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ULTRA-RAPID OPIATE DETOXIFICATION USING DEEP SEDATION AND PRIOR
ORAL BUPRENORPHINE PREPARATION : LONG-TERM RESULTS

THESE

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Sevrages opiacés de types ultra-courts, effectués sous sédation profonde après prémédication à la buprénorphine : résultats à longs termes.

Contexte : les méthodes de sevrage dit ultra-court pratiquées sous sédation intraveineuse font actuellement l'objet de controverses en raison du manque de données concernant leur suivi à long terme d'une part et leur sécurité d'autre part. La prémédication avec de la buprénorphine est préconisée puisqu'elle diminue les vomissements survenant au cours de la procédure de type ultra-courte. Enfin, les résultats des recherches antérieures ne se rapportent pas à des populations de patients socialement défavorisés.

Méthode : Seize patients dépendants des opiacés ont bénéficié d'un sevrage ultra-court puis ont été prospectivement évalués sur une période d'au moins 30 mois. Les données de cette procédure ont été comparées avec celles de notre étude précédente effectuée sans préparation avec de la buprénorphine. Des médecins généralistes ont entièrement géré la phase de pré et post-procédure (prémédication à la buprénorphine, suivi après sevrage).

Résultats : durant la procédure, seul un épisode de vomissement est survenu au lieu de 13 sur 20 dans notre précédente étude. Post-procédure, seuls deux patients se sont plaints durant 24 à 48 heures d'un état de manque modéré sous forme de nausées persistantes, crampes abdominales et vomissements au lieu de la plupart des patients dans notre étude précédente. Après une période d'au minimum 30 mois (36.0 ± 6.38), les 16 patients sont toujours en vie et régulièrement suivis par leur médecin généraliste. Deux d'entre eux sont restés totalement abstinents après le sevrage et quatorze ont rechuté. Parmi ces quatorze patients, douze ont suivi, après la rechute, un traitement de substitution à la méthadone. Deux sont resté héroïno-dépendants.

Conclusion : dans ce petit échantillon de patients, les données ont montré que la sécurité des sevrages de type ultra-court est significativement améliorée avec une prémédication à la buprénorphine. Aucun patient n'est décédé sur une période d'au moins 30 mois. De plus, la procédure a été effectuées avec des patients socialement défavorisés. Sur le long terme deux d'entre eux sont restés abstinents tandis que la majorité a opté pour un traitement de substitution après la rechute ce qui tend à montrer que le sevrage de type ultra-court peut s'inscrire comme l'une des étapes possibles dans une prise en charge à long terme.

Ultra-rapid opiate detoxification using deep sedation and prior oral buprenorphine preparation: long-term results

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Abstract

Background: New methods of ultra-rapid opiate detoxification (URD) under intravenous sedation have been criticized because of limited data on safety and long-term follow-up. Premedication with buprenorphine has been advocated to improve safety by decreasing vomiting. Prior research has not explored URD in socially impaired patients. **Method:** Sixteen patients were detoxified with URD and prospectively evaluated over at least 30 months. Data of this procedure were compared with those of our previous study without buprenorphine preparation (*Drug Alcohol Depend.* 52(3) (1998) 243). The 16 patients were followed up by a general practitioner (GP) before and after URD. The GPs also supervised the 7-day course of buprenorphine treatment prescribed for the 16 patients prior to URD. **Results:** During the procedure, only one episode of vomiting occurred instead of 13 out of 20 in our previous study. Post-procedure, only two patients experienced moderate withdrawal symptoms, such as persistent nausea, abdominal cramps and vomiting lasting from 24 to 48 h, in comparison with most patients in the previous study without buprenorphine. After a period of at least 30 months (36.0 ± 6.38), the 16 patients were still alive and were regularly monitored by their GP. Only two of the 16 never relapsed after URD and reported total opiate abstinence. Fourteen patients relapsed; 12 of these were prescribed a licensed methadone substitution program and two were still using heroin. **Conclusion:** In this small sample, the data indicated that URD with buprenorphine preparation was safe and that it markedly decreased post-procedure morbidity. No patient died over a minimum 30-month follow-up period. Furthermore, the procedure was employed with socially impaired patients. In the long term, a few patients were still free of opiates, while the majority opted for a methadone maintenance program, showing that URD can serve as one possible step in a long-term treatment program.

