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Substance Use & Misuse, 45:2076–2092 Copyright © 2010 Informa Healthcare USA, Inc. ISSN: 1082-6084 (print); 1532-2491 (online) DOI: 10.3109/10826081003791932 informa healthcare

# **Treatment: Retention**

# Effectiveness of Therapies for Heroin Addiction in Retaining Patients in Treatment: Results From the VEdeTTE Study

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Treatment is effective in reducing heroin use and clinical and social problems among heroin addicts. The effectiveness is related to the duration of treatment. "VEdeTTE" is an Italian longitudinal study funded by the Ministry of Health to evaluate the effectiveness of treatments provided by the National Health Services. The study involved 115

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We thank the staff of NHS treatment centers throughout Italy whose active support was essential for the VEdeTTE study. We especially thank Federica Mathis for acquisition of data, GianLuca Cuomo for data management, and Matthew Hickman for the comments on the first draft. This study was supported by a research grant from the National Fund for Drug Addiction provided by the Ministry of Health and by the Regional Fund for Drug Addiction of Piedmont Region.

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drug treatment centers and 10,454 heroin users. Clinical and personal information were collected at intake through a structured interview. Treatments were recorded using a standardized form. Survival analysis and Cox Proportional Hazard model were used to evaluate treatment retention. Five thousand four hundred and fifty-seven patients who started a treatment in the 18 months of the study were included in the analysis: 43.2% received methadone maintenance therapy (MMT), 10.5% therapeutic community, and 46.3% abstinence-oriented therapy (AOT). The likelihood of remaining in treatment was 0.5 at 179 days. The median daily dose of methadone was 37 mg. Psychotherapy was provided in 7.6% of patients receiving methadone and 4.9% of those in therapeutic community. Type of therapy was the strongest predictor of retention, with AOT showing the lowest retention. In MMT patients, retention improved according to dose. Living alone, psychiatric comorbidity and cocaine use increased the risk of dropout.

**Keywords** heroin addiction; treatment retention; methadone maintenance; methadone dose; therapeutic community; psychotherapy

#### Introduction

Treatment of heroin addiction is effective in reducing heroin use and related clinical and social problems (Amato, Davoli, Ferri, Gowing, and Perucci, 2004; Marsch, 1998; Mattick, Breen, Kimber, and Davoli, 2009; NIDA, 2000; Ward, Hall, and Mattick, 1999). Results from large-scale observational studies, such as the Drug Abuse Treatment Outcome Study (DATOS) (Simpson, Joe, and Brown, 1997b) and the National Treatment Outcome Research Study (NTORS) (Gossop, Marsden, Stewart, and Treacy, 2001), suggest that the extent of the reduction is associated with the duration of treatment. In this light, retention in treatment has been considered as an appropriate and measurable proxy of the effectiveness of treatment (Zhang, Friedmann, and Gerstein, 2003).

In Italy, treatment of heroin addiction is provided by the National Health Service (NHS) through a network of drug treatment centers (SerT). As of 2005, there were 535 treatment centers distributed throughout the country, and 180,117 patients were treated (Ministero della Solidarietà Sociale, 2006) (corresponding to 0.31% of Italy's population). The centers provide a wide range of individually tailored pharmacological and psychosocial treatments at no cost to the individual, mainly on an outpatient basis. When residential treatment is prescribed, the individual is referred to a therapeutic community. These communities are generally run by nongovernmental organizations (NGO), yet the cost of residential treatment is covered by the NHS, whose personnel supervise treatment.

In 1997, the Italian Ministry of Health decided to evaluate the effectiveness of the treatments provided by the drug treatment centers. Following the example of DATOS and NTORS, a large-scale follow-up study was launched. The study, known as "VEdeTTE" (an Italian acronym meaning "the evaluation of the effectiveness of treatment for heroin dependence") focuses on mortality (Davoli et al., 2007) and retention in treatment in relation to the treatment provided. In the present work, we describe the effectiveness of treatments in terms of retention.

### Methods

A pragmatic sample of 115 treatment centers were selected in 13 regional health offices as representative of the whole of regional treatment centers and participated in the cohort. To evaluate the representativeness of the cohort, the enrolled patients were compared to the population under treatment for opiate addiction in Italy in 1999, and no major differences

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were observed, apart from a lower proportion of new cases (11.5% in the cohort vs. 21.1% in the opiate addicted population, p < .01) (Bargagli et al., 2006).

During the study period (lasting 18 months, from September 1998 to March 2001), 10,454 heroin addicts provided informed consent and were enrolled. Upon enrollment, clinical history and personal information were collected by center personnel through a structured interview.

