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Cross-Sectional Study

Medication Compliance in Patients with Chronic Pain

Katherina Kipping, MD[1], Christoph Maier, Prof, MD[1], Heinz H Bussemas, MS[2], and Andreas Schwarzer, MD, PhD[1]

From: [1]Department of Pain Management, BG Universitätsklinikum Bergmannsheil GmbH, Ruhr University Bochum, Germany; [2]Healthcare center for laboratory medicine, Dortmund, Germany

Address Correspondence:
Andreas Schwarzer, MD
Department of Pain Management
Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH Bochum
Bürkle-de-la-Camp-Platz 1
D 44789 Bochum, Germany
E-mail: Andreas.Schwarzer@rub.de

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Background: Despite hints about the high incidence of pain patients misreporting their pain medication use, there are only a few non-controlled studies on the topic that focus solely on opioids.

Objective: Using toxicological analyses in a cross-sectional study, we investigated patients' reliability regarding their report of any current pain medication use.

Study Design: A cross-sectional study.

Setting: A comprehensive pain center and a surgical unit of a German University Hospital.

Methods: Consecutive outpatients at their first visit to the pain clinic (PG, n = 243) and pre-surgical control patients (SG, n = 100) suffering from pain reported on their current pain medication. The patients' reports were verified in serum and urine using specific toxicological methods. Two types of noncompliance were defined: under-reporting (detection of non-reported substances) and over-reporting (reported substances undetectable). The impact of clinical parameters on compliance was investigated using binary logistic regression.

Results: The incidence of noncompliance was significantly higher in the PG (43.3%) than in the SG (24%; $P < 0.05$). Under-reporting occurred similarly in both groups (31% PG; 23% SG), whereas over-reporting predominantly appeared in the PG (11% vs. 2%; $P < 0.05$). Opioids were not most frequently under-reported, but the highest proportion of under-reported drugs (under-reported in relation to detection incidence) was found for non-opioid analgesics (NSAIDs: 29% PG; 25% SG; other: 42% PG; 32% SG) and psychotropic drugs (35% PG; 53% SG). In the PG, logistic regression revealed high depression scores to be predictive for noncompliance (odds ratio 2.12).

Limitations: Due to lack of a structured follow-up interview motives of under- and over-reporting stay speculative.

Conclusions: Under-reporting of non-opioid analgesics is the main type of noncompliance, a disquieting fact in light of their toxicity and adverse effects. Further research is required in terms of drug assessment and compliance improvement strategies in pain clinics; therefore, toxicological monitoring is indispensable.

Clinical Trial: NCT01625065; Medi-3889-10

Key words: Medication compliance, adherence, chronic pain, toxicological analyses, urine drug testing, NSAID, opioids

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Medication noncompliance is important; as particularly for patients with chronic conditions, actual medication intake often does not comply with prescriptions (1-5). The average incidence of noncompliance in medical disciplines like cardiology, endocrinology, or oncology reaches 24.8% (6). In pain clinics, a particular issue in compliance research is the detection of opioid misuse, addiction, and non-reported opioid medication intake. The reason for this focus is "the rising tide of death" due to opioid overdoses in the US (7). Opioid prescriptions are increasing, and substance abuse among pain patients is frequent (8-15). Noncompliance regarding opioids in these patients reaches up to 45% (16-19). In the US, the implementation of routine screenings in patients on opioid therapy has been recommended (20-23). Unfortunately, data for noncompliance regarding other substances, not carrying the risk of addiction, is insufficient (24-26). Non-reporting of medication usage, particularly of non-steroidal anti-inflammatory drug (NSAID) usage, may pose a threat for the patients due to unknown side effects. There are few European studies available (24,27) and routine screening of pain patients is not yet recommended in Europe. Additionally, most of the available studies are non-controlled studies (28). Though no gold standard of compliance assessment exists (29), the use of specific toxicological methods has been evaluated as a good option for objective monitoring in pain management (30-33).

Using toxicological analyses in a cross-sectional study, we evaluated chronic pain patients' compliance in a comprehensive pain clinic, compared to a control group of patients from the surgical unit of the same hospital. We investigated both under-reported medication intake and over-reported substances by comparing the reports of current pain medications with objective detection of any type of pain medication. The purpose was to identify the types of substances being under-reported and over-reported and to find characteristic clinical parameters with a predictive value for noncompliance.

Compliance is a general term to describe patients' drug intake behavior in accordance with prescribed instructions (34). Because this term implies a certain level of inferiority of the patient, some authors recommend the use of the term adherence (35). In this study, we investigated patients' reliability regarding their reported current drug use, as we tested patients at their first visit. Due to the lack of alternative terms and to be consistent with terminology used in the literature, we use the terms "compliance" and "noncompliance" to describe this type of reliability without any judgmental intentions towards the patients.

Methods

Patients

After approval of the local ethics committee (registration number 3889-10) and after written informed consent, we assessed outpatients from a comprehensive pain center and pre-surgical outpatients. Two hundred forty-three consecutive patients were included over 6 months on their first visit to the pain clinic without any exclusion criteria. Control patients were recruited in the surgical section of the same university hospital. The inclusion criteria for the surgical patients were current pain. They were excluded from the control group in case of a current treatment in any kind of pain clinic.

