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SUBST-OP : Effectiveness and efficiency of substitutive drugs in opiates addiction treatment

Summary

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1. Introduction

The present work answers to a call for proposals made by the Belgian Federal Science Policy Office, within the framework of a research program supporting the federal policy document on addictive drugs. The main objective of this research was the assessment of the effectiveness[1] and the efficiency[2] of opiates addiction treatments using substances that could mimic the effects of street heroin. Such treatments are called substitution treatments in Belgium. Their goal is twofold : first, to get the patients into the treatment network and two, to have them remain within it as long as the medical-social-psychological-judicial situation preceding inclusion in the next stage of treatment isn't satisfactory enough. These are imperative conditions in order to maintain full abstinence in the future (Reggers et Ansseau, 2000) and the first stage of treatment is abstinence from street drug, i.e. heroin. The impact of psychosocial support and adjuvant treatments were also evaluated in this work.

The purpose of the research was thus to provide, on a scientific basis, evidences of the efficacy of various drugs in the treatment of opiates addiction. It was also to assess dosage accurateness in order to reach maximum efficacy. Moreover, the importance of additional psychological and adjuvant treatments was evaluated too. To achieve these objectives, the best statistical technique was a meta-analysis. Meta-analysis is a statistical procedure designed to combine data from multiple high methodological quality trials. This technique involves the use of a mechanism that synthesizes data across studies in a better way than each study taken one by one could provide.

Invented by researchers in Psychology and Educational Sciences in the early 80's, meta-analysis is a process by which the results of several therapeutic trials can be combined, in order to work out a reproducible and quantified synthesis (Cucherat, 1997). The meta-analytical technique is based on the selection of a maximum number of studies dealing with a given subject. The selected studies are then sorted out according to specific criteria. Meta-analysis is thus a systematic and quantified synthesis. It is systematic because it implies an exhaustive research of all published or not published trials. It is quantified because it uses statistical tools leading to a precise estimation of a treatment effectiveness. The main advantage lies in the high number of subjects included and in the possibility to draw different conclusions from those obtained in smaller scattered studies.

In our meta-analysis, only Randomised Controlled Trials - RCT were selected. Those quality trials are the only trials known as able to reach to highest scientific evidence. In our research, it means that patients presenting with similar problems were randomly allocated either to the studied drug group or to a control group, in which patients were given another treatment, an inactive drug dose or a placebo.

Finally, various aspects of opiate addiction are being discussed in our report as an introduction to the results. The extent of opiates addiction in Belgium and in Europe remains indeed a crucial issue. In Belgium, opiates addiction prevalence rates vary around half a percent, although definitive rates are cruelly lacking. These prevalence rates place the Kingdom in the European average as far as the reliability of the data gathered in other countries is satisfactory.

[1] Checks whether drug under study does better than a control procedure
[2] Checks which dose is efficient

Since the AIDS epidemic in the 80's, many drugs have been tested worldwide in this specific treatment stage during which heroin addicts are given a pharmacological agent belonging to the opiates family. The main objective was harm reduction through avoidance of intravenous contaminations by AIDS or hepatitis B and C. But in many countries, treatment accessibility, used drugs (methadone, buprenorphine, LAAM, diacetylmorphine, morphine, codeine, dextromoramide, suboxone, etc.), dosages, treatment objectives and duration still vary widely.

