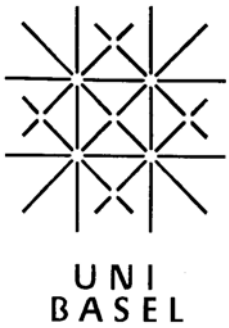

Fakultät für Psychologie der Universität Basel

Methadone Treatment for Opiate Dependent Patients in General Practice and Specialist Clinic Settings: Outcomes at One-Year Follow-Up

Inauguraldissertation
zur
Erlangung der Würde eines Doktors der Philosophie
vorgelegt der
Fakultät für Psychologie der Universität Basel

von
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Basel, 2004

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ASI	Addiction Severity Index
BZD	Benzodiazepines
CBT	Cognitive Behavioral Therapy
DARP	Drug Abuse Reporting Program
DATOS	Drug Abuse Treatment Outcome Studies
DC	Drug Counselling
ECA	Epidemiologic Catchment Area Study
FOPH	Federal Office of Public Health
GC	Good Cooperation
GP	General Practice
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDU	Intravenous Drug User
MET	Motivational Enhancement Therapy
MMT	Methadone Maintenance Treatment
MMTP	Methadone Maintenance Treatment Program
MTF	Monitoring The Future Study
NIDA	National Institute on Drug Abuse
NTORS	National Treatment Outcome Research Study
OD	Overdose
RCT	Randomized Controlled Trial
SC	Specialized Clinics
TAU	Treatment As Usual
TC	Therapeutic Community
TOPS	Treatment Outcome Prospective Study
UC	Unsatisfactory Cooperation

Acknowledgements

The author wish to thank Prof. Jürgen Margraf as principal leader of the project, Prof. Dr. med. Dieter Ladewig second referee, and Prof. Andreas Monsch for their help and advice throughout the project. Dr. Kurt Kräuchi, lic. phil. Ken Dürsteler, and Dr. phil. Urs Gerhard for their statistical advice. I also thank Prof. Rudolf Stohler, Dr. Bruno Bucheli, Dr. Georgette Schaller, and Prof. Gerhard A. Wiesbeck as experts in addiction medicine. Finally I thank the staff at the participating clinics, the general practitioners without whose active support this study would not have been possible, and the patients for agreeing to take part in the project. The views expressed in this paper are those of the author and do not necessarily reflect those of the Department of Health.

To all my colleagues, which always give me support and motivation to continue, my parents for the possibility to study clinical psychology, and over all I thank my husband Kurt Gottfried for his great support and comprehension.

Abstract

Few studies have investigated methadone maintenance treatment of opiate dependent patients in primary health care settings compared to specialist clinic settings. Using a prospective cohort design, the study investigated outcomes at one year for 660 patients treated by general practitioners (*n* = 70) or by drug clinics (n = 3) at sites across Basel, Switzerland. The main treatment outcome measures were: retention in treatment, attendance of consultations, prescribed methadone doses, and illicit drug use over time. Mean daily methadone dose for patients in general practice (GP) was 69.3 mg (SD = 44.7) and for patients in specialized clinics 76.7 mg (SD = 48.4). The overall one-year retention in treatment was 74% (GP, 75.6%; clinics, 72.2%). The proportion of reported concomitant heroin use was significantly lower in patients treated by GPs compared to the clinic sample (49% versus 72%; *P* < 0.0001), as well as the proportion of reported concomitant cocaine use (GP, 24%; clinics, 41%; *P* = 0.001). The same accounts for reported intravenous drug use (GP, 40% versus 58%; *P* < 0.0001). The concomitant use of benzodiazepines and alcohol did not differ between groups. Reductions in concomitant heroin and cocaine use were found in both groups at follow-up, by comparing admission, with average-stay and long-term samples. Patients in GP settings attended an average of 5.14 out of 6.19 scheduled consultations, patients in specialist clinic settings an average of 6.8 out of 7.86 scheduled consultations in a six-month period. The proportion of take-home medication for both groups was 69%. Comparing treatment outcome with the amount of consultations in both treatment settings, patients with a higher rate of consultations (4 to 7) had a significantly better retention rate in both groups (*P* = 0.002; *P*< 0.0001) compared to patients with a low rate of consultations (0 to 3). Results show substantial reductions in concomitant heroin use, among 'real world' patients treated in GP and in clinic settings, which were sustained at one-year follow-up. Our results support the success of methadone maintenance provided by primary care physicians' offices. Furthermore, our results provide evidence, that GPs treat an equal proportion of 'unstable patients' (25%) as do the clinics, indicating the knowledge and long clinical experience of this sample of GPs. However, providing better professional support, competence training and financial remains a goal for future developments in the primary health care field.

1. Introduction

Methadone prescribing to opioid-dependent individuals has become much more available over the past decade, both in countries with a history of its use like the UK, Australia, the Netherlands, Spain, Italy and Switzerland, and in countries round the world which previously had no methadone prescribing like France and Germany. In some of these countries (the UK, the Netherlands, Spain, Italy and Switzerland) methadone maintenance treatments (MMT) are provided by primary care and specialized clinics. In the United States the current narcotic treatment system is able to provide the most effective medical treatment for opioid dependence to only 170'000 of the estimated 810'000 oipoid-dependent individuals (National Consensus Development Panel, 1998). This lack of adequate treatments persists despite the demonstrated effectiveness of methadone maintenance in decreasing the medical, legal, and infections complications associated with heroin use (Ball & Ross, 1991; Metzger et al., 1991; Cooper et al., 1989). Critical statements against MMT argue, that the problem of methadone diversion is not solved. Methadone treatment has been researched for three decades and it has been reported that, when correctly implemented, this treatment can provide benefits for opioid dependent patients and the community and lower the mortality rate associated with opioid use (Caplehorn et al., 1994; Goldstein et al., 1973; Gunne et al., 1981; Kreek et al., 1981; Ball & Ross, 1991; Dole et al., 1969).

1.1 Opioid Abuse and Dependence

Before summarizing the research conducted in methadone maintenance treatment we will give a short overview of the APA Classification (American Psychiatric Association, 1994; DSM IV) and the WHO classification (WHO, International Classification of the World Health Organization, ICD-10, 1991) of opioid abuse and dependence. As we can see in the following section (substance dependence, criteria 6), the APA Classification outlines more the “important social, occupational (...) activities” that “are given up or reduced” (APA, 1994) than the WHO-Classification.

APA Classification: the Diagnostic and Statistical Manual – DSM-IV
Opioid Abuse and Dependence:

A. Characteristics and Major Features
1. Opioid dependence is a state characterized by behavioral and physiologic symptoms that result in continued use of opioid substances despite harm.
2. Hallmarks include prolonged self-administration of opioid substances despite significant adverse effects, often accompanied by tolerance and/or withdrawal.
3. Physiologic manifestations result from changes in brain receptor function and neurochemical signaling induced by chronic exposure to opioid agonist substances such as heroin.
4. Psychological and behavioral manifestations of opioid dependence are major causes of dysfunction and morbidity.

B. Criteria for Substance Abuse and Substance Dependence (DSM-IV)

1. **SUBSTANCE ABUSE** (American Psychiatric Association, 1994)

A. A maladaptive pattern of substance use leading to clinically significant impairments or distress, as manifested by 1 (or more) of the following occurring within a 12-month period:

1. recurrent substance use resulting in a failure to fulfill major role obligations at work, school or home
2. recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. recurrent substance-related legal problems

2. **SUBSTANCE DEPENDENCE** (American Psychiatric Association, 1994)

A. A maladaptive pattern of substance use leading to clinically significant impairments or distress, as manifested by 3 (or more) of the following occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect
b. markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following:
a. the characteristic withdrawal syndrome for the substance
b. the same (or closely related) substance is taken to relieve
3. The substance is often taken in larger amounts or a longer period than was intended.
4. There is persistent desire or unsuccessful effort to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple physicians), use the substance (e.g., chain-smoking), or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

The International Classification of the World Health Organization (ICD-10)

International Classification of Diseases (ICD-10, 1991):

The ICD-10 criteria of opioid dependence (F1) are very similar to the DSM-IV criteria. Three or more of the following must have been experienced or exhibited at some time during the previous year:

1. Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use
2. A strong desire or sense of compulsion to take the substance
3. Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects

4. Persisting with substance use despite clear evidence of overtly harmful consequences, depressive mood states consequent to heavy use, or drug related impairment of cognitive functioning
5. Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses
6. A physiological withdrawal state when substance use has ceased or been reduced, as evidence by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms

1.2 Epidemiology of Opioid Dependence

Heroin abuse and dependence are serious health problems with profound effects on individuals and society. Costs to society are estimated at $20 billion per year with $1.2 billion per year of direct health care costs in the U.S. (Fiellin et al., 2002). There are an estimated of 2.4 million Americans who reported using heroin at some time in their lives, thus the lifetime prevalence of people age 12 or older was 1.4 percent (National Household Survey on Drug Abuse, 1997). During 1991 – 1995 opioid-related deaths increased from 2300 to 4000 (Drug Abuse Warning Network, 1999).
Most of the new heroin users are under the age of 25. Evidence suggests that heroin snorting and smoking has become common in those areas of the United States in which high-purity heroin is readily available. This accounts also for the European Countries. Authors from the "Monitoring the Future Study" (MTF, 1999) analyzed heroin use by students in 1999. Although year prevalence rates for heroin use remained relatively low in 1999, these rates were about two to three times higher than those reported in 1991 and the use began to rise among 10th- and 12th-graders. The same accounts for cocaine use, the percentage of 8th-graders who had ever tried cocaine has increased from a low of 2.3 percent in 1991 to 4.7 percent in 1999 (table 1).

Table 1: Heroin Use by Students in the United States, 1999 (N = 49'866)

	8th-Graders	10th-Graders	12th-Graders
Ever Used	2.3%	2.3%	2.0%
Used in Past Year	1.4	1.4	1.1
Used in Past Month	0.6	0.7	0.5

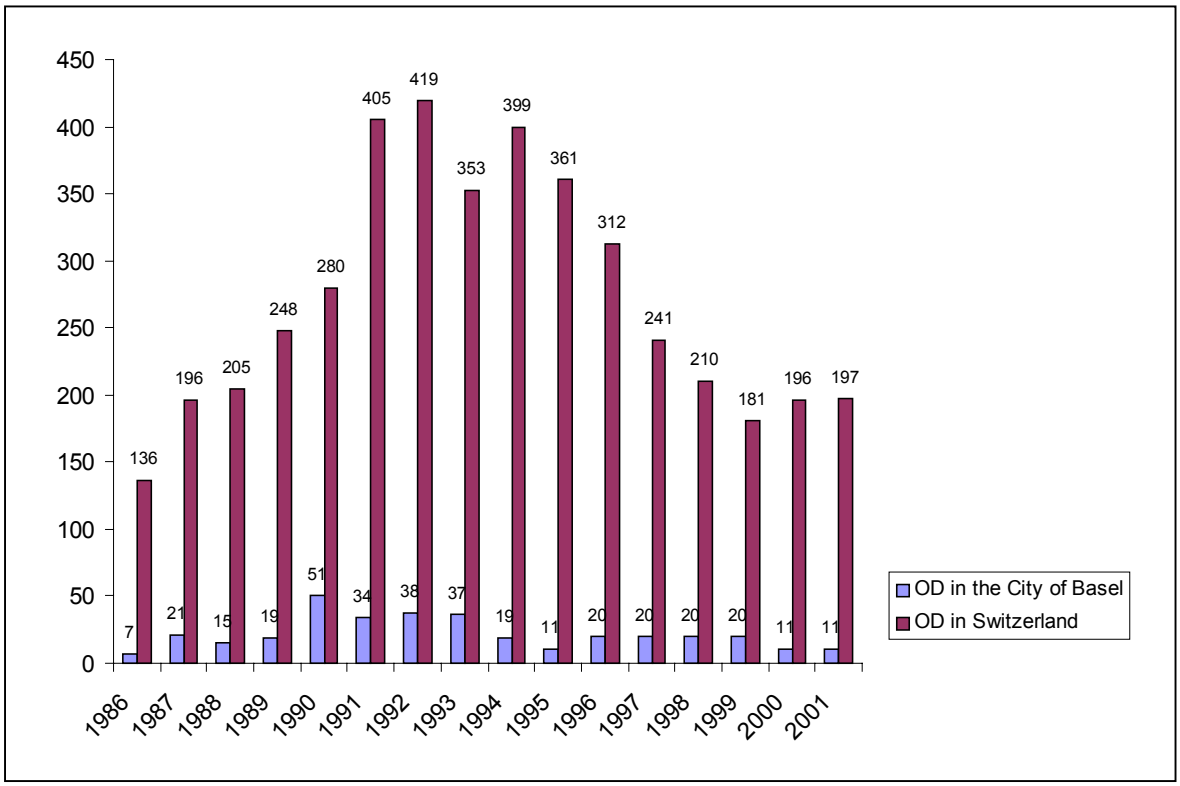
Monitoring the Future Study (MTF), 1999, National Institute on Drug Abuse (NIDA)

Recent estimates are that there are approximately 810'000 chronic heroin users in the U.S. However, only 170'000 of these are currently receiving treatment with the most effective form of therapy – an opioid agonist therapy such as methadone.

A recently published Swiss survey of 10'115 schoolgirls and schoolboys (aged 11 years to 16 years) reported a prevalence rate of 0.5% for heroin use and 3.4% for cocaine use (Schweizerische Fachstelle für Alkohol u. Drogenfragen, 2003). Heroin use remained unchanged in the past 10 years, whereas cocaine use increased significantly from 1.7% to 3.4% prevalence. This is similar to the American results from the MTF-study.
In Switzerland, there are an estimated of 1.3% of the total population who reported using heroin at some time in their lives, with a sex ratio of 3 to 1 for men (Schweizerische Fachstelle für Alkohol u. Drogenfragen, 1995). There are an

estimated of 30'000 persons having an opioid dependence (Esterman, 1996). 3% of the persons aged 15-39 years have tried heroin or cocaine at least one time in their life. For drugs like cannabis an estimated of 600'000 persons aged 15-39 years have tried cannabis at least one time in their life. In Switzerland, the number of heroin addicts has remained stable since 1990, and deaths from overdose have decreased from 419 in 1992 to 197 persons in 2001 (Bundesamt für Gesundheit, SPECTRA, 2002, Fig. 1). The category in the Federal statistic is not clearly defined and must be well understood: most persons died from multiple drug use, but there also suicide, accidents on the road or at work and persons dying from AIDS disease (Fig. 1). Nevertheless, there has been a considerable decrease drug-related deaths (ODs) since 1992 in Switzerland and in Basel (Fig. 1). This is due to the considerable efforts of the Swiss public health authorities and the experts in addiction medicine by expanding the drug treatment system in the last 25 years in Switzerland. In particular there has been a growth of the non-residential sector and the low-threshold programs, including methadone maintenance treatment, the establishing of injection rooms and controlled heroin prescription in specialized clinics (Klingemann, 1996).

Figure 1: Number of Persons Died from an Overdose (OD) Over Time, in Switzerland and in Basel



ODs in Switzerland: Adapted from, Bundesamt für Gesundheit, Statistik des Bundesamtes für Polizeiwesen BAP, polizeilich registrierte Fälle (2002).
ODs in the City of Basel: Adapted from, Statistisches Jahrbuch des Kantons Basel-Stadt (2001).

1.3 Pharmacology of Opioids

The most important pharmacological actions of the opioids are euphoria and analgesia; “they alter the response to the perception of pain in doses which have comparatively minor effects on other functions of the central nervous system “ (NIDA, 1986). There are three major types of opioid receptors: the Mμ receptor (mediates euphoria, analgesia, and sedation); the Kappa receptor (mediates dysphoria, analgesia); and the Delta receptor (Goldstein, 1991). Endogenous peptides which bind to these receptors are enkephalins, endorphins. Mμ receptors have a high affinity to opioids, enkephalins and beta-endorphins. Opioids mimic the action of the endogenous neurotransmitters in the brain by utilizing and activating the same receptor sites (Brown, 1976; Swan, 1997). Repeated (chronic) exposure to short-acting opioids (e.g., heroin) leads to neuronal adaptations resulting in tolerance, dependence, and craving. Replacement therapies with methadone aimed at stabilizing these neuronal circuits (Nestler & Aghajanian, 1997).
Different pharmacotherapies have been researched and developed in the last three decades for the treatment of opioid dependence. Full agonists (e.g. methadone) binds and activates the receptor, partial agonists (buprenorphine) binds and partially activates the receptor, antagonists (naloxone) binds but does not activate the receptor (table 2). Mμ, delta and kappa opioid receptors belong to a family of receptors know as the G-protein-coupled receptors – found on the cell surface. When these bind to drug (heroin), G-proteins activated within cell produce drug-inducted euphoria. Other effects include: analgesia, respiratory depression, constipation and miosis (Ling & Wesson, 1990; Kleber, 1994). Extended use of opioids that binds to the mμ receptor is associated with physical dependence and withdrawal syndrome when they are removed (Ling & Wesson, 1990). Natural opioids and their synthetic analogs are cross-tolerant and cross-dependent (Akers, 1992; table 2).

Table 2: Opioid Agonists and Antagonists

Agonists (naturally occuring)	Semi-synthetic Agonists	Synthetic Agonists	Partial Agonist and Mixed Agonist/Antagonist	Antagonists
Opium	Heroin (Diacethylmorphine)	Methadone (dl-6-Dimethylamino-4,4diphenyl-3-heptanon)	Buprenorphine (Subutex)	Naloxone (Narcan)
Paregoric	Hydromorphone	LAAM	Pentazocine	Naltrexone (Nemexin)
Morphine	Oxycodone	Propoxyphene	Nalorphone	Nalmefene
Codeine (Methylmorphine)	Hydrocodone	Fentanyl	Nalbuphine	

Akers, 1992

1.4 Opioid Abuse and Psychopathology

Psychiatric comorbidity in opioid dependence is common (Cacciola et al., 2001; Moggi, 2002). The following disorders are seen in association with opioid dependence in daily clinical practice: Abuse or dependence on another substance including tabacco, alcohol, cocaine or benzodiazepines; depression; anxiety disorders; antisocial personality disorder; and other personality disorders.

1.4.1 Abuse or Dependence on Another Substance or on Multiple Substances

Gossop and colleagues (1999, 2001, 2003) analyzed in a National Treatment Outcome Research Study (NTORS) in the UK the pretreatment diagnosis of 1075 patients before entering a methadone maintenance program and found, that multiple substance use before treatment is nowadays the norm (Gossop et al., 1999, 2001, 2003). 11% reported use of heroin and cocaine before treatment, 24% heroin, cocaine, and benzodiazepine use, 30% heroin, cocaine, benzodiazepine and alcohol use. Almost 98% percent used tobacco. Thus, most patients used beside heroin three additional substances. Nevertheless, most clinicians do not use the term "multiple dependences", but define for each substance a separate diagnosis, as it is defined in the DSM-IV and the ICD-10. The NTORS study also showed, that 50% of the patients dying from a so called "overdose" had 4 or more substances in their bodies and were heavy drinking subjects (autopsy reports).

1.4.2 Depression

Lifetime prevalence of depression in methadone maintained patients is estimated between 16-54% (Rounsaville et al., 1982; Brooner et al., 1997; table 3). Depression may have preceded the onset of drug abuse and a major depressive episode may develop in the context of opioid addiction. It occurs more commonly in women than in men. Treatment with antidepressants and psychotherapy is indicated and frequently helpful if the individual is abstinent from illicit drug use.

1.4.3 Anxiety Disorders

Panic disorder, obsessive-compulsive disorder, generalized anxiety disorder and phobia are seen in approximately 10% to 30% of opioid dependent persons (Khantzian et al., 1985; Regier et al., 1990; Cacciola et al., 2001; table 3). This group of persons is somewhat younger in age and higher in socioeconomic status and their drug use histories are not as extensive (Fiellin et al., 2002). Cacciola and colleagues (2001), found at methadone maintenance treatment entry 8% of the patients with panic disorder, 11% with a social phobia, 21% with a simple phobia and 33% with a post traumatic stress disorder (PTSD) (table 3). The high rate of PTSD is probably due to the high incidence of physical and sexual abuse among many opioid dependent patients (lifetime and current).

1.4.4 Personality Disorders

Antisocial personality disorders are the most commonly diagnosed with a prevalence rate between 25-35% (table 3). The majority are men. The second most diagnosed personality disorder is the borderline personality disorder with a prevalence rate of 10%, with no gender differences. "Personality disorders can be diagnosed historically in most individuals at a young age prior to onset of opioid dependence" (Fiellin et al., 2002, p. 11). The *Epidemiologic Catchment Area* (ECA) study (Regier et al., 1990) was a large-scale survey of the prevalence of psychiatric disorders conducted in the USA. The ECA findings are of interest, because the allow a comparison of lifetime rates in the general population with opioid users. Opioid users were found to be

seven times more likely to have experienced a psychiatric disorder than the general population (table 3).
In a Swiss study, Kuntze and colleagues (1998) found in 126 methadone maintained patients 70.7% with two or more diagnoses of substance related disorders. Personality disorders were found in 45% of the patients, depressive disorders in 25%, schizophrenic disorders in 14% and anxiety disorders in 5%.

Table 3: Estimates of Prevalence of Psychiatric Comorbidity in the Opioid Dependent and in the General Population

Author	Sample Type (N)	Prevalence rate (current[a] or lifetime[b])	Any psychiatric diagnosis %	Depressive disorder %	Anxiety disorder %	Alcohol use disorder %	Antisocial personality disorder %
Rounsaville et al. (1982)	Opioid dependent[c] 533	Current	70	26	3	14	27
Khantzian & Treece (1985)	Opioid dependent[c] 133	Current	93	56	11	14	35
Woody et al. (1983; 1985)	Methadone patients 110	Lifetime	-	43	7	26	15
Strain et al. (1991)	Methadone patients 66	Lifetime	47	23	2	49	30
Regier et al. (1990)	Opioid users 142	Lifetime	65	31	32	66	37
Brooner et al. (1997)	Methadone patients 716	Current	47	16	-	-	25
Cacciola et al. (2001)	Methadone patients 278	Current	75	35	24	14	28
Regier et al. (1990)	General Population sample 20'291	Current Lifetime 'Relative risk'[d]	13.0 22.5 6.7	5.2 8.3 5.0	7.3 14.6 2.8/	2.8 13.5 12.8/	0.5 2.6 24.3

Adapted from Ward et al., 1992, p. 259.
Notes. [a] 'Current indicates that the individual currently has the disorder; [b] 'Lifetime' indicates that the individual has had disorder at some time in life. [c] Refers to a mixed sample of opioid-dependent individuals, some of whom were in treatment some were not in treatment. [d] The figures on 'relative risk' are odds ratios reported by Regier et al. (1990) and indicate the increased likelihood that a person meeting diagnostic criteria for opiate abuse or dependence will also meet criteria for the diagnoses indicated.

1.5 The Early Methadone Maintenance Treatment Programs

In the early 1960s, Dole and Nyswander introduced orally administered maintenance doses of the synthetic opioid drug methadone as a drug-substitution treatment for opioid dependence. Methadone is a full agonist acting at the mμ receptors and replacing the shorter-acting heroin that is usually injected (Dole and Nyswander,

1965). Methadone is taken orally once a day because its long duration eliminates opiate withdrawal symptoms for 24-36 h, decreases craving for heroin and blocks its euphoric effects (table 4).

Table 4: Methadone versus Heroin

	Methadone	Heroin
Route	Oral	Intravenous, Intranasal
Onset	30 minutes	Immediate
Duration	24-36 hours	3-6 hours
Euphoria	Absent	Marked

Adapted from Dole & Nyswander, 1965

According to Dole and Nyswander, opioid dependence was perceived as "a physiological disease characterized by a permanent metabolic deficiency" (1965, p. 84). Thus, this deficiency was treated by administering to the opioid-dependent patient a sufficient methadone dose as a substitute to stabilize the metabolic deficiency. This allowed the patients to "improve his social functioning by taking advantage of the psychotherapeutic and rehabilitative services" that were an integral part of these early methadone maintenance programs (Dole & Nyswander, 1967, p. 22).

The early MMT were based on the following model of treatment process: entering treatment, induction phase, maintenance phase, detoxification phase, after care. This model of addiction treatment is derived from the early abstinence oriented therapeutic communities (1965, *Daytop, Synanon, Phoenix*) which comprised: detoxification, entering therapy, therapeutic phase with behavioral-emotional change, visiting after care services or self-help groups to maintain abstinence after the therapy. This 4-step model of addiction treatment was introduced in Europe first in the *therapeutic communities* (Petzold, 1974), and then later in non abstinence oriented treatments like MMT (Petzold et al., 2000). Nowadays, many clinicians, psychotherapists and experts in addiction medicine in the U.S. consider that for many patients the main objective of a MMT is abstinence from all non prescribed substances, and not a total abstinence from any substances.

In the early American MMT the inclusion criteria for a treatment with methadone were: a heroin dependence of at least 4 years, the patient had failed in at least two residential treatments, they were aged 21 or older, and had no alcohol or polydrug use. In the *induction phase* patients were hospitalized for six weeks to find the individual adequate methadone dose. In *the maintenance phase* takehome methadone medication were allowed after a stable phase without concomitant heroin use. Urinalysis were performed three times a week. In 1972 the U.S. indication criteria for MMT were revised and less stringent to allow more opioid-dependent persons to have access to these treatments. The actual criteria are: a heroin abuse of 1 year with a physical dependence, aged 18, an initial maximal methadone dose of of 30 mg (the maximum maintenance dose is 120 mg), clinical, medical examination before starting MMT, urinalysis and regular 6-month follow-up interviews. Takehome medications are only allowed for stable patients, without concomitant heroin use, and is only allowed for methadone doses below 100 mg. After the maintenance phase the patient has the possibility to stop the treatment and the methadone dose is gradually decreased until 0 mg. Post-treatment aftercare services are very important due to the high proportion of 82 percent of the patients relapsing to heroin use after one year post-treatment phase (Ball & Ross, 1991).

1.6 The Effectiveness of Methadone Maintenance Treatment

Methadone treatment has been researched for three decades. The most important active ingredient of MMT has been debated in the research community, asking, whether it is simply the provision in a controlled manner of a strong opioid or whether the counseling and the program structure are the most important factors promoting change (Strain et al., 1993).

1.6.1 Randomized Controlled Trials of Treatment Effectiveness

Carrying out rigorous research in the field of addiction is difficult. As a result controlled studies are rare. Only five randomized controlled trials have ever taken place in the 35 years since MMT was introduced (Ward et al., 1992; table 5). All five trials involved small numbers of patients who were rarely followed for longer than one year (Dole et al., 1969; Gunne et al., 1981). Dole and colleagues compared methadone maintenance in New York City in 1969 with a no treatment control and found at 12 month follow up that subjects in the control group were 92 times more likely to be using heroin daily than were those in the methadone group, and they were 53 times more likely to have been incarcerated. The other two RCTs were double blind, placebo controlled studies that compared methadone and a placebo, with support services available to all patients (Newman et al., 1979; Strain et al., 1993; table 5).

Table 5: Randomized Controlled Trials

No. Of groups	Maintenance duration	Number of subjects	Type of subjects	Design	Results	Reference
2	12 months and 12 months post-release	32	Opioid-dependent	Randomized Controlled Trial	Controls were 92 times more likely to use heroin daily, and 52 times more likely to be reincarcerated.	Dole et al. [1969] New York
2	24 months	36	Opioid-dependent	Randomized Controlled Trial, sequential design	Controls were 38 times more likely to use heroin daily, and had a significant higher mortality rate.	Gunne et al. [1981] Sweden
2	32 weeks, 3-year follow-up	100	Opioid-dependent	Randomized Double-blind placebo controlled	Treatment retention: control: 10% methadone: 76%	Newman et al. [1979] Hong Kong
2	45-day	240	Opioid-dependent	Randomized Controlled Trial	Treatment retention: control: 34% methadone: 76% heroin-positive urines: control: 53% methadone: 28%	Vanichseni et al. [1991] Bangkok
2	12 months	301	Opioid-dependent	Randomized Controlled Trial, waiting list	Heroin-positive urines: control: 60% methadone: 29%	Yancovitz et al. [1991] New York

All of these trials found, that methadone maintenance was superior to control conditions on several measures like illicit use of opioids, crime activity, and mortality. Another randomized study compared methadone maintained patients with patients in a gradual methadone withdrawal schedule (Vanichseni et al., 1991; table 5), and one

compared methadone maintenance without support services with controls in a waiting list (Yancovitz et al., 1991; table 5). Both of the studies found a superiority for the patients treated with methadone. “Taken together, the randomized studies of methadone maintenance show consistent positive results over vastly different cultural contexts (United States, Hong Kong, Sweden, Thailand) and over more than two decades of research “ (Farrell et al., 1994, p. 309).

1.6.2 Observational Studies of Treatment Effectiveness

The major observational studies have generally supported the results from the RCTs (Gearing et al., 1974; Hubbard et al., 1989; Simpson & Sells, 1982; Anglin et al., 1984; Ball & Ross, 1991; table 6). Observational studies of treatment effectiveness comprise two major types. „First there are comparative studies in which the outcomes are compared in persons who selected themselves into different treatments (i.e. methadone maintenance, therapeutic communities, drug-free counseling). Secondly, there are pre-post evaluations of treatment in which a group of people entering a single type of treatment are assessed at intake and at some time after treatment, assessing changes in ‘outcome’.” (Ward et al., 1992, p. 22). According to Ward and colleagues the major problem with all observational studies is weather the people receiving different forms of treatment were comparable prior to treatment. The strategy of quasi-experimentation provides a way of making inferences about treatment effectiveness.
Observational studies with some degree of control have surveyed large samples of opioid dependent subjects, enrolled in MMT and have confirmed that methadone maintenance has a major impact on illicit drug use and criminal activity, and that these positive outcomes were related to duration in treatment (Ball & Ross, 1991; Hubbard et al., 1989; Simpson & Sells, 1982; McGlothlin et al., 1981b; table 6). Several studies accumulated evidence that the prescribing of oral methadone is associated with lower rates of HIV infections for patients during treatment (Schoenbaum et al., 1989; Novick et al., 1990) and reductions in risky injecting and needle sharing behaviors (Ball & Ross, 1991; Selwyn et al., 1987; Darke et al., 1990).