Assessment of Current Medication

During the admission interview (surgical patients: study interview), we firstly inquired about current medication using a standardized documentation questionnaire. Patients were asked about any kind of pain or psychotropic medication, whatever long-term or rescue medication. For each substance, the exact doses and last intake times where supplied by their physician. Second, the patients were informed about the use of toxicological identification of the stated substances in blood and urine to check if all of the medication was present at an adequate level. After this instruction, no one made additional specifications about current drug use. Blood samples were taken within the interview, urine samples were given subsequent to the interview, and the sampling times were documented.

Interviews in the pain clinic were performed by an experienced pain physician. All of the surgical patients' interviews were conducted by one author (K.K.), without any treatment relationship to the surgical control patients.

For further analyses, medications were classified into substance classes: opioids (including tramadol and tilidine), non-opioids, coanalgesics (including anticonvulsants and antidepressants, such as tricyclic antidepressants [TCA] and serotonin-norepinephrine reuptake inhibitors [SNRIs]), as well as psychotropic drugs (including benzodiazepines, antidepressants such as selective serotonin reuptake inhibitors [SSRIs] and neuroleptics). Due to the different severity of side effects, we divided the group of non-opioid analgesics into NSAIDs and

other non-opioids (including metamizole, paracetamol, flupirtine, and baclofen). Other internal medications (antihypertensives, antidiabetics, antiarrhytmics, antibiotics, anticoagulants, diuretics, proton pump inhibitors, glucocorticoids, and immunsupressants) were not considered.

We initially tested a random sample of 50 patients (15% of each study group: 35 pain patients; 15 control patients) for illicit substances (amphetamines, cocaine), because rates of not reported illicit substances found in literature are high (16-19), in contrast to 10 years of clinical routine in our pain center with only very rarely detected illegal substances. As for this sample all tests were negative, for financial reasons we stopped the analysis of illicit substances for all study groups.

Toxicological Analyses

Documentation sheets with exact substance reports and last intake times, as well as blood and urine samples, were all transmitted to the same laboratory. For every patient we analyzed both blood and urine samples and used combined methods to maximize the likeliness of substance detection and to decrease false-negative interpretation errors.

Analyses in urine:

Urine samples were first analyzed for benzodiazepines and opioids using semi-quantitative immunoassays. Confirmation of every positive finding and analysis of further substances were performed using gas-chromatography mass-spectrometry (GC-MS). Analyses in urine especially GC-MS are considered the gold standard of analyses detecting substances and metabolites within one to 3 days (33,36,37).

Analyses in blood:

The serum was analyzed using high performance liquid chromatography (HPLC) and liquid chromatography – tandem mass spectrometry (LC-MS) to estimate quantitative levels of current medication. The LC-MS method has advantages over other chromatographic techniques regarding quantity of specimen and interferences with other substances (38,39). In patients with reported opioids (predominantly transdermal application) and with medication of expected low levels in blood samples (antidepressants, anticonvulsants), the samples were sent to a second referral laboratory.

To increase sensitivity we used both analyses in blood and urine, as in serum recent intakes, substances with short elimination half-lives and steady state concentrations of low dose medications (anticonvulsants) can be detected (40,41). Cut-off levels of the immunoassays are 200 ng/mL for opioids, 200 ng/mL for benzodiazepines, 300 ng/mL for amphetamines, and 200 ng/mL for barbiturates. Limits of quantification for HPLC and LC-MS analyses are listed in Table A1 in the appendix.

Interpretation of Laboratory Results, Plausibility

We defined 2 types of noncompliance: under-reported (additional substances detected) and over-reported (inability to detect reported substances). For further analyses and interpretation of toxicological results, each patient is classified as "compliant," "under-reporting," or "over-reporting." Classification algorithms are shown in Fig. 1. In case of suspected "under-reporting," the pharmacological plausibility was particularly important. Quantitative serum con-

