

The role of methadone in cancer pain treatment – a review

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SUMMARY

Background: Methadone is an opioid analgesic of step 3 of the World Health Organization (WHO) analgesic ladder. **Aim and Methods:** To outline pharmacodynamics, pharmacokinetics, drug interactions, equianalgesic dose ratio with other opioids, dosing rules, adverse effects and methadone clinical studies in patients with cancer pain. A review of relevant literature on methadone use in cancer pain was conducted. **Results:** Methadone is used in opioid rotation and administered to patients with cancer pain not responsive to morphine or other strong opioids when intractable opioid adverse effects appear. Methadone is considered as the first strong opioid analgesic and in patients with renal impairment. Methadone possesses different pharmacodynamics and pharmacokinetics in comparison to other opioids. The advantages of methadone include multimode analgesic activity, high oral and rectal bioavailability, long lasting analgesia, lack of active metabolites, excretion mainly with faeces, low cost and a weak immunosuppressive effect. The disadvantages include long and changeable plasma half-life, high bound to serum proteins, metabolism through P450 system, numerous drug interactions, lack of clear equianalgesic dose ratio to other opioids, QT interval prolongation, local reactions when administered subcutaneously. **Conclusions:** Methadone is an important opioid analgesic at step 3 of the WHO analgesic ladder. Future controlled studies may focus on establishment of methadone equianalgesic dose ratio with other opioids and its role as the first strong opioid in comparative studies with analgesia, adverse effects and quality of life taken into consideration.

Introduction

Methadone is a valuable opioid analgesic, which can be administered mainly in opioid rotation (OR) when other opioids failed. However, its use is more difficult than other opioids because of complicated pharmacokinetics, numerous drug interactions and possible QT prolongation; thus it should be used by physicians experienced in chronic pain management. In most cancer patients, pain is successfully relieved using opioids alone or in combination with adjuvant analgesics (co-analgesics) in accordance with the WHO analgesic ladder (1,2). Morphine is recommended by the Expert Working Group of the European Association for Palliative Care at the third step of the WHO analgesic ladder, which comprises also other opioids for moderate to severe pain intensity (fentanyl, oxycodone, hydromorphone and buprenorphine) (3). However, in case of insufficient analgesia and intense adverse effects of morphine or

another opioid, it can be switched to methadone (4), which may also be considered as the first strong opioid (5). The aim of this article is to outline pharmacodynamic and pharmacokinetic properties, drug interactions, equianalgesic dose ratio with other opioids, dosing rules, adverse effects and clinical studies of methadone in patients with cancer pain.

Methods

A search of Medline, Pubmed and Cochrane databases in English language was performed and articles with subheadings 'methadone' and 'cancer pain' was reviewed since 1975–2008 (last access on the 22nd November 2008). Articles regarding methadone use in cancer pain are included. Papers excluded concern methadone use in maintenance therapy, non-malignant pain and abstracts. Relevant papers on pharmacodynamics, pharmacokinetics and methadone interactions were also included. The full text articles

Review Criteria

A search of Medline, Pubmed and Cochrane databases in English language was performed and articles with subheadings 'methadone' and 'cancer pain' was reviewed since 1975–2008 (last access on the 22nd November 2008).

Message for the Clinic

Methadone is a valuable opioid analgesic, which can be administered mainly in opioid rotation (OR) when other opioids failed. However, its use is more difficult than other opioids because of complicated pharmacokinetics, numerous drug interactions and possible QT prolongation; thus it should be used by physicians experienced in chronic pain management.

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Disclosure

None.

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General characteristics of methadone

Methadone (Hoechst 10820) was synthesised in 1938 at J. G. Farbenindustrie in Hoechst-Am-Main in Germany by two physicians: Max Bockmuhl and Gustav Ehrhart. The name 'methadone' derives from the fragment of its chemical name: 6-dimethylamino-4,4-diphenyl-3heptanone (5). Methadone is available in oral and rectal preparations and in ampoules for parenteral administration (6). In clinical practice, methadone is administered mostly to patients with cancer pain who undergo OR. Methadone may be used in OR from morphine (7), transdermal fentanyl (TF) (8,9), hydromorphone (10) and other opioids (11), when insufficient analgesia and intractable adverse effects appear: neurotoxicity (drowsiness, confusion, hyperalgesia and myoclonus) and gastrointestinal symptoms (nausea and vomiting, constipation) (12). As a result of lack of active metabolites, methadone may be used in patients with pain and delirium (13). In comparison to morphine, 10 times less demand for laxatives (14–16) and twice less nausea and vomiting (7,17–19) were observed. Methadone may also be administered as the first strong opioid to patients who have been treated with opioids for moderate pain (tramadol, codeine and dihydrocodeine) or to opioid-naive patients (4,20–22). Methadone can be administered to patients with renal impairment (18,23) and to children with cancer pain (24,25). It is used also in patients with painful tenesmus refractory to morphine and ketorolac (26) and in patients with cancer-related neuropathic pain (27).

