

Heroin Addiction and Related Clinical Problems



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CONTENTS

Psychiatric comorbidity in substitution treatment of opioid-dependent patients in primary care: Prevalence and impact on clinical features <i>Martin Lieb, Hans-Ulrich Wittchen, Ulrich Palm, Sabine M. Apelt, Jens Siegert and Michael Soyka</i>	5
Methadone maintenance therapy and feto-maternal outcomes of pregnancy <i>Jide Igboekwu and Kim Wolff</i>	17
On opioid receptors <i>Andrea Vendramin and Annella Sciacchitano</i>	23
Psychotherapeutic management of heroin-addicted patients. Psychopathological, relational and organizing aspects <i>Emanuele Bignamini</i>	33
Treating heroin addicts. Blocking dosages and stimulation-stabilization of opioidergic system <i>Matteo Pacini, Angelo Giovanni Icro Maremmani, Luca Rovai, Fabio Rugani and Icro Maremmani</i>	41
It is time for a responsible administration of gamma hydroxybutyrate and methadone <i>Fabio Caputo</i>	49
Opiate maintenance treatment in primary health care in Germany <i>Rainer Ullmann</i>	53



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Psychiatric comorbidity in substitution treatment of opioid-dependent patients in primary care: Prevalence and impact on clinical features

Martin Lieb¹, Hans-Ulrich Wittchen², Ulrich Palm¹, Sabine M. Apelt², Jens Siegert², and Michael Soyka¹

¹ Ludwig-Maximilian-University, Dept. of Psychiatry, Munich, Germany, EU

² Technische Universitaet Dresden, Dept. of Psychology, Dresden, Germany, EU

Summary

Although elevated rates of psychiatric comorbidity in drug-dependent patients in methadone maintenance treatment are known, differences in comorbidity, maintenance medications, provider settings and somatic morbidities often remain unclear. Here, the prevalence and impact of comorbidity is described in a large, nationally representative sample of substitution patients with a cross-sectional naturalistic study in German buprenorphine or methadone substitution patients. Over two thirds of both the males and females were diagnosed by their physician as having a psychiatric diagnosis other than substance dependence. Depressive and anxiety disorders were the most common diagnoses. Men recorded higher rates for schizophrenic disorders, sleep disorders and antisocial personality disorder, while a higher percentage of women had a borderline personality disorder.

Key Words: Drug dependence; EuropASI; psychopathology; substitution; maintenance treatment; methadone; buprenorphine; comorbidity.

1. Introduction

In 2004 at least 57,700 opioid-dependent individuals received substitution treatment in Germany. Approximately 68% of these were treated with methadone, 15% with levomethadone and 16% with buprenorphine [1,2]. Despite these substantial treatment rates, little is currently known about the patients' problem profiles in terms of comorbidity, differences between provider models and treatment formats and, lastly, about the efficacy of either methadone or buprenorphine maintenance treatment in primary care.

There is a consensus that the major goal of substitution treatment is not primarily abstinence, but the reduction of behavioural and medical risks and harm associated with opioid dependence, improvements in social integration as well as the interruption of the vicious circle of drug intake and drug-related criminal acts. Although the ultimate goal

of substitution treatment might be complete abstinence or a change from maintenance treatment to other drug-free forms of treatments, little is known about the percentage of patients attaining this goal. A further positive aspect of maintenance therapy is that involving patients in a continuous medical treatment plan leads to better opportunities in treating or managing the wide range of associated mental and somatic morbidities (hepatitis, HIV). A critical question in this respect is to what extent patients in substitution regimens suffer from comorbid mental disorders and how mental disorder comorbidity influences their treatment, course and outcome.

Numerous studies have been carried out to measure the prevalence of psychiatric disorders and drug use patterns in the general population [3, 4], as well as among psychiatric patients and drug users in and outside treatment services [5, 6, 7, 8]. The results vary greatly in terms of both numbers and types of diagnoses, depending on the sampling char-

acteristics, sampling methods, diagnostic instruments and approach of each study. It has been shown that comorbidity is not merely an artefact of diagnostic criteria and the simple co-occurrence of disorder by chance, but provides important information on aetiology, natural course and treatment. In particular, symptoms of mental disorders and substance use disorders have been shown to interact and mutually influence each other.

Substance use disorders have been found to be associated with a wide range of all types of psychopathology, ranging from so-called externalizing (oppositional defiant disorder, conduct disorder, attention deficit/hyperactivity disorder) to internalizing mental disorders (anxiety and mood disorder) [9]. According to national reports, the prevalence of psychiatric comorbidity in opioid treatment settings in various countries of the EU ranges from 22 to 86%, depending on the diagnostic criteria selected, instruments used and time of diagnosis [10]. However, little is known about the question whether rates of comorbidity also differ by type of treatment setting. In the past substitution treatments were usually limited to specialized substitution centres, but by now the situation seems to have changed in most European countries. In recent years, substitution treatments have usually become available in smaller settings, for instance in primary care settings.

Comorbidity was found to be associated with a greater propensity to risk behaviour such as sharing injection equipment, or with lower rates of condom use [11, 12, 13]. More specifically, antisocial personality traits [14] or personality disorders [15] were associated with drug and sex-related risky behaviour or even HIV infection in most but not all investigations [16]. Personality disorders in methadone-maintained opioid addicts were found to be associated with a higher rate of employment, more family/social and psychiatric problems, an increased risk of HIV infection and poor social judgment or sensitivity [17]. Female gender, alcohol-related disorders and living without a partner were found to be associated with depression and intravenous drug abuse [18].

Less is known about comorbidity rates in methadone versus buprenorphine-treated patients. Two studies [19, 20] full reported mood improvement using low dose buprenorphine in non-opiate users with refractory depression. Another study [21] reported a rapid improvement in depressive symptoms during an open trial of buprenorphine, which the authors considered to be greater than that typically observed during stabilization in methadone maintenance treatment. However, no antidepressant effects of buprenorphine compared to methadone could be shown in any of the investigations [22].

In clinical practice, addicts treated with buprenorphine often describe a higher level of alertness compared to methadone treatment, but few clinical studies have evaluated cognitive performance under buprenorphine treatment. Recent studies suggest that buprenorphine treatment causes less impairment of psychomotor performance, especially driving ability in drug-dependent patients compared to methadone

maintenance patients [23, 24, 25, 26, 27].

In line with the cross-sectional character of the baseline investigation, our results reflect the present state of patients with psychiatric comorbidity who are undergoing substitution treatment in Germany, in terms of socio-demographic variables, setting size, allocation, addiction severity and substance use.

2. Materials and Methods

Baseline sampling referred to a nationwide register of over 2,500 substitution doctors in Germany in 2003, and to a percentage of roughly 10% in a stratified random sample (total baseline participating settings: $N = 223$) of small and medium-size providers as well as large-scale substitution centres. A total of $N = 2,694$ patients were enrolled in the baseline study. Physicians with more than ten opioid-dependent patients a day were instructed to list all patients on the predetermined recruitment week by type of substitution drug and recruit at least five methadone and five buprenorphine patients by using a prefixed algorithm. Small settings with less than 10 opioid-dependent patients were asked to recruit all patients. Each patient had to give written informed consent. The study was approved by the Medical Ethics Committee of the Technische Universität Dresden.

All patients who were at least 16 years of age had a past or current opioid dependence, and at that time were currently receiving an agonist maintenance therapy with either buprenorphine or methadone, were eligible for the study. Exclusion criteria were acute medical emergencies, cognitive impairments making the meaningful completion of the self-report forms unlikely and unwillingness to comply with study procedures, including the mandatory urine tests. A detailed description has been published in the COBRA study design [1].

2.1. Instruments

The baseline instruments consisted of a patients' questionnaire, a doctors' questionnaire and a standardized urine drug screening. A detailed description of the assessment tools and variables is given in the COBRA study design [1].

2.2. Patients' questionnaire

After receiving information about the study and filling in the informed consent form, patients were asked to complete a 12-page questionnaire. The questionnaire consisted of various components of established instruments, such as the European Addiction Severity Index (EuropASI, German version of the ASI) [28], as well as modules of the substance use questions of the WHO Composite International Diagnostic Interview (CIDI) [29]. The questionnaire covered the following domains: (I) basic biosocial and socio-demographic

information, (II) social and legal life developmental history and status rating, (III) past and current drug use and illness history module, (IV) diagnostic status (DSM-IV substance use and other mental disorders by CIDI) and severity, (V) self-reported physical disorders (e.g. hepatitis C, HIV), (VI) past and current impairments, disabilities and problems specific to drug use, (VII) past and current treatment history, (VIII) met and unmet subjective needs, (IX) current and past experiences with treatments and (X) quality of life and risk behaviours.

2.3. Subsequent assessment and appraisal of patients

Upon completion of the questionnaire, each patient – as part of the doctors' consultation – was assessed and evaluated by the doctor using a standardized appraisal form. This 7-page appraisal covered the following domains: (I) description of treatment frequency, medication and changes (lifetime and during the respective assessment period), (II) licit and illicit substance use and substance use diagnoses including severity ratings, (III) past and current physical and mental disorders by clinical global impression (CGI) and treatment status, (IV) multidimensional evaluation of social and psychological functioning, (V) description and appraisal of all past and ongoing current interventions or those being considered, (VI) compliance and problems of management profiles, (VII) individual treatment targets and considerations, (VIII) prognostic scales, (IX) health risk behaviours and EuropASI severity score.

2.4. Urine screens

In addition a standardized urine drug screening, supervised by a nurse, was obtained to confirm the patients' answers with regard to substance use and to validate doctors' ratings. Screening tools (Drugscreen Multi 7, von Minden GmbH, Regensburg, Germany) were provided by the study centre.

2.5. Subjects

Study participants at baseline were $N = 2,694$ opioid-dependent men (68.4%) and women (31.6%). The mean age of the sample was 34.8 years (SD 8.1; range 17-62 years); 8.6% were foreign citizens, 56.1% had never been married, 18.6% were separated or divorced and 12.4% were currently married. The mean duration of education in the whole sample was 11.1 years (SD 1.8; range 1-20 years) and 53.9% were unemployed. Women (34.1, SD 8.0 years) were younger than men (35.1, SD 8.1 years) (OR 0.98, $p=0.002$) and had more years of education (10.2 years [SD 1.8] vs. 10.0 years [SD 1.8], OR 1.08, $p=0.001$). The mean age at onset for any substance use (omitting nicotine) was 19.2 years (SD 3.9) for men and 18.9 years (SD 3.8) for women (OR 0.98, $p=0.068$). The mean age of first substance use treatment

was 23.9 years (SD 6.29) for men and 22.2 years (SD 5.94) for women (OR 0.95, $p=0.001$). 31.5%, 47.1% and 21.4% of patients were being treated in small, medium and large settings. 74.7% received methadone, 24.6% buprenorphine and 0.7% another substitution drug.

2.6. Statistical Analysis

Statistical analysis of data was performed using Stata 9.2. Descriptive Correlations (StataCorp LP, College Station, TX, USA) between the number of psychiatric diagnoses and other variables were performed using multinomial logistic regression. Exclusive groups were built for patients with one, two, three and four or more psychiatric diagnoses. Substitution drug, setting size, age, gender, HIV, hepatitis B and hepatitis C status were included in the model as independent variables to assess their influence on positive benzodiazepine and cannabis screening and the EuropASI global score.

3. Results

3.1. Rates of psychiatric diagnoses

About two-thirds of the total sample (68.4%), irrespective of gender, received at least one psychiatric diagnosis other than substance use disorder. Among those with psychiatric comorbidity, 53% had one additional diagnosis, 28.5% had two additional diagnoses, 12.5% had three diagnoses and 5.9% had four or more additional diagnoses. Prevalence rates are given in Table 1, together with OR (95% CI) comparing men with women.

Depression (56.6%) and anxiety disorders (25.3%) were the most common diagnoses. Men had higher rates of schizophrenic disorders (ICD10: F20-29), sleep disorders (ICD10: F51) and antisocial personality disorder. Women showed a higher risk of having a lifetime borderline personality disorder than men (Table 1).

Depressive disorders were the most commonly reported disorders in the "one comorbid disorder" group (44.1%). In the "two comorbid disorders" group the combination of depressive disorder and anxiety (22.8%) or sleep disorder (15.3%) was the item most commonly reported. In the "three comorbid disorders" group the most common combination was depression, anxiety and sleep disorder (16.2%), followed by depression, anxiety and borderline personality disorder (10.8%). In the "four or more comorbid disorders" group the quadruple combination of depression, anxiety, sleep disorder, and borderline personality disorder was the item most often reported (11.3%).

3.2. Psychiatric comorbidity and sociodemographic information including allocation, setting size and sero-status

Patients treated with buprenorphine had lower rates of

Table 1: Psychiatric comorbidity according to doctor's ratings: Percentages of clinical psychiatric diagnoses according to ICD-10 are shown separately for the total sample, and for males and females. OR: odds ratio from logistic regression (male is ref.)

	Total N = 2.694	Male N = 1.842	Female N = 852	OR	P
Dementia, amnesic disorder, other cognitive disorders (ICD-10: F00-F09)	2.31%	2.68%	1.55%	0.57	0.141
Schizophrenia, other psychotic disorders (ICD-10: F20-29)	5.02%	5.95%	3.10%	0.50	0.011
Manic / hypomanic disorder (ICD-10: F30-31)	1.97%	2.01%	1.89%	0.94	0.866
Depressive disorder (ICD-10: F32-33)	56.6%	57.33%	55.08%	0.91	0.368
Anxiety disorders (ICD-10: F40-41)	25.25%	25.06%	25.65%	1.03	0.791
Somatoform disorders (ICD-10: F45)	6.82%	6.62%	7.23%	1.10	0.634
Primary and secondary sleep disorders (ICD-10: F51)	21.20%	23.64%	16.18%	0.62	0.000
Acute and chronic stress disorder (e.g. adjustment disorder, PTSD) (ICD-10: F43)	11.33%	10.48%	13.08%	1.29	0.105
Antisocial personality disorder (ICD-10: F60.2)	6.82%	8.55%	3.27%	0.36	0.000
Borderline personality disorder (ICD-10: F60.3)	14.99%	11.65%	21.86%	2.12	0.000
Other personality disorders (ICD-10: F60-69)	13.70%	14.25%	12.56%	0.86	0.333
Others	8.23%	7.46%	9.81%	1.34	0.092

psychiatric co-morbidity compared to methadone patients (OR 0.76, $p=0.001$) (Table 2).

In comparison to small-scale settings, rates of mental disorders were highest in large-scale settings (OR 2.18, $p=0.001$), followed by medium size ones (OR 1.18, $p=0.045$) (Table 3). Comorbidity was not related to gender or education, but singles showed an increased risk for psychiatric comorbidity (OR 1.2, $p=0.014$), while employed persons had a lower level of risk (OR 0.49, $p=0.001$) (see Table 4 for a detailed description of sociodemographic variables). There was a greater number of HIV and hepatitis B- and C-positive patients in the comorbid group (Table 5).

3.3. Psychiatric comorbidity and addiction severity

The global score for addiction severity was associated

with the number of comorbid conditions: one comorbid disorder: $n=929$, mean 2.8, SD 1.4; two comorbid disorders: $n=498$, mean 3.2, SD 1.4, OR 1.27, $p<0.001$ compared to one comorbid disorder; three comorbid disorders: $n=220$, mean 3.6, SD 1.4, OR 1.51, $p=0.000$ compared to one comorbid disorder; four or more comorbid disorders: $n=105$, mean 3.9, SD 1.44, OR 1.71, $p=0.000$ compared to one comorbid disorder. Patients with any number of comorbid disorders revealed significantly more problems and were rated as having a higher need for treatment in the somatic, financial, legal, and social fields (Table 6). They also suffered more often from comorbid alcohol and drug abuse. Substitution therapy with buprenorphine (Coeff -1.9, $p=0.000$), female gender (Coeff -1.35, $p=0.003$) and being employed (Coeff -5.9, $p=0.000$) were all associated with lower EuropASI global scores, while medium (Coeff +2.4, $p=0.000$) and large

Table 2: Allocation according to psychiatric comorbidity

Allocation	Without comorbid disorders (n=920)	1 comorbid disorder (n=937)	2 comorbid disorders (n=509)	3 comorbid disorders (n=222)	4 or more comorbid disorders (n=106)
Methadone	72.4%	73.5%	79.2%	75.7%	82.1%
Buprenorphine	27.3%	25.9% 0.94 (0.09) p= 0.53	19.8% 0.66 (0.09) p=0.002	23.0 % 0.81 (0.14) p=0.22	15.1% 0.49 (0.14) p=0.011
Codeine/others	0.33 %	0.53% 1.6 (p=0.52)	0.98% 2.8 (p=0.17)	1.4% 4.0 (p=0.09)	2.8% 7.7 (p=0.01)

setting sizes (Coeff +1.1, p=0.022) and being single (Coeff +3.1, p=0.000) were associated with higher severity scores.

3.4. Psychiatric comorbidity and drug use

Patients with psychiatric comorbidity revealed higher rates of concomitant drug use (Table 6). Men (n=1,725, mean 1.6, SD 1.2) had more positive urine drug screenings than women (n=792, mean 1.4, SD 1.14) (OR 0.88, SD 0.03, p=0.001). The number of positive screenings increased with psychiatric comorbidity (one comorbid disorder: n=881, 1.53, SD 1.15; two co-morbid disorders: n=473, 1.8, SD 1.3, OR 1.18, p=0.001 compared to one comorbid disorder; three co-morbid disorders: n=211, 1.8, SD 1.3, OR 1.23, p=0.001 compared to one comorbid disorder; four or more co-morbid disorders: n=100, 2.16, SD 1.10, OR 1.49, p=0.000 compared to one comorbid disorder). Especially cannabis and benzodiazepine

use seemed to contribute to an increased risk of illegal drug abuse (Table 7). The influences of psychiatric comorbidity on positive cannabis and benzodiazepine screening remained significant, even when allocation, age, setting size, family status (married/living together vs. rest) and employment status (employed vs. rest) were taken into account (Table 8).

