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REVIEW

Precautions in the management of opioid agonist therapy: from target population characteristics to new formulations and post-marketing monitoring – a focus on the Italian system

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Abstract

Opioid use disorder (OUD) is a serious medical condition with vast social, health and economic impact. Individuals with OUD are prescribed opioid agonist therapies, such as methadone, levomethadone, buprenorphine or naloxone/buprenorphine, to reduce the risks associated with illegal substance abuse, eventually leading to opioid use abstinence. The OUD population has peculiar frailties, mainly related to the psychiatric sphere, which may jeopardize their therapeutic course. Amongst the possible phenomena that may contribute to treatment failure, opioid agonist therapy misuse and diversion are of utmost importance, leading to serious repercussions for patients as well as for national health systems. To minimize the consequences related to these practices, it is necessary to implement cross-cutting precautions, from the formulation of abuse-deterrent drugs to the implementation of a national monitoring system that oversees the health situation and signals when action is needed. Based on these premises, this article focuses on data and insights concerning the Italian territory.

Keywords: drug abuse, methadone, opioid agonist treatment, opioid misuse, opioid use disorder, public health.

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Introduction

Opioid use disorder (OUD) is a chronic and relapsing condition with serious social, medical and economic implications for the patient as well as for the national and international communities. In Italy, during 2021, the Services for Addiction Treatment (namely Ser.D. – *Servizio Dipendenze* – in Italian) assisted a total of 123,871 substance-dependent individuals, with a ratio of ~1:7 of new users to individuals already assisted, who were mostly men (85.5%) aged between 45 and 54 years old.[1] Most of the patients treated by Ser.D. in 2021 were former illicit opioid users, particularly of heroin, accounting for 61.5% of all Ser.D.-attending patients.[1] Heroin was responsible for 46.1% of overdose deaths in 2021 in Italy.[1] Trend analysis shows a decrease in opioid-related overdose deaths in Italy over the last 10 years (from 84.4% to 69.8%; percentages calculated from the total number of overdose deaths in 2021, excluding deaths from unknown substance); however, despite heroin remaining the main culprit, albeit with a decreasing trend, an increase in mortality from acute methadone intoxication was observed in the last 10 years (from 6.7% to 8.9%), reaching the highest value at the onset of the COVID-19 pandemic in 2020 (14.1%).[1]

Opioid agonist therapy (OAT) has been shown to alleviate cravings and withdrawal symptoms in individuals

struggling with opioid addiction. Moreover, OAT has proven efficacy in facilitating recovery, promoting sustained abstinence, and reducing the likelihood of relapse and fatal overdose.[2] However, the management of OAT requires special attention due to the delicate context in which it is applied. When dealing with patients with an OUD, factors such as the risk of illicit or dangerous behaviours must be considered. Additionally, it is of paramount importance to assess the social consequences related to the marketing of OAT drugs as they may be susceptible to diversion and non-medical use.

With a focus on the Italian context, this article provides an overview of the following aspects related to OAT: (1) the characteristics of the OUD population, (2) an overview on OAT and the potential related risks, and (3) cautions and precautions for proper drug formulation and post-marketing monitoring. Our aim is to provide useful information and insights for the management of OAT by providing an overview that ranges from the characteristics of OUD patients to the macroscopic phenomena of social-health significance on a national scale, with a particular focus on the Italian territory.

Review

Characteristics of the OUD population

The OUD population often presents with clinical comorbidities that characterize and distinguish them from those of other therapeutic areas. Amongst the most common comorbidities associated with OUD are blood-borne viral diseases due to sharing of syringes. According to the Ser.D. addiction report, amongst drug abusers in Italy, 41.0% are positive for hepatitis C virus (HCV), followed by 4.7% being positive for HIV and 2.4% for hepatitis B virus (HBV).[3] In addition to blood-borne diseases, psychiatric comorbidities are also highly prevalent in patients with OUD. Indeed, it is relevant to point out that psychopathological disorders can negatively influence OAT, even to the point of being considered true predictors of a poor treatment outcome.[4] It is therefore crucial to pay adequate attention to them both at OUD onset and during OAT.

