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Concomitant Drug Abuse of Opioid Dependent Patients in Maintenance Treatment Detected with a Multi-Target Screening of Oral Fluid

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INTRODUCTION

Opioid dependence is a severe, life-threatening disorder, and a major burden for public health worldwide. The European Drug Report 2016 recorded an increase in poly-substance-use patterns.[1,2] Deaths attributed to opioid drug overdose are often associated with mixed drug consumption.[3] The treatment of substance use disorders is traditionally focused on complete abstinence. However, this is only achieved by a limited number of patients with opioid dependence. The most effective therapy today is opioid maintenance treatment (OMT).[4–6] The reduction of concomitant use of psychoactive substances (other than the supervised consumption of substitution medicine) by patients is a primary goal of OMT.[7] Enrolled into a maintenance program, for example with methadone or buprenorphine, patients can achieve improvements of health and social stability. Stabilized opioid-dependent patients can receive maintenance medication for several days to take home besides daily dispensed dose.

Due to the potential abuse of take home medication, including the potential danger of children and third parties with contact to opioid users,[8–10] national and international guidelines recommend close monitoring of patients in OMT with take-home prescription.[11,12]

Data concerning concomitant substance abuse among opioid-dependent patients is poor. Specka et al. reported that 90% of opioid users consumed at least one other psychoactive substance at admission into their study. Among those, cocaine (55%), cannabis (65%), alcohol (60%), and benzodiazepines (53%) were found to be the most common.[13] Little research has focused so far on the extension of substance abuse among opioid-dependent patients participating in maintenance programs.

Urine drug testing or "other reliable biological tests for the presence of drugs, during the initial evaluation and frequently throughout treatment" are highly recommended according to the American national guideline on opioid use disorders.[14] Urine drug testing is an established method. However, in

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standard urine diagnostics in OMT only a few categories (opiates, benzodiazepines, cocaine, amphetamines, and THC) are included.[15] Oral fluid has become an increasingly popular matrix to assess compliance in addiction settings.[16,17] Oral sample collection is presumed to be less inconvenient for patients and less prone to manipulation like sample exchanges or sample dilutions.[18] Furthermore, oral fluid screening offers a shorter detection period compared to urine diagnostics.[19]

In our approach, we decided to perform a collection of oral fluid instead of standard OMT urine diagnostics with an extended spectrum of drug targets in order to assess substance abuse among OMT patients with regard to opioid substitution medication, take-home prescription, and contact with underage children.

METHODS

Participating Substitution Centers and Analysis Laboratory

For our study, two OMT centers in Munich, Germany, were selected. Both of which are specialized in OMT: the substitution office *Concept* (Center 1) and the outpatient clinic for maintenance treatment at the *Department of Psychiatry and Psychotherapy at the University Hospital of Munich* (Center 2). During the period of measurement, 280 patients received OMT with methadone, levomethadone, codeine, or buprenorphine at Center 1 and 150 patients received OMT with levomethadone, buprenorphine, or diacetylmorphine at Center 2. The study was performed in cooperation with the laboratory of *MVZ Labor Dessau GmbH*, Dessau-Roßlau, Germany, that analyzed all saliva samples at their special department for drug and medicament analysis, which operates at an international level. The study was approved by the ethics committee of the University of Munich (LMU).

Collective and Implementation

All multi-drug saliva screenings were carried out among patients in OMT within 1 week (end of March/April 2013) in both centers. All included patients fulfilled DSM V criteria of opioid use disorder and were in treatment for at least 1 week and received their individually adjusted opioid substitution dosage over at least 1 week.

Demographic and clinical data was collected from electronic patient records in both centers and based on the medical history. Regular contact to underage children was defined as living together with one or more underage children, both biological and not-biological, in one household.

The collection of samples took place unannounced and under supervision of a physician implemented in the regular drug screening of OMT. Since every patient had to appear personally at least once per week, a screening of the whole collective was possible. Patients were not informed in advance about the substances that were part of the multi-drug screening to prevent them from informing patients who had not been tested yet. The samples were collected and stored in a refrigerator (+4 °C) and sent daily to the laboratory.

In order to obtain longitudinal data for pregabalin abuse and to assess the frequency of this specific substance abuse, 134 patients in Center 2 were tested once per week for another 3 weeks. In total, those 134 patients were tested four times. Under these circumstances, drug screening days were varied.

Management of the Saliva Collection and Quantification System

Collection of saliva samples was performed with "Greiner Saliva collection and quantification system SCS pH 4,2" (Fa. Greiner Bio-One, Kremsmuenster, Austria). Patients had to put a saliva collection liquid in their mouth and keep it there for 2 min. Then, patients had to spit the saliva-buffer solution into a cup. Finally, liquid was stored in a sample tube.