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Keywords: Ultra-rapid opioid detoxification; Naloxone; Naltrexone; Buprenorphine

1. Introduction

Ultra-rapid opiate detoxification (URD), also known as anesthesia-assisted or 1-day opiate detoxification, is a procedure for detoxifying opioid-dependent patients with opiate antagonists, such as naloxone/naltrexone, administered either under general anesthesia or under deep sedation.

The method was first developed by Loimer et al. (1989) with patients under anesthesia and intubation and was based on earlier rapid detoxification methods published by the Yale group in the early 1980s (Riordan and Kleber, 1980; Vining et al., 1988). Numerous groups then worked on improving the technique. Loimer et al. (1991) refined the procedure with patients under deep intravenous midazolam sedation and proposed that patients should transfer to oral naltrexone 2–3 h post-procedure. Loperamide (Legarda and Gossop, 1994) or octreotide were added to prevent diarrhoea and ondansetron was prescribed against nausea (Loimer et al., 1993). Recently, the International Group for Rapid Opiate Detoxification (IGROD) reported on several

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developments, including the introduction of buprenorphine premedication prior to URD (Brewer, 1997).

This latter approach, first suggested by Stine and Kosten (1992), is based on the opiate agonist/antagonist properties of buprenorphine, which has less potential for drug dependence than a pure agonist. Its use as a substitution treatment at least 1 week before detoxification decreases the intensity of the withdrawal syndrome. Furthermore, this period of preparation is a good way to evaluate patient motivation.

However, much controversy currently surrounds URD because of its associated risks of mortality and morbidity (Dyer, 1998). Deep sedation without intubation involves the dangers of bronchial aspiration, nosocomial aspiration, pneumonia and the need for tracheal intubation in 1.3–2.6% of patients (Seoane et al., 1997). Even with intubation, Pfab et al. (1999) reported the onset of episodes of pulmonary and renal failure and thyroid hormone suppression during the procedure.

Nevertheless, limited data is available regarding patient outcome after URD. A literature review from 1989 to 1998 (O'Connor and Kosten, 1998) revealed studies with follow-up periods ranging from 1 week to 1 month. Most of these studies evaluated withdrawal scales rather than patient outcome. Recent reports indicated relapse rates from 36 to 80% after 6–12 months (Cucchia et al., 1998; Rabinowitz et al., 1998; Albanese et al., 2000).

Considering the lack of long-term outcome data after URD, this paper addresses the question by evaluating 16 opioid-dependent socially impaired patients at least 30 months after URD.

2. Method

2.1. General design

This study evaluated the follow-up of 16 opioid-dependent patients detoxed with a URD procedure after a 7-day course of buprenorphine. The 16 patients left hospital 24 h after URD to attend a residential or outpatient treatment program. Their GPs usually assumed responsibility for follow-up with a substance abuse treatment program (shared care). At least 30 months (36.0 ± 6.38) after the initial evaluation, the 16 patients (100% follow-up) were evaluated by a research assistant and asked to complete a questionnaire.

The study was approved by the Ethics Committee of the Department of Psychiatry of the University of Lausanne.

Descriptive statistics were used to present the results. In the data analysis, the Student's *t*-test was used for the dimensional variable, while the χ^2 -test was employed for data expressed as ratios. Correlations were incorporated

using the Pearson's coefficient. Statistical analyses were performed with SPSS for Windows (9.0). Continuous results are reported as means ± S.D.

2.2. Population studied

Sixteen patients were included; 12 men and four women with a mean age of 29 ± 5.98 years. Only five of the 16 patients were currently employed at the time of the URD. All had been opiate-dependent (DSM-IV) for at least 3 years, mean 8.1 ± 5.87 years (from three to 20). At the time of the URD evaluation, nine patients were receiving methadone maintenance therapy (mean dose 53.0 ± 33.44 mg). The other seven patients were heroin-dependent with daily drug use from two to five times a day (intravenously in five of the seven) and with a total estimated daily dose of 1–3 g. Three patients also admitted to occasional benzodiazepine use and one was dependent on cocaine. Three of the nine patients on methadone maintenance therapy used heroin approximately every other month.