Concerning patient characteristics, research found no good criteria as prognostic indicators for successful drug treatment (Hubbard et al., 1989; Simpson & Sells, 1982; McGlothlin et al. 1981a; Joe et al., 1991; table 6). Patients with good psychosocial adjustment before treatment and with good social support are more likely to benefit But patients with poorer psychosocial adjustment included in MMT are important from a public health perspective (HIV infection and hepatitis prevention). In the multicenter study of Ball & Ross (1991), treatment outcome was influenced negatively by a young age at first use of heroin, total years of drug use, and additional cocaine use. But these patient characteristics had less impact on the overall treatment outcome than did program characteristics (i.e. treatment policy, treatment facilities, treatment ‘philosophy’ and location of the MMTP).
The effectiveness of MMT in observational studies of community treatment programs has not been as impressive as that in the RCTs, indicating that half of those who enter treatment leave within 12 months and some of those who stay continue heroin and other illicit drugs. The proportion of continuing illicit drug use varies considerably from one program to another (10% to 56%; table 6). Ball and Ross (1991) found that this variability was may be due to characteristics of the patients and program variables (treatment philosophy, offered services, national policy).

Table 6: Observational Studies

No. Of groups	Study duration	Number of subjects	Design:	Results	Reference
1 program	1964-1971	17'500	Pre-Post study: - MMT	- 1-year retention = 90% - 2-year retention = 80% - 3-year retention = 75% mortality rate was 11 times higher in patients entering detoxification than in the MMT cohort.	Gearing & Schweitzer, 1974
52 programs	12 months	4627 out of 44'000 patients were interviewed	Comparative study: - MMT - Therapeutic Community - Outpatient drug-free - detoxification	- Patients from MMT, Ther. Communities or outpatient drug free had better outcomes than those from detoxification. - Improvement correlated with duration in treatment	Simpson & Sells, 1982 DARP* USA
41 programs	Every 3-month interviews	11'000	Comparative study: - MMT - Therapeutic Community - Outpatient drug-free	Retention in treatment: - MMT = 65% - Ther. Community = 44% - Outpatient drug-free = 40% - Improvement in the 3 groups correlated with duration in treatment	Hubbard et al., 1984 and 1989 TOPS** USA
3 programs	4-year and 8-year follow-up	439	- MMT - Therapeutic Community - active users	After leaving MMT, 54 % relapsed to heroin use and 70% were arrested	Anglin & McGlothlin, 1984 California
6 programs	1-year follow-up	633	- MMT	- 71% did not inject anymore. - Concomitant drug use in MMT varied from 10% to 56%. - Significant decrease of crime days - In the drop-out cohort, 68% relapsed to heroin use.	Ball & Ross, 1991 USA

*DARP (Drug Abuse Reporting Program)
**TOPS (Treatment Outcome Prospective Study)

1.6.3 Risks of Methadone Maintenance Treatments

Although clear benefits have been shown from MMT, there are risks to the individual and the community that need to be kept to a minimum through control of the administration of methadone. When adequate control measures are not used, patients may ingest more than their prescribed dosage, household members may accidentally drink the patients' methadone, and methadone may be sold or given to persons who are non-opioid-tolerant (Perret et al., 2000). A lethal oral dose is thought to be in excess of 40-60 mg in non-opioid-tolerant people. These risk factors can be controlled by prescribing initial doses of 10-40 mg in the induction phase of MMT and by giving take-home doses only to patients with a good response to treatment. Furthermore take-home doses should be stored in child-proof containers. Deaths associated with accidental methadone poisoning were reported, and the authors highlighted the importance of supervised dosing to prevent methadone-related deaths especially in the induction phase (Neeleman et al., 1997; Williamson et al., 1997).

1.6.4 Components of Effective Methadone Maintenance Treatments

In RCTs' a consistant relation between higher doses of methadone (>50 mg), less illicit opioid use, and higher retention rates in treatment was reported (Strain et al., 1993; Goldstein et al., 1973; Johnson et al., 1992). Observational studies showed, that the more effective clinics (in achieving significant reduction in heroin use) were characterized by prescribing adequate doses of methadone (50-120 mg per day) with a flexible dosing policy, and having a treatment goal of ongoing successful maintenance rather than abstinence (Ball & Ross, 1991; Payte et al., 1993; Eap et al., 2000; McGlothlin et al., 1981a; Joe et al., 1991; Caplehorn et al., 1994) (table 7). Furthermore, clinics with a better quality of medical and counseling services, better staff-patient relationships, low staff turnover rates, and better management were more effective (Ball & Ross, 1991).
Considering the facts that opioid dependence is a chronic relapsing disorder, several reports from clinicians suggest that abstinence from any substance (including methadone), may not be an appropriate treatment goal for many patients (c.f. Ball & Ross, 1991). There is also clear evidence that longer stays in treatment are associated with better overall outcomes (Dole & Joseph, 1978; Hubbard et al., 1989; Simpson & Sells, 1982; Ball & Ross, 1991). The reason for ending treatment is also highly predictive. Patients who end treatment with staff approval are doing much better than those who leave for other reasons (Des Jarlais et al., 1981; Dole & Joseph, 1978; Simpson et al., 1982). As outlined before, relapse rates are extremely high (70%-80%) for methadone patients once they left treatment (Anglin et al., 1984; Des Jarlais et al., 1981; Dole & Joseph, 1978; Ball & Ross, 1991; Magura & Rosenblum, 2001) but not higher than after drug-free residential treatments (Maddux et al., 1992).
In many MMT, urinalyses are used to monitor patients' illicit drug use and to ensure that they are taking their prescribed methadone. Observational studies showed, that the the monitoring itself does not reliably reduce illicit drug use (Havassy et al., 1981; Stitzer et al., 1993). To reward reductions in concomitant drug use with privileges, such as take-home methadone doses, has been shown to be effective. On the other hand, there is no evidence that the loss of privileges has an effect on concomitant drug use.

Table 7: Components of Effective Methadone Treatments

• Flexible but adequate dose of methadone after stabilization (usual range 50-150 mg)
• Adequate duration of treatment
• Goal of maintenance
• Rapid client-centered assessment and induction
• Psychosocial services to deal with social disadvantage and psychiatric comorbidity
• Trained staff with positive attitudes towards MMT and opioid-dependent patients
• Affordable cost of treatment
• Engagement with clients rather than punishment of continuing illicit drug use

Adapted from Ward *et al.,* 1999, p. 223

1.6.5 Predictors in Methadone Maintenance

Previous studies have looked at predictors of retention in treatment, but the findings are inconsistent (Simpson & Sells, 1982; Ball & Ross, 1991; McCaughrin & Price, 1992; Magura et al., 1998). Part of the reason is that most prior studies have focussed on "fixed", pretreatment variables, with little or no inclusion of "dynamic", intreatment variables that capture treatment processes (Fig. 4). Magura et al. (1998) demonstrated in a sample of 1206 admissions to MMT that intreatment variables are better predictors of retention than pretreatment variables. Only two of 16 pretreatment variables (age, involved with criminal justice), compared with five of six intreatment variables (adequate methadone dose, individualized interventions, cooperation, continued heroin and/or cocaine use) had significant effects on retention. These results suggest that events during treatment are crucial for patient retention.

1.6.6 Ancillary Interventions

The traditional role of counseling in MMT as delivered in specialized clinics in the USA has been case-management and crisis assistance to help patients resolve difficulties associated with their opioid dependence. Comorbid psychiatric disorders are not usually dealt with by counselors in such clinics (Mattick et al., 1998). When MMT is managed by a general practitioner (like in the UK, Switzerland, the Netherlands), the general practitioner usually provides this routine counseling or referrers the patient on to appropriate services for other areas (e.g. financial, employment, parenting, legal, accommodation).
There has been considerable debate over the role of counseling in maintenance substitution programs and the association between amount, quality of medical services, counseling and treatment outcome is not clear (Ball & Ross, 1991; Joe et al., 1991; McLellan et al., 1988, 1993). The model of MMT that has been effective in most studies has usually been clinic-based, and has included counseling, even though MMT without formal counseling has becoming increasingly common throughout the world (e.g. UK, Australia, the Netherlands, Switzerland, and Spain) but has "not been formally evaluated in Europe" (Farrell et al., 1994, p. 999). Recent studies with randomized designs have failed to show consistently that the provision of additional services, including counseling, achieve better outcomes than MMT without counseling (Mattick et al., 1998). Intensive services seems to render treatment more expensive with only marginal improvements in effectiveness (Kraft et al., 1997).

Nevertheless, the following findings remain important for clinical practice. The early practitioners of MMT argued that most patients' problems resulted from the heroin-seeking habits and their low socio-economic status (Dole & Nyswander, 1967; Newman et al., 1979) and highlighted the importance of developing an empathic alliance between the specialist respectively the general practitioner and the patient.
In 1991 Ball & Ross for the first time provided a detailed summary of what counselors actually do on a day-to-day basis in MMP, and how those services affect their patients. They found that the principal activities of a counselor can be described by 10 categories: Case management; liaising with other social services; assessing new admissions; one-to-one counseling; brief contacts; group therapy; family couples therapy; assessment of psychological problems; vocational counseling and

education. Most surveyed MMP/ clinics had regular (on average fortnightly) one-to-one counseling sessions with an average duration of 37 minutes.
The Treatment Outcome Prospective Study (TOPS; Hubbard et al., 1989) has also provided some information on counseling services delivered in 17 methadone maintenance units, and also the national survey of Calsyn and colleagues (1990). In these surveys 50 to 67 percent of the persons employed at MMT were counselors (one third of them were ex-addicts). Furthermore they reported 78 percent of the patients receiving mostly individual counseling, and only 7 percent receiving group therapy. Group sessions tended to be topic-oriented rather than generally therapeutic. Only the observational study of Joe et al. (1991) found an increase in retention (13%) as measured as survival rate for more intense psychological services.
In other countries (e.g. Australia, UK, Switzerland) the professionals most commonly employed in MMT are physicians and nurses. And in the mid eighties, with the spread of HIV, a lot of physicians in primary care enhanced their engagement for opioid-dependent patients. In Switzerland, according to the *National Treatment Guidelines* of the Federal Office of Public Health, such services should be available for patients who need them, either at the clinic or by referral, and carried out by qualified psychiatrists, psychologists and social workers (Bundesamt für Gesundheit, *Methadonbericht*, 1995).
Taken together, the evidence from methadone treatment studies suggests that counseling should be available to all patients, and tailored to patients' needs. All ancillary services should be offered on the basis of the patient freely consenting. One possibility to help professionals to decide if the patient need additional counseling is the semi-structured interview "Addiction Severity Index" (ASI) as developed by McLellan and colleagues (1980). This interview is widely used in the United States and in Europe.

1.6.7 Psychotherapy in Methadone Maintenance Treatment

Counseling approaches and psychotherapy, such as motivational interviewing (Miller & Tonigan, 1996), relapse prevention programs (Marlatt & Gordon, 1985) and social skills training (Myers & Smith, 1995; Monti et al., 1989), which are based on cognitive behavioral therapies, are frequently used in MMT and found to be effective. More intensive psychotherapy like the Interpersonal Therapy (Rounsaville et al., 1983) can be beneficial to people with concomitant affective disorders (e.g. depression, anxiety). Recent Behavioral Therapies combine these methods (e.g. *Relapse Prevention & Contingency Management* [RP & CM]) or develop new therapeutic interventions for specific patient populations (e.g. *Dual Diagnosis Relapse Prevention* (DDRP). A recent study compared *Motivational Enhancement Therapy* (MET) and *Drug Counseling* (DC) in methadone patients with a high versus a lower dose of methadone (Woody & McLellan, 2002). No clear advantage was seen for MET as compared to DC, but a better outcome for patients with higher methadone doses (Woody & McLellan, 2002; Carroll et al., 1994). Most of these psychotherapies are based on two important theoretical assumptions: the *behavioral change model* of Prochaska & DiClemente (1992), and a continuous, long-term treatment of opioid-dependent individuals (Petzold et al., 2000).

1.6.8 Methadone Maintenance in General Practice

Although rapid expansion of methadone programs has occurred in many countries (e.g. Spain, Switzerland, Australia, The Netherlands, UK), there are few studies on the impact of office-based treatment on treatment success. On the other hand there have been repeated calls from experts and clinicians for expansion of availability of methadone maintenance in several countries (United States, Germany, France, Sweden). These countries want to expand MMT to treatment providers in primary care settings like general practices (Weinrich et al., 2000; Lewis et al., 1999). Moreover, this would be a more efficient and less expensive way of delivering treatment, than in specialized clinics. Furthermore, this way could be more attractive to patients than the current models. “One alternative is to have general practitioners as prescribers and community pharmacies as dispensers of methadone, as in the UK, the Netherlands, in Spain and in some regions in Switzerland. However, new models for delivering MMT must be “properly assessed to ensure that the demonstrated effectiveness of the traditional treatment model is retained” (Farrell et al., 1994, p. 1000).

Until now, only one Randomized Controlled Trial exists, comparing methadone maintenance patients in primary care (n = 22) versus in specialized clinics (n = 24) (Fiellin et al., 2001). Results indicate no differences between groups concerning illicit heroin use or use on health or social services. Patients in primary care were significantly more satisfied with their treatment compared to patients in clinic.

Observational studies of patients receiving prescriptions in general practice have shown that they value care in general practice (Leaver et al., 1992; Speed et al., 2000). As Lewis states, “potentially primary care can allow easy access, holistic care for all medical problems, building of long term relationships, and avoidance of the stigma attached to attendance at drug clinics” (1999, p. 7).

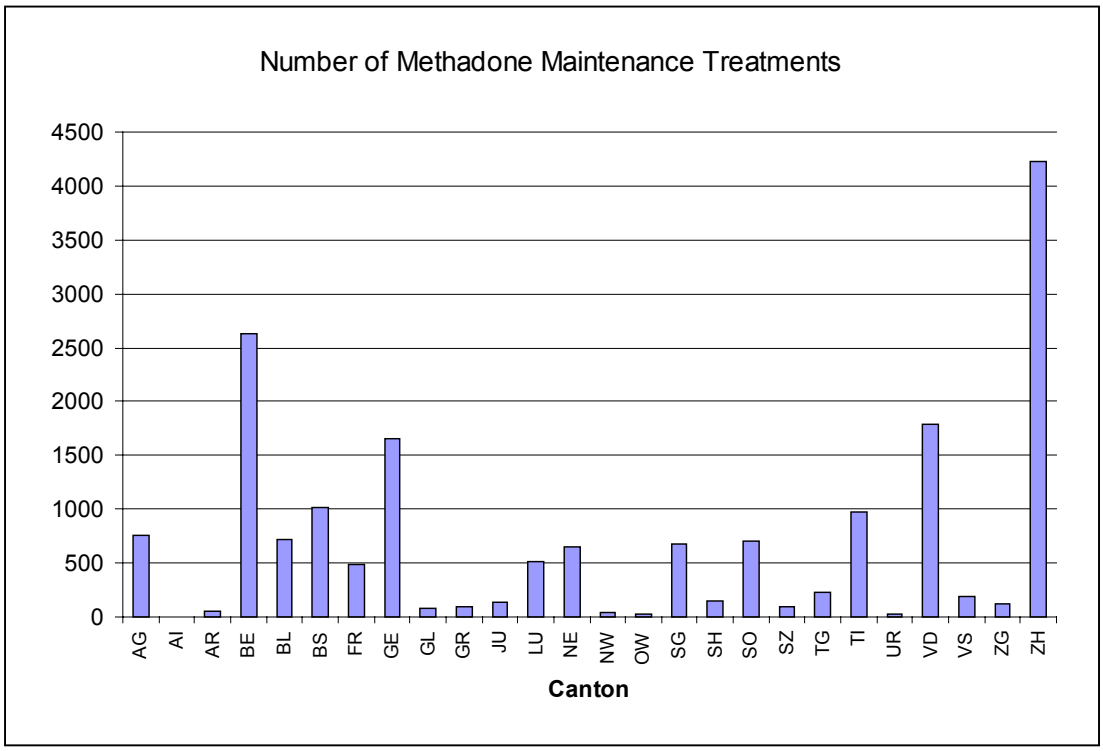
On the other hand, the provision of MMT in specialized drug clinics can show some advantages for the drug users: First, the greater experience of the doctors and secondly, they have more time available (Glanz, 1986), thirdly, they have specialists for the treatment of psychiatric comorbidities (affective disorders, psychosis, anamnestic attention deficit syndrome, and personality disorders) and somatic comorbidities (hepatitis, HIV, liver disease).

One British survey indicated, that most general practitioners felt “inadequately trained to prescribe methadone”, but would be encouraged to be involved in treatment if there were “better support from specialist services existed” (Davies & Huxley, 1997, p. 1173). A *National Treatment Outcome Research Study* (NTORS) in the UK recently compared six month treatment outcomes for patients receiving methadone maintenance either in a specialist clinic or general practice (Gossop et al., 1999). The two different settings showed comparable results, and patients were similar in age, sex, length of dependence, injecting habit, other drug use, and previous treatment attempts. Another study compared patients’ characteristics and treatment outcomes in primary (n = 89) or secondary care settings (n = 36) in a retrospective review of patient records. Patient characteristics were similar at the start of the treatment, and the proportion of patients with good outcomes were equally in either setting (Lewis et al., 2001). Langendam and colleagues (1998) compared 7 different methadone dispensing sites in a large cohort study (n = 444) in Amsterdam and found lower methadone dosages for patients treated by the general practitioners. Taken together, there are only a few observational studies and one RCT comparing MMT in primary care with MMT in specialist clinic settings.

1.7 Methadone Maintenance Treatments in Switzerland

In Switzerland, opioid addiction constitutes a major public health problem. Federal drug treatment policy in Switzerland consists of four pillars: harm reduction, therapy, prevention and repression (Bundesamt für Gesundheit, 1999; Klingemann, 1996). The organization and regulation of MMT varies widely from one canton to another and there are no explicit federal treatment guidelines for MMT to date. In contrast, countries like Australia and the United States have high levels of regulation and structured programs (Farrell et al., 1994; Parrino 1993). Some 30'000 persons are dependent on heroin and/or cocaine. Yearly, some 100 intravenous drug users die from AIDS, and another 200 die from other causes (suicide, incidents, liver disease, heroin overdoses, and intoxication from polydrug use) (compare figure 1). In the countries of the European Union (EU), approximately 1 to 1.5 million persons are dependent on opioids (Vader et al., 2002). In the EU 300'000 opioid dependent patients are actually in a MMT (Reisinger, 1997). In Switzerland, more than 60% of opioid addicts are engaged in some kind of addiction treatment: 2100 patients in inpatient abstinence-oriented community-based treatments, more than 15'000 patients in MMTs, and more than 1000 in medical prescriptions of narcotics [heroin] (Bundesamt für Gesundheit, 1999). Thus, considering the overall spectrum of all available treatments for opioid dependence in Switzerland, MMT play an important role (Hermann, 2001). The first MMTP started in the late 70ties in Geneva, Basel and Zurich. The number of MMTs in each canton are displayed in figure 2. 25 out of 26 cantons provide MMT places for opioid dependent subjects. Overall a total of 18'000 MMT treatment places*, thus 250 MMT places for 100'000 inhabitants. In Basel, the ratio is high, with 588 available MMT places for 100'000 inhabitants.

Figure 2: Results from the Swiss National Methadone Statistics



Adapted from: *act-info*, "Nationale Substitutionsstatistik für das Jahr 2000", Bundesamt für Gesundheit, Bern, 2000. The number of 18'000 MMT places corresponds to a total of approximately 15'000 patients.

1.7.1 Review of the Swiss Literature on MMT from 1995 to 2004

The review of the Swiss literature since 1995 by Rehm and colleagues (2001), included all published articles (controlled trials, reports from health authorities, and clinics) on MMT in Switzerland. Articles about detoxification with methadone were excluded. Only reports about methadone maintenance were included in the review, with particular interest to its effectiveness and cost-effectiveness in different clinical settings: general practitioners, psychiatric clinics and hospitals, counseling agencies, low threshold institution, and prisons. The review indicates that although the results of most studies favour methadone substitution treatments, they are often plagued by problematic methodological pitfalls, in particular, lack of an adequate control group. There are two exceptions, the study of Petitjean at al. (2001), and Ladewig et al. (1998). The review summarizes which indication criteria were used in the studies, which dosage schedules, insisting that studies with higher methadone doses appear to have better success rates than those with lower doses (Liechti et al., 2000). The report concludes with a recommendation for more high quality studies on effectiveness and cost-effectiveness on the global system level of MMT, for a re-examination of dosage schedules (in particular in relation to individual differences in methadone metabolism), consideration of psychiatric co-morbidities, and finally a better differentiation between indication criteria for substitution treatment and abstinence-oriented treatment. An additional literature review on Swiss MMT from 2001 to 2004 revealed two important reports, indicating better treatment retention in patients treated in general practice versus patients treated in specialized clinics (Petitjean & Schaller, 2002[b]; Falcato et al., 2002).

1.7.2 Review of International Literature on MMT from 1995 to 2004

The international literature review by van Beusekom and colleagues (2001) analyzed guidelines for methadone maintenance treatment from 17 different countries (except Switzerland), examining elements as admission criteria to MMT; initial, maximal and allowable take-home doses; and treatment services. The report concludes, that important advances have been done in the last 5 years, in particular concerning the pharmacokinetics of methadone (Eap et al., 1996; 2000). Some patients need higher methadone doses due to lower plasma concentrations. Furthermore, previous study results about the effectiveness of MMT have been confirmed in several studies, in particular studies indicating the effectiveness of higher methadone doses. Separate report sections outlines the needs of specific patient subgroups: patients with HIV-infection, hepatitis or tuberculosis, polydrug users, pregnant opioid dependent women. Furthermore the need for psychosocial treatment and other motivational interventions, and recommendations for treatment guidelines development. The guidelines are summarized according to the main phases of methadone treatment (initiation, maintenance and cessation of treatment). An additional international literature review on office-based MMT from 2001 to 2003 revealed two important studies, indicating good treatment outcomes for stable patients treated in general practice versus patients treated in specialized clinics (Gossop et al., 2003; Fiellin et al., 2002). A major purpose of researchers in the addiction field in the United States is, to develop office-based pharmacotherapies for opioid dependence (Fiellin & Barthwell, 2003).
Before starting the present study, a complete review of the literature was performed in May 2002 (MEDLINE, Cochrane Review), and main reports of the existing Swiss

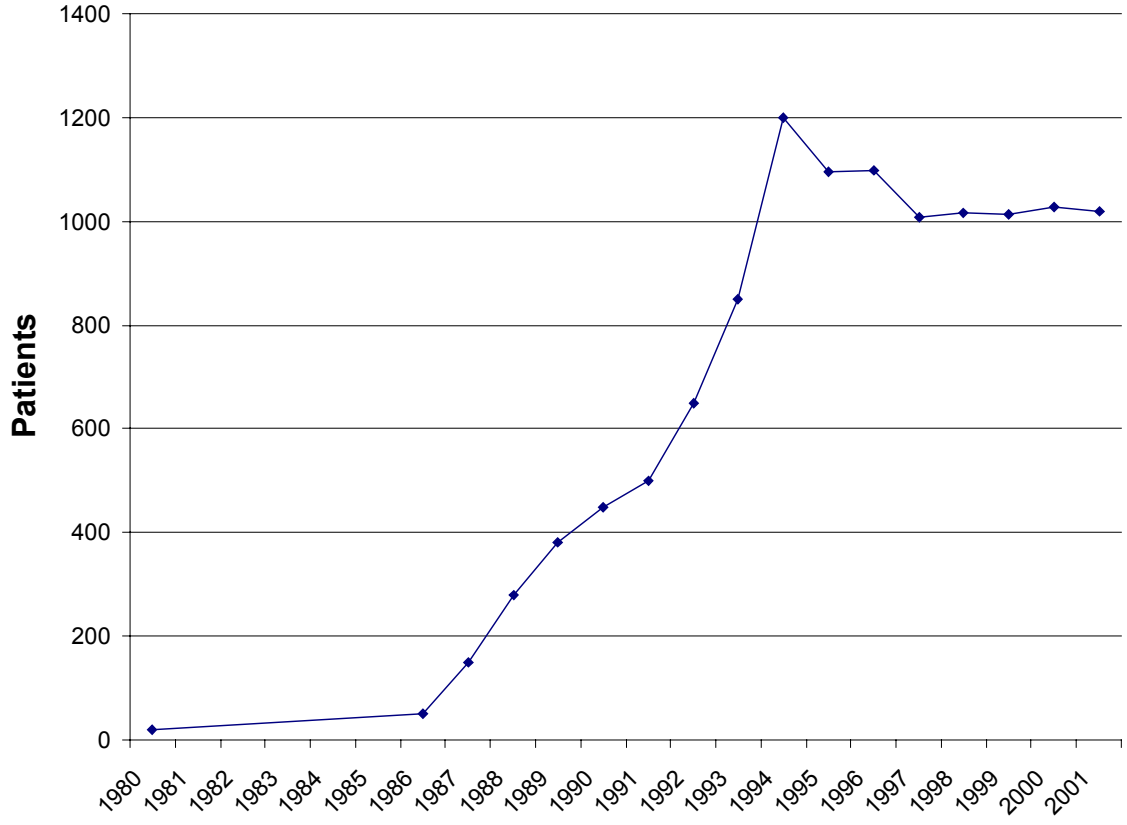
literature (Rehm et al., 2001; Van Beusekom et al., 2001; Hermann, 2001) were reviewed. An additional review of the literature was performed in May 2004.

1.8 Methadone Maintenance Treatments in the City of Basel

In Basel, a city of 188'000 inhabitants, opioid addiction began to be recognized as a health problem during the 1970s. 1976 the first methadone maintenance treatment programs (MMTP) were developed, based on the work of Dole, Nyswander and Kreek in New York (1966). Another small treatment program with codeine was also developed. The first MMTP were mainly carried out in specialized addiction treatment units in psychiatric clinics. Some engaged general practitioners treated also a few patients from the beginning. In Switzerland the prescription of oral methadone to patients dependent on opioids is regulated by federal laws since 1975. Only physicians holding a special permission may prescribe methadone. Generally, methadone maintenance is provided for patients aged 18 years or older who are not willing to undergo abstinence oriented treatments and incorporates individualized medical, psychological and counseling services. The most widely accepted objectives of methadone maintenance are: to reduce harmful opioid and other drug use, to improve the health of clients, to help reduce the spread of blood-borne diseases, to reduce deaths associated with opioid use, to reduce crime associated with drug use, and finally to facilitate an improvement in social functioning.
However, as a general treatment philosophy methadone programs in Basel favored long-term methadone maintenance, but always with the objective of abstinence. Patients' names are reported to the local authorities and treatment performance to specialized evaluation agencies. As a rule, since the mid nineties, there are no restrictions regarding dosing and treatment duration, but general methadone maintenance treatment guidelines (Stohler et al., 1995). Methadone treatments are paid for by health insurance. Nursing staff or pharmacist administer the medically prescribed dose of oral methadone daily on-site. After an induction period, maintenance methadone doses can be delivered as take-home doses. The methadone administered is a 2 percent methadonehydrochlorid solution (Racemat®). Methadone tapering procedures can be carried out in an inpatient unit or as an outpatient detoxification. Dose increases and decreases are decided on the doctor-patient level. Subjects receive medical examination and individualized psycho-social counseling. In the city of Basel, maintenance prescribing has always followed, from the beginning, a model of shared care. Maintenance prescribing and detoxification interventions are undertaken in a planned manner in collaboration with the patient and other parties, such as a general practitioner liaison physician, as appropriate. Shared care arrangements are important if the patients treated in primary care need psychiatric, somatic interventions in clinic or if the general practitioner is absent from his office.
The health authorities, the police and experts in addiction estimate that approximately 2000 drug users live in Basel. Since the late 1980s, with the advent of the AIDS epidemic in Switzerland, risk reduction and needle exchange programs and also an easier access to MMTP became available. The inclusion criteria respectively indication criteria for a MMT are nowadays, an opioid dependence according to DSM-IV (APA, 1994), aged 18 or older. The number of patients in methadone treatment has more than doubled since 1990, rising from 500 to 1019 in 2000 (Petitjean et al., 2000; Fig. 3).

Figure 3 shows an increase of MMT in Basel, from 1986 to 1994 parallel to the advent of the AIDS epidemic. The consequence of AIDS was an easier access to methadone programs. Since 1997, the MMT are stabilized at an average of 1000 patients.