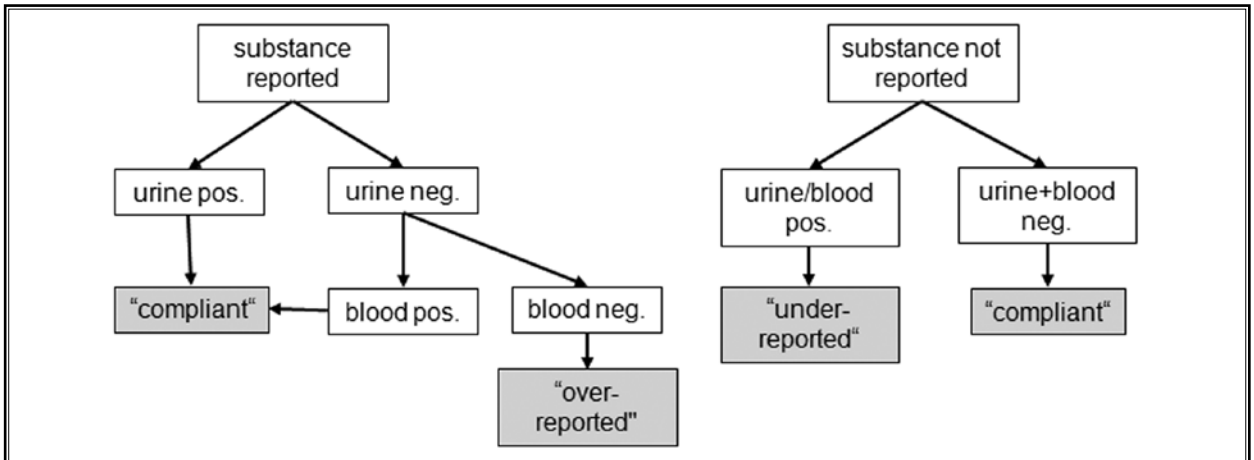

Fig. 1. Classification algorithms: compliant, over-reporting and under-reporting; urine positive: substance detection via GC-MS analysis; blood positive: substance detection via HPLC analysis; blood negative: negative result, pharmacologically plausible in HPLC or LC-MS analyses.

centrations were evaluated in a qualitative way: any positive finding (even below the therapeutic level) was considered to be "detected." In ambiguous cases, the chromatograms were rechecked with the laboratory to see if small peaks below the limit of quantification were overlooked. Considering peak plasma concentration values found in the literature (dose dependent), the limit of detection of the laboratory, and the elimination half-life of the substances, detection times in serum were estimated (40-43).

Clinical Data

Diagnoses were established in the course of admission to the pain clinic by a specialized pain physician. Diagnoses from the pre-surgical control patients were requested from the surgical department. The grade of depressive mood was assessed using the German validation (ADS, (44) of the Center for Epidemiologic Studies Depression Scale (CES-D; [45,46]). The depression score is missing from 24 patients from the pain clinic and 18 control patients. Patients estimated their current pain intensity (average and maximal) on a numeric rating scale (NRS; 0 – 10). The majority of the patients in the pain clinic (n = 145) underwent a psychological assessment by a psychologist. Psychopathologies were assigned according to ICD-10, including substance abuse coded as "mental and behavioral disorders due to psychoactive substance use" F10-19 (specification of the ICD-10 diagnosis). The diagnoses were made without the knowledge of the toxicological results.

Data Analysis

The statistical analysis was performed using the SPSS statistical software package, version 20 (SPSS Inc., Chicago II, USA). To analyze differences between clinical parameters in the 2 study groups, we used x^2-Tests for nominal data. The Mann-Whitney U-test was used to compare ordinal variables and non-normally distributed interval data. To analyze the distribution of metric variables, the Kolmogorov-Smirnoff-Test was used. We calculated Pearsons' and Spearmans' correlations to detect high intercorrelations among the clinical parameters included in multivariate analyses. Binary logistic regression was used to describe the relationships between the clinical parameters (age, gender, health insurance, duration of pain, pain intensity, ADS score, polymedication, pain diagnosis, psychological diagnosis, and diagnosis of substance misuse) and compliance, separately in both groups. Statistical significance was defined as *P*-values below 0.05.

Results

Clinical Data

A total of 11 patients from the pain clinic (PG) and 11 pre-surgical patients (SG) refused or were not able to give a urine sample. The blood sample was not sufficient for analysis or obtaining a sample failed in 3 cases (one patient from PG). From 103 pre-surgical control patients, 3 refused blood withdrawal after agreeing to participate and were excluded. Except for gender, the 2 groups differed significantly in all clinical parameters (Table 1). Seventy pain clinic patients suffered from neuropathic pain (28%), 72 from musculoskeletal pain (29.6%), and 73 from low back pain (30%). Among the pre-surgical patients, 92 had musculoskeletal pain (92%) and only 8 patients suffered from other pain (low back, neuropathic, or visceral pain; 8%). Etiologically, 27% of the pre-surgical patients with musculoskeletal pain were treated for chronic osteoarthritis and 73% had pain after traumatic injuries.

Compliance

In total, 122 (35.6%) patients in both study groups reported medication that differed from the findings in toxicological analyses; significantly higher rates were found in the PG (43.3%) than in the SG (24%; $P < 0.05$). Hence, the frequency of over-reported substances was significantly higher in the pain group (11% from PG vs. 2% from SG; $P < 0.05$). In contrast, rates of under-reported substances were high in both groups, with 31% in the PG and 23% in the SG (not significant).

Under- and Over-reporting

The distributions of reported medications, detected medications, and under- and over-reported substances for the different substance classes are shown in Fig. 2. Patients predominantly under-reported non-opioids, with a total of 19.4% in the PG and 12% in the SG (NSAIDs: 9.5% in PG; 8% in SG; other non-opioids: 11.5% in PG; 6% in SG; Fig. 2). The rate of under-reported psychotropic drugs was high (7% in PG vs. 8% in SG). Over-reporting was found primarily among the patients from the pain clinic, mainly concerning coanalgesics (4.1%) and opioids (4.1%). The highest proportion of under-reported drugs was found for non-opioid analgesics (NSAIDS: 29% in PG, 25% in SG; other: 42% in PG, 32% in SG) and psychotropic drugs (35% in PG, 53% in SG; Fig. 3). In the pain clinic group, there was an inverse relationship between under-reporting and detection in the different substance classes.

Table 1. *Clinical data*.

