mentioned, the mu opioid receptor is a G protein-coupled receptor, which increases potassium K+ conductance, hyperpolarizes thalamic neurons and increases the likelihood of the occurrence of the thalamic burst firing mode [13, 14]. As discussed above, agents that have agonist activity at receptors that also increase thalamic burst firing (GABAB, M2, A1) tend to have antipsychotic efficacy [94]. It appears that methadone and bupenorphine fit this pattern [12, 29, 40, 61, 62, 69, 76, 78, 96, 103]. Antagonism at the dopamine D2 receptor in the thalamus has also been found to increase the burst firing mode in rodents [16, 52]. As already mentioned, the burst firing mode in the HO thalamic nuclei was reported to be important for transthalamic cortico-cortical interactions [73], and its reduction in schizophrenia may contribute to psychosis. Agents that help restore the ability of the thalamus to display the burst firing mode (including mu opioid receptor agonists) tend to have antipsychotic efficacy [93, 94].

Zubieta et al. reported an interesting study that provides important insights into the potential relationship between dopamine overactivity, stress and opioidergic hypoactivity in the thalamus [104]. Namely, they utilized ligand positron emission tomography (PET) technology to image mu opioidergic activity in response to a painful stimulus in healthy individuals with and without valine (val) by methionine (met) substitution at the codon 158 of the cathechol-O-methyl transferase (COMT) gene. This variant of the COMT gene (val 158 met substitution) is associated with reduced activity of the COMT enzyme, which degrades the neurotransmitter dopamine. Homozygotes for the substitution gene (met/met) have the lowest activity of the COMT enzyme, and therefore, the highest brain dopamine levels. Those individuals with the val/met genotype have the highest level of COMT activity, and therefore, lower dopamine levels, while heterozygous individuals have intermediate activity of the COMT gene and intermediate dopamine levels. Importantly, the COMT polymorphism has been linked to a number of psychiatric disorders, including schizophrenia (for a critical review see 99), cannabis-induced psychosis [43] and PTSD [49]. Kolassa et al. (2010) found that the risk of developing PTSD depends on the interplay between traumatic load and COMT val 158 met polymorphism [49]. What Zubieta et al. (2003) found was that the activity of the COMT enzyme was positively related to mu opioidergic activation in the thalamus and ventral basal ganglia (with lesser statistical significance) [104]. In other words, COMT val 158 met substitution gene was associated with reduced mu opioidergic activity in the thalamus (and to a lesser degree in ventral basal ganglia) in response to a painful stimulus. More specifically, the areas of the thalamus affected by the reduction in mu opioidergic activity were the pulvinar and what the authors termed the “anterior thalamus.” As already mentioned earlier, the pulvinar nucleus is a HO nucleus, which is anteriorly continuous with another major HO thalamic nucleus, the mediodorsal (MD) nucleus [18]. Moreover, both are markedly affected...
in schizophrenia [18]. These results are important as they provide an important link between genetic psychosis risk (COMT val 158 met polymorphism), vulnerability to stress, and mu opioidergic hypoactivity in the thalamus. Interestingly, the COMT val 158 met polymorphism is also associated with opioid dependence in Hispanic women [67].

In summary, in some individuals who are genetically vulnerable to psychosis, stress, dopaminergic hyperactivity and opioidergic hypoactivity in the thalamus may conspire to impair the HO thalamic nuclei and their ability to display sustained hyperpolarization and subsequent shift to the burst firing mode, with the result of reduced transthalamic corticocortical communication, relative disconnection between associated cortical regions, and psychosis. This provides one potential neurobiological explanation for the reported efficacy of methadone and bupenorphine in the treatment of psychosis in patients who are dependent on opioid agonists. Namely, these agents may restore the ability of the thalamus to display the burst firing mode and to support transthalamic corticocortical communication. This type of corticocortical interactions is crucial for sensorimotor integration, as well as for a number of cognitive functions including the integration of a sense of self (for a review see 21).

8. Conclusion: The importance of trauma

Zubieta et al. study involved healthy participants [104]. Thus, it is possible to carry the COMT val 158 met substitution gene and to exhibit mu opioidergic hypoactivity in the thalamus in response to stress but not become opioid dependent or suffer from psychosis and/or PTSD. It is possible that these biological risk factors interact with severe environmental stressors (i.e., trauma) to produce those phenotypes. Indeed, anyone who cares for the opioid-dependent population, particularly within the setting of the methadone maintenance treatment programs, is struck by the very high prevalence of trauma amongst these individuals. The high prevalence of PTSD and trauma amongst the opioid dependent individuals is noted by the DSM-IV-TR [2]. One interesting and understudied issue is the comorbidity of PTSD and psychosis in individuals who are receiving treatment for opioid dependence.

It is possible that in vulnerable individuals, such as those with COMT gene polymorphisms, exposure to traumatic events disrupts the balance between intrinsic activation and external constraints on the thalamocortical information flow, which then in turn leads to psychotic experiences [7]. Mu opioidergic hypoactivation in the thalamus may be another and related contributing factor, and some individuals may go on to develop heroin dependence as a maladaptive behavioral response, with negative consequences for their quality of life. The resulting lifestyle leads to further exposure to trauma, thereby exacerbating the underlying biologic vulnerabilities.

Psychosis has been described as a uniquely human affliction [19]. Considering the importance of the thalamus in corticocortical interactions, and our argument here that an impairment in these interactions is a potential pathomechanism in psychosis, it is significant that relative to other primates, the growth of the prefrontal cortex (PFC) in humans has far outpaced the growth of its HO thalamic nucleus partner, the MD nucleus [38]. This by-product of the human evolution may help account for the human vulnerability to psychosis. Humans possess a highly evolved PFC capable of generating complex motor behaviors and plans, yet the relay that informs more posterior sensory cortical areas about those complex behaviors and plans does not appear to have kept pace, at least in terms of its size. Any disruption in the function of the MD nucleus (or other HO nuclei) may then lead to psychosis. The reduced volumes of the HO thalamic nuclei in schizophrenia (see discussion above) is likely one aspect of thalamic impairments associated with psychosis. Its neurophysiologic correlate may be a concomitant reduction in thalamic burst firing, as suggested by reduced sleep spindles in schizophrenia. As already discussed, this thalamic firing mode is itself important for the function of the HO thalamic nuclei and for cortico-thalamo-cortical interactions [73]. Mu opioidergic hypoactivity in the thalamus may be one contributing factor to the reduction in thalamic burst firing in a subgroup of individuals with psychosis.