4. Discussion

This cross-sectional study underlines the importance of psychiatric comorbidity in methadone and buprenorphine-treated opioid-dependent patients. According to the clinical diagnosis, almost two-thirds of the sample had at least one non-substance use disorder. Consistent with previous research, depression and anxiety were very common diagnoses [5, 6, 15, 30]. Comorbidity rates were similar in men and women, although men had higher rates of schizophrenic

Table 3: Psychiatric comorbidity according to setting size

Setting Size	Without comorbid disorders (n=920)	1 comorbid disorder (n=937)	2 comorbid disorders (n=509)	3 comorbid disorders (n=222)	4 or more comorbid disorders (n=106)
Small setting (up to ten substitution patients per day)	37.7%	29.1%	27.1%	25.7%	32.0%
Medium setting (10 to 40 substitution patients per day)	48.3%	50.1% 1.3 (p=0.005)	42.6% 1.2 (p=0.114)	42.3% 1.4 (p=0.164)	42.5% 1.03 (p=0.887)
Large setting (more than 40 substitution patients per day)	14.0%	20.8 % 1.9 (p=0.000)	30.3% 3.0 (p=0.000)	31.2% 3.4 (p=0.000)	25.5% 2.1 (p=0.006)

Table 4: Psychiatric comorbidity according to sociodemographic information. Family status

Family Status	Without comorbid disorders n=917	1 comorbid disorder n=891	2 comorbid disorders n=486	3 comorbid disorders n=212	4 or more comorbid disorders n=99
Unmarried	56.5%	55.4%	55.1%	61.1%	54.3%
Living together	14.6%	10.5% 0.73 (p=0.034)	12.2% 0.86 (p=0.362)	9.1% 0.57 (p=0.031)	8.6% 0.6 (p=0.184)
Married	13.0%	12.5% 0.99 (p=0.917)	10.8% 0.86 (p=0.38)	12.7% 0.9 (p=0.7)	14.3% 1.14 (p=0.66)
Separated	3.7%	6.1% 1.7 (p=0.021)	6.1% 1.7 (p=0.38)	5.0% 1.2 (p=0.548)	3.8% 1.07 (p=0.903)
Divorced	11.8%	14.8% 1.3 (p=0.083)	14.8% 1.3 (p=0.135)	10.0% 0.8 (p=0.33)	17.1% 1.5 (p=0.153)
Widowed	0.4%	0.8% 1.8 (p=0.373)	1.0% 2.3 (p=0.214)	2.3% 4.8 (p=0.021)	1.9% 4.5 (p=0.084)

Table 4: Psychiatric comorbidity according to sociodemographic information. Educational level

Education level	Without comorbid disorders n=870	1 comorbid disorder n=891	2 comorbid disorders n=486	3 comorbid disorders n=212	4 or more comorbid disorders n=99
No graduation	19.1	18.5	18.3%	17.3%	14.4%
Secondary School (9 years of education)	40.1	42.9 1.1 (p=0.6)	41.8 1.1 (p=0.6)	38.2 1.1 (p=0.8)	49.0 1.6 (p=0.12)
Secondary modern School (10 years of education)	19.9	20.8 1.1 (p=0.43)	18.9 0.99 (p=0.97)	23.6 1.3 (p=0.25)	21.2 1.4 (p=0.33)
Grammar school (13 years of education)	4.9	5.7 1.2 (p=0.43)	7.7 1.6 (p=0.054)	6.8 1.5 (p=0.22)	4.8 1.3 (0.63)
University	1.4	1.2 0.86 (p=0.72)	1.0 0.7 (p=0.6)	3.2 2.5 (p=0.07)	0.0
Vocational school	13.5	10.0 0.76 (p=0.12)	11.2 0.9 (p=0.48)	10.5 0.9 (p=0.59)	9.6 0.9 (p=0.9)
Others	1.1	1.0 0.9 (p=0.852)	1.0 0.9 (p=0.9)	0.5 0.5 (p=0.5)	1.0 1.2 (p=0.9)

Table 4: Psychiatric comorbidity according to sociodemographic information. Employment status

Employment Status	Without comorbid disorders n=870	1 comorbid disorder n=891	2 comorbid disorders n=486	3 comorbid disorders n=212	4 or more comorbid disorders n=99
Working	31.0	19.4	14.8	15.1	14.3
Unemployed	49.0	56.5 1.8 (p=0.000)	59.7 2.6 (p=0.000)	65.1 2.7 (p=0.000)	60.0 2.7 (p=0.000)
Pupil/student/ apprentice	3.4	2.8 1.3 (p=0.3349)	3.4 2.1 (p=0.028)	3.2 1.9 (p=0.150)	3.8 2.4 (p=0.136)
Not working/ House husband wife	6.7	9.3 2.2 (p=0.000)	8.9 2.8 (p=0.000)	5.1 1.5 (p=0.250)	8.6 2.8 (p=0.022)
Retired	2.9	4.3 2.4 (p=0.001)	5.5 4.0 (p=0.000)	6.0 4.3 (p=0.000)	6.7 5.1 (p=0.001)
Occupational retraining	3.8	4.2 1.7 (p=0.027)	3.7 2.0 (p=0.023)	3.2 1.7 (p=0.237)	3.8 2.1 (p=0.195)
Others	3.3	3.7 1.8 (p=0.032)	4.1 2.6 (p=0.002)	2.3 1.4 (p=0.49)	2.9 1.88 (p=0.340)

Table 5: Psychiatric comorbidity and hepatitis B, hepatitis C and HIV - status according to serology (RR comparing positive vs. negative, unassessed and missing data)

Serostatus according to:	Without comorbid disorders n=920	1 comorbid disorder n=937	2 comorbid disorders n=509	3 comorbid disorders n=222	4 or more comorbid disorders n=106
HIV					
Not assessed	8.91	8.75	4.91	5.86	6.6
Positive	4.78	4.91	5.30	6.31	9.43
Negative	77.93	76.4	72.7	77.03	69.81
Missing data	8.37	9.91	17.09	10.8	14.15
RR (p)		1.03 (0.899)	1.11 (0.66)	1.34 (0.355)	2.07 (0.047)
Hepatitis B					
Not assessed	6.1	6.4	3.5	4.5	6.6
Positive	22.93	25.72	31.83	28.23	36.79
Negative	62.3	57.5	50.1	57.2	45.3
Missing data	8.7	10.35	10.4	9.9	11.3
RR (p)		1.16 (0.162)	1.57 (0.000)	1.33 (0.89)	1.95 (0.002)
Hepatitis C					
Not assessed	5.2	5.12	2.55	3.2	4.7
Positive	55.54	58.59	64.44	58.11	63.21
Negative	36.0	32.0	26.7	35.1	28.3
Missing data	3.26	4.3	6.3	7.0	3.8
RR (p)		1.13 (0.185)	1.45 (0.001)	1.11 (0.49)	1.38 (0.13)

Table 6: Correlation between comorbid disorders, medical and social parameters

	Without comorbid disorders n=870	1 comorbid disorder n=891	2 comorbid disorders n=486	3 comorbid disorders n=212	4 or more comorbid disorders n=99
Somatic	1.80 (1.85)	2.40 (2.00) 1.19 (p<0.001)	2.78 (2.02) 1.23 (p<0.001)	3.12 (2.17) 1.40 (p<0.001)	3.63 (2.27) 1.53 (p<0.001)
Financial	3.14(2.15)	4.05 (2.26) 1.20 (p<0.001)	4.42 (2.19) 1.29 (p<0.001)	4.83 (2.32) 1.40 (p<0.001)	4.86 (2.33) 1.41 (p<0.001)
Alcohol	1.28(1.82)	1.52 (2.14) 1.06 (p=0.012)	1.90 (2.39) 1.15 (p<0.001)	1.84 (2.30) 1.14 (p<0.001)	2.92 (2.73) 1.33 (p<0.001)
Drugs	2.37 (2.30)	2.63 (2.30) 1.05 (p=0.014)	2.82 (2.45) 1.09 (p<0.001)	3.46 (2.53) 1.21 (p<0.001)	3.52 (2.24) 1.22 (p<0.001)
Legal	1.32(1.86)	1.68 (2.14) 1.09 (p<0.001)	1.92 (2.33) 1.15 (p<0.001)	2.45 (2.74) 1.25 (p<0.001)	2.13 (2.18) 1.19 (p<0.001)
Social	2.5 (2.13)	3.73 (2.32) 1.27 (p<0.001)	4.32 (2.42) 1.40 (p<0.001)	4.63 (2.46) 1.49 (p<0.001)	4.42 (2.55) 1.43 (p<0.001)
Psychiatric	1.52 (1.47)	3.44 (1.99) 1.95 (p<0.001)	4.47 (2.06) 2.48 (p<0.001)	4.90 (2.09) 2.73 (p<0.001)	5.68 (1.78) 3.27 (p<0.001)

disorders and antisocial personality disorder than women. Women had higher rates of borderline personality disorder.

In our nationally representative sample of opioid dependent patients in substitution treatment the results are in line with a smaller clinical cohort study by Krausz et al. [31]. In the course of this 5-year follow-up study of comorbidity in 350 opiate addicts mainly receiving methadone maintenance treatment, 55% were diagnosed as having at least one additional mental disorder according to ICD-10 (lifetime prevalence). In 43% of the opioid addicts, the predominant disorders were neurotic, adjustment and somatoform disorders (F4), and 32% of the patients had affective disorders (F3). Schizophrenic, schizotypic and delusional disorders (F2) were less frequent (5%). The average number of diagnoses was 1.3 per patient. In this study women were clearly more often affected by comorbidity than men.

Our study confirms the expected associations between psychiatric comorbidity and addiction severity as well as co-occurring substance abuse. Exclusive groups were formed according to the number of psychiatric diagnoses, and the data revealed that higher rates of psychiatric comorbidity were associated with increased addiction severity. Psychiatric comorbidity was associated with greater severity measures (EuropASI) and a need for specific therapy not only in psychiatric, but in somatic, alcohol and drug therapy too, as well as for financial, legal and social support, indicating a more intensive and burdensome nature of the disease. Social problems, as detected by the EuropASI, are probably reflected and objectified by the higher number of unemployed and singles in the comorbid disorder groups. The association

between a greater need for somatic therapy in dual diagnosis patients seems to be only partly explained by a larger number of HIV, hepatitis B- and C-positive patients in the comorbid groups, which did not always reach significance. The comorbid disorder group showed significantly more positive urine drug screenings, which reflects the increased drug-related problem ratings in the EuropASI. Especially cannabis and benzodiazepines contributed to these findings. In regression analysis the effects of the number of comorbid disorders on positive benzodiazepine and cannabis screening remained significant, even when corrected for allocation, substitution therapy, age, gender, setting size, HIV and hepatitis serostatus, as well as socio-demographic variables (single status, employed, housing situation). Bleich et al. [32] reported similar results from an investigation of benzodiazepine use in methadone patients. 148 patients who completed 1 year of substitution treatment with methadone underwent random and twice-weekly supervised urine analysis for various drugs of abuse, responded to self-report questionnaires (SCL-90-R; POMS; HIV/Hepatitis C risk-taking behaviours), participated in interviews (ASI) and were tested for Hepatitis C. After 1 year of methadone treatment, benzodiazepine users (n=63) had significantly more psychopathology, depressed mood and HIV/HCV risk-taking behaviour. In a cross-sectional investigation [33] heroin injectors with lifetime benzodiazepine dependence proved to be more likely to meet criteria for anxiety or depressive disorders. Epstein and Preston [34] performed a meta-analysis on 408 polydrug abusers meeting methadone-maintenance criteria to investigate whether cannabinoid-positive urine specimens in heroin-dependent

Table 7: Relationship between drug use (urine drug screen) and psychiatric comorbidity (RR). Percentages of negative, positive and missing urine screenings. §= (OR compared to “no comorbid disorder)

Urine drug screenings	Without comorbid disorder n=920	1 comorbid disorder (n=937)	2 comorbid disorders (n=509)	3 comorbid disorders (n=222)	4 or more comorbid disorders (n=106)
§ Opiate		0.97 (p=0.782)	1.17 (P=0.253)	1.31 (p=0.135)	1,56 (p=0,07)
Negative	68.48	70.33	66.21	66.6	59,43
Positive	18.7	18.57	21.22	23.8	25,47
Missing	12.83	11.10	12.57	9.46	15,09
§ Methadone		1.08 (p=0.44)	1.21 (p=0.115)	1.57 (p=0.01)	2,53(p=0,001)
Negative	32.28	32.44	29.86	25.68	16,98
Positive	50.98	55.5	57.37	63.51	67,92
Missing	16.74	12.06	12.77	10.81	15,09
§ Hallucinogen		0.51 (p=0.58)	2.14 (p=0.45)	1.89 (p=0.60)	
Negative	55.98	53.79	61.26	61.26	52,83
Positive	0.22	0.11	0.45	0.45	0
Missing	43.80	46.1	38.29	38.29	47,17
§ Codeine/DHC		2.61 (p=0.01)	4.78 (p<0.001)	3.30 (p=0.011)	2,96(p=0,11)
Negative	58.91	59.66	57.96	66.67	51,89
Positive	1.09	2.88	5.11	4.05	2,83
Missing	40.0	37.46	36.94	29.3	45,28
§ Cocaine		1.03 (p=0.845)	1.30 (p=0.188)	1.64 (p=0.042)	1,57(p=0,194)
Negative	78.15	78.44	77.41	77.48	68,87
Positive	7.50	7.79	9.63	12.16	10,38
Missing	14.35	13.77	12.67	10.36	20,75
§ Methamph/ Ecstasy		1.20 (p=0.785)	2.23 (p=0.233)	0.96 (p=0.974)	2,24(p=0,474)
Negative	78.8	80.47	79.76	84.68	79,96
Positive	0.43	0.53	0.98	0.45	0,59
Missing	20.76	19.00	19.25	14.86	19,45
§ Amphetamine		1.36 (p=0.602)	2.55 (p=0.112)	0.78 (p=0.823)	5,67(p=0,019)
Negative	81.2	82.18	80.55	86.04	74,53
Positive	0.54	0.75	1.38	0.45	2,83
Missing	18.26	17.08	18.07	13.51	22,64
§ Benzodiazepine		1.74 (p>0.001)	2.78 (p>0,001)	2.67 (p>0.001)	6,15(p>0,001)
Negative	73.7	67.45	58.74	61.7	44,34
Positive	12.50	19.85	27.70	27.93	46,23
Missing	13.80	12.70	13.56	10,36	9,43
§ Cannabis		1.29 (p=0.015)	1.51 (p=0.001)	1.62(p=0.003)	1,95(p=0,003)
Negative	49.78	45.89	42.63	41.44	37,74
Positive	31.96	37.89	41.45	43.24	47,17
Missing	18.26	16.22	15.91	15.09	15,09

outpatients predicted other drug use or impairments in psychosocial functioning. Cannabis use was not associated with retention rate, use of cocaine or heroin or the Addiction Severity Index. Cannabis-related disorders were weakly associated with psychosocial problems at post-treatment follow-up. A prospective investigation [35] in patients on methadone maintenance treatment found that cannabis abusers

were more often polydrug abusers than non-users, but did not suffer from more psychological distress or infectious diseases and did not engage in more HCV/HIV risk-taking behaviour and also did not leave treatment earlier than non-cannabis abusers.

Patients with psychiatric comorbidity were over-represented in large settings in our sample. On the one hand,

Table 8: Regression analysis of concomitant benzodiazepine and cannabis abuse

	Benzodiazepine positive	Cannabis positive
Without comorbid disorder	1	1
One comorbid disorder	1.65 (p=0.001)	1.24 (p=0.077)
Two comorbid disorders	2.70 (p=0.000)	1.56 (p=0.002)
Three comorbid disorders	2.00 (p=0.002)	1.52 (p=0.028)
More than three comorbid disorders	5.10 (p=0.000)	1.80 (p=0.026)
Substitution therapy with buprenorphine	0.58 (p=0.000)	1.00 (p=0.97)
Age (years)	1.01 (p=0.068)	1.01 (p=0.234)
Female gender	0.89 (p=0.355)	0.72 (p=0.003)
Medium setting size	0.82 (p=0.145)	1.09 (p=0.473)
Large setting size	1.08 (p=0.646)	1.69 (p=0.000)
HIV-positive	1.12 (p=0.662)	0.89 (p=0.623)
Hep.B-positive	0.96 (p=0.75)	0.91 (p=0.451)
Hep.C-positive	1.19 (p=0.206)	1.18 (p=0.134)
Single	1.03 (p=0.882)	1.64 (p=0.001)
Employed	0.70 (p=0.027)	0.74 (p=0.019)
Stable housing	0.70 (p=0.04)	1.12 (p=0.364)

this could be explained by the better therapeutic outcomes attainable in large settings for severely affected patients. On the other hand, our findings may reflect more sensitive psychiatric diagnosing in the larger settings. There seem to be relatively fewer comorbid patients in the buprenorphine group compared to the methadone group.

It was demonstrated by Wittchen et al. [1], that both the

doctor sample of physicians licensed for substitution as well as the sample of patients treated with either methadone or buprenorphine may be regarded as being representative of the situation of patients in German substitution centres, at least in terms of their regional distribution and the type of setting, as well as the type of substitution drug. In any of these core variables, available federal register data revealed a high concordance with our study data. With regard to the patient sample, the following critical remarks should be considered: the patients' sample does not reflect the total of all patients treated in the participating settings because patients not fluent in German (for example Eastern European opioid addicts without German language skills) as well as those experiencing severe suffering (like acute emergencies or cognitive impairment which prevented them from filling in the questionnaires) at the time of the study were excluded. Particularly for specialized centres in some areas, as many as a quarter of the patients were not eligible. Overall, our sample can be regarded as being reasonably representative of German substitution settings. The main weakness in our report is that the diagnosis of psychiatric comorbidity was made by the substitution doctor according to the clinical impression and not according to structured clinical interviews, which clearly have better reliability and validity to diagnose psychiatric disorders. The reported EuropASI scores founded on clinical impression are generally not comparable to the composite scores with regard to expressiveness, but they give an idea of the subjective severity estimation of addiction-associated problems and the need for treatment according to doctors' subjective opinions.

Our findings are of relevance with respect to social function, rehabilitation and psychotherapeutic strategies in substitution patients. A detailed psychodiagnostic examination should be performed at the start of and during substitution therapy, as co-occurring disorders are very common in these patients. Compared to the non-comorbid group, dual diagnosis patients do not only need a greater number of psychiatric and psychotherapeutic approaches, but integrated therapeutic opportunities in all addiction-related problem fields, too. The importance and transformability of key principles for substance abuse and mental health services – postulated by Power and DeMartino [36] – in treating dual diagnosis patients are emphasized: co-occurring disorders are both common and complex. Individuals with co-occurring disorders should be considered to be the rule, not the exception, in substance use and mental health treatment systems. Both mental illness and substance dependence are examples of chronic somatic illnesses, much like diabetes, elevated blood pressure, heart disease and asthma. If mental illness and substance use disorders coexist, both should be considered as primary, and integrated treatment is required with effective evidence-based practices.

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Contributors

The authors contributed equally to this article.

Conflict of Interest

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

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Methadone maintenance therapy and feto-maternal outcomes of pregnancy

Jide Igboekwu¹ and Kim Wolff²

¹ Ravens Wood Medium Secure Hospital, Fareham, UK

² Addiction Science Institute of Psychiatry, Kings College London, UK

Under the auspices of the International Programme in Addiction Studies (Kings College, London, University of Adelaide, Australia and West Virginia Common Wealth University, USA)

Summary

We studied a cohort of pregnant opioid dependent women ($n = 30$) on methadone maintenance therapy aiming to identify obstetrics, neonatal and pregnancy outcomes and characteristics including the level of antenatal contact and its effect. There were statistical significant associations between birth weight and use of illicit drug and between use of illicit drugs and gestational age (crack use and length of labour $r^2 = .57$ and $r^2 = .012$. $P = 0.05$; Cocaine use and type of delivery $r^2 = .515$ and $r^2 = .006$. $P = 0.05$; Birth weight and length of gestation $r^2 = .429$ and $r^2 = .041$. $p = 0.05$).