Contraindications to methadone administration are respiratory depression and allergy to the drug or preservatives (5). It is advisable to administer methadone cautiously to patients suffering from confusion, raised intracranial pressure syndrome, severe bronchial asthma and chronic obstructive pulmonary diseases, as its administration may exacerbate these symptoms (18). As a result of differences in pharmacology, a withdrawal syndrome can appear in few patients after switching from morphine to methadone, which requires to be treated with additional morphine dose (28). Methadone inhibits hyperplasia of lung cancer cells and induces their apoptosis (29); opposite to morphine it possesses a weak immunosuppressive effect and does not suppress natural killer cells function (30). Methadone is 10-fold less expensive than controlled release morphine, 25-fold cheaper than TF and it is particularly useful in patients requiring high opioid doses (31).

Pharmacodynamics and pharmacokinetics

Methadone is a racemate of dextrorotatory (*S*-methadone) and levorotatory (*R*-methadone) isomers. The *S*-methadone demonstrates mostly as an antitussive as well as an analgesic effect, whereas the *R*-methadone causes analgesia through affinity to opioid receptors (its analgesic effect is twice as potent as racemate) (32). Methadone activates mu, kappa and delta receptors (*R*-methadone), possesses moderate antagonistic effect to the *N*-methyl-D-aspartate receptor (both enantiomers) and strongly inhibits the reuptake of serotonin and noradrenalin in CNS (*S*-methadone) (33–35). These three mechanisms of action could explain better analgesia and less tolerance to analgesic effects of methadone in comparison to morphine, observed in experimental research (36) and in patients (37); another explanation may be different methadone receptor activity (38,39). When administered in high doses, methadone blocks potassium channels required for rapid cardiac muscle repolarisation, which may explain the risk for developing ventricular arrhythmia (40).

Methadone is a highly lipophilic and basic drug with a high distribution volume (4.1 ± 0.65 l/kg) and a high affinity to tissues, where it cumulates after multiple administrations (brain, lung, liver, gut, kidney and muscles) (41). The high affinity to tissues, together with a gradual, retarded release to plasma causes a prolonged half-life. Methadone cumulates in tissues after multiple administrations; in further stages of the treatment a balance emerges between the part of the drug that is bound in tissues and the part in plasma (42). About 1–2% of the drug appears in blood, where 60–90% of methadone links to plasma proteins, mostly with alpha-1-acid glycoprotein (AAG) and in part (13–17%) to gammaglobulins (28,42). Methadone free fraction is lower in cancer patients; this is caused by the rise of AAG level (32). The bioavailability of the drug after oral administration oscillates between 70% and 90% (41–43). The absorption is decreased and the clearance is increased in pregnancy, which may require higher methadone doses in pregnant patients with cancer pain. An opioid withdrawal postpartum syndrome may be observed in neonates born from methadone treated mothers. Breast feeding is relatively safe as only about 2.8% of maternal methadone dose gets into an infant, but it is not enough to prevent opioid withdrawal in a neonate exposed to methadone during pregnancy (40).

Methadone is detected in serum within 30 min since oral administration; the maximum plasma concentration is reached after 3–4 h. The half-life lasts

approximately 24 h, but it occurs in the range of 8–120 h, analgesia lasts for 6–12 h (18). After oral administration, a fast distribution phase occurs with half-life 14 ± 6 h, followed by a secondary elimination phase of 55 ± 27 h and a chronic phase with the elimination half-life 22.5 ± 7 h (43). After parenteral administration, half-life equals 2–3 h in the distribution phase and 15–60 h in the elimination phase (41). The elimination half-life varies individually to a large extent (42). Multiple administration of methadone may lead to a drug accumulation. It is particularly common in elderly patients with whom the elimination half-life could reach up to 120 h (44). Methadone long half-life plays an important role in patients with respiratory depression and requires naloxone administration either in repeated injections or in continuous infusion. A stable drug level is reached usually within 2–4 days (45).

