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Pharmacology and Neurochemistry of Methadone

Andrea Vendramin^{1,2} and Annella M. Sciacchitano³

¹ Drug Unit (SerT), Department of Drug Dependence, Padua, Italy, EU

² Medical Toxicology, University of Padua, Italy, EU

³ Drug Unit (SerT), Rovigo, Italy, EU

Summary

Contrary to what might be thought initially, the pharmacology of methadone is only partly known, and current research continues to investigate into its distinctive aspects. Clinical evidence provides key guidance to pharmacological research on the opiate system; on the other hand, evolving expectations from therapeutic drugs or putative agents for addiction treatment provide a key incentive to the broadening of pharmacological knowledge. Apart from the classic description of receptorial opioid agonism, narcotic blockade and tolerance/withdrawal dynamics, some crucial issues need to be clarified in a comprehensive way. For instance, studies have proved the importance of metabolic polymorphism in treatment planning and offered interpretations of apparent resistance to normal dosages, so authorizing the employment of high dosages on a sound pharmacological basis. Also, dosages should not be regarded as stable through time, especially in the first few months, and clinicians may schedule dose variations that take into account such expected variations while pursuing stabilization. Methadone's action profile in the central nervous system is not exclusively based on opioid receptors, and a thorough knowledge of its 'collateral' effects may explain its beneficial action against specific psychopathological abnormalities. The role of the inactive enantiomer in the context of racemous methadone's tolerability and action profile has also been outlined. Lastly, some of the therapeutic effects of methadone endure without being neutralized by the emergence of tolerance; one of these is its crucial anticraving property. In order to clarify this issue, the mechanisms of cell membrane endocytosis and signal transduction have been illustrated and compared between different opiates.

Key Words: Methadone; Pharmacology; Neurochemistry; Pharmacokinetics; Neurochemical properties; Receptor interactions; Side effects

1. Introduction

Methadone is a synthetic opioid with distinctive pharmacokinetic and neurochemical properties which account for its being, to date, the most effective agent for the treatment of heroin addiction. Studies have proved that, for 50-80% of unselected addicts, methadone-based treatment programmes are crucial in improving general health conditions and social functioning, while increasing compliance rates with other non-pharmacological interventions [66]. In particular, methadone maintenance treatment, as long as it is delivered at adequate dosages, under medical supervision and on a regular basis, is effective in reducing and eventually extinguishing the craving for fast-acting opiates and the drug-seeking behaviours that are rooted in it [27, 87]. Moreover, the administration of methadone makes it possible to restore the balance

between the functions that are typically impaired during phases of continued heroin use (e.g. the immune system, response to stress via the hypothalamic-pituitary-adrenal axis, and the hypothalamus-pituitary-genital one). On the other hand, it does not alter the level of pain sensitivity. More recently, methadone proved useful as one 'opioid rotation' solution for the management of severe pain, which is usually first treated by such opiates as morphine, codeine and buprenorphine [54, 93, 107].

2. Chemical profile

Methadone (Figure 1) was first synthesized in 1945 in the Hoechst Pharmaceutical Laboratories, in the context of a research project that aimed to find alternatives to morphine, with at least similar analgesic properties but fewer or milder side-effects. It is the first example

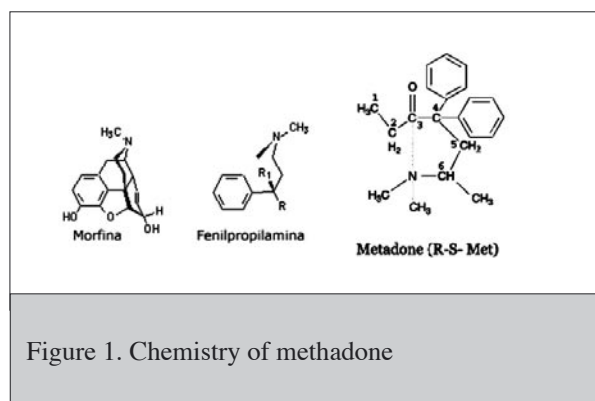


Figure 1. Chemistry of methadone

of a phenylpropylamine derivative that is structurally dissimilar from morphine, but acquires a similar conformation in an aqueous solution. Such derivatives (methadone and 1- α -acetylmethadol) are the results of the progressive simplification of original compounds such as epoxymorphinanes (nalorphine and nalbuphine), through morphinanes (levorphanol), benzomorphanes (pentazocine), phenylpiperidine (pethidine) and 4-aryl-piperidine (fentanyl). A methadone molecule consists of two aromatic rings tied to a 4-C, the sequence proceeding to C5, C6 and eventually to one N basic unit. C3 is tied to an electron-attracting ketonic part. Since the C6 atom is asymmetric, methadone has two isomeric variants, which share the same structure, mirroring each other, but have a different spatial array, referred to as S and R. As to other analgesics, the two isomeric variants (or enantiomers) have certain specific biochemical properties. Methadone hydrochloride (6-dimethylamine-4, 4-dephenyletan-3-one hydrochloride or 4, 4-diphenyl-6-dimethylamine-3-eptanone) is a white, basic, crystalline substance (pKa=9, 2), saturating water over 120 mg/ml, which may be made up of R-enantiomers (R-Met or l-Met), S-ones (S-Met or d-Met) or both in a racemic combination. Although most of the properties which make methadone useful in the treatment of heroin addiction and pain correspond to those of R-Met, methadone hydrochloride is usually employed as a 50% racemic mixture of the two enantiomers, in a variety of formulations that allow methadone to be administered in four different ways:

- 0.1, 0.2 or 0.5% syrup for oral administration;
- 5 or 10 mg tablets for oral administration;
- effervescent tablets containing 2,5, 5, 10 and 40 mg of the substance, for oral administration;
- 1 ml parenteral vials (10 mg/ml).

For analgesic purposes, R-S Met is available in enteral and spray formulations [23, 24].