Thus, one of the main arguments in this review is that mu opioidergic hypoactivity in the HO thalamic nuclei in individuals who are vulnerable to psychosis [104] provides (1) important insights into the underlying neurobiology behind the overlap between psychosis and opioid dependence, as well as (2) offers support for a theoretical framework that may help explain the reported antipsychotic efficacy of opioid replacement pharmacotherapies. This review is not meant to be conclusive, but rather its purpose is to be thought-provoking and to draw additional attention to this understudied yet clinically relevant issue.
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Successful long-term (3-year) treatment of gambling with naltrexone. A case report

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Summary

Pathological gambling (PG) is classified as an impulse control disorder in the Diagnosis and Statistical Manual of Mental Disorder (DSM-IV-TR). There is still no properly validated pharmacotherapeutic treatment of PG. The involvement of the mu-opioid system in reward processes leads to the hypothesis that opioid antagonists have an impact on addictive behaviors. In reality, opioid antagonists have been used not only in substance abuse illnesses (narcotics, alcohol), but also in a variety of psychiatric conditions, including anorexia nervosa, bulimia, schizophrenia, self-injurious behavior, autism, obsessive-compulsive disorder, Tourette’s disease and trichotillomania. We present a case report in which an Italian patient affected by pathological gambling was successfully given long-term treatment with naltrexone. Controlled studies on opiate antagonists from the literature have already shown positive results. This case report confirms these data, but the present innovative finding is, for the first time, focused on the long-term outcome of treatment without side-effects. The patient has, in fact, taken her medication for 3 years, and so far she has never relapsed into gambling.

Key Words: Pathological Gambling; Naltrexone; Long-term outcome

1. Introduction

1.1. Gambling and gaming definitions

Gambling is the wagering of money or something of material value (referred to as “the stakes”) on an event with an uncertain outcome, with the primary intention of winning additional money and/or material goods. Typically, the outcome of the wager is evident within a short period.

The term gaming [19] in this context typically refers to instances in which the activity has been specifically permitted by law. The two words are not mutually exclusive; i.e., a “gaming” company offers (legal) “gambling” activities to the public [20] and may be regulated by one of many gaming control boards, for example, the Nevada Gaming Control Board. This distinction, however, is not universally observed in the English-speaking world. In the UK, for instance, the regulator of gambling activities is called the Gambling Commission (not the Gaming Commission). Also, the word “gaming” is often used to describe activities that do not involve wagering, especially online.

Pathological gambling (PG) is a problem that typically affects men between 21 and 55 years of age, although gambling disorders are also commonly encountered in teenagers and people aged over 65. Women comprised 24 per cent of the problem gamblers who called the New Jersey gamblers’ hotline in 1997 – up from 13 per cent in 1990 [21]. No consistent data are available about the role that racial, ethnic,
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income or educational factors play in problematic or pathological gambling. A survey of self-reported behaviours administered to 21,297 students in 8th to 12th grades in Vermont revealed that 7 per cent of these students had problem gambling behaviours. In this study, drug and anabolic steroid use, violence and carrying a weapon to school were behaviours recorded at above-average frequencies in young people who gambled, especially in those who had problems as gamblers [16, 44].

1.2. Diagnosis

The term “pathological gambling” should only be attributed to people who meet the criteria included in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) for this condition (Table 1) [1].

“Problem gambling”, “probable pathological gambling” and “gambling addiction” are terms used to describe gambling-related behaviours that may not meet specific DSM-IV criteria. For a diagnosis of

<table>
<thead>
<tr>
<th>Table 1. Diagnostic Criteria for Pathological Gambling</th>
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<tbody>
<tr>
<td>A. Persistent and recurrent maladaptive gambling behaviour as indicated by five (or more) of the following:</td>
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<tr>
<td>Preoccupation with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)</td>
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<td>Needs to gamble with increasing amounts of money in order to achieve the desired excitement</td>
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<td>Has repeated unsuccessful efforts to control, cut back or stop gambling</td>
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<td>Is restless or irritable when attempting to cut down or stop gambling</td>
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<td>Gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety or depression)</td>
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<td>After losing money gambling, often returns another day to get even (chasing one’s losses)</td>
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<td>Lies to family members, therapist, or others to conceal the extent of involvement with gambling</td>
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<tr>
<td>Has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling</td>
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<tr>
<td>Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling</td>
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<tr>
<td>Relies on others to provide money to relieve a desperate financial situation caused by gambling</td>
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<td>B. The gambling behaviour is not better accounted for by a manic episode.</td>
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<th>Table 2. Gamblers Anonymous 20 Question Survey*</th>
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<tr>
<td>1. Did you ever lose time from work due to gambling?</td>
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<td>2. Has gambling ever made your home life unhappy?</td>
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<td>3. Did gambling ever affect your reputation?</td>
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<td>4. Have you ever felt remorse after gambling?</td>
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<td>5. Did you ever gamble to get money with which to pay debts or otherwise solve financial difficulties?</td>
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<td>6. Did gambling cause a decrease in your ambition or efficiency?</td>
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<td>7. After losing, did you feel you must return as soon as possible and win back your losses?</td>
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<td>8. After a win, did you have a strong urge to return and win more?</td>
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<td>9. Did you often gamble until your last dollar was gone?</td>
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<td>10. Did you ever borrow to finance your gambling?</td>
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<td>11. Have you ever sold anything to finance your gambling?</td>
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<td>12. Were you reluctant to use gambling money for normal expenditures?</td>
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<td>13. Did gambling make you careless of yourself or your family?</td>
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<td>14. Have you ever gambled longer than you had planned?</td>
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<td>15. Have you ever gambled to escape worry and trouble?</td>
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<tr>
<td>16. Have you ever committed or considered committing an illegal act to finance gambling?</td>
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<td>17. Has gambling caused you to have difficulty in sleeping?</td>
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<td>18. Have arguments, disappointment, or frustrations caused you to gamble?</td>
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<tr>
<td>19. Have you had an urge to celebrate any good fortune with a few hours of gambling?</td>
</tr>
<tr>
<td>20. Have you ever considered self-destruction as a result of your gambling?</td>
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</table>

*Seven or more positive responses suggest pathological gambling. Available from Gamblers Anonymous International Service Office, P.O. Box 17173, Los Angeles, CA 90017.
pathological gambling to be correct, a patient must have the habit of gambling in a persistent and maladaptive manner that disrupts relationships and daily activities, and is not caused by manic episodes. Suicide attempts, felony convictions, spouse and child abuse, and unemployment are common in pathological gamblers [9]. Gamblers may hide or deny gambling-related problems, and this makes pathological gambling an often overlooked, undiagnosed condition.

