Buprenorphine and methadone in the treatment of opioid dependence: methods and design of the COBRA study

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Abstract

Buprenorphine and methadone are the two established substitution drugs licensed in many countries for the treatment of opioid dependence. Little is known, however, about how these two drugs are applied and how they work in clinical practice. In this paper we present the aims, methods, design and sampling issues of a collaborative multi-stage epidemiological study (COBRA) to address these issues.

Based on a nationally representative sample of substitution physicians, the study is designed as an observational, naturalistic study, consisting of three major parts. The first part was a national survey of substitution doctors (prestudy, n = 379 doctors). The second part was a cross-sectional study (n = 223 doctors), which consisted of a target-week assessment of 2,694 consecutive patients to determine (a) the severity and problem profiles and treatment targets; (b) the choice and dosage scheme of the substitution drug; (c) past and current interventions, including treatment of comorbid hepatitis C; and (d) cross-sectional differences between the two drugs with regard to comorbidity, clinical course, acceptance/compliance and social integration. The third part consists of a prospective-longitudinal cohort study of 48 methadone-treated and 48 buprenorphine-treated patients. The cohort is followed up over a period of 12 months to investigate whether course and outcome of the patients differ by type or treatment received in terms of clinical, psychosocial, pharmaco-economic and other related measures. The response rate among substitution doctors was 57.1%; that among eligible patients was 71.7%. Comparisons with the federal registers reveal that the final samples of doctors and patients may be considered nationally representative with regard to regional distribution, training, type of setting as well as the frequency of patients treated with buprenorphine or methadone. The COBRA study provides a unique comprehensive database, informing about the natural allocation and intervention processes in routine care and about the course and outcome of patients treated with buprenorphine or methadone.

Key words: methadone, buprenorphine, epidemiology, opioid dependence, hepatitis C, course, outcome

Introduction

In many countries, considerable changes have occurred in the treatment modalities and care structure for opioid addicts over the past decade. In addition to existing drug-free psychosocial abstinence programmes, mostly in inpatient settings (McLellan et al., 1993; Vollmer and Krauth, 2001) there has been an increased emphasis on outpatient substitution

treatments. The goal of substitution treatment is not primarily abstinence but, in particular, the reduction of risks and harm associated with opioid dependence, the improvement of social integration as well as the interruption of the vicious circle of drug intake and drug-related criminal acts. By involving patients in a continuous medical treatment plan, doctors can presumably also establish better opportunities to treat the wide range of associated mental and somatic morbidities (HIV, hepatitis A, B or C, and so forth) with the long-term goal of helping patients ultimately to quit the use of drugs entirely.

There are currently two main types of substitution drugs available. Methadone, as a pure μ-opioid receptor agonist with corresponding pharmacological characteristics, has represented until recently the standard substance in substitution treatment. Efficacy in connection with various degrees of psychosocial support and psychological treatment has been demonstrated in numerous studies (Ling et al., 1976; San et al., 1990; Poser and Poser, 1996; Soyka et al., 1997; Layson-Wolf et al., 2002; Waal et al., 2003; Mattick et al., 2004), for example, with regard to (a) reduction of consumption of illicit opioids (such as heroin), (b) improvement of social situation as well as reduction of drug-related crime, (c) reduction of increased morbidity and mortality rates and the transmission rate of HIV, and (d) improvement of immunological, endocrinological and physiological parameters (Kreek, 1994). Reviewing safety, efficacy and treatment issues of methadone, Groß and Soyka (1999) have, however, summarized problems that may be associated with methadone treatments such as: (a) rare achievement of long-term drug abstinence, (b) frequent concurrent use of other substances, (c) increased mortality risk with concurrent use of heroin, (d) occurrence of psychopathological complications requiring additional psychopharmacological therapy, (e) sedation of the patients as well as (f) the occurrence of a frequently prolonged course of methadone withdrawal syndromes, which can lead to the dropout of the therapy. Not infrequently, methadone substitution also involves the problem of illicit dealing and intravenous injecting of the so-called 'take home' prescription.

Since the introduction of buprenorphine (Subutex) – a partial μ-receptor agonist and k-receptor antagonist – a second promising alternative has become available. Buprenorphine has been shown to be as efficacious as methadone. Among others, Petitjean et al. (2001), Kakko et al. (2003), Ling and Wesson (2003), Mattick et al. (2003), Gerra et al. (2004) claim that buprenorphine might have certain advantages over methadone (Johnson et al., 1992). These include the dosing scheme (2- or even 3-day dosage regimen), safety issues (for instance, lower risk of accidental overdose due to a ceiling effect on the opioid receptor, lower signal as regards analgesia, respiratory depression and euphoria), additional beneficial pharmacological properties (for example, antidepressive effects, better effects on cognitive functions, lower dependence potential (tolerance, withdrawal), lower direct and indirect psychotropic properties and improved measures of social adaptation/integration – Walsh et al., 1994; Kagerer et al., 2004). Several, but not all, clinical studies also seem to suggest that buprenorphine is equally effective in reducing the concomitant use of illegal drugs and stopping entirely the use of heroin, and they also reveal comparable dropout rates in trials. However, to date it is unclear whether patients with a high severity level of dependence also benefit from buprenorphine treatment as much as from methadone, because there are indications that methadone might have higher retention rates. Indications for the potential superiority of buprenorphine over methadone have also been suggested for patient cohorts with special needs (for example, patients with severe comorbid conditions such as hepatitis C and pregnant opioid addicts); there are also indications that buprenorphine rather than methadone may decrease the number of withdrawal symptoms in patients switching from heroin to substitution (see review by Groß and Soyka, 1999).