Methadone is metabolised mostly through microsomal liver enzymes, but also in the intestine wall via *N*-demethylation to two inactive metabolites: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine and 2-ethyl-5-methyl-3,3-diphenylpyraline (41,46). The main enzyme responsible for methadone *N*-demethylation is CYP3A4 with a lesser CYP1A2 and CYP2D6 involvement and a significant CYP2B6 role (47). Methadone may induce its own metabolism in a time-dependent fashion via CYP3A4, thus increasing its clearance over time (45). On the other hand, enzymatic inhibition develops quickly either secondary to competition between drugs or their metabolites for the same binding site or irreversible effects of a reactive metabolite. Methadone may inhibit CYP2D6 and therefore affect drugs metabolised by this enzyme (28).

The drug is excreted mainly via the alimentary tract, but also through kidneys depending on the urine pH (48). Methadone renal clearance is inversely proportional to the urine pH (32). Acidification of the urine ($\text{pH} < 6$) increases renal excretion of methadone and decrease methadone concentration; urinary alkalinisers may increase methadone levels (44). In chronic renal disease, methadone does not accumulate; methadone dose may remain unchanged as the drug and metabolites are increasingly excreted with faeces; in severe renal failure a dose reduction may be considered (40). Methadone is not eliminated in the process of haemodialysis (41,48). A comparison of methadone and morphine pharmacokinetic properties is presented in Table 1.

Drug interactions

Methadone is metabolised through cytochrome P-450 enzymes, mainly CYP3A4 but to a lesser extent

Table 1 A general comparison of pharmacokinetic properties of methadone and morphine, taken from Ripamonti and Bianchi (49)

Characteristic	Methadone	Morphine
Oral bioavailability	80%	35%
Protein binding	60–90%	35%
Elimination half-life	30 h	3–4 h
Active metabolites	No	Yes
Influenced by kidney disease	+	+++
Influenced by liver disease	+++	+

+ Slightly, +++ Highly.

CYP2D6 and CYP1A2. Methadone interacts significantly with drugs that cause hypoactivity or hyperactivity of these enzymes, especially CYP3A4 (49). More evidence indicates that CYP2B6 plays an important role in methadone metabolism (47). There are other factors that can influence methadone pharmacokinetics such as P-glycoprotein polymorphism, isoforms of CYP1A2, genotype of AAG, co-mediations and urine pH (40). Differences in CYP3A4 activity (30-fold in liver and 11-fold in gut), in CYP3A4 mRNA amount (50-fold), in the liver and CYP2D6 polymorphism also play an important role in large individual variations associated with methadone pharmacokinetics (50). Methadone drug interactions mediated via CYP2C9 and CYP2C19 enzymes alone seem to be not significant (51).

Antifungal azole drugs, selective serotonin reuptake inhibitors (SSRIs), macrolids and chinolones, diazepam, cimetidine, calcium channel blockers, desipramine, dihydroergotamine, grapefruit juice and single alcohol consumption inhibit metabolism, consequently causing a rise in methadone level and intensifying adverse effects (40). Among azole antifungals ketoconazole, fluconazole and itraconazole are potent CYP3A4 inhibitors and consequently these agents combinations with methadone may lead to QT prolongation or respiratory depression (52). From SSRIs group, fluvoxamine, fluoxetine and paroxetine display very significant (CYP3A4 and CYP2D6 inhibition), while sertraline and citalopram seem to have a small potential for methadone interaction (42). An interaction between venlafaxine (substrate and mild CYP2D6 inhibitor) and methadone has not been studied so far, but close monitoring is recommended for this combination. Chinolones inhibit CYP3A4 and CYP1A2, macrolides are potent CYP3A4 inhibitors both may prolong QT interval; cotrimoxazole (sulfamethoxazole and trimethoprim) may also prolong QT interval, sulfamethoxazole is CYP2C9 inhibitor, caution is

recommended in combining methadone with these agents (50).

