

Role of Medication and Background Variables in Dropout from Opiate Withdrawal Treatment – A Retrospective Chart Review

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Abstract

The present study aimed to examine whether retention in inpatient opiate detoxification was affected by the introduction of buprenorphine as a standard medication in opiate withdrawal, compared to older substances, when controlling for previous dropouts from detoxification, age, gender and current aftercare treatment planning. This chart review with a naturalistic design studied all inpatient opiate detoxifications in a detoxification unit during five years. In total, 375 patients with a total of 639 detoxification episodes were studied, with the withdrawal medication prescribed being buprenorphine, clonidine, dextropropoxyphene or methadone. In logistic regression, using buprenorphine as a reference, completion of detoxification was unrelated to the choice of medication, but associated with the presence of an aftercare plan upon admission, older age and a lower number of previous dropouts. However, dropouts remained significantly longer until dropout with buprenorphine, compared to clonidine and dextropropoxyphene. While the longer time to dropout suggests a higher effectiveness in withdrawal treatment with buprenorphine, no overall effect was seen on actual dropout rates. Lack of an aftercare plan and previous dropouts may be risk factors of dropout in opiate detoxification.

Keywords: Heroin; Opiate; Detoxification; Retention; Buprenorphine; Methadone; Clonidine; Dextropropoxyphene; Substance use disorder

Introduction

Withdrawal treatment (often referred to as detoxification) is a common procedure in the treatment of heroin-dependent patients coming off heroin or attempting to facilitate entry into psychosocial treatment or other interventions not involving opiate substitution treatment. Symptom relief and retention is crucial in withdrawal treatment, and subjective withdrawal symptoms are likely to lead to early dropout [1].

Pharmacological treatment during opiate detoxification may involve an opioid, achieving cross-tolerant treatment, or other symptom-oriented treatment such as alpha2-adrenergic agonists [2]. Alpha-2-adrenergic agonists, e.g. clonidine, lofexidine or guanfacine, have demonstrated some relative effectiveness in opiate withdrawal. The use of clonidine, however, may be somewhat limited by side effects including hypotension [2,3].

Dextropropoxyphene has been used in some settings for detoxification purposes, but the use of higher doses is limited by side effects [2]. Also, its toxicity in overdose, particularly in combination with alcohol, is well documented [4], and primary abuse of the substance has been documented [5]. Despite this, before being withdrawn from the market, dextropropoxyphene has been used for opiate detoxification in some settings, both according to older publications [6], and in somewhat more recent years in Spain [7] and Sweden [8], although little has been documented about its efficacy.

Since the introduction of buprenorphine, a partial opioid agonist, for the treatment of heroin detoxification [9], several studies have assessed its ability to alleviate opiate withdrawal symptoms. Early reports indicated that buprenorphine was more effective than clonidine against early symptoms of opiate withdrawal [10,11], and more recent studies demonstrated its superior efficacy expressed as retention in inpatient or outpatient detoxification, duration of retention and level of withdrawal symptoms [12-14] and expressed as the percentage

of patients who complete detoxification and continue to planned treatment [15]. Generally, withdrawal symptoms described during buprenorphine taper have been mild [16].

Methadone, which has been used for these purposes for many years, has demonstrated efficacy in placebo-controlled trials regarding its ability to retain patients in detoxification treatment, although it has not consistently proved to increase retention compared to other study medications [17]. For example, retention was not significantly different between methadone and buprenorphine [12].

The present study aimed to examine, retrospectively, whether the introduction of buprenorphine was able to improve retention in opiate withdrawal treatment in this inpatient setting, compared to older pharmacological options. While controlling for other factors potentially related to retention in detoxification, a secondary aim was to assess whether retention was influenced by previous detoxification history and by aftercare planning.

Materials and Methods

The present study is a retrospective chart review, using hospital records for pharmacological heroin detoxifications carried out in an inpatient detoxification unit of Malmö Addiction Center, Malmö, Sweden, during a five-year period. During this period, and during the decade prior to the study, this ward was the only unit for inpatient

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illicit drug detoxification in the catchment area of Malmö and its neighbouring city Lund, and with the closest inpatient detoxification ward (in the city of Helsingborg) being organizationally separated from the catchment area assessed here. Thus, a major number of opiate-dependent patients requiring inpatient detoxification in the region have been treated in the present detoxification unit.