In terms of incidence on the Italian territory, personality and behavioural disorders were found in 55.6% of the OAT population. Also common are neurotic syndromes and somatoform disorders (observed in 13.2% of patients), schizophrenia or other functional psychosis (12.5%), attention-deficit/hyperactivity disorder (ADHD; 11.2%), depression (2.7%), and bipolar affective disorder or various forms of mania (0.8%).[2] Interestingly, ADHD is, as an adult disease, more frequently found in the female population than in the male population with OUD, with an incidence almost 20 times higher than in the general population.[5] The female population is also more likely to be associated with the presence of psychiatric symptomatology requiring pharmacological intervention as well as with more severe socio-relational impairment.[6]

Furthermore, the presence of psychiatric comorbidities often results in the coexistence with psychotropic drug-based therapies, such as benzodiazepines, neuroleptics and antidepressants, which may interact with the mechanism of action of OAT. For example, the combined employment of opioid agonist drugs and benzodiazepines, indeed frequently coprescribed, correlates with negative outcomes, including increased risk of drug misuse, overdose, emergency room admission and reduced adherence to therapy.[7,8]

To summarize, psychopathological symptoms, psychiatric comorbidities and female sex are premises that may hinder the success of OAT and that should thus be considered in the treatment course of the patient with OUD.

Opioid agonist therapy

When planning the clinical management of individuals with OUD, the following main goals must be pursued: achieving opioid abstinence, reducing criminal behaviour, reducing the risks of infection related to the injection of substances, improving the social and work relationships of patients, and coping with potentially associated psychiatric disorders. The clinical management of patients with OUD is thus structured according to three main approaches: (1) harm reduction, (2) implementation of maintenance-oriented treatments and (3) implementation of opioid abstinence-oriented therapies. To this purpose, opioid agonist drugs are employed to alleviate and suppress withdrawal symptoms and, most importantly, to suppress opioid cravings. Individuals with opioid addiction should be encouraged to use opioid agonist treatments.[9] In less severe cases (e.g. non-injectors and individuals who have recently started), agonist treatments are recommended, but a significant number of individuals are also likely to respond well to treatments for the mitigation of withdrawal symptoms to facilitate abrupt discontinuation of opioids (e.g. lofexidine and/or benzodiazepine).[10] However, this article concerns the most severe cases, as these are the ones the addiction services deal with the most.

Initially, agonist opioid dosing is equivalent to prior heroin use; such dosing is continued until maintenance therapy is achieved and varies from patient to patient.[11,12] Only after can OAT be gradually reduced, until independence from opioids is achieved. In the Italian context, a polycentric study of about 1000 patients showed that the perceived quality of life of patients treated with

OAT is sufficiently good in 60% of cases, less good in 25%, and frankly worse in 15%, compared with the Italian general population.[13] Part of the national community remains sceptical of this therapeutic approach as it is based on strong and highly addictive opioids; however, the benefits of this therapy remain evident with significant improvement in quality of life and containment of the abstinence syndrome.[2]

Methadone and buprenorphine

Guidelines released by the National Institute of Health and Clinical Excellence (NICE) list methadone and buprenorphine as the recommended options for the management of OUD.[11] Nevertheless, methadone is the most employed opioid agonist drug, provided to about two-thirds of patients on OAT in the European Union,[14] whilst levomethadone is only available in some countries. Methadone has also been listed as an essential drug by the World Health Organization (WHO).[15] Three major meta-analyses attest to its clinical efficacy and report positive effects on opioid abuse retention, reduction in crime levels, HIV infection risk behaviours and mortality.[16–18] Positive evidence also emerges in favour of the fixed-dose methadone maintenance therapy, particularly at doses greater than 60 mg, as opposed to flexible dosing or no therapy at all.[17,18]

An extensive meta-analysis by Mattick et al.[19] compared buprenorphine and methadone, finding similar efficacy in suppressing heroin use at flexible doses, though methadone displayed ~17% greater likelihood in treatment retention, a superiority that was also confirmed at fixed doses.[19] Low doses of methadone (≤40 mg) are also found to be more effective than low (2–6 mg) or medium doses of buprenorphine (7–15 mg) in suppressing illicit opioid use.[19] In summary, this evidence shows that the employment of buprenorphine as the agonist treatment of heroin addiction is an effective intervention but not more effective than methadone at appropriate dosages.[19] Therefore, methadone should be considered a pillar in the management of OUD.

Misuse, non-medical use and diversion of opioid agonist drugs

During OAT, the patient must maintain firm motivation to continue the treatment as prescribed. Indeed, despite close monitoring by healthcare professionals, frequently, patients intentionally and intermittently fail to adhere to therapy. Consequently, there is a risk that highly problematic behaviours, such as misuse and diversion, can occur.

Understanding the motivations behind problematic behaviours is crucial. There are data showing that the main reason for the misuse of opioid agonist drugs is the need to alleviate the effects of abstinence (43.3% of cases), followed by the search for the sense of euphoria resulting from the abuse of these drugs (23.4% of cases); these results subtend more to a self-medication purpose than to a recreational one.[7,8] In addition, diversion gives access to these substances to people without any therapeutic supervision. In Italy, it is estimated that about 60% of high-risk opioid users are not under any kind of treatment,[14] and this constitutes a worrying reservoir of individuals at risk.