Despite a considerable body of research, there are several significant research deficits remaining.

A lack of long-term studies

Few of the claims relating to either type of drug have been firmly established in long-term studies and for routine care treatments, namely in samples of unselected substitution settings and unselected samples of patients. Thus, little is known about how methadone and buprenorphine work under routine care conditions. The evidence is still unclear as regards the benefits of one drug over the other concerning medical, psychological and social short-term outcome; compliance, ease of administration, tolerability, side effects and safety; advantages in various high-risk groups (in particular patients with comorbid hepatitis C); associated risks and critical incidences; and direct

and indirect costs. Long-term observational studies are needed to fill at least some of these gaps in our knowledge (Law and Nutt, 2003).

A lack of provider epidemiology data

Beyond the apparent need for long-term studies, the epidemiological database on the situation of substitution treatments in most countries is unsatisfactory. For example, little is known about (a) the effect of different provider models (for example, primary care-based versus specialized substitution centres) (Soyka et al., 2000; Mintzer and Stitzer, 2002; Ling and Wesson, 2003; Johnson et al., 2003). Such epidemiological data are of great importance for planning purposes, especially since the introduction of buprenorphine. Primarily because of its safety profile, and the lower abuse potential, buprenorphine treatments in primary care settings have become increasingly widespread in many countries (Farell et al., 2000). Whereas, in the past, substitution treatments were usually bound to substitution centres, offering a wide range of psychological, social and medical treatment options within the setting, the situation seems to be changing in most EU countries. In recent years, substitution treatments have also become increasingly available in smaller settings, for instance, in primary care settings, which usually do not have similarly comprehensive offers available. In Germany, for example, both types of settings are required by law to ensure the standards of a matched psychosocial intervention component (for instance through cooperation with addiction counselling centres offering a wider range of treatments and so forth), but data about the differences between provider models are lacking. Further deficits relate to (b) regional differences in the frequency in which methadone and buprenorphine are prescribed; (c) factors responsible for these different prescription patterns; (d) the frequency and the scope of additional psychological, pharmacological and social interventions; and (e) the situation in high-risk populations such as patients with concomitant HIV and hepatitis C infection.

A lack of data on allocation

Little is known about the heterogeneity of problem profiles of substitution patients in routine care and how substitution doctors manage the various complex problem constellations (Kuefner et al., 2004). Critical concerns relate here to questions such as:

- Are social, psychological and psychotherapeutic interventions applied at all and if yes, when and how?
- What proportion of patients receive appropriate treatment for serious medical illnesses?
- How do these intervention components affect the course and outcome of patients?

The lack of such data is clearly an obstacle to improved care and possibly also to more efficient care. Our basic assumption is that opioid addicts as a group are extremely heterogeneous in many ways (severity, stage of illness, motivation, expectations and so forth). Hence, it seems necessary to identify which patient, with which profile, is likely to benefit from which type of treatment and provider model.

Against this conceptual background, we designed and launched a stepwise and comprehensive cross-sectional and prospective-longitudinal epidemiological study in Germany. Initially named the COBRA project (COst-Benefit and Risk Appraisal of substitution treatments), the study takes into account – in greater detail than did previous studies – critical linkages between the patients and their problem profiles (type and stage of addiction and so forth), the psychosocial network, the treating physician and the system. The study approach is intended to allow for a comprehensive description of the current care and treatment situation for opioid addicts in Germany, to inform about the problems and attitudes and barriers of effective treatment in routine care, and to provide solid data about the relative benefits and problems of both methadone and buprenorphine treatments in various groups of opioid addicts.

Aims

The goal of this paper is to describe the aims as well as the design and methods of the COBRA project. We provide details about the sampling and fieldwork procedures and examine how well the COBRA study sample reflects the overall distribution of substitution doctors and their treatment modalities.

Methods

Core study goals

Part I (prestudy and cross-sectional component)

1. To describe the therapeutic management of various types of opioid-dependent patients (with/without hepatitis C, low versus high comorbidity) in substitution treatment by type of provider and type of substitution drug.
2. To identify the core clinical and non-clinical characteristics of patients treated with either methadone or buprenorphine (for example, addiction history and severity, mental and somatic comorbidity, social functioning, behavioural risk factors, motivation).
3. To identify doctor and patient variables affecting the treatment choice (for example, methadone or buprenorphine) and the short and long-term aims in the treatment.
4. To describe the most frequent allocation algorithms and strategies of substitution doctors.
5. To determine the degree of met and unmet needs of substitution patients.