For a five-year period, ranging from January, 2000, to December 2004, hospital records were reviewed for all treatment episodes described as a detoxification from opiates, and where any of the following medications were prescribed as withdrawal medication; buprenorphine, clonidine, dextropropoxyphene, or methadone. The present study period displayed a major transition in the choice of medication used for withdrawal treatment in opiate detoxification. Buprenorphine was introduced in clinical practice in Sweden in the very late 90's, although only on a pilot level [18], and during the study period, buprenorphine gradually replaced the previously predominating medications used, clonidine and dextropropoxyphene. During the same whole period, methadone was used in a lower number of patients, mainly for patients perceived to have a more severe prognosis in detoxification (see below). The distribution of medications prescribed for withdrawal treatment during the present study period is displayed in (Tables 1 and 2).

The present study excluded treatment episodes if they did not explicitly involve withdrawal treatment, i.e. if the patient was initiated on a continuous maintenance treatment with methadone or buprenorphine, or if the patient was observed for psychiatric reasons or did not need withdrawal medication. Also, in order to clearly examine the effect of each type of medication, treatment episodes were excluded if the patient's withdrawal medication was changed during the procedure. Also, treatment episodes were excluded if perceived to be carried out in a coercive context that was likely to influence the chance of retention. However, as this is a naturalistic retrospective study, aiming to assess the role of different prescription patterns in withdrawal treatment, patients were included if they dropped out very early after admission even if they did not even receive the first dose of withdrawal medication, provided it was explicitly stated in the hospital records that they were prescribed a specific substance (one of the four compounds assessed here) for the purpose of withdrawal treatment. Among 23 patients dropping out already during the first day of inpatient treatment, 13 patients never received the first dose of the medication they were explicitly prescribed.

We identified 639 detoxifications which fulfilled the inclusion criteria, including 375 unique individuals with one or more

	2000	2001	2002	2003	2004	Total
Clonidine	49	73	60	39	3	224
Dextropropoxyphene	59	55	56	64	2	236
Buprenorphine	0	1	8	19	88	116
Methadone	11	6	14	18	14	63
Total	119	135	138	140	107	639

Table 1: All included opiate detoxifications, 2000-2004. Number of detoxification episodes

	2000	2001	2002	2003	2004	Total
Clonidine	46	56	41	26	0	169
Dextropropoxyphene	41	27	21	32	1	122
Buprenorphine	0	1	4	11	45	61
Methadone	9	1	4	7	2	23
Total	96	85	70	76	48	375

Table 2: Included detoxifications 2000-2004, one detoxification (first episode) per patient

detoxification episodes. In secondary analyses, we included only the first treatment episode for each patient during this period of time.

Baseline characteristics of detoxification episodes were recorded for each type of withdrawal medication used, in order to identify potential differences between the groups. These data included gender and age of the patient, and for each episode, it was reported whether an aftercare plan was established before admission to the ward (Table 3). Also, in the present study, available data describe the number of previous detoxifications registered in the detoxification ward in Malmö and the number among these resulting in a dropout against medical advice, and these data were entered as absolute numbers in the model. These characteristics were compared using chi-square test for categorical variables and Student's t test for continuous variables, with patients who were prescribed buprenorphine as the reference.

In a multivariate analysis, assessing risk factors of dropout against medical advice, withdrawal medication were entered as one of the independent variables potentially predicting the risk of dropout, with the buprenorphine group as the category of reference. As the number of previous dropouts (and not the total number of previous detoxifications) differed significantly between groups in the binary analysis, this variable was entered in the multivariate analysis, along with age, gender and aftercare plan status. The present study was carried out within the context of a pre-graduate research project by the first author, which, according to Swedish legislation, does not require approval by an ethics committee.

Results

When including only the first detoxification of each patient, among 375 detoxifications, 47% (n=178) were successfully completed and 53% (n=197) were dropouts against medical advice. In binary comparison, completion of detoxification was significantly associated with a pre-treatment aftercare planning, older age, and fewer previous dropouts (Tables 4 and 5). However, successful detoxifications and dropouts did not differ with respect to gender or the total number of previous detoxification episodes.

Among all detoxification (N=639), 291 (46%) were successfully terminated and 348 (54%) were dropouts against medical advice. Here, in binary analysis, retention was significantly associated with a pre-treatment aftercare planning, and with a lower number of previous dropouts. Gender, age, and the total number of previous detoxifications did not differ significantly between the groups.

In logistic regression, and when analysing only the first treatment episode during the period, retention in detoxification was significantly associated with an aftercare planning upon admission, and with a lower number of previous dropouts, as well as with older age. However, no significant difference was seen between pharmacological treatment conditions, when comparing each of them to buprenorphine.