3. Pharmacokinetics of racemic methadone

3.1 Absorption

Methadone is well absorbed through any route of administration. After oral administration (as in the

treatment of heroin addiction) the absorption of racemic methadone takes place quickly, and almost reaches completion (range 35-100%, average 80%) [33, 79]. The methadone absorption rate is influenced by the expression of intestinal P glycoprotein (P-gp), as for several other compounds (such as amitriptyline, digossine, diltiazem, domperidone, fentanyl, indinavir, loperamide, morphine, nelfinavir, ranitidine, verapamil). P-gp is involved in the phenomenon of multidrug resistance to chemotherapeutic agents; these are, in fact, pumped out from cells by P-gp membrane units [73]. The physiologic function of P-gp, which is expressed in several normal tissues, is that of preventing the absorption of toxic substances through internal and external surfaces, and favouring their elimination [5]. P-gp is a twofold structure weighing 170 KD, consisting of 1,280 aminoacids with 12 transmembrane traits and 2 ATP-binding extracellular domains [48]. The genetic source, known by the acronym MDR1, leads to different levels of P-gp expression, with a ten-time interindividual variability. The induction of P-gp is a plausible reason for the loss of responsiveness to morphine and to antiretroviral agents. In the case of methadone, the P-gp transfers it outside the intestinal epithelium, into the bowel cavity. As a result, when P-gp is expressed at a high level, the administered drug is partly kept away from the blood stream [51, 70]. Moreover, this kind of action by P-gp across the blood-brain barrier is responsible for the passage of racemic methadone into the brain tissue, so affecting the binding rate of administered dosages and the incidence of therapeutic effects and side-effects [110]. The effects of orally administered racemic methadone are evident within 30'. At dosages between 3 and 100 mg/day, the enteric absorption rate is 92% [114]. The bioavailability of methadone is affected by the first-pass metabolism effect; it shows a lower rate with respect to other opiates (67-95%). The average time-to-peak is 2.5 hours for the syrup form [113] and 3 hours for the tablet form [82]. A single 100-120 mg oral racemic methadone dose causes a 0.5-0.9 mg/l plasma peak, and each 1 mg/kg oral dose increase corresponds to a plasma peak increase of 0.263 mg/l. Time-to-peak is 30' in cases of intrathecal administration, 15-20' for the epidural form and 12' for the intranasal. When administered intramuscularly or subcutaneously, the same methadone dose is one and a half times more powerful and more rapid, but its effects persist for a shorter time. Methadone 50% lethal dose is 95 mg/Kg in oral form in rats, or 20 mg/Kg intravenously in mice.

3.2 Distribution

As with any other lipophilic substance, methadone has a high tissue distribution rate in man and in the other animal models that have been studied. In pregnant rat females, racemic methadone spreads to the brain (4.6), bowels (37.2), kidneys (27.6), liver (44.2), muscles (14.7) and lungs (156.3) – the respective distribution coefficients are reported here in brackets [43]. In other words, methadone

spreads to blood and brain tissues only to a small extent, while reaching higher tissue concentrations in kidneys, spleen, liver and lungs. During pregnancy, it spreads through the placental barrier, so that its concentration in the amniotic liquid is similar to that in the maternal plasma. After single oral doses, its plasma kinetics can be described in terms of a two-phase open model. After absorption, about 98% of methadone passes from the central compartment (plasma) through to peripheral tissues (liver, spleen, kidneys, and lungs). On the other hand, in chronic administration regimens, a three-phase exponential model gives a better fit with actual observed kinetics. Anyway, as the concentration in tissues is higher than it is in plasma, the apparent distribution volume at the steady state (V_{ss}) is greater than the actual normal volume (4.2-9.2 l/Kg in the treatment of heroin addiction and 1.71-5.34 l in chronic pain treatment). About 2% of absorbed methadone remains in the plasma compartment: of this, 70-90% is bound to plasma proteins, while the remaining fraction is free, and it is this that is responsible for methadone's effects. In animal models, too, racemic methadone is bound to plasma proteins at similar rates [44, 47]. As it is weakly basic, methadone binds with a certain affinity to α_1 -acid glycoprotein (AAG), which has a high affinity site for a variety of small basic molecules [94, 112]. AAG concentration varies in some physiologic and pathologic conditions which also affect the bound/free ratio of methadone. In fact, since AAG concentrations are higher under stressful conditions [84], the free fraction is lower in cancer patients and heroin addicts than in healthy volunteers [2, 16]. One further factor arises from the fact that methadone only binds to the ORM2A allelic variant of the AAG, not the ORMF one. Although methadone also binds to albumin to some extent, the variation of albumin levels has an almost negligible influence, if any, on the concentration of free methadone. In heroin addicts, sex and weight are responsible for 33% of the inter-individual variability of V_{ss} : it is, in fact, higher in females, increases with weight and falls when the plasma concentration of AAG rises [96].

3.3 Plasmatic kinetics

Consistently with previously described mechanisms, the plasmatic clearance of racemic methadone after a single dose load takes the form of a biphasic curve: the first phase corresponds to distribution to the tissues followed by elimination through the kidneys ($t_{1/2\alpha} = 14$ hrs app.), while the second phase corresponds to its more gradual elimination from tissues ($t_{1/2\beta} = 54$ hrs app.). The overall result is that the drug tends to accumulate within tissues in cases of repeated administration, until an equilibrium is reached that shows only minor fluctuations, mostly depending on whether administration takes place once a day or under a split dose regimen. Once a steady state has been reached (corresponding to four times the $t_{1/2}$ during which the drug has been administered at stable doses and time intervals) methadone's half-life is

28 hrs on average (varying between 4 and 91 hrs) [111]. On the other hand, in chronic regimens methadone has the property of inducing its own metabolism, so that the eventual half-life, after enzymatic induction has brought it to a stable level, may be rather shorter.

3.4 Metabolism

The bio-transformation of a drug plays an important role in its neutralization, by the synthesis of inactive metabolites. This process mostly takes place in the liver, following two main metabolic pathways. The first consists in the para-hydroxylation of the benzene ring, after which there is the reduction of the ketonic group, two methylations and conjugation with glucuronic acid. The second pathway combines N-demethylation with its cyclization to 2-ethyl-5-methyl-3,3-diphenylpyrrolidine and 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), which has a half-life ranging between 39.8 and 48 hrs [23].

These two metabolites are further transformed into a common hydroxypyrrrolidinic product by aromatic hydroxylation. The second pathway combines N-demethylation with its cyclization to 2-ethyl-5-methyl-3,3-diphenylpyrrolidine and 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), which has a half-life ranging between 39.8 and 48 hrs [23]. These two metabolites are further transformed into a common hydroxypyrrrolidinic product by aromatic hydroxylation. Methadone's metabolism is performed by the P450 cytochrome system (CYP450), mostly by the isoform 3A4, which is prominently expressed in the bowels and the liver [28, 29, 41]. In addition, isoforms 2D6 and 1A2 play a prominent role in the process [32] (Table 1).