Figure 3: Number of Patients in MMT in Basel between 1980 and 2001



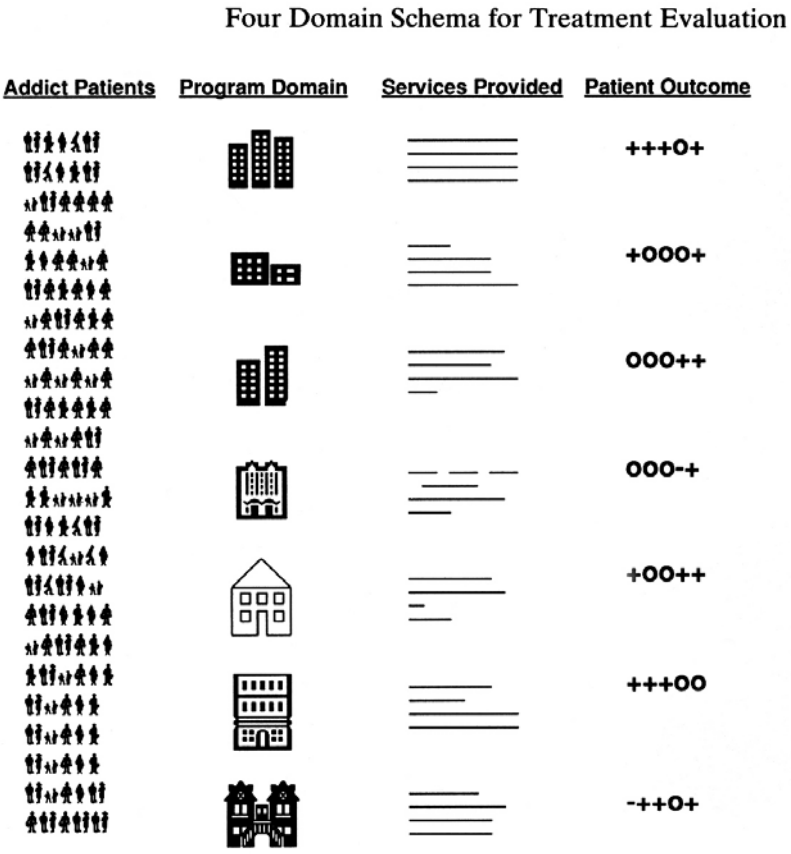
Adapted from: Petitjean et al., 2000

1.9 Treatment Outcome Evaluation of Methadone Maintained Patients in Basel

In contrast to the United States, where large-scale studies (e.g. TOPS [*Treatment Outcome Prospective Study*; Hubbard et al., 1989], Ball & Ross, 1991; DATOS [Drug Abuse Treatment Outcome Studies; Grella et al., 1999]) focus on long-term MMT outcomes, MMT in Switzerland has received no formal multi-site evaluation to date. Nevertheless, the idea of a Swiss multi-site MMT evaluation was developed in the early 1990s, and several expert panels have been organized, sponsored by the Federal Office of Public Health (FOPH) in Berne. The consensus of these meetings was the development of a nationwide standardized questionnaire, which was utilized by four cantons (Basel, Zurich, Geneva, and Tessin) in the last 10 years, and continuously adapted, making comparisons difficult. In the last decade, several reports have been published by the health authorities and addiction research units in Geneva (Petitjean & Schaller, 2002 [b]), Zurich (Falcato et al., 2002), Tessin (Cerutti & Cassis, 2004), and Basel (von Bardeleben et al., 1993; Petitjean et al., 2000 and 2002 [a]). Actually an expert panel from the Swiss FOPH tries to develop a multi-site MMT evaluation. This work is still going on (Vader et al., 2002).

In 1992 Ladewig and colleagues started to analyze the MMT at the two specialized clinics, the psychiatric university hospital and the psychiatric university policlinic in Basel, by sending a standardized questionnaire to the physicians. At that time, the general practitioners were not included in the data collection. But with the growing number of MMTs, the health authorities and research groups decided to include all patients registered in a MMT in Basel in a survey. Like the *National Treatment Outcome Research Study* (NTORS) in the UK, outcomes of patients treated in specialized drug clinics and in general practices (Gossop et al., 1999; 2003) were analyzed by face-to-face interviews.
To understand the complexity of treatment evaluation it is very helpful to look at the model of Ball & Ross (Fig. 4; 1991).

Figure 4: Four Domain for Treatment Evaluation (Ball & Ross, 1991)



Four domains in the evaluation of treatment.

From: Ball J.C.& Ross A. (1991).
Legend: In the present “four domain schema”, the first domain represents the heterogeneity of the patients [1], the second domain the treatment location/ facilities [2], the third domain the services provided [3], and the forth domain the treatment outcomes [4]. Thus, the outcomes can be understand as a combination and interdependence of the domains [1], [2], and [3].

Methadone maintenance treatment programs or general practices treat different subgroups of patients, these patients are treated in different settings, obtain different services (e.g. medical, psychological, counseling), and the patients at each treatment facility can have different outcomes. The question remains, which factors account in which proportion for a “good” or a “bad” treatment outcome? And how can we measure that ? This conceptual model was very important for the development of the research question and the interpretation of the results of the present study.

2. Methods

2.1 Research Question

The present study reports the outcomes of patients who received methadone treatment in either a specialized clinic or in a general practice setting. The overall objective was less to show *that* methadone treatment works, but more for what it tells us about *how* it works. We explored the major factors related to treatment outcomes. The specific research questions were: length of stay in treatment, one-year retention in treatment, concomitant drug use in the past 30 days, intravenous drug use in the past six months, average values of prescribed methadone doses, the amount of offered and attended consultations, HIV seroprevalence rates, hepatitis rates, and HIV risk behavior. These specific research questions were first analyzed for the total sample at two time points, and secondly by comparing patients treated in general practice versus in specialized outpatient clinics.

2.2 Hypotheses

For answering the main research questions, the following hypotheses were developed for the total sample:

A1) Data Analysis of the Total Sample (n = 660): Overall Outcome
H0: Does methadone maintenance as a general modality work in daily clinical practice? The objective is to demonstrate the clinical significance and the stability of treatment outcomes (retention, concomitant drug use) over time by a one-year follow-up.

A2) Data Analysis of the Total Sample (n = 660): Frequency of Consultations
H1: Patients attending more consultations have a better retention in treatment, and less illicit drug use.
H0: there is no association between the amount of attended consultations and retention in treatment; there is no association between the amount of attended consultations and illicit drug use.

A3) Data Analysis of the Total Sample (n = 660): Compliance
H1: Patients with a “good cooperation” [GC] (compliant patients) have a better social functioning, less concomitant drug use, less intravenous drug use, a lower rate of multiple substance use, and a lower rate of dual diagnosis than those with an “unsatisfactory cooperation” [UC] (non-compliant patients).
H0: There is no association between patient characteristics, patient behavior and compliance.

Definition:
[GC] = patients attending all scheduled consultations, or missed only one out of all scheduled consultations.
[UC] = patients missing more than one scheduled consultation.

The following hypotheses were developed for the comparison between patients treated in specialized clinics versus patients treated by general practitioners:

B1) Comparison Between Patients in General Practice and in Specialist Clinic Settings: Overall Outcome
H1: patients in general practice have better outcomes (retention, concomitant drug use) than those treated in specialized clinics.
H0: patients outcomes in general practice are as good or worse than those treated in specialized clinics.

B2) Comparison Between Patients in General Practice and in Specializist Clinic Settings: Consultations
H1: Patients in general practice attend more consultations than those in specialized clinics.
H0: Patients' compliance in general practice is as good or worse than in specialized clinics for the main outcome variable, number of attended scheduled consultations.

2.3 Treatment Programs

The present study is a prospective cohort study of patients recruited from all MMT programs in the City of Basel. The clinic sample was drawn from two state methadone clinics, and one private clinic. The GP sample from 120 GP practices. Two out of three specialist multimodal MMT centers are located in inner-city, one center is located at the border. The GP practices are located over the whole city. In the shared care system (chapter 1.8), two thirds of the general practitioners take responsibility for the prescription of methadone, provide medical care and consultations as required, and allow their patients to take the methadone on site in a authorized pharmacy. One third of the GP sample dispense methadone in their practice. The specialized clinics were providing MMT to much larger number of opiate dependent patients, including methadone prescription, dispensing and providing medical, psychological, and social services. The MMT programs were purposely (not randomly) chosen for participation.
There were no differences between GPs and clinics in the dispensing of methadone. Daily dispensing was as frequent among the GP agencies (21.5%) than for the clinics (20.9%).

2.4 Study Population

The present study sample comprised 660 patients, of whom 460 patients received methadone treatment from specialist drug clinics and 200 from GPs. This sample was constructed in the following ways. An initial sample of 815 patients was recruited from the clinic and GP programs in March 2000. Patient inclusion criteria for the prospective cohort study were: men and women, aged 18 or older, fulfilled DSM-IV criteria for heroin dependence (304.02: APA, 1994), maintenance with oral methadone, registered in a MMT for at least three months, inhabitant of the Canton Basel. The exclusion criteria were: patients with another maintenance medication than methadone (e.g. buprenorphine, morphine, codeine, naloxone), patients with less than 1 mg/d of prescribed methadone, patient with an incomplete questionnaire

(missing values like patient code, age, gender, dispensing site). Each client completed and signed a consent form to allow participation in the study. Relevant Human Research Ethics Committees approved the cohort study retrospectively (Ethikkommission beider Basel, 18.8.2003, see Appendix).
From the patients eligible for the 1-year follow-up study, a stratified random sampling procedure was used to include approximately the same percentages within the treatment modalities (SPSS sampling procedure). A total sample of six hundred and sixty patients was selected (table 8). The proportion of evaluable subjects did not differ significantly among treatment modalities: 83% from the GP sample, and 80% from the clinic sample (chi square = .894, df = 1, p = 0.199). Evaluable subjects were significantly older than the non-evaluable subjects (33.7 vs. 32.3 years; ANOVA; $F_{(1,814)} = 5.527$, d = 1, $P = 0.019$), but otherwise did not differ in any baseline subject characteristics (e.g. age, gender) [data not shown]. The first survey consisted of 660 outpatients with 641 patients in the in-treatment cohort and 19 in the admission cohort. At 12-month follow-up, 486 patients (73.6% of the 660 patients from the first survey) were successfully interviewed in March 2001 (table 9). The study sample (n = 660) was of sufficient size to give good accuracy in statistical analysis, and the follow-up interviews provided information about the stability of the MMT.

Table 8: Design of Data Collection for One Year

Patients at the three programs and the GPs				**Outcome for patients**
- review of patient register - census of patients (31.3.2000) Participants: 3 specialized clinics and 70 GPs - return of anonymous data to the research group	**First survey (t1)** - **660 patients*** - A sample of 60 or more at each program - Instrument: Standardized questionnaire		**Second survey (t2)** - **486 patients** - Still in treatment (486) - Drop-outs (171)	Change t1 to t2 - Drop-outs - Illicit drug use - IV drug use - Number of offered and attended consultations - Methadone doses - Other characteristics
- return of census findings to programs and GPs				

*(A) in-treatment cohort n = 641
(B) admission cohort n = 19; inclusion criteria, at least 3 months in MMT.

2.5 Measures and Procedures

Data were collected by structured face-to-face interviews at baseline and at one-year follow-up. The data collection procedures included confidential face-to-face interviews with a standardized questionnaire (see Appendix), and compilation of required data from case register records. The collected data were deemed confidential, and the results were not made available to either the treatment or the administrative staff of the respective program or general practice. Data was only available for the research group (a physician, a clinical psychologist). Anonymous data was kept in the Addiction Research Unit of the Psychiatric University Hospital in Basel.

The questionnaire contained items and scales developed specifically for this project, as well as measures adapted from published instruments. Subjects were interviewed by the physician responsible for the treatment at the specialized clinic or at the GP practice. Thus, the interviews were carried out in the natural visit/consultation context. If the subject did not reach the appointment, the physician filled out the questionnaire by examining the case report. The interview consisted of two pages of questions (see appendix) and provided measures of social and demographic variables, a section concerning actual methadone treatment variables, a section about consultations in the past 6 months, a section about lifetime illicit drug use and in the past 30 days (heroin, cocaine, alcohol, non-prescribed benzodiazepines) adapted from the *Addiction Severity Index* (McLellan et al., 1980), a section about hepatite serostatus, and a section about health risk behavior. Self-reports about illicit drug use should ideally be corroborated by urinalysis or other means where there is reason to believe that self-reports are biased in a way that undermines reported findings. There is no social pressure to lie and we can be confident, that the results about concomitant drug use are quasi objective. Additionally there were no financial resources available for using urine screening in the total sample.
Time in treatment was assessed in terms of number of years for which the patients remained in contact with treatment providers. These data were obtained directly from the treatment programs, as well as the reasons for leaving MMT. Measures of counseling sessions attended were obtained during interviews conducted with patients at baseline and at one-year follow-up.

2.6 Statistical Analyses

According to Bortz (1999), the proportion of missed variables had not to exceed 40 percent. Following this assumption, all assessed variables could be included. Student's *t*-test was used for continuous variables and the chi-square-test for categorical variables. Baseline/ follow-up comparisons for patients are presented using paired data sets. Changes for categorical dare are assessed with the McNemar test. A repeated measure analysis of variance was carried out on outcome measures. Time in treatment was assessed by Kaplan Meier survival analysis. Differences between the two groups were measured by a log rank test. Unless otherwise stated, all tests were two-tailed, and an α level of 0.05 was considered significant.
Cox regression procedures were used to compare retention times controlling for baseline differences between the two populations (age, length in treatment). To analyze self-reported drug use in the past 30 days prior interview, a missing information from patients who dropped out of the study before the end were considered as positive. Data analysis were first conducted on the 660 enrolled patients (intent-to-treat analysis [ITT-analysis]; all observed cases), and separately for 486 of the original 660 patients who completed the one-year follow-up (completer analysis).
For treatment x time effects, data were analyzed according to a two-factor repeated measures analysis of variance (ANOVA). Levene's test of equality of variance showed that ANOVA assumptions had not been violated for any factor except for 'self-reported cocaine use in the past 30 days'. All statistical analyses were performed using SPSS statistical software, version 11.

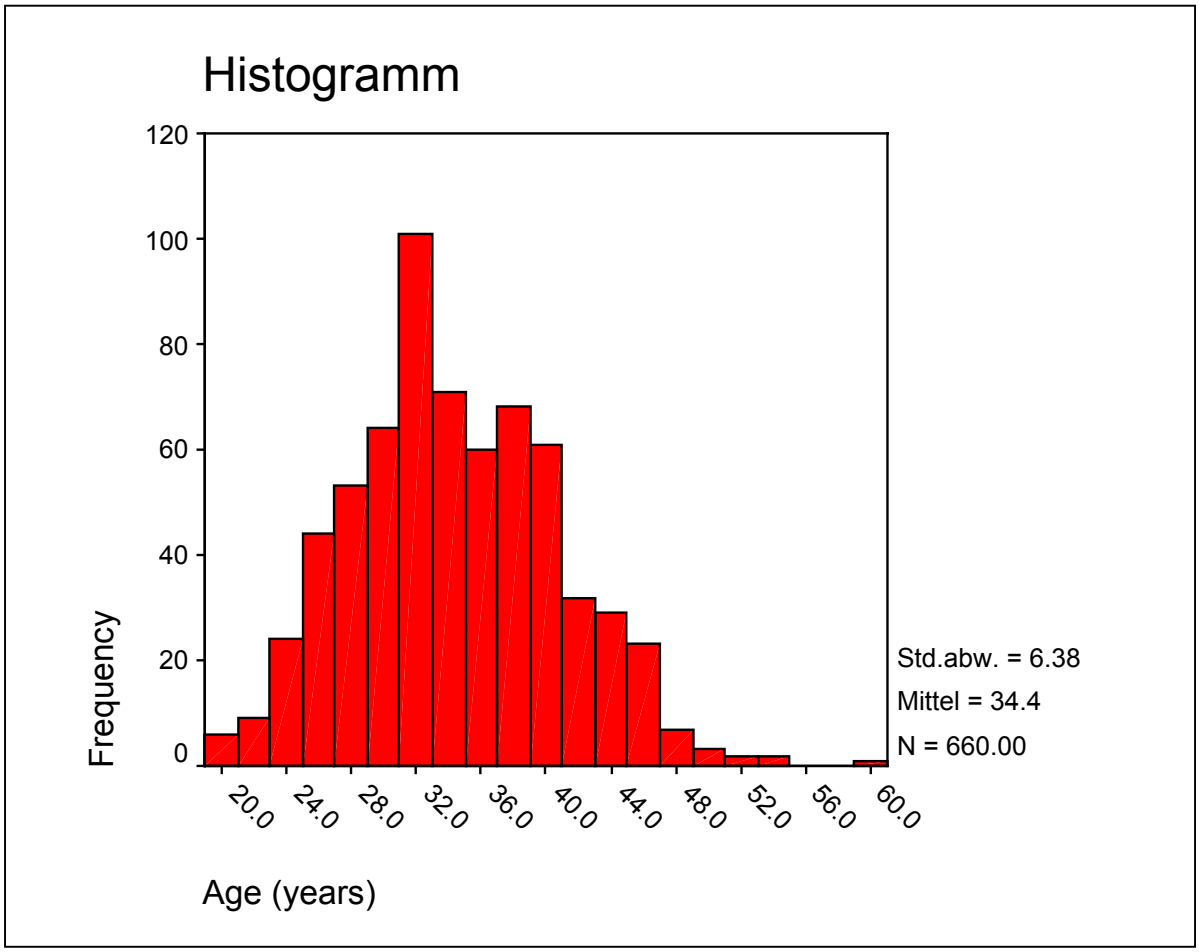
3. RESULTS

3.1 TREATMENT OUTCOMES OF THE TOTAL SAMPLE

3.1.1 Sociodemographic Characteristics of 660 Methadone Maintenance Patients

Of the six hundred and sixty patients, 19 were in the *admission sample* (up to 0.49 years), 227 were in the *average stay sample* (0.50-4.49 years) and 414 were in the *long-term sample* (4.5+ years). The baseline characteristics of all patients by gender are shown in table 9.
69% of the cohort were male, 31% were female. Age at first interview (t1): The 660 patients were primarily middle-age adults, with 74 percent of them being between 25 and 39 years old. Only 5.9 percent were under age 25. 20 percent were 40 or older. Their mean age at time of first interview was 34.4 ± 6.4 years (men 34.4 ± 6.4 years; women 33.8 ± 6.3 years; Fig. 5).

Figure 5: Age Distribution (n = 660)



The older age of these methadone maintenance (MM) patients reflects the fact that most have been in MMTs for several years. Most had a considerable history of heroin

addiction prior to their entry in a MMT. Their mean age at the beginning of the MMT was 28.4 ± 6.6 years, with a significant gender difference (table 10; women 27.5 years versus men 28.8 years; *P* = 0.023).
Basic demographic characteristics of 660 methadone maintenance patients were similar between gender, except for marital status, with a significantly higher percentage of unmarried men (77.6% versus 64.6%; Mann-Whitney-Test, Z = -3.447, *P* = 0.001), and significantly more women with children (23.3% versus 47.8%; Chi square, df = 1, *P* = 0.001; table 9).

Table 9: Demographic Characteristics of 660 Methadone Maintenance Patients

Variable	Male n=456	Female n=204	**Total (P1) n=660**	**P-value**
Age (years) (Mean ± SD)	34.7 ± 6	33.8 ± 6	34.4 ± 6	ANOVA
Range	20 – 59	20 – 49	20 – 59	0.103
Median	34.2	33.2	33.7	
95% CI	34.1 – 35.3	32.9 – 34.7	33.9 – 34.9	
Sex (M/F)	69 %	31 %	100 %	
Marital status:				
Unmarried	77.6 %	64.6 %	73.7 %	Mann-
Married	7.8 %	11.8 %	9.1 %	Whitney
Divorced/ separated	14.3 %	20.0 %	16.0 %	0.001
Widowed	0.3 %	3.6 %	1.2 %	
Parenthood:				Chi^2
With at least one child	23.3 %	47.8 %	29.2 %	0.001
Nationality:				
Swiss	85.8 %	89.5 %	86.9 %	Chi^2
European Union and other countries	14.2 %	10.5 %	13.1 %	0.128
Education:				
School absolved	43.3 %	51.9 %	45.8 %	Mann-
apprentice	52.2 %	46.6 %	50.6 %	Whitney
Higher degree school/ University	4.5 %	1.5 %	3.6 %	0.060
Education: Swiss population, 25+ years*:				
School absolved	8.8 %	15.9 %	19.0 %	
apprentice	57.0 %	66.8 %	56.8 %	
Higher degree school/ University	34.2 %	17.3 %	24.2 %	
Employment history:				
employed	32.8 %	21.6 %	29.4 %	Mann-
social welfare	21.4 %	30.2 %	24.0 %	Whitney
disability annuity	45.8 %	48.2 %	46.5 %	0.061
Employment: Swiss population,25+ years*:				
employed			52 %	
unemployed			2 %	
unemployed long term			15 %	
disability annuity			3 %	

*Bundesamt für Statistik (2002)

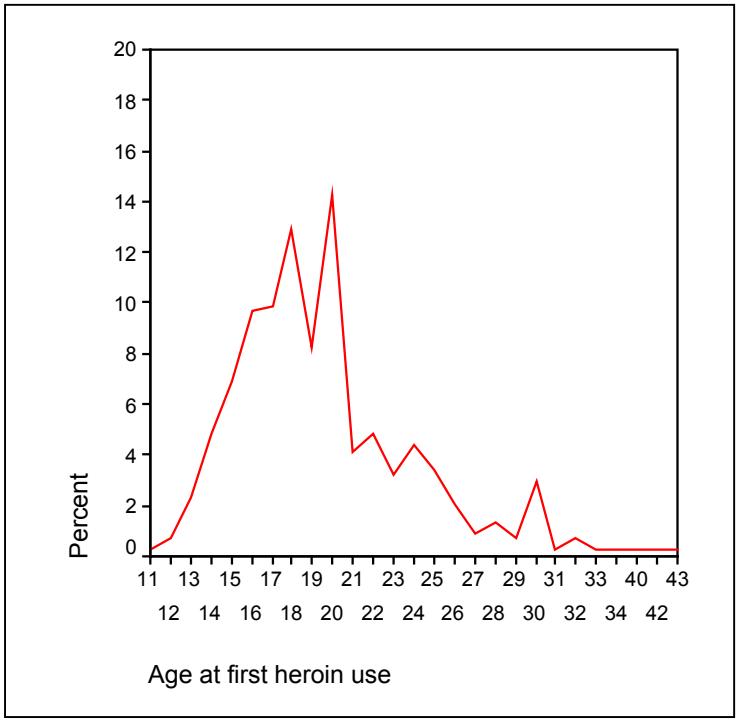
Nationality: 86.9 percent of the 660 patients were Swiss, and 13.1 percent were from other countries (table 9). In general, minority group position did not differ between the programs. However, there were considerably less patients from minority groups than

in the general population in the city of Basel (13.1% versus 27.7%; Bundesamt für Statistik, 2002, p. 28).
Education: When considering the life history of these 660 addicts in greater detail, we can see, that the years of formal education of the addict patients were considerably below that of the general Swiss population (Bundesamt für Statistik, 2002; table 9). Respectively the number of subjects with "absolved school" as highest degree of education was considerably higher compared to the general Swiss population (45.8% versus 19%). Looking at the proportion of subjects with an higher degree school or university, the difference is dramatic with a ratio of 3.6% versus 24.2%. These data demonstrate, that only a small group of subjects reach a higher school degree, probably due to the impact of the addiction on these areas. The proportion of missing values for this variable was quite high (33%), indicating a high proportion of the physicians responsible for the MMT having no idea of the education level of their patients.
Employment Status: When considering the life history of these 660 addicts in greater detail, we can see, that the proportion of employed patients was considerably below that of the general Swiss population (Bundesamt für Statistik, 2002; table 9, 29.4% versus 52%). About a third of all patients are employed, 24% live from the social welfare (including unemployed long term), and most of them have a disability annuity (46.5%, table 9). The proportion of missing values for this variable is quite high (29%), indicating that a high proportion of the physicians have no idea of the employment status of their patients. At 12-month follow-up, the sociodemographic variables were very similar.

3.1.2 Drug Use History

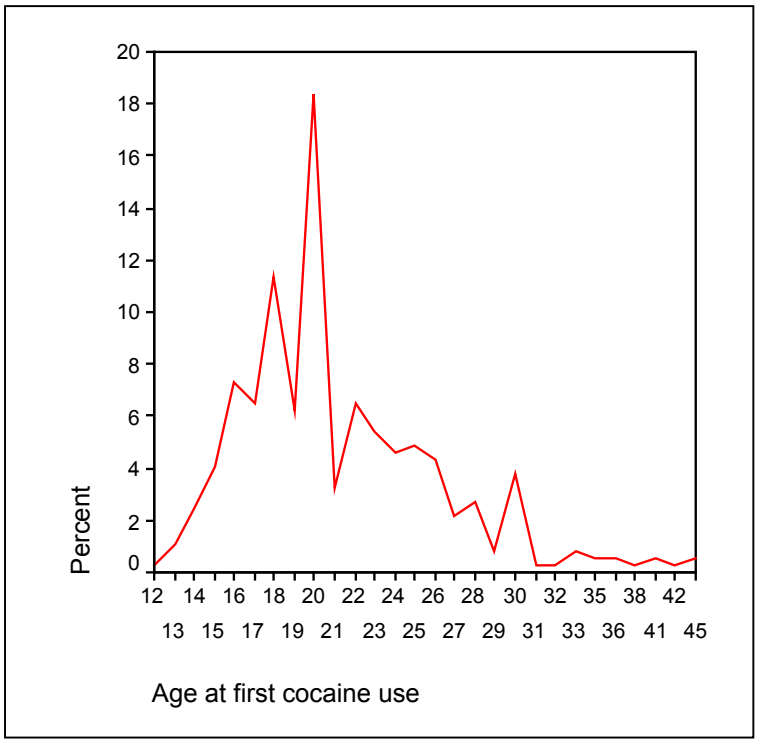
Variables about drug use history were available for 66% of the cohort. Patients were asked, about the age of onset of drug use. We got no information about the age at onset of drug dependence.
Most patients had a long history of regular heroin use. The early age at which opioid use commonly began was a crucial event in these patients' lives. With few exceptions, the onset of daily intravenous injections set the stage for a deviant course of life that was proved difficult to change. With respect to early onset, almost two-thirds had began use of heroin between 16 and 21 years (table 10; Fig. 6). The highest incidence years were ages 18 and 20.

Figure 6: Age at Onset of Opioid Use (n = 434)



Concerning the onset of cocaine use, half of the cohort had began use of cocaine between 16 and 20 years (table 10, Fig. 7). The highest incidence years were ages 17 and 20.

Figure 7: Age at Onset of Cocaine Use (n = 434)



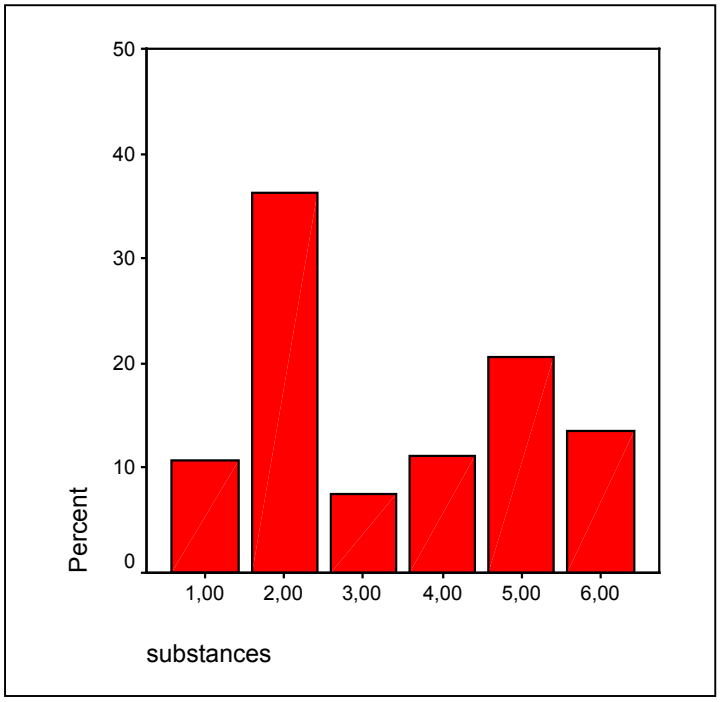
Concerning drug use history, there were no significant gender differences for onset of heroin, cocaine, cannabis, alcohol or benzodiazepine use (table 10).
Looking at the mean age of first heroin use (19.7 ± 5 years) and the mean age of entry in a MMT (28.4 ± 7 years), we can observe a period of approximately 8 years before getting enrolled in a MMT. Opioid dependent women were significantly younger when they entered a MMTP for the first time, compared to men (27.5 ± 7 years versus 28.8 ± 6 years; ANOVA, df = 1, $F_{(1, 656)} = 5.183$, $P = 0.023$; table 10).

Table 10: Drug Use History of 660 Methadone Maintenance Patients

Variable	Male n=456	Female n=204	Total (P1) n=660	**P-value**
Age (years) (Mean ± SD) Range Median 95% CI	34.7 ± 6 20 – 59 34.2 34.1 – 35.3	33.8 ± 6 20 – 49 33.2 32.9 – 34.7	34.4 ± 6 20 – 59 33.7 33.9 – 34.9	ANOVA 0.103
Age at admission to methadone maintenance treatment Range 95% CI	28.8 ± 6 16 – 54 28.2 – 29.4	27.5 ± 6.6 16 – 46 26.6 – 28.4	28.4 ± 7 16 – 54 27.9 – 28.9	ANOVA 0.023
Age at first heroin use Range 95% CI	19.9 ± 4 12 – 43 19.4 – 20.4	19.2 ± 5 11 – 42 18.3 – 20.1	19.7 ± 5 11 – 43 19.2 – 20.1	ANOVA 0.151
Age at first cocaine use Range 95% CI	21.5 ± 5 13 – 45 20.8 – 22.1	20.9 ± 5 12 – 41 20.0 – 21.8	21.3 ± 5 12 – 45 20.8 – 21.8	ANOVA 0.311
Age at first cannabis use Range 95% CI	15.7 ± 2 10 – 27 15.3 - 16.1	15.3 ± 3 10 – 25 14.6 - 16	15.6 ± 3 10 - 27 15.2 – 15.9	ANOVA 0.372
Age at first alcohol use Range 95% CI	15 ± 3 8 – 25 14.6 – 15.5	15.3 ± 4 6 – 35 14.2 – 16.4	15.1 ± 3 6 - 35 14.7 – 15.6	ANOVA 0.557
Age at first benzodiazepine use Range 95% CI	23 ± 6 6 – 42 21.9 – 24.3	21.7 ± 6 12 - 40 20 – 23.4	22.6 ± 6 6 - 42 21.7 – 23.6	ANOVA 0.192
Proportion of patients with intravenous drug use (lifetime prevalence)	342 (75)	165 (81)	508 (77)	Chi^2 0.104

89 percent of the patients had a multiple substance use before entering treatment. That is, multiple substance use seems to be the norm rather than the exception, leaving only 11% of the patients with a mono substance abuse of heroin (Fig. 8). 85% had a lifetime use of both heroin and cocaine. Both cannabis and alcohol were extensively abused prior to MMT: 52% had a a lifetime use of cannabis, 48% of alcohol, 33% a lifetime use of benzodiazepines, and 15% of amphetamines.
As shown in figure 8, before entering in a MMT, 36.2% of the patients had used two substances, 7.6% had used three substances, 11.2% four substances, 20.6% five substances, and 13.5% six substances (Fig. 8).