Part II (longitudinal component)

1. To determine to what degree treatment targets are reached or modified and to examine the effects of guidelines and/or legislative rules.
2. To identify baseline doctor and patient variables and allocation rules, associated with a favourable course and outcome (retention rates, quit rates, quality of life, functioning and so forth).
3. To test whether the extent to which psychological and social interventions have been provided influence the course and outcome,
4. To examine whether patients treated with methadone or buprenorphine differ in 12-month follow-up health outcomes. For this goal a wider range of criteria will be considered (natural course and outcome, quality of care, reduction of medical risks, retention rates, speed and stability of abstinence from illegal drug use, social functioning and quality of life, tolerability, direct and indirect costs).

Design

Building on a nationwide sample of substitution doctors in Germany in 2003, we adopted a complex sequential design with five steps and components (Figure 1):

1. Preliminary work to establish a *register*.
2. *Prestudy* in a random, stratified nationally representative sample of substitution doctors.
3. The *cross-sectional main study* with a target period assessment of unselected patients in the participating settings.
4. A 12-month prospective-longitudinal follow-up in patients treated with either methadone or buprenorphine.
5. A *health-economic appraisal* in these patients and settings (not dealt with in this paper).

Preliminary work – register

Due to restrictive data protection considerations, we were not able to use available official registers (Ärztekammer, Kassenärztliche Vereinigung, Bundesinstitut für Arzneimittel und Medizinprodukte). Therefore, sampling was based on a nationwide register compiled from all accessible sources (such as registers, local experts, societies, sales force registers and so forth) with the help from over 50 experts in the field. This list originally contained over 3,000 names and addresses. All these names were linked within one register and cross-checked by phone, letter, questionnaire and expert inquiries to find out which of the potential substitution providers were actually currently offering substitution treatment for opioid addicts. The eligibility criterion for the compilation of our study register was 'having treated at least one opioid-addicted patient with any substitution drug during the past month'. A comprehensive description of this preliminary register work has been described in a separate publication (Wittchen et al., 2004).

Initial sampling considerations

The goal of the COBRA study is to provide a representative picture of substitution doctors as well as their patients. No representative data are available for Germany to provide information about doctors' and patients' core characteristics, so the initial power calculations in the preparation of the protocol were largely based on assumptions by our advisors, rather than on data. We assumed that the main study should include a random sample of approximately 250 doctors to reflect sufficiently the variety of substitution settings in Germany, ranging from small primary care settings with few patients to large specialized centres with hundreds of patients per day, as well as the regional variation in their distribution. This number also seemed sufficient to yield a reasonably high

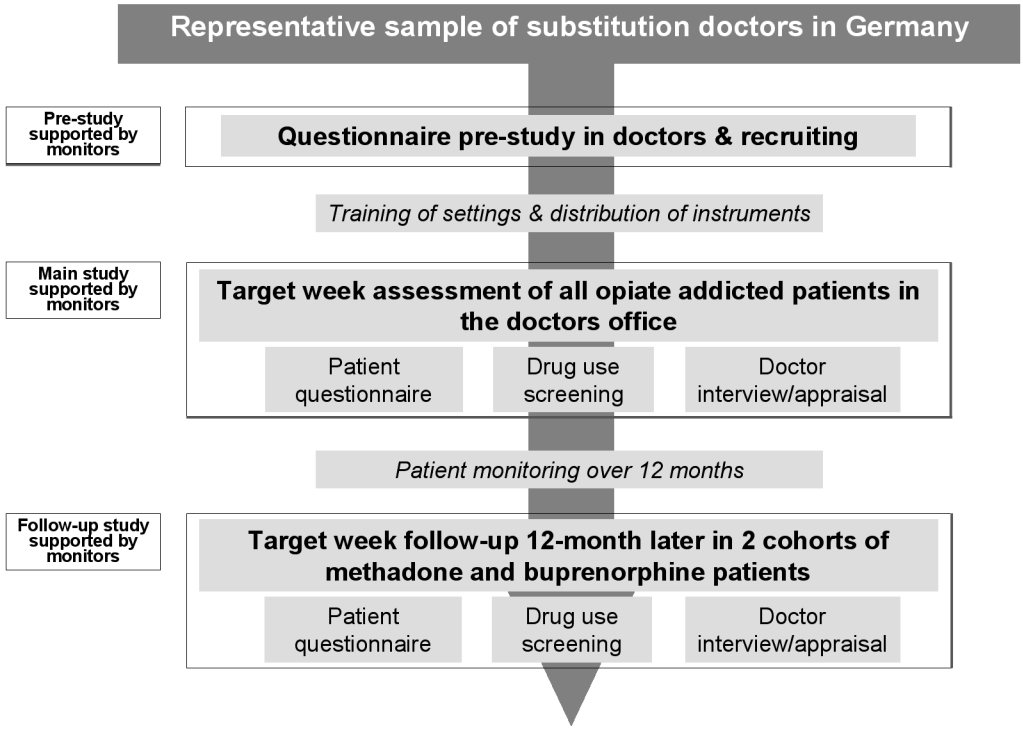

Figure 1.

number of patients in the main study. The main study was originally designed as a target day assessment, and we estimated that doctors could be expected to enrol and document on average 10 to 12 consecutive patients into the study. This fairly low number was due to a quite demanding assessment procedure requesting the doctors to spend at least 20 minutes face to face with each patient to complete the standardized clinical appraisal in addition to the informed consent, urine screening and the time for each patient to fill out the questionnaire. Based on these considerations – supported by initial power calculations to detect differences between the two substitution drugs – funding was ensured for the enrolment of at least 250 doctors with an estimated number of 10 patients per doctor and a total patient number of 2,500.