Parameters and Substances Tested by Screening

Table 1 shows the tested parameters and substances of the multi-target screening. The analyzed substances are included in a commercial multi-target screen panel offered by the laboratory of *MVZ Labor Dessau GmbH*.

Analysis of Saliva Samples

Collected samples were first checked for authenticity since the tested patients could have tried to manipulate the saliva sample or to give a fake sample. For this reason, saliva content and amylase concentration in the sample were determined photometrically via an Olympus AU 680 device (normal range of saliva content: 20–80%, normal range of amylase concentration in saliva sample >10.000 U/I). Tested substances and cortisol levels were analyzed with ultra-high-performance liquid chromatography (UPLC) and tandem mass spectrometry (MS). Since cortisol levels can be suppressed by methadone, the normal range for cortisol levels in saliva was defined between 0.1–6.0 ng/ml instead of 1.0–6.0 ng/ml.[20] Thresholds for positive results for EDDP, buprenorphine, norbuprenorphine were 0.1 ng/ml and for all other substances 1.0 ng/ml, in each case relating to native saliva.[1]

Statistical Methods

Statistical evaluation was performed with SAS 9.2 (SAS institute Inc., Cary, NC). Descriptive analysis was performed for socio-demographic characteristics. Differences between category data were compared via a chi-square-test or via Fisher's exact test. Differences were considered significant if $p < 0.05$. Due to the 4-week period of weekly sample collection at Center 2, the samples represented a sufficient "time under risk" and could be analyzed separately in a longitudinal analysis of pregabalin that was the substance of interest for the longitudinal analysis. The one-time collection of samples in Center 1 only allowed a cross-sectional analysis.

[1] For further information concerning detection periods and additional ion monitoring data of each single substance, please contact the corresponding authors.

TABLE 1. Parameters and analytes of the applied saliva multi-target drug screening (first and third column)

Substances	Patients tested positive	Substances	Patients tested positive
Opioid substitution drugs	351 (90.5%)	Opiates	63 (16.2%)
L-/D-Methadone	176	Morphine	61
Methadone	41	6-Acetylmorphine*	47
EDDP	41	Codeine	22
Buprenorphine	134	Norcodeine*	5
Norbuprenorphine	134	6-Acetylcodeine*	5
		Dihydrocodeine	2
Opioids	22 (5.7%)	Cannabis	182 (23.2%)
Naloxone	–	Tetrahydrocannabinol	182
Tramadol	5		
Desmethyltramadol*	3	Cocaine	17 (4.4%)
Tilidine	1	Cocaine	13
Nortilidine*	1	Benzoylecgonine*	–
Hydromorphone	1	Lidocaine	5
Fentanyl	13		
Oxycodone	6	Ketamine	–
Noroxycodone*	5		
Benzodiazepines	75 (19.3%)	Amphetamines	10 (2.6%)
Diazepam	46	D-/ L- Amphetamine	5
Nordiazepam	60	D-/ L- Methamphetamine	–
Oxazepam	26	MDMA	1
Flurazepam	–	Butylone	–
Desalkylflurazepam*	–	MDA	1
Temazepam	12	MDEA	–
Alprazolam	3	Mephedrone	–
Lorazepam	6	BDB	–
Flunitrazepam	–	MDPV	5
7-Aminoflunitrazepam*	–	Methylone	–
Midazolam	–		
7-Aminoclonazepam*	7		
Bromazepam	13		
Z-drugs	5 (1.2%)	Phenethylamines	11 (2.8%)
Zolpidem	2	Methylphenidate	11
Zopiclone	3	Ritalinic acid*	9
Zaleplon	–		
Anticonvulsants	77 (19.8%)	Perianalytics	388 (100%)
Pregabalin	73	Saliva content in sample	388
Gabapentin	4	Amylase in sample	388
		Cortisol in sample	388

Patients tested positive for each substance and substance classes (second and fourth column). Patients could be tested positive for one or several substances or substance classes.

*Metabolites.

RESULTS

In total, 388 patients were recruited during the study period from two OMT centers: 254 out of 280 patients from Center 1 (90.7%) and 134 out of 150 patients from Center 2 (89.3%) participated at our study. Missing patients refused participation. All 134 patients (100%) who participated at the first measurement at Center 2 were subsequently tested once per week for 3 more weeks. In total, we obtained four samples over 4 weeks of each patient at Center 2. Mean age of the patients was 40.1 years (SD = 8.1), 68% were men, 32% were women. Most patients (45.4%) received levomethadone as OMT, 34.5% buprenorphine, 10.6% methadone (only in Center 1), 9.3% diacetylmorphine, and one patient (0.3%) codeine (Table 2). Fifty-seven percent of all patients had take-home prescription, 49.7% for more than 2 days. Twenty-six percent reported regular contact with children younger than 18 years old.