Key Words: MMT; Pregnancy; Feto-maternal outcomes

1. INTRODUCTION

Opioid dependence in pregnancy is a multiplier of risks and will tend to introduce risk issues like abnormal physical, social, economic and environmental factors in pregnancy and birth [1]. Methadone maintenance therapy (MMT) is often the gold standard of treatment for opiate addiction in pregnancy [6, 24]. It is associated with reduced perinatal morbidity, recovery from illicit drug use and better preparation for parenting [19, 24]. However methadone does cross the placenta and has a dose related effect on the foetus. The dose and time of last methadone is related to the rate and time of neonatal abstinence syndrome [9,7] However Methadone has potential therapeutic benefit for the developing foetus by minimizing cycle of intoxication and withdrawal associated with variable timing of illicit opiate use [20]. Pregnancy for the drug dependent female is a window of opportunity

which can be exploited to address the opiate addiction once the dependent person is happy to commence on methadone maintenance therapy. The opportunity for regular antenatal checkups and regular urine drug screen presents itself if the addicted individual has to consume the methadone on site or even if they have to present themselves once in a while to collect their prescribed methadone [11]. Research has shown that methadone in conjunction with adequate prenatal care reduces maternal mortality, lowers the rate of foetal morbidity, foetal wastage, and pregnancy associated complications while promoting foetal stability and growth [12, 16, 17]

Total abstinence is not usually the goal of treatment for the drug dependent pregnant individual to avoid triggering premature labour, thus there are still instances when the individual on methadone maintenance will end up using on top opiates or heroin [16]. There are still instances of poly drug use as Methadone maintenance does not address crav-

ing for stimulant or cannabinoids. Thus those individual, who are addicted to opiates and other substance, could be on methadone while still using other drugs like cannabis or amphetamine. Thus there are evidence of certain untoward effect of methadone maintenance therapy on the mother and baby. Some studies provide the evidence that such negative effects should not be viewed in isolation from the psychosocial environment of the pregnant woman. Thus the presence of intimate partner violence, the chaotic life style of the addict and the unhealthy environment including housing and finance should be seen as contributing to the overall outcome in those maintained on methadone [21]. Research has shown that a critical component of behaviour change is knowledge of perceived riskiness of such behaviours [2, 26]. Could it be then that the perceived risk to the unborn baby is the driving force of the improvement in the behaviour of the expectant mother on methadone maintenance therapy? What we know is that the aim of methadone maintenance is to reduce harm, reduce a chaotic life style and reduce crime as well as maintain a healthy lifestyle. This study seeks to investigate and confirm effects of methadone maintenance therapy in pregnancy and immediate postnatal period.

2. Methods

Data for this prospective study were collected over a four year period from three sites in London United Kingdom namely-

- (a) The Primary Care Unit (PCU), London united kingdom
- (b) The Elizabeth Garrett Anderson Obstetric Hospital (EGA/OH); University College London Hospital (UCLH). London United kingdom
- (c) The Children Outpatient Department university college London hospital (UCLH). London, United Kingdom.

The data was collected by a research midwife working in the Primary Care Unit from all pregnant women using substances, which were either registered with the Primary Care Unit or booked for confinement at the Elizabeth Garrett Anderson/Obstetric Hospital. Misuse of substance was defined as any pregnant woman who currently or in the past has used opiates (including methadone), crack, cocaine or other illicit drug either alone or combination. Excluded were all pregnant women who were HIV positive and those unable to understand the information sheet.

Most pregnant drug users were offered full hospital care throughout their pregnancy, or if registered with General Practitioners and had a good relationship with the practice had shared care with their General practitioner. Patients were therefore expected to attend the Obstetrics Hospital every four weeks until the 28th week of pregnancy, fortnightly from 28-36 weeks and weekly thereafter until delivery.

At University College London Hospital (Elizabeth Garrett Anderson/Obstetric Hospital and Children's Outpatient Department), there were approximately 2500 deliveries per

year of which 20-30 of these were known to be drug users. Data was collected at three key periods namely antenatal period, perinatal period and postnatal period. The patient's name hospital number, date of birth, parity, gestation at delivery, type of delivery, antenatal and intra partum complications, substance misuse, baby's weight, and apgar score were recorded

2.1 Statistical analysis

Samples of the group were compared using one sample t-test. $P < 0.05$ were considered statistically significant. Null hypothesis were rejected when a one sample t-test found statistical significant results. Two tailed Pearson correlation was used to test for correlation between two parameters. Statistical significance was at 0.05 levels.

3. Results

3.1. Antenatal period

A total of 30 pregnant opioid dependent women were recruited and followed up within the four year period. The age ranges of the pregnant women were between 21 and 41. Mean age of 29.4 ± 4.7 (standard deviation SD). The base line demographic information recorded at booking included ethnicity which showed that 86.7% were Caucasians; 6.7% were black British; 3.3% were black others and the remaining 3.3% were Spanish.

At booking; 56.7% of the women were single and 30% were cohabiting. 40% of the women had never worked while 30% had semi regular employment and 16.7% had regular employment. The mean number of antenatal visits was 5.9 times throughout the entire period of gestation. The range varied between no visits at all to 20 visits (± 4.6). There was record of consistent methadone prescription with evidence shown by positive urine screen for 20 (67%) of the women. Two of the women (6.7 %) were detoxified from methadone during pregnancy.

There was no record of methadone prescription for 8 (27%) women who continued to use heroin as their primary drug of choice. Indeed, the Majority of the women 83% (n=25) admitted continued use of heroin at some point during gestation. Thirty percent (n=9) used cocaine while 7 women (23%) continued using benzodiazepines within the same period. Quite a number of women 60% (n=18) used crack. Only one woman agreed to have used amphetamine and the same number agreed to have used cannabis.

3.2. Perinatal period

Two women delivered more than once within the period but only the last pregnancy was documented and followed up. There were 30 live births consisting of 18 males (60%)

and 12 females (40%). 60% of the women had spontaneous vaginal delivery while 30% had emergency caesarean section only one woman was delivered using ventouse method. Concerning those women who had vaginal delivery, 20% incurred some form of vaginal tear requiring perineal repair, of those 13% had second degree tear. Only 13% of the subjects needed perineal suturing.

The mean gestational age for the neonates was 38.7 weeks \pm 2.3 (range is 33 to 41 weeks). There were eight premature births. All cases of birth before 38 weeks were classified as premature in this study. All women with prematurity 100% (n=8) used heroin during their gestational period. Seven out of eight of those women with prematurity (87.5%) were prescribed methadone. There was evidence that methadone was not the only drug used by this group as 75% (n= 6) of the women with premature infants also used crack. There was significant difference between the length of gestation among those women on heroin and those on methadone alone (100% in Methadone group Vs 87.5% in the Heroin group $P < 0.05$).

The mean length of labour was 7.9 hours (range 42 minutes to 24 hours). There were 8 cases of precipitate labour; a situation where the whole process of labour lasted less than five hours. For 48% of the women (n=14), labour started spontaneously while there was induction of labour for 7 women (23%). The method of induction of labour was by artificial rupture of membrane (ARM) in 27% of cases. There was no case of delayed third stage of labour a situation that leads to excessive blood loss. The mean amount of blood loss in labour was 373.8mls (Range 50mls to 1600mls \pm 347 SD).

There was a statistical significant correlations between methadone prescription and blood loss $r_2 = .58$ and $r_2 = .037$, $p = 0.05$. An indication that those on methadone maintenance lost less blood thus had better outcome in labour. Other statistical significant correlations at $p = 0.05$ are as follows: -

1. Crack use and length of labour $r_2 = .57$ and $r_2 = .012$; this meant more cases of precipitate labour in crack users. Precipitate labour tends to cause cervical injury which means more trauma during child birth.
2. Cocaine use and type of delivery $r_2 = .515$ and $r_2 = .006$; this meant more interventions in delivery among cocaine users. Possibly due to delay in all the stages of labour thus requiring more interventions.
3. Birth weight and length of gestation $r_2 = .429$ and $r_2 = .041$; the longer the gestation the higher the birth weight.
4. Antenatal visit and apgar's score $r_2 = -.962$ and $r_2 = -.038$; the more the number of visits the higher the apgar's score at the birth.
5. Antenatal visits and length of gestation $r_2 = .504$ and $r_2 = .033$. The higher the number of antenatal visit the longer the period of gestation and thus the more major the infant is at birth.

3.3. Postnatal period

The 30 pregnancies resulted in 30 live deliveries. 18 infants (60%) were male and 12 (40%) were female. Mean birth weight was 2798.6gm (Range 1982.00gm - 4237.00gm \pm 519.3 SD).

The mean apgar score for the newborns were 570.4 (range 56 - 910 \pm 337.7 SD). 70% of the newborns were bottle fed. All the newborn spent time in special care baby unit. The mean time spent in the said unit is 16 hours (range 10 hours - 25 hours \pm 2.8 hours).

All the pregnant women (100%) who were on methadone maintenance therapy continued to use heroin either by intravenous injection or smoking as documented previously. However there were differences in fetal-maternal outcome measures when there is Comparison between the groups who are on methadone with those who used crack or heroin on top of methadone. Those who used crack cocaine on top tended to be single 57%; were unemployed and never have worked. The proportion of black British among them is higher than those using methadone and heroin only (10.5%). Their mean antenatal visit was 6.7 times. Their mean length of labour was 11.8 hours. Mean blood loss in labour was 381.8mls. Their mean gestational age was 38.5 weeks. Their mean birth weight was 2728.7gms. The mean length of stay of their newborn in special care baby unit was 16.9 days. The mean apgar's score for their babies were 5.7

One sample t- test was conducted to see whether the group of women prescribed methadone who continued to use heroin (M =1.167) has a higher apgar's score for their new born. The test found that this sample of women did have a significant higher apgar's score $t(29) = 16.85$, $p < 0.001$.

A one sample t-test was carried out to see if a sample of those prescribed methadone who continued to use crack (M = 1.433) had a higher birth weight for their babies. The test found that this sample of women have a higher birth weight $t(29) = 13.84$, $p < 0.001$.

4. Discussion

We set out to investigate by analysis and statistical test, the maternal and neonatal outcomes in a group of opioid dependent pregnant women on methadone maintenance therapy. We investigated the effect of use of illicit substance and other factors on outcomes.

Following other studies [10, 16], this study found that the rate of use of additional illicit substances mainly heroin (85%), crack (60%) and cocaine during pregnancy was quite high and questions the efficacy of methadone maintenance therapy in the control of illicit drug use in pregnancy.

There were statistic significant correlation between antenatal visits and outcome variable mainly apgar's score and length of gestation, thus methadone maintenance therapy by helping improve antenatal attendance could have helped

improve the length of gestation and the baby's wellness immediately after birth.

This study found significant difference in the rate of premature birth among those prescribed methadone compared to those who continued to use crack and heroin (100% for methadone group Vs 85.7% for heroin group. $p \leq 0.05$) and (100% for methadone group Vs 75% for the crack group $p \leq 0.05$). The implication of the test above is that using either heroin or crack results in higher incidence of prematurity.

Illicit drug use in pregnancy has a known association with prematurity [3]. However one wonders whether this prematurity could be attributed solely to poly substance use when there were high rates of unemployment among the pregnant women as 40% of them have never worked in their entire life while 30% have semi routine employment an indication of their social circumstance. About 60% of the same group of women were single while a high proportion of them were only cohabiting with partners who probably are users. Adverse socio economic conditions could be a contributor to the observed rate of premature infants.

The substance abuse literature is unanimous concerning the use of illicit drug and growth retardation [8]. This effect is worse in babies born to poly substance users. In this study the average birth weight was 2,798.6gms. This is much lower than the 2905gms reported in a study in New York [8] and the 2810gms reported in Ireland [4]. This finding supports the meta-analysis by Hulse et al in 1997[16]. In that analysis the authors concluded that illicit drug use reverses the benefit of methadone maintenance therapy.

The statistical significant association found in this study between antenatal attendance and length of gestation and between antenatal attendance and the newborn apgar's score is not altogether a new finding. It supports the well documented findings that retention in treatment is associated with improved outcomes in drug dependent individuals [13]. One interpretation of this finding is that more regular attendance at antenatal clinics can enhance much needed stability in the often chaotic lifestyle of the pregnant drug dependent individual, thus giving her the opportunity not only for substitute prescription of methadone but also helps her resolve housing, employment and other social issues. The contribution of these social factors could be best estimated by further studies or by interviewing the women in this cohort.

This study is limited by the fact of being a secondary retrospective analysis of a small sample size. There are difficulties in drawing conclusions but the noticeable lower mean blood loss for those on methadone and the significant correlation between methadone and low blood loss indicates a positive effect of methadone as against the use of either heroin or crack when pregnant. Other noticeable positive parameters like length of labour and the length of time spent in special baby care unit does not suggest a departure from current trend of having methadone maintenance therapy as the gold standard of treatment for pregnant women with

heroin dependency syndrome. We recognise the effect of excluding those women with HIV and those who are unable to understand the information sheet as a quite a few drug users might tend to fall in this category.

5. Conclusions

Methadone maintenance therapy improves birth weight, increases gestational age of the infant, reduces blood loss at delivery and improves attendance at antenatal visits. Children born to women on methadone maintenance therapy are more likely to have higher apgar score, but they are more likely to spend more time in new born neonatal units. However, safe but adequate methadone dosing for the pregnant opiate dependent woman does not appear to control additional illicit drug use. Those who used crack cocaine on top while pregnant are more likely to have precipitate labour while those who use cocaine are more likely to have more interventions during the delivery process. Thus methadone maintenance therapy should continue to be the gold standard treatment for the pregnant opioid dependent females.

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Contributors

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On opioid receptors

Andrea Vendramin¹ and Annella Sciacchitano²

¹ Drug Addicition Department, Padova, Italy, EU

² SerT Rovigo, ULSS 18, Italy, EU

Summary

The system of opioid receptors is characterized by a high level of complexity and has received much attention from scientists all over the world. The aim of this article is to describe the present, updated situation regarding scientific knowledge on the subject. Each opioid receptor is distributed in CNS in a distinctive way. Some regions (striate body and dorsal horns of spinal medulla) indicate the three receptor types, although not necessarily in the same neurons. Conversely, other regions, such as the thalamic nucleus for μ or the claustrum for κ , show various sites for a single type of receptor. Each receptor is involved in functions that are implemented along different paths and extensions. At present, it seems clear that the role of each receptor in mediating biological actions or physiological effects needs to be deepened using methodologies that differ from the classic ones. It can now be predicted that molecular cloning, re-combining DNA, antisense holigonucleotides, knockout and knockdown techniques will soon make it possible to understand many of the problems which make this system so 'complicated'.

Key Words: opioid receptors

1. Introduction

The effects of all the natural, half-synthetic or synthetic opioids depend on their interaction with the endogenous opioid system, which is currently considered to be involved in the modulation and the control of behaviours such as response to stress, motivation, thermoregulation or breathing, which are essential for the survival of the individual and the species. In other words, this system, which was first identified only in the 1970s, is composed of specific membrane receptors whose natural ligands are some very peculiar neuropeptides. Therefore, from a neurochemical point of view, the effects of opioids have to be related to the interaction of these receptors, whether the interaction is phasic, tonic, partial or total, agonistic, antagonistic or inversely agonistic.

1.1 Brief history of a discovery

In 1972, thanks to the method created by Cuatrecasas during his studies on receptors for insulin, Pert and Snyder identified ligand sites specific to opioids, distinguishing the "signal" through the "background noise" of non-specific interactions. In that same year the research group led by Terenius and Simon reported similar results.

These sites, which interact with their ligands in a stereoselective way, have been recognized as membrane proteins, located on cellular surfaces of cerebral neurons.

In 1975 Hughes and Kosterlitz isolated two pentapeptides (met-enkephalin and leu-enkephalin), gifted with some of the pharmacological properties of morphine and with a high affinity for specific ligand sites available to opioids. At present, the endogenous opioid peptides are divided into enkephalins, endorphins, dynorphins and endomorphins [28].

Endorphins, enkephalins and dynorphins derive from three different precursors called pro-opiomelanocortin (POMC), pro-enkephalin (proENK) and pro-dynorphin (proDYN). The gene which codifies for POMC maps on chromosome 2 includes two exons and one intron in its sequence; the gene which codifies for proENK is likewise composed of two exons and one intron, but it is on chromosome 8. On the other hand, the gene that codifies for proDYN contains four exons and three introns in its sequence and maps on chromosome 20. The endomorphines' precursor(s) are still unknown [8].

Opioid peptides, derived from POMC and found in the neurons of the nervous brain system, are represented by β -endorphin (fragment 235-265) and by its derivatives (β -endorphin 1-27, β -endorphin 1-26, β -endorphin 1-17 or γ -endorphin, β -endorphin 1-16 or α -endorphin). Pro-ENK contains six copies of met-enkephalin and one copy of leu-enkephalin, whereas proDYN creates dynorphin A 1-17, dynorphin A 1-8, dynorphin B 1-13 and a-b-neoendorphin through endo-proteolysis. Compared to other endogenous peptides, which are not very selective for opioid receptors, endomorphins show a very high affinity and selectivity for receptors μ [28].

In spite of the initial scepticism, it is certain now that endogenous codeine and morphine are present in brain neurons of a variety of animal species, including human species [2]. This discovery has generated interest on the distribution, the action sites and functional meaning of these alkaloids. At present it is believed that morphine, in the form of 3-sulfoconjugate, represents an important endogenous ligand of μ receptors.

2. Opioid receptors

It is possible to identify three different types of opioid receptors by using pharmacological methods. They are identified by using the letters of the Greek alphabet μ , κ and δ , or by adopting the abbreviations introduced by Receptor Nomenclature Committee (IUPHAR) in 1996: OP3 for μ , OP1 for δ and OP2 for κ [1]. It has been suggested that the name of this family of receptors remain OP (opioid peptide) preceded by the symbols μ , δ or κ or M, D or K. Based on these considerations, the abbreviation MOP corresponds to the receptor μ , DOP to the receptor δ and KOP to the receptor κ . Alternatively, it is possible to use the acronym OR (opioid receptor) preceded by the letters M, D or K respectively for the μ , κ and δ receptors [1].

Opioid receptors show a higher affinity to morphine stereoisomer (-) than to (+) and a relatively high affinity to naloxone. Receptors μ and κ have been identified by applying the chronic spinal dog model, based on the different actions of morphine and ketocyclazocine, respectively. After the discovery of enkephalin, receptor δ has been characterized by comparing the activity of endogenous peptides and opioid drugs in different systems. Going into greater detail,

the stereo-specific relationship to etorphin, a non-selective agonist, allows the generic identification of opioid binding to specific sites, whereas U50488H, DAMGO and DPDPE, which are able to compete with three different fractions, allow differentiation between three different types of opioid receptors, which are identified by using the symbols κ (ketocyclazocine), μ (morphine) and δ (DPDPE). Further to the use of opioid ligands, more and more selective, hypothetical subtypes of these three main types of opioid receptors have been proposed, and the list is probably going to get longer, along with the identification of new components. On the basis of in vivo and in vitro pharmacological inquiries, there are three μ subtypes ($\mu 1$, $\mu 2$ and $\mu 3$), two δ subtypes ($\delta 1$ and $\delta 2$) and three κ subtypes ($\kappa 1$, $\kappa 2$ and $\kappa 3$), although only three types of complementary DNA (cDNA) have been identified, corresponding to μ , κ and δ receptors [18].

Over the past few years, the existence of two other classes of opioid receptors, indicated by the Greek letters s and e, has been hypothesized. Receptors s represent a heterogeneous group of sites characterized by a high affinity for many components, by a low affinity for naloxone and by a preference for the stereoisomer (+) of ligand opioids. In the literature the ligand site s is often indicated as PCP/s receptor, since it is implicated in the action mechanism of phencyclidine (PCP) and other arylcyclohexamines. It is likely that PCP/s is closely related to the NMDA receptor complex for glutamate. However, the functional consequences of the occupation of receptors remain unclear, and the s1 site has recently been identified as a mammalian homologue of yeast sterol-isomerase, a protein that fails to show analogies with the receptors paired to G proteins (GPCR) [23]. Receptors e have been proposed further to the observation that morphine antagonizes the actions of μ -endorphin in rat deferent; it has relatively few μ receptors and the partly agonist nature of morphine could have determined the wrong identification of a ligand site characterized by an apparently new pharmacology. Although some studies using radio-ligands show the existence of a non- μ and non- δ ligand site for beta-endorphin, the uncertainty on the molecular nature of e receptors has still to be overcome.

