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New Methadone Formulation in France: Results from 5 Years of Utilization

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Abstract – Background. In France, methadone has historically been less accessible than buprenorphine. In 2008, a dry formulation (capsule) was introduced into the market, aimed in particular to improve methadone accessibility. **Objective.** To describe the impact (prevalence of use, patient profiles and compliance with requirements) of the dry methadone formulation in France. **Method.** A retrospective cohort (from 2008 to 2012) was created from the data of the French General Health Insurance System which covers 80% of the French population. For each years, all subjects affiliated to this insurance system in southeast France (about 8.5 million inhabitants) with at least two reimbursements of methadone between 1st January and 31st December were selected. **Results.** In 2012, the proportion of capsule users was almost the same as that of syrup users (40.0% *versus* 43.1%; $p < 0.001$). The rise in the number of methadone users has followed the rise in capsule users. Over the study period, the proportion of patients using benzodiazepines or antidepressants was 6-9% ($p < 0.001$) higher for capsule users than for syrup users. On average over the study period, 18% of subjects had at least one concurrent issue of the two forms. **Conclusion.** The study has shown the rapid spread of the capsule formulation among methadone users. This may suggest that the capsule is well accepted by patients and the medical community. However, the monitoring of methadone-related deaths should continue because of the pharmacodynamic properties of methadone and the context of relaxed regulations concerning access to methadone maintenance treatement (MMT).

Abbreviations: see end of article.

1. Introduction

Among opioid maintenance treatments (OMT), methadone is the most commonly used to treat opioid dependence, before buprenorphine.[1,2] The conditions of access to methadone maintenance treatment (MMT) vary across countries, but are generally highly controlled because of methadone's pharmacodynamic properties.[3-8] In Europe (European Union-27, Norway and Croatia) in 2010, methadone was used by three quarters of patients on OMT while buprenorphine was prescribed to most of the remaining patients (other substances represented less than 5%).[9,10]

In France however, methadone has historically been less accessible than buprenorphine. In fact, three quarters of patients use buprenorphine and a quarter use methadone (n = 51 384 in 2014).[11] MMT must be initiated by a physician in a specialized addiction care center and prescriptions should be on a special form for scheduled drugs. In addition, the duration of prescription is limited to 14 days' supply and dispensing takes place in an addiction care center or in a pharmacy.[5,12]

From 1995 to 2008, methadone was only available in syrup form. In 2008, a dry formulation (capsule) was introduced into the market especially to improve methadone acceptability (a capsule is less stigmatizing) and thus increased its use among opioid-dependent patients. In addition, it facilitates storage in pharmacies and avoids some of the side effects of syrup (dental problems, taste…).[13-15] The introduction of capsules was accompanied by a

risk management plan (RMP) in order to minimize the risks associated with the use of the capsule form, such as abuse, diversion, injection, intoxication of children, overdose and black market.[16] Therefore, legal requirements concerning the use of the methadone capsule formulation are stricter compared to the syrup formulation. Only patients who are stabilized under the syrup formulation (in medical terms and for addictive behavior) for 1 year are allowed to switch from methadone syrup to capsule form.[5] The switch is performed at the same time and the same dose from one day to the next in a specialized addiction care centers. The aim of this study was to describe the impact (prevalence of use, patient profiles and compliance with requirements) of the dry methadone formulation in France.

2. Materials and methods

In France, the National Health Insurance Scheme comprises several specific regimes. Among them, the French General Health Insurance System (FGHIS) covers approximately 80% of the population residing in France, the exceptions being a few professions (students, storekeepers, farmers, self-employed, the army, the police force...).[17] Unemployed people and those in precarious social situations are also covered by the FGHIS. In this study, information was gathered from the FGHIS reimbursement database for three French administrative areas (Provence-Alpes-Côte-d'Azur, Corsica and Rhône-Alpes) corresponding to 8.5 million inhabitants. For each year of the study (from 2008 to 2012), all subjects affiliated to the FGHIS with at least two reimbursements of methadone between 1st January and 31st December were selected.

The database contained information on the patient (age, gender), the prescription (prescriber identifier, date of prescription), issue (medication, date, formulation, quantity, pharmacy identifier) and other medications dispensed (during the period of methadone issue). Methadone was identified by its anatomical therapeutic and chemical code (ATC) N07BC02 as indicated by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology. This code also enabled the other medications dispensed to be identified, such as opioid analgesics (ATC: N02A), antipsychotics (ATC: N05A), antidepressants (ATC: N06A) and benzodiazepines (ATC: N05BA, N05CD, N05CF, M03BX07 and N03AE01). In this study, patient, prescriber and pharmacy identifiers were sequential anonymous numbers chosen arbitrarily for each year, thus preventing any direct or indirect identification and follow-up beyond one year.

Three groups of patients were identified according to the two formulations of methadone. The syrup group (Sg): group of patients who had only Syrup. The capsule group (Cg): groups of patients who had only capsules. The syrup-capsule group (SCg): group of patients who had both formulations reimbursed in the course of the year. A descriptive and comparative analysis of the Sg and Cg groups was performed for each year (from 2008 to 2012). In the SCg, there was a focus on switches between the two forms of methadone. To study switches between methadone formulations, two pieces of information were assessed: the number of switches and the number of concurrent issues of the two forms. A switch was defined as instances where for a patient the formulation was different between two consecutive issues. However, if both forms were dispensed on the same day then the issue was considered "concurrent".

Descriptive statistics were used for the "general" profile (age, gender, number of pharmacies, physicians, number of drug issues, interval between two issues and doses issued) and the "other treatment" profile (at least one issue of another drug during the period of methadone issue). Proportions were compared using the approximate χ^2 test, or Fisher's exact test when necessary. The t-test was applied when groups were compared in terms of continuous variables, provided that they were fairly normally distributed. Mantel-Haenszel linear-by-linear association chi-squared tests were performed for trend data. Post-hoc comparisons (Bonferroni method) were performed when necessary. A p-value of less than 0.05 was considered statistically significant. The statistical analysis was performed with SPSS®, version 20 (IBM® SPSS Statistics, New York, USA).

3. Results

The evolution of the numbers of methadone users is presented in figure 1. The proportion of syrup users among methadone users decreased significantly ($p<0.001$) between 2008 (82.9%) and 2012 (43.1%). In contrast, the prevalence of capsule users among methadone users increased significantly ($p<0.001$) between 2008 (1.4%) and 2012 (40.0%). There was no significant trend ($p=0.77$) during the study period for the proportion of SCg.

The general profile comparison for each year between syrup users and capsule users is presented in table I and the "other treatment" profile in table II. Capsule users were older and had a higher dose per issue than syrup users. In addition, the proportions of patients with at least one benzodiazepine (BZD) or antidepressant (ATD) issue were greater in the capsule group (+6.6% for BZD in 2012 and +7.8% for ATD in 2012). The number of switches and the number of concurrent issues in the SCg are presented in table III. In the SC group, most patients made one switch (61.6% in 2012) or two (17.6% in 2012). However, some patients in the SC group did not switch (10.1% in 2012). These were patients who had at least one concurrent issue. The proportion of patients with concurrent issues significantly increased over the study period (+3%, $p<0.001$). For 98% of concurrent issues, both formulations were dispensed on the same day by the same pharmacist for the same prescription.

4. Discussion

The purpose of this work was to describe the impact (prevalence of use, patient profiles and compliance with requirements) of