Evidence points to the common existence of narcissistic personality characteristics and impulse control problems in pathological gamblers. High rates of personality disorders (e.g., obsessive-compulsive, avoidant, schizotypal and paranoid) are noted in several studies [4, 7]. Personality profiles of persons who are alcoholics and pathological gamblers have shown similarities in some studies. Some experts view pathological gambling as an addictive disorder, citing as evidence the tolerance and withdrawal symptoms exhibited by pathological gamblers because of debt escalation behaviours [42]. However, no physical or biochemical markers exist to help physicians make the diagnosis.

1.3. Screening tools

Several surveys are available to assist physicians in diagnosing this condition. The 1998 Gambling Impact and Behaviour Study [7] used a new screening tool based on DSM-IV criteria. The South Oaks Gambling Screen (SOGS) is the only extensively used, validated screening tool for the evaluation of patients who are pathological gamblers [31, 39]. Although it has not been validated, the Gamblers Anonymous Survey (Table 2), which includes 20 questions, may be helpful in providing clinical information, and can orient the gambler to the Gamblers Anonymous programme. Seven positive responses to the survey questions suggest a diagnosis of pathological gambling. A similar survey, “Are you living with a compulsive gambler?” [39] can be used to assist family members in coping with a problem gambler.

The easiest instrument for the family physician to use is the LIE/BET questionnaire [22], which is similar to the CAGE questions asked as part of screening for alcoholism. It consists of two questions that are sensitive to the core issues of pathological gambling: “Have you ever had to lie to people important to you about how much you gambled?” and “Have you ever felt a need to bet more money?”

1.4. Treatment

Central to the problem and treatment of pathological gambling is helping the patient overcome irrational thoughts. Pathological gamblers believe they have the ability to control random or chance events by relying on superstitious behaviour or methods [11].

Treatment goals for patients who are pathological gamblers or patients who are being treated for depression or alcoholism tend to be similar in that they focus on restoring a normal way of thinking and living to patients. A variety of approaches have been used in the treatment of pathological gamblers (Table 3). Modelled after Alcoholics Anonymous, Gamblers Anonymous is the primary self-help group and uses a 12-step, abstinence-based treatment programme. The efficacy of Gamblers Anonymous has not been demonstrated in controlled studies and, unlike alcoholism, some researchers have discovered that complete abstinence from gambling may not be necessary for successful treatment.

Behavioural, cognitive and cognitive-behavioural therapy appear to be the most successful treatment approaches [19]. Pharmacotherapy appears to have a role in the treatment of coexisting depression, rather than as a primary treatment for pathological gambling.

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<th><strong>Table 3. Treatment for Pathological Gamblers</strong></th>
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<tr>
<td>Screen patients for pathologic gambling if financial problems, alcoholism or depression are present.</td>
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<td>Intervene if the patient is at risk for suicide.</td>
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<tr>
<td>Refer the patient to Gamblers Anonymous and family members to Gam-Anon.</td>
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<tr>
<td>Enlist support from the family to help the patient follow through with treatment recommendations.</td>
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<tr>
<td>Counsel (or seek consultation, if appropriate) to assess and address the patient’s reasons for gambling, confrontation of defences and cessation of pathologic gambling behaviours; challenge the patient’s errors in thinking and reverse “learned behaviour” by systematic exposure, desensitization and skill development.</td>
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<tr>
<td>Actively participate throughout the patient’s treatment plan to continue assessment of related risk factors (e.g., suicide, alcoholism, depression); ensure follow-up with treatment recommendations, reinforce counselling and refer to self-help groups.</td>
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Contemporary psychotherapeutic approaches stress the identification of reasons for gambling, confrontation of defences and cessation of chasing behaviours. Cognitive treatments focus on challenging and correcting the patient’s errors in thinking; for example, exploring and understanding the illusion of control over chance events [30]. Behavioural therapy considers pathological gambling a behaviour that has been learned, and relies on techniques such as systematic exposure or desensitization and skill development (e.g., relaxation techniques and improving social skills) [51]. Cognitive-behavioural therapy combines elements from both the behavioural and cognitive treatment approaches, using systematic exposure or desensitization, relaxation techniques, training in social skills, and covert sensitization, as well as relapse prevention [51].

2. Case Report

A 64-year-old housewife presented with complaints of hypomania and a lifelong history of PG. There was an additional history of family psychiatric disease: her grandfather committed suicide, her father was aggressively violent, and her mother liked raffles, but both her brothers had the habit of betting a lot of money on horses. The patient had worked in a supermarket for 13 years, and was a housewife until 1970. In the previous three years, she had lost over 80,000 € playing the state lottery. Her spouse was concerned about possible economic and personal ruin if his wife’s gambling persisted. He was brusque and violent, but let her be responsible for their financial situation. The patient had worked in a supermarket for 13 years, and was a housewife until 1970.

In the previous three years, she had lost over 80,000 € playing the state lottery. Her spouse was concerned about possible economic and personal ruin if his wife’s gambling persisted. He was brusque and violent, but let her be responsible for their financial situation. The patient acknowledged that she had claimed non-existent winnings, gambled more than intended, felt guilty, had difficulty in stopping, hid the evidence of her gambling and secured loans to cover gambling debts. She related a history of gambling beginning as a middle-aged woman (54 years old). She started by betting 100 € on the laggard number of “Lotto” (Italian state lottery). For 3 months she played once a week, than she began to unflaggingly bet more money (500-2000 €) two or three times a week. At first she was against it; then she couldn’t stop betting, and gambling dominated her thoughts.