3. Aspects of molecular biology

The molecular bases of the pharmacological classification of opioid receptors μ , δ and κ have been proposed by techniques of molecular clonation in various animal species. Up to now only one type of μ , δ and κ receptor has been cloned in those species, even if some functional variants of μ receptors in human beings and in rats have been identified. The gene codifying for μ receptors contains in its sequence four exons and three introns, a map on chromosome 6 and is indicated as MOR1 gene or OPRM1. The gene codifying for δ receptor consists of three exons and two introns, it is on chromosome 1 and is indicated as DOR1 gene or

OPRD1. Also the gene codifying for κ receptor contains in its sequence three exons and two introns. It is indicated by the abbreviations KOR1 or OPEK1 and a map on chromosome 8. Despite the efforts made to clone the different sub-types of opioid receptors, it has been impossible to identify any corresponding cDNA. The pharmacology of opioid receptor subtypes cannot be explained, therefore, on the basis of multiple genes that codify for the different varieties of μ , δ and κ receptors, although one cannot exclude that there are other genes that have not been cloned. The different sub-types that have been defined pharmacologically could represent variants, even if unidentified so far, of cloned genes for μ , δ and κ receptors, protein products of the same mRNA, which have undergone a different post-translational transcription, or identical receptor proteins associated with different G proteins in the cellular membrane. It is currently believed that they are the expression of the phenomenon of sequential re-arrangement (splicing) alternative to the gene primary transcription [9].

4. Structure of opioid receptors

The cloning of opioid receptors has shown that they belong to the GPCR super-family, which includes a group of proteins corresponding to about 1-3% of the genes in the human genome. Comparison between the ways the amino acid sequences of GPCR line up makes it possible to identify the structural characteristics of this super-family's members.

They comprise one amino acid chain, with seven hydrophobic transmembrane domains (TM), connected by relatively short intra-cellular and extra-cellular loops.

In relation to the plasma membrane, the amino-terminal part is on the extra-cellular side, whereas the carboxyl-terminal part is located within the cell.

Ligands interact with the receptors from the extra-cellular part, inducing the interaction with proteins G, which are on the intra-cellular side of the plasma membrane.

The amino acid sequence of opioid receptors compared with the sequence of other GPCR shows a homology no higher than 30%. On the other hand, comparison between μ , δ and κ shows a significant concordance in the trans-membrane sectors, in the intra-cellular loops and in a small intra-cellular portion close to the seventh trans-membrane region (TM7). The most divergent areas are the second and third extra-cellular loops and the extra- and intra-cellular tails, which terminate with the NH1 amin group and the carboxylic group COOH, respectively [18].

Receptors δ , μ and κ are membrane proteins of about 67 kDa comprising 398, 372 and 380 amino acids, respectively. By lining up the amino acid sequences one can observe identity of composition between δ and μ at a level of 62%; with δ and κ , and with μ and κ the levels of this parameter are 61% and 57%, respectively.

GPCRs have structural determinants which mediate their

properties, and a great number of structurally different ligands pair with them. They also pair with various G proteins, thus determining the specificity of every single interaction.

As far as opioid receptors are concerned, some ligands (bremazocin, ethorphin and diprenorphine) bind to μ , δ and κ receptors with similar degrees of affinity, whereas others (D-Ala, DAMGO, SB222941 and DPDPE) are selective by type.

The analysis of chimera receptors μ/κ and δ/κ has shown that the κ second extra-cellular loops are necessary for another affinity compared to dynorphine 1-17, dynorphine 1-13, a-neo-endorphine and dinorphine B.

The situation is different with the chimera receptors μ/δ ; in this case it has been possible to observe that the first extra-cellular loop of the μ receptor is essential for the DAMGO binding and that the Lys-108 residue is permits discrimination for the possible binding of DAMGO to δ instead of μ .

The residue glu-297 in the third extra-cellular loop of receptor κ has an influence on the interaction with the selective antagonist norbinaltorphimine, while its mutation does not influence the interaction with diprenorphine or naloxone.

By contrast, the binding of δ -selective peptides depends on the paired residues in the region from TM5 to TM7 of receptor δ and the mutation of the close couple of Arg- in the third extra-cellular loop is essential for the DSLET high binding affinity [3].

5. Receptor μ (MOP or MOR)

Receptor μ mediates the analgesic, sedative and toxicomanic properties which characterize the opioid agonists. In the knockout rat for the MOR1 gene, the lack of receptor μ implies the complete loss of the main biological actions of morphine, which indicates that both therapeutic properties and the adverse effects (including respiratory depression, constipation and immunosuppression) of this alkaloid depend on its interaction with a single gene product. As a result, analgesia and the adverse effects of morphine are maintained in knockout rats for KOR1 gene or for DOR1 gene [13].

Receptors μ preferably correlate with proteins Go1, Go2, Gi2, Gi3 and Gz. The interaction with Gi1 is proved, but its functional meaning is uncertain [6].

The subdivision of receptor μ in subtypes derives from the peculiarities of some highly selective antagonists.

It is known that the morphine effects are antagonized by β -funaltrexamine, which is used to define an effect as mediated by receptor μ .

Unlike β -funaltrexamine, naloxazone and naloxonazine antagonize only some of the effects of morphin. Due to this peculiarity they are selective antagonists of subtype m1 of receptor μ . The insensitivity to naloxonazine includes respiratory depression and inhibition of gastro-intestinal transit, suggesting that the possible m1-selective agonists could lack two of the main collateral effects of morphine. The sub-type $\mu 1$, only supraspinal, is located in the grey periaqueductal

substantia, in the medial hypothalamus and in the raphe magnus nucleus. It mediates analgesia, psychomotor arrest and prolactin hyper secretion. Sub-type $\mu 2$ is located in the same site as $\mu 1$, but it is also present at spinal level. By integrating with $\mu 1$, it mediates the analgesic effects and is responsible for respiratory depression and constipation, as well as the contraction of the urinary bladder and of the sphincter of Oddi.

The complexity of the receptor μ system is amplified by recognition of the properties of morphine-6--glucuronide (M6G), an active metabolite of morphine [17]. M6G binds to μ receptors selectively and with high affinity. Its pharmacological profile is similar to that of morphine, and its analgesic effects are antagonized by naloxonazine. However, antagonist 3-O-methylnaltrexone (3-methoxynaltrexone), in doses ineffective for morphine, selectively blocks analgesia induced by M6G, whose analgesic properties also appear in CXBK rats, which are normally insensitive to morphine [4]. These data would suggest that, together with $\mu 1$, $\mu 2$ and $\mu 3$ subtypes (all of which appear to mediate the physiological effects of downregulation through the release of nitroxide), there is also another variant specific for M6G analgesia and similar phenomena, which are characterized by substitution in position 6, like heroin and 6-acetylmorphine [19].

Anti-sense sondes for exon 1 of the MOR1 gene block the supraspinal effects of morphine but not analgesia induced by M6G, while with exons 2 and 3 the opposite effect is achieved [22]. Anti-sense sondes for exon 4 block the effects of morphine at the spinal level, too. This difference is in accordance with the results obtained with naloxonazine, on the basis of which spinal analgesia from morphine implies receptor targets that are different from those implicated in the supraspinal type. Knockout rats for exon 1, insensitive to morphine, respond to the analgesic effects of both heroin and M6G, and analgesia from M6G is pharmacologically indistinguishable from that observed in wild-type rats. A possible explanation for this complexity is the existence of the so-called splicing variants of the same gene [15]. Initially two variants were described which differ from each other due to the presence or absence of 8 amino acids in the intra-cellular carboxyl-terminal part of the receptor. The gene for the first variant lacks exon 4, which takes the place of exon 5 in the second variant. Since that finding, many variants have been described, in which exon 4 is replaced by combinations of supplementary exons. All variants whose brain distribution is inhomogeneous have a high affinity for ligands of receptor μ , even if there are some functional differences [16].

6. Receptor δ (DOP or DOR)

Further to what has been observed in knockout rats for MOR1 gene, the specific functions of receptor δ are difficult to define [20]. The abolition of spinal analgesia induced by the selective agonist δ DPDE characterizes the knockout rat

for the DOR-1 gene [29]. It is common opinion that, to be able to show their effects, δ receptors need the cooperation of other opioid receptors, particularly μ receptors .

Receptors δ preferably correlate with proteins Go1, Go2, Gi1 e Gi2. The interactions with Gi3, Gz e G16 are proven, but their functional meaning has only been preliminarily defined [6].

The sub-types of receptor δ can be distinguished by adopting one of two different classifications (δ_1 e δ_2 o δ_{cx} e δ_{ncx}), though these may reveal a basic form of overlapping. Through in vivo studies with selective molecules δ_1 and δ_2 have been identified. In rodents the antinociceptive supraspinal activity of DPDPE is mediated by the δ_1 sub-type and is selectively antagonized by 7-benzylidenaltrexone (BNTX) or by DALCE. Instead, the analgesic effects of deltorphine II and DSLET are mediated by δ_2 and are antagonized by naltriben and by nantrindole 5-isotiocinato (5-NTII). Moreover, tolerance to the effects of repeated injections of DPDPE does not seem to be crossed compared to deltorphine II. In vivo, receptors δ_1 and δ_2 induce analgesia which can, however, be antagonized through the blocking of different types of K⁺ channels. In vitro, the best experimental proof supporting the subdivision into subtypes of receptors δ receptors comes from adenylyl cyclase (AC) inhibition in membranes of the rat brain and from the increase in intracellular Ca²⁺ in the line ND8-47. In these two models, the effects of DPDPE and deltorphine II are selectively antagonized by BNTX and naltriben, respectively.

The subdivision of receptors δ in δ_{cx} and δ_{ncx} is based on the hypothesis that the subtype δ_{cx} , unlike δ_{ncx} , is able to form heterodimers with receptors μ and maybe also with κ receptors. It is common opinion that δ_{ncx} corresponds to receptor δ_1 , while δ_{cx} corresponds to δ_2 [27].

7. Receptor κ (KOP or KOR)

As previously mentioned, the first characterizations of ligand sites of type κ derive from the use of ketocyclazocine and its radioligand trizium derivative [18]. Pharmacological findings on subtypes κ have come almost entirely from studies of binding with radioligands [9].

The use of marked ethylketocyclazine (³HEKC) has, in the spinal cord medulla of guinea pigs, revealed the existence of an inhomogeneous population of ligand sites with high affinity, and has lead to the first identification of sites κ_1 e κ_2 , which are marked out by their sensitivity to DADLE. Another study conducted by using ³H-EKC and ³H-etorfine has identified two other sites in surrenal gland bovine medulla, one with high affinity for met-enkephalin-Arg-Gly-Leu and similar to κ_2 , the other indicated by κ_3 , and characterized by a high affinity for [Met⁵]enkephalin-Arg-Phe-.

The terminology κ_1 , κ_2 , κ_3 has been applied to other putative subtypes, too; they have been defined in various models, but it is unclear whether the common nomenclature reflects

similar pharmacological properties.

Receptors κ preferably correlate with proteins Go1, Gi2 e Gi3. The interaction with Gz has been proved, but its functional meaning is unclear [6].

Despite the fact that the results of the analgesia tests often show differences, κ -agonists are traditionally classified among analgesic drugs of limited power. At present, receptors κ , located in the CNS, in hypothalamic nuclei, in the ventral tegmental area, in the mienteric plexus, in the placenta and in the miocardium are often described as showing certain effects that contrast with those that characterize receptors μ . In particular, κ -agonists seem to be able to antagonize analgesia, reward, tolerance and memory processes mediated by μ receptors. Moreover, the in knockout rat for gene KOR1, selective κ -agonist U50488H does not show spinal or supraspinal analgesic effects, and it is much less effective, compared to what is observed in wild-type rats, in determining hypolocomotion and dysphoria.

8. Receptor NOP (ORL1, OP4 or LC132)

Soon after the cloning of receptors μ , δ and κ , a ligand site was identified which, as it has an amino-acid sequence homologous with that of opioid receptors (approximately 60%), is characterized by a very low affinity for most opioid ligands, including naloxone [10].

Cells with the human homologues of this protein, classified as “opioid receptor like”, indicated by the acronym ORL1 or currently as NOP, have been used, by a process of reverse pharmacology, to facilitate the isolation of a possible endogenous agonist for the receptor identified as a peptide called nociceptine or orphanine (FQ). Orphanin FQ/nociceptin (OFQ/N) is a 17-amino-acid peptide that shows structural similarities to the traditional endogenous opioid peptides, and to dynorphin A (1-17) in particular.

OFQ/N correlates to dinorphine, through structural rather than functional analogies. Unlike the other opioid peptides, it does not have tyrosine in N-terminal position, and NOP, its ligand to receptors, is currently classified by IUPHAR as a non-opioid member of the opioid receptor family. It is located mostly in central neurons of superficial layers of spinal dorsal horns, in the sensory complex of the trigeminus, in grey periaqueductal substantia and in the raphe nucleus. OFQ/N precursors contain another bioactive heptadecapeptide indicated as nocistatine, which is able to diminish various types of pain sensations (for example, those evocated by prostaglandin E2 and by OFQ/N itself), although it does not interact either with opioid receptors or with NOP. The NOP is coupled with the same effector systems. Thus, activation of the NOP leads to inhibition of the enzyme “adenyl” cyclase and calcium channel conductance. Furthermore, the activation of inwardly rectifying potassium channels is associated with the stimulation of NOP. The net effect of these cellular actions is to reduce neuronal excit-

ability and neurotransmitter release. Indeed, a wide range of neurotransmitter systems are modulated by N/OFQ and these include glutamate, catecholamines and tachykinins. NOP activation also modulates mitogen-activated protein (MAP) kinase, extracellular signal-regulated kinase (ERK) and JUN activity. NOP may also be involved in phospholipase C (PLC)-mediated phosphatidylinositol bisphosphate hydrolysis. The peptide N/OFQ is involved in a wide range of physiological responses, with effects noted in the nervous system (central and peripheral), the cardiovascular system, the airways, the gastrointestinal tract, the urogenital tract and the immune system. Its effects on the nervous system are complex: when given spinally, N/OFQ is antinociceptive, with many features that are common to the classical opioids, but when given supraspinally, N/OFQ reverses the effects of opioids (anti-opioid action) with a whole-animal response that manifests as hyperalgesia. In the brain, this peptide is also hyperphagic and affects responses to stress, anxiety and locomotion. In the cardiovascular system N/OFQ produces bradycardia and hypotension; this response is similar to that produced by classical opioids, especially to morphine as used in the clinic.

9. Double state receptor model

Nowadays one plausible view is that opioid receptors are in two different functional states, one inactive but activatable and another constitutionally activated in a way that is independent of the agonist ligand. The latter is phosphorylated and interacts with effectors through a specific G protein. The functional balance is maintained by the relationship between phosphorylated receptors (activated) and non-phosphorylated (inactive). Agonists have high selective affinity for the activated affinity form, and by binding to it, they keep it active; they withdraw it from the basic pool and shift the ratio activated/disactivated molecules in favour of the latter. In order to quickly reach an equilibrium in the residual pool, it is necessary to increase the number of phosphorylated receptors. Partial agonists show affinity for the activated selective form of intermediate degree, which allows a change in the balance between the phosphorylated and non-phosphorylated forms, in a less radical way compared to agonists. Antagonists, by binding without selective affinity with one of the two functional forms of receptors, do not alter the basic balance, but they can prevent or wrong-foot the agonists' ligand. Some substances bind selectively with the inactive receptor, keep it unchanged and move the ratio between the remaining receptors in favour of those that are constitutionally activated, and whose number decreases to re-establish the balance. Consequently, one observes an increase in the number of inactive receptors and a functional result opposite to that for the agonists. These active principles are inverse agonists, and their effects, similar to those of agonists, are blocked by antagonists. Inverse partial agonists are characterized by their

affinity for the inactive and selective forms, although to an intermediate degree. The double state receptor model has a significant relevance from a clinical perspective, and has a useful role in offering an explanation for some phenomena whose pathophysiology had been hard to understand.

10. Signal transduction

10.1 The role of G proteins

As previously stated, cloning has confirmed the biochemical evidence that opioid receptors are part of the GPCR superfamily. GPCRs are the signal transduction means for many small transmitters and molecular peptide modulators through their interaction with G proteins, a term which is the abbreviation of guanosin-triphosphate protein (GTP). G proteins are heterotrimers which bind and hydrolyse GTP by transferring the amplified signal from receptors to effectors. Each protein G has three subunits, called α , β e γ ; at present we only know the α , β and γ subtypes. At rest, a guanosine-triphosphate molecule (GTP) is bound to a subunit, and the whole protein complex is close to the internal surface of the cell membrane. The carboxy-terminal end of an α subunit interacts with the receptor, allowing recognition between itself and the G proteins, which have at least 20 variants, thanks to the various possible α , β and combinations. Different receptors correspond to different G proteins, although some types of G proteins can be activated by many receptors, as there are more transmitters than proteins. Opioid receptors bind preferably, though not exclusively, with G proteins that are sensitive to the pertussis toxin (PTX) of G_i and G_o families [6]. Both α , β and sub-units of G proteins interact with cellular effectors, but there are doubts about the implications of the different combinations of β and γ sub-units for the receptor/effector coupling. β and γ sub-units are always strongly associated, so they are indicated as a β/γ functional complex.

The cloning of μ , δ and κ opioid receptors, as well as of many G proteins, has made it possible to combine receptors and G proteins in quite well defined systems. These researches have confirmed that opioid receptors couple with G_{i1-3} and G_{o1-2} proteins, sensitive to PTX, which share the capacity to inhibit AC. In particular, it is believed that in these systems a sub-unit reduces adenylcyclase activity, and that β/γ complex activates ion channels for K^+ , inhibiting other, voltage-dependent channels that are specific to Ca^{2+} .

Opioid receptors can couple to G proteins, too, whose functional role is less defined [6]. The interactions that are best characterized are those with G_z e G_{16} proteins.

G_z protein, which is strongly correlated with G_o , can inhibit AC, but lacks the cysteine residue necessary for ADP ribosilation and PTX inactivation. When embryonal cells of human kidney HEK 293 are transfected with μ , δ , κ receptors or ORL1, the activation of these receptors inhibits the endogenous AC in a PTX-sensitive way. When G_z is co-

transfected with any of the opioid receptors, AC inhibition becomes only partly PTX-sensitive; this implies a functional interaction between receptors and G_z .

G_{16} , which is strongly correlated with G_q , belongs to a family of G proteins which also includes G_{11} , G_{14} e G_{15} ; these activate phospholipase C (PLC) [25]. When G_{16} is co-transfected in ovary cells of the Chinese hamster (CHO) with any of the opioid receptors, the subsequent receptor activation stimulates PLC. μ opioid receptors couple with G_{15} , too, but not with G_{11} and G_{14} . δ receptors and ORL1 seem to couple more efficiently with G_{16} compared to μ o κ receptors. Coupling with G_{16} has shown significant differences in the opioid receptors' capacity to activate various G proteins in well-defined systems.

HEK 293 cells transfected with opioid receptors and with type-II AC have been used to determine which a sub-units of protein G do not couple with opioid receptors. Type-II AC is a form of enzyme that can be activated by Gs; it can be further stimulated by a variety of β/γ complexes of G proteins. When HEK 293 cells are co-transfected with a constitutionally active Gs sub-unit and type-II AC, the activation of any heterotrimer of G protein in the cell determines an increase in AMPc levels through the release of β/γ complexes. Co-transfection of the above components with G_z determines an increase in AMPc stimulated by opioid receptors that persist during treatment with PTX, confirming that μ and δ can couple with G_z . When a μ receptor is co-transfected with G_q , G_{12} or G_{13} , no increase in the AMPc levels further to treatment with PTX is observed, thus indicating that μ receptors are unable to couple with a sub-units of these types of G proteins. By omitting constitutionally active Gs, neither μ nor δ receptors activate type-II AC, indicating with strong evidence that these receptors do not couple with the endogenous GS of HEK 293 cells [6].