The 16 URD candidates were personally interviewed by a senior psychiatrist (G.B.) who assessed the diagnosis of opiate dependence according to DSM-IV. Unmotivated patients or those with severe psychiatric disorders, such as schizophrenia or bipolar disease, were excluded. The indications for URD were: detoxification before admission to a therapeutic community (*n* = 4), a new occupation or training (*n* = 10) or a long journey abroad (*n* = 2). All had previously experienced outpatient detoxification and had left hospital with a naltrexone treatment (50 mg per day).

2.3. Ultra-rapid opiate detoxification procedure

One week before URD, all the patients switched from heroin or methadone to buprenorphine at a starting dose of 3 mg when withdrawal symptoms appeared. Accordingly, patients on methadone waited 40–60 h before starting buprenorphine. Those with methadone doses exceeding 30 mg per day received clonidine (0.075 mg four to six times a day) during this period of 40–60 h. Buprenorphine doses were added to achieve complete resolution of withdrawal symptoms. The patients determined the minimum dosage needed to make them feel comfortable. This dose generally decreased from 7.4 ± 4.61 mg on the first day to 4.3 ± 2.66 mg on the day preceding URD. Each patient underwent a physical examination, an electrocardiogram and blood tests, including blood count, electrolytes, urea, creatinine and transaminases.

On the day of URD, patients were admitted to our hospital at 07:30 h with an empty stomach. The procedure started with simultaneous oral administration of clonidine 0.300 mg, midazolam 60–135 mg (according to the subject's experience with benzodiazepines),

ondansetron 16 mg and loperamide 16 mg. When the first signs of sleepiness appeared, patients received 50 mg of naltrexone. Thirty to 60 min later, they entered the most acute phase of the withdrawal for 2–4 h. During this and the initiation phase, a nurse and a physician were responsible for the monitoring (permanent control of cardiac activity and oxygen saturation as well as blood pressure every 30 min). Oxygen therapy by mask, broncho-aspiration and tracheo-intubation material was available in the room and the physician on duty had been trained to use them.

Patients remained under constant nursing attention until they awoke spontaneously and remained awake for sufficient time (sometime between 6 and 10 h after the initiation). When they showed excessive global or specific withdrawal symptoms, additional medication was administered by mouth or by intramuscular injection in case of vomiting or abdominal cramps. During the first 24 h, the mean (± S.D.) medication was as follows: clonidine 0.51 ± 0.16 mg, benzodiazepines 127.5 ± 43.47 mg, ondansetron 19.3 ± 3.66 mg and loperamide 20.3 ± 5.74 mg. Patients left hospital after 24 h under naltrexone (50 mg per day) with a 2–3 day supply of clonidine and benzodiazepine. The GPs, in collaboration with the substance abuse therapeutic network, were responsible for the buprenorphine preparation and post-treatment phase.

2.4. Follow-up

Patients were located with the help of their GP and were mailed a follow-up questionnaire. The questionnaire evaluated aspects of the post-treatment phase, such as duration of abstinence, naltrexone intake, use of unprescribed medication, use of illegal drugs, number of new detoxification attempts, introduction of a new methadone maintenance therapy, physical or mental illnesses after URD. Visual analogue scales ranging from zero to ten points were used to determine the patients' satisfaction regarding URD. The corresponding statements were: 'I never underwent such a hard/easy detoxification'; 'I would choose another/the same method if I needed to undergo another in-patient detoxification'; 'I think that URD was of no use/extremely useful in my progress towards abstinence'.

3. Results

The 16 patients (100%) successfully completed the detoxification process and were discharged on naltrexone. Complications were limited to one episode of vomiting during the procedure instead of 13 out of 20 found in our previous study without buprenorphine preparation (Cucchia et al., 1998) (*P* < 0.001). Thus, in our present study, the mean (± S.D.) dose of ondansetron during the first 24 h was 19.3 ± 3.66 vs. 28 ± 12 mg (*P* < 0.05) in the previous study. No tracheal intubation was required. Only two patients experienced moderate withdrawal symptoms, such as persistent nausea, abdominal cramps and vomiting lasting from 24 to 48 h post-procedure, whereas most patients had complained of digestive symptoms in our previous study. However, all patients in both studies complained of psychic symptoms, insomnia and anxiety in the week following the procedure.

The 16 patients were located at least 30 months after URD and were interviewed (100% follow-up rate). Twelve patients (75%) returned completed questionnaires and four (25%) answered over the telephone. Of the 16 patients, four (25%) had been abstinent after 1 year and two (12.5%) remained abstinent after at least 30 months (see Fig. 1). Finally, of the 11 patients who had been unemployed at the time of the study, six were back in work at the time of the interview.