Recently, on the basis of findings from in vitro studies, it was hypothesized that isoforms 2C9, 2C19 and, especially, 2B6 contribute to the metabolism of methadone [13, 33, 45, 70, 79, 109]. Isoform 2C19 seems to be involved to a higher degree during pregnancy, and to be responsible for the enhanced metabolic rate that appears during the second and third trimesters [80]. Differences in the expression of P450 isoforms are a primary factor affecting the inter-individual variability of methadone's metabolism. CYP450 can be induced, which means that the clearance of methadone by the cytochrome system is not easy to predict on general grounds. In a steady-state condition, heroin addicts develop a metabolic rate that is three times what it was at the time of treatment initiation (first dose load) [96]. Since methadone can, over time, induce its own metabolism, long-term treatment may require dose increases in order to maintain the previously effective plasma level. The 3A4 induction apparently causes a 15% reduction in the average R-Met plasma level, although the level of 3A4 expression varies by as much as 11 or 30 times from one individual to another, in the bowels and the liver, respectively. The 2D6 isoform is expressed by 90-95% of Caucasian people. Those who lack this isoform (due to the absence of functional gene sequences) are referred to as low metabolizers, whereas

Table 1. Metadone and P450 cytochrome

CYP3A4	It has a primary role in R-S methadone metabolism. It can be induced in the initial phase of MMT.
CYP2D6	It has a secondary role in R-S methadone metabolism, which can, in some cases, inhibit the enzyme itself.
CYP1A2 CYP2C9 CYP2C19	They are isoenzymes probably involved in R-S methadone metabolism, but their role is still under review.
CYP2B6	It could play an important role in R-S methadone metabolism
References: [13, 33, 45, 70, 79, 80, 109, 116]	

those who have a normal activity (one or two copies of functioning genes) are labelled as extensive metabolizers. The characterization of the patient's metabolic status may be performed either with genetic or phenotypical methods. Among extensive metabolizers, a subgroup of ultrarapid metabolizers, expressing three or more gene copies, can be identified by genetic probing: this subpopulation is 1.5% of the total population in Germany, 7% in Spain and 29% in Ethiopia. The same metabolic system is shared by a variety of compounds, and cannot be induced: some commonly used drugs, such as fluoxetine and paroxetine, can inhibit its activity. Methadone itself can cause 2D6 enzymatic inhibition to a certain extent [116]: extensive metabolizers who have added fluoxetine or paroxetine to an ongoing methadone regimen show an increase in R-Met (but not in S-Met) plasma levels with respect to the period before the introduction of the antidepressant [10, 30]. This finding suggests that 2D6 is somewhat stereo-selective for R-Met. In low metabolizers, amitriptyline, which is one 2D6 substrate, reduced methadone clearance, and methadone itself reduces that of desimipramine (another 2D6 substrate), probably through a competitive mechanism. CYP 1A2 is involved in the metabolism of several drugs, including clozapine and olanzapine. Its activity can easily be probed by caffeine administration, and is induced by tobacco smoking and inhibited by some drugs, the most common of which is fluvoxamine. The combination of fluvoxamine treatment with racemic methadone causes a major increase in both R-Met and S-Met plasma levels, so suggesting that CYP A12, unlike 2D6, is equally responsible for the metabolism of both enantiomers.

3.5 Elimination

Methadone hydrochloride is mainly eliminated through the kidneys. As much as 15-60% of a single dose is excreted in urine over the next 24 hours. On average, 20% of the administered dosage is excreted unchanged and 13% as EDDP. After repeated administration that

kind of ratio is inverted [9]. Due to its lipophilic and basic properties, pH changes are crucial in determining the rate of methadone excretion: in fact, over a pH of 6, excretion through the kidneys falls to only 4% of the total. On the other hand, when pH is over 6, that rate may be as high as 30% [6, 55, 56]. In comparing situations in which pH values are equal, the interindividual variability in the clearance of methadone through the kidneys is reduced by 27% [96]. As for liver excretion, methadone can be classified as a drug with a low rate of hepatic clearance, around 3.1 ml/min/kg in heroin addicts or 1.5 ml/min/kg in chronic pain patients. Hepatic clearance also depends on the free rate of plasma methadone and on intrinsic hepatic clearance, which means the level of metabolic activity. As observed previously with reference to AAG levels, the rate of plasma protein binding also affects the value of hepatic clearance [2, 16]. Methadone is present in bile, too: as much as 20-40% of a single dose is excreted with feces, after its metabolization and glucuronidation. In some patients, methadone reaches higher concentrations in sweat than in urine. In cases of kidney failure, the interval between administrations should be adequately widened to allow for the degree of functional impairment. On the other hand, in stable hepatic disorders with different degrees of severity, cirrhosis included, dosage schedules may be maintained. Racemic methadone is also excreted through the breasts: almost 3% of the daily dose administered to a mother is taken in by her newborn through her milk. In 6 cases out of 10 this quantity is not enough to prevent the onset of neonatal withdrawal. The data now available support the trend not to prohibit or avoid breast-feeding by racemic methadone-treated mothers.

4. Neurochemical properties

Like all other opioidergic drugs, methadone exerts its action by interacting with a system of three receptors, which, taken together, are referred to as "opioid receptors"; they are linked to G₀ or G₁ proteins, and are normally