The patient was referred to a psychiatrist and psychotherapist, who treated her with Paroxetine 20mg/day and cognitive-behavioural therapy (CBT) (20 sessions). She felt less distress, but she had a weight gain of 10kg, so she switched from Paroxetine to Venlafaxine at a dose of 75mg/day. She didn’t stop lying to her husband and planned new ways of finding money: she asked her aunt to help her, and then her personal friends. When her spouse found out about her debts, he cut off funds and threatened her. She received assistance from community mental health services. She was treated with Carbamazepine at 400mg/day and Fluoxetine at 10mg/day. Although she said she could control her behaviours, she continued to attend CBT sessions and to take tablets. She did not stop playing the state lottery.

We gave her Quetiapine at 200mg/day, but she didn’t stop betting. The patient’s manic symptoms and behaviour improved. She stopped gambling, but only for one or two months. The patient and her husband both reported improvements in their relationship and communication. Finally we treated her with Naltrexone at 100 mg/day. No side-effects were found, and so far she has not gambled for 3 years. Just once she tried betting 3 € on the state lottery, but she didn’t feel like doing it again.

3. Discussion

Evidence from the literature and suggestions from clinical practice converge in indicating solid grounds for the hypothesis that opiates may be effective in a wide range of psychopathological conditions [15]. The endogenous opioid system – either directly, or through its influence on other neurotransmitter systems – has far-reaching effects on normal as well as abnormal (maladaptive) behaviours, thoughts and mood states [12]. Despite this, the role of antagonist opiates in psychiatry and on psychopathological symptoms has not been fully investigated. Regarding mood disorders, naltrexone was reported to have anti-manic properties, which may be due to its capacity to counterbalance rising endorphin levels, which is the source of euphoria and elation states [52]. On the other hand, manic relapses were not prevented during naltrexone maintenance [50]. Naltrexone may be a partial obstacle to the display of certain manic symptoms (manic euphoria), without blocking the onset or course of psychomotor excitement, so that the outcome is dysphoric mixed mania or mixed states. Looking at the antipodes of mania, depression is not positively influenced by the effects of opiate antagonists. At treatment entrance depression is, in fact, one of the negative predictors of the one-year retention in naltrexone maintenance treatment of heroin addicts [38]. The incidence of thoughts of death and of ending one’s life is considerably higher in the case of naltrexone maintenance than in that of methadone or...
buprenorphine maintenance, regardless of treatment response, which suggests that the effects of opiate antagonists may be independent of the mental status of inactive heroin addicts (Maremmani, unpublished data). Even so, naltrexone-induced dysphoria is exceptional during the first three months of a low-dose (50mg) naltrexone programme [14, 40], but it may be more common under 100 mg and/or in the long term [8, 35]. Encephalin (together with serotonin) is known to modulate the projection originating from the dorsal nucleus of the raphe and leading to the amygdala [32], which finds its resolution in peak anxiety and somatic symptom modulation. Panic attacks that have no link with opiate withdrawal have been reported in non-addicted patients after the administration of naltrexone [33, 37] or mu-agonists [26]. On the other hand, naloxone did not produce any panic symptoms in patients already suffering from panic disorders [3], which suggests a probable difference between acute opiate antagonism and enduring antagonism, the latter being effective in eliciting pathological anxiety. Opiate antagonism has also been considered in relation to psychotic symptoms. Naloxone administration, for instance, did produce any improvement of symptoms in selected schizophrenic patients, but the results were not homogenous [52]. The negative impact of opiate antagonism on psychosis is indicated by the evidence of psychotic symptoms worsening during long-term naltrexone treatment [50], and by the low retention rate of psychotic heroin addicts during naltrexone maintenance [38]. Thus, the predictable interaction between opiate antagonism and certain psychotic disorders, when combined with opiate addiction, is unfavourable.

Naltrexone has been shown to have poor results on unselected populations of heroin addicts. Studies from many groups have also shown the lack of effectiveness of opiate antagonists in the treatment of a majority of long-term heroin addicts [28]. An effective treatment for heroin addiction is based on two important pharmacological concepts: the drug used has to prove (a) an ‘antagonist’ effect against the abused substance; and (b) an ‘anticraving’ effect against drug-seeking behaviour, by stimulating the substance of the abuse-related affected system [43]. These two concepts stand as the basis of methadone treatment [13]. Naltrexone only provides patients with an ‘antagonist’ effect, which does not appear to be the crucial feature of the ‘narcotic blockade’ originally described for full agonists, since levels of global effectiveness differ markedly. The balance between the level of narcotic blockade and other properties corresponds to the level of global effectiveness of a treatment regimen, which may explain why complete blockade brings poorer results in the absence of other anticraving actions [43]. Naltrexone use is mostly confined to detoxification-related procedures, whereas its long-term effects and properties have been largely neglected, partly due to its limited effectiveness in the long-term control of addictive behaviours [38].

Studies focusing on the use and efficacy of naltrexone in cocaine dependence are rare. Naltrexone treatment seems to be effective in decreasing cocaine and alcohol use in men, but not in women with co-occurring cocaine and alcohol dependence [49]. Still, these are weak findings, suggesting that pharmacological and behavioural interventions that have shown their efficacy in the treatment of a single drug dependence disorder may not provide the coverage needed in targeting dual drug dependence [46]. The association of a copy skill treatment with the consumption of naltrexone may be able to reduce cocaine use [47].

Naltrexone was the first medication since disulfiram to be approved by the United States of America Food and Drug Administration for the treatment of alcohol dependence [48]. A recent Cochrane review concludes that naltrexone is an effective and safe strategy in treating alcoholism [45]. In particular, naltrexone has been found to be effective in reducing heavy drinking and craving. A longer period of required abstinence before treatment is associated with stronger medication effects [34]. Trials testing standard-dose naltrexone (50 mg/day) have generated mixed results; high-dose naltrexone may serve as a viable treatment option for alcohol-dependent patients with prominent alcohol craving [53]. Naltrexone is not effective for every patient and, looking at response predictors, an expression of “sweet preference” has a strong correlation with positive treatment outcomes [29].

Opioid antagonists have been used not only in substance abuse illnesses (narcotics, alcohol), but also in a variety of psychiatric conditions, including anorexia nervosa, bulimia, schizophrenia, self-injurious behaviour (as part of borderline personality disorder and other conditions), autism, obsessive-compulsive disorder, Tourette’s disease and trichotillomania [12].

