12 years of Substitution treatment with buprenorphine for opioid addicts in Austria– obstacles and challenges

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Abstract: Buprenorphine (Subutex®; Suboxone® - buprenorphine and naloxone in combination) is since more than 12 years a fully accepted treatment choice for opioid dependence in Austria. In Austria up to now buprenorphine has reached like in France the status of a first choice medication together with methadone maintenance treatment. Until now the potential of buprenorphine as a treatment choice is not fully used.

Key-Words: : Buprenorphine, Subutex®; Suboxone®, first choice medication, maintenance treatment

1 Introduction

Buprenorphine (Subutex®; Suboxone® - buprenorphine and naloxone in combination) is since more than 12 years a fully accepted treatment choice for opioid dependence in Austria. In Austria up to now buprenorphine has reached like in France the status of a first choice medication together with methadone maintenance treatment.

At our department buprenorphine is normally used as part of a complete treatment plan to include counseling, psychological and psychosocial support. At the university hospital of Innsbruck buprenorhine is now administered in nearly 35% of all treatment cases. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. Therefore, clinical monitoring appropriate to the patient's level of stability is essential. Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits.

Buprenorphine can be abused but not in a manner similar to other opioids, legal or illicit. Regarding our experience the abuse potential lies therefore more by sniffing it than an intravenous consumption and can be regarded as very low in comparison to slow-release morphine abuse. This abusing manner lowers potentially the risk of a Hep C infection [1-9].

2 Buprenorphine or other maintenance agent in the management of opioid dependence?

In the last 12 years we`ve investigated a number of different studies regarding the effectiveness of buprenorphine.

Although other forms of treatment for opioid dependence continue to be explored, in Austria and internationally, methadone maintenance treatment remains the most widely used form of treatment for people who are dependent on opioids. Methadone maintenance treatment has been demonstrated to be an effective treatment for opioid addiction and curbs the incidence of HIV [1; 2; 9].

Although methadone maintenance treatment has been successful, it is associated with a number of problems [1-13]. Up to 50% of methadone patients withdraw from treatment in the first 6 months. Daily dosing can be a burden for treatment facilities, some of which provide doses to over 900 patients a day. Patients prefer take-home doses, but they are often associated with diversion.

Virtually there are a number of alternatives to methadone as a maintenance agent in the management of opioid dependence.

The most promising of these involve pharmacotherapies which treat patients with a pharmaceutical grade opioid which has a longer duration of action than methadone. These include

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the opioid partial agonist buprenorphine and the full agonist levo-alpha-acetylmethadol (LAAM), which is yet not available in Austria [11]. Buprenorphine was found to be a potent synthetic opioid analgesic initially used for the management of acute pain [11].

Pharmacologically, buprenorphine causes morphine-like subjective effects and produces cross-tolerance to other opioids. Unlike methadone and heroin (which are full agonists), buprenorphine is a partial agonist and exerts weaker opioid effects at opioid receptor sites. This partial agonist action appears to make buprenorphine safer in overdose. Other benefits of buprenorphine may include an easier withdrawal phase and, because of the longer duration of action, the option of alternate day dosing.

Nevertheless, it is buprenorphine that has gained more and more importance in addiction treatment in Austria in the last 12 years because the correlation between dose and therapeutic effects is not linear, indicating a ceiling on the effects in patients due to its opioid agonistic–antagonistic characteristics [12]. Buprenorphine is therefore a relatively safe substance, and its effectiveness in maintenance therapy has been proved in many studies. It has been used in Austria as a substitution drug since 1999 [1; 9].

3 Driving impairment on buprenorphine and slow-release oral morphine

As mentioned already above, in several studies sublingual buprenorphine was found to be nearly as effective as methadone and a useful alternative for maintenance and detoxification therapy of opioid-dependent subjects.
Preliminary data of a randomized experimental study on slow-release oral morphine's effect on driving ability under steady-state conditions in drug-dependent patients, using a standardized test battery are reported here [7].

The traffic-relevant performance dimensions of the participants in one of our studies for example were assessed after receiving synthetic opioid maintenance therapy, by a series of tests constituting the Vienna Reaction Test System (RG), Vienna Determination Test (DT), Visual Pursuit Test (LVT), Tachistoscopic Traffic Test Mannheim for Screen (TAVTMB) and Cognitrone Test (COG) (methods are described by [9; 13].

Results are shown in the table 1 below. There were differences between the synthetic slow-release oral morphine-maintained subjects investigated in the current study and buprenorphine controls. The data indicate a better psychomotor performance in patients under buprenorphine, especially within the Visual Pursuit Test (LVT).