The degree of satisfaction was closely related to the duration of abstinence: 'I would choose another/the same method if I needed to undergo another in-patient detoxification', *r* = 0.55 (*P* < 0.01); 'I never underwent such a hard/easy detoxification', *r* = -0.49; 'I think that URD was of no use/extremely useful in my progress towards abstinence', *r* = -0.56. The global satisfaction level (based on the mean scores for the three questions for each patient) was 6.0 ± 3.91 (*P* < 0.0001) and showed that the global satisfaction level was significantly higher among those patients (*n* = 10) who remained abstinent for more than 1 month Fig. 2.

At the time of the study, two (12.5%) out of the 16 patients reported total abstinence after URD and never relapsed. Both were under methadone maintenance before URD. All other patients (*n* = 14, 87.5%) relapsed on opiates after URD. Twelve were prescribed a licensed methadone substitution program. At the time of the study, two of the 12 had completed their methadone treatment and had been abstinent for more than 1 year, while ten were still following methadone treatment. Finally, two (12.5%) of the 14 relapsers attempted

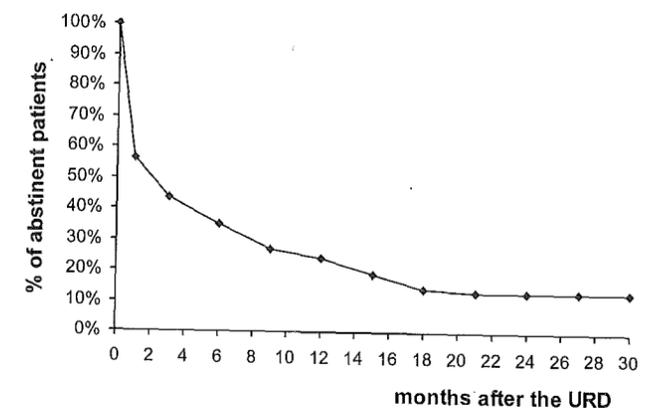


Fig. 1. Thirty-month survival (abstinence) profile after URD (*n* = 16).

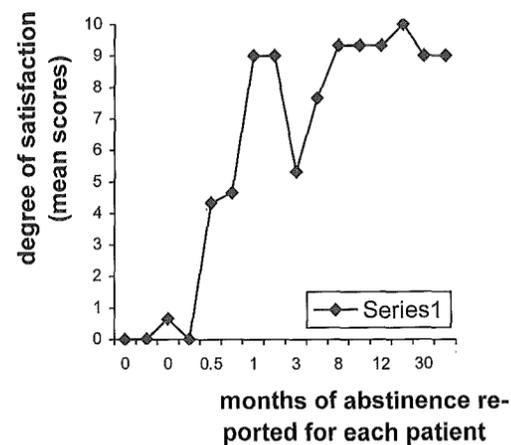


Fig. 2. Degree of satisfaction reported during the period of abstinence after URD.

another detoxification (not URD). They were still dependent on heroin at the time of the study, but still receiving treatment from their GP and connected to social services. Among the 14 relapsers, seven were heroin dependent and seven methadone dependent. Relapsers who were on methadone before URD returned to methadone, while five heroin dependent patients switched to methadone substitution treatment. Fig. 3 categorizes the different forms of outcome for the 16 patients, 30 months after URD.

Among the 14 relapses, seven occurred during the first month after URD, five between the second and twelfth month and two between the thirteenth and eighteenth month. The seven earliest relapsers explained that they had suffered severe residual withdrawal syndrome and had stayed in close contact with drug dealers, while the others mentioned emotional problems and a general lack of satisfaction with their lives.

Fig. 4 evaluated the relationship between the duration of abstinence (month) and the duration of naltrexone use. None of the seven first-month relapsers were on naltrexone, while those on naltrexone for more than 30 days remained abstinent for at least 6 months. Two out of the three patients who had taken naltrexone for just 1 day and remained abstinent for 6 months, entered a therapeutic community directly after URD. The third immediately left the country in a very isolated context. Naltrexone intake was similar between the heroin dependent patients and those under methadone maintenance (mean of 17 vs. 19 days, respectively, $P = 0.9$).