Moving on now to eating disorders, naltrexone had been studied in the treatment of bulimia [23, 24]. Higher dosages (200-300mg/die) appear to be more effective than those commonly used in the treatment of opiate drug addiction [6, 25, 41]. Moreover, the association of fluoxetine with naltrexone seems to
be able to reduce episodes of “stuffing oneself”, the sense of loss of control during these episodes and the tendency to fast after episodes of “stuffing oneself” [36]. An obvious area for targeted research is that marked by “impulsivity”, a tendency that can lead to severe occupational, familial or social disability, such as that associated with compulsive/impulsive gambling, shopping or sexual activities. Indeed, certain compulsions, when primarily associated with pleasure in and of themselves, may be referred to as “impulsive” and this is true, for instance, of compulsive gambling [12].

The effect of opioid antagonists on the mu-opioid system in reward processes leads to the hypothesis of their usefulness in treating gambling [18]. To date, there is no properly validated pharmacotherapeutic treatment of PG [2], even if controlled studies on opiate addicts show positive results on pathological symptoms [2]. Naltrexone seems to be effective in reducing disease symptoms [27]. Subjects treated with naltrexone demonstrated statistically significant reductions in gambling urges and irresponsible behaviour in pathological gambling. Low-dose naltrexone (50 mg/day) appeared as effective as higher doses (100 mg/day and 150 mg/day) and all doses were well tolerated [17]. Pathological gambling could also be a serious complication in Parkinson’s disease treated with dopamine agonists, but it seems to respond to treatment with opioid antagonists such as naltrexone [5].

4. Conclusions

The best of our knowledge, there have been no studies so far that have looked at the long-term outcome of naltrexone treatment for gambling. The longest study lasted only about 12 weeks [10]. The present case report again shows once more the efficacy of naltrexone in pathological gambling, but the innovative brand-new finding is about its long-term outcome. This patient has, in fact, stayed in treatment for 3 years, and till now she has not relapsed into gambling, while showing no side-effects.

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All the authors contributed to, and have approved, the final manuscript.

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Recommendations for measuring treatment outcomes in opioid dependence management: consensus from the GLADD meeting

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1. Experience in measurement of outcomes in opioid management: how does it influence decision making

Provider experience– Emilis Subata

1.1 Reforming drug treatment in the Baltic States

In Lithuania, the pathway to a modern service for OD care began in the 1990s with a journey from abstinence treatment to a modern integrated system. Post 1990, treatment for OD in Lithuania has rapidly moved forwards with the introduction of the Minnesota model with 28 days of inpatient treatment (1992), residential drug-free rehabilitation (1994), opioid substitution treatment (OST) with methadone (1995) and buprenorphine (2006), mobile harm reduction services for intravenous drug users (2000), case management for medication assisted and court-mandated treatments (2007) and a mobile clinic for OST (2011). From a coercive approach under the ‘Narcological’ system, the current system in Lithuania aims to provide services that are effective and attractive for patients.

1.2 The need for outcomes data

There have been difficulties in moving from the ‘narcological’ system to a service-based integrated system. Politicians have found some treatment options, such as residential drug-free programmes, to be acceptable, and hence these types of programmes are more easily funded. Other treatment options, such as OST programmes, are viewed with suspicion or hostility by some groups and have faced opposition from politicians. For example, in 2011, 56 members of the Lithuanian Parliament signed a resolution questioning the role of OST in Lithuania. Only intervention from the World Health Organisation (WHO) and the Lithuanian Association of Psychiatrists persuaded the Lithuanian Parliament to adopt a much more balanced resolution that stated the need to ensure the quality of, and to increase support to, drug treatment services [4].
1.3 Outcomes in a local context

Against the background of such opposition to essential services for patients with OD, it was of vital importance to have high quality outcomes data to prove the effectiveness of treatments in a Lithuanian setting. The first such local specific data was provided by the WHO collaborative study on substitution therapy for OD and HIV, which was conducted in seven countries including Lithuania [5]. This study demonstrated positive outcomes in terms of decreased heroin use, risk behaviour and criminality; and improved health and quality of life (Figure 1). However, despite the positive outcomes from the WHO study there was still a strong demand for further confirmatory local outcomes data.

Further support for the need for robust and convincing outcomes data is provided by a study of OST in a Kyrgyzstan prison [6]. OST in prisons is controversial in many countries; however, this study demonstrated significant reductions in risk behaviours, criminality, drug use severity of dependence as well as an improvement in quality-of-life.

Based on the need to improve outcomes reporting for OD treatment services, in 2012 a National Drug Treatment Database was set up in Lithuania and will provide its first outputs in 2013. This database includes outcome measures for OST, which will be important in order to support and ensure continued funding for these services. In addition, the database will include data from an obligatory monitoring form that is filled at least annually for each individual patient. While there have been issues in processing these data on a national level, it is hoped that they will provide an important source of outcomes information for Lithuania in the coming years.

Since 2012 there has been a web-based National Database of drug treatment including medical OD therapies. In addition, the Addiction Severity Index (ASI) web-based database is available for use by service providers. This database includes assessment of addiction severity and clinical, social and psychiatric status and is completed at treatment initiation and every 12 months. As both databases evolve they are expected to have an important role in documenting treatment outcomes. In an era of where health resources are being stretched, the outcomes information from these databases should play an important role in ensuring continued funding for a range of services to treat OD.

It is hoped that these databases will provide high quality outcomes data on both an individual patient level and from a national perspective. However, in the future the aim is to develop the databases to provide ‘above individual patient level information’ in order to be able to assess and compare individual treatment programmes. Only by doing this can the most cost effective services for patients be identified.

Figure 3: Proportion of patients* reporting they were currently receiving psychosocial counselling
1.4 Summary

Locally relevant outcomes data has been vital in Lithuania to support effective treatment programs in the face of sometimes strong opposition. With the new national databases in place, Lithuania will have detailed information available at a patient and national level. In the future it is hoped to extend the databases so that they can measure outcomes at ‘an above patient level’ so that they can provide valuable data the outcomes associated with different treatment interventions for OD, which will enable the most cost effective programmes to be identified.

2. Making provision and payer based choices based on outcomes in opioid dependence services

Payer experience–Mark Gilman

2.1 Harm reduction

Treatment for OD is associated with a number of important outcomes including reduction in acquisitive crime, reduction in blood-borne infection risk and the potential for patients to progress to long-term recovery. Harm reduction has been the main focus of treatment for OD in the UK over the past 30 years. In the 1980’s needle syringe programmes were developed to prevent HIV transmission and AIDS. In the 1990’s, OST programmes were expanded in part as an attempt to reduce acquisitive crime.