Figure 8: Multiple Substance Use before Treatment (n = 434)



3.1.3 Somatic Health State of 660 Methadone Maintenance Patients

One section of the questionnaire asked questions about infectious diseases like HIV seropositivity, hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). A third of the physicians did not fill out this part of the questionnaire or wrote "unknown HIV state" and "unknown "hepatitis state" in the first interview.

The prevalence rate of HIV seropositivity was 8.6 percent for the total sample (table 11). These results were similar to those reported in 1999 for all patients in a MMT (9.4 percent; Petitjean et al., 1999). Women had a significantly higher HIV prevalence rate than men (Chi^2 = 12.373; df = 1; *P* = 0.002). The physicians responsible for the treatment reported, that 20 percent of the HIV infected patients had AIDS. They also reported, that an approximate of 70 percent of HIV infected were treated with a retroviral medication. At 12-month follow-up the prevalence rate of HIV seropositivity was 10.9 percent (table 12).

Table 11: HIV Seroprevalence in MMT at t1 by Gender

			2000 t1
Variable	Male n = 456	Female n = 204	Total n = 660
HIV seropositive (N/%)	29 (6.4)	28 (13.7) **	57 (8.6)
HIV negative (N/%)	299 (65.6)	111 (54.4)	410 (62.1)
Unknown state (N/%)	128 (28.0)	65 (31.9)	193 (29.3)
Total	456 (100.0)	204 (100.0)	660 (100.0)

**P < 0.01

Table 12: HIV Seroprevalence in MMT at t1 and at 12-Month Follow-Up

	2000 t1	2001 t2
Variable	Total n = 660	Total n = 486
HIV seropositive (N/%)	57 (8.6)	53 (10.9)
HIV negative (N/%)	410 (62.1)	310 (63.8)
Unknown state (N/%)	193 (29.3)	123 (25.3)
Total	660 (100.0)	486 (100.0)

For the hepatitis seroprevalence rates, we had a third of missing values in the questionnaire. HAV, HBV, and HCV seroprevalence in MMT were high, with a third with hepatitis A virus, and half of the patients infected with the hepatitis B and hepatitis C virus (table 13). No significant gender differences were found for HAV, HBV and HCV). The physicians responsible for the treatment reported, that 7 percent of the HCV infected patients were enrolled in a medical treatment (interferon therapy).
At 12-month follow-up we had a decrease in the amount of missing values. This was due to the sensibilization of the physicians responsible for the MMT of the importance of this section of the questionnaire for the evaluation of the MMT. The results at follow-up reflect more realistic prevalence rates. HBV seroprevalence was 55 percent, and HCV seroprevalence was 54 percent (table 13).

Table 13: Hepatitis A, B, and C Seroprevalence in MMT at t1 and t2

	Baseline	1 year	Baseline	1 year	Baseline	1 year
Variable	**HAV**	**HAV**	**HBV**	**HBV**	**HCV**	**HCV**
Positive (N/%)	236 (35.8)	96 (19.8)	309 (46.8)	266 (54.7)	308 (46.7)	260 (53.5)
Negative (N/%)	169 (25.6)	206 (42.4)	131 (19.8)	130 (26.7)	142 (21.5)	128 (26.3)
Unknown state (N/%)	255 (38.6)	184 (37.8)	220 (33.4)	90 (18.6)	210 (31.8)	98 (20.2)
Total	660 (100.0)	486 (100.0)	660 (100.0)	486 (100.0)	660 (100.0)	486 (100.0)

3.1.4 Reported Drug Use

One section of the questionnaire focussed on the illicit drug use and the doctor asked the patients, if they had used heroin, cocaine, cannabis, benzodiazepines or alcohol during the past 30 days prior to interview. According to this section in the ASI, the doctor had to fill out the number of days: if the patient asked “I take cocaine daily”,

then he would code [30], if the patient asked “I take cocaine monthly”, then he would code [01], and so on. Illicit drug use was one of the main treatment outcome measures for treatment effectiveness.

3.1.4.1 Reported Concomitant Drug Use During the Past 30 Days Prior First Interview

45 percent of the patients reported they had not used any heroin, and 55 percent reported they had an illicit heroin use in the past 30 days prior interview. Heroin was abused on an average of 7 out of 30 days. For cocaine use we found 34 percent with cocaine use in the past 30 days prior interview on an average of 6 days (table 14). For cannabis use, we found 56 percent of the patients with cannabis use in the past 30 days prior interview, 56 percent with alcohol use and 16 percent with benzodiazepine use. There were no significant gender differences in the proportion of any concomitant drug use, except for cannabis. women reported significantly more days with cannabis use (ANOVA; $F_{(1,56)} = 0.733$; $P = 0.034$). Men reported more heroin use in the past 30 days than women, but on a non significant level (trend; $P = 0.066$).

Table 14: Drug Use in the Past 30 Days Prior First Interview (t1)

Drug	Male n=456	Female n=204	Total n=660	P-value
Heroin Use:				Chi^2
None (%)	42	52	45	0.066
1day or more (%)	58	48	55	
mean days (mean, SD)*	7.0 ± 6	6.9 ± 6	7.0 ± 6	ANOVA
CI	5.96 - 8.00	5.0 8- 8.81	6.08 – 7.86	0.971
Cocaine Use:				Chi^2
None (%)	65	67	66	0.361
1day or more (%)	35	33	34	
mean days (mean, SD)	5.2 ± 5	7.3 ± 7	5.8 ± 6	ANOVA
CI	3.92 – 6.44	4.87 – 9.71	4.66 – 6.91	0.094
Cannabis Use:				Chi^2
None (%)	44	45	44	0.466
1day or more (%)	56	55	56	
mean days (mean, SD)	19.3 ± 11	22.8 ± 11	20.3 ± 11	ANOVA
CI	17.57 – 21.03	19.99 – 25.65	18.85 – 21.82	0.034
Benzodiazepine Use:				Chi^2
None (%)	83	86	84	0.293
1day or more (%)	17	14	16	
mean days (mean, SD)	9.9 ± 10	18.7 ± 11	11.5 ± 11	ANOVA
CI	5.29 – 14.47	6.70 – 29.62	7.30 – 15.75	0.098
Alcohol Use:				Chi^2
None (%)	42	51	44	0.095
1day or more (%)	58	49	56	
mean days (mean, SD)	17.0 ± 11	16.7 ± 11	16.9 ± 11	ANOVA
CI	15.21 – 18.72	13.66 – 19.74	15.39 – 18.40	0.881
Intravenous drug use past 30 days prior to interview	44	49	45	Chi^2 0.149

*Range: 1 – 30 days

As expected, the most common way of using heroin and cocaine was the intravenous way followed by snorting or smoking these substances. Of the 216 patients which

reported a heroin use in the past 30 days, 45% said they had applied heroin intravenously, 27% had snorted and 27% had smoked (table 15). Of the 126 patients who had used cocaine in the past 30 days, 57% reported they had applied cocaine intravenously, 22% had snorted and 21% had smoked (table 15). The proportion of patients using drugs intravenously was higher for cocaine than for heroin.

Table 15: Current Way of Using Substances (Past 30 Days):

	heroin	**cocaine**
Intravenous drug use (IDU) (N/%)	96 (45.2)	72 (57.1)
Smoked/ inhalation (N/%)	60 (27.4)	28 (22.2)
Sniff/ snort (N/%)	60 (27.4)	26 (20.7)
Total	216 (100.0)	126 (100.0)

Frequency of Opiate Use During the Past 30 Days for Three Treatment Cohorts:

The 660 patients were divided in three different cohorts to compare the amount of concomitant opiate and non-opiate use: There were 19 new admissions (up to 0.49 years), 149 average-stay patients (0.50 – 4.49 years), and 231 long-term patients (4.5+ years). These three cohorts were compared in drug abuse by time already spent in treatment. The extent to which drug abuse among these patients decreased during methadone maintenance treatment is shown in table 16.

As expected, the extent of opiate use among the admission sample was high, with 68.4 percent of concomitant heroin use. 57.1 percent had used cocaine, 46.2 percent had used cannabis, 76.9 percent had used alcohol, and 7.7 percent sedatives.

Patients in the average-stay sample had a significantly lower prevalence of concomitant heroin use (62.4%) compared to the admission sample (68.4%). Mean days of reported heroin use were significantly lower (5.4 days out of 30 days versus 11.5 days out if 30 days) compared to the admission sample (ANOVA, $F_{(1,\ 105)}$ = 11.247, P = 0.001). Also for cocaine, there was a significant decrease from 57.1 percent (admission sample) to 40.4 percent (average stay sample; P = 0.01), but no decrease in the mean number of days cocaine was used. There was no decrease in cannabis, alcohol and sedative use (table 16).

In the long-term stay sample, compared to the admission and the average-stay sample, there was a trend for decreased heroin use (Kruskal-Wallis-Test, Chi^2 = 5.537, df = 2, P = 0.063) and a significant decrease of cocaine use (Kruskal-Wallis-Test, Chi^2 = 8.895, df = 2, P = 0.012). Thus 48.5 percent reported no use of heroin and 71.6 percent reported no use of cocaine in the long-term sample. High rates for alcohol (60.5 percent), cannabis (52.9 percent) and benzodiazepine use (18.6 percent) persisted and remained unchanged (table 16).

Looking at the proportion of patients in the three different cohorts sharing needles with others, there was a significant decrease over time.

Table 16: Frequency of Opiate and Non Opiate Drug Use During the Past 30 Days for Three Treatment Cohorts of Methadone Maintenance Patients

	Admission sample (up to 0.49 years) (n = 19)			Average stay sample (0.50-4.49 years) (n = 149)			Long-term sample (4.5+ years) (n = 231)		
Drug of abuse	No.	%	Mean days	No.	%	Mean days	No.	%	Mean days
Heroin*	13	68.4	11.5	93	62.4	5.4	119	51.5	7.6
Cocaine	8	57.1	3.5	59	40.4	4.7	59	28.4	7.3
Cannabis	6	46.2	21.3	94	61.0	20.4	117	52.9	20.3
Sedatives	1	7.7	4.0	17	12.3	12.8	40	18.6	12.1
Alcohol	10	76.9	18.9	70	47.0	17.6	133	60.5	16.4

Reduction in prevalence by time in treatment was significant at the 0.001 level for heroin, and at the 0.01 level for cocaine.

3.1.4.2 Reported Concomitant Drug Use at One-Year Follow-Up

Compared to the first interview, the completer-analysis yielded no significant self-reported increase or decrease of illicit heroin or cocaine use at 12-month follow-up. However, there was a significant increase in the proportion of patients using cannabis, non prescribed benzodiazepines and alcohol, but not in the average mean days they had used it in the past 30 days prior interview (table 17). Thus, MMT had no impact on the reduction of cannabis, benzodiazepine or alcohol use.

Table 17: Annual Change in Drug Abuse Among MMT Patients (t1 – t2)

	Percent of patients using drug, past 30 days	Percent of patients using drug, past 30 days	Frequency of use (Mean days of use in the past 30 days)	Frequency of use (Mean days of use in the past 30 days)
Drug	Baseline	1 year	Baseline	1 year
Heroin	55.5	52.6	8.0	7.7
Cocaine	34.0	35.0	7.2	6.9
Cannabis	52.9	61.5***	19.8	20.1
Sedatives	17.0	25.1***	17.9	18.0
Alcohol	52.2	56.7**	16.5	16.0

McNemar-Test; significantly higher proportion of cannabis-users ($P < 0.0001$), of benzodiazepine-users ($P < 0.0001$); and alcohol-users ($P < 0.001$) at 12-month follow-up.

3.1.4.3 Reported Intravenous Drug Use at One-Year Follow-up

At 12-month follow-up, 241 out of 486 patients reported, they had have continued intravenous drug use in the past six months prior second interview (49.6 percent, table 18). There was no difference in the proportion of IDUs between the three treatment cohorts. 168 out of these 241 IDUs reported risk behavior in the past six

months by sharing needles with others (table 18). The proportion of patients with HIV risk behavior through needle sharing differed significantly between the three treatment cohorts (Kruskal-Wallis-Test, Chi^2 = 6.505, df = 2, P = 0.039). Thus, the proportion of needle sharers was significantly lower in the long-term sample (table 18).

Table 18: Frequency of Intravenous Drug Use and Needle Sharing During the Past Six Months for Three Treatment Cohorts

	Admission sample (up to 0.49 years) (n = 19)	Average stay sample (0.50-4.49 years) (n = 149)	Long-term sample (4.5+ years) (n = 231)
Intravenous drug use, past six months (%)	50.0	55.5	51.8
Needle sharing, past six months (%)	42.9	50.0	36.7*

*P < 0.05

Additionally we analyzed changes in lifetime intravenous drug use for patients enrolled in a MMT. After 12 months, a total of 6.3 percent of the patients who had never injected (lifetime) had switched from non-intravenous heroin use (smoking, snorting, sniff) to intravenous drug use. This increase of intravenous drug users was highly significant (McNemar-Test; Chi^2 = 20.833; P < 0.0001) (table 19). Unfortunately there were no results available from the "new admission cohort", because they had terminated their methadone maintenance treatment at 12-month follow-up and could not be contacted anymore.

Table 19: Annual Change in Intravenous Drug Use, Lifetime (t1 - t2)

	Intravenous drug use, lifetime (%)		Percent of use change
Group	2000	2001	2000-2001: Significant Change
Average stay sample (%)	75.9	83.0	+7.1
Long-term sample (%)	79.3	85.1	+5.8
Total	78.1	84.4	+6.3***

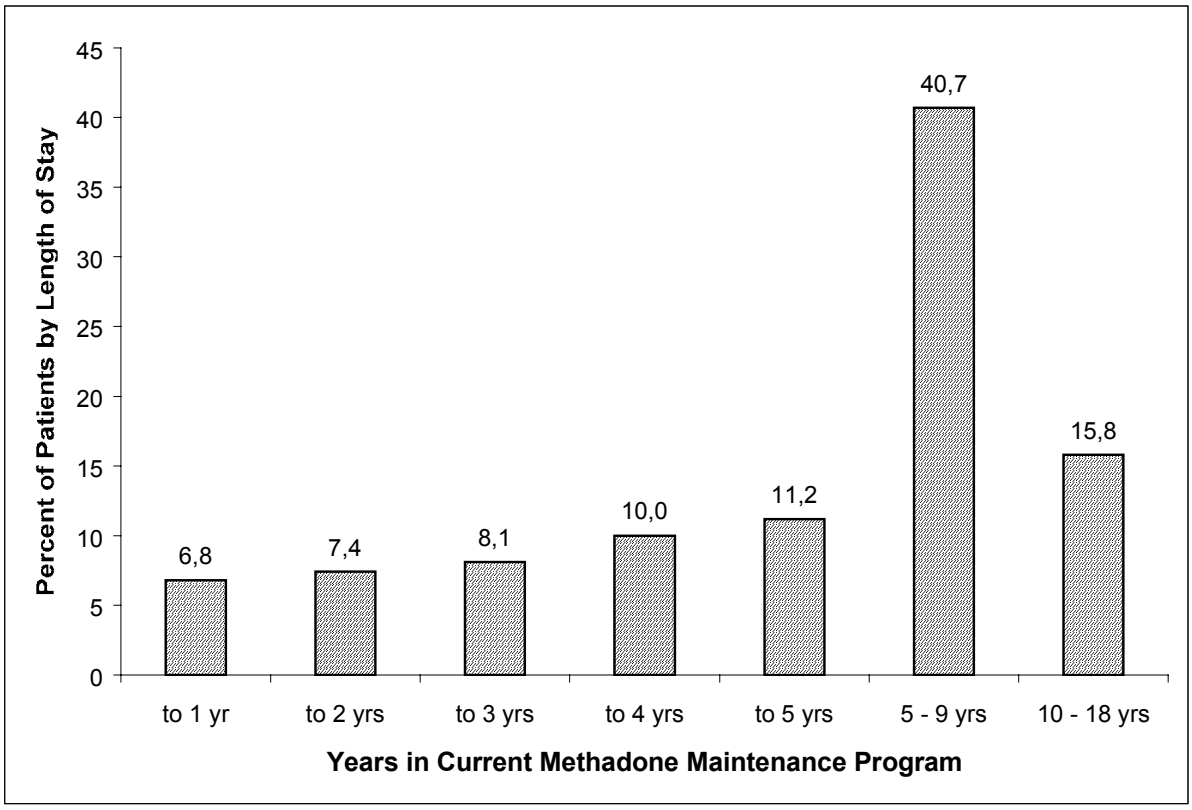
***P < 0.0001

3.1.5 Length of Stay in Treatment

The length of stay in treatment is an important measure of patients' progress in outpatient MMT and of treatment success: Newly admitted and less motivated patients tend to leave, those who remain in treatment tend to become rehabilitated over the years (Ball et al., 1992). Patients' progress in treatment and rehabilitation is commonly associated with time in treatment. Thus. The longer patients stay in a MMTP, the better. The average length of stay in treatment for the total sample at first interview was 6 $\pm$ 4 years (median, 5.4 years; range, 3 months to 25 years). There were no gender differences concerning the average length of stay in treatment.

Almost 7% of the 660 patients had been in treatment for one year or less, 7.4 percent for two years and 8.1 percent for three years. The majority of the patients (57 percent) had been in MMT for more than five years (Fig. 9).

Figure 9: Length of Stay in Treatment for 660 Methadone Maintenance Patients

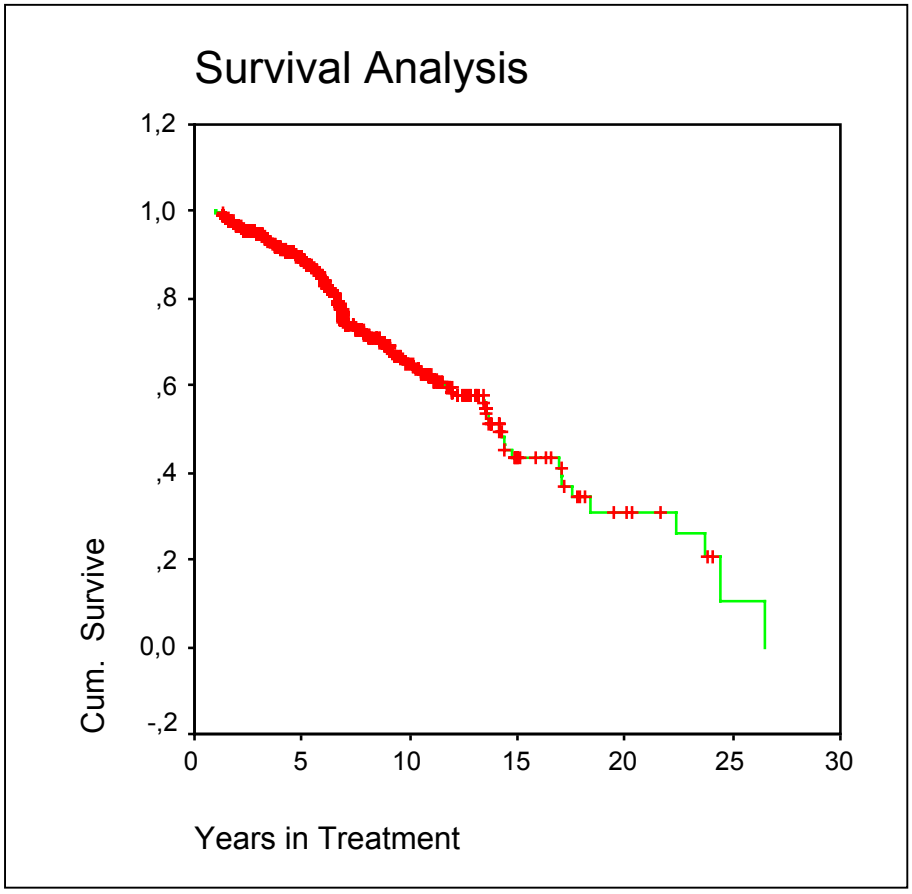


3.1.6 Retention in Treatment

At one-year follow-up, 73.6 percent of the patients were still in treatment. The proportion of patients leaving MMT did not differ between gender (Chi^2 = 1.293, df = 1, *P* = 0.149). The same accounts for different age categories: Younger aged patients (18 to 29 years) did not drop out of treatment more frequently, than did the older aged patients (30 to 60 years) (Chi^2 = 1.998, df = 1, *P* = 0.157).

To estimate the survival curve for the total cohort, we calculated a Kaplan-Meier survival curve (Fig. 10). The outcome of interest was the time to an event. The event was dropping out of treatment. The mean survival time in MMT for men was 14.6 years (95% CI = 13.2, 16.7), and for women 15.06 years (95% CI = 12.9, 17.2) (log rank, df = 1, *P* = 0.989; Fig. 10). As shown in figure 10, most dropouts occurred in the first years of treatment. The longer the patients are in treatment, the more rarely they drop out of treatment.

Figure 10: Survival Analysis of 660 Patients (Kaplan Meier)

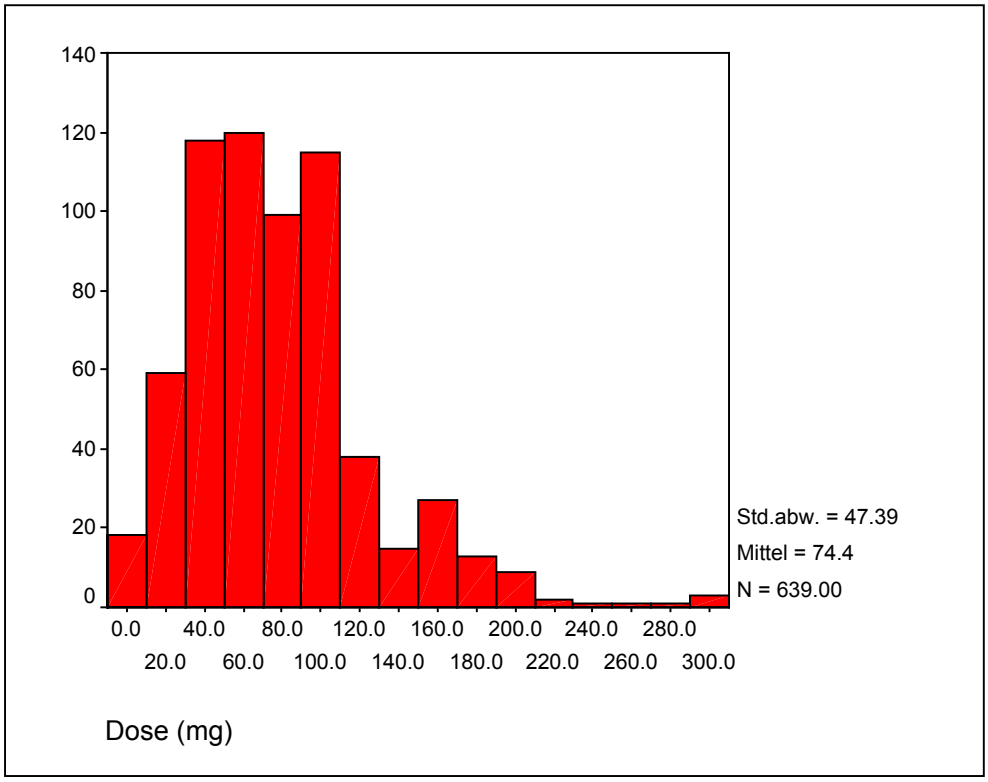


Legend: each cross represents the time point of an event, thus one patient dropping out of methadone maintenance treatment.

3.1.7 Methadone Dispensing Practices

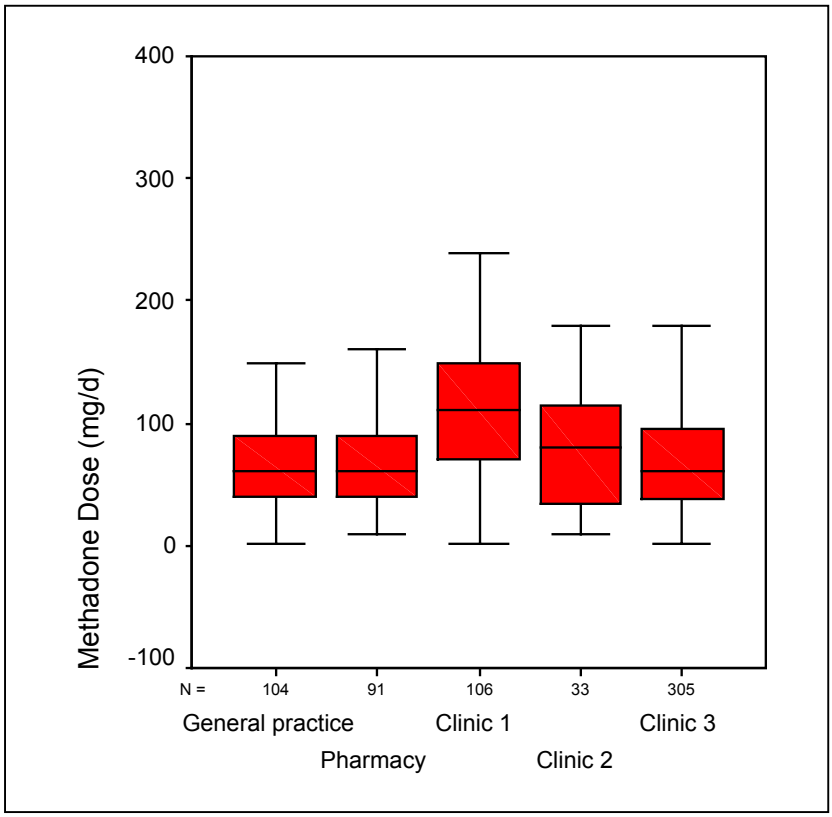
During the regular work week, all three of the clinics dispensed methadone in both the morning and evening hours. Two of the clinics had two dispensing periods (4 hours a day), and one had one long continuous dispensing period from 7:00 a.m. to 7:00 p.m. It should be noted, that the last clinic had an automated dispensing procedure. All three clinics were open on Saturdays, and one was open on Sundays.
In general practices, during the regular work week, all dispensed methadone in both the morning and evening hours. 60 percent of the GP patients received their medication in the pharmacies.
The dosage policy of methadone maintenance programs are influenced by recommendations of federal, state, and local governments, previously established dispensing practices at each clinic, and knowledge about effective clinical doses. Dispensed daily methadone doses to 639 patients are shown in figure 11. Most patients, were prescribed doses between 30 mg and 110 mg (68 percent were in this dosage range), 12 percent of the patients received doses below 30 mg, and 20 percent had doses of 110 mg or higher. The mean methadone dose dispensed to these 639 patients was 74.4 $\pm$ 47.39 mg (range: 1 mg to 300 mg/d) (Fig. 11).

Figure 11: Methadone Dose Distribution to 639 Patients



Mean daily methadone doses differed significantly between the different MMTPs (ANOVA, $F_{(4/634)}$ = 22.771; df = 4, P < 0.0001) (Fig. 12). Patients treated in general practice had a mean methadone dose of 68.2 ± 42 mg/d, in pharmacies of 70.5 ± 47 mg/d, at clinic1 of 110.9 ± 62 mg/d, at clinic 2 of 82.3 ± 52 mg/d, and at clinic 3 of 64.2 ± 35 mg/d (Fig. 12).

Figure 12: Mean Methadone Doses at the Five MMTPs



Legend: Prescribed mean methadone doses (mg/d; SD) at three specialized clinics, in general practice and in pharmacies.

The year to year variation in the mean daily methadone dose dispensed at each of the MMTPs was minimal (74.4 ± 47 mg versus 76.4 ± 51 mg (paired T-Test; T = -,666; *P* = 0.506). In detail, these results indicate, that there is a considerable stability in prescribing practices in specialized clinics and in general practice.
Surprisingly, there were no gender differences in prescribed methadone doses, and the mean methadone dose was even higher in women. Due to the higher mean weight of men (73 kg), compared to the lower mean weight of women (61 kg), we expected a lower methadone dose in women. Adequate methadone doses are defined by the physicians, looking at the corresponding body weight. The mean dose prescribed to men was 73.6 ± 45 mg and to women 76.4 ± 52 mg (ANOVA; $F_{(1, 624)}$ = 1012, *P* = 0.497). This result remained consistent at 12 month follow-up (men, 75.3 ± 52 mg versus women, 78.7 ± 50 mg; *P* = 0.450).
Mean methadone doses differed significantly between the three treatment cohorts: Patients in the *admission sample* had a prescribed mean methadone dose of 58.1 ± 23 mg, in the *average stay sample* of 64.4 ± 41 mg, and in the *long-term sample* of 80.6 ± 50 mg (ANOVA; $F_{(2,636)}$ = 9.709; *P* < 0.0001).
Usually, take home medication is allowed by the physician responsible for the MMT for stabilized patients. Patients with a good compliance, low concomitant drug use (e.g. heroin, cocaine, alcohol) and good psychosocial functioning can come once a week to the dispensing site, take one methadone dose orally and take the methadone medication for six days at home. 'Take-home' was defined as taking the methadone at home for at least 3 days or more (table 20). 70 percent of all patients had allowed take-home methadone medication (table 20). For this group the mean days of take-home medication were 5.9 ± 3 days [95% CI; 5.6 – 6.2]. For 21 percent of the 'problematic' patients, take-home medication was not allowed, or only on weekends (table 20). Usually the physicians responsible for the MMT allow take-home medication for stable patients. For unstable patients it would be to dangerous (e.g. injecting the methadone solution, diversion of methadone, risk of respiratory depression by taking the methadone with non prescribed benzodiazepines or with alcohol, access to non tolerant persons).