4. Discussion

All patients (100%) were located and interviewed after almost 3 years, despite their initial socially impaired situation. All were alive and still being regularly monitored by their GPs. At the time of the study, 75%

of the patients had followed, or were still following, a methadone substitution program. This means that the 30-month relapse rate was high (87.5%). Nevertheless, patients globally reported a high degree of satisfaction (mean 6.0 ± 3.91) for URD. This paradoxical high degree of satisfaction was probably linked with the integration of the patients in a therapeutic addiction network after the URD. This shared-care program, involving close collaboration between GPs, specialists, pharmacists and social services, offered the patients the possibility of avoiding the social, legal and infectious complications of opiate addiction. The prescription of methadone substitution treatment under the supervision of GPs probably decreased the stigmatization of the patients and may have helped attract them to the therapeutic network and to keep them within it. Consequently, for most of the patients unemployment decreased and parallel illegal drug consumption disappeared.

To our knowledge, this study involves the longest follow-up of patients after URD. In contrast with previously published data, this study did not include high-functioning patients with a good prognosis, since the main acceptance criterion for URD was simply the motivation for detoxification. Most of the patients were unemployed and none had to pay for their treatment. In such conditions and by way of comparison, our relapse rate at 6 months (56.25%) was similar to that observed after classical in-patient detoxification programs (Gosop et al., 1989; Broers et al., 2000). Our results also matched those of Albanese et al. (2000), who obtained a 45% relapse rate with a comparable procedure on a sample of 123 patients. At 6 months, we found better results than those of Cucchia et al. (1998), who reported an 80% relapse rate with the same URD procedure but without buprenorphine preparation. The lower level of side effects provided by the buprenorphine preparation may have contributed to the difference (see below). At 1 year however, our relapse rate was 75% compared with 43% observed by Rabinowitz et al. (1998). Here, the main difference seems to be in the patient compliance for naltrexone treatment after URD. Rabinowitz et al. (1997) reported that the non-relapsed patients completed at least 5 months of naltrexone treatment. In our study, only four patients (25%) took naltrexone for more than 30 days, but all remained abstinent for more than 6 months. This confirms the results of Rabinowitz et al. (1997) and proves that more prolonged use of naltrexone is associated with less chance of relapse.

The major controversy about URD concerns the associated risks of mortality and morbidity. Our experience shows that, with the deep sedation technique, buprenorphine preparation can improve safety since it significantly decreases the side effects observed during URD. Only one patient experienced vomiting during the procedure with buprenorphine preparation, compared