Evidence becoming available from the preparatory register work soon revealed two significant, interrelated complications that required us to adopt a modified, complex sampling strategy for both the sampling of doctors and the sampling of patients.

Final sampling of doctors

Despite fairly strict regulation, substitution settings differ considerable and systematically with regard to structural characteristics (for example, personal and social interventions) as well as the predominant and preferred treatments applied. For example, in small provider settings (mostly primary care type, with a few patients per day only), the proportion of patients treated with buprenorphine to those treated with methadone is 1:2. In contrast, in large substitution centres, the proportion is 1:10. Similar marked differences are apparent with regard to the breadth and scope of additional intervention components (social and psychological interventions) within the setting. These marked provider differences suggest the need for stratification in the sampling process to ensure that separate group analyses by type of provider model could be performed with sufficient statistical power. We thus stratified the providers into (a) small settings with less than 10 opioid addicted patients a day, (b) medium-size providers with 10–40 and (c) large settings with more than 40 patients a day.

Prestudy sampling and response rate

Because of the quite demanding protocol characteristics, we expected a doctors' response rate of

approximately 50%. Aiming for a total of 250 study doctors to be enrolled, we thus randomly sampled N = 683 doctors from the register (37% sample of all addresses). All N = 683 substitution doctors were approached and invited to participate. The doctors received a letter of invitation from the study centre, an overview of the study protocol, and they were asked (a) to fill out the prestudy questionnaire and (b) to agree to participate in both the main and the follow-up component – by filling out a contract and honorarium form. For each patient enrolled and documented in the main study, the doctors received 10. Trained study monitors performed the enrolment of the doctors.

Of the 683 doctors, 19 turned out to be ineligible (stopped working n = 12, no current opioid-addicted patients or no substitution n = 5, not allowed to participate n = 1, moved n = 1). Of the remaining 664 (100%) doctors, 379 were enrolled in the first part of study, constituting a *response rate of 57.1%*. Main reasons for non-participation were 'protocol too demanding/no interest' (71.7%), personal reasons and time restrictions of other type (22.8%), ethical and content reasons (2%) and others (3.5%). Because funding did not allow us to enrol all 379 settings into the main study, we randomly selected from these 379 settings participating in the prestudy a total of N = 267 doctors in Germany.

Table 1 shows the estimated true distribution of settings (column A; for details, see Wittchen et al., 2004), the prestudy sample distribution (column B) and the distribution of the 267 doctors sampled for the main study (column C).

Main study response rate

Of all eligible doctors for the main study (N = 267), 44 (16.5%) dropped out prior or during the patient recruitment period because of the following reasons: time and personal reasons (n = 8), protocol too demanding (n = 31), no substitution patient available, meeting inclusion criteria (n = 1), ethical concerns (n = 1), unknown reasons (n = 3). Table 1 (column D) shows the final distribution by type of setting in this main study sample.

Final sampling of patients

Further evidence from the preparatory work revealed that the number of buprenorphine patients in some provider strata would have been too low to allow for meaningful analyses if a simple random target day sampling design had been chosen (for example, estimated proportion of buprenorphine patients in medium or large settings: 2:10 and 1:10, respectively). Therefore, we adopted a more complex *patient sampling scheme* in each of the participating settings with more than 10 patients a day. The settings were requested to list all consecutively attending patients first by type of substitution drugs, before an equal number of at least five methadone and five buprenorphine patients were approached for participation by a prefixed algorithm. This ensured a sufficiently high number of patients in each group without introducing systematic selection biases. Furthermore, it allowed us to estimate roughly the true prevalence of methadone- and buprenorphine-treated patients.

On the basis of these two considerations, we adopted a complex sampling scheme that consisted of

Table 1. Distribution of substitution doctors in Germany (estimated), the prestudy and the main study sample

	A. Germany	B. Prestudy doctor sample		C. Main study sample		D. Final main study sample	
Setting	%	N	%	N	%	N	%
Small[1]	39	169	44.6	101	37.8	86	38.6
Medium[2]	45	154	40.6	121	45.3	101	45.3
Large[3]	16	56	14.8	45	16.9	36	16.1
TOTAL	100	379	100.0	267	100.0	223	100.0

[1] Small = <10 patients
[2] Medium = 10–40 patients
[3] Large = >40 patients

(a) a stratified (by type of setting) random sample of substitution doctors and (b) a stratified (by type of drug) sampling scheme for patients in the participating settings.