Table 20: Doses Dispensed On-Site and Take-Home Medication

	Total patients	
	No.	%
Dispensed daily on-site*	139	21.1
Take-home, 3 days or more	457	69.2
missing	64	9.7
Total	660	100.0

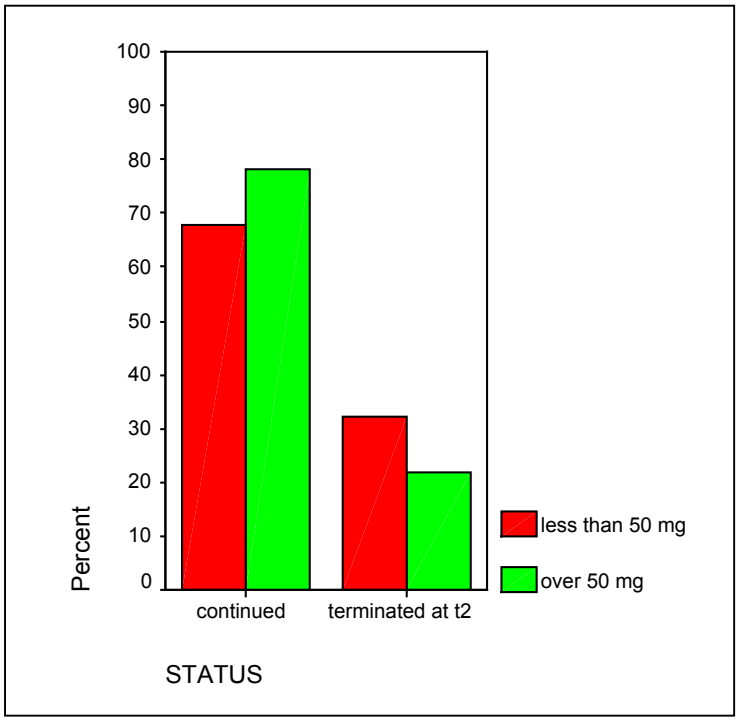
*except on weekends

The proportion of allowed take-home privileges did not differ between women and men (80.2% versus 75.1%, *P* = 0.105). Patients with take-home medication for three days or more had a significantly lower proportion of any concomitant heroin (55.0% versus 67.6%, Chi2 = 3.612, df = 1, *P* = 0.038) and a significantly lower proportion of any cocaine use (31.2% versus 53.0%, Chi2 = 11.148, df = 1, *P* = 0.001) compared to the on-site dispensing sample.

3.1.7.1 Methadone Dose, One-Year Retention and Concomitant Heroin Use

Daily methadone doses ≥ 50 mg are known to be more effective than methadone doses ≤ 50 mg (Johnson et al., 1992; Strain et al., 1993). At 12-month follow-up, patients with more than 50 mg of prescribed methadone had a significantly higher retention rate (78%) compared to those with less than 50 mg (67.9%) (Chi^2 = 8.058; df = 1; *P* = 0.003; Fig. 13).

Figure 13: Prescribed Methadone Dose and Retention (n = 484)



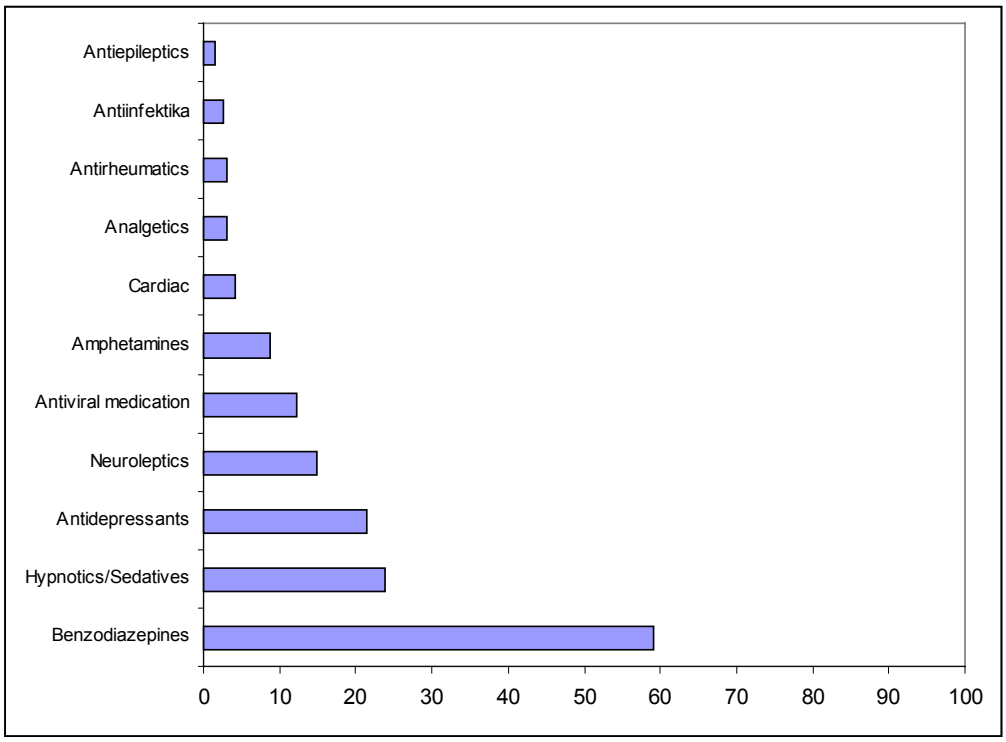
P = 0.003

Patients receiving less than 50 mg of methadone reported 8.47 ± 7 days with concomitant heroin use out of 30 days, patients receiving more than 50 mg of methadone reported 6.7 ± 6 days with concomitant heroin use (ANOVA, $F_{(1/245)}$ = 3.007, df = 1, *P* = 0.084).

3.1.8 Comedication

Besides the methadone medication, 39.5 percent of all patients (n = 261) received other medications like antidepressants, neuroleptics, benzodiazepines due to a diagnosed comorbidity (Fig. 14). The most frequently prescribed medications were benzodiazepines (59%), followed by Sedatives (23.7%), antidepressants (21.4%) and neuroleptics (14.9%).
Of these 261 patients, 40 percent had two prescribed medications and 15 percent three prescribed medications. There was a trend for women to have more prescribed comediaction (44 percent versus 37.5 percent; Chi^2 = 2.582; df = 1; *P* = 0.064). At 12 month follow-up we found the same proportion of patients with a comedication (39%) (Fig. 14).

Figure 14: Prescribed Comedication to 261 Patients



Multiple responses, n = 401

In the general population there is an estimated number of 13% of subjects with a current psychiatric disorder (Regier et al., 1190) compared to an estimated number of 47% to 75% of patients in a MMT with a current psychiatric disorder. Benzodiazepines are more often prescribed for opioid-dependent patients in a MMTP compared to the general population in Switzerland (8.7%; Ladewig et al., 1996).

3.1.9 Provided consultations to the Patients in 2000 and 2001

The second main purpose of this study was to assess the amount of provided consultations to each patient. Measurement focused on the frequency of contacts between physicians and patients within the past six months prior interview. The frequency of provided consultations was measured at baseline and at 12-month follow-up. In general, the scheduling of services to patients in MMTPs is organized around the provision of methadone. Thus, hours of consultations and medical services are usually coordinated with the dispensing hours for the convenience of both patients and staff.
The medical staff at the three MMTP and partly in general practice can be divided into three groups: (1) physicians, psychiatrist; (2) nurse practitioners and physicians' assistants; and (3) dispensing nurses or pharmacists. At one program (Clinic1) the actual amount of coverage provided by physicians was 63 hours per week, or 1.5 full-time equivalent (FTE) for 140 patients. At the second program (Clinic 2) the actual amount of coverage provided by physicians was 29 hours per week, or 0.7 full-time equivalent (FTE) for 70 patients. At the clinic 3, there was a 4.8 full-time equivalent

(FTE) for 480 patients. General practitioners treat an average of three patients in their general practice.

3.1.9.1 Scheduled and Attended Consultations in the Past Six Months Prior Interview

The general practitioners and the medical staff at the specialized centres were asked, how often they scheduled consultations, counseling, or medical sessions in the past six months prior interview. For this variable, there were only 5% of missings. Overall, 98.2 percent of the patients had at least one offered consultation by their physicians within six months, and 95.4 percent attended these consultations (table 21). There were no significant gender differences in the proportion of offered and attended consultations (table 21). The mean number of scheduled consultations in the past six months by the physicians were 7.4 ± 5.3 consultations, thus a little more than monthly sessions (table 21). Patients attended a mean of 6.3 ± 4.9 consultations, thus approximately one consultations less than scheduled.

Table 21: Scheduled and Attended Consultations to 660 Methadone Maintenance Patients During the Past Six Months

Variable	Male n =456	Female n=204	Total n=660
Offered, none (%)	1.8	1.6	1.8
Offered, one or more consultations (%)	98.2	98.4	**98.2**
Offered consultations (Mean ± SD)	7.3 ± 5.4	7.5 ± 5.0	**7.4 ± 5.3**
Range	1 – 41	1 – 25	1 – 41
Median	6.0	6.0	6.0
95% CI	6.8 – 7.8	6.8 – 8.2	6.9 – 7.8
Attended, none (%)	4.4	5.2	4.6
Attended one or more consultations (%)	95.6	94.8	**95.4**
Attended consultations (Mean ± SD)	6.4 ± 5.1	6.2 ± 4.5	**6.3 ± 4.9**
Range	1 – 40	1 – 24	1 – 40
Median	6.0	6.0	6.0
95% CI	5.9 – 6.9	5.6 – 6.9	5.9 – 6.7

3.1.9.2 Scheduled and Attended Consultations Over Time

There was only minimal change over time in the number of scheduled and attended consultations over time (table 22, table 23). The Wilcoxon-Test revealed an non significant change over time: First for the sum of scheduled consultations, and second for the sum of attended consultations. As expected, number of scheduled consultations showed great variability between the different treatment facilities (table 22).

Table 22: Annual Change in the Provision of Consultations by Dispensing Site

	Offered consultations* Mean [95% CI]		Change in year	Percent of patients with one or more scheduled consultation		:
Program	2000	2001		2000	2001	% Change
Clinic 1	11.1 [9.4-12.8]	9.4 [8.2-10.6]	-1.7	99.0	100.0	+1.0
Clinic 2	5.6 [3.9-7.2]	4.6 [3.2-6.0]	-1.0	100.0	96.7	-3.3
Clinic 3	6.9 [6.5-7.2]	7.0 [6.7-7.3]	+0.1	99.0	99.3	+0.3
General practice	6.9 [5.8-7.9]	6.5 [5.5-7.6]	-0.4	95.0	95.3	+0.3
Pharmacies	4.9 [4.0-5.8]	5.5 [4.5-6.4]	+0.6	97.7	98.1	+0.4
Total	**7.2** [6.8-7.7]	**6.9** [6.6-7.3]	-0.3	98.2	98.5	+0.3

Table 23: Annual Change in the Attendance of Consultations by Dispensing Site

	Attended consultations* Mean [95%CI]		Change in year	Percent of patients with one or more attended consultation**		
Program	2000	2001		2000	2001	% Change
Clinic 1	8.9 [7.4-10.5]	7.7 [6.6-8.8]	-1.2	98.1	100.0	+1.9
Clinic 2	4.5 [3.3-5.7]	3.4 [2.4-4.4]	-1.1	97.1	93.3	-3.8
Clinic 3	6.0 [5.7-6.3]	6.0 [5.7-6.3]	+0.0	96.3	97.7	+1.4
General practice	5.4 [4.4-6.5]	5.5 [4.4-6.5]	+0.1	93.1	94.2	+1.1
Pharmacies	3.9 [3.0-4.8]	4.4 [3.6-5.3]	+0.5	90.9	92.3	+1.4
Total	**6.0** [5.6-6.4]	**5.8** [5.5-6.1]	-0.2	**95.4**	**96.5**	+1.1

3.1.9.3 Frequency of Attended Consultations and Treatment Outcome

We were first interested, if there was a association between the number of attended consultations and main treatment outcome measures (e.g. treatment retention, the proportion of concomitant heroin use). We expected, that patients with a high amount of consultations (4 to 7 consultations) would have a higher retention in treatment and a lower proportion of concomitant opiate drug use, compared to those with less consultations (0 to 3 consultations).
Overall, major baseline variables (age, gender) and in-treatment variables (e.g. methadone dose, comedication) did not differ between patients with a high amount of attended consultations, and those with a low amount of consultations (table 24). As to be expected, patients with a high rate of consultations were significantly more often treated in specialized clinics ($P < 0.0001$; table 24).

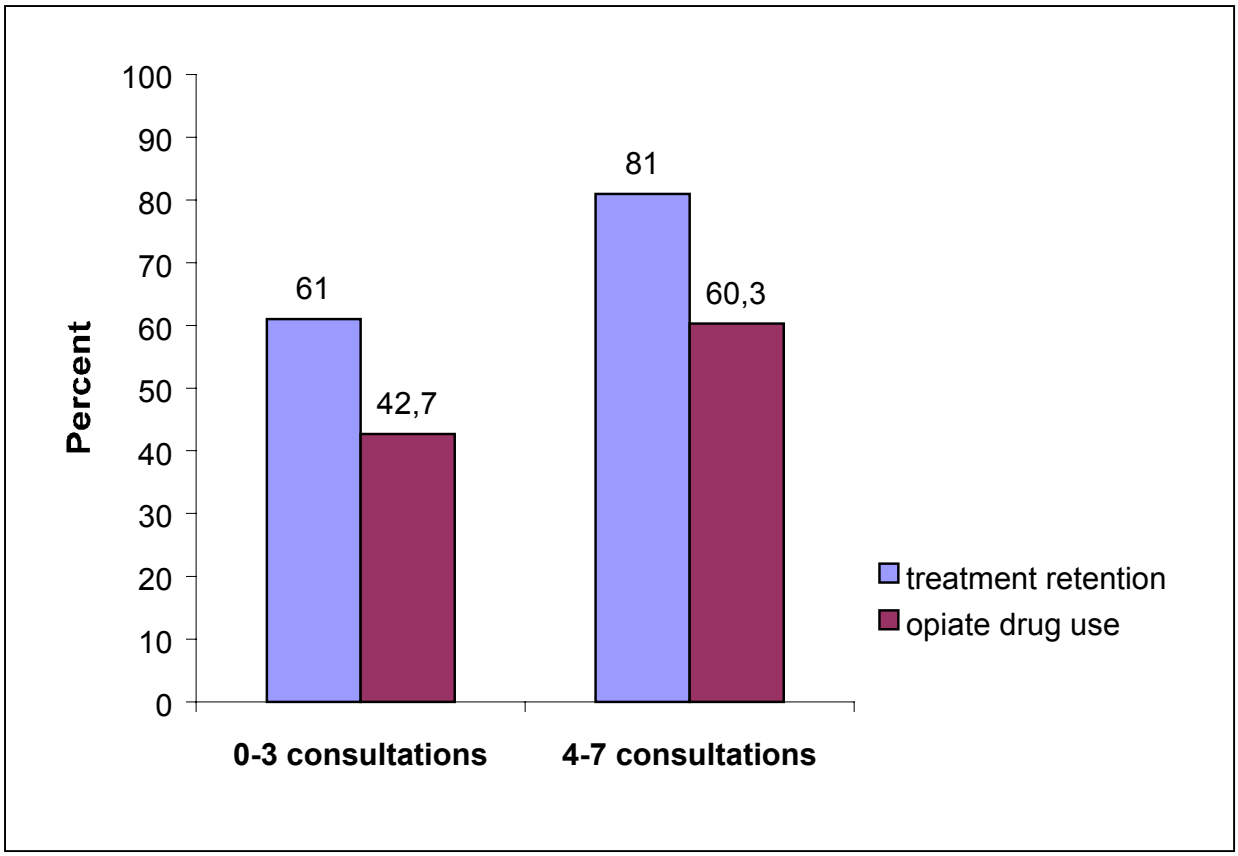
Table 24: Differences Between Methadone Maintenance Patients with a Low Rate of Attended Consultations (0 to 3) and a High Rate of Attended Consultations (4 to 7) During the Past Six Months (n = 616)

Variable	0 to 3 attended cons. n=169	4 to 7 attended cons. n=447	P-value
Male (N/ %) Female (N/ %)	111 (65.7) 58 (34.3)	315 (70.5) 132 (29.5)	p = 0.282
Not married Nationality, Swiss	113 (69.8) 135 (87.7)	328 (74.9) 374 (87.0)	p = 0.431 p = 0.889
Age (years; mean, SD)	35.2 ± 6	34.1 ± 6	p = 0.45
Age at first MMT (years)	28.3 ± 7	28.4 ± 7	p = 0.915
Age at first heroin use (years)	20.3 ± 5	19.1 ± 6	p = 0.514
Treated in General practice (N/ %) Treated in Specialized clinic (N/ %)	101 (59.8) 68 (40.2)	81 (18.1) 366 (81.9)	**p > 0.0001**
Retained in Methadone Maintenance Treatment (%)	61%	81%	**p < 0.0001**
Take-home (only on weekends) Take-home (3 days or more)	43 (28.7) 107 (71.3)	87 (20.7) 334 (79.3)	p = 0.054
No heroin use past 30 days (N/ %) Heroin use, at least 1 day (N/ %)	47 (57.3) 35 (42.7)	121 (39.7) 184 (60.3)	**p = 0.006**
No cocaine use past 30 days (N/ %) Cocaine use, at least 1 day (N/ %)	63 (81.8) 14 (18.2)	171 (60.9) 110 (39.1)	**p = 0.001**
No intravenous drug use (N/ %) Intravenous drug use past 6 months (N/ %)	61 (62.9) 36 (37.1)	131 (45.5) 157 (54.2)	**p = 0.006**
Without a comedication (N/ %) With a comedication (N/ %)	107 (63.3) 62 (36.7)	257 (57.5) 190 (42.5)	p = 0.20
Daily methadone dose (mg/d)	73.7 ± 49	75.6 ± 46	ANOVA p = 0.66

As we hypothesized, there was a strong association between the amount of attended consultations and the retention rate. Patients with a higher rate of consultations (4 to 7 consultations) had a significantly better retention rate compared to patients attending a lower rate of consultations (0 to 3 consultations) (81% versus 61%; Chi^2 = 24.53; df = 1; *P* > 0.0001; table 24; Fig. 15).

The hypothesis of a significant association between a high amount of consultations and a low amount of concomitant heroin use had to be rejected. Patients with more consultations (4 to 7 consultations) had significantly more illicit opiate use in the past 30 days (60.3%) than those with less consultations (0 to 3 consultations, 42.7%) (Chi^2 = 8.809; df = 1; *P* = 0.006; table 24, Fig. 15).

Figure 15: Number of Attended Consultations, Retention in Treatment and Concomitant Opiate Drug Use



One-Year Treatment Retention; P < 0.0001
Proportion of concomitant opiate use; P = 0.006

Furthermore, patients with more consultations had significantly more intravenous drug use in the past six months prior interview (54.2% versus 37.1%; *P* = 0.006, table 24), and significantly more illicit cocaine use (39.1% versus 18.2%; *P* = 0.001; table 24). Thus, it seems, that the physicians offer more consultations for the more 'problematic patients' with multiple substance use and intravenous drug use. For the more stabilized patients, they seem to schedule less consultations.

3.1.9.4 Attendance of Consultations as a Measure of Patients' Cooperation

Secondly, we were interested to analyze the differences between patients with a "good cooperation" and those with a "unsatisfactory cooperation" with their physicians. For this purpose we divided the patients into two subgroups with the following categories: patients with a "good cooperation" (GC) were defined as patients who attended all scheduled consultations or missed only one consultation; patients with an "unsatisfactory cooperation" (UC) were defined as patients who missed more than one scheduled consultation. We analyzed a total of 19 variables, 8 pretreatment patient variables and 11 in-treatment variables (table 25, 26).
The two subgroups differed significantly in 3 out of 4 pretreatment variables: patients with a "good cooperation" (GC) were more likely to be men, employed and with less multiple substance use (table 25).

Table 25: Comparison Between Methadone Maintenance Patients with a "Good Cooperation" (GC) and Patients with an "Unsatisfactory Cooperation" (UC) [Patient Variables]

	Good Cooperation (GC) n=478	Unsatisfactory Cooperation (UC) n=149	P-value
Male / Female (%)	78.8/ 21.2	70.5/ 29.5	**p = 0.024**
Age (years) [mean, SD]	34.5 ± 6	34.0 ± 6	p = 0.378
Employed (%)	29.8	14.0	**p = 0.002**
Multiple substance use at entry in MMT (mean, SD)	2.7 ± 1	3.6 ± 2	**p < 0.0001**

Concerning the in-treatment variables, the two subgroups differed significantly in 3 out of 8 in-treatment variables: patients with a "good cooperation" (GC) were more likely to have less cocaine use in the past 30 days prior interview (P = 0.024), less contacts to the injection rooms in the past 14 days (P = 0.023), and more take-home medication allowed (P < 0.0001; table 26). The GC and the UC group did not differ with regard to treatment retention, prescribed methadone dose, treatment setting and concomitant heroin use (i.e., the less addicted, the better the compliance or treatment cooperation).

Table 26: Comparison Between Methadone Maintenance Patients with a "Good Cooperation" (GC) and Patients with an "Unsatisfactory Cooperation" (UC) [In-Teatment Variables]

Variable	Good Cooperation (GC) n=478	Unsatisfactory Coop. (UC) n=149	P-value
Retained in Methadone Maintenance Treatment (%)	82	78	p = 0.285
General practice/ Specialized clinic (%)	75.1 vs. 76.7	24.9 vs. 23.3	p = 0.670
Retained in Methadone Maintenance Treatment (%)	82	78	p = 0.285
Take-home allowed for (3 days or more, %)	81.3	60.6	**p < 0.0001**
Heroin use, 1 day or more in the past 30 days (%)	6.8	56.6	p = 0.974
Cocaine use, 1 day or more in the past 30 days (%)	32.0	46.4	**p = 0.024**
Contacts to the injecting rooms in the past 14 days prior interview (%)	27.5	38.6	**p = 0.023**
Daily methadone dose (mg/d)	73.2 ± 46	80.6 ± 51	p = 0.103

3.1.10 Comparison of Treatment Failures with Those who Remained in MMT

3.1.10.1 Reasons for Leaving MMT

At 12-month follow-up, the practitioners and medical staff noted, if the patients had left treatment within the past 12 months and why the patients had left methadone treatment. For this variable we had a high rate of missing values (67%). At follow-up, 171 out of 660 patients had left MMT and the information could be provided only for 74 out of 171 subjects. Consequently, we had to screen the methadone case register to complete the missing data about the reasons of leaving MMT by March 2001. After this analysis, 131 out of 171 patients were considered as "treatment failures" and the remaining 40 patients (23.4 %) were considered as treatment successes or losses unrelated to the MMT: 16 had withdrawn from opiates, 21 were transferred to another general practitioner and 3 died of AIDS. Patients which were considered as "treatment failures" (arrested [n = 6], discharged by program [n = 5], dropped out voluntarily [n = 26]).
For the majority of the patients (94 patients) the physician responsible for the MMT had no follow-up information. This fact could be due to the behavior of both, the patients and the physicians. The Patients do not take contact anymore and the physicians do not have the time to re-contact their patients. An additional important result was, that all the 19 patients from the "admission cohort" had dropped out at 12-month follow-up.

3.1.10.2 Comparison of Treatment Failures With In-Treatment Patients

As outlined in the previous section, treatment failures were considered as losses related to the MMT. A comparison between the in-treatment cohort and the 131 treatment failures showed significant differences in 4 out of 18 analyzed variables (table 27). Treatment failures had significantly more prescribed methadone doses below 50 mg (32.1% versus 22%, Chi^2 = 8.058, df = 1, *P* = 0.003), a significantly lower rate of allowed take-home medications (64.9% versus 79.5%, Chi^2 = 0,557, df = 1, *P* = 0.001), a significantly lower rate of prescribed comedication (29.8% versus 42.4%, Chi^2 = 6.872, df = 1, *P* = 0.009), and attended significantly less scheduled consultations (90.8% versus 96.6%, Chi^2 = 7.070, df = 1, *P* = 0.008) compared to the in-treatment sample (table 27).

Table 27: Pretreatment Characteristics of Methadone Maintenance Patients: In-Treatment versus Treatment Failure Samples

Variables	In-treatment at t2 n = 486	Treatment Failures n = 131
Age (mean years, SD)	34.6 ± 6	33.5 ± 7
Gender M/F (%)	67.9 / 32.1	69.6 / 30.4
Age at onset of opiate use (mean years)	19.8 ± 5	19.5 ± 4
Intravenous drug use (lifetime) (%)	79.0	82.0
Age at begin of MMT (mean years, SD)	28.4 ± 6	28.1 ± 7
Duration in current MMT (mean years, SD)	6.2 ± 4	5.4 ± 4
Swiss Nationality (%)	87.8	81.8
Not married (%)	73.2	76.0
Employed (%)	25.5	29.1
Daily Methadone Dose, less than 50 mg (%)	34.2	49.2**
Mean Methadone dose (mg/d, SD)	76.8 ± 47	69.8 ± 51
Take-home medication, three days or more (%)	79.5	64.9**
With Comedication (%)	42.4	29.8**
Attended one or more consultation in the past 6 months (%)	96.6	90.8**
Intravenous drug use past six months (%)	51.0	58.0
Use of any heroin during past 30 days (%)	58.5	54.7
Use of any cocaine during past 30 days (%)	34.1	35.2
Multi substance use during past 30 days (%)	88.7	92.4

** $P < .01$

3.1.10.3 Predictors of Treatment Failure: Cox Regression Analysis

To find predictors of treatment failure, respectively to gain a better understanding of the process that may be involved in leaving methadone maintenance, we undertook a forward stepwise regression in which variables representing three kinds of factor were included as potential predictors of attempts to stop methadone maintenance at follow-up: baseline demographic variables, attendance of consultations, take-home privileges, concomitant opiate drug use, methadone dose, dispensing site (table 28).
A forward stepwise multiple regression revealed the following results: Intravenous drug use in the past six months prior interview (*P* = 0.009) and a reported cocaine use in the 30 days prior interview (*P* = 0.039) predicted leaving treatment at follow-up (table 29). A similar result was obtained when a backwards stepwise regression was used. Expected percent of patients remaining in treatment was: 74.1

Table 28: Relative Risks of Treatment Failure, by Patient Characteristics at First Interview (bivariate associations)

Independent variable	**RR**	**Sig. p-value**
Sex (Male, female)	.038	0.845
Age	1.96	0.161
Intravenous drug use, lifetime	0.10	0.747
Employment status	1.82	0.176
Dispensing site	1.54	0.215
Methadone dose	1.46	0.226
No Take-homes	1.01	0.750
having attended no consultations	1.04	0.747
Intravenous drug use in the past six months prior interview	14.8	0.001
Heroin use past 30 days	0.82	0.366
Cocaine use past 30 days	2.20	0.138
Having no prescribed comedication	0.99	0.320

Intravenous drug users (in the past 6 months prior interview) were more likely to drop out of treatment than non intravenous drug users. Cox regression analysis showed a relative risk (RR) of 2.9. Patients with any cocaine use during past 30 days prior interview, show a relative risk of 2.6 to drop out of treatment compared to patients without concomitant cocaine use (table 29). Thus. The less addicted the patients the more likely a methadone maintenance treatment will be successful.

Table 29: Final Model from Forward Stepwise Regression of Predictors of Leaving MMT (n = 616)

Variable	Odds ratio	Significance
Intravenous drug use in the past six months prior first interview	2.89	*P* = 0.009
Any cocaine use during last 30 days prior first interview	2.66	*P* = 0.039

3.2 TREATMENT OUTCOMES IN GENERAL PRACTICE AND IN SPECIALIST CLINIC SETTINGS

After it had been found that the three methadone maintenance programs and the general practices were effective in markedly reducing intravenous drug use, and other deviant behavior among patients who remained in treatment, the question arose if the 200 patients treated in general practice had similar or even better outcomes than the 460 patients treated in specialized clinics ?

In 2000 in the city of Basel, approximately 674 physicians worked in private practice (BFS, T 14.2.2.3). A total of 120 physicians were providing office-based methadone maintenance treatment (MMT), thus 18 percent of all private practitioners.
In this cohort study a total of 70 private practitioners (GP) participated and each had an average of 3 patients in his practice (range: 1 to 33). Looking at the specialty of the physicians, we found a third of GPs, a third in internal medicine and a third of psychiatrists. For 32% of the patients with office-based MMT, the dispensing site for the methadone was a pharmacy, whereas the GP regularly sees the patient in his practice for consultations.

3.2.1 Comparison of Patient Characteristics in General Practice versus in Specialized Clinics

The sociodemographic characteristics of the two treatment groups differed in 2 out of 7 variables (table 30). Patients treated in general practice (GP) were significantly older (35.8 $\pm$ 6 years versus 33.8 $\pm$ 6 years; T-test; $T_{(1,659)} = 3.702$, $P < 0.001$), and had a significantly lower proportion with an employment (18.3% versus 29.0%; $Chi^2 = 5.570$, df = 1, $P = 0.018$) compared to the patients in specialized clinics (SC). There were no significant differences between groups in gender, in marital status, in parenthood, in nationality or education (table 30).

Table 30: Comparison of Demographic Patient Characteristics in General Practice versus in Specialized Clinics (t1)

Variable	General practice n=200	Specialized clinics n=460	Total Sample n=660
Age (years) (Mean $\pm$ SD)	35.8 $\pm$ 6***	33.8 $\pm$ 6	34.4 $\pm$ 6
Range	21 – 55	20 – 59	20 – 59
Median	36.02	32.80	33.75
95% CI	34.9 – 36.7	33.2 – 34.4	33.9 – 34.9
Sex, M (%)	69.0	69.0	69.0
Marital status:			
Unmarried (%)	76.7	73.7	74.6
Married (%)	8.0	9.7	9.1
Divorced/ separated (%)	15.3	16.6	16.3

Parenthood:			
With child (%)	27.0	30.0	29.8
Without child (%)	73.0	70.0	70.8
Nationality:			
Swiss (%)	90.6	85.4	86.9
European Union and other countries (%)	9.4	14.6	13.1
Education:			
School absolved (%)	45.2	46.2	45.9
Apprentice (%)	46.8	52.2	50.7
Higher degree school/ University (%)	8.0	1.6	3.4
Employment history:			
Employed (%)	26.6*	31.1	29.8

* $P < .05$; *** $P < .001$

3.2.2 Comparison of Drug Use Histories

There were no significant differences in drug-use history between the GP and the clinic samples, except for age at first alcohol use and multiple substance use (table 31). Patients treated in GP started alcohol use at a significantly older age (16.8 ± 6 years versus 15.0 ± 3 years; T-Test, $T_{(1,207)} = 2.341$, $P = 0.020$), and had a significantly lower rate of multiple substance use (75% versus 93%; Mann-Whitney-Test, $Z = -6.853$, $P < 0.001$) than the clinic sample. The prevalence rate of patients with intravenous drug use (IDU) did not differ between groups. Patients in both groups entered MMT at an average age of 28 years (table 31).