Information about treatment was collected for 18 months from the start of the study. Using a standardized form, the personnel of the centers collected detailed information on each episode of the following treatments: methadone maintenance; detoxification with tapering doses of methadone; detoxification with nonopiate drugs (in- and outpatient based); maintenance with naltrexone; therapy with psychotropic drugs; psychotherapy; counseling; job guidance; social advice; and residential and semiresidential treatment (semiresidential patients do not spend the night at the facility).<sup>1</sup> All treatments were provided on an outpatient basis by the centers' personnel, except for residential and semiresidential treatments and, in certain cases, inpatient detoxification. The following information was collected: type of treatment; mean dose (for methadone treatments), starting and closing date. For further details about the study design and population, see Bargagli et al. (2006).

In order to study the retention in treatment and its determinants, the analysis was limited to the first therapy started during the study period. This selection limited the study population to 5,457 subjects since the 4,816 patients who have an ongoing therapy at the beginning of the study and that did not start a second therapy in the 18 months of the study were not included in the analysis. Patients' therapies ongoing at the beginning of the study were excluded from the analysis because they referred to a selected group of patients who had "survived" to the treatment within the whole group of patients who started the treatment before the beginning of the study. The inclusion of these therapies would have caused an underestimation of the risk of dropout.

For the purpose of the analysis the included patients were classified according to the undergone treatment as follows:

- 1. Therapeutic community (TC), whatever additional treatment they received;
- Patients not in TC, undergoing a methadone maintenance therapy (MMT), whatever additional treatment they received;
- Patients not in a TC and not undergoing a MMT, receiving solely treatments aimed at abstinence (i.e., naltrexone maintenance, semiresidential treatments, detoxifications, psychotherapy, counseling, social advice, job guidance, psychotropic drug treatments).

This set of treatments was identified as a specific strategy of treatment called "abstinence-oriented therapy" (AOT).

When abstinence-oriented treatments were offered closely before a therapeutic community or a methadone maintenance (n = 1,260/2,931), they were considered as a preliminary

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<sup>&</sup>lt;sup>1</sup>Treatment can be briefly and usefully defined as a planned, goal directed, temporally structured change process, of necessary quality, appropriateness and conditions (endogenous and exogenous; micro to macro levels)), which is *bounded* (culture, place, time, etc.) and can be categorized into professional-based, tradition-based, mutual-help-based (AA,NA, etc.), and self-help ("natural recovery") models. There are no unique models or techniques used with substance users—of whatever types and heterogeneities—which are not also used with nonsubstance users. In the West, with the relatively new ideology of "harm reduction" and the even newer Quality of Life (QOL) treatment-driven model there are now a new set of goals in addition to those derived from/associated with the older tradition of abstinence driven models. Editor's note

phase of the following MMT or TC and not as a therapy itself. The preliminary phase was analyzed as a covariate of the therapy, and it was excluded by the calculation of the duration of therapy.

For the purposes of the survival analysis, any abandoning of treatment longer than 21 days, whatever the reason, was considered a failure. Therapies still ongoing at the end of the study period (18 months), or those stopped within 21 days from the end of the follow-up, were treated as right-censored. Kaplan–Meier product-limit estimator was calculated overall and for each group stratification, according to relevant patients' characteristics; log-rank test was used to assess statistical significance. A Cox Proportional Hazard model was built for the maximum likelihood estimation of the risk of dropout (Kleinbaum, 1996). Models were fitted following a backward procedure from a saturated model, including the most relevant information collected in the interview, particularly those suspected to play as confounders. Gender was always retained in the model independently by significance. Likelihood-ratio test was used to assess the fitness of models. Because of the difference in the distribution of type of patient between the cohort and the total of patients treated in Italy and because type of patient was an effect modifier in the graphical analysis, the model was stratified for new and reentry patients.

# Results

A total of 5,457 heroin users were included in the analysis: 1,216 (22.3%) were seen for the first time by the treatment center (new patients) and 4,241 (77.7%) had already been seen by the center in the past (retreated patients). In Table 1 are described the main characteristics of the study population.

Methadone maintenance was the first therapy for 43.2% of cases (n = 2,356), both in new and retreated patients (Table 2). The median dose of methadone was 37 mg; 15.1% of patients receiving 60 mg or more; 75.9% between 20 and 59 mg; and 9.0% less than 20 mg (data not shown). Before starting a MMT, 41.4% of patients underwent a preliminary period of treatment (Table 3), a quarter of them (27.0% new patients vs. 25.1% retreated patients; p = .377—data not shown) including tapering methadone.

Therapeutic community was the first therapy for 10.5% of cases (n = 575) (Table 2): 11.6% and 6.7% (p < .001) for retreated and new patients, respectively. Half of patients started the therapeutic community with a preliminary treatment (Table 3), 20% of them including a tapering methadone and 30% other abstinence-oriented treatments (data not shown).