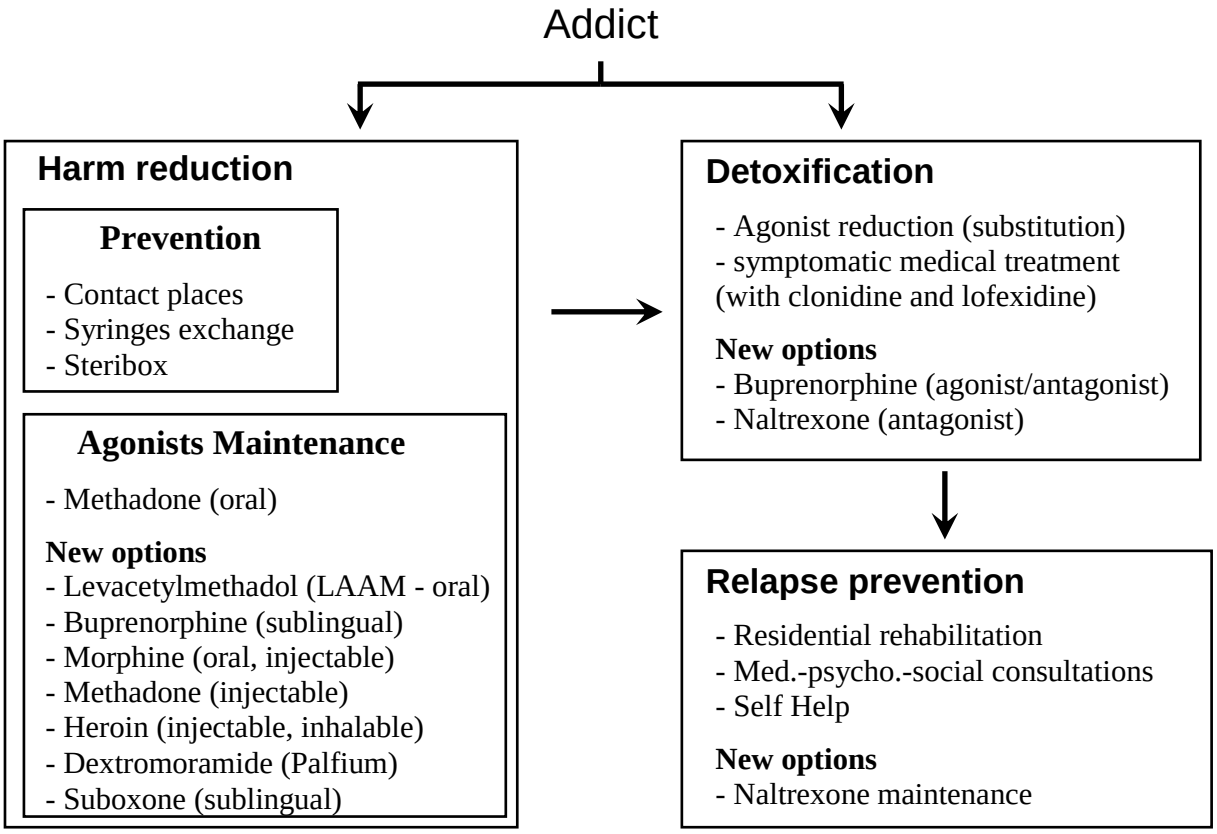
The following table sums up the situation for methadone only.

Country	Eligibility Criteria	Initial Dosage	Maximal Dosage	Injectable Methadone	Methadone (take-home)	Methadone Administration
Australia				Yes but disputed		
Austria						General Practitioners
Belgium	> 18 years of age, opiates dependence for at least one year	30 to 40 mg/day		No		Pharmacist
Canada					After stabilisation	
Denmark	ICD-10 Opioid dependence		120 mg/day			State employed MDs
Finland	> 20 years of age, > 4 years heroin use, previous attempts of detoxification failed		270 mg/day		If patient co-operates well. Max. take-home treatment : 7 d.	Hospital
France	ICD-10 or DSM-IV opiates dependence			No	No	Limited number of treatment centres
Germany	ICD-10 or DSM-IV opiates dependence - Abstinence goal		3 g/month		After stabilisation	Treatment Centre
Greece	> 22 years of age; daily consumption; previous attempts of detoxification failed; no severe psychopathologies; priority to pregnant and HIV-Infected addicts and to partners of MMT-patients			No		Limited number of treatment centres
Ireland	> 18 years of age; ICD-10 opiates dependence, > 1 year i.v. drug use; Pregnant and HIV-infected addicts and Partners of MMT-patients	Average: 55 mg/day		No		General practitioners, treatment centres and their satellite clinics
Italy	n.a.		No maximum	No		Medical doctors in co-operation with treatment centres
Netherlands	> 6 months heroin dependence					Any Medical Doctor
Portugal	> 18 years of age; HIV-infected, pregnant, long addiction history, failed detoxification attempts, psychiatric comorbidity, severe medical disease	No maximum	No maximum	No		Treatment Centres
Spain	Opioid dependence	60 mg/day		Not much used	yes	Treatment Centres
United Kingdom	n.a.	10 - 40 mg/day	60 -120 mg/day	Only in exceptional cases	yes	Shared care: medical doctors and treatment centres
USA	n.a.	40 mg/day	80 - 100 mg/day			Treatment Centres