	Patients from Pain Clinic n = 243	Pre-Surgical Patients n = 100	*P*
Gender (female, n (%))	113 (46.5 %)	43 (43 %)	0.554
Age (years), mean±SD (range)	55.2 ± 14.8 (21…85)	51.6 ± 12.1 (18…78)	<0.05
Worker´s Compensation (n (%))	61 (25.1 %)	37 (37 %)	<0.05
Duration of Pain (disease)[a] (month; mean±SD)	85.2 ± 112.6 (1…641)	44.4 ± 83.6 (0…494)	<0.001
Pain Intensity (NRS 0-10)			
Average Pain Intensity mean±SD (range)	7 ± 2 (0…10)	5 ± 2 (0…9)	<0.001
Maximal Pain Intensity mean±SD (range)	9 ± 1 (3…10)	8 ± 2 (1…10)	<0.001
Depression Score (ADS)[b] mean±SD (range)	26 ± 12 (3…56)	21 ± 11 (2…53)	<0.001
Current Psychological Diagnosis[c,d,e] (n (%))	94 (38.7%)	-	-
Depressive Disorder (F32-34) (n [%[f]])	48 (51.1%)	-	-
Somatoform Disorder (F45.4) (n [%[f]])	8 (8.5 %)	-	-
Reaction to Severe Stress or Adjustment Disorder (F43.2) (n [%[f]])	19 (20.2 %)	-	-
Psychological Diagnoses (phobic or personality disorders) (n [%[f]])	25 (26.6%)	-	-
Aberrant Opioid Use (substance misuse) (F11.1-3) (n [%[f]])	36 (38.3 %)	-	-
Aberrant Behavior Due to Alcohol or Cannabinoids (F10.2; 12.1; 12.2) (n [%[f]])	3 (3.2 %)	-	-

NRS: numeric rating scale (0 = no pain 10 = worst pain possible)
[a]in the pain group duration of pain disease, in the pre-surgical group duration of current pain. [b] mean from n = 219 in PG, n = 82 in SG;
[c]Psychological assessment by experienced psychologists was performed only in the pain group; [d]according to ICD-10 criteria,
[e]multiple classification possible; [f]percent of total psychological diagnosis (n = 94)

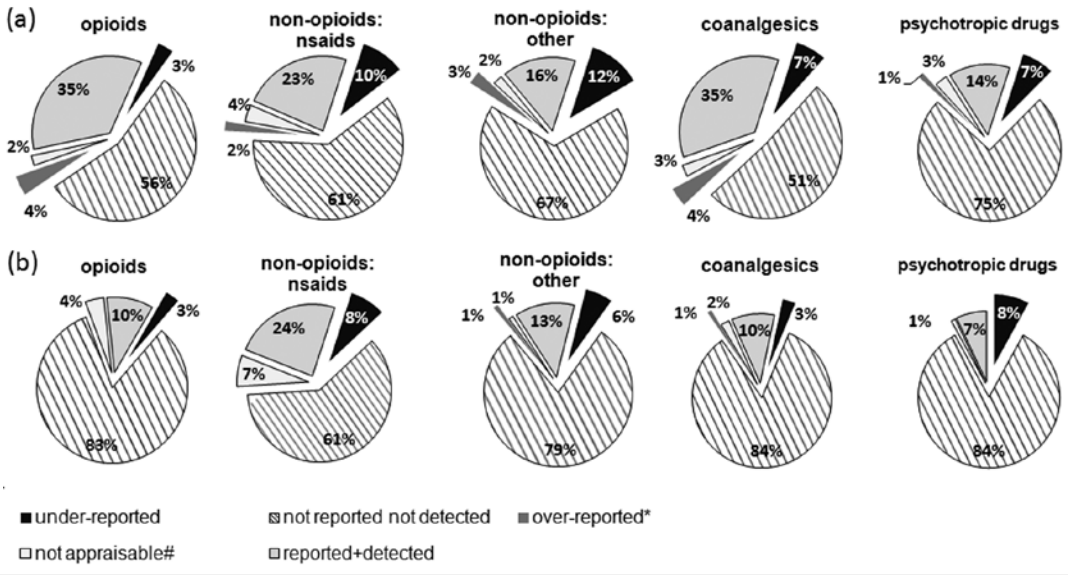

Fig. 2. *The distribution of reported medication, detected medication, under- and over-reporting in the pain clinic group (a) n = 243 (100%) and the pre-surgical group (a) n = 100 (100%). Thirty-nine patients in the pain clinic group and 53 patients in the control group were without any current medication. Non-opioid analgesics are separated into 2 groups: NSAIDs and others (metamizole, paracetamol, muscle relaxants); coanalgesics include anticonvulsants and antidepressants (TCA and SNRIs) and psychotropic drugs include benzodiazepines, antidepressants (SSRIs), and neuroleptics.*
**classified according to pharmacokinetic plausibility algorithms; # negative screening result is pharmacologically plausible, patients are classified as compliant.*