The unsupervised voluntary use of opioid agonist drugs endangers, in terms of usage precautions and dosages, the health of the individual who is most at risk of overdose. Indeed, many substances interfere with the mechanism of action of opioids by generating serious or even fatal adverse effects. These include centrally acting analgesics, alcohol, benzodiazepines, phenothiazine derivatives, barbiturates, hypnotics and narcotics, tricyclic antidepressants, and monoamine oxidase inhibitors. For those who abuse opioid agonist drugs recreationally, particularly in the case of methadone, which has a less euphoric effect than heroin, the concomitant use of illicit substances emphasizes the risk of fatal overdose. Indeed, methadone, even at low doses, can be toxic in those who have not developed drug tolerance, and 55% of drug-related deaths are due to opioid use, including 11% from methadone overdose.[20]

On the other hand, little is known on this matter about opioid agonist drug diversion. Supply channels may be internal to the national supply systems or occur, albeit to a lesser extent, through cross-border trafficking. Amongst commonly encountered practices, counterfeiting prescriptions or procurement through family members or acquaintances who have regular access to the drugs are to be mentioned.

Finally, it is important to note that another potential victim category of diversion dynamics is represented by those individuals who are accidentally exposed to the drug, particularly children as well as family members of patients undergoing OAT. Accidental intake of opioid agonist drugs in adults who are not tolerant to therapy can be life-threatening already at a dosage of 50–100 mg, whilst even as little as 10 mg can be fatal in children.[21] This is due to differences in the pharmacokinetics of the molecule in the presence of low body weight such as in children, in whom metabolic functions are still immature (i.e. catalysed by delayed maturation of liver enzymes, immature renal function and limited ability to bind serum proteins), making these substances more dangerous than in adults. Therefore, it is crucial to ensure that patients store drug appropriately when in the presence of minors.

All of these conditions place additional burdens on public health, including an increased risk of blood-borne

virus spread, increased somatic complications associated with the use of opioid agonist drugs by unconventional routes (see The role of excipients, below), other adverse outcomes related to the drug use and misuse, culminating with an excess in mortality.[15] All this can endanger the reputation of treatment services and compromise the public acceptance of OAT.[15]

Possible routes of drug misuse

The misuse of opioid agonist drugs mainly occurs via oral, parenteral, nasal or injection routes. The most common is the oral route, followed by the injection route, with an incidence between 5% and 36%.[5] The use of the latter improper route is more common in patients who are young, female and with ADHD,[5] and it is also associated with an increased risk of blood-borne infections, venous thrombosis, pulmonary side-effects (see The role of excipients, below), allergic reactions, respiratory depression and local injection site damage, such as fasciitis and compartment syndrome.[7,8] Although methadone abuse via the nasal route is not very commonly detected in Italy, this route of intake remains very risky because of the rapid absorption and high bioavailability of the active component – higher than that of other nasal opioids – and is followed by a rapid onset of action, similar to that occurring intravenously.[22] Importantly, an Italian study revealed that 27.7% of the analysed population (criteria: age ≥18 years, having been on oral OAT for at least 3 months, willing to participate to the study) misused OAT through injection, though the phenomenon appears to be less serious and widespread in Italy than in other countries.[7,8]

Precaution for a proper opioid agonist drug formulation and the importance of a national monitoring system

The phenomena of diversion and misuse of opioid agonist drugs are of great public health concern and require adequate vigilance of this important therapeutic option. Herein, we will discuss some crucial cautions and precautions that should be taken to minimize abuse, misuse and, in particular, potential harm to public health that might be observed in the post-marketing phase of a new OAT formulation.

Ideal features of drug formulations

Special attention should be given to the features of opioid agonist drug formulations. Indeed, the possibility of administration via a route other than the prescribed one must be prevented or at least reduced.[23] In this regard, the FDA has drafted specific guidelines regarding abuse-deterrent formulations that are considered to be of high public health priority.[24]

According to guidelines, solid formulation products should be designed to resist (1) crushing, (2) chewing and (3) physical tampering. To this end, gelling agents can be included to prevent pulverization, nasal abuse, water solubilization and intravenous administration.[25] Liquid formulations are required to have a density and/or viscosity grade that discourages intravenous administration. A final recommendation concerns the possibility of merging agonist and antagonist drugs into a fixed combination such that, if used for non-medical purposes, the antagonist drug would prevent the user not only from feeling the euphoric effects of the opioid but also from causing a mild withdrawal syndrome. However, recommendations for the use of the fixed buprenorphine-naloxone combination, which is often hastily believed to solve the abuse issue, have shown very controversial results in studies designed to evaluate its efficacy on injection misuse.[7,8] Indeed, in one of these studies, the buprenorphine-naloxone combination showed a significantly higher rate of repeated misuse (once: 15%, 2–20 times: 35%, >20 times: 50%) than buprenorphine alone (37%, 26% and 37%, respectively; p=0.008).[7]