Guidelines for and clinical practice in methadone maintenance in 16 countries (tailored from Van Beusekom & Iguchi, 2001)

For some years now, substance dependence has been viewed as a chronic illness of the central nervous system. As in other neurobiological diseases, its treatment is complex because it involves various areas of the patient's life (somatic, psychic and social). This treatment has therefore to be carried-out under the supervision of a specialised medical team. As previously stated, treatment lies not only in the management of abstinence or in relapse prevention : it also depends on previous stages such as drug substitution or maintenance treatment.

The following picture sums up the current views on treatment stages.



Before dealing with the assessment of efficacy and efficiency of substitutive drugs, a strict definition of maintenance and substitution as treatment stages must be given. The main goal of a maintenance treatment is to provide the patient with a close-to-heroin drug that may avoid withdrawal symptoms. Along with help and sustain from the medical team, this is supposed to allow an acceptable quality of life prior to detoxification. One the other hand, substitution treatments can be viewed as a detoxification technique. In such a case, the goal is to taper off drug consumption as quickly as possible in order to definitively stop it.

2. Research Methodology

First, data (1902 studies) were collected from various databases (MEDLINE, PSYCHinfo, EMBASE and the Cochrane Library) from November 2005 till May 2005 . Unpublished studies were not taken into account. According to selection criteria (see below), 43 studies[3] (out of 62) were selected in the three following domains: drugs[4] (28 studies), psychosocial treatments (11 studies) and adjuvant treatments (4 studies).
Studies selection criteria:

- Date of publication after 1980
- ICD-10 or DSM-IV heroin dependent subjects;
- RCT studies or opiates drugs comparisons;
- Psychosocial treatments studies must include at least one opiate drug as the main treatment;
- Adjuvant treatments protocols must include another adjuvant medication than the initial opiate maintenance treatment.

Four substances were found in a satisfactory number of studies permitting meta-analysis. These substitutive drugs are described as agonist or agonist/antagonist because they partially or fully mimic the physiological response to opiates through specific neuromediators. The agonists are methadone, Levacetylmethadol or LAAM (a kind a of 'long lasting' methadone) and the agonist/antagonist, buprenorphine. The agonist diacetylmorphine was assessed elsewhere (Ansseau et al., 2005).

Efficacy and efficiency are assessed through 2 variables: treatment retention and street heroin abstinence.

The efficacy analysis compared substitutive drugs to control procedures as described in the following table.

Control	Drug(s) under study	Studies
placebo	buprenorphine	Fudala et al. (2003)
placebo	methadone, buprenorphine	Johnson et al. (1995)
placebo	buprenorphine	Krook et al. (2002)
waiting list	methadone	Dolan et al. (2002)
waiting list	methadone	Yancovitz et al. (1991)
abstinence	methadone	D'Ippoliti et al. (1998)
abstinence	methadone	Strain et al. (1993)
1mg buprenorphine	methadone, buprenorphine	Ahmadi et al. (2003)
1mg buprenorphine	buprenorphine	Ling et al. (1998)

The efficiency analysis measured drug efficacy at the ideal dose. In order to standardise procedures, drug dosages were split into high vs. low dosages. This clustering was made following scientific and guidelines recommendations criteria.

Substance	Low dose	High dose
Methadone	10 – 59 mg/day	> 59 mg/day
Buprenorphine	2 – 7 mg/day	> 7 mg/day
LAAM	10 – 60 mg/day	> 60 mg/day

Note that dosages lower than 'low dosages' are used as control doses.

[3] Selected studies are detailed section 6 page 8

Because treatment settings and goals varied widely round the world, a geographic origin variable was drawn. This lead to split studies in two clusters: North American vs. Others trials.