In the analysis of all detoxifications during the period, retention remained significantly associated with an aftercare planning, older age, and a lower number of previous dropouts and no significant associations were seen between pharmacological treatments, when comparing to buprenorphine, respectively.

When analysing buprenorphine versus each of the other substances, when controlling for co-variables studies here (age, gender, number of previous dropouts, and aftercare planning), differences in dropout between buprenorphine and other substances remained non-significant for all comparisons. In the analysis of all detoxifications,

	Buprenorphine (n = 116)	Clonidine (n = 224)	Dextropropoxyphene (n = 236)	Methadone (n = 63)
Mean age	32.4 yrs	30.6 yrs (p=0.10)	34.0 yrs (p=0.14)	35.7 yrs (p=0.02)
Number of previous detoxifications	1.97	1.31 (p=0.02)	3.19 (p<0.001)	5.22 (p<0.00001)
Number of previous dropouts	1.01	0.66 (p=0.04)	1.77 (p<0.001)	3.21 (p<0.00001)
Aftercare planning confirmed	67 (58%)	133 (59%, p=0.77)	115 (49%, p=0.11)	28 (44%, p=0.09)
Male gender	71 (61%)	177 (79%, p<0.001)	151 (64%, p=0.61)	19 (30%, p<0.0001)

*significant (p<0.05) difference compared to buprenorphine group

Table 3: Baseline characteristics in all treatment episodes, Comparisons with buprenorphine as reference

	All subjects (N=375)	Completed detox (n=178)	Dropouts (n=197)	p value
Male gender	266 (71%)	127 (71%)	139 (71%)	0.87
Aftercare planning confirmed	188 (50%)	114 (64%)	74 (38%)	<0.001*
Mean age	31.8 yrs	32.9 yrs	30.8 yrs	0.02*
Number of previous detoxifications	1.32	1.20	1.43	0.32
Number of previous dropouts	0.67	0.47	0.86	<0.01*

*significant (p<0.05) difference between dropouts and completers

Table 4: Binary comparison between completers and dropouts. One detoxification per patient.

	All subjects (N=639)	Completed detox (n=291)	Dropouts (n=348)	p value
Male gender	418 (65%)	199 (68%)	219 (63%)	0.15
Aftercare planning confirmed	343 (54%)	193 (66%)	150 (43%)	<0.001*
Mean age	32.7 yrs	33.4 yrs	32.1 yrs	0.08
Number of previous detoxifications	2.51	2.37	2.62	0.32
Number of previous dropouts	1.38	1.07	1.64	<0.001*

*significant (p<0.05) difference between dropouts and completers

Table 5: Binary comparison of completers and dropouts. All detoxifications.

in the comparison against methadone, retention was associated with aftercare planning (OR 2.42 [1.29-4.52]), against clonidine, retention was associated with aftercare planning (OR 1.86 [1.18-2.91]) and lower number of previous dropouts (OR 0.85 [0.72-1.01]), and against dextropropoxyphene, retention was associated with aftercare planning (OR 3.93 [2.48-6.24]), older age (OR [1.04 (1.01-1.07)]) and lower number of previous dropouts (OR 0.84 [0.75-0.95]). When analysing only the first treatment, in the comparison against methadone, retention was associated with aftercare planning (OR [3.32 (1.31-8.42)]), against clonidine, retention was associated with aftercare planning (OR 2.50 [1.45-4.29]), and against dextropropoxyphene, retention was again associated with aftercare planning (OR 5.02 [2.60-9.71]) and with a lower number of previous dropouts (OR 0.68 [0.48-0.95]).

In contrast, while the completion of detoxification in the detoxification group was not different from the clonidine and dextropropoxyphene groups, in patients who dropped out against medical advice, retention was markedly longer in the buprenorphine group, both compared to clonidine (p<0.001) and dextropropoxyphene (p<0.001). The same comparison remained highly significant when analysing only one detoxification per patient (p<0.01).

Discussion

The present retrospective chart review examined retention in inpatient opiate detoxification with the choice of withdrawal medication as a potential predictor of retention. However, the study failed to demonstrate an increased rate of completion with the use of buprenorphine, compared to every other drug; however, the study found large and highly significant differences in the length of retention for patients who eventually dropped out, possibly favouring

the prescription of buprenorphine during opiate withdrawal. Also, the study rather demonstrated that the presence of an aftercare plan upon admission may be associated with a higher retention rate, and that dropout was predicted by previous dropouts from inpatient detoxification.