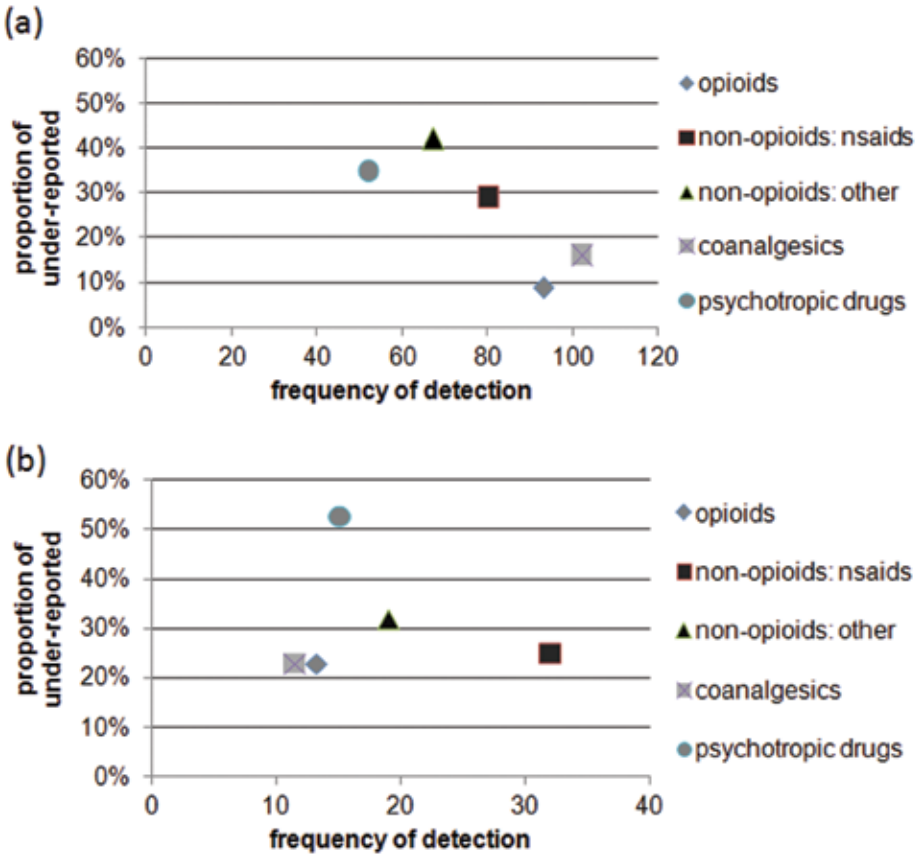

Fig. 3. *The proportion of under-reported drugs as the quotient of the number of under-reported substances and the frequency of detected substances in each medication class for the pain clinic group (a) and pre-surgical group (b). Non-opioid analgesics are separated into 2 groups: NSAIDs and others (metamizole, paracetamol, muscle relaxants); coanalgesics include anticonvulsants and antidepressants (TCA and SNRIs) and psychotropic drugs include benzodiazepines, antidepressants (SSRIs), and neuroleptics.*

Risk Factors for Noncompliance

The clinical data for patients classified as compliant, under-reporting, and over-reporting are reported in Table 2.

In the pain clinic group, the univariate calculation of odds ratios (ORs) identified 3 factors with an increased OR: high ADS scores (OR 2.12, confidence interval [CI] 1.18; 3.80), reporting of opioids (OR 1.7, CI 1.01; 2.86), and a duration of pain longer than 40 months (OR 1.66, CI 1.00; 2.79; Fig. 4). Whereas 29 of 243 patients had none of these 3 risk factors, 78 had 2 of them (mostly ADS + long duration, n = 30 or ADS + reported opioids, n = 31), and 30 had all 3 risk factors. The presence of at least 2 risk factors was associated with an increased risk (significant CI; Fig. 4). Notably, patients with missing ADS scores (n = 24) had an increased risk for noncompliance (OR 4.92, CI 1.53; 15.88).

The binary logistic regression (Table 2) confirmed only high ADS scores as a risk factor with a significant OR for noncompliance ($P < 0.05$; $R^2 = 0.41$; OR 2.12). Any type of current psychological diagnosis (n = 94), polymedication (> 4 substances, n = 21), or the reporting of opioid medication or worker's compensation insurance status had no predictive value for noncompliance.

Upon the inclusion of the same clinical parameters for the pre-surgical group, the logistic regression found no independent factor with an impact on compliance.