stimulated by endogenous opioids. These opioid receptors are commonly indicated by the Greek letters μ , κ and δ or by the acronyms OP3 or MOR for μ , OP1 or DOR for δ and OP2 or KOR for κ [4]. Due to its negligible affinity for δ (IC_{50} nM 752 ± 686) and for κ (IC_{50} nM 1817 ± 573 , in both cases in the bovine caudate nucleus) racemic methadone can be classified as a selective agonist of μ receptors (IC_{50} nM 5.73 ± 1.5 for μ_1 and 10.0 ± 3.1 for μ_2 in the bovine caudate nucleus) [68]. It was possible to map μ opioid receptors in thirteen brain areas of healthy individuals who had had a ^{18}F -Cyclofoxy probe administered to them, by using Positron Emission Tomography (PET) brain scan sequences. In a descending order of density values: thalamus, amygdala, caudate, insula, anterior cingulate and putamen, followed by medial frontal cortex, parietal cortex, cerebellum, lower temporal cortex, hippocampus, white substance and occipital cortex [59]. The human μ receptor unit is a surface protein of 67kDa consisting of a sequence of 372 aminoacids organized in seven hydrophobic transmembrane (TM) domains, with short extra- and intracellular loops. The N-terminal segment is extracellular, whereas the C-terminal segment is intracellular. Ligands interact with the extracellular portion of the receptor, and induce the activation of intracellular G proteins. The activation of G proteins causes neuronal inhibition by the reduction of adenylyl-cyclase activity, the opening of a series of receptor-dependent K^+ channels and the blocking of voltage-dependent Ca^{2+} channels. This cascade takes place around a relatively rigid self-regulating pathway involving the receptor-coupled protein-kinase units (GRK), by its recruitment, consequent receptorial phosphorylation and eventual interaction with β -arrestin. The μ receptor is the main feature responsible for several opioidergic effects, and its stimulation directly produces analgesia, respiratory depression, tolerance to narcotic effects and addiction. In MOR1 knockout mice (expressing no MOR), the lack of μ receptors renders these mice refractory to the main effects of morphine, both those with a therapeutic value and those that can be considered toxic: the same genetic product is thus responsible for an ensemble of effects. As expected, both analgesia and morphine toxicity persist in KOR1-knockout mice and DOR1-knockout ones [74]. Although only one gene encoding for the μ receptor has been cloned (located on chromosome 6 and comprising 4 exons and 3 introns), some variants were described, dependent on the use of selective ligands such as β -funaltrexamine (β -FNA), naloxonazone, naloxonazine and 3-methoxynaltrexone. β -FNA produces a dose-dependent stimulation of the receptor, and is used to recognize its presence and involvement in any supposed effect [3]. Unlike β -FNA, naloxonazone and naloxonazine prevent some of the effects that are mediated by morphine, but not others, since they interact selectively with the μ_1 variant. Insensitivity to naloxonazine is responsible for respiratory depression and the inhibition of bowel motility, suggesting that possible μ_1 -selective agonists may not share these

two important collateral effects with morphine. The μ_1 subtype, which is exclusively supraspinal, is located in the periaqueductal grey substance, the medial hypothalamus and the great raphe nucleus. It mediates analgesia, psychomotor retardation and the increased secretion of prolactin. The μ_2 subtype has a similar distribution, but is found in the spinal cord, too. When coupled with μ_1 it mediates analgesia and is the one feature responsible for constipation, respiratory depression, and the improved muscular tone of the bladder and Oddi's sphincter. Studies on the properties of morphine's metabolite, morphine-6- β -glucuronide (M6G), made things even more complex [86]: in fact, M6G binds to μ receptors selectively and with a high affinity. Its pharmacological profile is close to that of morphine and its analgesic effect is antagonized by naloxonazine. However, 3-methoxynaltrexone is effective against M6G-mediated analgesia at doses which are ineffective against morphine-mediated analgesia. On the other hand M6G also exerts analgesic effects in CXBK mice, which are refractory to morphine [18]. These data lead to the conclusion that another variant exists, apart from the already known μ_1 e μ_2 ; this third variant appears to mediate an analgesic effect through M6G or other 6-substituted analogues, such as heroin or 6-acetylmorphine [95]. One possible explanation is the existence of splicing variants from the same gene, exon 4 being replaced by other supplementary exons [85]. Also, two receptors may interact with each other and build a μ/μ or μ/δ complex, which could comprise various μ subtypes with partly dissimilar pharmacological properties. Studies have always indicated methadone's strong affinity for its receptor, but some differences have emerged. In Blake's study, based on the use of μ -transfected HEK 293 rat cells, methadone has a lower affinity than morphine (K_1 3, 51nM vs. 1, 41nM, respectively) [11]. On the other hand, in Raynor's study on COS-7 cells transfected with rat μ receptors, methadone has a higher affinity than morphine (K_1 0, 78nM vs. 14nM, respectively) [90]. In this latter study, methadone had a negligible ($K_1 \geq 1000nM$) affinity for δ and for κ receptors. The same authors showed that methadone and other opioid drugs have a higher affinity for human μ receptors in transfected COS-7 cells [91]. In conclusion, racemic methadone is a complete agonist of the μ receptor population, which swings between an available state and an inactive state. The affinity is higher for the active form than for the inactive. Methadone raises the absolute number of active (or activated) receptors (i.e. phosphorylated) and exerts maximal receptor-mediated effects, in a dose-dependent manner. Another distinctive feature of R-S-Met with respect to morphine is its non-competitive antagonism with respect to the NMDA receptor. The inhibition curve and its K_1 for the displacement of its ligands are very similar to those of dextrometorphan, which is a typical NMDA antagonist. In particular, K_1 of R-Met is $\mu mol/L$ 3, 4 and that of S-Met is $\mu mol/L$ 7, 4. NMDA antagonists are characterized by the property of preventing the onset of tolerance to

morphine without interfering with its analgesic effects. The non-competitive antagonism exerted by R-S-Met should therefore favour the stability of its analgesic action in protracted treatment regimens, and would explain its negligible abuse potential, together with the absence of complete tolerance to some of its effects during long-term MMT at stable dosages [25]. Lastly, racemic methadone interferes with the reuptake of serotonin (5HT), and, to a lesser extent, with that of norepinephrine (NE) [20]. In rat cortical synaptosomes racemic methadone has a K_i of $\mu\text{M } 0.27 (\pm 0.038)$ against 5HT reuptake, which means a level close to that of desimipramine ($\mu\text{M } 0.43 \pm 0.037$) and minimal in comparison to fluoxetine's ($\mu\text{M } 0.049 \pm 0.0046$). This property is not maintained, however, after chronic exposure, at least in the rat model [46].

5. Specificity of the methadone- μ receptor interaction

5.1 Receptorial site binding

At oral dosages between 80-150 mg/day, as administered to tolerant individuals, racemic methadone does not saturate available receptors: in fact, the self-administration of heroin at doses higher than those usually employed can produce narcotic effects. Likewise, the administration of morphine, hydromorphone or fentanyl upon methadone for pain control is effective in counteracting breakthrough pain peaks. A study was conducted employing ^{18}F -Cyclofoxy in MMT patients taking dosages of 30-90 mg/day and plasma levels of 127-673 ng/ml (350 ng/ml on average): a PET scan was performed 22 hrs after daily oral dose, and showed a 19-32% reduction in the expected binding rate in all the brain areas examined (thalamus, amygdala, caudate nucleus, anterior cingulate cortex, putamen) with respect to the brain of healthy controls [59]. In other words, approximately 24 hours after the previous administration, methadone has saturated 19-32% of μ receptors, including those which have been internalized. The rate of ^{18}F -Cyclofoxy binding reduction, though limited, is significantly related to plasma levels of racemic methadone. As a result, 60-80% of available μ receptors are free to interact with endogenous opioid peptides. Since opioid peptides are involved in the control of the immune and endocrine systems, with special regard to the hypothalamic-pituitary-adrenal axis, it can be hypothesized that the normalizing effect of MMT on these functions depends on the low occupancy of receptors at therapeutic dosages. In other words, methadone at dosages high enough to suppress the craving for heroin tends to have a rather conservative effect on the physiology of endogenous brain opioid systems.