Preliminary phase was observed in similar proportion in new and retreated patients (53.7% vs. 48.9%; p = .423—data not shown) with a median duration of approximately one month and half for both MMT and TC (Table 3).

During MMT and TC, patients received various supporting treatments, as counseling, social advice, and job guidance. Psychotherapy was provided to 7.6% of patients in MMT and to 4.9% of those in TC. Tapering methadone was rarely carried out in TC (0.9%) and limited to the very beginning of the treatment (Table 3).

AOT was the most frequent first therapy (46.3%; n = 2,526), in both new (49.7%) and retreated patients (45.3%). These patients received a great variety of pharmacological and nonpharmacological treatments: naltrexone (13.9%); single (37.5%) or repeated methadone detoxifications (14.3%); psychotherapy (12.7%); counseling, social support, or nonopiate detoxifications (55.0%) (data not shown). If patients receiving abstinence-oriented interventions as preliminary treatment were also taken into account (23.1%) (Table 3), the overall proportion of patients first treated with this type of treatments increased to 69.4%.

 Table 1

 Characteristics of the VEdeTTE study population

Gender M						I	
		New patients	ients	Retreated patients	l patients	Total	al
	I	N	%	u	%	u	%
W	en	1,010	83.1	3,670	86.5	4,680	85.8
	omen	206	16.9	571	13.5	LLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLL	14.2
Age 18	3–24	407	33.5	626	14.8	1,033	18.9
	25-29	340	28.0	1,254	29.6	1,594	29.2
30	)-66	469	38.6	2,361	55.7	2,830	51.9
Household Al	lone	146	12.0	579	13.7	725	13.3
Ó	Own family	1,070	88.0	3,662	86.3	4,732	86.7
Unemployment No	0	834	68.6	2,579	60.8	3,413	62.5
	SS	382	31.4	1,662	39.2	2,044	37.5
Prison No	0	1,067	87.7	3,438	81.1	4,505	82.6
Ye	SS	149	12.3	803	18.9	952	17.4
Education Hi	igh	257	21.1	667	15.7	924	16.9
M	edium/Low	959	78.9	3,574	84.3	4,533	83.1
Duration of 0–	4	465	38.2	497	11.7	962	17.6
addiction 5-	-19	683	56.2	3,359	79.2	4,042	74.1
20	)–33	68	5.6	385	9.1	453	8.3
HIV No	No	1,184	97.4	3,929	92.6	5,113	93.7
Ye	SS	32	2.6	312	7.4	344	6.3
Dual diagnosis No	0	1,103	90.7	3,661	86.3	4,764	87.3
Ye	SS	113	9.3	580	13.7	693	12.7
Age at first use 9–	-18	519	42.7	2,104	49.6	2,623	48.1
19	)-55	697	57.3	2,137	50.4	2,834	51.9
Tc	otal	1,216	100	4,241	100	5,457	100

	New p	atients	Retreated	l patients	А	.11
First therapy	n	%	n	%	n	%
Methadone maintenance	530	43.6	1,826	43.1	2,356	43.2
Therapeutic community	82	6.7	493	11.6	575	10.5
Abstinence-oriented therapies	604	49.7	1,922	45.3	2,526	46.3
Total	1,216	100	4,241	100	5,457	100

 Table 2

 Therapies observed during the 18-month period of the study among the VEdeTTE patients selected for the analysis of retention

Overall, 44.1% patients were still under treatment at the end of the study period (54.4% of MMT, 47.8% of TC, and 33.7% of AOT). Within the study period, overall 33.0% of patients restarted a second therapy (28.1% of MMT, 39.0% of TC, and 36.1% of AOT), while 23% stopped the therapy and did not come back (17.5% of MMT, 13.2% of TC, and 30.2% of AOT) (Table 3).

#### Retention in MMT, TC, and AOT

The overall likelihood of remaining in treatment was 0.5 at 179 days, i.e., 50% of patients were still under treatment after 179 days of therapy. The most significant predictor of retention in treatment was type of therapy, with some differences between new and retreated patients (Figure 1). Regardless to the type of therapy, the association with psychotherapy improved treatment retention: the median likelihood of retention was 315 days with psychotherapy vs. 167 days without (p = .001).

Among new patients in MMT, 50% were still under treatment after 307 days (Figure 1), as well as those in TC; however the difference among the two therapies was not statistically significant (p = .087). Among retreated patients, the median likelihood of retention were 300 days for patients under MMT and 169 days for patients in TC (p < .001). In this group,

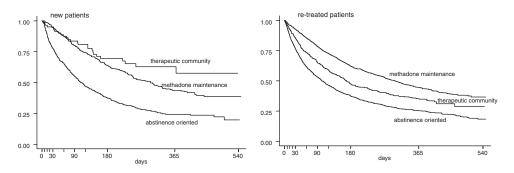


Figure 1. Kaplan–Meyer survival estimate of retention in treatment, by type of therapy and type of patient. n = 5,457.