The clinical conclusions from this study are preliminary. Still, the more favourable values of patients under buprenorphine compared with slow-release oral morphine maintenance, especially in the Visual Pursuit Test (LVT) is an interesting finding that deserves attention. It may indicate a less marked effect on cognitive-motor performance of a mixed agonist/antagonist opioid than a full agonist such as slow-release oral morphine.

It actually is planned to carry out a controlled study to compare clinical effects of buprenorphine, buprenorphine and naloxone as well as slow-release oral morphine on psychomotor performance and driving ability in drug-dependent patients.

4 Patterns of drug use among opioid addicts treated with methadone and buprenorphine - results of a 4-year trial

Another study designed to evaluate urinalyses of methadone and sublingual buprenorphine maintenance programme participants made a retrospective analysis of drug screening tests, aimed at comparing drug consumer patterns of oral methadone with sublingual buprenorphine, as measured by the results of urinalyses over a period of 4 years.
Regarding the discussion raised in the previous section, this study offers a descriptive tool with which to characterize the typology of patterns of drug use in a methadone programme compared with a sublingual buprenorphine treatment. Some of the results of this study have been published and are still in the process of discussions [1; 5].
All opioid-dependent patients (N = 693) admitted to a methadone or sublingual buprenorphine maintenance programme were considered in this study. The only requirement for inclusion in the methadone or sublingual buprenorphine programme was a confirmed diagnosis of opioid dependence (DSM-IV 304.0).
History and physical examination supported the judgment on the part of the physician that the

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patient was a candidate for methadone or buprenorphine maintenance programme and that such treatment was indicated on the basis of a thorough clinical evaluation.
An open-label, flexible dosing regimen based on a methadone or sublingual buprenorphine programme was used, with increasing doses depending on the severity of withdrawal symptoms and the patient's opinion during the induction period of 6-7 days to a stable dose thereafter. The clinical management included follow-up visits to assess the patient's medical condition and treatment response. The initial dose was therefore based on the physician's evaluation of the history and present physical condition of the patient with added knowledge of local conditions, such as the relative purity of the appropriate street drugs. Benzodiazepines were generally not prescribed for these patients at our clinic
Urine screening tests were carried out regularly but at random time intervals to detect additional consumption. Urine samples of each client were taken at least every 4 weeks and were always temperature-tested. Patients with positive urine toxicology results were not re-tested more often. All urine samples were tested at the Institute of Forensic Medicine in Innsbruck.
All urine samples were immunologically screened on a Hitachi 902B according to the manufacturer's instructions.
The original data set consisted of 92,234 records including informations of a variety of clinical parameters (e.g. other substitution groups, pH values, invalid data, etc.). The data set was reduced down to 42,610 (33,057 methadone, 9,522 sublingual buprenorphine) urine records of patients admitted for outpatient maintenance treatment of opioid addiction to the Univ. Department of Psychiatry Innsbruck. Maintenance programme changers were taken into consideration. Substance concentrations of illicit drug abuse in urine samples were communicated in a semi-quantitative way: extent of drug was reported on the interval [0, 3]; 0 = negative, 1 = weak positive, 2 = positive, 3 = strong positive.

Inspection of the data showed some clear differences regarding the patterns of additional drug consumption between the two maintenance groups. Table 2 presents the summarized percentages of positive urine sample results in each maintenance group during the entire observation period. The sublingual buprenorphine maintenance clients showed significantly less consumption of opioids ($p = 0.000$). Furthermore, the sublingual buprenorphine maintenance group showed significantly less consumption of benzodiazepines ($p = 0.000$), cocaine ($p = 0.001$) and ethanol ($p = 0.000$) compared with the methadone group. Generally, the sublingual buprenorphine group showed only about a third of the additional consumption than methadone maintenance clients did ($p = 0.000$). Results indicate that amphetamines, cocaine, codeine, dihydrocodeine, ethanol and monoacetylmorphine (heroin) did not have a major impact on additional drug consumption compared with benzodiazepines and morphine. Consumption of morphine had evidently more impact on additional consumption in both maintenance groups than traditional monoacetylmorphine (heroin).

Until now the potential of buprenorphine as a treatment choice is not fully used. Problems in accepting Suboxone® by the client are yet not fully understand and need to have a further and deeper investigation including patients' opinions. A further challenge will be the planed long time depot administration of buprenorphine for special treatment populations all along together with new developed possible cocaine treatment options.

4 Conclusion

Until now the potential of buprenorphine as a treatment choice is not fully used. Problems in accepting Suboxone® by the client are yet not fully understand and need to have a further and deeper investigation including patients' opinions. A further challenge will be the planed long time depot administration of buprenorphine for special treatment populations all along together with new developed possible cocaine treatment options.