TABLE 2. Demographic data and substitution treatment according to substitution treatment centers 1 and 2

		Both centers		Center 1		Center 2	
		n	%	*n*	%	*n*	%
Patients (total)		388	100	254	100	134	100
Sex	Male	264	68	173	68,1	91	67,9
	Female	124	32	81	31,9	43	32,1
Age (years)	Mean (SD)	40,1 (8,1)		40,3 (8,3)		39,9 (7,6)	
Substitution treatment	Polamidone	176	45,4	99	39	77	57,5
	Buprenorphine	134	34,5	113	44,5	21	15,7
	Methadone	41	10,6	41	16,1	0	-
	Diacetylmorphine	36	9,3	0	-	36	26,9
	Codeine	1	0,3	1	0,4	0	-

Fifty-one percent of all patients (199/388) tested positive for at least one non-prescribed substance (concomitant abuse of single substances: Table 1). For routinely screened substances, most patients with concomitant substance abuse consumed THC (22.2%), followed by benzodiazepines (19.3%), opiates (8.2%), cocaine (4.4%), and amphetamines (2.6%). Thirty-two percent of patients (104/388) tested positive for substances that were not part of routine drug screenings. Pregabalin was the dominant substance in this subgroup. Eighteen percent of all patients (73/388) tested positive. Women were significantly more likely to be pregabalin-positive than men ($p = 0.0371$, Chi^2-Test). In general, there was a significantly higher prevalence among younger patients ($p = 0.0337$, Chi^2-Test). Concomitant pregabalin abuse was significantly higher among patients in OMT with methadone or levomethadone (25.8%) compared to the also very frequent used buprenorphine (9.7%, $p < 0.0001$, Fisher's Exact Test). Statistical trend was observed compared to diacetylmorphine (11.1%, $p = 0.059$) (Table 3). In the 4-week longitudinal analysis at Center 2.61% of the 134 patients had a pregabalin-positive result in 3 or 4 samples.

Through multi-target screening, a concomitant substance abuse of 43.5% among patients with take-home prescription was revealed (34.7% with take-home medication for >2 days, 60.7% with take-home medication for ≤ 2 days) compared to 68.9% among patients in OMT without take-home medication. Eighteen percent of the patients with take-home medication for >2 days had concomitant substance abuse of THC plus another substance. In total, 52.5% of patients with contact to underage children were positive for non-prescribed substances compared to 50.9% of patients without contact to underage children.

DISCUSSION

Aim of the study was to assess concomitant substance abuse among opioid dependent patients in OMT and to further assess certain subgroups such as those patients who have regular contact with underage children and those patients who are considered as more stable and receive opiate take home prescription for a maximum of 7 days. Initial studies suggested that immunochemical urine drug screening could be replaced by a multi-target screening of oral fluids based on LC-MS/MS.[21,22] In oral fluid the detection time of substance abuse is shorter compared to urine drug screening.[19] LC-MS/MS turned out to be a sensitive method for detecting single substances in a given sample and allowed confirmation and differentiation analysis to be foregone.[23,24] This method is efficient because all analytes of several samples can be measured within 6 min. Furthermore, the collection of oral fluids is a non-invasive method that respects the sphere of privacy of the patient.[18] To our knowledge, no multi-target screening in oral fluid samples of patients in OMT has as yet been performed. In the applied commercial drug screening, substances of OMT routine diagnostics (THC, BZD, cocaine, opiates, amphetamines) were further differentiated and extended by additional substances (Table 1). True-positive rates for cocaine and for amphetamines were significantly higher in the applied multi-target oral fluid screening compared with immunochemical drug screening, whereas the true-positive rates for BZD and opiates were similar.[22,23]

In a previous and so far largest ($>$2,500 participants) nation-wide study in Germany (COBRA) urine drug routine diagnostics were performed among OMT patients at substitution doctors at the time point of inclusion (2004) and in a 6-year follow up. However, the applied urine drug screenings only included methadone, buprenorphine, opiates, cocaine, amphetamines, methamphetamines, benzodiazepines, and cannabis.[25,26]

In our study, 388 patients were recruited for a multi-target screening of oral fluids: 254 out of 280 patients from Center 1 (90.7%) and 134 out of 150 patients from Center 2 (89.3%). According to COBRA parameters, our Centers 1 and 2 are defined as large specialized centers ($>$40 patients/day). Compared to COBRA data from 2004 we detected a higher rate of amphetamine-positive samples (2.6% vs. COBRA: 0.3%) in our cohort. Other routinely measured substance groups were observed in a lower percentage: opiates 7.4% versus COBRA 18.5%, cocaine 4.4% versus COBRA 6.0%,