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Table 3

		Preliminary phase	hase		During therapy		At	At the end of follow-up	dn-mc	
Therapy	Yes %	Median duration p50	Tapering methadone %	Tapering methadone %	Psychotherapy %	Other <sup>a</sup> %	Ongoing %	Stopped and did not come back %	Stopped and restarted a second therapy %	Patients n
Methadone	41.4	45	25.5		7.6	49.0	54.4	17.5	28.1	2,356
maintenance (MMT)				ć						נ נ נ
Therapeutic community	49.6	49	19.8	0.9	4.9	39.1	47.8	13.2	39.0	575
(TC)										
Abstinence- oriented therapy	I	I	I	51.9	12.7	55.0	33.7	30.2	36.1	2526
(AOT)										
Total therapies	23.1	45	$24.4^{b}$	37.4	9.7	50.7	44.1	22.9	33.0	5,457

MMT had a better retention among those who underwent a preliminary phase compared to those who did not: the median likelihood of retention corresponded to 340 days and 274 days, respectively (p = .004). Among patients undergoing MMT, retention improved according to dose.

In both groups of patients, AOT showed the lowest retention (p < .001, in comparison with the other two therapies): after 107 and 101 days of treatment, 50% of new and retreated patients, respectively, were still under treatment.

#### **Results of Cox's Multivariate Analysis**

In Cox's multivariate analysis (Table 4), few sociodemographic and clinical characteristics significantly confounded the relationship between type of therapy and retention. Since therapies had different patterns of prediction between new and retreated patients, two models were carried out. Type of therapy was confirmed as the strongest predictor of retention. Among new patients, those who were treated in TC showed nonsignificant differences compared to those who underwent MMT at 60 mg or more daily. Compared to the latter, all other therapies showed significant increases of risk of dropout. Living alone, psychiatric comorbidity, and cocaine use significantly increased the risk of stopping therapy.

Among retreated patients, those who underwent MMT at 60 mg or more daily showed the best retention. Among MMT patients, the lower the dose, the higher the risk of stopping therapy. Compared to MMT at 60 mg or more, the risk of stopping therapy was 1.85 (95%CI: 1.47–2.34) times higher among patients treated in TC and 3.27 (95%CI: 2.65–4.03) among those who received AOT. The risk of stopping therapy was associated to young age, and a slight additional risk of stopping was seen among patients living alone (1.18; 95%CI: 1.05–1.33).

In both groups of patients, regardless to the type of therapy, if no psychotherapy or no psychosocial treatment was associated to therapy, the risk of stopping increased of approximately two times. The absence of a preliminary phase before MMT increased the risk of stopping of 29% (1.29; 95%CI: 1.14–1.46; the risk was estimated in a model restricted to patients in MMT—data not shown).

#### Discussion

The analysis of the VEdeTTE study, a large Italian cohort of heroin addicts, showed the greatest retention for MMT when administered at a daily dose of 60 mg or more. Patient's history determines retention differences: among patients undergoing their first treatment, retention was similar when receiving TC and MMT, except for those receiving very low doses of methadone. Among retreated patients, who return for a new treatment after a relapse, TC as well as AOT, and AOT for all patients, show a higher risk of dropout and should be, therefore, considered with caution.

These findings were fairly expected and are consistent with the results of cohorts (Gossop et al., 2001; Simpson et al., 1997a), randomized controlled trials (Johnson, Jaffe, and Fudala, 1992; Johnson et al., 2000; Strain, Bigelow, Liebson, and Stitzer, 1999), and systematic reviews (Faggiano, Vigna-Taglianti, Versino, and Lemma, 2003; Mattick et al., 2009). They are also highly consistent with the results of the analysis on mortality in the same cohort: MMT showed the lowest mortality both during treatment and after the end of the treatment (Davoli et al., 2007).

This evidence raises the concern on the treatments offered by the Italian NHS drug treatment centers: 46.3% of patients received AOT as first treatment, most consisting of