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Table 1 Psychomotor test performance of drug-dependent patients taking slow-release oral morphine compared with clients taking buprenorphine

Test	Buprenorphine (n = 13)	Slow-release oral morphine (n = 14)	p-value
RG	**Mean ±SD**	**Mean ±SD**	
Reaction time	518.2 ± 92.2	511.4 ± 99.1	0.314
Correct reactions	7.8 ± 0.4	7.9 ± 0.4	0.282
Incorrect reactions	0.3 ± 0.6	1.6 ± 3.7	0.330
DT			
Reaction time	0.8 ± 0.1	0.8 ± 0.1	0.226
Correct reactions	480.1 ± 43.7	474.6 ± 55.5	0.376
Incorrect reactions	27.8 ± 17.7	37.7 ± 23.4	0.127
Delayed reactions	106.2 ± 61.6	122.0 ± 69.0	0.331
Missing reactions	48.9 ± 42.0	53.1 ± 48.9	0.367
TAVTMB			
Correct answers	31.2 ± 4.4	30.0 ± 5.5	0.313
LVT			
Correct answers	39.5 ± 0.9	38.7 ±1.2	0.016
Incorrect answers	1.3 ± 2.3	3.2 ± 2.8	0.025
Working time [min]	2.45 ± 0.34	3.09 ± 0.40	0.047
Time for correct answers	3.8 ± 0.8	4.2 ± 0.8	0.087
COG			
Working time [min]	21.27 ± 12.58	28.0 ± 15.51	0.122
Time for correct reactions	2.9 ± 0.7	2.8 ± 0.4	0.331

Note: Vienna Reaction Test System (RG); Vienna Determination Test (DT); Tachistoscopic Traffic Test Mannheim for Screen (TAVTMB); Visual Pursuit Test (LVT); Cognitrone Test (COG).

Significant at $p < 0.05$.

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Table 2 Summarized percentage of positive urine sample results

	Methadone (N = 33.057)					**Buprenorphine (N = 9.522)**					
	N					**N**					
	[%]					**[%]**					
Urine samples	negative	weak positive	positive	strong positive	total positive percentages	negative	weak positive	positive	strong positive	total positive percentage	p-values between total positive percentages
	701	5	3	19	27	265	3	0	30	33	
Amphetamine	96.3	0.7	0.4	2.6	3.7	95.0	1.1	0.0	3.0	5.0	0.374
	1273	59	66	1969	2094	627	16	19	391	426	
Benzodiazepines	37.8	1.8	2.0	58.5	62.2	59.5	1.5	1.8	37.1	40.5	0.000
	6816	54	33	452	539	2132	16	11	95	122	
Cocaine	92.7	0.7	0.4	6.1	7.3	94.6	0.7	0.5	4.2	5.4	0.001
	2090	170	103	175	448	834	38	19	24	81	
Ethanol	82.3	6.7	4.1	6.9	17.7	91.1	4.2	2.1	2.6	8.9	0.000
	5442	115	76	1699	1890	1760	26	29	412	467	
Opioids (total) [a]	74.2	1.6	1.0	23.2	25.8	79.0	1.2	1.3	18.5	21.0	0.000
	1942	29	95	116	240	486	11	17	26	54	
-Codeine	89.0	1.3	4.4	5.3	11.0	90.0	2.0	3.1	4.8	10.0	0.536
	1845	31	59	247	337	497	9	6	28	43	
-Dihydrocodeine	84.6	1.4	2.7	11.3	15.4	92.0	1.7	1.1	5.2	8.0	0.000
	0	-	-	-	2772	540	4	12	10	26	
-Methadone	0.0	-	-	-	100.0	95.4	0.7	2.1	1.8	4.6	-
	792	270	363	756	1389	196	90	102	151	343	
-Morphine	36.3	12.4	16.6	34.7	63.7	36.4	16.7	18.9	28.0	63,6	1.000
	2036	21	45	80	146	502	5	13	20	38	
-Monoacetylmorphine	93.3	1.0	2.1	3.7	6.7	93.0	0.9	2.4	3.7	7.0	0.774
	16322	403	281	4314	4998	5618	99	78	933	1110	
Total	76.6	1.9	1.3	20.2	23.4	83.5	1.5	1.2	13.9	16.5	0.000

[a] If urine samples were tested positive for opioids, a further chemical differentiation for codeine, dihydrocodeine, methadone, morphine and monoactetylmorphine was accomplished.

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