

Methadone: An Assessment of Side Effects and Their Impact on Treatment Adherence

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Abstract

Original Research Article

Objective: To evaluate the side effects of methadone in patients undergoing Opioid Agonist Therapy (OAT) and to determine their impact on treatment adherence. **Methods:** A prospective descriptive study conducted among a sample of 67 patients enrolled in the Methadone Program at the Ar-razi University Psychiatric Hospital in Salé (Morocco). Inclusion criteria were: age ≥ 18 years, a diagnosis of opioid use disorder according to the DSM-5 TR, and treatment with methadone for at least 3 months. Data were collected through medical consultations and a pre-designed questionnaire, then analyzed using Microsoft Excel. **Results:** The sample was predominantly male (79.1%), aged 31 to 40 years (61.2%), single (47.8%), of average socioeconomic status (50.7%), unemployed (49.3%), and 44.8% had a criminal history. Prior to enrollment, heroin was the most commonly used substance (68.7%), primarily smoked (64.2%). The most common side effects were constipation (70.1%), excessive sweating (68.7%), drowsiness and nausea/vomiting (40.3% each), erectile dysfunction (20.9% of all patients, all cases in men), and amenorrhea (10.4% of all patients, all cases in women). These effects were most pronounced at the start of treatment (55%). Only 13% of patients felt that these effects had influenced their adherence to treatment; 78% reported an improvement in their quality of life while on methadone. **Conclusion:** Methadone, like most opioids, is not without adverse effects that could potentially impact treatment adherence. However, these effects compromised adherence in only a minority of patients, while the majority experienced a marked improvement in their quality of life. Appropriate care and close monitoring, particularly at the start of treatment, remain essential to minimize these effects and optimize treatment adherence.

Keywords: Methadone; Opioid Agonist Therapy; Side effects; Treatment adherence; Opioid use disorder.

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INTRODUCTION

Opioid dependence is currently one of the major global public health challenges. According to the most recent estimates, nearly 40 million people suffer from a substance use disorder, with opioids remaining the class of substances most frequently implicated in drug-related deaths worldwide [1]. This addiction has far-reaching consequences—medical, social, and economic—affecting both individuals and the healthcare systems responsible for their care.

In response to this issue, Opioid Agonist Therapy (OAT) has emerged as one of the most well-evidenced therapeutic approaches. Several studies have shown that this type of treatment not only significantly reduces the use of illicit opioids and helps patients remain in care, but also reduces long-term mortality associated with opioid use [2, 3]. Among the compounds

used for this purpose, methadone hydrochloride plays a central role. This synthetic opioid, characterized by a prolonged half-life, allows for a gradual stabilization of plasma concentrations, thereby limiting withdrawal symptoms and the clinical fluctuations often observed with other substances. In Morocco, it was introduced in June 2010 as part of the “Opioid Substitution Treatment Program” initiative to develop substitution programs for the management of patients with opioid use disorder [4].

However, like other opioid treatments, methadone is not without adverse effects, the intensity and impact of which vary considerably from one patient to another. These side effects, when poorly tolerated or insufficiently anticipated, are among the main reasons cited by patients for prematurely discontinuing treatment and are thus likely to undermine treatment adherence [5]. It is within this context that our study was conducted; its

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objective was to evaluate the side effects of methadone reported by patients enrolled in the Methadone Program, as well as their impact on treatment adherence.

MATERIALS AND METHODS

Study Type and Setting

We conducted a prospective descriptive study within the Methadone Program at the Ar-razi University Psychiatric Hospital in Salé, a facility affiliated with the Ibn Sina University Hospital and the Faculty of Medicine and Pharmacy in Rabat, Mohammed V University in Rabat. This study was part of a clinical evaluation aimed at better characterizing the tolerance profile of methadone among patients receiving care through this substitution treatment program.

Study Population

The sample consisted of 67 patients receiving care through the Ar-razi Hospital Methadone Program. Patients were consecutively enrolled from among those meeting the inclusion criteria as they attended their appointments.

Inclusion Criteria

- Age 18 years or older;
- Confirmed diagnosis of opioid use disorder according to DSM-5 TR criteria;
- Undergoing methadone treatment for at least 3 months; this duration was selected to allow for a representative assessment of side effects observed beyond the initial treatment induction phase.

Data Collection

Data were collected during follow-up medical visits using a pre-designed questionnaire administered directly to patients. This questionnaire explored several complementary areas:

- The patients' sociodemographic characteristics (age, sex, marital status, socioeconomic status, educational level, employment status);
- Criminal and psychiatric history;

- Substance use patterns prior to enrollment in the program, including the types of substances used and their routes of administration;
- Parameters related to methadone treatment;
- Side effects experienced by patients, as well as their perceived impact on treatment adherence and quality of life.

Data Analysis

The collected data were entered and processed using Microsoft Excel, enabling descriptive statistical analysis (calculation of frequencies and percentages) to identify the most frequently reported side effects, the timing of their occurrence during treatment, their impact on patients' quality of life, and their influence on treatment adherence. Ultimately, this analytical approach aimed to identify ways to optimize the care of patients on methadone.