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	New	New patients $(n = 1,216)$	()	Retre	Retreated patients ( $n = 4,241$ )	,241)
Predictor of treatment interruption	Hazard ratio	95% C.I.	Failure/N	Hazard ratio	95% C.I.	Failure/N
Therapy						
Methadone maintenance $\geq 60 \text{ mg daily}$	1	I	26/74	1	I	96/282
Methadone maintenance 20–59 mg daily	1.43	0.95 - 2.17	173/404	1.41	1.14 - 1.75	645/1,384
Methadone maintenance <20 mg daily	3.22	1.94 - 5.34	37/52	2.33	1.76 - 3.09	98/160
Therapeutic community	0.88	0.51 - 1.51	26/82	1.85	1.47 - 2.34	274/493
Abstinence oriented therapies	3.68	2.46 - 5.50	395/604	3.27	2.65 - 4.03	1,280/922
Concurrent psychosocial treatments						
Yes	1	I		1	Ι	
No	1.93	1.64 - 2.26		1.81	1.67 - 1.97	
Concurrent psychotherapy						
Yes	1	I	69/137	1	I	176/390
No	2.03	1.57 - 2.63	588/1,079	2.01	1.72 - 2.34	2,217/3,851
Gender						
Woman	1	I	101/206	1	I	308/571
Man	1.12	0.9 - 1.39	556/1,010	0.98	0.87 - 1.1	2,085/3,670
Age						
30-66 years		I	246/469	1	I	1,261/2,361
25–29 years	1.02	0.84 - 1.24	187/340	1.13	1.03 - 1.24	726/1,254
18–24 years	1.15	0.95 - 1.38	224/407	1.36	1.22 - 1.53	406/626
Household						
Living with his/her own family	1	I	562/1,070	1	I	2,058/3,662
Alone, with friends, homeless	1.37	1.09 - 1.73	95/146	1.18	1.05 - 1.33	335/579
Dual diagnosis						
No	1	Ι	586/1,103	1	I	2,062/3661
Yes	1.50	1.17 - 1.94	71/113	1.11	0.99 - 1.25	331/580
Cocaine use						
No		I	473/897		I	1,539/2,680
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repeated detoxification attempts, supported by counseling and social advice. Centers often combine these treatments as a first stage of any therapy, presumably to establish a better relationship with patients and to increase motivation and acceptance of therapy itself. However, these treatments do not allow to maintain long-term abstinence (Amato, Davoli, Minozzi, Ali, and Ferri, 2005; Caplehorn, McNeil, and Kleinbaum, 1993; D'Ippoliti, Davoli, Perucci, Pasqualini, and Bargagli, 1998) and do not ensure good compliance to treatment; in the VEdeTTE study subjects receiving AOT did not continue these therapies for more than 100 days and showed the worst retention. The limited retention of AOT could be inherent to treatment, since it is aimed at abstinence, and consequently is a definitive recovery associated with treatment,<sup>2</sup> but, considering the short term of the VEdeTTE follow-up, it is properly a failure. Given the defined chronic nature of addiction<sup>3</sup> (McLellan, O'Brien, Lewis, and Kleber, 2000), a medium to long-term treatment should be always set up after detoxification to prevent relapse.

The proportion of patients under MMT is 43.2% and it can be considered to be quite low if considering the higher effectiveness of MMT reported by randomized-controlled trials (Strain, Stitzer, Leibson, and Bigelow, 1993; Vanichseni et al., 1991; Yancovitz et al., 1991). Furthermore MMT was on average prescribed at ineffective doses: only 15% of patients receive at least a daily dose of 60 mg, as recommended by scientific literature (Faggiano et al., 2003), whereas about 10% of them receive less than 20 mg of methadone daily, and their risk of discontinuing therapy is three times higher among new patients and two times higher among retreated patients, compared to patients receiving 60 mg or more. The great majority of patients underwent MMT at doses between 20 and 59 mg daily, and they showed a risk of discontinuing therapy about 40% higher than patients receiving 60 mg or more. These data reflect the effect of a more than 10 years-long pressure against MMT driven by some Italian political parties and by the religious contexts, pressure that seems to be lasted in the last years of 1990s.

Some components of treatments seem to increase retention. Psychosocial treatments, when added to whatever therapy, showed a higher than 80% significant increase in retention. Randomized-controlled trials showed an effect of psychosocial components on MMT, especially on heroin use (Amato, Minozzi, Davoli, Vecchi, Ferri, and Mayet, 2008; McLellan, Arndt, Metzger, Woody, and O' Brien, 1993), but not on retention (Amato et al., 2008). It is likely that when these combined interventions are offered to clients together with an under-dosed methadone maintenance, they may improve the effectiveness in preventing relapse, as already shown in alcohol-dependence research (Stout, Rubin, Zwick, Zywiak, and Bellino, 1999). Psychotherapy in particular increased retention rates even more than other psychosocial treatments, regardless the type of therapy associated. It is possible that psychotherapy may have been prescribed to selected patients with low severity and/or higher level of motivation, who had an increased likelihood of experiencing high retention rates. Although this result was adjusted for main confounders, including patients' severity, it is possible that some degree of residual confounding still remained. Nevertheless, given the strength of the estimated hazard ratio (HR = 2.03 and HR = 2.01 in new and retreated

<sup>&</sup>lt;sup>2</sup>The reader is referred to Hills's criteria for causation which were developed in order to help assist researchers and clinicians determine if *risk factors* were causes of a particular disease or outcomes or merely associated, (Hill, 1965). The environment and disease: associations or causation? *Proceedings of the Royal Society of Medicine 58:* 295–300.). Editor's note.