5.2 Tolerance and endocytosis

Continued opioid use is characterized by the onset of pharmacodynamic tolerance, possibly combined with a pharmacokinetic component, at least for some compounds.

Due to tolerance, when drugs are used continually, they lose their effect, so that higher dosages are needed to restore the desired effect. Tolerance also involves some therapeutic effects, such as analgesia, as typically happens in cases of pain treatment through the chronic administration of morphine [54]. Tolerance to morphine does not depend on increased biotransformation, but is typically pharmacodynamic. Cross-tolerance is one of the key phenomena on which the agonist treatment of heroin addiction is based. Fortunately, tolerance can be forestalled or can be made incomplete by the anticraving effect of opiate agonists. A variety of strategies can be resorted to in investigating the mechanism of tolerance and the distinctive features of each opiate agonist: on general grounds, it is agreed upon that tolerance is a result of a range of pharmacological and behavioural mechanisms, different circuits being involved, beyond the known roles of opioid receptors. On the other hand, it is likely that methadone tolerance is also due (quite probably, mainly due) to variations in the level of μ receptor expression [117]. The internalization of receptors was long considered to be the primary mechanism inducing change in the sensitivity of neurons to agonists. Research on populations of native neurons or transfected cell lines has shown that a cascade of events leads to the rapid desensitization and endocytosis of μ receptors. The trimeric G protein, which comprises α , β and γ subunits, becomes detached from the receptors: while the α subunit inhibits adenylyl-cyclase activity, the β/γ ensemble interacts with K^+ and Ca^{++} channels, and is linked to a GRK-specific kinase which phosphorylates the μ receptor. The phosphorylated receptor interacts with a cytosol protein called β -arrestin, which becomes bound to it and prevents further interactions between the receptor and the G protein. The arrestin-receptor complex is internalized by a clathrin-mediated process of endocytosis, and is stored in the intracellular endosomal compartment. Afterwards, the receptor may be dephosphorylated by a phosphatase and be placed back within the cell membrane, which restores the neuron's sensitivity. Otherwise it may be catabolized in lysosomes without being dephosphorylated, which would correspond to a down-regulation of sensitivity. Opioids differ in their capacity to induce receptorial endocytosis, even if the pharmacological peculiarities that account for these differences are not clear. Etorphine, surfentanyl, methadone and DAMGO produce endocytosis to a greater extent than codeine, buprenorphine, heroin, morphine-6-glucuronide and, especially, morphine. DAMGO (Tyr-D-Ala-Gly-MePhe-Gly-ol-enkefalin) is similar to endogenous opioid peptides, and is referred to as a term of comparison with exogenous opioids. Some studies have referred to the capacity of opioid agonists to induce endocytosis as an inverse function of the so-called RA/VE ratio, indicating the relationship between relative G protein-related activity and endocytosis. Morphine has a higher RA/VE, which means it produces a high level of G protein activation coupled with a low μ receptor

endocytosis. By contrast, endorphins and opioids such as etorphine and methadone induce endocytosis to a greater extent with respect to their capacity to produce intracellular signal transmission (low RA/VE) [38]. More recently, it has been proved that the capacity of opioids to activate G-protein-dependent cascades, and thus to induce rapid desensitization, is a separate property with respect to their capacity to cause receptor internalization. Bearing in mind that DAMGO's properties in both cases are 1, the values for methadone and morphine are 0.98 and 0.59, and 0.58 and 0.07, respectively [14]. In other words, morphine's effectiveness in causing internalization (0.07) is far lower than DAMGO's (0.98) and methadone's (0.59), and does not reflect its capacity to activate G-proteins and promote desensitization (0.58). While it was previously believed that endocytosis is the reason for pharmacodynamic tolerance, lately evidence has been growing that internalization may play a role in counterbalancing the development of tolerance [38]. Moreover, morphine and heroin are not only capable of inducing tolerance, but are strongly addictive. Apart from this problem, methadone, which also produces endocytosis, does induce a lower degree of tolerance, and is effective in the treatment of heroin addiction. It has been hypothesized that those opioid agonists which induce a higher degree of tolerance do so because they endure longer in their interactions with the receptor: on this view, tolerance develops as a consequence of prolonged interaction with receptors, whereas endocytosis counterbalances this property by reducing the duration of ligand-receptor interaction, eventually limiting the degree of acquired tolerance. Chronic morphine treatment, both in cell lines and animal models, is associated with a compensatory up-regulation of cAMP synthesis, which may be one consequence of prolonged μ stimulation coupled with a low capacity of that ligand to induce endocytosis. On the other hand, the cAMP response to methadone exposure is significantly lower, which may reflect its greater capacity to induce endocytosis. The agonist-mediated activation of receptors, and then their desensitization and internalization, seem to constitute the three physiological phases of a functional dynamic cycle of normal opioid receptors. Tolerance to opioids may develop due to an abnormal activation profile, rather than to the down-regulation phenomenon alone. Abnormal activation would produce a response that differs from the normal functional recycling of receptors. In conclusion, methadone seems to resemble endogenous opioids in the profile that emerges from its receptor interactions; this may account for some of its therapeutic properties and its favourable long-term interactions with the opioid system.

6. Specificity of stereoselective enantiomers

Absorption and bioavailability are similar for R-Met and S-Met [67], although the former is twice as strongly