RESULTS

1. Sociodemographic Characteristics

The sample for our study consisted of 67 patients enrolled in the Methadone Program at the Ar-razi University Psychiatric Hospital in Salé. In terms of age, the 31–40 age group was the most represented, accounting for 61.2% of the patients, indicating that the majority of the population was of working age. A clear predominance of males was also observed, with men accounting for 79.1% of the sample, compared to only 20.9% women. Regarding marital status, 47.8% of the patients were single, which may reflect a certain degree of social isolation often associated with substance use disorders. Socioeconomically, half of the sample (50.7%) had a medium socioeconomic status, while 62.7% of patients had completed only high school and had not pursued higher education. Furthermore, nearly half of the patients (49.3%) were unemployed at the time of the study, illustrating the significant socio-occupational repercussions of opioid dependence. Finally, a criminal history was reported in 44.8% of patients, highlighting the medico-legal dimension frequently associated with this population.

Table 1: Sociodemographic characteristics of patients (n = 67)

Characteristic	Proportion
Age between 31 and 40 years	61.2%
Male	79.1%
Single	47.8%
Average socioeconomic status	50.7%
High school graduates	62.7%
Unemployed	49.3%
Criminal record	44.8%

2. Substances Used Prior to Enrollment and Route of Administration

An analysis of substance use patterns prior to enrollment in the Methadone Program revealed a clear predominance of heroin, used by 68.7% of patients

(46/67), far ahead of codeine, reported by 35.8% of patients (24/67), tramadol, used by 23.9% of patients (16/67), and morphine, used less frequently by 6% of patients (4/67).

Table 2: Substances used prior to program enrollment (n = 67, multiple responses allowed)

Substance used prior to enrollment	Number of patients	%
Heroin	46	68.7%
Codeine	24	35.8%
Tramadol	16	23.9%
Morphine	4	6.0%

Regarding the preferred route of administration, smoking was the most common at 64.2% (43/67),

followed by oral administration at 44.8% (30/67), and finally injection, reported by 11.9% of patients (8/67).

Table 3: Route of administration of substances used prior to enrollment (n = 67, multiple responses allowed)

Route of administration	Number	%
Smoked	43	64.2%
Oral	30	44.8%
Injection	8	11.9%

These results confirm that heroin, primarily smoked, was the most common gateway to opioid dependence in our study population prior to enrollment in the substitution program.

3. Side Effects Reported with Methadone

Regarding treatment tolerance, the side effects most frequently reported by patients were, in descending order, constipation, present in 70.1% of patients (47/67),

followed very closely by excessive sweating, reported by 68.7% of patients (46/67). Next were drowsiness and nausea and/or vomiting, each reported by 40.3% of patients (27/67). In terms of neuroendocrine effects, erectile dysfunction was reported in 20.9% of all patients (14 patients, all men), while amenorrhea was noted in 10.4% of all patients (7/67). Other, more varied effects, such as weight loss or weight gain, were reported by 13.4% of patients (9/67).

Table 4: Side effects reported with methadone (n = 67, multiple responses possible)

Reported side effect	Number of patients	%
Constipation	47	70.1%
Excessive sweating	46	68.7%
Drowsiness	27	40.3%
Nausea and/or vomiting	27	40.3%
Erectile dysfunction (men)	14	20.9%
Amenorrhea (women)	7	10.4%
Other (weight loss, weight gain, etc.)	9	13.4%

4. Timing of Onset and Peak Intensity of Adverse Effects

An analysis of the timing of these adverse effects showed that they were particularly pronounced at the start of treatment, a period reported by approximately 55% of patients (37/67) as the time when side effects

were most intense. A smaller proportion of patients reported that peak intensity occurred during the dose-escalation phase (18%, or 12/67), while 27% (18/67) reported peak intensity during the stable phase of treatment.

Table 5: Timing of the peak intensity of side effects (n = 67)

Time of onset	%
Start of treatment	55%
Dose increase	18%
Stabilization phase	27%

These results suggest that the induction phase of treatment is the most critical period in terms of clinical tolerability, warranting increased vigilance at this stage of care.

5. Impact of Side Effects on Treatment Adherence

Despite the high frequency of these adverse effects, only 13% of participants reported that these effects had an impact on their treatment adherence, while 85% felt they had no impact, with the remaining 2% reporting an occasional impact ("sometimes").

Table 6: Perceived impact of side effects on treatment adherence (n = 67)

Perceived impact on adherence	%
No impact	85%
Occasional impact (“sometimes”)	2%
Reported impact	13%

Among patients who reported an impact on their adherence, half (50%) also stated that they sometimes felt the urge to stop treatment because of these side effects.