Retention is crucial in inpatient opiate detoxification, facilitating transfer to long-term treatment of opiate use disorders. The present study suggests a more favourable course in detoxification if an aftercare treatment plan is present already when the patient is admitted. Despite this finding, when controlling for demographic data, previous dropouts and withdrawal medication (Tables 6 and 7), the present study does not allow for the causality to be established, and it cannot be excluded that patients with a higher perceived risk of dropout were less likely to have an established plan made before hospitalization, but the association of these variables after attempting to control for clinical severity (number of previous dropouts) does not indicate this. With this in mind, the present findings support a clinical routine where an aftercare plan is established prior to admitting the patient for detoxification.

Also, previous failure in inpatient detoxification was an independent predictor of dropout in the present study, both in the all-episode analysis and in the analysis of only one index episodes per patient. This finding may seem intuitive, and it was confirmed in the binary analysis where the total number of previous treatment episodes did not differ between completers and dropouts, whereas dropouts had a significantly higher number of previous dropouts against medical advice. These data were dichotomous and the exact characteristics of these earlier treatment episodes could not be thoroughly investigated, but they occurred in the same ward and with a high likelihood of being detoxifications in a majority of cases. The role of previous treatment

	Retention, one treatment episode per client, n (%)	P value compared to buprenorphine	Retention, all treatment episodes, n (%)	P value compared to buprenorphine
Buprenorphine	32/61 (52%)		61/116 (53%)	
Clonidine	49/169 (49%)	0.60	103/224 (46%)	0.25
Dextropropoxyphene	58/122 (48%)	0.53	105/236 (44%)	0.15
Methadone	6/23 (26%)	0.03*	22/63 (35%)	0.02*
Total	178/375 (47%)		291/639 (46%)	

*significant (p<0.05), compared to buprenorphine

Table 6: Retention with different types of withdrawal medication.

	One treatment episode per patient (N=375)	All treatment episodes (N=639)
Age	1.05 (1.02-1.08)*	1.03 (1.01-1.05)*
Gender	0.75 (0.45-1.25)	1.14 (0.77-1.61)
Aftercare planning	3.22 (2.07-5.00)*	2.82 (2.02-3.96)*
Number of previous dropouts	0.75 (0.62-0.92)*	0.85 (0.78-0.94)*
Drug (buprenorphine reference)		
- Methadone	0.37 (0.12-1.18)	0.68 (0.34-1.36)
- Dextropropoxyphene	0.95 (0.50-1.76)	0.82 (0.51-1.31)
- Clonidine	0.94 (0.50-1.76)	0.72 (0.45-1.16)

Table 7: Predictors of retention, Logistic regression.

failure as a predictor of subsequent failure was consistent with the findings of Kovas et al. who reported observational data comparing detoxification outcomes in two subsets of patients, treated with either buprenorphine or clonidine, and where prior treatment completion predicted completion of the index detoxification episode [19]. In clinical practice, patients with previous dropouts against medical advice may need particular attention and further focus on optimizing detoxification, such as the aftercare plan discussed above and possibly in-depth analysis of the reasons for previous failures.

The paradigm for withdrawal medication changed completely during the period studied here, and although not in a controlled study design, these changes allowed for a comparison of different withdrawal medication paradigms, given that other procedures surrounding detoxification was similar throughout the study period. The findings of the present study relating to withdrawal medication were somewhat ambiguous; on one hand, the study demonstrated large differences in the length of stay in dropouts, with buprenorphine patients remaining almost twice as long in the ward than patients receiving clonidine or dextropropoxyphene. On the other hand, the actual completion of detoxification, expressed dichotomously, was not improved with the newer medication, neither in binary analysis, nor when controlling for other variables included in the study. Consistent with previous data indicating an improved course in patients treated with buprenorphine [10-14], compared to alpha-adrenergic agonists such as clonidine, the marked difference in the number of days until dropout may be interpreted as an improved symptom-relieving effect with buprenorphine, compared to older agents (Table 8). Importantly, with clonidine and dextropropoxyphene, a significant minority of patients dropped out during the first few days of treatment, whereas many patients treated with buprenorphine remained long enough to complete the whole or large parts of the medication regime (data not shown). However, the lack of effect on actual treatment completion is more difficult to interpret, but may potentially indicate that despite an assumingly more favourable course throughout detoxification, the actual completion of the inpatient episode may depend on other factors, such as contextual factors including the type of treatment – or lack of treatment – planned after leaving the ward. The observational study of Kovas and co-workers demonstrated – similar to the findings

of the present study – a longer retention in patients treated with buprenorphine compared to patients treated with clonidine, but also saw a significant difference in actual completion of detoxification between the two drugs [19].