Table 2. *Impact of compliance on clinical data*

		Pain clinic n = 243						Surgical Patients n = 100					
		pain clinic (all)	Compliant	Noncompliant				surgical patients (all)	Compliant	Noncompliant			
					concealed	feigned	concealed + feigned				concealed	feigned	concealed + feigned
		n = 243 (100%)	n = 145 (100%)	n = 98 (100%)	n = 71 (100%)	n = 24 (100%)	n = 5 (100%)	n = 100 (100%)	n = 76 (100%)	n = 24 (100%)	n = 22 (100%)	n = 1 (100%)	n = 1 (100%)
gender n (%)	female	113 (46.5 %)	69 (47.6 %)	44 (44.9 %)	33 (46.5 %)	10 (45.5 %)	1 (20 %)	43 (43 %)	34 (44.7 %)	9 (37.5 %)	9 (40.9 %)	-	-
	male	130 (53.5 %)	76 (52.4 %)	54 (55.1 %)	38 (53.5 %)	12 (54.6 %)	4 (80 %)	57 (57 %)	42 (55.3 %)	15 (62.5 %)	13 (59.1 %)	1 (100 %)	1 (100 %)
age n (%)	<30	13 (5.35 %)	8 (5.5 %)	5 (5.1 %)	4 (5.6 %)	1 (4.5 %)	-	5 (5 %)	4 (5.3 %)	1 (4.2 %)	1 (4.5 %)	-	-
	30 - 49	81 (33.3 %)	51 (35.2 %)	30 (30.6 %)	18 (25.4 %)	10 (45.5 %)	2 (40 %)	35 (35 %)	31 (40.8 %)	4 (16.7 %)	4 (18.2 %)	-	-
	50 - 65	79 (32.5 %)	50 (34.5 %)	29 (29.6 %)	19 (26.8 %)	9 (40.9 %)	1 (20 %)	46 (46 %)	31 (40.8 %)	15 (62.5 %)	13 (59.1 %)	1 (100 %)	1 (100 %)
	>65	70 (28.8 %)	36 (24.8 %)	34 (34.7 %)	30 (42.3 %)	2 (9.1 %)	2 (40 %)	14 (14 %)	10 (13.2 %)	4 (16.7 %)	4 (18.2 %)	-	-
insurance company n (%)	workers comp.	61 (25.1 %)	39 (26.9 %)	22 (22.4 %)	10 (14.1 %)	10 (45.5 %)	2 (40 %)	37 (37 %)	31 (40.8 %)	6 (25 %)	5 (22.7 %)	-	1 (100 %)
	GKV/ PKV	182 (74.9 %)	106 (73.1 %)	76 (77.6 %)	61 (85.9 %)	12 (54.5 %)	3 (60 %)	63 (63 %)	45 (59.2 %)	18 (75 %)	17 (77.3 %)	1 (100 %)	-
duration of pain (disease)[a] n (%)	<40 month	120 (49.4 %)	79 (54.5 %)	41 (41.8 %)	27 (38 %)	13 (59.1 %)	1 (20 %)	72 (72 %)	53 (69.7 %)	19 (79.2 %)	18 (81.8 %)	1 (100 %)	-
	>40 month	123 (50.6 %)	66 (45.5 %)	57 (58.2 %)	44 (62 %)	9 (40.9 %)	4 (80 %)	28 (28 %)	23 (30.3 %)	5 (20.8 %)	4 (18.2 %)	-	1 (100 %)
pain intensity mean±SD (range)	maximal pain intensity (NRS 0-10)	8.8 ± 1.3 (3…10)	8.8 ± 1.3 (4…10)	8.9 ± 1.3 (3…10)	8.8 ± 1.3	9 ± 1	8.6 ± 1	7.6 ± 1.8 (1…10)	7.5 ± 1.9 (1…10)	8 ± 1.5 (5…10)	8 ± 1.6	7 ± 0	9 ± 0
depression score (ADS) n (%)	ADS ≤23	94 (38.7 %)	67 (46.2 %)	27 (27.6 %)	21 (29.6 %)	4 (18.2 %)	2 (40 %)	54 (54 %)	43 (56.6 %)	11 (45.8 %)	11 (50 %)	-	-
	ADS >23	125 (51.4 %)	67 (46.2 %)	58 (59.2 %)	41 (57.7 %)	15 (68.2 %)	2 (40 %)	28 (28 %)	19 (25 %)	9 (37.5 %)	7 (31.8 %)	-	-
	missing	24 (9.9 %)	11 (7.6 %)	13 (13.3 %)	9 (12.7 %)	3 (13.6 %)	1 (20 %)	18 (18 %)	14 (18.4 %)	4 (16.7 %)	4 (18.2 %)	1 (100%)	1 (100%)

Table 2 (cont.). *Impact of compliance on clinical data*

	Pain clinic n = 243						Surgical Patients n = 100					
	pain clinic (all)	Compliant	Noncompliant				surgical patients (all)	Compliant	Noncompliant			
				concealed	feigned	concealed + feigned				concealed	feigned	concealed + feigned
	n = 243 (100%)	n = 145 (100%)	n = 98 (100%)	n = 71 (100%)	n = 24 (100%)	n = 5 (100%)	n = 100 (100%)	n = 76 (100%)	n = 24 (100%)	n = 22 (100%)	n = 1 (100%)	n = 1 (100%)
reported opioids n (%)	105 (43.2 %)	55 (37.9 %)	50 (51 %)	35 (49.3 %)	11 (50 %)	4 (80 %)	14 (14 %)	9 (11.8 %)	5 (20.8 %)	5 (22.7 %)	-	-
polimedication n (%) >4 substances	21 (8.6 %)	9 (6.2 %)	12 (12.2 %)	7 (9.9 %)	4 (18.2 %)	1 (20 %)	1 (1 %)	-	1 (4.2 %)	1 (4.5 %)	-	-

GKV/PKV: compulsory or private German health insurance; worker`s compensation insurance company; #in the pain group duration of pain disease, in the pre-surgical group duration of current pain; NRS: numeric rating scale (0=none 10=worst pain possible);

Fig. 4. *Odds ratio (box) and 95% confidence interval (plot) in the pain clinic group (n = 219; 24 missing); ADS > 23: high depression score (n = 125), reporting of opioids (n = 105), and long duration of pain over 40 month (median split; n = 123); 2 risk factors: mostly ADS + long duration of pain (n = 30) or ADS + reporting of opioids (n = 31); 3 risk factors: n = 30.*

Discussion

Patients from a comprehensive pain clinic indicated significantly more incorrect statements regarding current medication with 43%, compared to 24% in the control group. In particular, over-reporting of medication intake was higher in the pain clinic group (11% vs. 2%). Our findings of 43% noncompliance in pain patients are in agreement with the reported incidences in the literature presenting a median of 29% (9 to 45%) (16-19,24-27). There has been no progress in patients' compliance rates over the last 2 decades. However, regarding the reported worries about increasing opioid use and misuse (7-15), it is an unexpected finding that in our pain clinic opioids were not under-reported most often, but non-opioids were. Nevertheless this is a disquieting fact because of the large spectrum of adverse effects of these substances.