Most research conducted in animal models has led to conclusions similar to those obtained through neuron cell lines and cloned receptors. When opioid receptors from the rat cellular membrane have been purified, it has been observed that it is also possible to purify G_i and G_o proteins. Moreover, it has been demonstrated that the coupling of μ receptors with AC inhibition in rat cellular membrane is sensitive to antibodies directed against G_o and G_{i3} . Studies conducted on membranes prepared by rat periaqueductal grey substance show that GTPase activity stimulated by μ receptors is diminished by antibodies directed against G_{i2} or G_z , whereas the activity stimulated by δ receptors is diminished by antibodies against G_{i2} , thus suggesting a differential coupling of μ and δ receptors, at least under these experimental conditions.

Opioid receptors raise K^+ conductance and inhibit Ca^{2+} flux in many isolated neurons. In any case, these effects are mediated by G proteins, sensitive to PTX, probably through β/γ complexes. The G proteins involved have been studied in greater depth in neurons of the dorsal roots of rat ganglia,

where it has been demonstrated that antibodies against Go represent a strong obstacle to any inhibiting modulation of a Ca^{2+} ionic current due to the activation of μ or κ receptors, whereas those against Gi do not show significant effects. In guinea-pig sub-mucosa neurons, PTX eliminates the coupling of δ receptors both with K^+ currents and Ca^{2+} . The latter coupling is re-established by including Gi/Go-purified proteins in the recording pipe. Direct antibodies against various G proteins have been used to define the coupling of μ , δ and κ receptors in isolated circular muscle of the guinea-pig intestine. Activation of all opioid receptors promotes binding with GTP γ S, a non-hydrosoluble GTP analogous, with Gi2 and Go, but not with Gi1, Gi3, Gs or Gq. The functional consequences of the activation of opioid receptors in this tissue include PLC-b stimulation and AC inhibition, which are both blocked by PTX: The inhibition of adenylyclastic activity by part of the three opioid receptors is diminished by over 80% when antibodies are co-applied against Gi2 and Go. Conversely, PLC-b3 stimulation is significantly influenced only by antibodies against the b/g complex of G proteins, in line with the idea that the b and g sub-units of G proteins, which are sensitive to PTX, stimulate this PLC isoform [6].

As to the Go gene in knockout rats, the activation of μ receptors still inhibits Ca^{2+} flux in the gangli cells of dorsal roots, but the types of G proteins responsible for the inhibition of Ca^{2+} flux in wild-type and in knockout rats for Go have not yet been determined. It is feasible that the coupling of non-Go proteins with Ca^{2+} currents in Go-negative rats represents a compensatory mechanism in mutant animals, which does not reflect animal coupling in the natural state.

The attempts to delineate the opioid/G protein coupling through the *in vivo* injection of antibodies or anti-sense oligonucleotides for different sub-units of G proteins (knock-down *in vivo*) must be interpreted with great caution; it is impossible to establish whether these agents interrupt the interactions of opioid receptors with respective G proteins or whether they influence neuron activity in regions treated with anti-sense, so altering the coupling with G proteins of other receptors. This problem is exemplified by many studies, where Gas or Gaq knockdown *in vivo* has selectively influenced the response to a type of opioid receptor, even if no interactions with these a sub-units through the use of better defined methodologies have been observed.

10.2 Effects independent of G proteins

The importance of heterotrimeric G proteins in the responses mediated by opioid receptors is well established. However, G protein activation may not be the foundation for all the effects obtained by the stimulation of opioid receptors [6].

In cultures of bovine surrenal medullary chromaffin cells, the activation of μ and D2 dopamine opioid receptors increases the activity of the K^+ channel (BK) activated by Ca^{2+} [26].

The modulation of BK channel activity by μ agonists is not blocked by treatment with PTX, nor is it influenced by the inclusion of nucleotide inhibitors or heterotrimeric G protein activators in the recording electrode. On the other hand, the effect of D2 receptor activation on the BK channel is blocked both by treatment with PTX and by analogous guanine nucleotides. A similar observation has been reported with rat sensorial neurons, where nociceptine inhibits both Ca^{2+} high voltage-dependent flux (HVA) and T-type low-voltage dependent flux. The inhibition of Ca^{2+} HVA flux mediated by nociceptine shows sensitivity to guanine nucleotides, a finding to be expected from a process mediated by G proteins; the inhibition of Ca^{2+} type-T flux fails to show any sensitivity to G protein inhibitors or activators. In the same cells where ORL1 receptor activation inhibits both Ca^{2+} HVA and T-type flux, μ receptor activation only modulates HVA currents. One might argue that, similarly to b_2 -adrenoceptors, some opioid receptors could interact directly with ionic channels or with other effectors different from G proteins, but there is no evidence to support this line of argument.

Generally, the consequences of any opioid receptor activation depend on the profile and stoichiometry of G proteins and of the effectors expressed by cells, rather than on the kind of receptor involved. One should avoid the statement that different types of opioid receptors couple preferably with one particular type of effector. Coupling of all types of opioid receptors with the main cell effectors has been demonstrated in a variety of tissues. Although this principle has still not been confirmed for some less well-known effector mechanisms mediated by G proteins activation, there is no reason to believe that they differ from the main ones. This would be prove to be false for interactions independent of G proteins, if the finding that some types of opioid receptors interact specifically with other signal proteins should be confirmed.

Although each opioid receptor can activate a specific range of G proteins, differential activation as a necessary feature of conditions where different agonists act on one type of receptor still needs to be studied extensively. There is emerging evidence that the profile for the effectiveness of μ opioid agonists (as well as agonists for other GPCR types) is distinguished by its capacity to signal events like receptor phosphorylation and internalization, presumably establishing specific receptor configuration. It is now reasonable to expect the development of agonists acting on a single type of receptor and preferably stimulating specific G proteins expressed in some neurons sensitive to opioids, even if not in all of them.

11. Opioid receptor dimerization

The seeming interaction with various ligand sites of selective components for a particular type of receptor, found in pharmacological and functional tests, has led to the hypothesis of the existence of μ/δ e δ/κ "receptor complexes", recently

indicated as “heterodimer receptors” [14]. It is impossible to exclude that the μ/δ heterodimer corresponds to one of the δ subtypes and that the δ/κ heterodimer is one of the κ subtypes [12].

A previously observed, morphine analgesia is mainly mediated by μ , but this effect disappears in knockout rats for this kind of receptor. However, agonists selective for δ receptors do modulate morphine analgesia.

Leu-enkephaline, an agonist mildly selective for δ receptors, when supplied in doses insufficient to determine temporary analgesia, can cause a move towards the left of the morphine dose-response curve. Similarly, the provision of δ -selective ligands in non-analgesic doses increases morphine analgesia. When using components selective for μ receptor in the same way, that same phenomenon does not happen. The functional interaction between μ and δ receptors has been observed too in other experimental conditions, like the turn of endotoxic shock induced by opioids.

The powerful analgesia, the rise in increase of the pain threshold and the decline in possible tolerance that happens during pregnancy are mediated by δ and κ spinal receptors; they can also be blocked by the provision of suboptimal doses of δ or κ selective antagonists, which shows synergy between these elements.

This mechanism could prove to be important in minimizing the risk of possible pharmacological tolerance and dependence during pregnancy [7].

In rat deferent and in guinea-pig ileum, morphine and enkephalin in dimeric form seem to be significantly more similar to opioid receptors than to corresponding monomers. The increased power suggests that receptors, too, can take the form of dimers. Consistent evidence exists on other GPCR forms of dimerization, whereas there are only a few studies showing the existence of oligomers of opioid receptors. The first proof of a potential opioid receptor oligomerization comes from a number of studies on neuroblastoma cells, in which δ receptors, properly marked with rhodamine and enkephalin analogues, seem to be placed on the cell surface in non-uniform clusters, kept together by disulphide ligands.

Another proof is that the β -endorphin cross-linking in rat striatal membrane. β -endorphin ligand to the band of about 80 Kda can be inhibited both by both μ selective DAMGO compost and δ selective DSTBULET. This observation suggests that β -endorphin creates a cross-linking with a δ/μ complex, although it is unclear whether the 80 Kda band represents a δ/μ receptorial complex related to β -endorphin or, more simply, a peptide separately related to μ receptors and δ receptors [21].

The first direct evidence of dimerization has been found further to the cloning of cDNA opioid receptors, which has allowed its heterogeneous expression in a variety of cellular lines. By using cross-linking agents it is possible to observe that δ receptors exist as dimers when expressed in heterologous cells. In polyacrylamide gel the band molecular

weight is about twice that expected for δ receptors. By using a MYC epitope, this band is confirmed as the dimer species of a δ receptor.

κ receptors, too, exist as dimers. A significant difference between the two types of dimers has to do with their SDS stability: δ dimers are unstable and require a cross-linking agent, whereas κ dimers are stable. δ dimer monomerization is observed when δ -selective agonists are present, providing a possible functional correlation between dimers, monomers and occupied receptors.

Regarding κ dimers, the selective ligands are unable to modulate the number of dimers, which depends on the level of receptor cellular expression. The stability of κ dimers suggests that covalent ligands could mediate this interaction. However, they are sensitive to reducing agents and one could imagine they are of disulphide type.

Having established that δ and κ receptors can form homodimers, it is necessary to evaluate the possibility of their forming heterodimers. κ receptors can heterodimerize with δ receptors, but not with μ receptors and the biochemical nature of this interaction is similar to κ homodimers, since κ/δ heterodimers are stable to SDS but sensitive to reducing agents [11]. Moreover, these heterodimers are stable in a variety of detergents and are not modified in conditions of solubilization or extraction. Ligands binding to cellular membranes characterized by κ/δ complexes shows receptor sites for opioids distinguished from the other κ and δ receptors. These sites can be identified by using lower concentrations of a non-selective antagonist of opioids diprenorphine, appropriately radio-marked.

κ/δ heterodimers are insensitive to and δ selective agonists, but sensitive to non-selective ligands like bremazocin, ethylketocyclazocine e dynorphin.

Furthermore, sensitivity to selective ligands reappears when κ -selective and δ -selective are used simultaneously, thus suggesting that there may be cooperation in their respective binding.

These results could explain the functional synergy observed in vivo among selective ligands for different types of opioid receptors. δ receptors, but not κ receptors, are known to be able to internalize quickly in response to non-selective agonists like etorphan. In the cells that express κ/δ heterodimers, δ receptors are unable to internalize in response to endorphins, suggesting that heterodimerization has an influence on the movement of these receptors. Moreover, in cells expressing both κ and δ receptors, cell stimulation with selective agonists for both receptors determines a dose-dependent inhibition of major AC compared to the inhibition caused by a single ligand. A similar function increase has been observed when comparing the ability of a single agonist on protein-kinase phosphorylation with the combination of various agonists. The cooperative and synergic effect observed in pharmacological and functional experiments regarding the phenomenon of heterodimer receptors indicates that a significant number of

δ receptors interact with a very high number of μ receptors. This has happened both in vivo and in vitro.

The demonstration of co-localization of two different receptors on the same cell, as well as their ultra-structural position, is very interesting. μ and δ receptors can be co-localized in the same cells, as demonstrated in studies on the binding of the two receptors' ganglia of dorsal roots and on measuring the frequency of the single neuron's discharge potential.

The ultra-structural data are insufficient; it has only been demonstrated that δ receptors are localized in the core of big dense vesicles. This information is certainly not in contrast with the fact that they can also exist as homodimers or heterodimers [5].

The fact that κ receptors can heterodimerize with δ receptors suggests the need to compare these complexes with the respective receptor subtypes.

Complexes of δ/κ receptors couple with high affinity to benzomorphans like bremazocina, but they are unable to bind U69593, a highly selective antagonist of κ_1 subtype.

From a pharmacological point of view these characteristics make them similar to the κ_2 subtype of κ receptor [30]. Similarly, δ/μ receptor complexes correspond to δ_2 subtype of δ receptor from a functional and pharmacological point of view [27].

The phenomenon of homo-hetero dimerization strongly implements the concept of opioid receptors' 'complexity' [3]. One could speculate that some of the opioid receptor subtypes actually correspond to heterodimer receptors, thus providing a nice justification for the lack of any identification of respective cDNAs.

12. Conclusions

Each opioid receptor is distributed in CNS in a distinctive way. Some regions (striate body and dorsal horns of spinal medulla) indicate the three receptor types, although not necessarily in the same neurons. Conversely, other regions, such as the thalamic nucleus for μ or the claustrum for κ , show various sites for a single type of receptor.

Each receptor is involved in functions that are implemented along different paths and extensions. At present, it seems clear that the role of each receptor in mediating biological actions or physiological effects needs to be deepened using methodologies that differ from the classic ones [24]. It can now be predicted that molecular cloning, re-combining DNA, antisense oligonucleotides, knockout and knockdown techniques will soon make it possible to understand many of the problems which make this system so 'complicated'.

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Psychotherapeutic management of heroin-addicted patients. Psychopathological, relational and organizing aspects

Emanuele Bignamini

Addiction Department, Turin, Italy, UK

Summary

Addiction is a pathological condition which is still only partly understood. The complexity of reality exceeds our capacity to elaborate and synthesize the information that is currently available, so compelling us to operations of simplification, in order to become operative. In this exposition I will discuss how, starting from a view of addiction as a pathology of relationships, and from a pragmatic vision of the available therapeutic techniques as tools of intervention rather than interpretive theories of reality, it is possible and necessary to evaluate the psychotherapeutic approach.

Key Words: Psychotherapeutic management; Heroin dependence

Addiction is a pathological condition which is still only partly understood.

Many data continue to be accumulated all the time, and important steps have been taken that cover the whole field of the neurosciences, but it is still difficult to put together an overall picture. Clearly, the question is not strictly limited to addiction, but ramifies out to include the mind-brain problem in general.

The way in which we interpret an unknown object cannot be isolated from the prejudices that form part of our cognitive and emotional systems of reference.

We welcome and appreciate the earliest indications of the unknown object by relying on data that already occupy a place within our system of knowledge. In this sense, one might say that the diagnostic system is incapable of describing the pathology, but still stands as our only access to its comprehension.

Furthermore, the complexity of reality exceeds our capacity to elaborate and synthesize the information that is currently available, so compelling us to operations of simplification, in order to become operative.

Obviously, if one forgets that simplification is a cultural operation rather than being a form of magic thanks to which reality suddenly becomes simpler, one makes a false move from a research hypothesis to an ideological position.

This preamble is an appropriate precaution, given the incredible growth which the neurobiological paradigm in the sphere of addiction has undergone in these last few years and the cultural primacy it has assumed. In this scenario, it seems that psychotherapy has become increasingly restricted to being treated as if it were an 'Indian reserve'. At best, behavioural techniques which do not trespass on to the dark, slippery terrain of the intrapsychic are tolerated.

In this exposition I will discuss how, starting from a

view of addiction as a pathology of relationships, and from a pragmatic vision of the available therapeutic techniques as tools of intervention rather than interpretive theories of reality, is it possible and necessary to evaluate the psychotherapeutic approach.

1 Concept of addiction

Addiction is the result of an interaction between subject and substance which comes about in a certain environment (Figure 1). This particular condition permits, modulates and directs the effects of the substance in relation to the patient's own biological reactivity, affective and emotional order and culture. The substance modifies the functioning and the structure of the subject. The environment may favour or complicate interaction, besides conditioning timing and modalities. From this interaction, and from the subject-object relationship which develops in certain environmental conditions, different types of linkage originate.

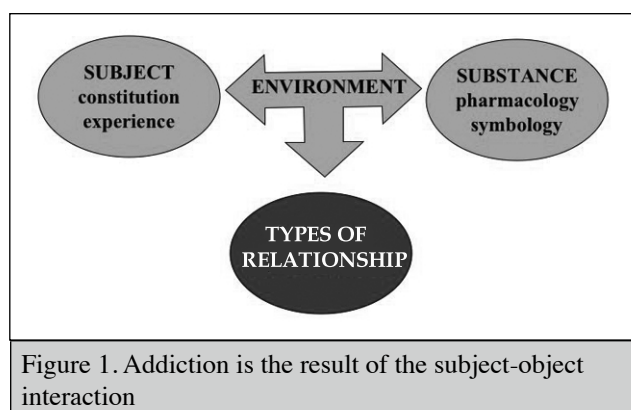


Figure 1. Addiction is the result of the subject-object interaction

We may briefly describe these as:

Use: a relationship of normal drug use, without any pathological consequences, is certainly possible; in this connection one need only think of the relationship with alcohol in cultures where it is legal.

Abuse: this occurs where the use of the substance comes about through the violation of norms and regulations without reference to specific alterations of the biopsychological balance of the subject.

Dependence: this is the outcome whenever the substance becomes indispensable to the biopsychological balance of the subject.

Mania: we refer to mania when the use of the substance determines an imbalance in the subject, who tends to increase the frequency, dose and duration of his/her consumption until exhaustion supervenes.

These possibilities provide patterns of the different possibilities resulting from the characteristics of the subject and the drug as they interact.

The mechanisms that are set in motion by the process due to which addiction is structured may be summarized as follows:

- Induction of positive sensations or relief from negative ones, whether physical or psychological.
- Fixation of the experience in the memory as the key experience for forming an assessment of every other gratification.
- Modification of the normal biological, cognitive and emotional reward processes.
- Modification of the processes of desire and development of craving.
- Alteration of the affective order (mood, ambivalence).
- Alteration of responses to stress.
- Cognitive impairment.

All these mechanisms, whose biological correlations have been studied a great deal, implicate a radical change in the subject, and in his/her biological, cognitive, emotive and value systems, behavioural strategies and life aims.

2. Addictive personality

Naturally enough, the change induced by drugs leads to different results in different people. For a long time, research has been conducted on the personalities of addicts so as to verify if there is a personality profile that predisposes towards specific or frequent addiction. A lot of interesting data on vulnerability have been gathered by following different paths (from genetic profiles, to psychic traumas, to problems of parental care, and on to the development of object relationships), but the essence is that no recognition of a prepathogenic personality for addiction has been attainable. For example, Bergeret [1] recognizes addicts with a neurotic personality structure, others with a psychotic structure, and others with a depressive structure. Other authors describe addicts with previous pathological personalities of different types, but they admit that it is possible to structure an addiction even from a normal personality [9].

At this point it can be observed that the transformative process which drugs determine in different subjects tends to produce a likeness in the characteristics and functioning of very different personalities. Thanks to the capacity of drugs to modify the subject who takes them, they seem to have the power to mould the personality of the individual; the end-result is that all addicts seem to show similarities.

The high frequency with which diagnoses are made among addicts of Borderline Personality Disorder and of Antisocial Personality Disorder could be the consequence of dependence, not a condition preceding its development. The transformative effect of the substance on the subject makes him/her function as if possessing a pathological personality organization (belonging to cluster B), without this necessarily being part of any previous functional mode.

We might say that, if a real prepathogenic personality does not exist, we can at least delineate the common characteristics of a postpathogenic personality:

Coercion of desire (corresponding to the neurofunctional

and neurostructural modifications that occur): the subject limits his/her desire to drugs alone, and displays no real interest in anything else. More precisely, the affective drive of desire is exclusively oriented towards drugs, while other things can only be desired through processes of reasoning and cognitive effort.

Giving up and/or mourning over the loss experienced (corresponding to the idealized affective state and to the chance to recall it through memory): the drug becomes an object which structures the identity and the existence of the subject, as occurs for a significant affective relationship. Giving up the drug corresponds to a feeling of grief which the patient feels for the loss of a loved one. The possibility of easily recalling the presence of the loved object sets up a continuous affective but also cognitive oscillation and ambivalence of willpower.

Regret for the tragic-heroic dimension (correlated with allostatic regulation). The life of the addict is made up of emotions and intense and deep experiences. The loss of the capacity to feel such enthralling emotions or sustain and reproduce a lifestyle of this kind leads to the onset of nostalgia and amplifies the emotive and cognitive oscillations. Obviously, the emotive states activated by drugs may be positive or negative; the desired drug not only induces pleasure, but suffering, too. Thus a strong ambivalence develops and the drug is both loved and hated; intense passion is a constant feature.