For patients treated with methadone, retention was lower in binary comparison, but in logistic regression analysis, it also did not differ significantly from buprenorphine (Table 7). Here, the role of methadone may be seen as a study limitation, as it has been used typically for patients suspected to be more difficult to retain in treatment, and this was somewhat confirmed by a higher number of previous dropouts in the methadone group. The effect of methadone in opiate detoxification has been demonstrated previously, and here, when controlling for other variables, its influence on retention was not significantly inferior to that of other substances, despite the assumingly more severe group of patients treated with methadone.

Although beyond the scope of the present study, it has to be borne in mind that in the treatment of heroin addiction, opiate maintenance treatment with methadone or buprenorphine has robust evidence from the literature [20]. The present study refers to a treatment situation where the patient undergoes withdrawal treatment after discontinuation of opiate use, and without transfer to agonist maintenance treatment such as methadone or buprenorphine maintenance treatment. This is a situation likely to occur when opiate-dependent individuals in ongoing opiate use are hospitalized, incarcerated or in any other setting where the patient is undergoing opiate withdrawal. However, detoxification also still remains a routine treatment in many settings aiming to transfer the patient to a non-agonist treatment regime, including psychosocial treatment programmes.

The present study has limitations. First and foremost, this study is retrospective, such that the dosing of medication was not standardized and not possible to control for. Also, the present study has a naturalistic design, and despite the authors' general impression that regulations in the ward were comparable throughout the study period, the retrospective and naturalistic design did not allow for a controlled design in comparing groups of patients with different medications. Also, given the naturalistic nature of the present analyses, and given the purpose of comparing different medication paradigms

	Completed detox, all detoxifications	Dropouts, all detoxifications	Completed detox, first detox only	Dropout, first detox only
Buprenorphine	13.0 (n=61)	8.1 (n=55)	12.3 (n=32)	7.3 (n=29)
Clonidine	10.6 ^{***} (n=103) p=0.001	4.3 ^{***} (n=121) p<0.00001	10.5 (n=82) p=0.08	4.2 ^{**} (n=87) p=0.002
Dextropropoxyphene	11.7 (n=105)	4.5 ^{***} (n=131) p<0.00001	11.7 (n=58)	4.5 ^{**} (n=64) p=0.004
Methadone	15.0 (n=22)	8.4 (n=41)	14.2 (n=6)	9.2 (n=17)

Significance compared to buprenorphine, ^{*}p<0.05, ^{**}p<0.01, ^{***}p<0.001

Table 8: Duration of stay in completers and dropouts (number of days).

with respect to dropout, patients were included if they were explicitly (according to hospital records) planned to receive one particular withdrawal medication even if they left the ward before the first dose was administered. Although this is a limitation to the generalizability of pharmacological effects of different medications, it still permits the comparison of dropout rates while the medication guidelines have changed over time, still controlling for individual characteristics of the patients. This also limits the medication-related findings to an indication of the *effectiveness* of prescription patterns, rather than the pharmacological *efficacy* per se. In addition, the role of methadone as a second-line treatment for assumingly more difficult detoxifications limits the generalizability of the findings related to that substance, although the statistical model controlling for previous dropouts did not demonstrated a significant inferiority to buprenorphine, although in a relatively limited number of patients. Also, the present chart review has not allowed the authors to include other individual characteristics, such as psychiatric disorders or social context, which are variables which could potentially have an impact on treatment retention in detoxification.

Conclusions

In conclusion, although heroin-dependent individuals being prescribed buprenorphine as withdrawal medication were able to remain longer in detoxification until they dropped out, the rates of actual completion of detoxification were not significantly better in the buprenorphine group, compared to clonidine or dextropropoxyphene. Instead, the presence of an aftercare planning upon admission was associated with completion of withdrawal treatment, and clients with a higher number of previous dropouts against medical advice were more likely to drop out than other patients. Despite limitations in the present retrospective chart review, it may indicate that inpatient withdrawal treatment in heroin users should involve a structured aftercare planning, and that patients with a history of dropping out from inpatient detoxification may need enhanced efforts attempting to lower the risk of non-completion. Despite the lack of difference in actual completion, buprenorphine may be superior to clonidine and dextropropoxyphene in retaining patients longer in opiate detoxification treatment.

Conflicts of interests

The authors do not have any conflicts of interest to report related to the present paper.

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