lipophilic as the latter (57 of oil/water coefficient vs. 28). The difference in elimination half-life between the two enantiomers may depend on a different binding to plasmatic proteins (14% for R-Met vs. 20% for S-Met) [34]. Although that is not a large difference, it may be enough to account for the fact that R-Met's half-life is 38 hrs vs. 29 hrs. for S-Met. Average clearance of R-Met is 158 ml/min, while S-Met's is 129 ml/min. Apparent Distribution Volumes are quite variable, around 7 L/Kg for R-Met and 4 L/Kg for S. R-Met has a double affinity for the μ with respect to racemic methadone, similar to that of morphine. As for the μ_1 subtype, it is ten times higher for S-Met in bovine caudate than for R-Met (IC_{50} of nM 3, 01 \pm 0, 18 nM 26, 4 \pm 3, 7) while values for μ_2 subtype are nM 6, 94 \pm 1, 3 for R-Met and nM 87, 5 \pm 9, 0 for S-Met [68]. Consistently with these premises, R-Met is 50 times more analgesic than S-Met [41]. R-Met prevents the onset of opiate withdrawal even at low dosages, while S-Met does so when administered at dosages of 650-1000 mg/day. S-Met has the distinctive property of its non-competitive antagonism to the NMDA receptor, which accounts for its capacity to antagonize NMDA-induced hyperalgesia and the development of morphine tolerance, after systemic or intrathecal administration. R-met is therefore able to replace the racemic form in the treatment of heroin addiction and pain, but the racemic formulation does show some advantages from a long-term perspective. S-Met alone, or when combined with morphine, may be effective against neuropathic hyperalgesia, or in increasing the analgesic effect in chronic morphine administration regimens [25]. As previously mentioned, racemic methadone inhibits the reuptake of serotonin (K_i of μ mol/L 0, 014 for R-Met and μ mol/L 0, 992 for S-Met) and norepinephrine (K_i of μ mol/L 0, 702 and μ mol/L 12, 7 respectively). In other words, it is 5 times more selective for serotonin than for norepinephrine, as R-Met has a greater affinity for both uptake systems [20]. S-Met is effective against coughing in the absence of any risk of producing respiratory depression. Several studies agree on the fact that methadone's effectiveness depends on the administration of certain dosages. The higher the dosage, the lower the risk of treatment dropout, so dosage adequacy is the main factor affecting the rate of therapeutic failure. Although 100 ng/ml was initially thought to be enough to ensure a good outcome, a stable response requires a level of 400 ng/ml. Recently, a correlation between R- and S-Met concentrations and treatment response has been defined: 250 ng/ml of R-Met are usually predictive of a response to treatment. Nevertheless, effective plasma concentrations of R- and S-Met, in cases where oral doses of racemic methadone are equal, and after accounting for body weight, vary widely between individuals – up to 16/17 times in the case of R-Met. In other words, oral dosages corresponding to effective plasma concentrations do vary widely, and may also depend on further variables, such as combined treatments that give rise to pharmacokinetic interactions.

For some individuals 55 mg/day may produce effective plasma concentrations, whereas over 900 mg/day may be required in other subjects [31, 32].

7. Side effects

On the whole, MMT is well tolerated from a long-term perspective [83]. Possible side-effects which may develop and endure during opiate agonist treatment regimens depend on a variety of factors, including duration of treatment, dosage, the route of administration, age, concurrent organ impairment and combined treatments or psychoactive substance use. Transient adverse events such as rash or nettle rash may happen in cases of subcutaneous or intramuscular injection. Frequently reported effects include somnolence, hypotension, bradycardia, nausea, vomiting, swelling of hands or (more frequently) feet, disorders involving emetics, menstrual abnormalities, anorgasmia or delayed achievement of sexual orgasm, insomnia, constipation or excessive sweating. Since tolerance develops at variable terms for different symptoms, a low baseline tolerance is usually predictive of more severe side-effects in the early phases of treatment. It is very unlikely that side-effects will be so intense as to require treatment termination. They usually improve with dose adjustment or transition to an oral route of administration, although some cases may require symptomatic treatment. Sweating, constipation, sexual dysfunctions and sleep disorders tend to endure in the long term [62]: in patients taking dosages between 80 and 120 mg/day, sleep disorders, constipation and loss of libido are still present after three years in as many as 15-20% of cases, while excessive sweating persists as often as in one case out of two. Sedation is frequently reported in the early phases of treatment, after the first few days of steady administration. In these circumstances, sedation depends on the progressive increase of plasma concentration due to methadone's longer half-life, which corresponds to a rising narcotic effect in non-tolerant individuals. Temporary dose reduction or splitting the dose into two or three fractions during the day may be sufficient to counteract the sedating effect of peaking methadone. Once sedation has been extinguished, one may proceed with further dose increases as requested by treatment goals. In other circumstances, sedation may be induced by a combination of alcohol with CNS depressants, bearing in mind that these depressants should not be co-prescribed to such patients anyway. As with other opiate agonists, another effect of methadone is that it reduces bowel secretion and motility, so causing constipation and/or awkward defecation due to the dehydration of feces. The development of tolerance to opioid-induced constipation is quite slow, so that constipation is usually a persistent side-effect. Diet supplements or changes, lubrication of bowels or pharmacological stimulation of motility may be beneficial. Nausea and vomiting, which are quite rare in untreated heroin addicts,

depend on the stimulation of the Chemoreceptor Trigger Zone (CTZ) but also on the alteration of vestibular sensitivity, bearing in mind that the incidence of this disorder is greater in outpatients. In some cases, antiemetic drugs may be a rapid solution to acute symptoms. In elderly patients urinary retention may develop, due to the increased contraction of the inner urethral sphincter, so that untreated prostatic hypertrophy and urethral stenosis are not compatible with methadone treatment. Some patients experience weight gain, which is usually related to improved life quality but may also be a sign of increased alcohol consumption. Methadone is not toxic to the liver, and no abnormalities of liver function are expected during methadone maintenance, apart from those depending on concurrent liver disorders, which may worsen independently [64]. A history of acute hepatitis should be regarded as a reason for starting methadone treatment as a matter of urgency, since it usually indicates a higher risk of toxic effects caused by a lack of hygiene in injection practices. Methadone increases the liver synthesis of albumin, which is even greater in alcohol-using patients [60, 97]. Thyroxin and Thyroxin-binding-globulin levels are higher during MMT, but no reduction of free T4 was observed [62]. Possible higher values of total globulins or IgG and IgM may derive from pre-existing liver diseases. False positive results at tests for syphilis were observed [65] in over 30% of MMT patients, whereas absolute lymphocytosis can be found in 20%. However, MMT is not related to abnormalities in immune functioning [8, 21]. Methadone is responsible for some changes in endocrine functions: during the first three months of treatment a reduced response to metopirone due to the depletion of ACTH and cortisol can be observed [22, 61, 62, 65]. Abnormalities of this kind are fully reversible during treatment within four to five months after treatment initiation. As for sexual hormones, LH levels tend to fall, whereas FSH has no predictable variations. After one year of treatment, LH and FSH values are expected to fall to within normal ranges, while testosterone levels may continue at lower levels than normal. Delayed ejaculation, which is complained about by quite a few patients, may be handled by shifting the time of dose administration away from times of sexual intercourse, according to individual habits. Methadone causes an increase in prolactin levels during the first 2-8 hrs after administration. Differently from what can be observed with antipsychotics, a flattened circadian secretion rhythm has been documented, which does not seem reversible while on treatment [65]. High prolactin levels may contribute to sexual dysfunctions, and also cause breast hypertrophy and galactorrhoea. Bromocriptine may be useful in this case. No teratogenic effects have been attributed to methadone, nor have any been attributed to morphine or heroin to date [15]. Nevertheless, no appropriate studies on its possible mutagenic or teratogenic properties have been performed yet. Infants of mothers who use street heroin have a 50%