Discontinuity of the Self (in the sense of one's personal history: the addict seems to live different lives – those experienced before, during and after drug use) and in the Self (that is, the the patient's sense of identity, with feelings which cover the whole range between the ideal state of the Ego to feelings of self-contempt).

To these basic characteristics, some modalities of the typical functioning of the addict can be added:

Impulsivity/compulsion. After the first 'honeymoon' phase with the drug, dominated by impulsivity and corresponding to the highest grade of cognitive impairment, a partial recovery of the functioning of the prefrontal cortex and a downregulation of the reward-response relationship determine the appearance of a compulsive type of dynamics.

Designified relationships: interpersonal relationships are emptied of the significance which these had had in the subject's life. The affectivity and cognitive processes are completely absorbed by the relationship with the drug, which is viewed as if personified, while other people are reduced to inanimate things, or are viewed as obstacles or means related to the cultivation of the only important relationship.

Transformation of the emotions into somatic sensations and secondary alexithymia. Emotions are perceived as physical states, so that the body becomes the main means through which the addict communicates. Any mood is transformed into a somatic sensation which is confused with the abstinence syndrome and treated as if part of the experience of

drug-taking. By consequence, the addict loses any real sense of the words that are used to express feelings, so becoming an 'illiterate' on the affective plane.

Dementialization and acting out. The representation of one's own mental processes and those of others are reduced to elementary dynamics, in general of the paranoid and 'arch reflex' type. Together with the previous characteristics, this amplifies the tendency to action and to motory discharge without reflection.

3. Pathogeneses and shades of addiction

We have seen that it is possible to become an addict starting from a range of different personalities. We should also consider different pathogeneses.

Classically [11, 12, 14], it has been argued that addiction is secondary to a psychic pathology for which the subject searches for self-therapy. This theory is also very widespread among professional people and indeed seems very plausible, even though [13] it has no solid evidence to support it.

Other authors [16, 17] state that the push towards self-therapy is not only determined by serious psychic uneasiness, but may alternatively be due simply to a desire to be better than one is, to give a better performance, to be more powerful. In speaking of addiction, it is also considered a secondary condition.

However this may be, addiction may be considered primary [2-6] when the experimentation with drugs which then leads to addiction in the context of the subject's readiness to gratify him- or herself. In this case, the subject is healthy and satisfied, and it is in this positive state, in a favourable environment, that he/she decides to try the drug while perceiving this as another opportunity to attain gratification. The experience of drugs, which in a reactive subject is particularly intense, then becomes a pleasurable experience of comparison, which reveals that a previous state of well-being was not gratifying after all. The drug reveals that, in reality, until that moment, the subject had never really experienced true enjoyment

Similarly, it can be considered that the transformative effects brought about by drugs and the successive allostatic repercussions determine a completely new and unknown state of suffering to the subject. The condition of suffering which maintains toxicomaniac behaviour has to be considered primary and must not be confused with a pre-existing malaise as in the first two conditions.

In relation to different pathogeneses, we can therefore differentiate between different conditions of addiction (Figure 2):

If we connect different pathogeneses up with the different types of pathological relationships that are possible, and the results of the encounter of the drug with a variably vulnerable subject, the outcome is a multiplicity of different shades of pathological dependence (Figure 3).

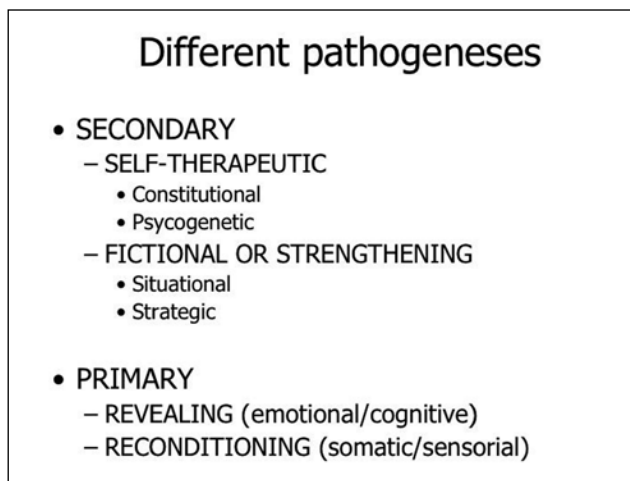


Figure 2. Pathogeneses of Addiction

PATHOGENESES \ RELATION	Secondary self-therapeutic	Secondary fictional	Primary emotional-cognitive	Primary somatic-sensorial
ABUSE				
DEPENDENCE				
MANIA				

Figure 3. Multiplicity of different shades of pathological dependence

4. Limits and breadth of psychotherapy

After clarifying how addiction is to be interpreted and dwelling on the psychopathological aspects to be treated in this way, we still need to formulate a few considerations on psychotherapy and its scope.

Whatever is intended by ‘psychotherapy’ and whatever theory or technique is considered, we will do well to declare where the limits lie.

The limits must be understood as boundaries which mark a move towards other disciplines and other ways to read keys to reality.

In synthesis, we may say that the most important limits are those provided by the boundaries with the neurosciences, the organizational dimension, the individuality of the therapist, the end of life and the end of individual lives. An in-depth discussion would require ample space; here I can only recall the essential points.

The limits of the neurosciences have led to the production

of an enormous mass of research and theories: these comprise neopositivism and neomaterialism, then functionalism and neuroanalysis, and also the discussion on whether there is continuity between nature and culture (that is, between the transmission and expression of genetic properties and environmental learning and personal history), right up to the most recent studies which propose new connections between affective states, cognitive processes and neurobiological modifications. This makes boundary between psychotherapy and neurosciences seem more and more permeable and confused.

The boundary with the organizational aspects regards the definition of the outcomes of therapy, the social aims for which it is done and the management of the interpersonal relationship between therapist and patient in a context which also takes account of other variables. In summary, the therapy does not produce health, but prompts changes in how the patient understands his/her problems. It is thanks to these changes (cognitive, emotive, motivational), that patients collaborate with a therapy and consent to it, including its pharmacological aspects, to allow positive effects on health to develop.

The limit imposed by the individuality of the therapist refers to the interpretation he/she gives of therapeutic techniques. Therapy and psychotherapy, in particular, are strongly dependent on the personality of the therapist [15]. In cases of addiction, which are characterized by a pathology of the relationship between subject and object, the therapist personally manipulates objects which are loaded with symbolic significance and the relational present, which is evocative of past experiences and of desire and fear. These objects are perceived as “environmental-somatic transformers” [7].

The search for a transformative object becomes a constant in some phases of life. Preverbal memories are repeatedly put into action; the emotional aspects which they drag with them offer a chance to form a deep subjective relationship with the object: an upsetting fusion with the object, evoking psychosomatic fusion.

The search for a transformative object assumes characteristics that are necessarily modulated by personality and pathology; in toxiphilia: a need for maternal care, distortion of the transitional phenomena, with inhibition of the development of one’s own psychic capacities and a continuing search for an external solution; in addiction: drugs, alcohol and medicines substitute the transitional objects which once freed the child from total dependence on its mother and become fetish objects to be sought after because external to the self and destroyed by incorporation.

The project of care itself comprises a hope of finding a transformative object. A therapist (or even a non-psychotherapist) is always a transferral figure [10]. The transference is established on traces of the memory of the relationship with the first transformative object, in the face of which the therapist may experience contrasting feelings: agitation and perplexity over regression and omnipotent expectation; ele-

ments of hope and evolutionary movement that are rooted in the question.

The (therapeutic) object proposed by the therapist is loaded with significance deriving from the affective investment of the patient (food, gifts, intrusions, controls, threats).

Moreover, if the therapist has not resolved for him- or herself the mind/body dualism, he/she will tend to transfer any 'non-solutions' into the therapy itself (addiction: illness of biological origin; or else: useless pharmacological therapy?).

Lastly, psychotherapy has to frame a reply to the question 'why be treated, if any subject is bound to die eventually?'. This is the limit of psychotherapy, which inevitably tends to represent the end of life and, tightly interlaced with that, the end of individual lives. The life project of every individual appears, under Nature's glance, to be radically senseless: memory is a constant reminder to man (in Greek mythology, animals can live happily because, unlike man, they have no memory). At the same time, addiction offers an escape and a separation from memory, which nurtures the tragedy of living. The search for life's meaning and happiness is mistaken by the addict (where the mistake may take the form of being ambiguous or a trade-off or a choice in favour of deviation) for pleasure (or relief from pain), which is tied to the moment, not to the project.

In addiction, the memory is modified, both on the neurobiological and psychological planes, and the reference points for significance change. One passes from the sense to the sensorial, from the verbal to the non-verbal, from action to acting out and from the psychic to the somatic plane. Or, speaking more precisely, they become confused.

As defined by the elements we have recalled above, psychotherapy occupies a space whose breadth is variable: it may be extended or reduced in relation to several factors (Figure 4).

The extent of the search: the integration of the psychological perspective with others (whether these are social, philosophical, neurobiological or organizational) in relation

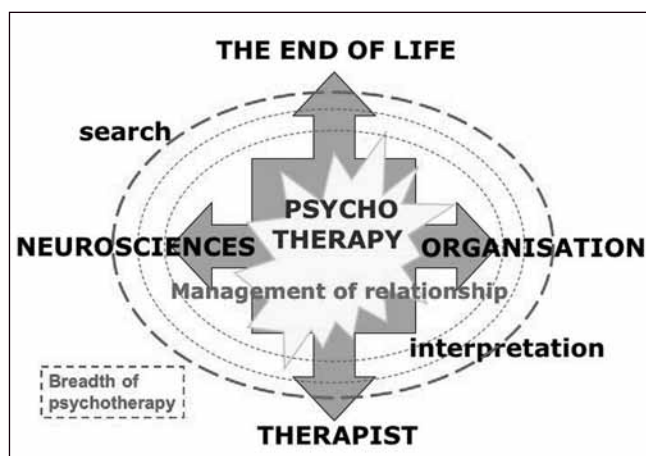


Figure 4. Space occupied by psychotherapy

to cultural development and the prevalent point of view at a given historical moment.

The strength of clinical thought: management of the therapist-patient relationship may be considered more or less important with respect to other objectives.

The interpretive dimension (with reference to the planes of thought and action): between psychopathology and specific techniques there may be remoteness and diversity tied to the fact that one is not always able to treat on the practical plane what one understands on the phenomenological plane.

5 Psychotherapeutic approach

Having shared the preamble, we may now consider the elements which a psychotherapeutic approach suggests in relating to the addict.

- 1 - Firstly, the patient's body is recognized and treated as the place where mental contents are expressed too. The therapist must be able to stand firm in this confusion, distinguishing between the planes, but accepting that the patient will be unable to do so. Patients very often speak about their physical problems to the psychologist and about their psychic discomfort to the doctor.
- 2 - It follows from this that verbal language becomes evocative and ambiguous: when discussing his/her physical problems with the patient (ranging from phlebitis to hepatitis), this is bound to bring back a whole variety of and psychological questions, just as it also involves the relationship with the therapist and his/her project for further care.
- 3 - The therapist has to take in hand and manage the patient's needs, taking care not to fragment them, but keep them together by representing the patient as a coherent unit. The capacity to carry out this role, concretely represented by multidisciplinary collective work and avoiding specialistic fragmentation, itself constitutes a fundamental therapeutic function.
- 4 - The relationship with such fragile subjects, who have an absolute need for help, but are strongly diffident and manipulating, calls for a capacity to manage objects that mediate the relationship, deviate attention and tension, transfer significances and values which, in their concreteness, reduce persecutory anxiety. Medicines themselves should be considered a partial object bearing intrinsic peculiarities of ambivalence (pharmakon in Greek means both 'medication' and 'poison'): it may become superinvested with value and identifiable as the central object of the relationship for which the exchanges come about only through medicine. Or it may be a vehicle-mediator, that is, an object that permits access to other objects (mental ones in this case) and which may be integrated by words. (This is also true, incidentally, of the tools used in reducing damage, like syringes or condoms).
- 5 - Furthermore, given the alexithymia and the inadequacies

of mentalization, what one wants to transmit to patients should be communicated through action, not exclusively through words: mime, gestuality, timing, attitude, context and setting should be accurately thought out and used, as they are the most effective vehicles of communication attainable through discourse.

6 - The therapeutic agent is the 'care group', which is stable, continuous and persistent. The context of care becomes like a figure of maternal attachment to whom one turns when one is "afraid, tired, ill" [8]. To be 'there', waiting, allows one to 'recognize oneself in the other', presupposing a subject who has never had access to stable, receptive attachment figures and lives an 'unpredictable' life

These modalities of managing a relationship are certainly specific to a psychotherapeutic intervention; despite this, they are inevitably present in every therapeutic relationship with an addict. By concentrating on pharmacological therapy, many doctors assume that these aspects can be overlooked; in reality, they give an unconscious solution to these problems. In the same way, the design of clinical services for addicts cannot be reduced to purely formal aspects, but should utilize this knowledge to organize services that already have therapeutic value built into their architecture.

6 Integrating techniques and organizing treatment

An attitude open to knowledge and experimentation, pragmatic without being ideological, allows the use of various specialistic techniques in an integrated way.

Firstly, an addict usually presents problems and needs of a physical type, which are expressed as the threat of a crisis of abstinence and a psychophysical imbalance induced by using opiates of short duration; in this case, the use of agonistic medicines constitutes the primary intervention.

Subsequently, the aim of suspending the use of illegal substances to stabilize the patient, thanks to the use of pharmacological therapy, should be maintained through a the definition of rules of behaviour that include exercising control. These are associated with cognitive-behavioural and motivational techniques that help the patient to recover consciousness of his/her pathological patterns and mobilize his/her resources towards making the change.

At a still later stage, it will be necessary to sustain and encourage the patient to maintain the plan with constancy while developing hisher life project further. At this point, it will become indispensable to help the patient adopt a new lifestyle free of drugs, characterized by by a series of renunciations, but also by the identification of new possibilities.

This is a theoretical path, described in a linear way, which aims to illustrate how a pragmatic approach, as long as it is integrated with new techniques, is necessary.

The Service should be structured as a relational network whose nodes constitute places, timing and modalities of diversified relationships (Figure 5).

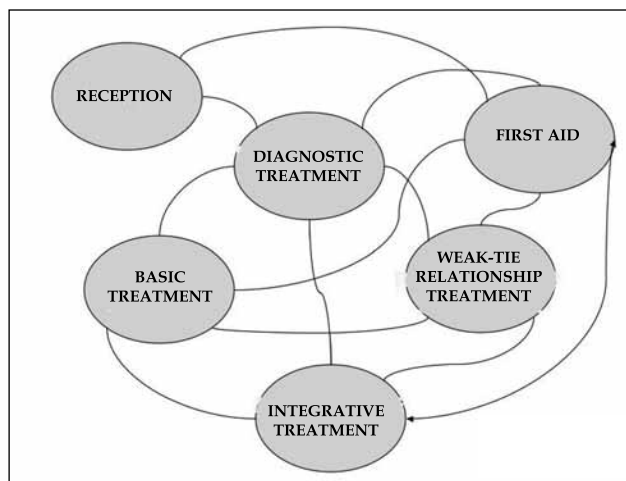


Figure 5. The relational network

These nodes point to relationships that may be strongly or weak correlated with those of maternal care, intervention in crises, dialectal project comparison (and others might be added).

The tensions which the addict has to go through are numerous and each may may comprise a set of different problems and undergo different evolutions (Figure 6). Dependence on external control, with the push towards conformism and the development of a false Self, a strong affective and physical tie with the drug, the conditions it sets and a negative social environment (both on an economic and a cultural plane) and the presence of associated psychic disorders represent risks and problems which need to be correlated with their possible positive evolutions.

Management of the complex challenge set by how addicts should be treated calls for a judicious selection within the range of available means.

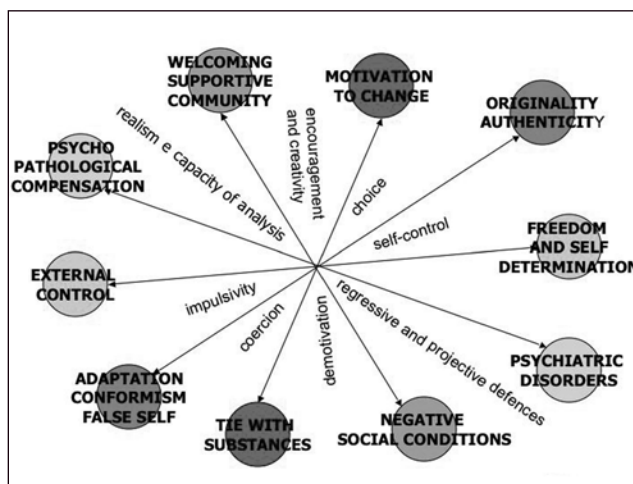


Figure 6. Tensions, problems and evolutions

7. Conclusions

The therapeutic function is tightly linked with the capacity for organizing thought (with reference to itself, to work objectives, to action scenarios and to the relationships between parts).

Psychotherapeutic thought, in preference even to psychotherapeutic techniques, must be assigned an indispensable role in the clinical management of patients.

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Treating heroin addicts. Blocking dosages and stimulation-stabilization of opioidergic system

Matteo Pacini³, Angelo Giovanni Icro Maremmani^{1,2}, Luca Rovai¹, Fabio Rugani¹, and Icro Maremmani^{1,2,3}

¹ "Vincent P. Dole" Dual Diagnosis Unit, Santa Chiara University Hospital, Department of Psychiatry, NPB, University of Pisa, Italy

² Association for the Application of Neuroscientific Knowledge to Social Aims (AU-CNS), Pietrasanta, Lucca, Italy, EU

³ "G. De Lisio", Institute of Behavioral Sciences Pisa, Italy, EU

Summary

The paper that follows is an attempt to conceptualize a clinically based classification of treatments for heroin addiction. In fact, a distinction is drawn in classifying treatments between those that are antagonists and those that are agonists; the latter can be further subdivided into full and partial. On this view, the effectiveness of full agonists cannot be displayed as dependent on a key antagonist action, originally described as an 'opioid blockade' and regarded as the main therapeutic mechanism available against addiction. On the other hand, the differences in levels of effectiveness between antagonists and full agonists cannot be understood either in terms of the presence of absence of antagonism, or as opposing two radically different mechanisms of action (it remains true that they both produce an opioid blockade). In proceeding further, the authors propose the concept of optimal antagonism, which is centred around the original 'opioid blockade' mechanism and also accounts for agonist potency providing a direct anticraving effect and aversive effects. Also, acquired tolerance to opiates does function as a drawback deriving from abrupt treatment termination or steep reduction, so as to favour stability of the anticraving coverage. In practice, optimal antagonism is a concept that helps to define the gold standard of retention, clinical response and rehabilitative potential. Naltrexone only provides patients with antagonism, 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 eventually explains why complete blockade brings poorer results in the absence of other anticraving actions. Methadone and buprenorphine appear to provide optimal antagonism; in other words, they offer patients opioid blockade combined with tolerance to euphoria and direct anticraving action.