Overall, the development and availability of abuse-deterrent opioid formulations represent a significant step towards reducing the risks of abuse, misuse and diversion of OAT-prescribed medications.[26,27] Data about their efficacy are becoming evident, particularly in the USA context, where the opioid epidemic is a major social and sanitary issue.[26] However, post-marketing data are necessary to fully understand the impact of abuse-deterrent formulations in reducing drug abuse.[23] Finally, the increasing availability of long-acting OAT formulations is also worth mentioning, involving depot injections of the drug or its gradual release through a subcutaneous implant, which would allow for a reduction in diversion and misuse practices as well as reduce the frequency of visits to the addiction centre (to receive treatment), thus reducing the associated stigma.[28,29]

The role of excipients

The features of each excipient should be carefully considered in the event of drug misuse. Excipients should be essentially inert, besides ensuring the stability of the active component, protecting against microbial contamination, optimizing administration and even adapting the absorption rate of the active ingredient. Interestingly, povidone (PVP), a polymeric excipient used in many oral methadone-based medications as a suspension agent that increases viscosity and acts as a tablet binder, has been shown to induce serious consequences once misused by intravenous injection, such as subcutaneous granuloma and panniculitis, the latter even several years after PVP misuse. Moreover, cases of renal failure, bone marrow disorders and anaemia have also been reported following intravenous injections.[30] PVP has indeed been shown to possess high antigenicity associated with its high-molecular-weight form when

used intravenously. In light of these serious manifestations, the Pharmacovigilance Risk Assessment Committee (PRAC) stated that high-molecular-weight PVP was not an appropriate excipient for OAT and therefore recommended reformulation of the oral solution and the use of lower-molecular-weight PVP following specific instructions. This regulation was finally adopted on 24 July 2014, and implemented by all European regulatory authorities, including the Italian Medications Agency (*Agenzia Italiana del Farmaco*).[30]

Furthermore, excipient-induced lung disease (ELD), mostly reported as a consequence of the addition of talc into the methadone formulation in 1964, is another issue deserving close attention.[31] As with PVP, ELD occurs because of the improper use of the drug intravenously: injected particulate is deposited in pulmonary arterioles and capillaries, triggering foreign-body pulmonary granulomatosis that may lead to a fatal outcome.[32] Individuals who survive ELD report up to a 10-fold increased risk of acute and chronic pulmonary complications, pneumonia included.[31,32] In addition to talc, microcrystalline cellulose and starch are also excipients that may cause ELD. Microcrystalline cellulose is widely used as a binder/diluent in oral tablet and capsule formulations, whilst starch is used as a diluent of tablets and/or capsules.

Finally, oral tablet injection is related to many serious complications, including infection, pseudo-aneurysms, rhabdomyolysis, compartment syndromes and distal ischemia with limb loss. The amputation rate after an oral opioid injection has been estimated to be 37%, and that of benzodiazepines is 50%.[33]

The importance of national monitoring: the example of France

For all the earlier-mentioned reasons, introducing a new OAT formulation on the market requires special precautions, as this event might trigger macro-scale dynamics amongst opioid users that will end up concerning public health on a national scale.

It is therefore worth mentioning the example of France, where a new solid formulation of methadone was introduced in 2008. This formulation entailed certain precautions to minimize the risk of abuse and misuse: (1) the drug was formulated in capsules containing gelling agents that, when in contact with water, generate an insoluble mass that is difficult to inject; (2) the authorized dosage was limited to a maximum of 40 mg/capsule; (3) the product was packaged in blisters and was protected by a child-proof film; and (4) this solid formulation could only be prescribed to patients stabilized for 1 year with syrup, another common formulation amongst methadone-based drugs. Indeed, patient stabilization is critical during OAT and correlates usually with a lower risk of abuse or misuse.

As an additional precaution to protect the health system following the introduction of the drug in the market, a national monitoring circuit was established; its purpose was to keep track of the proper and potentially improper use of the new formulation and to study its characteristics and the potential occurrence of health complications. This monitoring was based on a multi-source approach that used surveillance and health systems from the French drug addiction network.