Table 2. Substances which can produce opiate withdrawal when combined to methadone (modified from Leavitt, Addiction Treatment Forum)

Drug name	Notes/References
Buprenorphine, butorphanol, dezocine, nalbupine, pentazocine	Displace methadone from μ receptors [26, 57]).
Naltrexone, nalmefene, naloxone	Displace methadone from μ receptors [26, 57, 102].
Tramadol	Displaces methadone from μ receptors [105].

Table 3. Substance which can interfere with methadone's metabolism and produce unpredictable effects when combined to it (modified from Leavitt, Addiction Treatment Forum)

Drug name	Notes/References
Alprazolam, alorazepate, estazolam, flurazepam, midazolam, triazolam	Potential interactions due to a common metabolic pathway through P450 [52]. May increase methadone's depressant effects on the CNS [102].
Cannabis	Presumable interaction due to a common CYP3A4 metabolic pathway [52].
Didanosine	Reduces DDL concentration [89], not observed with gastro-resistant capsules [36, 42]
Dextrometophan	Methadone may increase its plasma concentration and effects [71].
Alpha-interferon + ribavirine	Adverse events may mimic opiate withdrawal, so that methadone dose increase may be decided on a wrong basis [99, 103].
Monoaminoxidase inhibitors	Potential adverse reactions reported [78].
Nifedipine	Methadone may increase nifedipine's concentration [71, 102].
Alfentanil, idrocodone, fentanil, meperidine, morphine, oxycodon, propoxyphen	Possible enhancing effects due to common metabolic pathways. Long half-life metabolites of meperidine and propoxyphen may reach toxic concentration [52].
Stavudine (d4T)	Methadone reduces d4T plasma level. d4T has no effect on methadone's plasma level [89].
Amitriptiline, desipramine, imipramine, nortriptiline	Association with methadone increases TCA toxicity [26, 88, 92]. TCA have a variable effect on methadone's plasma level [33, 79, 102].
Zidovudine (AZT)	Methadone increases AZT level by 40% ; adverse events of AZT are more likely [76].

likelihood of being born underweight. Low birth weight (below 2500 gr) and a shorter head circumference were reported in newborns from mothers under R-S methadone treatment. On the other hand, methadone treatment is related to a decreased incidence of spontaneous abortion, premature discharge or hyaline membrane disease. Despite a report that 33% of a group of newborns were born

underweight, and that 60-70% showed signs of opiate withdrawal (neonatal withdrawal syndrome), no clear correlations with dosage and treatment status were defined [15]. Residual irritability, restlessness and episodes of desperate crying may recur, though to a milder extent, throughout the first two or three months of life. Between 4 and 6 months of age those symptoms usually fade

completely, and the rhythm of growth accelerates with respect to normality, so that by 12 months those newborns can be expected to be normal as to weight and height, that is, similar to infants of mothers without any history of addiction. Head circumference still remains around the 25th percentile at 6 months, and takes over 24 months to normalize. During the first two years, the course of mental and psychomotor development is normal, apart from a tendency not to express one's needs verbally or respond to verbal requests. The developmental outcome does not seem to relate to the duration of dosage of methadone treatment, or to neonatal withdrawal severity or APGAR score at 5' minutes after birth. Attention

and language abnormalities fade by the time children start to go to school, since comparisons with control children show minimal differences. In general, children of addicted parents show rigid temperamental features, so that the initial features are more likely to persevere unchanged throughout the process of development. Some experience regular neurological and behavioural growth, and maintain the acquired stage of development later on, while others show early defects which are likely to persist throughout the process of growth. Those who have not shown neurological or behavioural abnormalities by 36 months of age are characterized by a higher cultural level of the mother and a stable family environment. On

Table 4. Substances which may reduce levels of methadone in plasma and/or lower its effects (modified from Leavitt, Addiction Treatment Forum) .

Drug name	Notes/References
Abacavir (ABC)	Levels of methadone fall, as does the peak value of ABC [49].
Amprenavir	The induction of CYP3A4 may reduce methadone's plasma level [19, 33]. The level of Amprenavir may be reduced too, for the same reason [36]
Butobarbital, mefobarbital, phenobarbital, pentobarbital, secobarbital, others	All of these induce P450 [63]; phenobarbital may cause a rapid decrease in concentrations of methadone [49]. An increase in methadone dose is usually required.
Carbamazepine	A strong induction of CYP3A4 may cause withdrawal . Valproate does not have this effect and may be a safe alternative [12, 98].
Cocaine	Increases the elimination of methadone [79].
Desametasone	Induces CYP3A4 [33].
Efavirenz	The induction of CYP3A4 often results in abstinence from methadone. After three weeks of treatment with efavirenz, if the dosage is not raised appropriately, the peak concentration of R-S-Met fall by as much as 48% [33, 75].
Ethanol in chronic exposure	Induces P450 [88].
Fusidic acid	Induces CYP3A4 [33, 106].
Heroin	Reduces the free fraction of methadone [79].
Lopinavir + ritonavir	Withdrawal may develop and dose increases be required. Ritonavir alone fails to cause any such effect [19, 77].
Nelfinavir	Induces CYP3A4 and P-gp [33], but withdrawal is rare [77]. The level of nelfinavir too may be slightly decreased [19].
Nevirapine	Its induction of CYP3A4 may may lead to withdrawal [33].
Phenytoin	Rapid reduction of methadone due to CYP3A4 induction [33, 63].
Rifampicine and rifampicine/isoniazid	These induce P450 and may cause severe withdrawal [33, 63]. Rifabutin doesnot produce these effects [49, 71].
Spirolactone	Induces CYP3A4 [33].
St. John's Wort (hypericum perforatum)	Induces CYP3A4; the level of methadone is reduced by 47% [35, 100].
Tabacco (habitual smoking)	Most reports indicate a reduction in the effectiveness of methadone in habitual smokers [79, 104].
Urinary acidifiers (e.g. ascorbic acid)	The excretion of methadone through the kidney occurs more quickly at acid pH values [81, 102].

the whole, MMT should be considered the standard treatment for pregnant heroin addicts [80]. In treating pregnant heroin addicts, a couple of issues call for definitive clarification: neonatal withdrawal syndrome and methadone addiction. Neonatal withdrawal is elicited by the abrupt interruption of methadone supply to the fetus after the development of tolerance through regular exposure throughout pregnancy. Its distinctive features are its delayed onset and prolonged course. As for methadone addiction, authors agree that R-S methadone, when administered orally as in MMT for heroin addiction, has no addictive liability.