Moreover amongst the 28 selected trials, treatment durations ranged from 2 to 64 weeks. This variability could lead to biases concerning efficacy and efficiency. A supplementary analysis taking this fact into account was thus performed. The underlying question was to determine which drug could be efficient (or more efficient) and at which dosage at the beginning or during the treatment. Considering clinical and statistical views, the selected studies were stratified in 2 groups: shorter or equal to 5 months and longer to 5 months trials.

In this study, all meta-analysis were performed under the protection of a publication bias analysis. Publications biases were assessed through the Egger et al. (1997) funnel plot analysis.

3. Results

No publication bias was discovered into any meta-analysis.

Efficacy results are shown drug by drug using retention and abstinence as main criteria. Efficiency results are exhibited similarly.

Methadone is more efficient than control procedures both in treatment retention and in abstinence from street heroin. High doses (> 60 mg/day) are more efficient for both retention and abstinence. As for buprenorphine, similar results are found when doses are above 7 mg/day. Due to lack of data, a meta-analysis could not be performed to assess LAAM's efficacy. However its efficiency was proved for high doses (> 60 mg/day).

Drugs were then compared one to the other. , Methadone proved better than buprenorphine in maintaining retention. Both drugs showed the same efficacy as far as abstinence was concerned, with a short advantage in favour of buprenorphine however. Methadone and LAAM were equal in terms of retention and abstinence. Buprenorphine and LAAM were not compared because of a lack of data due to the fact that these substances appeared at different times on the market.

The analysis of confounding factors, such as geographical origin or duration of the studies, did not change the main conclusions of our study.

Finally, the analysis of the impact of psychosocial treatments did not show any significant effect. This could be explained by the short duration of the trials: from 3 to 6 months. Furthermore, adjuvant treatments showed no significant effects either. Of course, the small number of studies may explain the absence of significant results.

4. Conclusions

Substance	Efficacy	Efficiency
Methadone	Yes	> 60 mg/jour
Buprenorphine	Yes	> 7 mg/jour
LAAM	N/A	> 60 mg/jour

This meta-analysis showed once again that any opioid agonists does better than control procedures on retention and abstinence, in a dose-dependent way. However, the short duration of the selected trials (over 95% of the studies lasted less than one year) doesn't allow to draw clear conclusions in terms of long term efficacy of long-lasting substitutive treatments.

It was also regrettable not to have the opportunity to include in our analysis other relevant factors such as gender. Indeed, a recent study by Jones et al. (2005) showed that methadone did better than buprenorphine in both men and women as far as retention was concerned, but that buprenorphine-mediated abstinence was higher in women than methadone-induced abstinence. On the other hand, LAAM-mediated abstinence was higher in men when compared to buprenorphine.

Various other variables should be taken into account in further studies: patients presence rates at different times, psychiatric co morbidities, etc. It is appreciable though to notice that some recent studies deal with adjuvant and psychological treatments.

Finally, if meta-analysis is a good tool because of its power, it does not allow more refined comparisons. Unfortunately, it is indeed technically impossible to perform confounding factors combinations analysis yet.

5. Recommendations

These recommendations are based on a March 2004 Royal Decree, mainly on two axis. The first considers the necessity of both a basic university training and a Continuing Medical Education on such a complex disorder as addiction. The second axis focuses on the medications that should be considered effective and efficient in the substitutive stage of addiction treatment. This meta-analysis exhibited a clear dose-dependent superiority of any pharmacological agent over control procedures. Any of the tested drugs (methadone, buprenorphine, LAAM, diacetylmorphine or suboxone) should therefore be proposed as a substitutive agent, in specific settings, by trained general or specialized medical practitioners.
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6. SUBST-OP studies synoptic : efficacy and efficiency