Despite regulated and stricter access than, for example, syrup solution, this new formulation had rapid market penetration, reaching 70% of patients on methadone-based therapy.[34] In parallel, there was a clear increase in abuse-associated and misuse-associated factors between 2008 and 2018: reports of illegal methadone use quadrupled, the number of capsule injections increased fivefold, and the number of serious cases requiring hospitalization increased by more than tenfold.[34–37]

It is therefore informative to observe how, despite the cautions adopted, the marketing of a new drug formulation that had been used for several years before led to profound changes in the health situation in such a fragile population as patients with OUD. The concern of these changes is what has led another country – the United Kingdom – to withdraw all applications for the approval of methadone tablets. Indeed, according to the document released, British physicians have not deemed necessary to introduce a new pharmaceutical formulation for OAT into the market, as this was believed to possibly become an additional source of opioid misuse, abuse and diversion.[38] On the other hand, a monitoring system such as the one established by France made it possible to fully understand the extent and direction of the evolution of those phenomena, and the possible factors driving changes in methadone use. This example should be taken as a reminder of vigilance and of the need to achieve a safe balance between prescription, benefits and risks.

In Italy, since 2016, the Department of Anti-Drug Policies has entrusted the Istituto Superiore di Sanità – Centro Nazionale Dipendenze e Doping (CNDD), with the operational coordination of the Sistema Nazionale di Allerta Precoce (SNAP), constituting one of the activities of the Permanent Observatory, to check the trend of the drug addiction phenomenon in Italy. The main tasks of SNAP are (1) identifying new circulating drugs and the patterns of consumption of the previously known substances, and (2) assessing the presence of adulterants, dangerous additives, other psychoactive/pharmacologically active

substances in combination with psychotropic substances, or high concentrations of active ingredients of previously known substances.[39] The indicators considered by the Italian monitoring system describe a situation in delicate balance, with a growth in the illegal opioids market observed in 2018.[39] Finally, the Italian pharmacovigilance system coordinated by the Italian Medicines Agency, promotes active pharmacovigilance programmes and studies with the aim of increasing knowledge of medicines and better defining their safety profiles. All these activities are currently applied also for new methadone-based drugs, with the aim of monitoring their safety profile in clinical practice. The Italian post-marketing surveillance system, together with the specific expertise of medical toxicologists, allows and will enable the precise assessment of prescribing patterns and the safety of methadone use in the real-world setting.

Conclusions

The implementation and introduction of a new treatment programme require careful assessment of the potential risks arising from the specific features of the OUD population. Indeed, patients with OUD are characterized by a peculiar psychiatric vulnerability that may powerfully influence treatment course outcomes. Involving patients as active participants of their treatment is essential; they must participate in goal planning and progress monitoring and must be informed about good drug-use practices and especially oriented to preventing overdose risks and proper drug storage when in the presence of minors. Although misuse and diversion practices cannot be completely avoided, preventive measures can be implemented to limit their impact, such as the application of abuse-deterrent formulations of opioid agonist drugs and the appropriate choice of excipients. To better train medical personnel, it is also necessary to update clinical guidelines that direct towards virtuous behaviours, include training paths that consolidate their skills, and adequately educate the staff working in the Ser.D. Finally, at a more macro level, it is essential to implement a monitoring plan that assesses the impact of opioid agonist drugs on the national health system and that is capable of detecting an adverse development early in time, thus allowing it to be corrected.

Based on what has been discussed, we propose the following conclusive statements:

- OATs have the potential to lead to detoxification from illicit opioids, reduce criminal behaviour, lower the risk of blood-borne infections, and improve social and work relationships as well as associated psychiatric disorders.
- Although methadone, levomethadone and buprenorphine are all recommended first-line options for OUD management, methadone is the most commonly used.
- The presence of psychiatric comorbidity often involves prescribing concomitant psychopharmacological therapies that, in the case of misuse, could significantly increase the risk of fatal overdose (particularly benzodiazepines).
- OAT diversion and misuse phenomena have been shown to be widely prevalent, albeit with marked differences and a source of great concern for public health. In particular, intravenous OAT misuse requires crucial precautions to minimize potential health hazards.
- Solid formulation products should be designed to resist tampering; the inclusion of gel-forming agents has proven useful in this regard.
- The use of both agonist and antagonist medications in a fixed combination to discourage injectable misuse, often strongly recommended as highly effective, has paradoxically yielded very controversial outcomes that are worthy of further investigations.
- Excipients can also cause adverse reactions in case of intravenous misuse (e.g. povidone, talc, microcrystalline cellulose, starch). Therefore, care must be taken in this regard.
- Special attention should finally be directed to the packaging of OAT formulations, which must be strictly child-proof.

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