Definitely, in laboratory testing the presence of false-positive and false-negative results is an issue (33). With the choice of com-

bined methods we intended to reduce false-positive results due to cross-reactivity, misinterpretation of metabolites, or long elimination half-lives (47). Minimization of false-negative results due to low doses or short half-lives was pursued by the additional analysis of blood samples.

A major discrepant result versus the findings from previous studies was the low incidence of under-reported opioids with 3% in the group from our pain clinic vs up to 37% in U.S. studies (16,18,19,26). Furthermore in the pain clinic group, the lowest proportion of under-reported drugs of 9% was found for opioids, despite the high incidence of opioid detection. These discrepancies could result from the fact that most cited studies exclusively included patients on stable opioid therapy (16,18,19,26). In our investigation, only 43.2% of the pain clinic patients reported a current opioid medication, in contrast to reported rates of 94% opioid medication prior to treatment in a multimodal pain center (48). Additionally the great concerns of opioid misuse, addiction, and death due to opioid overdoses seem to be more important in the US (8,11). In fact, the 2 European trials found equally low overuse of opioids (27) and low under-reporting of codeine preparations (24). In general patients know that in comprehensive pain centers opioid medications are quite accepted. What would be the point of concealing opioids then?

Another notable result of this study was the high number of under-reported non-opioids among the pain patients (19.4%). Ten percent of the pain patients did under-reported NSAIDS, and 12% under-reported other non-opioids such as metamizole or paracetamol, thus resulting in a high proportion of under-reported drugs in both groups of non-opioid analgesics (29% for NSAIDs and 42% for other non-opioids). Unfortunately, the interpretation of these results stays speculative, as we did not perform a follow-up interview of the patients inquiring potential concealing motives. One reason of under-reporting could simply be that patients tend to have problems with memory and forget to report certain substances. This seems to be unlikely, as the rates of noncompliance in this study are in accordance with results from previous investigations (16-19,24-27) and noncompliance in the patients from the pain clinic differs significantly from a control group. Besides it is remarkable that the same patient group with reliably reported opioids showed an increased OR for noncompliance regarding other drugs. We thus hypothesize that their pain is not sufficiently treated by the opioid medication (49). Patients could concomitantly use NSAIDs or benzodiazepines as escape medication as it has already been found for patients with neuropathic pain (50). Additionally, reasons for non-reporting non-opioid use could be that their use is trivialized by society; they are frequently used by the general population for minor complaints. Patients may underestimate the necessity of reporting these substances to a physician.

Also the point in time of the compliance testing in this study could explicate our findings. We tested patients before starting the pain treatment on the day of referral. Other groups tested patients' compliance weeks, months, and sometimes years after the beginning of their specialized pain treatment, meaning that in many patients, the pre-treatment medication may have been changed and most likely optimized by the pain specialists. In our pre-treatment patients, the reasons for patients to report their medication usage inadequately could be the shame of taking medication without the knowledge of the referring physician. In previous investigations the spectrum of analyzed substances was often a priori restricted to benzodiazepines, opioids, and illicit substances; therefore, noncompliance regarding non-opioids was often not detectable.

Moreover, in this study the percentage of under-reported psychotropic drugs was not negligible. In agreement with the findings from Berndt et al (24), we found mostly benzodiazepines and antidepressants among the under-reported psychotropic drugs. Patients may often conceal the use of psychotropic drugs to avoid the suspicion of benzodiazepine addiction (51) or to avoid stigmatization.

Of the substances leading to over-reporting in the pain clinic group, one third was coanalgesics and one third opioids. By over-reporting substances, patients could pretend to take medication. Pretending could be a hint for medication underuse due to fear of addiction (27,52), avoidance of unpleasant side effects, or ineffectiveness of medication (53). In some patients the failure to detect medication could further result from irregular intake habits, when medications are taken symptomatically rather than regularly. In addition, patients may have a tendency to catastrophize the severity of their pain by pretending the intake of substances.

This is the first study investigating medication compliance in pain management that includes a control group in a cross-sectional study design. Compared with the pain patients, rates of noncompliance are significantly lower in the control group, especially regarding over-reporting of medication intake. Therefore, this study contributes evidence of a significantly higher in-

cidence of noncompliance in chronic pain patients. Certainly, the value of the pre-surgical group as a control is limited due to major differences in clinical parameters versus the patients from the pain clinic. In contrast to the pain clinic patients, there is no therapeutic relationship to the control patients in the study interview. There is no personal interest to report certain substances and patients are conscious of the lack of consequences of misreports. Nevertheless under-reporting found in 23% of the patients is disquieting, particularly in a pre-surgical division, where unknown substance intake may cause adverse effects during anesthesia. Because the types of not reported substances in the control group are the same as those of the pain clinic group (mainly non-opioids), similar concealment motives are hypothesized.