Patients: recruitment and in-and exclusion criteria
During the assessment period from February to April 2004, on preset days (in settings with a large number of patients) or week/s (in settings with few substitution patients), the doctors were requested to list all substitution patients attending the setting on a *recruitment list* in the order of their visits in the assigned time period. The list was stratified by type of substitution drug, and it showed the distinction between patients with new onset (up to 4 weeks ongoing) and those with ongoing treatment (more than 4 weeks ongoing). Each doctor was requested to sample at least 12 patients according to a prefixed random designation sheet. In order to ensure a roughly equal number of buprenorphine and methadone/levo-methadone patients, sampling for each drug strata should stop whenever at least five patients agreed to participate. This burdensome recruitment list procedure was chosen to avoid systematic selection of special patients and to allow for the estimation of the prevalence of buprenorphine- and methadone-treated patients in each setting. Note that small settings with only a few patients (= total assessment) were not required to use the list procedure.

Each eligible patient should be asked to participate by explaining the study rationale, handing over the study information and signing the informed consent form. This procedure was chosen to avoid systematic selection of special patients. As we conducted a non-interventional naturalistic study, inclusion and exclusion criteria were minimal. All consecutive patients 16 years or older with a past or current opioid addiction problem were eligible. Exclusion criteria applied for patients with acute emergencies, those who were cognitively so impaired that they could not fill out the questionnaire and those with no informed consent and ethical considerations.

As shown in part C of Table 2, among the eligible patients, the *total response rate was 71.7%;* 26.9% refused participation or did not give a signed informed consent form. Disregarding the few cases receiving 'other' substitution drugs, the response rate was highest in small-scale settings (81% and 83%) and slightly lower in medium- and large-scale settings. Overall 2,694 patients were enrolled, of which n = 2,013 patients were on methadone and 662 patients on buprenorphine. It should be noted that the absolute number of buprenorphine cases was quite low for large settings (N = 117).

Table 2 shows the total number of patients listed by type of setting and drug and the response rate along with information about patients refusing participation. The upper two portions of the table show separately the findings for settings that either used or did not use (part A) the listing procedure. The upper portion (part A) reveals that some of the medium-scale (N = 27) and large-scale (N = 14) settings violated the protocol; the small settings were not required to use the listing procedure at all. The middle part B shows the rates for all settings with a valid recruitment procedure.

As can be seen in the row of total patients listed (C total), a considerably higher number of patients treated with methadone/levomethadone were listed in total, as well as among those eligible for enrolment. It is also evident that among methadone patients a higher proportion was not eligible because they did not meet the inclusion criteria. The most frequent reason for ineligibility was that a sufficient number of patients for the respective condition had already been enrolled successfully (strata full). Other relatively frequent reasons for non-inclusion were severe impairment and language problems; both were considerably more frequent in the methadone group.

Representativeness of the prestudy and main study sample
To examine whether our doctors sample could be regarded as roughly representative for all substitution settings in terms of their geographical distribution, we compared the nationwide distribution of our prestudy and the final main study sample with the official BfArM nationwide regional distribution (by Laender). Using the official, yet confidential, federal data for 2003 as the standard, in Table 3, we present overall relatively similar distributions in each of the COBRA sampling stages. We used the federal registers, stratified by type of setting (small, medium and large scale), *and* the respective proportions of methadone/levomethadone versus buprenorphine treatments as a yardstick against which we compared the final COBRA sample distribution to derive the appropriate weighting scheme.

Table 4 reveals that our sample matches well the true distribution of small- versus medium- and large-scale settings as found in the 2003 BfArM data register.

Table 5 further illustrates the number of eligible

Table 2. Total number of patients listed by type of setting and drug, non-eligible and eligible patients and response rate

	Type of setting									
	small				medium			large		
	total	Meth.[2]	Bup.[3]	Oth.[4]	Meth.[2]	Bub.[3]	Oth.[4]	Meth[2]	Bub[3]	Oth.[4]
A. settings w/o list										
N of settings	55	(14)			(27)			(14)		
Total listed patients	697	81	31	4	304	66	6	167	33	5
Non-eligible patients	37	0	1	0	27	4	0	4	0	1
Total eligible patients	**660**	**81**	**30**	**4**	**277**	**62**	**6**	**163**	**33**	**4**
Unwilling/no consent	52	0	1	0	42	7	0	0	2	0
Incomplete[1]	29	10	3	4	5	0	4	1	0	2
Total enrolled patients	**579**	**71**	**26**	**0**	**230**	**55**	**2**	**162**	**31**	**2**
B. settings with list										
N of settings	170	(73)			(75)			(22)		
Total listed patients	4146	751	326	22	1713	494	31	596	203	10
Non-eligible patients total	1047	127	33	8	513	154	7	144	60	0
too impaired	148	28	5	1	74	10	1	24	5	0
emergency	8	4	0	0	1	1	0	2	0	0
language problems	143	15	12	0	64	23	1	19	9	0
sample strata full	502	53	5	1	254	75	6	68	40	0
other/unknown	246	27	11	6	120	45	0	31	6	0
Total eligible patients	**3099**	**624**	**293**	**14**	**1200**	**340**	**23**	**452**	**143**	**10**
Unwilling/no consent	960	119	51	7	437	115	15	154	54	8
Incomplete[1]	24	2	0	0	9	3	2	5	3	0
Total enrolled patients	**2115**	**503**	**242**	**7**	**754**	**222**	**6**	**293**	**86**	**2**
C. total										
Total eligible patients (n)	3759	705	323	18	1477	402	29	615	176	14
Total eligible patients (%)	**77.6**	**84.7**	**90.5**	**69.2**	**73.2**	**71.8**	**78.4**	**80.6**	**74.6**	**93.3**
Unwilling/no consent (n)	1012	119	52	7	479	122	15	154	56	8
Unwilling/no consent (%)	26.9	16.9	16.1	38.9	32.4	30.3	51.7	25.0	31.8	57.1
Incomplete[1] (n)	53	12	3	4	14	3	6	6	3	2
Incomplete[1] (%)	1.4	1.7	0.9	22.2	0.9	0.7	20.7	1.0	1.7	14.3
Total response (n)	2694	574	268	7	984	277	8	455	117	4
Total response rate (%)	**71.7**	**81.4**	**83.0**	**38.9**	**66.6**	**68.9**	**27.6**	**74.0**	**66.5**	**28.6**