TABLE 3. Pregabalin abuse according to sex, age, and substitution treatment: Pregabalin abuse was significantly higher in female and younger patients ($^{*}p < 0.05$; $p = 0.0371$ for female vs. male patients, $p = 0.0337$ for patients <35 years of age vs. older patients)

	Total		Sex				Age						Substitution treatment							
			Male		Female		<35 y		35–45 y		>45 y		Levomethadone + methadone		Buprenorphine		Diacetylmorphine		Codeine	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Patients	388	100	264	100	124	100	108	100	184	100	96	100	217	100	134	100	36	100	1	100
Pregabalin positive	73	18,8	42	15,9	31	**25***	29	**26.9***	31	16,8	13	13,5	56	**25.8****	13	9.7	4	11.1	0	0
Pregabalin negative	315	81,2	222	84,1	93	75	79	73,1	153	83,2	83	86,5	161	74.2	121	90,3	32	88.9	0	100

Pregabalin abuse was significantly higher among patients with levomethadone and methadone as OMT compared to buprenorphine ($^{**}p < 0{,}0001$), statistical trend compared to diacetylmorphine ($p = 0.059$).

BZD 19.3% versus COBRA 23.2%, THC 22.3% versus COBRA 5%.[15] Different rates in substance abuse could be due to different screening sensitivities between oral fluid and urine samples, regional differences (our study was performed in one city and not nationwide), differing maintenance treatment quality and a switch to other substances. An exact differentiation of specific BZD can uncover abuse and, if BZD are prescribed, monitor compliance in maintenance treatment. Concomitant substance abuse of substances that were not covered in routine drug-monitoring was detected in 32% of all patients.

Surprisingly, all substances that are normally not screened in OMT routine diagnostics, but screened in our study, were barely abused in our cohort including prescription opioids (such as fentanyl, oxycodone, tramadol, or tilidine), Z-drugs and phenethylamines (for details see Table 1). However, the large amount of pregabalin abuse was striking. Pregabalin is an anticonvulsant that is prescribed for epilepsy, neuropathic pain, and generalized anxiety disorder. Studies suggest that pregabalin helps patients reduce their use of benzodiazepines.[27] Since pregabalin is not tested in common drug screening, patients might prefer to take pregabalin instead of benzodiazepines in order to avoid sanctions (e.g., the loss of take-home prescription). This theory is supported by the fact that 34.7% of the patients with take-home prescription (>2 days) tested positive for pregabalin in our study. Among 134 patients that were tested for 3 consecutive weeks, longitudinal analysis of pregabalin-positive results in oral fluid samples was performed to obtain longitudinal data concerning pregabalin abuse. Longitudinal analysis of other substances than pregabalin was not performed since pregabalin was our focus of interest. Fourty-three percent of pregabalin consumers (19/44) had pregabalin-positive samples every week implying a regular intake. This finding might indicate an addictive potential of pregabalin in OMT. Carry-over between subsequently samples of one single patient can be excluded. In the applied commercial oral fluid drug screening, pregabalin can be detected only until 1.34 days after use). Subanalysis revealed a significantly higher pregabalin abuse among patients in OMT with methadone or its active enantiomer levomethadone compared to the also very frequently used buprenorphine. Statistical trend was observed compared to diacetylmorphine and should be reevaluated in studies with higher case numbers. Since pregabalin is increasingly detected among autopsied opiate-dependent persons it seems a major issue in different OMT centers and should be prescribed very cautiously among opioid dependent patients.[28–30] Screening for pregabalin might prevent potentially dangerous situations for patients in OMT, such as sedation, overdoses, or epileptic seizures after abrupt high-dose pregabalin withdrawal.

Concomitant substance abuse was higher among patients without take-home prescription (68.9%) compared to patients with take-home prescription (43.5%). Intriguingly, 34.7% of patients with take-home prescriptions longer than

2 days tested positive for at least one non-prescribed substance even though this subgroup was considered as stable according to OMT standards. Alarming 52.5% of patients with contact to underage children had concomitant substance abuse.

A multi-drug screening standard could possibly prevent medical and legal risk situations for patients, their environment and practitioners. Around half of the patients reported regular contact to underage children who might be also better protected by achieving greater treatment security. However, since our findings were observed in a local study, further investigations in larger multicenter and international studies with higher case numbers are needed to validate the striking pregabalin abuse among OMT patients. Conducting studies with a broad and long-term analysis of substances including those that are not part of routine drug screening among OMT patients could bring new insights into unknown abuse patterns and interrelations between certain substances. Furthermore, those studies might assess the potential benefit of multi-target screening.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper. Part of the data were subject of the doctoral thesis of GM.

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