Key Words: Dependence, Addiction, Substance Use Disorder, Normalization, Craving, Treatment Duration

1. From normality to normalization

Addiction is a behavioural disease centred upon the inability to take control of one's drive to consume certain substances, and stably interrupt one's drug-using habit according to one's own plans [9]. The disease model is rooted in a neurofunctional system usually bridging the positive memory linked to a substance with a behavioural drive towards its

future consumption (positive reinforcement). Nevertheless, addiction comes as a distortion of this physiological function, in a hypertrophic and steadfast way [21]. The abnormality of addiction with respect to its physiological correlates (habit and vice) is expressed as an acquired inability to get one's drive to repeat a pleasure-seeking behaviour (at one stage activated throughout the mesolimbic system and across the nucleus accumbens), possibly modulated and neutralized

by other variables deriving from elaborated cortical signals, and corresponding to a complex experience [1, 2, 6, 12, 22]. Such inhibitory signals may correspond to the lack of recent reward, experienced risk or damage associated with drug-seeking or drug use, the weakening of self-effectiveness and general well-being, and the loss of other major or preferable sources of reward. As this abnormality determines the pathophysiological model, normalization is the therapeutic objective – an objective which amounts to the restoration of the correspondence between pleasure-seeking instincts and one's pleasure-related plans, and to reattaching automatic cravings to weaker drives that can be influenced by stable cognitive constructs (i.e. intentions that modulate rather than merely witness unwanted instinctual drives) [3, 20].

The development of addiction seems to require some sort of critical mass or level of exposure to a necessary and sufficient factor, which is a substance possessing a behavioural-reinforcing intrinsic property. This looms like a learning process, even if it is directed towards a dysfunctional result, of a plastic neuronal network which is capable of self-maintaining its acquired state in the long term. As a result, whatever therapeutic process we may engage in order to reverse this learned dysfunction, it will presumably require quite a long time to sort out its results. Expressed differently, the uncoupling between instinct and intentions is likely to require that a long-term artificial readjustment be neutralized, which in very severe cases corresponds to a permanent chemical prosthesis, providing the patient with an opportunity to recover a normal functioning of his/her pleasure-seeking brain circuitry [3, 17]. In other cases too, even assuming that the damage may actually be reversed and reset to a state of complete healing, treatment duration will presumably remain a long-term question.

On psychopathological grounds, a normalized subject is someone who is enabled to stop drug-seeking, as long as he/she plans to act in that way, and rehabilitate according to individual inclinations and potential. By contrast, an addicted subject is willing to do so, but cannot help craving for the opposite outcome. The achievement of normalization does not mean the disappearance of any pleasant memory of the substance, or a failure to dream of the possibility of controlled use. In fact, normalized behaviour will not be affected by persistent physiological desires for the substance, so that the patients will put up with being abstinent according to their own plans, despite residual desires and positive memories of substance-induced highs. In patients who have actually become disgusted with the substance and with a drug-related lifestyle, normalization tends to coincide with an unregretful, stable and complete abstinence.

2. Therapies against addiction: antagonism, anti-craving action, aversive action.

The current classifications of therapies for addictions re-

veal at least two flaws. The first is the employment of generic terms which fail to clearly specify the addictive dynamics or therapeutic properties. For instance, the classification adopted by the Italian Ministry of Health accounts for three categories, namely: “pharmacological”, “non-pharmacological” and “pharmacologically integrated”. Therapies employing non-exclusively pharmacological means are also referred to as “psychosocial” or “rehabilitation-oriented” [16]. Such labels do not account for the simple fact that pharmacological treatments, whether alone or integrated with psychosocial interventions, are those which provide patients with the best rehabilitative potential of treatments in a way that can be scientifically planned and developed. The parameters used to define and plan effective methadone treatment, for example, were originally related to rehabilitative purposes, beyond symptomatic resolution. On the other hand, the concept of integration is centred on psychosocial interventions which may be integrated by pharmacological treatment, but not vice versa, as it should be (pharmacological treatment possibly integrated by psychosocial interventions). The second flaw concerns the conceptualization of treatment dynamics: pharmacological treatments for addiction are rated as “substitution” or “other solutions”, the latter amounting to only a tiny percentage. The distinction based on a time criterion (short/medium/long-term) is itself meaningless on clinical grounds, since all known effective treatments against the relapsing course of addictive drug use can be interpreted as a long-term regimen based on a maintenance phase. Any other definition of effectiveness so far expressed cannot be understood in terms of relapse prevention, or must otherwise refer to clinical pictures of substance abuse in the absence of a diagnosis of drug addiction. We propose an alternative classification, in an attempt to account for the different therapeutic mechanisms proposed to counteract the dynamics of drug addiction:

- Antagonist drugs, which prevent the substance from producing its sequential effects. Antagonism may be exerted by a receptorial blockade or pre-receptorial substance inactivation.
- Anti-craving device or drug that is effective against drug-seeking behaviour. These drugs mimic the presence of an overload of the abused substance without actually overstimulating its receptorial system due to a sharply different kinetic profile. Drug-seeking is held in check as a consequence. Agonist drugs are usually direct receptor agonists, so that they can also be used against withdrawal syndromes. Due to this closeness to the abused drug's functional targets, some agonist drugs may be faulty and reveal a certain level of abuse liability.
- Aversive drugs. Such drugs induce negative reinforcement, a behavioural barrier between substance use and consequent effects due to a toxic syndrome elicited by substance use. This relationship may either take the form of a toxic effect overlapping with substance-related pleasant

effects (e.g. disulfiram and alcohol), or an unfavourable modulation of substance-induced effects (e.g. disulfiram and cocaine).

The basic pharmacological properties listed above may be combined with one another. In some cases a unique drug possesses more than one basic property, so that its action can count on two distinct mechanisms, possibly with different latency of action and relevance according to the specific stage of the illness. Methadone maintenance treatment, the most effective form of intervention against opiate addiction, is based on methadone's properties, which comprise an anticraving action (produced through the agonism of the opioidergic system) but also determines an opioid blockade (antagonism to heroin). On the whole, methadone-mediated opioid blockade is radically different from that obtained by naltrexone, since it induces a state of tolerance to opiates and is coupled with a direct anticraving action.

3. Methadone as optimal antagonist (blocking dosages and stimulation/stabilization of opioidergic system).

The blockade of substance-elicited effects is crucial to the achievement of behavioural normalization in addictive diseases. To achieve this, the blockade should be a persistent state that is not rapidly or easily reversible. The blockade should not be liable to disactivation during a time interval of as little as 24 hours, so that skipping one dose will not be enough to restore full sensitivity to opiates. It is also important that the possible reversal of opiates is rather uncomfortable if it is not achieved gradually, so that those who aim to get rid of a blockade in order to respond to drugs of abuse are held back by expected symptoms of discomfort [4].

In order to achieve a response to an agonist treatment, patients must be induced to accept blocking dosages, though cautiously and in a controlled manner (at least 80-120 mg/die 8-24 of buprenorphine). On the other hand, some patients stop craving for drugs at lower dosages [10]: in other words, some patients stop using drugs despite the absence of any opioid blockade. This latter property (direct anticraving effect) characterizes all agonist drugs, whereas antagonism may be activated by full agonists (methadone), partial agonists (buprenorphine) or antagonists (naltrexone). It should be added that the therapeutic response differs quite sharply whenever a direct anticraving property is present. A direct anticraving effect, independently of the level of acquired tolerance to opiates, does contribute to the therapeutic response, together with the blockade effect. Agonist drugs, in fact, counteract addiction by two mechanisms, the first direct (reduction of craving) and the second indirect (reduction of craving after the experience of blockade, bringing interference with short-term reward). These combined effects also mean that, as long as the system is deprived of the exogenous action of abused drugs, the endogenous function is supported in a stable way, or replaced if damaged. The agonist action usually implies

the maintenance of a certain level of tolerance (so-called 'somatic dependence'), but susceptibility to withdrawal is a crucial condition. Patients are somehow induced to take their medication again, as long as no heroin dose would be enough to buffer withdrawal or exceed a level of tolerance capable of producing a high. Despite residual cravings, patients will find it preferable to take their medication rather than drop out of treatment in order to become sensitive to their abused drug again. Treatments which have no power to tie patients to medication-taking are less effective in retaining patients in treatment, which is typical of addictive diseases, due to their lack of insight and the relapsing drive towards drug-seeking [14].

So, while the patient is being treated with adequate dosages which correspond to a state of opioid blockade, before any actual relapse has happened, retention in treatment due to somatic dependence does favour the eventual outcome of long-term treatment, by preventing short-term treatment termination and favouring the patient-doctor interaction. Being susceptible to abrupt methadone discontinuation, far from being a limitation on this treatment option, is a favourable feature, both on clinical grounds and on ethical ones, as long as it increases the achievement of eventual therapeutic results and rehabilitation in the long term.

4. To what extent is treatment duration relevant to the rehabilitative outcome ?

Normalization is the target, but expected treatment duration depends on the spontaneous disposition of the damage incurred to heal in the absence of recurrent renewal. The time-span in question may be virtually lifelong, but it may be hypothesized that effective treatment is able to shorten it and this makes it realistic that patients treated in the earliest phase of their disease can achieve full recovery on biological grounds, or at least display a very low susceptibility to relapse in standard environments after they have completed long-term treatment programmes.

To date, however, judgements on concerns over the effectiveness of treatment, including the urgent need to prevent relapses, can only be formulated during the maintenance phase of long-term treatment programmes, and they have to face the problem of the likelihood of relapse while on treatment. Otherwise, a decision to assess an intervention as successful simply on the basis of the accomplishment of a treatment schedule is meaningless if there is no long-term follow-up of treatment completers. In this sense, detoxification interventions have proved to be feasible for most addicts, but have no relevant impact on the course of the disease. Consequently, any programme that has a predetermined duration term is unreliable, since it is likely to have been conceived on the basis of the intrinsic needs of some kinds of interventions (i.e. what an intervention requires to be performed), rather than on the features of the disorder. Short-term treatments tend

to involve simple mistakes on the topic of which function or functions need normalization, and about the collateral role of acquired tolerance and withdrawal in the self-maintaining dynamics of drug addiction. In terms of time perspective, detoxification is often lived or practised as a way that speeds up the process, whereas maintenance is viewed as a way to slow down and take time. The underlying idea that tolerance reversal will turn the clock back on the biology of the disease is itself a great misconception. So-called 'detox' procedures, no matter how rapid, last a certain time for those who practise them, but have longer-term time implications, since relapsing addicts will not apply for another intervention, of whatever type, as long as they are engaged in another cycle of addictive drug use. It could be said that a short-lasting detox intervention overlooks the question of preventing a longer-lasting relapse.

Referring patients to programmes with a predetermined duration appears to be a form of malpractice, since it corresponds to the omission of effective long-term regimens and induces the enhancement of relapse-related risks after a programme has been completed in a state of non-tolerance to opioids [19]. Generally speaking, any prefixed term functions as a time-limit to the maintenance of possibly acquired therapeutic results. Correctly managed maintenance treatment programmes also have an end-phase characterized by slow dose reduction, but that procedure is not decided a priori or by any pre-fixed time term.

In ongoing agonist treatment programmes, another mistake is that of applying an uncoupled treatment duration to early or medium-term objectives, without adjusting treatment parameters according to the therapeutic response: patients often find themselves obliged to continue ineffective treatment for a long time, in the meaningless expectation that time itself will draw patients towards rehabilitation, even if they are still active drug users and do not show even minor progress [11, 13]. This is the case of low-threshold methadone programmes which do not even aim to achieve a later leap to higher threshold programmes (blocking dosages and stimulation/stabilization of the opioid system) [8]. Schifano and coll. [18] report and comment on some common elements of malpractice by which methadone dosages do not show an increasing trend according to the patient's toxicological status, with average dosages falling below 60 mg/day regardless of treatment duration in as many as 8 heroin addicts out of 10. This kind of case, which is probably registered as being based on a long-term treatment programme lasting over 6 months does not correspond to the basic standard, let alone the gold standard, of methadone maintenance: in fact, a case of this kind only appears to maintain inadequate dosages, while the maintenance of rehabilitative results is itself impossible if they are not first pursued in a scientific way.

On the whole, the interest in duration is not centered upon the state of remission, but on the endurance of abstinence, which means adopting a perspective rather than a retrospective

view. Patients are enrolled in relapse-prevention programmes after detoxification, as if detoxification could be considered the first necessary step to recovery and as if it could provide the first relevant strand of immunity against relapse proneness. In any case, in line with the nature of addictive disorders, relapse proneness is a certainty in the long-term if no treatment is resorted to, and detoxification is neither necessary, nor propedeutical to the actual treatment of addiction. Obviously, the view presented here clarifies the fact that treatment does not aim to encourage abstinence, but to prevent relapse, while relapsing patients are not those who were encouraged but failed to take advantage of their opportunity, but are just genuine sufferers from drug addiction. The achievements of detoxification may be useful sometimes, or respond to urgent needs, but they never represent a change of route in the natural course of the disorder. We might say that detoxification may actually serve as an excuse to get patients with poor insight (as addicts are, on average) involved in a treatment context which will refer them to the correct programme. This happens in the case of opiate agonists, which are often initially employed against withdrawal but are then used to increase dosages in order to extinguish craving.

5. Agonism, antagonism and treatment duration

Agonist treatment programmes (methadone, buprenorphine) are often regarded as being at risk of becoming one long-term therapeutic engagement, despite the patient's initial intention, in opposition to antagonist treatment (naltrexone), which can last as little as one may decide. As a consequence, some patients and doctors tend to avoid agonist treatment or regard it as an extreme measure. This trend can in no way be justified on clinical grounds. Naltrexone treatment is meaningless unless it is applied in the long term, since a state of opiate blockade works through the patient's relapsing into use, not in the absence of it. Patients abstaining from their very first day of naltrexone treatment are unassessable in terms of treatment response; in particular, their ongoing treatment is not assessable in terms of relapse prevention. Otherwise, a course beginning with relapses of some importance followed by a progressive extinction of relapsing behaviour could be assessed as favourable. Practically speaking, a two-month naltrexone treatment without episodes of heroin consumption cannot be evaluated as successful, since no sign of remission is measurable in terms of dwindling engagement in drug use, and the temporary absence of drug use is no different from what addiction itself displays along its natural course. Moreover, if a short-term duration of antagonist treatment is no more than the result of a premature treatment termination of a drop-out, that outcome is equivalent to an ongoing or expected relapse, so that it could in no way be considered an achieved short-term cycle of addiction treatment with a positive outcome. The long-term perspective, the need to observe the change in the course of

symptoms, and the need to carry out a comparison with the pretherapeutic situation are usually lost when the doctor's and the patient's interest are focused on the long term. On technical grounds, the mechanism of antagonist drug action against reinforcement may be completely misunderstood, so that patients come to believe they are not drinking because of their latest naltrexone dose. In reality, it has been proved that patients may also use the drug for relapse prevention after long-term stabilization, deciding to take it only on presumed drinking days, without actually creating a major interference with immediate alcohol-induced effects, but preventing the rewarding and reinforcing phenomena during the following days (in other words, keeping a slip a slip, so avoiding any real relapse) [5]. This strategy is unlikely to be feasible in heroin addiction, since the effects of heroin would be blocked, and craving would not allow the patient to voluntarily produce a preventive blockade.

The duration of treatment before any assessment of treatment effectiveness can vary according to the patient's abstinence history. On general grounds, the assumption that the longer the period of abstinence, the lower the likelihood of relapse cannot be relied upon, regardless of the time span. During the first year after detoxification, patients diagnosed as addicted will relapse, so that the cumulative rate of relapse will rise progressively, usually reaching a short-term peak and then other later peaks. The likelihood that one patient who has not relapsed yet will do so in the future does not vanish after other peers have relapsed, but actually increases: in other words, given that they all share the same diagnosis and a risk disposition to relapse, the ones who are 'left standing' after others have relapsed are those who are at equal risk, but over a longer term. Short-term and longer-term relapsing patients may be distinguished in this way, but longer-term abstinence should not be misinterpreted as a non-relapsing disposition. One possible method for estimating the effectiveness of treatment in the medium-term is to compare the abstinence endurance of patients who are still on treatment with that displayed during the last one or two years of illness in a treatment-free condition. This kind of evaluation is also useful prior to treatment planning, in order to spin out any judgement on treatment effectiveness beyond the endurance of pre-treatment spontaneous abstinence. In other words, it would be meaningless to rate a patient as a responder to treatment after three months of abstinence if that same patient had been able to stop for a maximum of four months during the year previous to treatment enrolment [15]. Clinical monitoring, along with treatment, should proceed with no premature downranking of relapse risk. In some cases, treatments are extended, apparently in an expectation that extinction will become complete, but are terminated soon after a period of negative urinalysis, so that the achievement of stability is mistaken for healing. It should always be kept in mind that the improvement of symptoms, no matter after how long or by what method, never amounts to the eradication of a

disposition to relapse. All the same, if acquired by following an extinction paradigm, the remission of symptoms is a sign of treatment-sustained neutralization of relapse risk.

On one hand, initiating treatment from a condition of acquired abstinence (detoxification) is not a necessary starting point; on the other, it may also delay the capacity to detect treatment effectiveness, which can be noted earlier from a condition of active use. A positive change from regularly to infrequently positive urinalyses carries with it a precise clinical meaning even in a short-term perspective, whereas stably negatively urinalyses after detoxification are not enough to imply effectiveness unless a very long period of observation has passed [7]. Accepting the conceptualization proposed by Sinclair about naltrexone as a treatment for alcoholism, opioid agonist drugs too may be conceived and handled as a means of extinction and not as a way to maintain results obtained through an initial phase of detoxification [5, 7]. Treatment for addiction may thus be described as a way of maintaining results achieved during the extinction phase. Although opiate blockade by agonist drugs is much more effective against craving than that produced by antagonist drugs, a long-term perspective is still imperative.

Obviously, one needs to accept the idea that addiction is a chronic relapsing disease, whose core symptoms may actually worsen through time, not just recur: many absurd treatment strategies, on the other hand, seem to be rooted in the assumption that addiction may remit spontaneously after the interruption of drug use, and that the ability to control one's craving may considerably improve over time without any treatment.

Collateral damage due to incorrect short-term interventions also derives from the groundless conviction that the treatment (identified with its agent) either does not fit the patient, if he/she relapses after its conclusion; or that the treatment was, indeed, effective, despite a relapse, so that is worth trying the same treatment again (in that same short-term formulation). For instance, a patient relapsing after naltrexone-assisted detoxification may resort to a fresh attempt at naltrexone-assisted detoxification, on the assumption that something did not work despite the effectiveness of the intervention (during which he/she had stayed abstinent). On the other hand, a patient relapsing during low-dose methadone treatment after three months of abstinence after methadone-assisted detoxification, may conclude that the treatment was not, after all, as effective as it had seemed, and drop out, instead of responding to an increased dose. On the whole, the short-term perspective has as its immediate consequence an overrating or a premature evaluation of apparently good or bad outcomes.

On pathophysiological grounds, opioid blockade itself does not imply a reduction in craving, but an awareness of opioid blockade, as long as it cannot be overcome, does condition a patient's behaviour as a secondary factor that is continually operative. A normal drug user would give up

use of the drug as long as he/she was still under blockade, whereas an addict simply experiences a gradual reduction of craving after an initial exacerbation (associated with attempts to overcome it or skip doses of the blocking drug). The response to blockade can be assessed as long as the abused drug is available in the environment. If blockade is not coupled with a direct anticraving action (e.g. naltrexone), reinforcement will proceed uninterrupted for a while before facing possible counteraction, so that the exacerbation of craving may become an important factor in the meantime. This is the why an enforced departure from protected environments (jail, closed communities, hospitals) while a patient is under pure antagonist treatment should never be regarded as a state of protection against relapse or drug-related accidents. On the other hand, drug-related risks, overdosing included, are amplified due to the loss of tolerance attributable to detoxification and the need to use larger drug doses to overcome a blockade. When such a departure takes place under agonist treatment, possible blockade is inevitably coupled with an anticraving effect and a state of tolerance to opiates which at least shields patients from the most severe drug-related accidents.