Tab. 31: Drug Use History, Patients in General Practice versus in Specialized Clinics (t1)

Variable	General practice n=200	Specialized clinics n=460	Total Sample n=660
Age at admission to methadone maintenance treatment (mean, SD)	28.2 ± 6	28.5 ± 6.8	28.4 ± 6.6
Range	16 – 50	16 – 54	16 – 54
95% CI	27.4 – 29.1	27.8 – 29.1	27.9 – 28.9
Age at first heroin use (mean, SD)	19.1 ± 4	19.8 ± 5	19.7 ± 5
95% CI	18.3 – 20.0	19.3 – 20.3	19.2 – 20.1
Age at first cocaine use (mean, SD)	21.5 ± 5	21.3 ± 5	21.3 ± 5
95% CI	20.1 – 22.8	20.7 – 21.9	20.8 – 21.8
Age at first cannabis use (mean, SD)	15.6 ± 2	15.6 ± 3	15.6 ± 3
95% CI	14.5 - 16.8	15.2 - 16	15.2 – 15.9
Age at first alcohol use (mean, SD)	16.8 ± 6*	15.0 ± 3	15.1 ± 3
95% CI	13.9 – 19.7	14.6 – 15.4	14.7 – 15.6
Age at first benzodiazepine use (mean, SD)	22.5 ± 4	22.7 ± 6	22.7 ± 6
95% CI	19.8 – 25.1	21.7 – 23.7	21.7 – 23.6
Proportion of patients with multiple substance use (%)	75.0***	93.0	89.0
Proportion of patients with intravenous drug use (lifetime) (%)	80.0	76.0	77.2

* $P < .05$; *** $P < .001$

3.2.3 Comparison of the Somatic Health State

One section of the questionnaire asked questions about infectious diseases like HIV seropositivity, hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). A third of the physicians did not fill out this part of the questionnaire or wrote "unknown HIV state" and "unknown "hepatitis state" in the first interview. Missing rates had decreased at one-year follow-up interview due to an intervention of the health authorities, by directing the physicians' attention to the importance of this section of the questionnaire for the evaluation of the MMT. Thus, the results at follow-up reflect more realistic prevalence rates.
The prevalence rate of HIV seropositivity did not differ significantly between office-based MMT and MMT in specialized clinics (8.2 versus 11 percent; $Chi^2 = 4.119$, df = 1, $P = 0.128$; table 32). The same accounts at 12-month follow-up. As outlined before, the increase of the prevalence rates over time is biased, due to a greater number of physicians, completing this section of the questionnaire.

Table 32: HIV Seroprevalence in General Practice versus Specialized Clinics at t1 and at One-Year Follow-Up

	Baseline (t1)		1 year (t2)	
Variable	**General practice n=200**	**Specialized clinics n=460**	**General practice n=200**	**Specialized clinics n=460**
HIV seropositive (%)	8.2	11.0	12.3	15.2
HIV negative (%)	62.0	61.0	81.2	81.7
Unknown state (%)	29.8	28.0	6.5	3.1
Total	100.0	100.0	100.0	100.0

Comparing HAV, HBV, and HCV seroprevalence rates in patients treated in GP versus in specialized clinics, the analysis revealed a significantly higher proportion of patients infected with the hepatitis A virus ($Chi^2 = 14.666$, df = 1, $P < 0.0001$) and with hepatitis B ($Chi^2 = 8.735$, df = 1, $P = 0.003$) in the clinic sample. Hepatitis C seroprevalence did not differ between groups (table 33).

Table 33: Hepatitis A, B, C Seroprevalence in MMT (t1)

Variable	**General practice**			**Specialized clinics**		
Hepatitis	**HAV**	**HBV**	**HCV**	**HAV**	**HBV**	**HCV**
Positive (%)	22.3	50.0	54.6	33.8***	64.0**	66.0
Negative (%)	57.7	40.0	25.4	36.2	25.7	24.0
Unknown state (%)	20.0	10.0	20.0	30.0	10.0	10.0
Total	100.0	100.0	100.0	100.0	100.0	100.0

** $P < .01$; *** $P < .001$

At 12-month follow-up we had a decrease in the amount of missing values. Thus, the results at follow-up reflect more realistic prevalence rates. Patients treated in specialized clinics had significantly higher proportions of HAV, HBV and HCV prevalence rates ($P < .05$; table 34).

Table 34: Hepatitis A, B, C Seroprevalence in MMT at 12-month follow-up (t2)

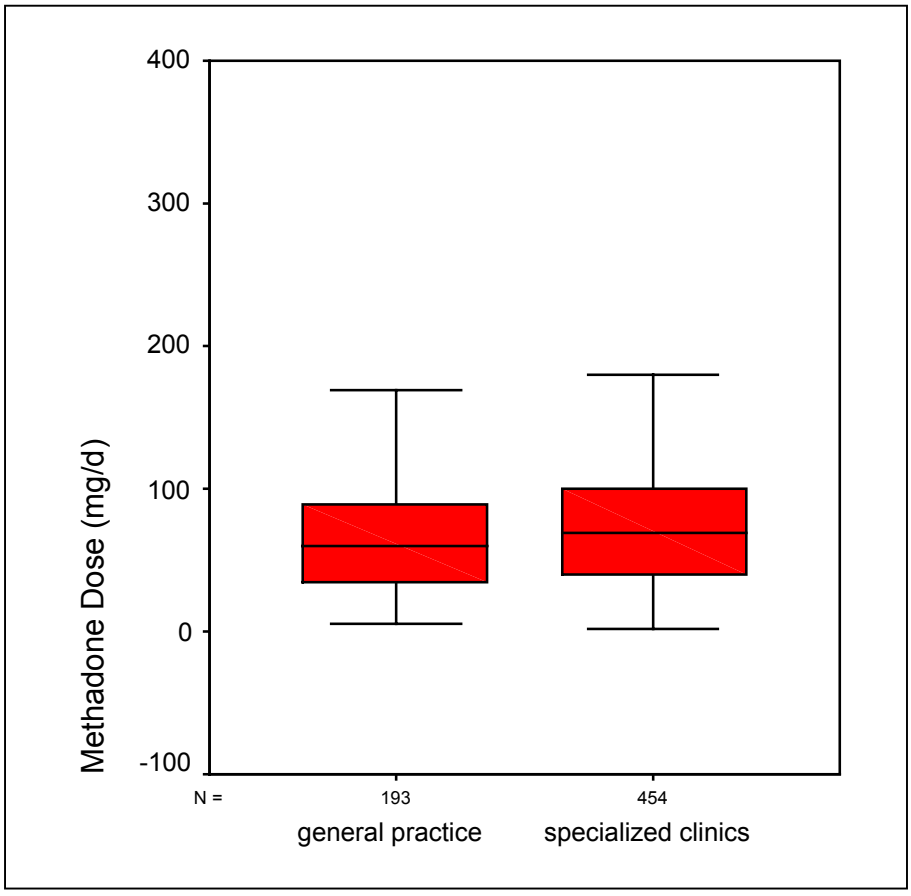
Variable	General practice			Specialized clinics		
Hepatitis	**HAV**	**HBV**	**HCV**	**HAV**	**HBV**	**HCV**
Positive (%)	22.1	52.6	51.3	28.5*	65.1*	65.3*
Negative (%)	55.2	35.1	32.2	57.3	26.8	27.1
Unknown state (%)	22.8	12.3	16.4	14.2	8.1	7.6
Total	100.0	100.0	100.0	100.0	100.0	100.0

* $P < .05$

3.2.4 Comparison of Methadone Dispensing Practices

There were no statistically significant difference in the main daily doses of methadone prescribed to the patients by the GPs (69.3 ± 44.7 mg), and in the clinics (76.7 ± 48.4 mg) at first interview, but a trend ($P = 0.068$). At 12-month follow-up, the mean daily doses of methadone prescribed to the patients by the GPs (68.6 ± 46.3 mg) was significantly lower compared to the methadone doses prescribed by specialized clinics (79.6 ± 52.4 mg; ANOVA; $F_{(1,645)} = 6.348$; $P = 0.012$; Fig. 16).

Figure 16: Prescribed Mean Methadone Doses by the GPs and the Clinics



There were no statistically significant difference in the proportion of low doses of methadone prescribed to the patients by the GPs (39.5%), and in the clinics (37.2%). To measure methadone dose changes over time, we carried out a repeated measures analysis of variance with the study completers. There was a significant effect over time (ANOVA; $F_{(1,621)} = 18.914$; $P < 0.001$) and a significant interaction (ANOVA; $F_{(1,621)} = 18.914$; $P < 0.009$). Thus, methadone doses prescribed by GPs decreased significantly over time, whereas methadone doses prescribed by clinics increased significantly over time.

There were no significant differences between the general practices and the clinics in the proportion of allowed take-home medication (GPs group 69.0 versus specialized clinics 69.3%) (table 35). Considering the higher proportion of patients with concomitant drug use in the clinic sample, we expected a lower rate of take-home privileges in this group. Patients with a prescribed comedication did not differ between groups (table 35).

Table 35: Methadone Doses Dispensed On-Site and as a Take-Home Medication

	General practice		Specialized clinics	
	No.	%	No.	%
Dispensed daily on-site*	43	21.5	96	20.9
Take-home, 3 days or more	138	69.0	319	69.3
With comedication	83	42.1	172	37.4

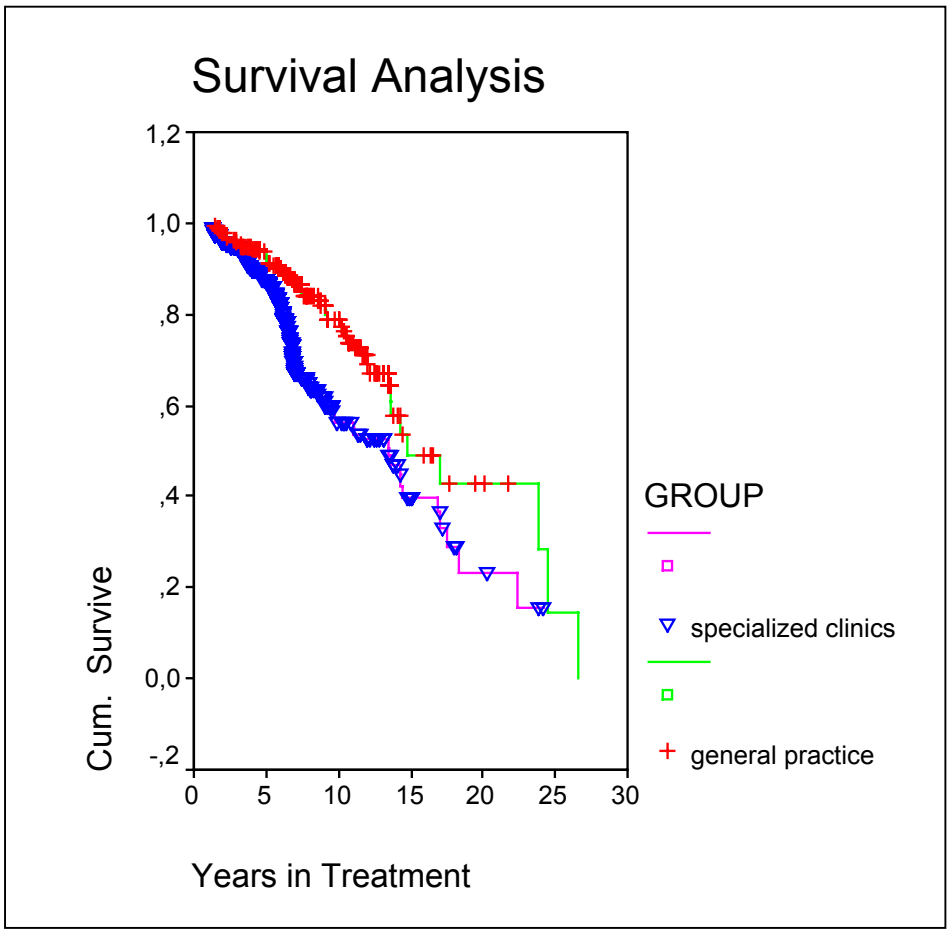
*except on weekends

3.2.5 Treatment Retention in General Practice versus in Specialized Clinics

At one-year follow-up, 75.6% of the GP patients and 72.2% of the clinic patients were still in their treatment (Chi2 = 0.842, df = 1, $P = 0.359$). Thus, the one-year retention rate did not differ between groups. The reasons for leaving treatment were shown in chapter 3.9. A Cox regression procedure was used to compare retention times controlling for baseline differences between the populations.

To compare the survival experience of the two groups of patients, we calculated the Kaplan-Meier survival curves separately for each group (Fig. 17). The mean survival time for patients treated by GPs was 17 years (95% CI = 14.8, 18.9), and 13.2 years (95% CI = 11.8, 14.6) for clinic patients. Log rank testing of the survival curves revealed a significantly better retention for patients in general practices (Log rank test = 14.18, df = 1, $P = 0.0002$; Fig.17). Thus, the survival probability (remaining in treatment) of a patient treated by a GP was significantly higher, than for a patient treated by a specialized clinic.

Figure 17: Survival Analysis of Patients treated by GPs and in Clinics



Legend: The survival time was significantly longer for patients treated in general practice (Kaplan Meier survival analysis, log rank-test, P = 0.0002). A cross (+) represents the time point, when a patient treated by a GP is dropping out of MMT; a delta (∇) represents the time point, when a patient treated by a clinic is dropping out of MMT.

3.2.6 Reported Concomitant Drug Use During the Past 30 Days Prior to the First Interview for Patients treated by GPs an in Clinics

As outlined in chapter 3.1.4, patients were asked by their physician responsible for the treatment, if they had used heroin, cocaine, cannabis, benzodiazepines or alcohol during the past 30 days prior to the first interview. Concomitant drug use is one of the main treatment outcome measures for MMT effectiveness.
We first carried out an intention-to-treat analysis (ITT-analysis, all patients enrolled in the study, including drop outs), and secondly a completer analysis (only the patients still in treatment at 12-month follow-up).

The intention-to-treat analysis yielded the following results: In the GP group a significantly higher proportion of patients (46 percent) reported they had not used any heroin in the past 30 days prior first interview compared to 26 percent in the patients treated in specialized clinics (Chi^2 = 21.056, df =1, P < 0.0001; table 36). For cocaine

use we found again, a significantly higher proportion without any cocaine use in the GP group (79 percent versus 59 percent; $Chi^2 = 14.631$, df =1, $P < 0.0001$).
Patients were also asked if they had used drug intravenously in the past 6 month prior to the first interview: a significantly lower proportion of patients treated by GPs reported intravenous drug use compared to the clinic sample (37 percent in versus 58 percent; $Chi^2 = 16.083$, df =1, $P < 0.0001$; table 36).

Table 36: Reported Drug Use at First Interview, Patients treated by GPs versus Specialized Clinics (ITT-analysis) [a]

	First Interview (t1)		
Drug	**General practice n=200**	**Specialized clinics n=460**	**P-value**
Heroin use:			Chi^2
None (%)	46	26	p < 0.0001
1day or more (%)	54	74	
mean days (mean, SD)	6.9 ± 6	7.4 ± 6	ANOVA
95% CI	5.10 – 8.78	6.47 – 8.37	0.629
Cocaine use:			Chi^2
None (%)	79	59	p < 0.0001
1day or more (%)	21	41	
mean days (mean, SD)	5.3 ± 5	5.7 ± 5	ANOVA
95% CI	3.23 – 7.42	4.73 – 6.81	0.694
Cannabis use:			Chi^2
None (%)	50	42	p = 0.156
1day or more (%)	50	58	
mean days (mean, SD)	20.9 ± 11	20.1 ± 11	ANOVA
95% CI	18.17 – 23.66	18.35 – 21.92	0.641
Benzodiazepine use:			Chi^2
None (%)	81	86	p = 0.238
1day or more (%)	19	14	
mean days (mean, SD)	11.4 ± 10	14.3 ± 11	ANOVA
95% CI	7.20 – 15.70	11.66 – 17.70	0.395
Alcohol use:			Chi^2
None (%)	42	46	p = 0.510
1day or more (%)	58	54	
mean days (mean, SD)	17.6 ± 11	16.7 ± 11	ANOVA
95% CI	15.01 – 20.25	14.77 – 18.53	0.550
Intravenous drug use past 6 months prior to the first interview (%)	37	58	Chi^2 p < 0.0001

[a] *Intention-to treat analysis*

The completer analysis yielded similar results as the previous ITT-analysis: In the GP group a significantly higher proportion of patients reported they had not used any heroin and cocaine in the past 30 days prior first interview compared to the patients treated in specialized clinics. The same accounts for the proportion of intravenous drug use (table 37).

Table 37: Reported Drug Use at First Interview, Patients treated by GPs versus Specialized Clinics (COMPLETER-ANALYSIS)

	First Interview (t1) [a]		
Drug	**General practice n=114**	**Specialized clinics n=244**	**P-value**
Heroin use: None (%) At least 1day or more (%) mean days (mean, SD)	 51 49 8.4 ± 6	 28 72 7.4 ± 6	Chi^2 p < 0.0001 n.s.
Cocaine use: None (%) At least 1day or more (%) mean days (mean, SD)	 76 24 4.7 ± 4	 59 41 6.7 ± 6	Chi^2 p = 0.001 n.s.
Cannabis use: None (%) At least 1day or more (%)	 52 48	 44 56	Chi^2 p = 0.254
Benzodiazepine use: None (%) At least 1day or more (%)	 82 18	 85 15	Chi^2 p = 0.601
Alcohol use: None (%) At least 1day or more (%)	 43 57	 50 50	Chi^2 p = 0.259
Intravenous drug use past 6 months prior to the first interview (%)	40	58	Chi^2 p = 0.009

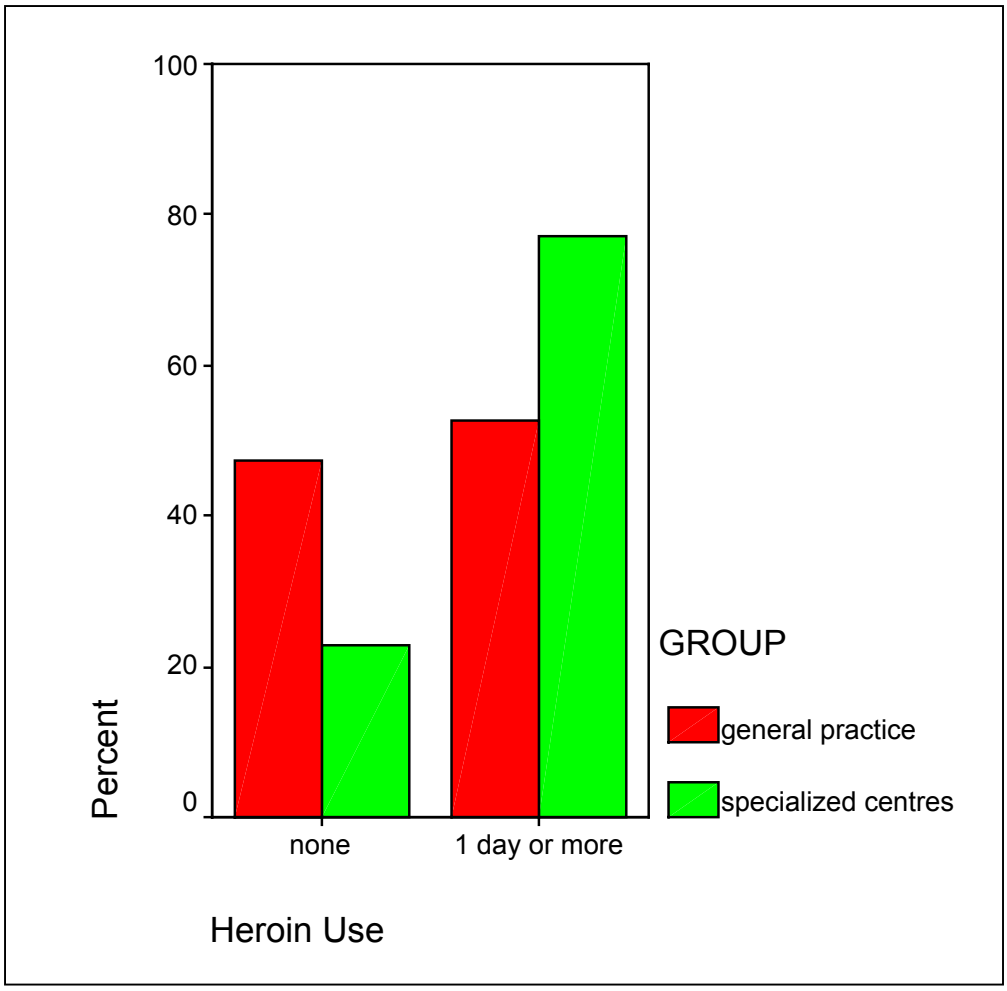
[a] *Completer analysis*

3.2.6.1 Concomitant Heroin Use Over Time: Completer Analysis

Proportions of concomitant heroin use over time were analyzed for study completers. The results from self-reported heroin use at one-year follow-up are displayed in figure 18. For patients remaining in MMT, the percentage of any self-reported heroin use (during the last 30 days) throughout the study differed significantly between groups with 49% in the general practice group and 72% in the specialized clinics group (Chi^2 = 17.808; df = 1; *P* < 0.0001), and with 53% versus 78% at the second interview (Chi^2 = 23.018; df = 1; *P* < 0.0001; Fig.18). The proportion of self-reported heroin use increased over time in both groups: on a significant level for patients treated in specialized clinics (72% to 78%; Wilcoxon-Test; Z = -2.121; *P* = 0.034) and on a non-significant level for patients treated in general practice (49% to 53%; Wilcoxon-Test; Z = -,784; *P* = 0.433).

Furthermore, frequencies of concomitant heroin use over time were analyzed for study completers. At first interview, mean days of heroin use of 8.4 ± 6 days were reported in the general practice group and of 7.4 ± 6 days in the clinic sample respectively (1 to 30 days). At 12-month follow-up, mean days of heroin use of 9.7 ± 7 days were reported in the general practice group and of 7.6 ± 6 days in the clinic sample respectively. The two groups did not differ in the frequency of heroin use (mean days of heroin use in the past 30 days) (ANOVA; $F_{(1,212)}$ = 2.755; p = 0.098). A repeated measures of variance revealed no significant increase of concomitant heroin use over time ($F_{(1,\ 424)}$ = ,242; p = 0.623). A covariate analysis of age and length in treatment revealed that these variables had no impact on the results.

Figure 18: Heroin Use at t2, Completer Analysis



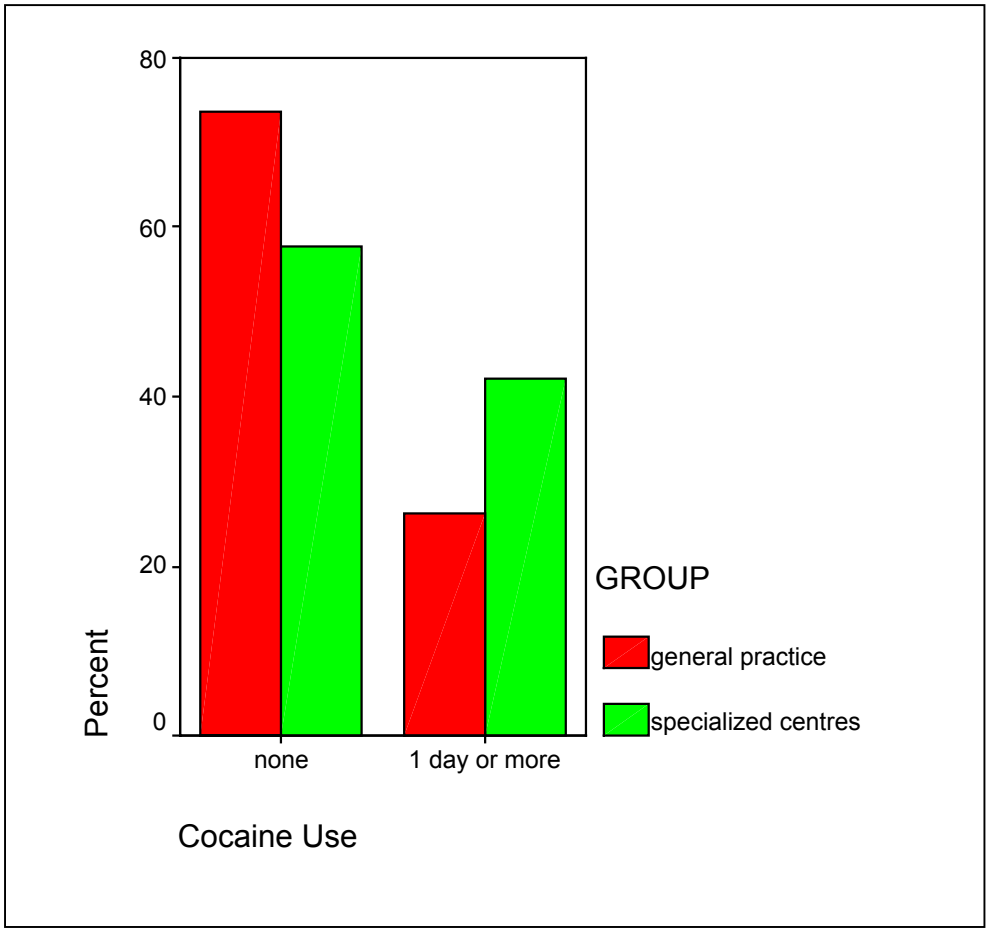
Legend: a significant higher proportion of heroin use in patients treated in specialized clinics (Chi^2 = 23.018; df = 1, p < 0.0001)

3.2.6.2 Concomitant Cocaine Use Over Time: Completer Analysis

The results from self-reported cocaine use at one-year follow-up are displayed in figure 19. For patients remaining in methadone maintenance treatment, the percentage of any self-reported cocaine use (during the past 30 days) throughout the study differed significantly between groups with 24% in the GP group and 41% in the clinic group (Chi^2 = 10.608; df = 1; *P* = 0.001) at first interview, and with 26% versus 42% at the second interview (Chi^2 = 8.410; df = 1; *P*= 0.004; Fig. 19). The proportion of self-reported cocaine use remained stable over time in both groups and accordingly there was no effect over time (*P* = 0.593; *P* = 0.655).
Furthermore, frequencies of concomitant cocaine use over time were analyzed for study completers. At first interview, mean days of cocaine use of 4.7 ± 4 days were reported in the general practice group and of 6.7 ± 6 days in the clinic sample (during the past 30 days). The two groups did not differ in the frequency of cocaine use at first interview (ANOVA; $F_{(1,129)}$ = 1.922; *P* = 0.168), and at 12-month follow-up (GP group, 7.8 ± 7 days; SC group, 7.1 ± 6 days; ANOVA, $F_{(1, 252)}$ = 2.660; *P* = 0.105). For patients treated in general practice, there was a significant increase of cocaine use

over time (ANOVArm; $F_{(1, 252)}$ = 4.499; *P* = 0.036). A covariate analysis of age and length in treatment revealed that these variables had no impact on these results.

Figure 19: Cocaine Use at t2, Completer Analysis



Legend: a significant higher proportion of cocaine use in patients treated in specialized clinics
Chi^2 = 11.975; df = 1, *P* < 0.001

3.2.7 Comparison of Scheduled and Attended Consultations in General Practice versus in Specialized Clinics

At first and second interview, the physicians responsible for the MMT had to report the number of scheduled consultations and the number of attended consultation by the patient in the past six months.

3.2.7.1 Comparison of Attended Consultations, ITT- Analysis

At first interview, patients in general practice attended an average of 5.15 out of 6.19 scheduled consultations, patients in specialized clinics attended an average of 6.80 out of 7.86 scheduled consultations in a six-months period (table 38). This means, that patients in both groups attended approximately one consultation less than

scheduled by their physicians. As expected, patients in specialized clinics had significantly more scheduled consultations, and as a consequence, attended significantly more consultations (table 38). These results were similar at follow-up (table 38).

Tab. 38: Scheduled and Attended Consultations, Patients treated by GPs versus Specialized Clinics at First Interview and at One-Year Follow-Up (t1-t2)

Variable	General practice n=182	Specialized clinics n=434	Total Sample n=616	P-value
Number of scheduled consultations in the past 6 months (Mean ± SD) at t1 Range 95% CI	**6.19** ± 5 1 – 26 5.46 – 6.97	**7.86** ± 5 1 – 41 7.35 – 8.36	7.37 ± 5 1 – 41 6.95 – 7.78	ANOVA P < 0.0001
Number of scheduled consultations in the past 6 months (Mean ± SD) at t2 Range 95% CI	6.14 ± 5 1 – 29 5.42 – 6.87	7.42 ± 4 1 – 30 7.04 – 7.80	7.04 ± 4 1 – 30 6.70 – 7.39	ANOVA P < 0.001
Number of attended consultations in the past 6 months (Mean ± SD) at t1 Range 95% CI	**5.15** ± 5.88 1 – 25 4.41 – 6.97	**6.80** ± 5 1 – 40 6.34 – 7.27	6.32 ± 5 1 – 40 5.93 – 6.71	ANOVA P < 0.0001
Number of attended consultations in the past 6 months (Mean ± SD) at t2 Range 95% CI	5.25 ± 5 1 - 23 4.55 – 5.95	6.28 ± 4 1 – 30 5.94 – 6.61	5.98 ± 4 1 – 30 5.67 – 6.30	ANOVA P < 0.004

3.2.7.2 Comparison of Attended Consultations Over Time: Completer Analysis

Frequencies of attended consultations over time were analyzed for study completers. At first interview, the mean number of attended consultations reported in the GP group were 4.7 ± 4 consultations and 6.6 ± 4 consultations in the clinic sample (range: 1 to 30 consultations). At 12-month follow-up, the mean number of attended consultations reported in the GP group were 6.4 ± 5 consultations and 6.1 ± 4 in the specialized clinics group respectively. The two groups differed significantly in the frequency of attended consultations (ANOVA; $F_{(1,538)} = 8.369$; $P = 0.004$). As shown in the ITT-Analysis, this was due to more offered consultations in specialized clinics. A repeated measures of variance revealed a significant increase of consultations in the GP group over time (ANOVA; $F_{(1,538)} = 14.13$; $P < 0.0001$). A covariate analysis of patients' age and length in treatment revealed that these variables had no impact on the results.