[1] no doctors quest
[2] Methadone/levomethadone
[3] Buprenorphine
[4] Codeine/others

patients and the number of cases included (total response) by size of setting and type of treatment and reveals the weighting scheme (BfArM; Federal Centre for Drugs and Medical Devices).

Follow-up cohort and follow-up procedures

Assuming a loss of 100 per group as a result of dropout or other reasons, we aim at a successful follow-up of N = 500 methadone- and N = 500 buprenorphine-

Table 3. Comparison of proportions of substitution doctors by federal state and to the true BfArM distribution

State	Number of substitution doctors							
	Prestudy sample		Main study sample		Final main study sample		BfArM (2003)	
	N	%	N	%	N	%	N	%
Bayern	56	14.8	42	15.7	35	15.7	295	11.3
Baden-Württemberg	54	14.2	40	15.0	39	17.5	426	16.4
Hessen	31	8.2	22	8.2	17	7.6	223	8.6
Saarland	6	1.6	4	1.5	4	1.8	26	1.0
Rheinland-Pfalz	16	4.2	10	3.7	8	3.6	79	3.0
NRW	89	23.5	66	24.7	52	23.3	743	28.5
Niedersachsen	51	13.5	37	13.9	30	13.5	257	9.9
Schleswig-Holstein	9	2.4	4	1.5	2	0.9	134	5.1
Bremen	5	1.3	4	1.5	3	1.3	66	2.5
Hamburg	8	2.1	5	1.9	5	2.2	115	4.4
Berlin	24	6.3	17	6.4	14	6.3	164	6.3
Sachsen	5	1.3	2	0.7	2	0.9	13	0.5
Sachsen-Anhalt	7	1.8	4	1.5	3	1.3	26	1.0
Mecklenburg-Vorpommern	15	4.0	9	3.4	8	3.6	13	0.5
Thüringen	1	0.3	0	0.0	0	0.0	12	0.5
Brandenburg	2	0.5	1	0.4	1	0.4	13	0.5
Total	379	100	267	100	223	100	2,605	100

Table 4. Cross-tabulation of the proportions of small vs. medium/large settings in the COBRA main study sample and the BfArM register data

	COBRA main study		BfArM register (2003)	
	n	%	n	%
Small	46	12.14	317	12.17
Medium/large	333	87.86	2288	87.83
Total	379	100.00	2605	100.00

Chi-squared test of independence: Pearson chi2(1) = 0.0003, Pr = 0.986

treated patients. We therefore randomly sampled almost all buprenorphine patients and N = 600 methadone patients for the 12-month follow-up study. Immediate selection as part of the editing of the baseline cross-sectional forms allowed the participating doctors to mark their patient files, in an attempt to reduce changes from avoidable loss and attrition and to increase their awareness that particular patients were part of the follow-up study. In the 12-month interval, it is likely that relying on retrospective information only will result in a considerable loss of data. Every 3 months, therefore, physicians receive a course evaluation card to code continuously and describe over the follow-up period information about significant changes in the domains of substance use, prescription of drug, changes in dosage or drug, emergencies, changes in the treatment plan, adverse events, compliance and significant life events. This card should also allow intermediate interviews to be planned and conducted with those patients who stop treatment with their doctors in the follow-up interval. Furthermore, a dropout interview for all patients stopping substitution treatment at any point in the follow-up period is used, as well as a proxy interview for patients who might die

Table 5. Scheme of the weighting of COBRA final main study – sample of patients by strata