The evolution of drug treatment in the UK has been associated with increasing costs. For example, in 1982 the budget for interventions for OD was in the region of 18 million pounds sterling and the total budget approached a figure near to 1 billion pounds sterling in 2013, an approximately 55-fold increase over the past 30 years. Despite the costs, the focus on harm reduction has been viewed as successful in some quarters based on a number of outcomes such as crime reduction, control of HIV spread in injecting drug users and an aging heroin-user population in the UK with fewer young people using the drug.

2.2 If this is success, what does failure look like?

It is possible, however, that the focus on harm reduction in the UK has resulted in an approach that prioritized long-term maintenance on OST over achieving long-term social recovery. Individuals on long-term OST had improved odds of survival, reduced need to participate in criminal activity and reduced infection risk compared with those not receiving treatment. However, continued dependence meant that individuals on long-term OST remained isolated without the social support networks to assist in their long-term recovery and potentially without being given appropriate opportunities to recover. This lack of recovery options was highlighted by the manager of a residential rehabilitation facility reporting to a UK Home Affairs Parliamentary committee, she said: “It is not unusual to receive a referral from somebody who has been on methadone for over five years and has never been offered the opportunity of residential rehabilitation” [2]. For those questioning the focus on harm reduction, this type of evidence supported their opinion that addicts were being ‘parked’ on OST therapy without being offered the means to move forwards to full recovery.

2.3 The goals of treatment have changed

Providing individuals with the best possible opportunity to achieve long-term recovery requires a range of support services to support their medical, psychological and social needs. Since 2010 in the UK there has been an increasing focus on recovery as a treatment goal for individuals with OD. An English public health view of this recovery process, recognises three broad social outcome areas in which individuals on OD treatment should demonstrate improvement, these are: economic– such as gaining paid employment, being in training/education or participating in voluntary work; autonomy–meaning having a stable home environment; and social function–having a network of family, friends and healthcare professionals to support the recovery process. A strong social support network is vital for individuals attempting opioid withdrawal and studies looking at this area have demonstrated that strong social networks can have as great an impact on health outcomes as smoking cessation, physical activity and to programmes to address obesity [3].

2.4 Outcomes are key to policy and provision decisions

In England, drug treatment services are commission by 152 local administrative areas funded by public health grants along with local investment. These bodies commission services from providers such as the UK National Health Service (NHS) and Crime Reduction Initiatives (CRI). By modifying the
‘success criteria’ on which they commission services and by looking at the range of services that they commission, payers can have a major impact on health outcomes. Commissioners will often consult patients and provider service ‘user groups’ to consult on service design and for input on the quality of the services. In order to support recovery a range of services such as recovery coaches, asset based community development, health trainers and expert patient programmes may be offered to patients. In addition, other approaches such as switching to more recovery-friendly medication, intensive day programmes, detoxification, residential rehabilitation and sober living accommodation may be appropriate. Therefore, payers have an important role in improving health outcomes in OD individuals by commissioning both the range of services that provide individuals with appropriate support for recovery, and by basing commissioning on outcomes (including medical, psychological and social) that provide individuals with their ‘best chance’ of recovery.

Once the commissioning group has formally identified the outcome goals for their OD treatment programme, these goals will be used to measure provider performance. If providers fail to achieve suitable results their contracts will not be renewed and other providers would be asked to tender for those services. This is a ‘payment by results’ system that aims to improve services by having clear metrics for measuring success.

2.5 The need for better outcomes in commissioning

In order to commission the appropriate services to aid recovery appropriate treatment outcome metrics are required. The current metrics in use are: 1. successful completion of treatment and 2. no return to treatment within 6 months. These outcomes are limited in terms of patient recovery as they do not address some of the broad social outcome areas seen to be important in the recovery process, such as having a job, a stable home environment and a strong social support network. In addition, these outcomes could easily lead to services that promote a rapid drive to detox and discharge without addressing the wider needs of patients. Therefore, service commissioners need to look at a range of outcomes metrics that will results in services that provide patients with ‘their best chance’ of recovery.

2.6 Summary

Treatment for OD in the UK is changing. Over the past 30 years a great deal of funding has been put in place to limit the harms associated with OD. From some perspectives this programme has been viewed as a great success as associated crime is down, HIV in drug users has been controlled, the users of heroin are getting older, and younger people are less likely to use heroin. However, the downside of this approach has been the emphasis on harm reduction over recovery that has often meant that individuals have been placed on OST for the long-term without being given the support needed for withdrawal. With a renewed focus on recovery, the commissioners who pay for OD services are being asked to deliver services with new metrics for success. Choosing the appropriate outcomes on which to measure success is vital in terms of measuring provider performance and for emphasising key health goals. However, there is a need for new outcomes measures in OD as the currently widely used metrics for treatment success are limited and may not sufficiently drive service providers to develop treatment programmes that give patients the ‘best chance’ of recovery.

3. A systematic way to measure outcomes in opioid dependence treatment

Hannu Alho

3.1 Issues with outcomes from a European perspective

There are currently two major limitations in the way outcomes data for opioid dependence treatments are collected. Firstly, there is no standardised set of outcomes measures, so the quality of outcomes measurement will vary by...
outcomes of opioid dependence treatment. Instead, a set of metrics are needed to capture mortality in treatment, individual and societal benefits as well as harm-related outcomes. In addition, because OD dependent populations are highly variable in terms of their clinical presentation and their personal goals for therapy, there needs to be some flexibility in scoring success. Therefore, population or system-wide outcomes measurement in OD management should be based on a scorecard of a number of metrics. Qualifying as a ‘responder’ would be determined based on the achievement of defined goals for the selected outcome measures (Table 2).

### 3.2 A pan-European approach

These issues have led to the proposal for a pan-European approach to linking existing outcomes databases related to medical-assisted therapy for opioid dependence [1]. Databases of harms associated with medically-assisted therapy for OD should be commenced at a European level. In addition, the authors proposed that funding for the EMCDDA should be enhanced to widen its remit and to ensure that it has the capacity to oversee the submission of more meaningful data for individual countries.