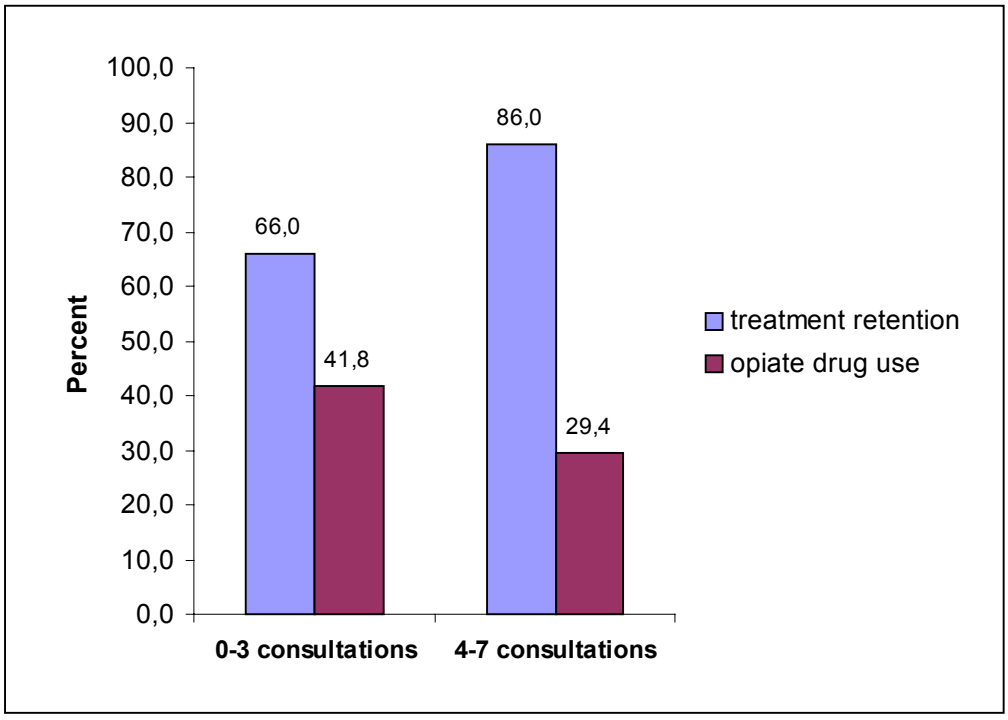
3.2.7.3 Frequency of Attended Consultations and Treatment Outcome

Additionally, we analyzed the proportion of patients attending a low rate (0 to 3 consultations) and a high rate (4 to 7 consultations) in each treatment setting (see chapter 3.1.9.3). Specialized clinics had a significantly higher proportion of patients attending a high rate of consultations compared to general practices (83% versus 49%; $Chi^2 = 76.737$; df = 1, $P < 0.0001$). The ratio for patients attending a low rate of consultations was 51% for the GP group versus 17% for the clinic sample.

As shown for the total sample in chapter 3.1.9.3, there was a strong association between the number or attended consultations and retention in treatment. For patients treated in general practice, there was a strong association between the amount of attended consultations and retention in treatment. Patients with a high rate of consultations had a significantly better retention rate (86%) compared to patients attending a low rate of consultations (66%) (Chi^2 = 9.977; df = 1; *P* = 0.002) (Fig. 21). This result was also consistent for patients treated in specialized clinics (78.7% versus 54.2%; Chi^2 = 19.019; df = 1; *P* < 0.0001) (Fig. 20).

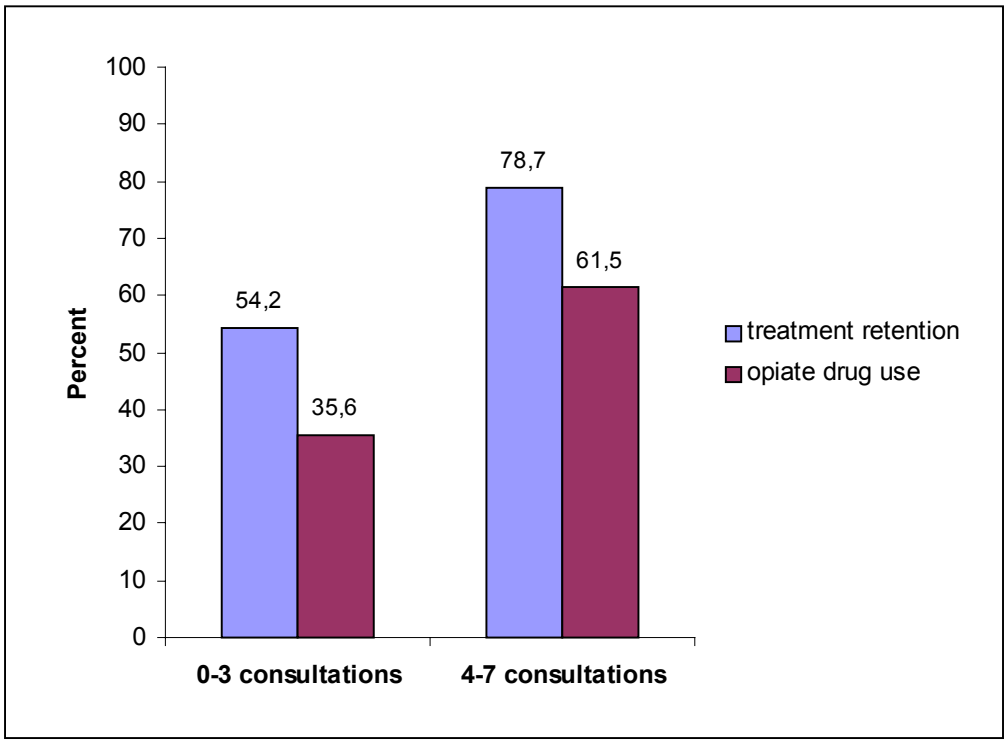
The hypothesis of an association between a high rate of consultations and a low rate of concomitant heroin use could be demonstrated, but only for patients treated in general practice (Fig. 20). Patients with a high rate of consultations had a significantly lower rate of concomitant heroin use (29.4%) compared to patients attending a low rate of consultations (41.8%), but this difference was not significant (*P* = 0.133) (Fig. 20). Thus, for the GP group, the amount of consultations probably do not have an impact on concomitant heroin use.
For the clinic sample an association between a high rate of consultations and the proportion of concomitant heroin use could be demonstrated, but in an inverse way.
Patients with a high rate of consultations had a significantly higher proportion of concomitant heroin use (61.5%) compared to those with a low rate of consultations (35.6%) (Chi^2 = 10.776; df = 1; *P* = 0.001) (Fig. 21). Thus, for the clinic sample, patients with concomitant drug use seem to get more treatment contacts and treatment services, than patients with no or less concomitant heroin use.

Figure 20: Number of Attended Consultations, Retention in Treatment and Concomitant Opiate Use in General Practice



One-Year Retention; *P* = 0.002 Proportion of Concomitant Opiate Use; *P* = 0.133

Figure 21: Number of Attended Consultations, Retention in Treatment and Concomitant Opiate Use in Specialist Clinic Settings.



One-Year Retention; $P < 0.0001$ Proportion of Concomitant Opiate Use; $P = 0.001$

As demonstrated the results in chapter 3.1.9.4, patients with a good cooperation (75.1% versus 76.7%) and a unsatisfactory cooperation (24.9% versus 23.3%) were equally distributed in the GP group and in the clinic sample ($P = 0.670$).

4. Discussion

4.1 Treatment Outcomes of the Total Sample

To our knowledge, this is the first large-scale study comparing treatment outcomes of methadone maintained patients in general practice versus in specialized clinics in terms of psychosocial support. The first part of the discussion focus on the results of treatment outcomes in the total sample (n = 660), the second part focus on the comparisons between patients treated in general practice and in specialist clinic settings.
There were no significant *baseline gender differences*, except for women with a younger age when entering a MMT and a higher proportion of married women compared to men. The overall mean age was 34.4 years with 69% of men. The result of less patients from minority groups in MMT (13%) than in the general population in the city of Basel (27.7%) indicates, that more efforts are needed to attract these groups of opioid dependent subjects in addiction treatments. Furthermore efforts for the amelioration of the formal education, apprentice, and higher degree school of addicted patients must be undertaken, as well as an increase of the proportion of patients with an employment. This worser formal education and employment status of opioid dependent subjects compared to the general population could also be demonstrated in the methadone treatment outcome studies of Hermann (1986), and Petitjean & Schaller (2002[b]).

The mean age at first heroin and cocaine use is comparable to earlier findings of MMT outcome studies in Basel (Petitjean et al., 2000), in Geneva (Petitjean & Schaller, 2002 [b]), and in the United States (Ball & Ross, 1991, p. 41). The high rate of *multiple substance use* before entering a MMT of 89% is consistent with a recently published study of Gossop et al. (2003), who reanalyzed the baseline characteristics of 1075 methadone maintained patients in the UK and found 87% of patients with prior multiple substance use. These pre-treatment characteristics are very important and until now, they have not been considered in the whole literature of the effectiveness of MMT, which are all predicting on one substance, heroin. Thus, these results should be considered in new clinical interventions, in future clinical studies and in the interpretation of treatment outcomes.

The prevalence rates of *HIV seropositivity* between 9% (at t1) and 11% (at t2) are within the expected range of previous studies in Basel (Petitjean et al., 2000) and the statistics of the federal public health authorities (BAG, Aids und HIV in der Schweiz, 2000). Maintenance treatments in other cantons in Switzerland, like Vaud (B. Favrat, 2001) reported a HIV prevalence rate of 9% in 1040 methadone maintained patients; in Geneva a HIV prevalence rate of 11.5% was reported in 2000, respectively 13.2% in 2001 (Petitjean & Schaller, 2002[b]). In the present study, we found significantly higher rates of *HIV seropositivity* in women. This is consistent with the results of a recently published study of Morrow & Costello (2004). They developed a targeted prevention program for women and emphasized the importance of such interventions in daily clinical practice. Furthermore, the high proportion of patients with a retroviral medication could be explained by a high engagement of internists in hospitals

(treatment and research) for this subgroup of patients (Opravil et al., 2002). Observing the HIV prevalence rates in MMT in the City of Basel and the number of MMTs over time, we can see a significant decrease of HIV infected patients and an increase of MMTs over the last decade.
Looking at the *prevalence rates of hepatitis A (36%), B (55%) and C (54%)*, we found similar rates as reported in earlier MMT evaluation studies (Petitjean et al., 2000; Petitjean & Schaller, 2002[b]). Due to the 30% of missing values, the results must be interpreted with caution because of possible under representation. Cullen and colleagues (2003) identified in a GP sample (n = 380) in Ireland, 73% of the MMT patients being HCV positive. Fitzgerald and colleagues (2001) found in 138 client records a 79% having antibodies to hepatitis C and 16.37% were HIV positive.

Retention in treatment: compared to earlier large-scale observational studies, where the authors found an overall retention rate between 63.5 percent (Ball & Ross,1991), respectively 65 percent (Hubbard et al., 1989) and 90 percent (Gearing et al., 1974), the one-year retention rate of 74 percent in this cohort study can be judged as very good. Furthermore the results show that 78% of the patients are in MMT for more than 3 years, demonstrating the effectiveness of these treatments and the capacity to retain opiate-dependent patients in treatment. Consistent with the results from previous RCTs' and observational studies (Ball & Ross, 1991; Payte et al., 1993; Eap et al., 2000; McGlothlin et al., 1981a; Joe et al., 1991; Caplehorn et al., 1994), patients receiving over 50 mg of methadone in our study, had a significantly longer length of stay in treatment compared to those receiving less than 50 mg daily, and a significantly better retention in treatment rate.

Methadone dispensing practices: Most patients were prescribed methadone doses between 30 mg and 110 mg, thus 68% were in this dose range. The mean daily methadone dose of 74 mg indicates, that most patients are in a good clinically recommended dosage range. Surprisingly, we found even higher mean methadone dosages in women. Looking at the lower weight of women we would expect lower methadone doses, corresponding to the body weight. This gender specific result should be explored in future clinical trials, due to a lack of existing gender comparison studies. The proportion of 70% of the patients with allowed take-home methadone medications can be interpreted on one hand as a 'laisser faire' policy of the physicians, or on the other hand as a high proportion of 'unproblematic patients' having matched (according to patients needs) treatment modalities. The evidence, that patients with take-home privileges have a significantly lower proportion of patients with concomitant heroin and cocaine use do support this hypothesis. One can be confident, that the physician have a good judgement. Prescribed comedication in 40% of the patients indicates, that nearly a half of the patients have a co-occuring disorder (somatic disorder, one or more psychiatric disorders, one or more disorders related to other substance use). This is bellow known prevalence rates from previous studies (Table 3, p. 7).

Reduction in opioid use is one of the main treatment outcome variables to measure the effectiveness of MMT: As expected, the comparison of the three treatment cohorts (admission sample 68% concomitant heroin use; average-stay sample 62%, long-term sample 52%) clearly showed a significant reduction of opioid use in MMT over time. But the reduction was not as impressive as the results reported from the multi-site study of Ball & Ross, where the concomitant opioid use decreased from 66.7% to 7.6% (Ball & Ross, 1991, p. 164).

Proportion of patients (n = 660) without opioid use: the proportion of patients without any heroin use in the past 30 days prior interview was 45 percent. This results are not as good as the results reported in the meta-analysis of Marsch (1998), which found an overall proportion of patients without opioid use of 67 percent, as well as Vanichseni (72%; 1991) and Yancovitz (71%; 1991). On the other hand, Ball & Ross (1991) could demonstrate that there was a considerable variation of abstinent patients from one program to another (range: 44% to 90%). Our results do not support the evidence of an association between high methadone doses (more than 50 mg) and less concomitant heroin use, as was found by Gossop et al. (2003), Hartel et al. (1995), Johnson et al. (1992, Stohler et al. (1998), Strain et al. (1999), and Preston et al. (2000).

Reduction in cocaine use: Furthermore, a significant reduction of cocaine use could be observed in the three treatment cohorts (admission sample 57%; average-stay sample 40%, long-term sample 28%) over time. This is consistent with the results from Magura et al. (2002), indicating that MMT can help dually-addicted patients to reduce their cocaine use.
Evidence was found, that the MMT had no impact on the reduction of concomitant use of cannabis, sedatives and alcohol, thus there was even an increase over time for these substances. These results are consistent with the results from Ball & Ross (1991) and Gossop (2003). This result should be of concern for the physicians responsible for the MMT, and patients should be instructed about the risks of a respiratory depression by taking methadone and alcohol together, as well as their alcohol use could be controlled by breath tests.

Intravenous drug use: Surprisingly, there was an significant increase of lifetime intravenous drug use in the cohorts (average-stay sample from 76% to 83%; long-term sample from 79% to 85%), representing 6% of the non IDUs' switching to intravenous drug use within one year. One possible explanation could be an increase of cocaine dependent patients, due to an increase of available cocaine in European countries, or "heroin chasers" switching from smoking to intravenous heroin use. These findings should be of concern for the clinicians treating opioid-dependent patients in MMT. However, the evaluation showed a significant decrease of needle sharing over time, indicating a decrease of risk behavior in the cohort.

Offered number of consultations and treatment outcome in the total sample: A second research question hypothesized that patients with more scheduled consultations would have better treatment outcomes, than those with less scheduled consultations. Our findings are consistent with previous studies, demonstrating that patients with more consultations had a significantly better retention in treatment (81% versus 61%) compared to patients with less scheduled consultations. Thus, demonstrating that the H1-hypothesis is true. This result is consistent with the findings of McLellan et al. (1988, 1993) and Joe et al. (1991), demonstrating that the "dose" of treatment services can determine treatment outcomes: In the study of McLellan (1993), patients with methadone dispensing alone had a 6-month retention rate of 31%, those with methadone + standard counseling a retention rate of 59%, and those with methadone + enhanced counseling (counseling, medical/ psychiatric, employment, and family therapy) had a retention rate of 81%. An association between amount of counseling and improved outcomes has been reported in several other studies (Ethridge et al., 1995; Fiorentine & Anglin, 1996).

An association between a high amount of consultations and less concomitant heroin use was not found and the hypothesis H1 has to be rejected for this outcome measure. Our results showed, that patients with less consultations had significantly less concomitant drug use, those with more consultations had significantly more concomitant heroin use (43% versus 60%). This result is not consistent with the results of McLellan and colleagues (1993) which demonstrated that none of the patients with methadone dispensing alone achieved a 16 consecutive weeks of negative urines, 28% of those with methadone + standard counseling achieved 16 consecutive weeks of negative urines, and those with methadone + enhanced counseling achieved 55%. On the other hand, recent studies with randomized designs have failed to show consistently that the provision of additional services, achieve better outcomes than MMT without councselling (Mattick et al., 1998; Kraft et al., 1997). In the present study, one possible explanation could be that physicians schedule more consultations for the more "problematic patients", whereas the "well functioning patients" receive less consultations, according to clinical evidence. Evidence for this interpretation was additionally found in a significantly higher proportion of patients with concomitant cocaine use as well as intravenous drug use in the 'high rate' consultation group. Taken together the results indicate, that improved treatment outcome is associated with a higher rate of offered consultations. Compared to an earlier survey conducted by von Bardeleben and colleagues (1993), the number of offered consultations by physicians in a six-month period has decreased from a mean of 9.0 $\pm$ 7 to 7.4 $\pm$ 5, and proportionally the number of attended consultations by the patients decreased from 8.4 $\pm$ 6 to 6.3 $\pm$ 5 in the last 10-year period. Overall, scheduled and attended consultations showed considerable variations from one program to another, probably due to different fulltime equivalents (FTE) between specialized clinics and general practice. The number of scheduled and attended consultations remained stable over time, indicating consistency of treatment services at one-year follow-up. In summary these findings in 1993 and 2001 indicate, that patients' behave in attending approximately one consultation less than scheduled by their doctors.

Treatment cooperation and treatment outcome: In order to get a more precise impression of the relation between the attendance of consultations and treatment outcome, we compared patients with a "good cooperation" (GC) (compliant patients) and those with a "unsatisfactory cooperation" (UC) (non-compliant patients) and found evidence-based results. We hypothesized, that patients with a worse social functioning, multiple substance use and a higher proportion of dual diagnosis would show a unsatisfactory treatment cooperation. Our results showed, that patient with a "good cooperation" were significantly more often employed (better social functioning), had less multiple substance use at entry in MMT, and a lower rate of co-morbidity, significantly less concomitant cocaine use and more take-home privileges. These results provide further support of the relation between patients' co-morbidity, compliance, and treatment outcomes which has been demonstrated in previous studies (Gold & Slaby, 1991; Cacciola et al., 2001). Interestingly, a significantly higher proportion of women was found in the non-compliant group. One possible explanation could be, that women are more involved in parenthood obligations, have more often a relation to an addicted spouse, and as a consequence have less time to attend the consultations compared to men (Hser et al., 2003).

Treatment failures versus in-treatment patients: Evidence was found, that treatment failures had significantly lower methadone doses, less prescribed co-medication, less

take-home privileges and attended less consultations than patients remaining in MMT. Thus, as discussed in the previous section, in-treatment variables (methadone dosage policy, take-home medication, attendance of consultations) seem to have a higher impact on retention in treatment than patient variables. This was postulated by Ball & Ross in their large-scale study (1991). These results were emphasized by the analysis of potential predictors of treatment failure in this cohort study. Only two in-treatment variables were identified as predictors for treatment failure: continuous intravenous drug use in MMT and concomitant cocaine use.
In conclusion, patients in this large-scale study with a one-year follow-up showed improvements on most of the key outcome variables in a MMT. Their use of heroin was halved, and substantial reductions were found for cocaine. There were also improvements in physical health status at follow-up. The present study showed substantial reductions in a range of problem behaviors among unselected samples of opioid dependent patients which are sustained to one-year follow-up. An association between amount of consultations and improved outcomes could be demonstrated for retention in treatment.

4.2 Methadone Maintenance in General Practice versus in Specialized Clinics

The second part of the discussion focus on the results comparing treatment outcomes in general practice (n = 200) versus in specialist clinic settings (n = 460). We hypothesized that patients treated in general practice would have better or equal treatment outcomes compared to patients treated in specialized clinics with GPs' treating more stable patients. Thus, we aimed to demonstrate the clinical significance and the stability of treatment outcome in the two treatment modalities over time. A second research question focussed on the relation between the number of attended consultations and treatment outcome in MMT in primary care versus in specialized clinics. We hypothesized, that patients in general practice would proportionally attend more scheduled consultations than those treated in specialized clinics.

Patients treated in both the general practices and the specialized clinics settings showed improvements on most of the main outcome variables. We compared to populations with similar *baseline variables*: gender, marital status, nationality, age at begin of heroin, cocaine use, and age at begin of MMT. However, the two populations differed significantly in age (33.8 yrs versus 35.8 yrs). Furthermore patients treated in GP had a lower proportion of patients with multiple substance use at MMT entry and started at an older age with alcohol use, indicating a lower rate of co-morbidity. Prevalence rates of HIV and HAV, HBV and HCV differed between groups, again showing patients in general practice with a better health status.

The main findings for the *one-year retention in treatment* were the following: The overall retention rate was 73.6%. The one-year retention rate for patients in general practice was 76%, and for patients in clinics 72%, thus did not differ significantly. As we hypothesized, the mean survival time for GP patients was significantly longer, than for clinic patients (16.9 years vs. 13.5 years). Our results are consistent with those in the Swiss methadone case register analysis of Falcato et al. (2002) in Zurich, including a total of 524 in general practice versus 550 patients in specialized institutions over five years. They found a significantly longer retention time for patients treated in general practice (Kaplan-Meier; $P < 0.001$). Consistent with our

results was a methadone case register analysis of Petitjean & Schaller in Geneva, including a total of 1034 patients (454 in general practice versus 580 patients in specialized institutions) (Petitjean & Schaller, 2002[b]). They found a significant longer survival time in treatment for patients treated by GPs. The results in our study are not consistent with the findings in a RCT of Fiellin et al. (2001) and the observational study of Gossop et al. (1999). They found no differences in retention between the GP and the clinic group. One explanation could be, that Fiellin included only highly selected stable patients in his study without dependencies on other substances, without psychiatric co-morbidity, and without concomitant drug use.

Reduction of heroin use: Evidence was obtained that *concomitant heroin use* decreased in both treatment settings over time for patients retained in the study (completer analysis). Concomitant cocaine use remained stable over time. As we hypothesized, the proportion of patients with self-reported Illicit heroin and cocaine use in the past 30 days was significantly lower in patients treated by GPs (heroin: 42% versus 64%; cocaine: 19% versus 42%) compared to patients treated in clinics. Patients in general practice had also a significantly smaller proportion of patients with multiple substance use (75%) compared to those treated in clinics (93%), and a significantly lower proportion of patients with intravenous drug use in the past six months prior interview (34% versus 49%). Alcohol use outcomes were poor for both groups with little change in frequency of drinking. Poor drinking outcomes have been reported elsewhere (Gossop et al., 1999; 2003; Hubbard et al., 1989). Concomitant alcohol use is a problem for both settings of MMT. Cannabis use remained unchanged too and the use of non prescribed benzodiazepines is high in this population (Ladewig & Simoni, 1996).

An association between the amount of consultations and improved outcomes has been reported (Etheridge et al., 1995; Fiorentine et al., 1996; McLellan et al., 1988, 1993). To our knowledge, this is the first study demonstrating, that the *provision of more consultations* is more effective for MMT outcomes, both in general practice and in specialist clinic settings. Consistent with previous studies, the provision of services in addition to the administration of methadone has been shown to lead to improved outcomes (Ball & Ross, 1991; McLellan et al., 1993). Individual counseling sessions are the base of all treatment modalities in MMT, and they constitute one of the most frequent forms of therapeutic contact within methadone programs. Simpson et al. (1982) also reported that program participation as measured by session attendance was related both to improved drug use outcomes and to higher patient satisfaction ratings.
For patients treated in general practice in our study an association between session attendance and improved drug use outcomes was found, but on a non significant level. GP patients with a high rate of consultations had less concomitant heroin use compared to GP patients a low rate of consultations (29.4% versus 41.8%). For patients treated in *clinics* this association was not found. Clinic patients with a high rate of consultations had significantly more concomitant heroin use compared to clinic patients with a low rate of consultations (61.5% versus 35.6%). Indicating, that physicians in the clinics schedule more consultations for the more “problematic patients”, thus providing individually targeted interventions.
Somewhat surprising was the fact, that the equal proportion of non-compliant patients in both the GPs and the specialist clinic settings (25% versus 23%). We expected that GPs would have a smaller proportion of patients with an unsatisfactory cooperation (UC) than the clinics. One explanation could be the fact, that most GPs

provide MMT to opioid-dependent patients since the late seventies in the area of Basel, and as a consequence have a lot of experience, allowing them to treat and to cope with difficult patients.
The finding that patients do attend approximately one consultation less than scheduled by their physicians in private practices as well as in specialized clinics indicates, that the cooperation between the patients and their physician is as good in both settings. Patients in primary care attended an average of 5.14 out of 6.19 scheduled consultations, patients in clinics attended an average of 6.80 out of 7.86 scheduled consultations in a six-month period. As expected, the patients treated in general practice had significantly less scheduled, respectively attended consultations than those in specialized clinics. This could be explained by a higher physician-patient ratio in specialized clinics, thus physicians having more time for their patients compared to general practices.
One limitation of the study is, that we have to be aware, that the amount of consultations/ counselling *per se* may not be the active ingredient of treatment. It may be more important to provide specifically targeted interventions (Avants et al., 1998). We do not know the ingredients of the assessed number of consultations in this cohort study.

Methadone doses prescribed by GPs' were lower, but differed not on a statistically significant level at the first interview. Daily methadone doses were in a good therapeutic range (69.3 $\pm$ 44.7 mg versus 76.7 $\pm$ 48.4 mg) (Payte et al., 1993). Doses prescribed by clinics increased significantly over time and this result is consistent with the results of a multi-site observational study in Amsterdam of Langendam et al. (1998). Surprisingly, the amount of take-home medication did not differ between groups as well as the proportion of patients with a comedication. This result is surprising, because the three specialized clinics were supposed to treat more "problematic patients" with more co-morbidities (somatic, psychiatric, social) than the GPs. Therefor we would expect less patients with take-home medication and more patients with a comedication. On the other hand, this result could reflect, that GPs with a long experience in MMT treat a substantial subgroup of patients with co-morbidities. These results are consistent with the results about cooperation.

Multi-site, prospective studies of this kind have the merit of representing patients and services in the real world, and have high external validity and allow a generalization of the findings (Simpson et al., 1999). This prospective observational study has some *limitations* which needs to be addressed. First the absence of random assignment and a non-treated control group (Fletcher et al., 1997). Due to ethical purposes, opioid dependent patients are nowadays not allocated anymore to "waiting lists" or treated with a placebo. The lack of random assignment requires great caution in making any inferences from the outcomes achieved by patients in the two treatment settings. However, although the patients in this study were not randomly allocated to the different treatment modalities, the patients receiving methadone treatment from GPs or from clinics were similar in their demographics, and in the type and severity of their substance use behaviours and other presenting problems at intake. There was no systematic selection process by which patients were allocated to either physicians in general practice or to clinics. The main problem drug in both treatment groups was heroin and multiple substance use was common.
Greater caution is needed with regard to interpreting the findings of the GP sample in our study. This group of GPs may not be representative for all GPs, because they represent approximately 20 percent of all GPs in the City of Basel. But they are

representative for a typical setting of a general practice, having a major part of other non-substance use patients and a mean of 3 patients with substance use disorders in each private practice. Nevertheless, in an recent representative Swiss survey of private practitioners (n = 129), 80 percent of the private practitioners' noted, that they would encourage a physician colleague to take some methadone maintained patients in his practice, and only 10 percent would not recommend their colleagues to take a patient in a MMT, due to "personal problematic experiences" (Hermann, 2001). This result indicates a high acceptance within physicians for addicted patients.

The reliability of self-reports of the use of drugs over a defined time period is open to question. While underreporting of concomitant heroin use is common (Harrison et al., 1995), there is some evidence according to Farabee & Fredlund (1996), that people who have participated in a replacement therapy with methadone may be more likely to report that they have used drugs than are those who have not been in any treatment. To control concomitant drug use or alcohol use, physicians in both settings collect urine specimens or do a breath test with their patients if appropriate. These urinalyses are done on a individually targeted way. That is, some doctors control concomitant drug use weekly, others monthly. These urinalyses results were not asked in the questionnaire, because earlier surveys provided 80% of missing values in this section. The fact that some patients did not tell the truth by underreporting concomitant drug use or HIV risk behaviour to their doctors could be a limitation of the present study.

A further limitation of the study could be the lack of information of the contents and the length of the consultations and counseling. As Zanis states, "regardless the source, recording treatment service data on the individual patient level is a complex task that involves the assessment of multiple factors including the type, frequency, quality and quantity of treatment services" (1997, p. 31). Results of their study showed that measures of treatment service delivery can vary, based on who provides the information (e.g. patient or physician/ treatment staff) and what different procedures are used for data collection (self-report versus record abstraction). Nevertheless, there was a good correspondence between the estimates of the physicians/ treatment staff and the patients. As Simpson states, "although much remains unknown about the "black box" of methadone maintenance treatment, and what occurs during the treatment process, the measure of the frequency of offered and attended consultations to the patient provides some insight into this area" (Simpson & Sells, 1982, p. 27).

5. Conclusions

In conclusion, this study yielded positive results and improvements for patients in MMT in general practice and in specialized clinics in terms of attended consultations treatment cooperation, concomitant drug use and retention time in treatment. There were some differences between treatment in general practice and in clinics. Results show substantial reductions in concomitant heroin use, among samples of opiate-dependent patients treated in GP and in clinic settings, which are sustained to one-year follow-up. Our results support the effectiveness of methadone maintenance provided by primary care physicians' offices and favour a stronger participation of private practitioners in MMT. Providing better professional support and financial compensation may enhance their engagement.