<sup>&</sup>lt;sup>3</sup>The reader is referred to the "natural recovery" literature which documents cessation of use of a range of psychoactive drugs without professional-based, tradition-based, or mutual-help-based (AA,,NA,.). Editor's note.

patients respectively), residual confounding do not appear to completely explain the result obtained.

Retention in MMT seemed to be enhanced by adding to MMT and TC a preliminary phase, consisting in a set of psychosocial treatments together with some attempts of detoxification. Although this result confirms the crucial role of patient–clinician relationship, particularly in first contacts in order to motivate patient to undertake a long therapy, it could be nation-specific effect, to motivate patients unwilling to enter in a long-term methadone therapy, conditioned by the ideological pressure against MMT.

#### Study's Limitations

The results presented here came from an observational study with an 18-month individual follow-up, and this is the origin of some limitations: for example, treatments were considered concluded when the interruption was longer than three weeks: therefore, any treatment stopped during the study period was considered as a failure, though some of those therapies may have concluded successfully, according to clinician. The threshold of three weeks was chosen a priori for clinical considerations. Moreover, in order to limit the effect of selection bias we excluded ongoing therapies at the start of the study, and treatments were regrouped in three simplified patterns of therapy to synthesize the information collected. These choices limit the external validity of the study, together with any comparison of VEdeTTE treatment durations with those observed in other similar studies. Besides, even if the regression models have been adjusted for various potential confounders, VEdeTTE study remains an observational study with the typical limitations in the interpretation of results due to residual uncontroled biases. Nevertheless, under the assumption that addiction is a chronic condition (Leshner, 1997; McLellan, 2002) requiring treatments longer than two years (McLellan et al., 2000), retention can be considered as an appropriate indicator of the effectiveness of treatment started during the 18 months of the study.

In spite of all possible limitations, studies like VEdeTTE have a basic importance for the evaluation of the effectiveness of therapies: in fact they provide the unique possibility to study the occurrence of outcomes in the "real world," where patients are not randomized, treatments are not optimal, resources are limited. As reported by McLellan, treatment is expected to produce symptoms reduction only as long as the patient is actively involved in that treatment (McLellan, 2002). Results from VEdeTTE study suggest that appropriate choice of treatment and dose, correct evaluation of patient's treatment history, and association with psychosocial treatments can have a relevant impact in patient outcomes even in daily practice.

#### **Declaration of Interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

# RÉSUMÉ

Le traitement est efficace pour réduire l'usage de l'héroïne, ainsi que les problèmes médicaux ou sociaux des usagers d'héroïne. L'efficacité du traitement est liée à sa durée. Vedette est une étude italienne longitudinale financée par le ministère de la Santé qui a pour objectif d'évaluer les traitements dispensés par les services de santé nationaux. L'étude a concerné 115 centres de traitement de la toxicomanie et 10454 usagers d'héroïne. Des

données personnelles et cliniques ont été recueillies au moment de la mise sous traitement au cours d'un entretien structuré. Les données concernant les traitements ont été recueillies à l'aide d'un formulaire standardisé. Une analyse de survie avec modèle de Cox a été effectuée pour évaluer la rétention en traitement. Au total, 5457 patients qui ont commencé un traitement pendant la période d'étude ont été inclus dans l'analyse: 43,2% recevaient un traitement de substitution par méthadone, 46,3% des thérapies orientées vers l'abstinence et 10,5% étaient en communautés thérapeutiques. La dose journalière médiane de méthadone était de 37 mg. 7,6% des patients sous méthadone et 4,9% de ceux en communautés thérapeutiques bénéficiaient d'une psychothérapie. La probabilité de rétention en traitement était de 50% à 179 jours. Le type de thérapie était le facteur prédictif de rétention en traitement le plus fort, les thérapies de sevrage étant associées à la probabilité la plus faible. Chez les patients recevant un traitement de substitution par méthadone, la probabilité de rétention en traitement augmentait avec la dose de méthadone. Vivre seul, une comorbidité psychiatrique et une consommation de cocaïne augmentait le risque d'abandon du traitement. L'association d'une psychothérapie au traitement réduisait de moitié le risque d'abandon du traitement.