6. Cognitive treatment of addicts and their therapeutic response

Considering addiction that continues over a period of years, patients develop deep changes in their ability to encode and decode their drug-related experiences. Addicts always undergo alterations at a cognitive level during their periods of active drug use, but in less severe cases significant improvement follows the reduction of craving at an early stage during treatment. In the remaining cases cognitive faults endure and stand as a major obstacle to prolonged, specific treatment.

A common mistake is that of dealing with an addicted person without accounting for the features of an addicted brain which displays no consistency between rational judgement and the ability to be effective according to individual intentions. Unlike other people, addicts are not supposed to have a free will in dealing with drugs, as a direct consequence of their inability to understand or judge themselves 'from the outside'. When patients criticise their substance use, that signals no real progress, at least no stable progress. Moreover, addicts who correctly judge the dynamics of substance use continue to act inconsistently with their correct judgement, because they are unable to cope with their hypertrophic appetition instinct (craving). The relapses of detoxified addicts do not correspond to a loss of judgement skills (cognitive relapse) or to an inability to handle emotions (affective relapse); these patients simply rot in a hypertrophy of instinctual drives towards substance use, which call for no further or superior explanation. On the other hand, as long as craving and drives towards drug-seeking persist, insights into one's addictive condition are impossible, as if

one had to look ahead despite having one's head turned in the opposite direction. Basically, the addict's illusion will either be that of denying his/her condition ('I need treatment, but am not an addict') or that of expecting to find a solution within substance use, but with a higher capacity for control. In severe cases, the cognitive settings of the addicted brain become rigid and irreversible, and function as a new mental resource dedicated to addictive purposes (more effective drug use and avoidance of treatment). The chronology of therapeutic responses goes through different stages, the last of which takes shape as cognition, which is actually the first and strongest obstacle to treatment initiation. The first effect of treatment is to interrupt reinforcement, then it normalizes desire and neutralizes cravings, and eventually reaches the stage of improving insight, if that is at all possible. Reversing these considerations, a lack of insight will be the first function to favour relapse and impede the continuation of treatment, even over a period of years.

7. Conclusions

Substances of abuse produce structural changes in a user's brain, which correspond to psychopathological and behavioural features of acute and chronic phases, from controlled use to addiction. Addiction is the most problematic form of involvement in substance use, and is displayed as a behavioural problem. Addictive behaviours are not only sociopathic – they are basically dysfunctional with respect to substance use itself, since they create the worst conditions for organizing oneself for satisfactory future substance use. From this point of view, an addict is a person who has irreversibly lost the capacity to take drugs in a controlled and satisfactory way. In order to reverse alterations like these, treatments shall normalize behaviours, and detach the patient's intention to desist from his/her overwhelming instinct to repeat drug use, which is none other than the pathophysiological pathway of addiction seen in reverse. Spontaneously, normalization does not tend to stability, but to relapse, so that maintenance is needed. The process of normalization is based on dosage and opioid blockade, whereas stability is based on treatment continuation. The promotion of normalization treatments which are conceived to be long-lasting – lifelong if necessary – is a major medical and cultural challenge.

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It is time for a responsible administration of gamma hydroxybutyrate and methadone

Fabio Caputo

Department of Internal Medicine, SS Annunziata Hospital, Cento (Ferrara), Italy, EU

TO THE EDITOR: Gamma hydroxybutyrate (GHB) is a short-chain fatty acid structurally similar to the inhibitory neurotransmitter γ -amino-butyric acid, which exerts an ethanol-mimicking effect on the central nervous system by acting on its own receptor and on the GABA_B receptor [26]. Several European trials have demonstrated the efficacy of GHB in suppressing alcohol withdrawal syndrome (AWS) [2,13,22,20], and in alleviating the craving for alcohol, while maintaining alcohol abstinence [1,6,14]. A recent Cochrane analysis has shown that GHB (50 mg/kg/day) is more effective than placebo in coping with alcohol withdrawal syndrome; it must be added that this drug fails to give better results than BDZs or clomethiazole in preventing AWS. On the other hand, GHB has proved to be more effective than placebo in preventing 3-month relapses in previously detoxified alcoholics; in particular, GHB performs better than naltrexone (NTX) and disulfiram in maintaining abstinence and has a greater effect on craving than placebo and disulfiram. Moreover, the side-effects of GHB do not differ from those seen with BZDs, NTX or disulfiram [18]. Unlike methadone [23,28], a withdrawal syndrome does not occur at GHB discontinuation, so that GHB withdrawal does not even require a tapering procedure [3]. It must, however, be borne in mind that about 10% of alcohol-dependent patients manifest episodes of craving for this drug during treatment [1,7], and 40-90% of alcoholics with previous heroin or cocaine dependence develop a craving and a propensity for the abuse of GHB [8]. In Anglo-Saxon Countries, where GHB is widespread as a recreational drug of abuse, several cases of intoxication have been reported, and 1-3% cases of death

after a single self-administered dose of the street formulation can be attributed to this drug [16,21,25]. In clinical trials, however, only rare episodes of sedation due to GHB abuse [1,7,8] have been reported, and none at all of intoxication, coma or death.

Methadone is a synthetic μ -opioid receptor agonist currently used for the treatment of heroin dependence [23,28]. This drug has no serious long-term side-effects; even if the 16-34% of patients treated with high dosages (>120 mg/day) present QT interval prolongation and episodes of torsades de pointes ventricular tachycardia [11,17,24]. A study performed on a population of heroin addicts of Copenhagen showed that methadone doses were associated with a longer QT interval (affecting almost 30% of treated patients), while no association between buprenorphine and QT prolongation was found; expressed differently, a 50 mg higher methadone dose was linked with 1.2 times higher odds for syncope [12]. Besides this, a study performed on Norwegian heroin addicts has shown that 4.6% of patients treated with methadone had QT intervals above 500 milliseconds, 15% had a QT interval above 470 milliseconds, and 28.9% had a QT above 450 milliseconds. Furthermore, in a study involving patients who had completed a methadone maintenance treatment, a smaller number of deaths due to heroin was unsuccessfully counterbalanced by a higher number of methadone-related deaths [15]. Thus, a wide range of deaths attributable to QT prolongation (from 0.06% to 30%) have proved to be correlated with high methadone dosages in treating heroin-addicted patients [5,19,27,29].

In the light of these data, another question is warranted:

have the potential risks of the clinical use of GHB been overemphasized while, on the other hand, have the threats linked with methadone administration been considerably underestimated? Even though these drugs have different sites of action in the central nervous system [23,28], their effects are quite similar, and both act as a replacement therapy. On the other hand, their potential side-effects seem to raise different concerns. As methadone administration can lead to QT interval prolongation, and even a low dose (50 mg/day) is effective in treating heroin addiction [30], definite rules should be followed once the decision to administer this drug has been taken. The dosage should not exceed 60-120 mg/day, baseline and ongoing treatment ECGs should be performed, while medications that may per se prolong the QT interval (i.e. antidepressants and/or mood stabilizers) [30] should be withdrawn. Patients should also be helped to abstain from alcohol, as that may interfere with blood methadone levels. As far as GHB is concerned, to avoid episodes of craving and abuse, GHB should be avoided in alcohol addicted patients with poly-drug dependence; its dosage should not exceed 50-100 mg/kg/day divided up into three to six daily administrations, and a strict medical surveillance needs to be put in place [4,9,10].

In conclusion, we believe that physicians should attribute greater importance to the potential side-effects of methadone clinical use and be less concerned by the risk of GHB intoxication, as episodes of poisoning and deaths have only occurred with uncontrolled self-administration with this latter drug. Indeed, in clinical settings, GHB intoxication has never been reported during controlled administration, whereas cases of arrhythmias and deaths due to methadone have been clearly ascertained.

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Opiate maintenance treatment in primary health care in Germany

Rainer Ullmann

General Practitioner, Hamburg, Germany, EU

TO THE EDITOR: The first physicians to offer opiate maintenance treatment (OMT) and those who prescribed methadone for withdrawal had to face criminal prosecution. Public opinion, including influential psychiatrists, was strongly against methadone maintenance. With the onset of the AIDS epidemic, public opinion changed. By now OMT is accepted as an important part of the drug helping system by all political parties. That system comprises syringe and needle exchange, injecting rooms, methadone drug clinics in bigger cities, an opportunity to withdraw from drugs (mainly alcohol, benzodiazepines, cocaine, heroin) under OMT in specialized hospital wards, psychosocial services, long-term residential treatment, and in the last few years injectable heroin programmes in special drug clinics set up in some cities.

Methadone maintenance started in 1988 in a drug clinic and in 1989 in a private practice setting. The first regulations introduced into the health care system for the treatment of heroin addicts in 1991 accepted OMT only for addicts who were severely ill (e.g. addicts with AIDS, tuberculosis or cancer) or who were pregnant besides being heroin addicts. Starting in 2003 addiction itself became a sufficient indication. Now over 65,000 out of roughly 150,000 heroin addicts get OMT, in most cases paid for by social health insurance (SHI). Most patients are treated by general practitioners. In the early years a physician was not allowed to treat more than 10 SHI patients. Physicians can prescribe methadone, levomethadone, buprenorphine and in some cases dihydrocodeine. With the narcotic prescription regulations now in force, the government tries to curtail the black market in

prescribed opiates. It demands that opiates be taken under supervision at the doctor's office or in a pharmacy as long as the patient misuses drugs. On the other hand, patients with a job need take-home doses. This is a difficult decision for the doctor to take.

Beside regulation by criminal law, the SHI imposes quality control. Because of many regulations and much bureaucracy, only 2,700 general practitioners out of 60,000 treat addicts. Besides that, in the 90s there were some press campaigns against physicians offering OMT (headlines included: "dealer in white", "codeine deaths", "methadone deaths"). Now, especially in southern Germany, some physicians have to deal with criminal proceedings, because of offences against formal regulations. These proceedings have the effect of discouraging other physicians. In some rural regions, no treatment is offered.

In 1926 the psychiatrist Gaupp, the main speaker on morphinism at the annual meeting of German physicians, called openly on doctors to ignore what were then new regulations: "Of course, ladies and gentlemen, life mocks all paragraphs. The difficulties it brings with it do not always allow the exact implementation of the above-mentioned principles anywhere" (6).

The earliest implementation of opiate maintenance treatment (OMT) took place thanks to a few GPs in Germany in the 1970s. They were treated as black sheep, and were criminally prosecuted. At that time it was difficult to even discuss OMT. Abstinence was the only goal – whatever the cost in terms of lives, AIDS or social destruction. As a judge wrote in 1975: "OMT is malpractice, this is well

known. I need no expert in my trials to prove that” (18). The German Federal Medical Association announced in 1985: “The medically reasonable indications for methadone occur rarely and are very few. They are: life-threatening situations in withdrawal with long-lasting convulsions; withdrawal in severe illnesses like tuberculosis, heart failure, postoperative pain, and, besides that, there is a – disputed – indication that a pregnant woman can take a low dose of Polamidon beginning in Month VI” (1). So the Government could say in 1986: “OMT is medically contraindicated and therefore unlawful” (4).

Looking back, Robert Newman wrote in 1995: “For some doctors, the result was shattered lives and permanently destroyed careers. For others, civil and criminal proceedings dragged on for years, robbing them of their time, energy, and their financial resources” (13).

At that time, about 400 people died every year because of their drug abuse, and AIDS was spreading. Some politicians dared to consider Methadone Maintenance Treatment. A scientific colloquium was held in Düsseldorf in 1987 by the then social and health minister Hermann Heinemann in North Rhine Westphalia. After that a programme was started with 250 addicts. They had to be 22 years old, with several years of addiction to heroin and with at least two failures in attempting residential drug-free treatment. The HIV-infected addicts were accepted after they had failed residential drug free treatment once (15). In 1989 in Hamburg, a treatment within the Social Health Insurance (SHI) system started with GPs prescribing L-Polamidon – the only form of methadone then available. Polamidon was to be taken in the pharmacy with take-home for Sundays. A methadone treatment clinic was installed for patients not presentable in a GP’s office and to help in difficult situations. A committee of physicians and drug counsellors had to approve each treatment. It started very slowly: 50 patients in the 2nd year, 200 in 1991. Now 4,000 of the about 10,000 heroin addicts are being treated.

In those times MMT was not accepted for all heroin addicts, only those with severe diseases beside addiction. In Hamburg, the SHI, the medical association and politicians accepted 2 other indications: “malign course” and “successfully treated with dihydrocodeine” (DHC). The reason for the use of DHC was the criminal prosecution of physicians who prescribed L-Polamidon, which fell under the narcotics act. One of the pioneers, the GP Hannes Kapuste in Munich, was sentenced because of an unjustified prescription of narcotics. A psychiatrist reported “methadone paranoia”. That was the reason Gorm Grimm, GP in Kiel, started prescribing DHC to heroin addicts in 1975. DHC did not fall under any of the narcotics regulations. But there were problems with the SHI-companies, which expected and ordered him to pay for the DHC prescription himself.

Many addicts from Hamburg became his patients. Because the discussion about methadone was a matter of great controversy, the social authority decided to pay for DHC in

1988. In Hamburg OMT started to use the very expensive DHC capsules. Diversion was a problem, but heroin addicts were the only ones to use diverted DHC capsules, not naïve opiate addicts. A committee gave some advice about treatment: daily distribution of the capsules in the pharmacy, weekly contact with the physician, drug counselling (2). From the beginning in Hamburg there was drug counselling, especially for opiate-maintained patients. In other regions drug counsellors only prepared the patients for residential drug free treatment. Often there was open hostility between opiate-maintaining physicians and drug counsellors.

Many physicians were afraid to prescribe DHC at the expense of SHI. They prescribed a DHC syrup. This was cheaper but more dangerous than the slow-acting capsules. This treatment spread fast: in 1997 about 20-30,000 addicts were treated with DHC syrup. Some socially integrated patients were enabled to manage their lives by using DHC syrup. For other addicts the syrup was a drug rather than a remedy. In Munich especially, a black market emerged. Some physicians prescribed large amounts of 2.5% DHC solution without any control over consumption. There were drug deaths attributed to DHC. After a long-lasting controversy, DHC was brought under the narcotics regulations in 1998 if prescribed to opiate addicts. As a result, many physicians stopped treatment. Many of the patients found other physicians and were switched on to methadone. Others couldn’t find another doctor, or the MMT regulations were incompatible with their work schedule. The number of drug deaths began to rise again.

In 1991, the Supreme Court allowed OMT, even if not accepted by the medical association (3), and, starting in 1992, the narcotics regulations explicitly allowed OMT for addiction treatment. Supervised consumption in a physician’s office was required. Later the narcotics regulations defined the necessary qualifications of the prescribing physicians, conditions for access and discharge of their patients, the opiates accepted for OMT (the use of any other kind is a crime), the number of daily doses that can be prescribed and the conditions for take-home (the maximum is 7 days, with an exception for a stay abroad lasting up to 30 days). The physician must register the patient at a central registration office, see the patient regularly (usually once a week), urge participation in drug counselling wherever necessary, document all relevant patient and treatment data and turn the files over to the relevant state authorities if required (20). All guidelines and regulations ignore the difficulties involved in treating heroin addicts in rural regions; there are few physicians treating heroin addicts, only a few pharmacies participate in supervising consumption, and there are often long distances to travel despite inadequate public transport.

Prosecuting attorney Dr. Körner wrote:

“An overdose is always harmful, even an overdose of criminal law. The amendments of the criminal regulations mean an overdose of criminal law. They are not helpful, but

harmful. They can lead to degrading criminal proceedings and deter physicians from maintenance treatment” (10).

Even though narcotic regulations accepted heroin addiction as a sufficient indication for OMT, the SHI Guidelines did not. About 90% of the population belong to the SHI. Most of our patients need treatment costs to be covered by the SHI. But in the case of OMT, the SHI refused to pay for a long time. In the 1991 SHI Guidelines, heroin addiction was not a sufficient indication for getting treatment. SHI only paid for OMT if patients had other severe illnesses: “drug addiction in pregnancy until delivery; drug addicts suffering from manifest AIDS in an advanced stage; if patients had severe diseases like cancer or tuberculosis, life-threatening status in withdrawal; if a withdrawal is not reasonable during a necessary treatment in a hospital (16). At that time, a physician was not allowed to treat more than 10 patients at the cost of the SHI. The comment of the federal organization of physicians in SHI (KBV) sounds scornful: “The methadone maintenance guidelines serve the ill addicts and the protection of their physicians” (9).

It was a process involving struggles that lasted for years and years until addiction itself was accepted as an indication. Not until 2003 did manifest opiate addiction become a sufficient indication for OMT. The maximum number of patients per physician is now restricted to 50. Eight per cent of all patients are controlled each year by a committee of physicians and representatives of the SHI, and this committee decides if a patient may be discharged. In some regions, the committee demands that treatment be stopped if a physician or consulting psychiatrist prescribes benzodiazepines. The commentary of the KBV at this time: “The SHI first refused the new regulations. They were afraid that they had to pay for too many treatments. But applying strict criteria to quality will prevent any rise in payments” (8). The main goal of all those regulations was to restrict the number of patients the SHI had to pay for. They did not succeed: in 5 years the number of treatments rose by 50%. Now over 65,000 out of about 150,000 heroin addicts get OMT, which is normally paid for by the SHI. Most patients are treated by general practitioners, about 20% of them in drug clinics. There are only a few psychiatrists offering OMT. Most of them work in drug clinics (7,21).

The results of treatment by GPs in Germany are comparable with the international results reported. Retention rates are high: about 80% in the first year, about 60% after 5 years. Rates of death from drugs for people in treatment fell to 1/3 of the original value in that period. HIV infection rates are low at less than 6%. There are less than 200 infections with HIV per year affecting over 100,000 heroin addicts. Besides OMT, the following also led to a fall in HIV-infection rates: educational work, the availability of anonymous HIV-testing, syringes, needle exchange and supervised injecting centres (12). Every year at least 1% of OMT patients are able to withdraw gradually from opiates in an outpatient setting or

change to residential opiate-free settings (5). A recent study showed that treatment in small practices works as well as in drug clinics and OMT-focused practices (14).

Although physicians offering OMT have shown good results, they are often publicly criticized. Physicians who do not work carefully gave a pretext for opposing OMT in general. In some cases physicians start with doses that are too high or give take-home doses to unstable patients. This has led to the death of the patient or his/her friends. “Dealer in white” was a popular name for opiate-maintaining physicians some years ago. “New death drug” (DHC), “38 deaths – the dangers of methadone”, “Drug substitutes for self-service”, “Doctors in drug swamp”, “Raid on dope doctors”: these were some of the newspaper headlines. Another point is that SHI demands that money be paid back by doctors for providing medication (often amounting to some ten thousand Euros) if they think the physician made a mistake. In other words, they argue that OMT is not allowed if there is another dependence, mostly benzodiazepines or alcohol.

Examples of prosecution

- a) A physician is suspected of prescribing too high doses. Nobody asks the physician about the doses, but there is a raid at his/her office and home. Order of summary punishment: 3000 Euro.
- b) Fines are given because of take-home outside a practice, instead of take-home only at a pharmacy.
- c) A court decides: “There are no grounds that can justify early take-home. A long journey to the physician, a patient’s interest in keeping his/her job or the risk of falling back into the drug scene do not justify overruling the narcotics regulations” (11).

The efficacy of OMT is as great in Germany as elsewhere, but this is feasible only because physicians treat their patients as well as possible, despite the regulations. Sometimes the risks they run comprise fines, prison and the revocation of their permission to practise. Other reasons that induce physicians to refuse to offer OMT are bureaucratic hassles, a bad image associated with this treatment, all the time and energy required to deal with those sometimes difficult patients, and low fees (19). Those are the reasons why less than 5% of all GPs and less than one third of the physicians who have special permission to offer OMT actually do so.

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