6. Impact of Treatment on Quality of Life

Finally, despite the frequency of reported adverse effects, a large majority of patients felt that

methadone treatment had a positive impact on their quality of life: 77.6% of patients (52/67) reported a significant improvement, and 19.4% (13/67) reported a slight improvement, for a total of 78% of patients reporting an improvement in their quality of life while on methadone. Only 3% of patients (2/67) reported no improvement.

Table 7: Effect of treatment on perceived quality of life (n = 67)

Impact on quality of life	Sample Size	%
Significant improvement	52	77.6%
Slight improvement	13	19.4%
No improvement	2	3.0%

These results suggest that, in our series, the overall perceived benefit of methadone on quality of life far outweighs the discomfort caused by its side effects for the vast majority of patients followed.

DISCUSSION

In our study, the main side effects experienced by patients on methadone, particularly at the start of treatment, were constipation (70.1%), excessive sweating (68.7%), drowsiness, and nausea and/or vomiting (40.3% each), as well as erectile dysfunction (20.9% of all patients, all cases in men) and amenorrhea (10.4% of all patients, all cases in women). Despite the high frequency of these symptoms, only 13% of patients in our cohort felt that these effects had influenced their treatment adherence, and 78% reported an improvement in their quality of life while on methadone.

From a pharmacological standpoint, the adverse effect profile we observed largely corresponds to what is described for methadone in the specialized literature. Like other opioid agonists, this compound is associated with a well-characterized set of clinical manifestations: slowed gastrointestinal transit leading to constipation, a sedative effect that can result in drowsiness, effects on the autonomic nervous system that explain excessive sweating, as well as disruptions to the hormonal axis responsible for sexual dysfunction in men and menstrual irregularities in women [6]. The consistency of our results with this known pharmacological profile tends to confirm that the effects reported by our patients are indeed attributable to the pharmacodynamics specific to methadone, rather than to factors specific to our study population.

With regard specifically to sexual dysfunction, a meta-analysis of patients undergoing methadone maintenance therapy estimated the overall prevalence of

this disorder at 52%, with a 95% confidence interval ranging from 39% to 65%⁷. This figure is significantly higher than the rate observed in our series (20.9% of the total sample, occurring exclusively in men). This discrepancy could be explained by several factors: on the one hand, the meta-analysis in question grouped together all sexual function disorders (decreased libido, erectile dysfunction, orgasmic disorders), whereas our study focused solely on erectile dysfunction itself, which automatically limits the reported proportion; on the other hand, the data collection method used in our study—based on spontaneous patient reports during consultations rather than on a standardized tool such as the International Index of Erectile Function—may have led to underreporting of this disorder, which is often perceived as a private matter or embarrassing to discuss.

Beyond the mere frequency of these side effects, it is especially important to assess their actual impact on patients’ daily functioning, as a common side effect is not necessarily synonymous with a clinically disabling one [8]. This is precisely what our results suggest: although constipation and excessive sweating affected more than two-thirds of our sample, only 13% of patients felt that these effects had impacted their adherence to treatment, which indicates a generally satisfactory level of tolerance when close medical follow-up is provided, particularly during the induction phase, which our study identified as the period of highest risk.

This relatively good tolerance perceived by our patients contrasts, however, with certain observations reported in other healthcare settings. For example, the experience of the Integrated Addiction Treatment Center in Dakar revealed that the adverse effects of methadone—notably constipation, insomnia at the start of treatment, and decreased libido—were among the

concerns expressed by some patients enrolled in that program, and these complaints could occasionally lead to threats to discontinue treatment [9]. This parallel underscores the importance of providing patients with clear and advance information about the expected effects of methadone—particularly during the first few weeks of treatment—in order to prevent treatment discontinuation due to perceived poor tolerance rather than actual treatment ineffectiveness.

Finally, regarding the overall impact of treatment on quality of life, a survey conducted in French general practice among patients who had been on opioid substitution therapy for more than ten years showed that this type of treatment, when prescribed long-term, was perceived by the majority of patients as a factor that helped stabilize, or even improve, their social and economic situation [10]. This finding is fully consistent with our own results, in which 78% of patients reported an improvement in their quality of life while on methadone despite the presence of frequent side effects. Taken together, these findings support the conclusion that the treatment offers an overall benefit which, in the vast majority of cases, far outweighs the discomfort caused by its adverse effects.

CONCLUSION

Our study confirms that methadone is associated with frequent side effects—constipation, excessive sweating, drowsiness, and sexual dysfunction—but that these are generally well tolerated, with symptoms being particularly pronounced at the start of treatment. These effects compromised treatment adherence in only a minority of our patients; on the contrary, the majority reported a net improvement in their quality of life. This finding is consistent with the literature, which indicates that unanticipated side effects are among the main reasons for discontinuing treatment [5], hence the importance of increased vigilance during the induction phase, identified here as the period of highest risk.

A patient-centered approach, which emphasizes listening to patients' concerns and involving them in treatment adjustments, could improve adherence and enhance long-term outcomes [11]. Close monitoring and tailored information about expected effects remain essential for optimizing the care of patients on methadone.

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