### RESUMEN

El tratamiento para adicción a opiáceos es efectivo, reduce el uso de la heroína y las consecuencias clínicas y sociales de los adictos. La efectividad del tratamiento depende de la duración del mismo. "VEdeTTE" es un estudio de cohorte italiano financiado por el Ministerio de la Salud con el objetivo de evaluar la eficacia de los tratamientos procurados por el Servicio Público de Salud para la tóxico dependencia. Participaron 115 Centros y 10,454 adictos a la heroína. La información clínica, personal y socio-demográfica de los pacientes fue recogida a través de una entrevista estructurada. La información sobre los tratamientos recibidos fueron relevados mediante instrumentos estandarizados. Para evaluar la retención al tratamiento se utilizaron análisis de sobrevida y el modelo de Cox. Fueron incluidos en el análisis 5,457 pacientes que iniciaron el tratamiento durante el período de 18 meses: el 43.2% recibió un tratamiento de mantenimiento con metadona, el 10.5% un tratamiento de comunidad terapéutica residencial y el 46.3 una terapia orientada a la abstinencia. La probabilidad de restar en tratamiento fue del 0.5 después de 179 días de tratamiento. La dosis mediana de metadona diaria fue de 37 mg. El 7.6% de los pacientes que recibieron metadona y el 4.9% de aquellos enviados en comunidad terapéutica recibieron también un tratamiento psicoterapéutico. El tipo de terapia mostró ser el más fuerte determinante de retención al tratamiento. De las terapias utilizadas, las orientadas a la abstinencia han mostrado la peor retención. Entre los pacientes que recibieron un tratamiento de mantenimiento con metadona, la retención mejora con el aumento de la dosis. Vivir solo, tener comorbilidad psiquiátrica y el uso de cocaína aumentan el riesgo de abandono del tratamiento, mientras que recibir un tratamiento psicoterapéutico lo disminuye.

# RIASSUNTO

Il trattamento per la dipendenza da oppiacei è efficace nel ridurre l'uso di eroina e le conseguenze cliniche e sociali dell'uso tra i tossicodipendenti. L'efficacia del trattamento dipende dalla sua durata. "VEdeTTE" è uno studio di coorte italiano finanziato dal Ministero della Salute allo scopo di valutare l'efficacia dei trattamenti offerti dai Servizi Pubblici



per la dipendenza da sostanze (SerT). Allo studio hanno partecipato 115 SerT e 10,454 tossicodipendenti da eroina. Informazioni sulle condizioni cliniche e socio-demografiche dei soggetti sono state raccolte all'arruolamento tramite intervista. I trattamenti ricevuti dal soggetto sono stati registrati mediante strumenti standardizzati. Per valutare la ritenzione in trattamento sono stati utilizzati l'analisi di sopravvivenza e il modello di Cox. Sono stati inclusi nell'analisi 5,457 pazienti che hanno iniziato un trattamento nei 18 mesi dello studio: tra essi, il 43.2% ha ricevuto un trattamento di mantenimento con metadone, il 10.5% un trattamento di comunità residenziale, ed il 46.3% una terapia orientata all'astinenza. La probabilità di restare in trattamento è 0.5 dopo 179 giorni di trattamento. La dose mediana giornaliera di metadone somministrata è 37 mg. Il 7.6% dei pazienti che hanno ricevuto metadone ed il 4.9% di quelli inviati in comunità terapeutica hanno ricevuto anche un trattamento di psicoterapia. Il tipo di terapia si è rivelato essere il più forte determinante della ritenzione in trattamento, e tra le terapie quelle orientate all'astinenza hanno mostrato la peggiore ritenzione. Nei pazienti che hanno ricevuto trattamenti di mantenimento con metadone, la ritenzione migliora con l'aumentare della dose. Vivere da solo, avere comorbidità psichiatrica e usare cocaina aumentano il rischio di abbandono del trattamento, mentre ricevere un trattamento di psicoterapia dimezza il rischio di abbandono.

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# References

- Amato, L., Davoli, M., Minozzi, S., Ali, R., Ferri, M. (2005). Methadone at tapered doses for the management of opioid withdrawal. *The Cochrane Database of Systematic Reviews*, (3) CD003409.
- Amato, L., Davoli, M., Ferri, M., Gowing, L., Perucci, C. A. (2004). Effectiveness of interventions on opiate withdrawal treatment: an overview of systematic reviews. *Drug and Alcohol Dependence*, 73(3):219–226.
- Amato, L., Minozzi, S., Davoli, M., Vecchi, S., Ferri, M., Mayet, S. (2008). Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *The Cochrane Database of Systematic Reviews*, (4) CD004147.
- Bargagli, A. M., Faggiano, F., Amato, L., Salamina, G., Davoli, D., Mathis, F., et al. (2006). VEdeTTE, a longitudinal study on effectiveness of treatments for heroin addiction in Italy: study protocol and characteristic of study population. *Substance Use and Misuse*, 41:1861–1879
- Caplehorn, J. R. M., McNeil, D., Kleinbaum, D. G. (1993). Clinic policy and retention in methadone maintenance. *International Journal of the Addictions*, 28(1):73–89
- Davoli, M., Bargagli, A. M., Perucci, C. A., Schifano, P., Belleudi, V., Hickman, M., Salamina, G., Diecidue, R., Vigna-Taglianti, F., and Faggiano, F., for the VE de TTE Study Group. Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE Study, a national multisite prospective cohort study. *Addiction*, 102: 1954–1959.