The results of this study provide further support for the feasibility and effectiveness of methadone treatment provided within a primary care setting, and show that treatment outcomes for such patients can be as satisfactory as for patients in specialist drug clinics. These results support the findings in studies from Britain and Australia, which reported on the feasibility of prescribing methadone within primary health care settings (Byrne et al., 2000; Gruer et al., 1997; Weinrich & Stuart, 2000). Furthermore these results demonstrate that GPs' treat a substantial subgroup of problematic patients in their practices (25%) , showing a great experience in the field of addiction, due to a long duration of patient-doctor contacts over years, in some cases for nearly 20 years.

Despite the positive findings of this study, our results also raise questions about certain GP and clinics prescribing practices. A subgroup of patients have methadone take-home privileges despite regular concomitant heroin and cocaine use, continuing risk behavior, and attending less consultations. Furthermore, targeted interventions should be developed and provided for different subgroups of patients (e.g. prevention and treatment of blood-borne infections, especially for women; CBT for cocaine and alcohol dependent patients). Additionally more employment and educational possibilities should be developed and implemented for MM patients. Resolving such difficulties with "problematic patients" represents a major challenge for future provision of methadone treatment in general practice and in specialist clinic settings.

Finally knowledge and training to provide medical maintenance should be provided by the health authorities and the specialist clinic settings to the physicians.

6. References

Act-info, "Nationale Substitutionsstatistik für das Jahr 2000" (2000) Bundesamt für Gesundheit, Bern. Available at: http://*www.suchtundaids.bag.admin.ch/themen/sucht/forschung/actinfo*.

Akers R.L. (1992) Drugs, alcohol and society – Social structure, process and policy. Belmont, CA: Wadsworth.

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders (4th edition) Washington D.C.: American Psychiatric Association.

Anglin M.D., McGlothlin W.H. (1984) Outcome of narcotic addict treatment in California. In: Tims FM, Ludford JP, eds. Drug abuse treatment evaluation: strategies, progress, and prospects. Rockville, MD: *National Institute of Drug Abuse*, *(NIDA research monograph 51).*

Avants S.K., Margolin A., Kosten T.R., Rounsaville B.J., Schottenfeld R. (1998) When is less treatment better? The role of social anxiety in matching methadone patients to psychosocial treatments. *Journal of Consulting and Clinical Psychology*, 66(6), 924-931.

Ball J.C. & Ross A. (1991) *The Effectiveness of Methadone Maintenance Treatment.* Patients, Programs, Services, and Outcome. New York, Springer.

Bortz J. (1999) *Statistik für Sozialwissenschaftler*. 5. Aufl., Berlin, Springer 1999.

Brooner R.K., King V.L., Kidorf M., Schmidt C.W. Jr, Bigelow G.E. (1997) Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Arch Gen Psychiatry*, 54 (1), 71-80.

Brown J.K. (1976) Heroin – Some information. *The Pharm Chem Newsletter*, 5 (9), 1-2; 7.

Bundesamt für Gesundheit (1995): *Methadonbericht*. *Suchtmittelersatz in der Behandlung Heroinabhängiger in der Schweiz.* 3. Aufl., Bundesamt für Gesundheit, Bern, 1995.

Bundesamt für Gesundheit (1999) *Die schweizerische Drogenpolitik. Strategie der vier Säulen mit spezieller Berücksichtigung von Heroin.* Bundesamt für Gesundheit, Bern, 1999.

Bundesamt für Gesundheit (2000) *Aids und HIV in der Schweiz. Epidemiologische Situation Ende 2000*. Bundesamt für Gesundheit, Bern, 2000.

Bundesamt für Gesundheit (2002) *SPECTRA*, Zitiert aus der "Statistik des Bundesamtes für Polizeiwesen BAP". Bundesamt für Gesundheit, Bern, 2002.

Bundesamt für Statistik (2002) *Kantone und Städte in der Schweiz*. Statistische Übersichten 2002. Hrsg. Bundesamt für Statistik (BFS), Neuchâtel 2002.

Byrne A. (2000) Nine-year follow-up of 86 consecutive patients treated with methadone in general practice, Sydney, Australia. *Drug and Alcohol Review*, *Vol* 19(2), 153-158.

Cacciola J.S., Alterman A.I., Rutherford M.J., McKay J.R., Mulvaney F.D. (2001) The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. *Drug Alcohol Depend*, 61, 271-280.

Calsyn D.A., Saxon A.J., Blaes P., Lee-Meyer S. (1990) Staffing patterns of American methadone maintenance programs. *Journal of Substance Abuse Treatment*, 7, 255-259.

Caplehorn J.R., Dalton M.S., Cluff M.C., Petrenas A.M. (1994) Retention in methadone maintenance and heroin addicts' risk of death. *Addiction*, 89, 203-207.

Carroll K.M., Rounsaville B.J., Gordon L.T., Nich C., Jatlow P., Bisighini R.M., Gawin F.H. (1994) Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry* 51(3), 177-187.

Cerutti B. & Cassis I. (2004) Les traitements de substitution à la méthadone des toxicomanes au tessin. Etude de cohorte 2000-2002. Ufficio del medico cantonale. Dipartimento della sanità e della socialità Bellinzona. *Salute pubblica No 22*.

Cooper J.R. (1989) Methadone treatment and aquired immunodeficiency syndrome. *Journal of the American Medical Association* 262, 1664-1668.

Cullen W., Bury G., Barry J., Kelly F.D. (2003) Hepatitis C infection among drug users attending general practice. Irish J. Med. Sci., 172(3), 123-127.

Darke S., Hall W., Carless J. (1990) Drug use, injecting practices and sexual behavior of opioid users in Sydney, Australia. *British Journal of Addiction*, 85, 1603-1609.

Davies, A., Huxley P. (1997) Survey of general practitioners' opinions in treatment of opiate users. *British Medical Journal*, 314, 1173-1174.

Des Jarlais D.C., Joseph H., Dole V.P. (1981) Long-term outcomes after termination from methadone maintenance treatment. *Ann NY Acad Sci,* 362, 231-238.

Dole V.P., Nyswander M.E. (1965) A medical treatment for diacetylmorphine (heroin) addiction.: a clinical trial with methadone hydrochloride. *JAMA, 193*, 80-84.

Dole V.P., Nyswander M.E., Kreek M.J. (1966) Narcotic blockade – a medical technique for stopping heroin use by addicts. *Trans Assoc Am Phys*, 79, 122-136.

Dole V.P., Nyswander M. (1967) Heroin addiction – a metabolic desease. *Archives of Internal Medicine*, 120, 19-24.

Dole V.P., Robinson J.W., Orraca J., Towns E., Searcy P., Caine E. (1969) Methadone treatment of randomly selected criminal addicts. *New Engl Journal Med, 288*, 1372-1375.

Dole V.P., Joseph H.J. (1978) Long-term outcome of patients treated with methadone maintenance. *Ann NY Acad Sci*, 311, 181-189.

Eap C.B., Finkbeiner T., Gastpar M., Scherbaum N., Powell K., Baumann P. (1996) Replacement of R-methadone by a double dose of (R,S)-methadone in addicts: interindividual variability of the (R/(S) ratios and evidence of adaptive changes in methadone pharmacokinetics. *Eur Journal Clin Pharmacol,* 50(5), 385-389.

Eap C.B., Bourquin M., Martin J.L., Spagnoli J., Livoti S., Powell K., Baumann P., Déglon J.J. (2000) Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. *Drug Alcohol Depend,* 61, 47-54.

Estermann J. (1996) Sozialepidemiologie des Drogenkonsums. VWB Berlin, 130.

Etheridge, R.M., Craddock S.G., Dunteman G.H., Hubbard R.L. (1995) Treatment services in two national studies of community-based drug abuse treatment programs. *Journal of Subst Abuse*, 7, 9-26.

Falcato L., Stohler R., Dürsteler K.M., Nordt C., Rössler W. (2002) Effektive Methadonbehandlungen. Behandlungsdauer spezialisierter Institutionen und Privatpraxen im Vergleich. Resultate aus der Begleitevaluation der Methadonbehandlungen im Kanton Zürich, *PUK Zürich*.

Farabee, D., Fredlund E. (1996) Self-reported drug use among recently admitted jail inmates: Estimating prevalence and treatment needs. *Subst. Use Misuse,* 31, 423-435.

Farrell M., Ward J., Mattick R., Hall W., Simson G.V. Des Jarlais G., Gossop M., Strang J. (1994) Methadone maintenance treatment in opiate dependence: a review. *British Medical Journal,* 309, 997-1001.

Favrat B. (2001) Evaluation des programmes méthadone dans le canton de Vaud. *Oral communication*.

Fiellin D.A., O'Connor P.G., Chawarski M., Pakes J.P., Pantalon M.P., Schottenfeld R.S. (2001) Methadone maintenance in primary care: a randomized controlled trial. *JAMA,* 286 (14), 1724-1731.

Fiellin D.A., Storti S.A., Schottenfeld R.S., Biscoe J.D., Pantalon M.V., O'Connor P.G. (2002) Methadone medical maintenance: a training and resource guide for office-based physicians. Center for substance abuse treatment, *SAMSA*, Rockville.

Fiellin D.A. & Barthwell A.G. (2003) Guideline Development for Office-Based Pharmacotherapies for Opioid Dependence. *Journal of Addictive Diseases*, 22(4), 109-120.

Fiorentine R., Anglin M.D. (1996) More is better: counseling participation and the effectiveness of outpatient drug treatment. *Journal of Subst Abuse Treatment*, 13, 341-348.

Fitzgerald M., Barry J., O'Sullivan P., Thornton L. (2001) Blood-borne infections in Dublin's opiate users. Irish J. Med. Sci., 170(1), 32-34.

Fletcher B.W., Tims F.M., Brown B.S. (1997) Drug Abuse Treatment Outcome Study (DATOS): Treatment evaluation research in the United States. *Psychology of Addictive Behaviors*, 11, 216-229.

Gearing F.R., Schweitzer M.D. (1974) An epidemiologic evaluation of long-term methadone maintenance treatment for heroin addiction. *Am Journal Epidemiol, 100*, 101.

Glanz A. (1986) Findings of a national survey of the role of general practitioners in the treatment of opiate misuse: views on treatment. *British Medical Journal,* 293,543-545.

Gold M.S. & Slaby A.E. (eds) (1991) *Dual Diagnosis in Substance Abuse*. Marcel Dekker Inc., New York.

Goldstein A., Judson B. (1973) Efficacy and side effects of three widely different methadone doses. In: *Proceedings of the Fifth National Conference on Methadone Treatment*. New York: National Association for the Prevention of Addiction to Narcotics.

Goldstein A. (1991) Heroin addiction: Neurobiology, pharmacology and policy. *Journal of Psychoactive Drugs*, 23, 123-133.

Gossop M., Marsden J., Stewart D., Lehmann P., Strang J. (1999) Methadone treatment practices and outcome among opiate addicts treated in drug clinics and in general practice: results from the National Treatment Outcome Study. *British Journal of General Practice*, 49, 31-34.

Gossop M., Marsden J., Stewart D., Treacy S. (2001) Outcomes after maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug and Alcohol Depend*, 62, 255-264.

Gossop M., Stewart D., Browne B.A.N., Marsden J. (2003) Methadone treatment for opiate dependent patients in general practice and specialist clinic settings: Outcomes at 2-year follow-up. *Journal of Substance Abuse Treatment*, 24, 313-321.

Grella C.E., Hser Y.I., Joshi V., Anglin M.D. (1999) Patient histories, retention, and outcome models for younger and older adults in DATOS. *Drug Alcohol Depend,* 57, 151-166.

Gruer L., Wilson P., Scott R., Elliot L., Macleod J., Harden K., Forrester E., Hinshelwood S., McNulty H., Silk P. (1997) General practitioner centred scheme for treatment of opiate dependent drug injectors in Glasgow. *British Medical Journal*, 314, 1730-1735.

Gunne L.M, Grönbladh L. (1981) The Swedish methadone maintenance program: a controlled study. *Drug Alcohol Depend,* 7, 249-56.

Harrison L. (1995) The validity of self-reported data on drug use. *Journal Drug Issues*, 25, 91-111.

Hartel D.M., Schoenbaum E.E., Selvyn P.A., Kline J., Davenny K., Klein R.S., Friedland G.H. (1995) Heroin use during methadone maintenance treatment: the importance of methadone dose and cocaine use. *Am. Journal Public Health,* 85, 83-88.

Havassy B., Hall S. (1981) Efficacy of urine monitoring in methadone maintenance. *Am Journal Psychiatry* 138, 1497-1500.

Hermann E. (1986) Verlaufsuntersuchung Opiatabhängiger in staatlichen Methadonbehandlungen im Kanton Zürich. *Dissertation*, Universität Zürich, Juris Druck + Verlag, Zürich 1986.

Hermann H. (2001) *Aktuelle Praxis der Substitutionsbehandlung mit Methadon in der Schweiz, 2000.* Bundesamt für Gesundheit, Bern.

Hser Y.I., Huang D., Teruya C., Anglin M.D. (2003) Gender comparisons of drug abuse treatment outcomes and predictors. *Drug Alcohol Depend*, 72, 255-264.

Hubbard R.L., Marsden M.E., Rachal J.V., Harwood H.J., Cavanagh E.R., Ginzburg H.M. (1989) *Drug abuse treatment: a national study of effectiveness*. Carey: University of North Carolina Press.

Joe G.W., Simpson D.D., Hubbard R.L. (1991) Treatment predictors of tenure in methadone maintenance. *J. of Substance Abuse*, 3, 73-84.

Johnson R.E., Jaffe J.H., Fudala P.J. (1992) A controlled trial of buprenorphine treatment for opioid dependence. *J. Am. Med. Assoc.,* 267, 2750-2755.

Khantzian E.J. & Treece C. (1985) DSM-III psychiatric diagnosis of narcotic addicts: Recent findings. *Arch Gen Psychiatry*, 42, 1067-1071.

Kleber H.D. (1994) Assessment and treatment of cocaine-abusing methadone-maintained patients [Treatment Improvement Protocol Series (TIPS) 10, DHHS Publication No. (SMA)94-3003]. Rockville, MD: U.S. *Department of Health and Human Services.*

Klingemann H.K. (1996) Drug treatment in Switzerland: harm reduction, decentralization and community response. *Addiction*, 91, 723-736.

Kraft M.K., Rothbard A.B., Hadley T.R. (1997) Are supplementary services providing during methadone maintenance really cost-effective? *Am Journal Psychiatry,* 154, 1195-1197.

Kreek M.J. (1981) *Medical management of methadone-maintained patients*. In Lowinson J.H., Ruiz P. (eds): Substance Abuse: Clinical Problems and Perspectives. Baltimore: Williams & Wilkins, 660-673.

Kuntze M.F., Ladewig D., Stohler R. (1998) Art und Häufigkeit der Komorbidität bei methadonsubstituierten Opiatabhängigen in der ambulanten Versorgung. *SUCHT* 44(2), 104-119.

Ladewig D. & Simoni H. (1996) Basler Befragung von Opiatabhängigen zur Medikamentengruppe der Benzodiazepine, *SUCHT* 42(3), 167-175.

Ladewig D., Hug I., Stohler R., Battegay M., Gyr K., Erb P., Rohr H., Uchtenhagen A. (1998) A randomized trial with methadone, morphine and heroin in the treatment of opiate dependence. In: *Bundesamt für Gesundheit*, Buch zur Berner Konferenz, Bern.

Langendam M.W., van Haastrecht H.J., van Brussel G.H., Reurs H., van den Hoek A.A., Coutinho R.A., van Ameijden E.J. (1998) Differentiation in the Amsterdam methadone dispensing circuit: determinants of methadone dosage and site of methadone prescription. *Addiction,* 93(1), 61-72.

Leaver E.J., Elford J., Morris J.K., Cohen J. (1992) Use of general practice by intravenous heroin users on a methadone programme. *British Journal of General Practice*, 42, 465-468.

Lewis D.C. (1999) Access to narcotic addiction treatment and medical care: prospects for the expansion of methadone maintenance treatment. *Journal Addict Dis.* 18(2), 5-21.

Lewis D.C., Bellis M. (2001) General practice or drug clinic for methadone maintenance ? A controlled comparison of treatment outcomes. *International Journal of Drug Policy* 12, 81 – 89.

Liechti F., Falcato L., Dürsteler K., Eich D., Stohler R. & Rössler W. (2000) Methadondosierung und Heroinkonsum. Ein matched pairs design. Zürich: Sozialpsychiatirsche Forschungsgruppe der *Psychiatrischen Universitätsklinik Zürich*. (Resultate aus der Begleitevaluation der Methadonbehandlungen im Kanton Zürich – Nr. 7: November 2000).

Ling W., Wesson D.R. (1990) Drugs of abuse – opiates. *West J Med*., 152, 565 – 572.

Maddux J.F., Desmond D.P. (1992) Methadone maintenance and recovery from opioid dependence. *Am Drug Alcohol Abuse* 18, 63-74.

Magura S., Nwakeze P.C., Demsky S. (1998) Pre- and in-treatment predictors of retention in methadone treatment using survival analysis. *Addiction* 93(1), 51-60.

Magura S., Rosenblum A. (2001) Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. *Mt Sinai Journal Med, 68*, 62-74.

Magura S., Rosenblum A., Fong C., Villano C., Richman B. (2002) Treating cocaine-using methadone patients: predictors of outcomes in a psychosocial trial. *Subst. Use Misuse*, 37(14), 1927-1955.

Marlatt G.A., Gordon J.E. (1985) *Relapse prevention:* Maintenance strategies in the treatment of addictive behaviors. Guilford, New York London.

Marsch L.A. (1998) The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction,* 93(4), 515-532.

Mattick R.P., Ward J., Hall W. (1998) The role of counseling and psychological therapy. In: Ward J., Mattick R.P., Hall W., eds. *Methadone maintenance treatment and other opioid replacement therapies*. Amsterdam Harwood Academic, 206-304.

McCaughrin W.C., Price R.H. (1992) Effective outpatient drug treatment organization: program features and selection effects. *International Journal of Addictions*, 2, 1335-1358.

McGlothlin W.H. & Anglin M.D. (1981a) Long-term follow-up of clients of high and low dose methadone programs. *Arch Gen Psychiatry*, 38, 1055-1063.

McGlothlin W.H. & Anglin M.D. (1981b) Shutting off methadone: Costs and benefits. *Arch Gen Psychiatry*, 38, 885-892.

McLellan A.T., Luborsky L., Woody G.E., O'Brien C.P. (1980) An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. *J of Nerv Ment Dis., 168*, 26-33.

McLellan A.T., Woody G.E., Luborsky L., Goehl L. (1988) Is the counselor an "active ingredient" in substance abuse rehabilitation? An examination of treatment success among four counselors. *J of Nerv Ment Dis*, 176, 423-430.

McLellan A.T., Arandt I.O., Metzger D.S., Woody G.E., O'Brien C.P. (1993) The effects of psychosocial services in substance abuse treatment. *JAMA* 269, 1953-1959.

Metzger D., Woody G., De Philippis D., McLellan A.T., O'Brien C.P., Platt J.J. (199) Risk factors for needle sharing among methadone-treated patients. *American Journal of Psychiatry*, 148, 636-640.

Miller W.R., Tonigan J.S. (1996) Assessing drinkers' motivation for change: The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). *Psychol Addict Behav*, 10, 81-89.

Moggi F. (2002) *Doppeldiagnosen: Komorbidität psychischer Störungen und Sucht.* 1. Aufl., Bern, Huber: Klinische Praxis.

Monitoring the Future (MTF) (1999) National Clearinghouse for Alcohol and Drug Information, NIDA-Publication 1-800-729-6686. *National Institute on Drug Abuse.* Rockville.

Monti P.M., Abrams D.B., Kadden R.K., Cooney N.L. (1989) *Alcohol Dependence: A Coping Skills Training Guide*. New York: Guilford Press.

Morrow K. & Costello T. (2004) HIV, STD and hepatitis prevention among women in methadone maintenance: a qualitative and quantitative needs assessment. AIDS Care, 16 (4), 426-433.

Myers R.J., Smith J.E. (1995) Clinical Guide to Alcohol Treatment: The Community Reinforcement Approach. New York: Guilford Press.

National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction (1998) *JAMA* 280, 1936-1943.

National Institute on Drug Abuse (NIDA) (1986) *NIDA capsules – Heroin*. An drug information published by the National Institute on Drug Abuse, Rockville, MD.

National Institute on Drug Abuse (NIDA) (1997) National Household Survey on Drug Abuse: population estimates 1997. Washington D.C.: U.S. government printing office.

National Institute on Drug Abuse (NIDA) (1999) Drug Abuse Warning Network: Epidemiologic Trends in Drug Abuse. NIH-Publication, Rockville, MD.

Neeleman J., Farrell M. (1997) Fatal methadone and heroin overdoses: time trends in England and Wales. *Journal Epidemiol Community Health,* 51, 435-437.

Nestler, E.J. & Aghajanian G.K. (1997). Molecular and cellular basis of addiction. *Science*, 278, 58-63.

Newman R.G, Whitehill W.B. (1979) Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. *Lancet*, 485-488.

Novick D.M., Joseph H., Croxson T.S., Salsitz E.A., Wang G., Richman B.L., Poretsky L., Keefe J.B., Whimbey E. (1990) Absence of antibody to human immunodeficiency virus in long-term, socially rehabilitated methadone maintenance patients. *Arch Internal Medicine*, 150, 97-99.

Opravil M., Hirschel B., Lazzarin A., Furrer H., Chave J.P., Yerly S., Bisset L.R., Fischer M., Vernazza P., Bernasconi E., Battegay M., Ledergerber B., Gunthard H., Howe C., Weber R., Perrin L. (2002) Randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection. Swiss-HIV-Cohort-Study. *Journal Infect. Dis.,* 185 (9), 1251-1260.

Parrino M.W., ed. (1993) State methadone treatment guidelines. USA: *US Department of Health and Human Services*.

Payte J.T., Khuri E.T. (1993) Principles of methadone dose determination. In: Parrino M.W., ed. State methadone treatment guidelines. USA: *US Department of Health and Human Services*, 47-58.

Petitjean S, Bucheli B., Kuntze M., Ladewig D. (2000) *Resultate aus der Begleitevaluation der Methadonbehandlungen im Kanton Basel-Stadt.* Nr. 5, Forschungsgruppe: Psychiatrische Universitätsklinik Basel.

Petitjean S., Stohler R., Déglon J.J., Livoti S., Uehlinger C., Waldvogel D., Ladewig D. (2001) Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend, 62 (1),* 97-104.

Petitjean S, Bucheli B., Kuntze M., Ladewig D. (2002[a]) *Resultate aus der Begleitevaluation der Methadonbehandlungen im Kanton Basel-Stadt.* Nr. 6, Forschungsgruppe: Psychiatrische Universitätsklinik Basel.

Petitjean S, Schaller G. (2002 [b]) *Cures de méthadone à Genève; 1999-2001.* Analyse des données recueillies par le service du médecin cantonal. Rapport de la direction générale de la santé, Genève.

Perret G., Déglon J.J., Kreek M.J., Ho A., La Harpe R. (2000) Lethal methadone intoxications in Geneva, Switzerland, from 1994 to 1998. *Addiction*, 95(11), 1647-1653.

Petzold H.G., (1974) *Drogentherapie – Methoden, Modelle, Erfahrungen*. Klotz, Frankfurt.

Petzold H.G., Scheiblich W., Thomas G. (2000) *Psychotherapeutische Massnahmen bei Drogenabhängigkeit.* In: Uchtenhagen A., Zieglgänsberger W. (Hrsg.): Suchtmedizin: Konzepte, Strategien und therapeutisches Management, Urban & Fischer.

Preston K.L., Umbricht A., Epstein D.H. (2000) Methadone dose increase and abstinence reinforcement for treatment of continued heroin use during methadone maintenance. *JAMA*, 57(4), 395-404.

Prochaska J.O., DiClemente & Norcross J.C. (1992) In search how people change. Applications to addictive behaviors, *American Psychologist*, 47, 1102-1114.

Rehm J., Uchtenhagen A., Dombrowski D. (2001) *Metaanalyse Schweizerischer Arbeiten zur Verwendung von Methadon als Substitutionsmittel bei der Behandlung von Opioidabhängigkeit*. 133, 1-42. Zürich, Institut für Suchtforschung. Report.

Regier D.A., Farmer M.E., Rae D.S., Locke B.Z., Keith S.J., Judd L.L. & Goodwin F.K. (1990) Comorbidity of mental disorders with alcohol and other drug abuse: Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association*, 264, 2511-2518.

Reisinger M. (1997) Trends in substitution treatment in Europe [Review. Journal]. *Research and Clinical Forums, 19/3*, 9-15. CO.

Rounsaville B.J., Weissman M.M., Kleber H., Wilber C. (1982) Heterogeneity of psychiatric diagnosis in treated opiate addicts. *Arch Gen Psychiatry*, 39, 161-166.

Rounsaville B.J., Glazer W., Wilber C.H., Weissman M.M., Kleber H.D. (1983) Short-term Interpersonal Psychotherapy in Methadone-Maintained Opiate Addicts. *Arch Gen Psychiatry,* 40, 629-636.

Schoenbaum E.E., Hartel D., Selwyn P.A., Klein R.S., Davenny K., Ogers M., Feiner C., Friedland G. (1989) Risk factors for human immunodeficiency virus infection in intravenous drug users. *New England J of Medicine*, 321, 874-879.

Schweizerische Fachstelle für Alkohol- und andere Drogenprobleme (1995) *Informationen über Drogen*. Hrsg.*:* SFA, Lausanne, 57-58.

Schweizerische Fachstelle für Alkohol- und andere Drogenprobleme (2003) *Trends im Konsum psychoaktiver Substanzen von Schülerinnen und Schülern in der Schweiz.* Forschungsbericht Nr. 39, SFA, Lausanne.

Selwyn P.A., Feiner C., Cox C.P., Lipshutz C., Cohen R.L. (1987) Knowledge about AIDS and high-risk behavioer among intravenous drug users in New York City. *AIDS*, 1, 247-254.

Simpson D.D., Sells S.B. (1982) Effectiveness of treatment for drug abuse: an overview of the DARP research program. *Advances in Alcohol and Substance Abuse, 2*, 7-29.

Simpson D.D., Joe G.W., Fletcher B.W., Hubbard R.L. & Anglin M.D. (1999) A national evalaution of treatment outcomes for cocaine dependence. *Arch Gen Psychiatry*, 56, 507-514.

Speed S., Janikiewicz S.M.J. (2000) A comparison of levels of satisfaction of stable drug users treated in general practice and an outpatient (community-based) drug treatment service. *Health and Social Care in the Community*, 8, 436-442.

Statistisches Jahrbuch des Kantons Basel-Stadt (2001).

Stitzer M.L., Igushi M.Y., Kidorf M. (1993) Contingency management in methadone treatment: the case for positive incentives. In: Onken L.S., Blaine J.D., Boren J.J., eds. Behavioral treatments for drug abuse and dependence: *NIDA research monograph 137*. USA: National Institute on Drug Abuse, 19-35.

Stohler R., Ladewig D., Rohr H.P. (1995) *Behandlungsempfehlungen für Substitutionstherapien.* Gesundheitsamt Basel-Stadt; Psychiatrische Universitätsklinik Basel. Oktober 1995.

Stohler R., Petitjean S.., Ladewig D. (1998) Methadone dose and recent heroin use in methadone maintenance treatment. *College on Problems of Drug Dependence*, 142.

Strain E.C., Stitzer M.L., Liebson I.A., Bigelow G.E. (1993) Dose-response effects of methadone in the treatment of opioid dependence. *Ann Intern Med, 119*, 23.

Strain E.C., Bigelow G.E., Liebson I.A., Stitzer M.L. (1999) Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *JAMA, 281(11),* 1000-1005.

Swan, N. (1997) Scientists unlock the secrets of the opioid receptor. In *NIDA Notes* – Heroin prevention treatment, and research (NN0023) (p.17). Washington D.C.: National Institute on Drug Abuse.

Vader J.P., Hämmig R., Besson J., Eastus C., Eggenberger C., Burnand B. (2002) Appropriateness of methadone maintenance treatment for opiate addiction: Evaluation by an expert panel. *Swiss Federal Office of Public Health eds*.

Vanichseni S., Wongsuwan B, Staff of the BMA Narcotics Clinic No 6, Choopanya K., Wongpanich K. (1991) A controlled trial of methadone maintenance in a population of intravenous drug users in Bangkok: implications for prevention of HIV. *Int J Addict, 26,* 1313-1320.

Van Beusekom I., Igushi M.Y. (2001) Developments in methadone maintenance treatment between 1995 and 2000: a literature review. *RAND Europe*.

Von Bardeleben U., Stohler R., Petitjean S., Ladewig D. (1993) Drogen-substitutionsbehandlungen mit Methadon. *Therapeutische Umschau*, Bd. 50 (3), 139-147.

Ward J., Mattick R., Hall W. (1992) Key Issues in Methadone Maintenance Treatment. New South Wales University Press, Australia.

Ward J., Hall W., Mattick R. (1999) Role of maintenance treatment in opioid dependence. *The Lancet*, 353, 221-226.

Weinrich M. & Stuart M. (2000) Provision of methadone treatment in primary care medical practices: review of the Scottish experience and implications for US policy. *JAMA, 283(10*), 1343-1348.

Williamson P.A., Foreman K.J., White J.M. et al. (1997) Methadone-related overdose deaths in South Australia, 1984-1994. *Med J Aust,* 166, 302-305.

Woody G.E. & McLellan A.T. (2002) Continuing drug use by methadone patients: high vs lower dose and MET vs DC. *Drug Alcohol Depend, 66*, 198.

World Health Organization (1991) Tenth Version of the International Classification Diseases, *Chapter V (F): Mental and Behavioural Disorders*. Clinical Descriptions and Diagnostic Guidelines. © World Health Organization.

Yancovitz S.R., Des Jarlais D.C., Peyser N.P., Drew E., Friedmann P., Trigg H.L. (1991) A randomised trial of an interim methadone maintenance clinic. *Am J Public Health, 81,* 1185-1200.

Zanis D.A., McLellan A.T., Belding M.A., Moyer G. (1997) A comparison of three methods of measuring the type and quantity of services provided during substance abuse treatment. *Drug Alcohol Depend*, 49, 25-32.

Appendix A

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