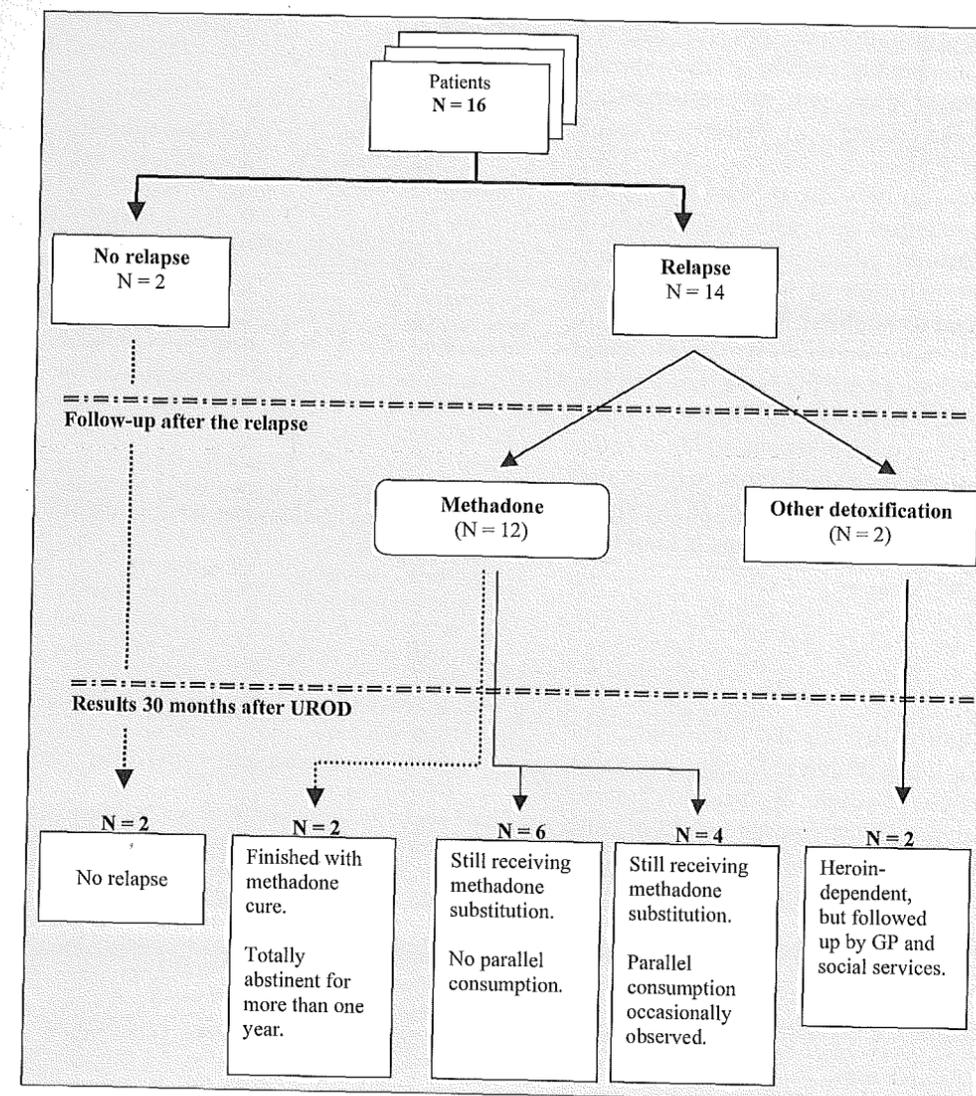


Fig. 3. Global situation 30 months after URD.

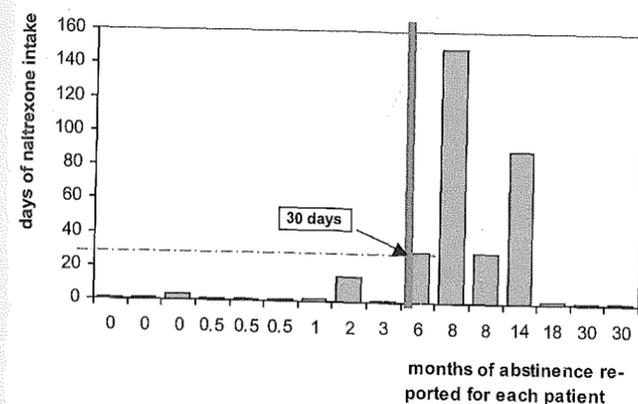


Fig. 4. Months of abstinence in relation to the period of naltrexone intake.

to the two-thirds of patients who experienced vomiting in the study reported by Cucchia et al. (1998). Nevertheless, even though none of these vomiting episodes

had required the use of tracheal intubation, a risk of bronchial aspiration does exist and explains why general anaesthesia with intubation may appear to be the safest method. Nevertheless, the mortality associated with anaesthesia itself remains between one in 1185 and one in 6789 for unselected patients (Brown, 1992). In such a context and since URD is an expensive procedure that can cost as much as 2500–7500 US\$ per patient (O'Connor and Kosten, 1998), it appears that the method should be evaluated individually for each patient and the costs carefully balanced against the potential savings afforded by this procedure.

Our study has several limitations. Firstly, we studied only a small number of patients and secondly, we did not use a control group. These results need to be replicated in a larger sample with a control group. Furthermore, GPs were contacted primarily to obtain the patients' addresses. Although we observed close similarities between their information and that of the

patients, we did not formally ask GPs for detailed follow-up information. Finally, future studies should evaluate more accurately those patient characteristics that could predict the success or failure of such procedures.

In conclusion, this study showed that the URD procedure with deep sedation was easier and safer with buprenorphine preparation than without as in our previous study. After a period of 30 months, two of the 16 patients reported total opiate abstinence, 12 were on methadone maintenance and two were still opioid dependent. All the relapsers remained integrated within the therapeutic addiction network that they had joined after relapse. However, long term results were no better than those of classical detoxification. This suggests that in a context of socially impaired patients, URD may be an alternative option in detoxification even if long term abstinence is weak.

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