Small settings					
	Type of treatment				
	Meth.[1]	Bup.[2]	Oth.[3]	Total	M1:B2 ratio BfArM ratio 2:1
Total eligible patients (n)	705	322	19	1046	2.2 : 1
Total response patients (n)	574	268	7	849	2.1 : 1
Weights	0.978	1.047	1.000		
Weighted total response (n)	561	281	7	849	2 : 1
Medium settings					
	Type of treatment				
	Meth.[1]	Bup.[2]	Oth.[3]	Total	M1:B2 ratio BfArM ratio 5:1
Total eligible patients (n)	1480	404	29	1913	3.7 : 1
Total response patients (n)	984	277	8	1269	3.6 : 1
Weights	1.068	0.759	1.000		
Weighted total response (n)	1051	210	8	1269	5 : 1
Large settings					
	Type of treatment				
	Meth.[1]	Bup.[2]	Oth.[3]	Total	M1:B2 ratio BfArM ratio 10:1
Total eligible patients (n)	611	175	14	800	3.5 : 1
Total response patients (n)	455	117	4	576	3.9 : 1
Weights	1.143	0.444	1.000		
Weighted total response (n)	520	52	4	576	10 : 1
Total	2013	662	19	2694	
Total weighted	2132	543	19	2694	

[1] Methadone/levomethadone
[2] Buprenorphine
[3] Codeine/others

in the observation period. The 12-month follow-up interviews are scheduled to take place between February and May 2005, approximately 12 months after the main study.

Instruments

Prestudy

The prestudy was based on a 12-page questionnaire with a total of 48 items, which included the following domains: availability and organization; number and type of patients by substitution drugs; comorbid patterns; practice characteristics in terms of staff, services, attitude to guidelines and indication, allocation and withdrawal decisions of substitution therapy. As part of the recruitment, the doctors willing to participate were asked to complete the questionnaire with the following items: the doctors' specific characteristics; attitudes and preferences regarding treatments; number of opioid patients treated per week and day; their illness profiles; doctors' past experiences with treatments; as well as past, current and future challenges and barriers for adequate care. In addition, a standardized questionnaire (Christl and Gerlach,

2003) was provided to assess attitudes and beliefs of doctors with regard to methadone and buprenorphine.

Main study

The main study included a patient questionnaire, a doctor's interview and questionnaire and a standardized urine screening.

Patient questionnaire

Upon signing the informed consent form, the patients were asked to complete a 12-page patient questionnaire. This consisted of various components of established instruments such as the Addiction Severity Index (German Version of the EuropASI, Gsellhofer et al., 1999) as well as modules of the substance-use questions of the WHO Composite International Diagnostic Interview (CIDI, Wittchen et al., 1994; Wittchen et al., 1998, see Table 6). The questionnaire covered the following domains:

- basic biosocial and socio-demographic information;
- social and legal life developmental history and status rating including ASI information;
- past and current drug use and illness history module;
- diagnostic status (DSM-IV substance use and other mental disorders by CIDI);
- severity (EuropASI);
- self-reported physical disorders (e.g. hepatitis C, HIV);
- past and current impairments, disabilities and problems specific to drug use;
- past and current treatment history;
- met and unmet subjective needs;
- current and past experiences with treatments; and
- quality of life and risk behaviours.

Subsequent doctor assessment and appraisal of all these patients

Upon patients' completion of the questionnaire, each of the 2,694 patients – as part of the doctors' consultations – was assessed and evaluated by the doctor using a standardized appraisal form. This seven-page appraisal covers the following domains (see Table 3):

- substance use severity rating;
- physical and mental disorders (comorbidity) by CGI (Guy, 1976) severity and treatment status;
- multidimensional evaluation of functioning;
- description and appraisal of all past and ongoing current intervention (current treatment considerations if a new case, respectively);
- compliance and problems of management profiles;
- individual treatment targets and considerations;
- prognostic scales; and
- EuropASI and preference rating.

Urine screens

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

Field testing and training

The study materials were field tested in a total of 21 settings to explore feasibility and time needed for each component and to identify items and domains that were difficult to administer or to complete. Subsequent modifications were field tested again. In this process, the overall length of all assessment tools was considerably reduced. For the patient questionnaire, a small test-retest study (25 patients, two administrations 3 days apart) was conducted in one centre. Administration time for the patient questionnaire was extremely variable ranging from 18 minutes to 2 hours, with an average of 24 minutes. Test-retest reliability findings are currently being analysed (Wittchen et al., in preparation). The intermediate analyses for reports of substance use were good with kappa values ranging from 0.62 (for cannabis) to 0.86 (for opiates). These data were also compared with doctors' urine screenings in 19 individuals, resulting in good concordance as well, with conformation rates of subject reports ranging from 78 (cannabis) to 100% (opiates).

With regard to the doctors' questionnaire a manual was developed with explicit instructions for all items, supplemented by an abbreviated manual for the addiction severity ratings. The doctors received the final study material at least 2 weeks before the start of the main study, had to complete at least two practice assessments up-front and had the opportunity to contact the study telephone hotline to clarify issues.