### 3.3 Developing a system to measure outcomes at an ‘above individual patient’ level

In order to identify appropriate outcome measures, it is important to look at various aspects of the treatment including the patient population, treatment goals and setting (Table 1). One single metric cannot quantify the range of outcomes of opioid dependence treatment. Instead, a set of metrics are needed to capture mortality in treatment, individual and societal benefits as well as harm-related outcomes. In addition, because OD dependent populations are highly variable in terms of their clinical presentation and their personal goals for therapy, there needs to be some flexibility in scoring success. Therefore, population or system-wide outcomes measurement in OD management should be based on a scorecard of a number of metrics. Qualifying as a ‘responder’ would be determined based on the achievement of defined goals for the selected outcome measures (Table 2).

### 3.4 Summary

Increasing access to OD management calls for better understanding of outcomes in this area. A range of measures describe effectiveness and long-term safety of buprenorphine and methadone in opioid dependence management, however, there is a need for a universal or at least European system, as proposed here, to allow comparison at the “above-individual-patient” level. Further work and pilots to develop such a tool are essential and should be supported by the community.

### 4. Consensus

In order to gauge audience opinion three questions were posed at the end of the symposium:
1. Measuring outcomes in opioid dependence can improve care provision?
2. Current approaches for measuring outcomes in opioid dependence are inadequate and should be improved?
3. Developing a universal system for measuring outcomes would be a useful advance in opioid dependence management?

There was broad agreement from the audience that measuring outcomes can improve care provision, that current approaches are inadequate and need to be improved and that a universal system for measuring outcomes would be useful.

5. Overall conclusions—Icro Maremmani

To improve care in OD we need to better understand outcomes across different systems and geographies. To achieve this goal, there needs to be a change in the way outcomes are measured. The new system should be simple and practical, so that it is easy to implement in different healthcare systems. A pan-European outcomes system would help to identify those countries that are achieving better outcomes and enable other countries to learn from their approach. Here we have proposed one option for the systematic measurement of outcomes in OD therapy based on a patient ‘response’ across a range of outcomes in four main categories: mortality, individual, society and harm reduction. Initial feedback from clinicians and policy makers in the addiction medicine field has been positive. We look forward to an informed debate on the implementation of a universal pan-European outcomes measurement system.

References


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Contributors

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Conflict of interest

ES was a Principal Investigator in 2 clinical trials on opioid dependence treatment, which were supported by “Schering Plough, UAB”. He has also received unrestricted grants from Merck Sharp & Dohme, UAB and Medikona, UAB for the development of Clinical Guidelines for Management of Opioid Dependence, which were commissioned by the Lithuanian Psychiatric Association. MG has received support from Reckitt Benckiser to attend and present at conferences and seminars. HA has been an advisory board member for Lundbeck, Reckitt Benckiser, Actavis and Mundipharma. IM was a member of the Scientific Board supported financially by Reckitt Benkiser, D&A Pharma, Lundbeck.

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The Food and Drug Administration in the United States has approved three medications for the treatment of chronic opioid addiction: methadone, buprenorphine, and Vivitrol/Naltrexone. There are approximately 310,000 patients being treated in 1,250 federally certified and approved Opioid Treatment Programs (OTPs) in the United States. The vast majority of these patients (300,000) receive methadone as a part of comprehensive treatment offered by the OTPs. The remaining 10,000 patients use buprenorphine as part of their comprehensive treatment.

At the present time, there are a small number of patients receiving Naltrexone/Vivitrol through the OTPs and it is anticipated that this number will increase in the coming years.

There are two important trends which will have an effect on patient access to treatment in OTPs in the coming years in the United States. The first major policy initiative is Health Care Reform. The administration of the White House and the Department of Health and Human Services anticipates that 30 million Americans will have greater access to healthcare as a result of being able to get public health insurance. We expect that a significant number of opioid addicted individuals will also gain access to care through such public health insurance coverage (Medicaid) as a direct result of this policy change.

The second major initiative is the likelihood of increased referrals to OTPs through the Criminal Justice System. We understand that representatives from the Criminal Justice System; including Drug Courts, probation and parole offices, and correctional facilities; seem to prefer the use of Naltrexone/Vivitrol to treat chronic opioid addiction. A number of such Criminal Justice representatives also appear to support the use of buprenorphine for such treatment, and a smaller number appear to support the use of methadone at the present time. What all representatives from the Criminal Justice System appear to agree on is that such medications should be used to treat chronic opioid addiction as part of comprehensive care services, which...
include counseling and other importance medical ancillary services. The AATOD Board of Directors, through its Medications Committee (Chaired by Dr. George Stavros and written by Dr. Brian McCarroll), developed the Naltrexone/Vivitrol Guidelines to provide guidance to member programs about the use of this medication to treat chronic opioid addiction. We do not anticipate that a large number of patients will be inducted in the OTPs using Naltrexone/Vivitrol products at the present time. We do anticipate that programs will have a greater interest in using this medication as a relapse prevention tool as patients decide to end the use of methadone or buprenorphine as part of a maintenance treatment program. The AATOD Board believes that all OTPs should use the three federally approved medications to treat chronic opioid addiction, depending on the clinical needs of the patient and where they happen to be as part of their recovery process. From AATOD’s point of view, recovery is not defined as ending methadone or buprenorphine treatment but part of a continuum of care, which may include withdrawal from medications like methadone and buprenorphine as the individual sees fit. If this is the case, then Naltrexone/Vivitrol may be an appropriate relapse prevention medication to be used at the end stage of maintenance treatment.

We also understand that for the vast majority of patients who are treated for opioid addiction in OTPs, that recovery will come through maintenance on either methadone or buprenorphine. Once again, the issue of recovery is not related to ending the use of either methadone or buprenorphine. The AATOD Board also worked with many of its colleagues in the medical community in developing these guidelines over the course of nine months prior to publication. They are simply meant as a method of informing our associates about the value of all appropriate and federally approved medications to treat chronic opioid addiction.