Anticonvulsants, tuberculostatics, antiretrovirals, high corticosteroid doses, risperidone, fusidic acid, spironolactone, St. John's Wort, regular alcohol consumption (through inducing CYP3A4) and smoking cigarettes (CYP1A2 inducer) speed up methadone metabolism, reduce analgesia and may cause withdrawal (28). From the other hand, a withdrawal from CYP3A4 inducers (carbamazepine, rifampicin and high corticosteroids doses) administration may lead to methadone toxicity (52).

Pharmacodynamic interaction between methadone and benzodiazepines may increase the risk of toxicity (respiratory depression). Because of the possible pharmacokinetic interaction with diazepam (CYP3A4 inhibition), midazolam, alprazolam and triazolam (CYP3A4 substrates), drugs that do not undergo phase I metabolism may be preferred (buspirone, lorazepam, oxazepam and temazepam) if there is a need for methadone combination with benzodiazepines (52). Synergistic analgesia occurs when methadone is administered with ibuprofen (53), diclofenac (54) or tetrahydrocannabinol although the latter was noted in animal study (55).

Methadone causes a rise of zidovudine levels in blood serum (5). Tricyclic antidepressants (amitriptyline, nortriptyline, imipramine and doxepine), propranolol, chlorpromazine, prochlorperazine and thioridazine bind with AAG and may cause methadone to be removed from bonds with plasma proteins, nevertheless bonding of methadone is strong and requires high concentration of these drugs; therefore the removal is highly improbable (56). Methadone excretion could be limited because of an AAG elevated level caused by cancer itself, but this mechanism is unlikely to be significant (57).

Caution and careful monitoring is recommended when combining methadone with tricyclic antidepressants (amitriptyline and trazodone), because it increases the risk of QT interval prolongation (50). Methadone is CYP2D6 inhibitor and during simultaneous administration it may cause rise in drug levels metabolised by this enzyme e.g. SSRIs, tricyclics, venlafaxine, mianserine and neuroleptics (risperidone, haloperidol and chlorpromazine), β -blockers and opioids (dextromethorphan, tramadol, codeine and dihydrocodeine) (58). Similarly, many drugs that are CYP3A4 substrates may also be affected by methadone administration and vice versa (42). Methadone therapy with monoamine oxidase inhibitors should be avoided as it can produce serotonin syndrome (50). A combination of antiarrhythmics (quinidine and lidocaine are substrates and amiodarone CYP3A4 inhibitor, quinidine is a strong CYP2D6

inhibitor), which prolong QT interval and may cause ventricular arrhythmia with methadone if possible should be also avoided (50).

Selected methadone drug interactions are presented in Table 2. Many drugs listed are administered to patients with cancer pain, which calls for caution, especially when an interaction may intensify adverse effects or symptoms of over dosage. Generally, it is advisable to avoid agents metabolised through CYP3A4 especially CYP3A4 inhibitors and inducers, possibly limit CYP2D6 inhibitors and substrates during methadone therapy (59). Special attention should be paid on older population (over 65 years), because these patients are particularly vulnerable to drug interactions because of coexisting chronic diseases requiring pharmacotherapy and age-related decline in P450 activity (50).

Equianalgesic dose ratio with other opioids

Literature lacks one method of calculating equianalgesic dose ratio of other opioids to methadone and the most optimal dosing. Equianalgesic dose ratio should be individualised with comprehensive evaluation of pain and adverse effects intensity. Furthermore, comorbidities and concomitant drugs need to be taken into consideration (60).

There are two ways of switching methadone: immediate (stop and go or stop-start approach), when previous opioid is replaced by methadone completely since the beginning of treatment (7,8,20,61–63) and partial (gradual), when change is progressive, usually over 3 days (64–66). Authors from Europe (7,8,20,61–63,67), Australia (68) and Brazil (69) recommend the stop-start approach. Most authors in America withdraw previous opioid and introduce methadone gradually (65,66). However, the stop-start approach allows achieving rapidly effective analgesia and stable plasma concentration of methadone with quick adverse effects relief because of elimination of previous opioid and its metabolites (69–72). A progressive replacement of morphine or hydromorphone with methadone, usually over 3 days (11,64–66) or longer (73) seems to be less adequate because of the delay in achieving satisfactory analgesia and an overlap of adverse effects of previous opioid with methadone (69–72). In few reports, equivalent methadone dose calculation was independent from morphine daily dose: ratio 5 : 1 (oral route) (61,70) and 5–7 : 1 (subcutaneous morphine to oral methadone) (65).