Analysis

The sampling scheme for doctors and patients required weighting to adjust for the different sampling

Table 6. Construct and instruments by time of administration

Construct	Source: physician	Source: patient	Time of assessment		
			T_0	T_1	T_2
Biosocial data					
age. gender		x		x	x
height. weight. educational and occupational status. marital status.	x				
living situation. social status		x		x	x
current patients' mental and health condition	x observed			x	x
Current reason for consultation (11 items)	x	x		x	
Health-related quality of life (WHO EQ 5)[1] and mobility/exercise index	x observed	x		x	x
Patient-rated depression symptoms (DSQ)[2]					
major depression. dysthymia rating		x		x	x
dimensional severity		x		x	x
age at onset – first episode		x		x	x
number of episodes		x		x	x
History and current drug consumption (CIDI. EuropASI. SODQ. SOWS)[3]					
use, misuse and dependence (patient)	x	x		x	x
helpseeking		x		x	
reduction		x		x	
withdrawal		x		x	
substitution	x	x		x	x
Readiness to change (RCQ)[4]		x		x	x
Medical and psychosocial support (PREDI)[5]					
expectations		x		x	x
satisfaction		x		x	x
Social environment (EuropASI)					
drug scene. drug history in the family		x		x	
Social and penal problems (history and current)					
general		x		x	
drug-related		x		x	x
Multiaxial caseness rating (4-point rating – physician. 5-point rating – patient)					
somatic morbidity. psychological morbidity. psychosocial functioning status. independent living	x	x		x	x
Doctors' treatment targets and goal attainment (4-point rating – physician)					
targets for substitution	x		x	x	x
procedural and management targets	x		x	x	x
behavioural targets	x			x	x
Prognostic outlook (12 months; doctors' 4-point ratings)					
overall medical prognosis	x			x	x
target therapy	x			x	x
Patients' compliance problems and reasons (rating. and yes/no)	x	x		x	x
Cognitive behavioral risk index					
6 items health behavior domains		x		x	x
3 items disease-related distress		x		x	x
Hepatitis C and HIV					
infection	x	x		x	x
therapy	x	x		x	x

T_0: Prestudy T_1: Baseline T_2: Follow-up

[1] (WHO EQ 5, Brooks et al., 2003) [2] (DSQ, Wittchen et al., 2001) [3] [(CIDI, Wittchen 1998) (EuropASI, Gsellhofer et al., 1999) (SODQ, Sutherland et al., 1986) (SOWS, Gossop, 1990)]. [4] (RCQ, Carey et al., 1999) [5] (PREDI, Kuefner et al., 2001)

probabilities (setting and type of drug); furthermore, we adjusted for non-response in each strata. The statistical analyses for the cross-sectional study will largely be descriptive. Associations for categorical variables will be analysed by odds ratios with 95% confidence intervals calculated from logistic regressions. We will examine the effects of predictors from the prestudy using simple and multiple logistic regression analyses. For the follow-up primary outcome criteria, discrete time survival modelling will be applied for selected outcome criteria (maintenance rates/time, dropout rates/time, targets: discontinuation of concomitant drug use). With regard to the comparisons between treatments, the study is powered to detect differences even when provider strata are considered.

Discussion

This paper has provided an overview of the COBRA project, its aims and methods. In the core of the presentation was a discussion of the complex sampling strategy for both the sample of German substitution doctors as well as their patients.

The core aim was to ensure a reasonably representative sample for Germany. The challenge was that we were not allowed to use the federal registers for sampling but only for a post hoc verification; thus we relied on our own laborious register work initially. The outcome was by and large satisfactory with a moderate response rate of 57.1% for the doctor sample and, more importantly, a response rate of 71.7% for the patient sample. We demonstrated that both the doctor sample of physicians licensed for substitution as well as the sample of patients treated with either methadone or buprenorphine may be regarded as being representative for patients in German substitution centres, at least in terms of their regional distribution, the type of setting as well as the type of substitution drug. In any of these core variables, available federal register data revealed a good fit with our study data. This was quite unexpected because, due to the relatively high refusal rate among doctors approached in the initial prestudy, almost one-third of all substitution doctors initially declined participation. Some of these refusing doctors obviously had considerable political objections – at least initially – to the conduct of the study. Even worse, some refusals occurred clearly clustered in two southern regional districts. Although this effect is also noticeable in the regional distribution of our final study sample, it obviously had no significant effect on those variables examined so far. The fact that our COBRA proportions of small versus large settings are almost identical to those in the Federal Register, as are the rates of buprenorphine versus methadone versus other drugs, adds to the credibility of our methods approach.

With regard to the patient sample, the following important limitations should be considered. First, some centres evidently were not properly sampling the patients for the study randomly. Although this refers to only a few patients sampled from these settings, it might have led to an overinclusion of methadone-treated patients. Second, the patient sample does not reflect the total of all patients treated in the participating settings because patients not fluent in German (for example Eastern European heroin addicts without German language skills) as well as those experiencing severe suffering at the time of the study were excluded. Particularly for specialized centres in some areas, this meant that up to a quarter of the patients were not eligible.

Overall, COBRA can be regarded as being reasonably representative for German substitution settings. Incorporating quite comprehensive doctor and patient data on 2,600 patients, this study is among the largest naturalistic cross-sectional and longitudinal studies of substitution treatment in heroin/opiate addicts available so far. The study is expected to provide additional evidence about the relative benefits and advantages of substitution drugs early in 2005.

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