Up to this time the normally accepted treatment for opiate addiction has included methadone (an opiate agonist) which is only available through federal and state licensed specialized clinics, as well as buprenorphine which can be prescribed by specially licensed physicians out of their private practices. Both of these medications have been proven to be highly successful in the treatment of opiate addiction especially when they are combined with regularly scheduled counseling sessions. Both of these medications require the patient to dose on a daily basis. They also both suppress withdrawal and craving. Certain patients find it difficult to comply with daily dosing regimens and have been known to miss days of dosing which could result in relapse. Vivitrol is an extended release formulation of naltrexone, which is an opioid receptor antagonist. This medication was officially approved in October of 2010 by the US Food and Drug Administration (FDA) for the treatment of opiate addiction. It works by binding to opiate receptors in the brain for up to a one month duration. The experimental data indicates that Vivitrol blocks neurotransmitters in the brain and experts believe that these blocked neurotransmitters are associated with the pleasurable effects of recreational drugs such as alcohol, heroin, and morphine. This antagonist binding appears to nullify the euphoric and psychotropic reaction of opiates. Since the recovering opioid addicts do not get the reinforcing euphoria or “high” from occasional opiate use, their self-administrative behavior pattern of drug abuse is decreased. Ultimately, over time, this lack of reinforcement gradually results in “extinction” of such behavior. The medication had originally been approved by the FDA in 2006 for the treatment of alcohol addiction, however, it has now been approved for opiate addiction based on the findings of clinical research predominantly performed on heroin addicted patients in Russia. Not only has it demonstrated its effectiveness in preventing relapse to drug use following opioid detoxification, but has also been shown to decrease cravings. Currently it is the only approved medication for opiate dependence that is not a controlled substance. Vivitrol does not display abuse potential, offers a safe alternative for treatment expansion, and has been successfully used in highly motivated groups i.e. impaired professionals, parolees, and probationers. This medication is supplied as a depot intramuscular injection that the patient receives in the gluteal region on a monthly basis. Safety and efficacy of Vivitrol have been studied. In one six-month study Vivitrol treatment was compared to placebo treatment in patients who had finished opioid detoxification and were no longer physically dependent on opioids. The results demonstrated that patients who were treated with Vivitrol were more likely to stay in treatment and to refrain from using illicit drugs. Further analysis of the data revealed that 36% of the Vivitrol treated patients were able to continue in treatment for the full 6 months of the study without using drugs, compared to 23% in the placebo group. It must be noted that all formulations of naltrexone carry a “black box warning” for liver damage or hepatitis (hepatotoxicity) but in actuality this side effect is rare. Regular clinical evaluations with a serial liver function studies are recommended. Furthermore, patients who have been on prolonged treatment with Vivitrol may be more sensitive to lower doses of opioids after Vivitrol treatment stops. This, of course, could lead to serious injury, coma, or death. In order to prevent the occurrence of acute opiate withdrawal in opiate dependent patients, the patients must be completely opioid-free for a minimum of 7-10 days before starting Vivitrol treatment. One must keep in mind that the absence of an opioid in a urine drug screen is quite often not sufficient proof the patient is opioid free. Therefore, a naloxone challenge test is recommended prior to beginning Vivitrol therapy. One must also realize that there is always the possibility that patient treated with Vivitrol could overcome the opioid blockade effect of the medication. The blockade of the opioid receptors by Vivitrol is not insurmountable. Patients who administer large amounts of exogenous...
opioids in an attempt to overcome the opioid blockade of Vivitrol could face a fatal overdose due to respiratory arrest and circulatory collapse. The FDA has reported certain side effects associated with Vivitrol use. The most common adverse events (occurring greater than 2% and at least twice as frequently with Vivitrol than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Local effects at the injection site were predominantly pain and induration. Serious allergic reactions including skin rash, facial or tongue swelling, trouble breathing, wheezing, chest pain, dizziness, and feeling faint have also been documented. Further reported side effects are nausea, vomiting, headache, fatigue, and mild to moderate muscle cramps. There have been rare cases of severe allergic pneumonia. Other possible serious side effects include depression (5%), suicidal thoughts(5%), suicidal behavior(5%), dysphoria, and generalized malaise. However, the majority of side effects were reported as "mild to moderate". In regard to the dosing requirements of Vivitrol there are two distinct differences between Vivitrol and methadone/buprenorphine. Unlike methadone and buprenorphine both of which are taken orally, Vivitrol is administered via an intramuscular injection. Unlike methadone and buprenorphine (both of which must be taken daily) Vivitrol is effective for 30 days. Furthermore there is no need to adjust the doses of Vivitrol for weight, height, age, gender, or health status. A single injection of 380 mg maintains the patient's blood levels above 1 ng/cc 4-5 weeks. Vivitrol should be administered only by a health care provider as an intramuscular injection, using special administration needles that are provided with the product. Vivitrol should not be injected using any other needle.

Since Vivitrol is an opioid blocker, pain patients are a considerable challenge. Patients undergoing emergency or elective surgery will not respond to the normal therapeutic doses of intravenous or oral opioid analgesics. The pain-relieving effects of any opioid agonists are blocked while on Vivitrol. This would include pure mu agonists such as methadone or morphine derivatives, partial agonists, as well as mixed agonist/antagonists. In order to overcome the pharmacologic blockade of Vivitrol, extremely high doses of opioid analgesics are required to achieve adequate analgesia. This could lead to accidental overdoses using this class of pain medications. Therefore it is recommended that non-opioid analgesics be prescribed for elective pain management in these patients when possible. This would include the non-steroidal anti-inflammatory agents which are not blocked by Vivitrol. Regional nerve blocks and dissociative analgesics such as ketamine have also been recommended. However, expert consultation by an informed experienced pain specialist would be optimal.

As with any other medication intended for the treatment of addiction, Vivitrol was never intended to be used alone without other conventional accepted modalities for treatment. It should never be regarded as any type of "cure". It is simply a tool which, when used in combination with inpatient drug rehabilitation, counseling, and NA/AA meetings could improve the patients' chances for a successful recovery. Furthermore, it is an expensive medication. The average cost of a single monthly injection averages between $850.00 and $1,100.00 depending on the patient population being treated through insurance coverage. However, it is covered by many third party carriers. Virtually all carriers have criteria that the patients must meet in order to qualify for the prescription. Most require that they currently be abstaining from all opioid use and are also receiving documented psychosocial support. Many provider also require that the patients have tried and failed at least a 30-day trial with oral naltrexone; or the member's physician has documented inappropriateness of treatment with oral naltrexone. In many states Vivitrol is covered by Medicaid. Due to the variation of coverage criteria from state to state and between insurance carriers it would be best to check on an individual basis.

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