In most studies, equianalgesic dose ratio of morphine to methadone is higher in patients receiving bigger morphine doses (7,20,64), and much

Table 2 Methadone selected drug interactions, based on Fishman et al. (5), Davis and Walsh (28), Davies (40), Ferrari et al. (42), Weschules et al. (50), Haddad et al. (52), Kostka–Trabka and Woron (57), Bruera and Sweeney (59), modified

Type of interaction and clinical effect	Type of enzyme P-450	Group of drugs	Possible alternative drugs, comments
Inhibiting the metabolism of methadone, intensification of analgesia, higher risk of over dosage and adverse effects	CYP3A4	Antifungal agents: ketoconazole, fluconazole, itraconazole Antibiotics* Macrolides: erythromycin, clarithromycin Chinolones: ciprofloxacin Tuberculostatics: isoniazid† H2 receptor blockers: cimetidine Proton pump inhibitors: omeprazole‡ Benzodiazepines: diazepam§ Calcium channel blockers†: verapamil, diltiazem, nifedipine Dihydroergotamine§ Grapefruit juice, single alcohol consumption	Terbinafine, caspofungin Azithromycin Levofloxacin Famotidine, ranitidine After ingestion large amounts for several days, orange juice as an alternative
	CYP3A4, CYP1A2, CYP2D6	SSRIs¶: nefazodone, fluvoxamine, norfluoxetine, paroxetine, fluoxetine, duloxetine, tricyclic antidepressants/mirtazapine: desipramine†	Citalopram, escitalopram, sertraline, venlafaxine¶, mirtazapine
Speeding up the metabolism of methadone, risk of insufficient analgesia and withdrawal symptoms	CYP3A4	Anticonvulsants: carbamazepine**, phenytoin, phenobarbital Tuberculostatics: rifampicin**, rifabutin Corticosteroids: dexamethasone Antiretroviral therapies Protease inhibitors: ritonavir, lopinavir Nucleoside reverse transcriptase inhibitors: abacavir Non-nucleoside reverse transcriptase inhibitors: efavirenz, nevirapine Diuretics: spironolactone Neuroleptics: risperidone* St. John's wort* Antibiotics: fusidic acid Regular alcohol consumption	Valproic acid, gabapentin, lamotrigine, levetiracetam Possible at higher doses (16–24 mg/day)** Careful monitoring suggested
	CYP1A2 CYP2D6	Smoking cigarettes Tricyclic antidepressants*: amitriptyline, nortriptyline, imipramine, desipramine Other antidepressants¶: venlafaxine, duloxetine	Caution and careful monitoring is advised when combining drugs

Table 2 (continued)

Type of interaction and clinical effect	Type of enzyme P-450	Group of drugs	Possible alternative drugs, comments
Increased analgesia		Neuroleptics: risperidone*	Olanzapine
		Nucleoside reverse transcriptase inhibitors: zidovudine**	
Increased risk of toxicity		Opioids: dextromethorphan, tramadol, codeine, DHC††	
		NSAIDs, delta-9-tetrahydrocannabinol†	Combining drugs is recommended
		Benzodiazepines: alprazolam, diazepam	Buspirone, lorazepam, oxazepam, temazepam

*Tricyclic antidepressants, macrolides and chinolones may cause QT interval prolongation. St. John's Wort increases serotonin concentration. Risperidone is CYP2D6 and CYP3A4 weak substrate and a weak CYP2D6 inhibitor, risperidone interaction with methadone (opioid withdrawal) was reported in two patients, probably not P450 mediated. †Verapamil, diltiazem and isoniazid are potent inhibitors and nifedipine is a substrate of CYP3A4, but no studies were performed so far; delta-9-tetrahydrocannabinol and desipramine increase analgesia, verapamil increases methadone bioavailability, all in animal studies. ‡Probably because of increase of methadone bioavailability, not P450 mediated. §Data reported in the form of the *in vitro* studies. ¶Selective serotonin reuptake inhibitors (SSRIs) in order from the strongest to the weakest CYP3A4 inhibitor (with the exception of duloxetine). Paroxetine and fluoxetine are strong and sertraline mild CYP2D6 inhibitor; furthermore fluvoxamine, paroxetine, sertraline, fluoxetine, norfluoxetine and nefazodone inhibit CYP1A2 in decreasing order. Duloxetine is CYP2D6 substrate and inhibitor. Venlafaxine is a mild inhibitor and a substrate of CYP2D6. **Methadone slows down zidovudine glucuronidation, therefore the dose of the latter should be reduced. Carbamazepine, rifampicin and corticosteroids withdrawal may cause methadone toxicity toxicity. ††Codeine and dihydrocodeine (DHC) a theoretical interaction, no studies performed so far.