Study	Country	Treatment	Dosages (mg)	Duration	N	Outcome	Significant results
Ahmadi et al. (2003)	Iran	Methadone Buprenorphine Buprenorphine Control	30 8 3	18 weeks	41 41 41 41	Retention	M > Control B 8 > Control B 8 > B 3
D'Ippoliti et al. (1998)	Italy	Methadone Control	44	24 weeks	731 566	Retention	M > Control
Dolan et al. (2002)	Australia	Methadone Control	60	24 weeks	129 124	Abstinence	M > Control
Eder et al. (1998)	Austria	Methadone Buprenorphine	66 7	24 weeks	16 18	Abstinence	B > M
Eissenberg et al. (1997)	USA	LAAM LAAM LAAM	113 57 28	17 weeks	62 59 59	Retention Abstinence	- L 113 > L 28
Fisher et al. (1999)	Austria	Methadone Buprenorphine	63 7	24 weeks	31 29	Retention Abstinence	M > B M > B
Freedman et al. (1981)	USA	Methadone LAAM	26 14	52 weeks	24 24	Retention Abstinence	- -
Fudala et al. (2003)	USA	Buprenorphine Control	16	4 weeks	105 109	Retention Abstinence	B > Control B > Control
Johnson et al. (1992)	USA	Methadone Methadone Buprenorphine	60 20 8	17 weeks	54 55 53	Retention Abstinence	B > M 20 -
Johnson et al. (1995)	USA	Buprenorphine Buprenorphine Control	8 2	2 weeks	30 60 60	Retention Abstinence	- -
Johnson et al. (2000)	USA	Methadone Methadone Buprenorphine[5] LAAM	80 20 24 100	17 weeks	55 55 55 55	Retention Abstinence	L > M 20 M 80 > L M 80 > M 20 L > M 20
Karp-Gelernter et al. (1982)	USA	Methadone LAAM	Not described	40 weeks	46 49	Retention Abstinence	- -
Kosten et al. (1993)	USA	Methadone Methadone Buprenorphine Buprenorphine	65 35 6 2	24 weeks	35 34 28 28	Retention Abstinence	M 35 > B 6 -
Krook et al. (2002)	Norvway	Buprenorphine Control	16	12 weeks	55 51	Retention	B 16 > Control
Ling et al. (1996)	USA	Methadone Methadone Buprenorphine	80 30 8	52 weeks	75 75 75	Retention Abstinence	- -
Ling et al. (1998)	USA	Buprenorphine Buprenorphine Buprenorphine Control	16 8 4	16 weeks	181 188 182 185	Retention Abstinence	B 16 > Control B 8 > Control B 4 > Control B 16 > Control B 8 > Control B 4 > Control
Marcovici et al. (1981)	USA	Methadone LAAM	46 51	40 weeks	52 78	Retention	-
Mattick et al. (2003)	Australia	Methadone Buprenorphine	45 8	13 weeks	205 200	Retention Abstinence	- -
Pani et al. (2000)	Italy	Methadone Buprenorphine	60 8	24 weeks	34 38	Retention Abstinence	- -
Petitjean et al. (2001)	Suisse	Methadone Buprenorphine	70 10	58 weeks	31 27	Retention Abstinence	M > B -
Schottenfeld et al. (1997)	USA	Methadone Methadone Buprenorphine Buprenorphine	65 20 12 4	24 weeks	28 30 29 29	Retention Abstinence	M 65 > B 4 -
Strain et al. (1993)	USA	Methadone Methadone Control	50 20	20 weeks	84 82 81	Retention Abstinence	M 50 >Control M 20 >Control M 50 >Control

[5] Studies doses ranged from 16 to 32 mg buprenorphine, twice higher than the « high dose » of this meta-analysis, thus data not included.

Study	Country	Treatment	Dosages (mg)	Duration	N	Outcome	Significant results
Strain et al. (a) (1994)	USA	Methadone Buprenorphine	67 11	16 weeks	27 24	Retention Abstinence	- -
Strain et al (b) (1994)	USA	Methadone Buprenorphine	54 9	16 weeks	80 84	Retention Abstinence	- -
Strain et al. (1999)	USA	Methadone Methadone	90 45	40 weeks	97 95	Retention Abstinence	- -
Uehlinger et al. (1998)	Suisse	Methadone Buprenorphine	70 10	6 weeks	31 27	Retention Abstinence	M > B -
White et al. (2002)	Australia	Methadone LAAM	76 82	12 weeks	32 30	Abstinence	-
Yancovitz et al. (1991)	USA	Methadone Control	80	64 weeks (maintenance) 4 weeks (abstinence)	147 148	Maintenance Abstinence	M > Control M > Control

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