A further aim of this study was the identification of potential risk factors for noncompliance. On this issue, results between different studies vary vastly. In contrast to Berndt et al (24), we could not prove polymedication to be predictive. Other authors described a coherence for age and gender with an increased risk for men and younger patients (19,26). As indicated in other studies, patients meeting ICD criteria for substance misuse (F10-13) had no evidence for increased rates of noncompliance (10). Similarly, insurance status did not influence noncompliance in the pain patients. This result is unexpected, as the effects of therapy, particularly in pain patients, are negatively correlated with worker's compensation status after work injuries (54-56).

However, high depression scores (ADS) seemed to be predictive for noncompliance in chronic pain patients. Furthermore, the combination of high ADS, reporting of opioids, and a long duration of pain led to an increased risk of noncompliance, which was 4.7 times higher than in patients without one of these risk factors. The ADS primarily measures the current mood and depressive tendencies of patients. An association between depression and noncompliance has been published, not only in the context of chronic pain (57) but also in other medical disciplines (58-62). Nevertheless, in our study, only 29% of all patients having an increased ADS score indicated a current depressive disorder (F32-34). It is thus plausible that a high depression score in this context revealed a certain "distressed" patient group rather than depressive psychopathologies. In pain management institutions, the ADS can be used as a yellow flag, especially in the short period of a first admission interview.

Conclusion

To summarize, medication noncompliance is still a relevant problem in the treatment of chronic pain patients. Forty-three percent of the pain clinic patients in this investigation made incorrect statements regarding their intake of pain medication. Compared with a control group, over-reporting of medication intake was more frequent. In contrast to research from American studies, non-opioid analgesics were more often under-reported than opioids. High rates of non-reported NSAID intake increases the risk of gastrointestinal, renal, and cardiac impairment (63-65). Measures to improve compliance should be part of comprehensive pain care. Interventional programs to enhance compliance including validated assessment questionnaires, as successfully established for opioids (66-69), are necessary in the future. Therefore, toxicological drug monitoring in comprehensive pain centers is indispensable.

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Appendix I. *Analyses in serum: methods, elimination half-lives and limits of quantification.*

Substance	Half – live in h	Method serum	Limit of quantification
Ibuprofen	2–3	HPLC	<1.0 ug/ml
Pregabalin	6,3	LC – MS/MS	<0.2 ug/ml
Tilidine *Nor – Tilidine	ca. 3	HPLC	<20 ng/ml
Amitriptyline	30 – 50	HPLC	<20 ng/ml
Acetyl salicylic acid	ca. 3	HPLC	<1.0 ug/ml
Oxycodone	2 – 5	LCMS	<1.0 ng/l
Metamizole (Dipyrone)	6 – 8	HPLC	<0.5 ug/ml
Gabapentin	5 – 7	LC – MS/MS	<0.2 ug/ml
Tramadol	5 – 10	HPLC	<50 ng/ml
Morphine	1 – 4	GC/MS	<5.0 ng/ml
Diclofenac	1 – 2	HPLC	<0.1 ug/ml
Carbamazepine *Carbamazepine – epoxid	12 – 60	HPLC	<1.0 ug/ml <0.1 ug/ml
Fentanyl (transdemal)	1 – 3	LC – MS	<0.2 ng/ml
Paracetamol (Acetaminophen)	2 – 4	FPIA	<2.0 ug/ml
Duloxetine	8 – 17	LC – MS/MS	<5 ng/ml
Flupirtine (Aminopyridine)	7 – 11	HPLC	<0.1 ug/ml
Tetrazepam	10 – 26	HPLC	<20 ng/ml
Citalopram	33 – 36	LC – MS/MS	<10 ng/ml
Doxepin	8 – 25	HPLC	<10 ng/ml
Mirtazapine	20 – 40	HPLC	<10 ng/ml
Hydromorphone	2 – 3	LC – MS/MS	<1.0 ng/ml
Lorazepam	10 – 40	HPLC	<20 ng/ml
Zopiclone	3,5 – 8	HPLC	<10 ng/ml
Baclofen	6,8	LC – MS/MS	<0.05 ug/ml
Diazepam *Nordiazepam	24 – 48 40 – 80	HPLC	<20 ng/ml
Trimipramine	10 – 20	HPLC	<10 ng/ml
Opipramol	6 – 23	LC – MS/MS	<10.0 ng/ml
Oxazepam	6 – 20	HPLC	<20 ng/ml
Paroxetine	16 – 24	HPLC	<20 ng/ml
Zolpidem	2 – 5	HPLC	<20 ng/ml

Substances and elimination half-lives (42,43) methods and limits of quantification of toxicological analyses of the laboratory; ordered by frequency of occurrence with a minimum of 3 cases; HPLC: high performance liquid chromatography; GC-MS: gas-chromatography mass-spectrometry; LC-MS: liquid chromatography – tandem mass spectrometry; FPIA: fluorescence polarization immunoassay; *relevant metabolite.

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