8. Potentially lethal adverse events

Acute methadone intoxication involves the automatic

regulation of breathing, and is characterized by the triad: miosis, coma and respiratory depression.

Intoxication may happen accidentally, as when children ingest amounts of methadone left unlocked and within their reach. Otherwise, it may be due to a deliberate suicide attempt or an impulsive act of self-injury or suicidal behaviour by tolerant individuals. During the induction phase of MMT, patients run an overdosing risk which is 6 to 7 times that of untreated heroin addicts, and 42% of racemic methadone-related deaths take place in the first week of treatment [17, 118]. Lethal accidents often happen in the first three days [108]. That is why it is advisable not to administer more than 30 mg/day on the first few days, bearing in mind that the repeated administration of a stable dose will result in a progressive increase in peak levels for the first 4-5 days, that is, before

Table 5. Substance which may increase levels of methadone in plasma or enhance its effects (modified from Leavitt, Addiction Treatment Forum)

Drug name	Notes/References
Cimetidine	Inhibits P450 [12, 102].
Ciprofloxacin	Inhibits CYP3A4 and CYP1A2 [33, 53]).
Delavirdine	Inhibits CYP3A4 [49].
Diazepam	The mechanism is unknown [33]. Sporadic reports [71].
Diidroergotamine	Inhibits CYP3A4 [106].
Disulfiram	Reported sedation after high disulfiram doses [12].
Ethanol in acute exposure	Competition for P450 [88].
Fluconazole	Inhibits CYP3A4 [33]; Increases methadone's plasma level [49]; Uncertain clinical relevance [71].
Grapefruit	Inhibits bowel CYP3A4 [51] and Pg-P [33]. This effect is not observed with other fruit's juices [58].
Ketoconazole	Inhibits CYP3A4 [33].
Eritromicine, claritromicine	Strongly inhibits CYP3A4. No cardiac or metabolic effects are reported for azitromicine [33].
Moclobemide	Inhibits CYP2D6 and CYP1A2 [33].
Herbal products such as: uncaria tomentosa, matricaria recutita, echinacea angustifolia, hydrastis canadensis, quercetina	Strongly inhibit CYP3A4, though no specific reports about methadone are available [100, 106].
Omeprazole	May obstacle methadone's absorption[102]).
Fluoxetine, fluvoxamine, paroxetine, nefazodone, sertraline	Mainly inhibit CYP2D6, but also CYP3A4 and CYP1A2 [33, 71, 92].
Troleandomicine	Inhibits CYP3A4 [106].
Urine-alkalinizers (e.g. sodium bicarbonate)	Alkaline urine pH reduces the elimination of methadone through the kidneys [57, 102].
Verapamil	Inhibits CYP450 [71] Substance influencing cardiac conduction to a variable extent with potential arrhythmic properties in combination with methadone.

the steady state is achieved. Urinalysis before admission by single-use sticks for morphinuria with a cutoff level of 2000 ng is advisable as a rule to check anamnestic data and identify low-tolerance individuals: in fact, some of those who have undergone self-handled detoxification may still have intense dysphoria, insomnia or diarrhea, despite the loss of tolerance, a factor that may itself lead to overmedication. Respiratory depression by methadone develops within 2-3 hours after intake, or within a few days after treatment initiation. In cases of intoxication, naloxone administration may quickly restore an adequate breathing function, and flumazenil may be useful, too. The patient must be hospitalized and closely monitored, repeating naloxone administration throughout the first 48 hours, in order to avoid re-intoxication after the fading of short-term antagonism from a single naloxone dose. Recently, authors have expressed concerns about the incidence of methadone-related ventricular arrhythmias [69, 115]. In January 2004 the Swiss Regulatory Agency indicated a risk of QT lengthening in patients receiving methadone for the treatment of addiction or pain. Between 1990 and 2003, out of a total of 272 methadone-related adverse event reports, physicians reported 42 cases of arrhythmia in 25 patients (20 males and 5 females, aged 40 on average) who had had a prescription of methadone for addiction treatment. Between April 2001 and August 2003, 7 torsade de pointes and 14 QT prolongation cases were reported. Daily methadone dosages ranged between 40 and 1400 mg/day. In almost all these cases, known risk factors for arrhythmias were documented, such as a long QT, atrio-ventricular delay, bradycardia and electrolyte abnormalities. Several patients were HIV-positive or suffered from viral hepatitis. In some cases interaction with antidepressants, antimicrobial drugs or protease inhibitors was plausible. The OMS database includes 14 cases of torsade de pointes and 16 cases of QT lengthening, mostly reported in the USA. The Italian Ministry of Health recorded just one case of ventricular tachycardia in a male patient taking methadone as a supplementary medication. Patients taking racemic methadone who are also affected by cardiac diseases (such as cardiac failure, bradycardia, left ventricular hypertrophy, long QT syndrome) or electrolyte abnormalities (such as low magnesium, potassium, primary or secondary to diuretic treatment) should be cautiously evaluated through time. Likewise, factors which may cause a sudden increase in methadone concentrations in plasma should also be known and prevented. Lastly, chronic combined treatment with QT-prolonging drugs, such as class I and II antiarrhythmic drugs and antidepressants, should be assessed with great caution. One recent study by Maremani et al. showed no correlation between methadone dosage and QT length in methadone-only treated addicts [72].

9. Pharmacological interactions

Tables 2,3,4,5 report an updated list of known interactions with methadone. The progressive introduction of

new active principles, together with the use of multiple drug treatment regimens, have raised the likelihood of significant interactions and complicated the parameters of clinical assessment and decision-making [1, 7, 50]. Up-to-date knowledge about the pharmacogenetics of drug treatment makes it easier to understand most of the pharmacokinetic and pharmacodynamic mechanisms involved in these interactions [37, 39, 40, 101]. Unfavourable and sometimes dangerous interactions may come from other drugs, over-the-counter products, legal and illegal recreational substances, or sometimes simply from certain types of food.

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