- D'Ippoliti, D., Davoli, M., Perucci, C. A., Pasqualini, F., Bargagli, A. M. (1998). Retention in treatment of heroin users in Italy: the role of treatment type and of methadone maintenance dosage. *Drug and Alcohol Dependence*, 52:167–171.
- Faggiano, F., Vigna-Taglianti, F., Versino, E., Lemma, P. (2003). Methadone maintenance at different dosages for opiod dependence. *The Cochrane Database of Systematic Reviews*, (3): CD002208.
- Gossop, M., Marsden, J., Stewart, D., Treacy, S. (2001). Outcomes after methadone maintenance and methadone reduction treatments: two year follow-up results from the National Treatment Outcome Research Study. *Drug and Alcohol Dependence*, 62:255–264.
- Johnson, R. E., Chutuape, M. A., Strain, E. C., Walsh, S. L., Stitzer, M. L., Bigelow, G. E. (2000). A comparison of levomethadyl acetate, buprenorphine and methadone for opiod dependence. *New England Journal of Medicine*, 343:1290–1297.
- Johnson, R. E., Jaffe, J. H., Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. JAMA, 267(20):2750–2755.
- Kleinbaum, D. G. (1996). Survival analysis. New York: Springer.
- Leshner, A. I. (1997). Drug abuse and addiction treatment research: the next generation. Archives of General Psychiatry, 54:691–694.
- Marsch, L. A. (1998). The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction*, 93(4):73–92.
- Mattick, R. P., Breen, C., Kimber, J., Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Database of Systematic Reviews*, (3): CD002209.
- McLellan, A. T. (2002). Have we evaluated addiction treatment correctly? Implications from a chronic care perspective. Addiction, 97:249–252.
- McLellan, A. T., Arndt, I. O., Metzger, D. S., Woody, G. E., O' Brien C. P. (1993). The effects of psychosocial services in substance abuse treatment. JAMA, 269(15):1953–1959.
- McLellan, A. T., O'Brien, C. P., Lewis, D., Kleber, H. D. (2000). Drug addiction as a chronic medical illness: implications for treatment, insurance and evaluation. *JAMA*, 284:1689–1695.
- Ministero della Solidarietà Sociale. (2006). Relazione annuale al parlamento sullo stato delle tossicodipendenze in Italia, 2005. Ministero Solidarietà Sociale, Roma.
- NIDA.nih.gov. (2000). Principles of drug addiction treatment. Bethesda: National Institute of Health Press. Accessed 9 April 2010 from http://www.drugabuse.gov/PODAT/PODATindex.html.
- Simpson, D. D., Joe, G. W., Broome, K. M., Hiller, M. L., Knight, K., Rowan-Szal, G. A. (1997a). Program diversity and treatment retention rates in the Drug Abuse Treatment Outcome Study (DATOS). *Psychology Addictive Behaviors*, 11(4):279–293.
- Simpson, D. D., Joe, G. W., Brown, B. S. (1997b). Treatment retention and follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psychology Addictive Behaviors*, 11(4):294–307.
- Stout, R. L., Rubin, A., Zwick, W., Zywiak, W., Bellino, L. (1999). Optimizing the cost effectiveness of alcohol treatment: a rationale for extended case monitoring. *Addictive Behaviors* 24:17–35.
- Strain, E. C., Bigelow, G. E., Liebson, I. A., Stitzer, M. L. (1999). Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *JAMA*, 281(11):1000–1005.
- Strain, E., Stitzer, M., Leibson, I., Bigelow, G. (1993). Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine*, 119:23–27.
- Vanichseni, S., Wongsuwan, B., The Staff of BMA Narcotics Clinic No. 6, Choopanya, K., Wongpanich, K. (1991). A controlled trial of methadone in a population of intravenous drug users in Bangkok: implications for prevention of HIV. *International Journal of the Addictions*, 26(12):1313–1320.
- Ward, J., Hall, W., Mattick, R. P. (1999). Role of maintenance treatment in opioid dependence. *Lancet*, 353(9148):221–226
- Yancovitz, S., Des Jarlais, D., Peskoe Peyser, N., Drew, E., Friedman, P., Trigg, H., et al. (1991). A randomized trial of an interim methadone maintenance clinic. *American Journal of Public Health*, 81:1185–1191.
- Zhang, Z., Friedmann, P. D., Gerstein, D. R. (2003). Does retention matter? Treatment duration and improvement in drug use. *Addiction*, 98(5):673–684.

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