stronger methadone analgesic effect is observed (74–76). Ripamonti et al. (64) proved stronger methadone analgesia when administered to patients rotated from higher morphine and hydromorphone doses (77). There is a significant correlation between equivalent dose ratio of morphine to methadone and morphine dose administered before switch – Spearman's correlation coefficients 0.91, 0.86 and 0.78 in Ripamonti et al. (64), Lawlor et al. (76), Cornish and Keen (78) studies respectively. These findings justify lower methadone doses in patients treated with high equivalent daily dose of oral morphine (ddom), especially over 1000 mg (79). The conversion ratio of ddom to daily dose of oral methadone (ddomet) for patients receiving over 1000 mg ddom before switch is 20 : 1 (68,80) and not exceed 30 mg of a single oral methadone dose (62). In a recent systematic review, no superiority of one method of rotation of methadone over another was found with a successful rate of rotations 46–89%; this review confirmed correlation of previous morphine dose with a final methadone dose and dose ratio although ratios varied widely (81).

Although methadone dose titration during OR is performed usually at the in-patient unit (82), Hernansanz et al. (83) advocate OR to methadone to be performed at home with 24 h access to possible naloxone administration in case of respiratory depression. Table 3 presents an overview of equianalgesic

dose ratio of morphine and methadone. In contrast to equivalent doses of other opioids to methadone, the suggested conversion ratios when replacing methadone with another opioid are usually lower. In a study when rotation from methadone to morphine took place, the ratio was 8 : 1, but when switching from morphine to methadone it was 11 : 1 (76). Unsuccessful substitution of methadone with another opioid in almost all patients in clinical (84) and experimental studies (85) cause difficulties in establishing correct equivalent doses when switching from methadone to another opioid (41,60,75). In a retrospective study, the mean dose ratio of ddomet to ddom was 1 : 4.7 and for intravenous methadone to ddom was 1 : 13.5 when rotating from methadone to other opioids; these ratios relate to a stable ddom after OR. Authors recommend in practice to use a more careful approach with even lower ratio than predicted from results of the study. Methadone dose was significantly correlated to a stable ddom after switch for oral (0.72, $p = 0.0024$) and intravenous (0.86, $p = 0.0001$) route (86).

Dosing and breakthrough pain treatment

Frequency of methadone administration depends on analgesia duration and adverse effects intensity.

Table 3 Overview of dose calculations of other opioids to methadone – conversion ratios of ddom to ddomet are presented, taken from (7,20,61–69,86)

References	Conversion ratio of daily oral doses of morphine:methadone
Mercadante et al. (7)	For ddom: Below 90 mg 4 : 1 90–300 mg 8 : 1 Over 300 mg 12 : 1
De Conno et al. (20)	For ddom: Below or equal to 60 mg 3 × 5 mg of methadone 70–90 mg 4 : 1 Over or equal to 100 mg 6 : 1
Mercadante et al. – Palermo model (61)	5 : 1
Morley and Makin – British model (62)	10 : 1*
Nauck et al. – German model (63)	For ddom over or equal to 600 mg: 5–10 mg of R-methadone, every 4 h and not more frequently than every 1 h in case of pain†
Ripamonti et al. – Milano model (64)	For ddom: 30–90 mg 4 : 1 90–300 mg 8 : 1 Over 300 mg 12 : 1
Gagnon and Bruera (65)	5–7 : 1‡
Bruera et al. – Edmonton model (66)	10 : 1§
Leppert – Polish model (67)	For ddom: Below 100 mg 4 : 1 100–300 mg 6 : 1 301–1000 mg 12 : 1 over 1000 mg 20 : 1
Ayonrinde and Bridge – Australian model (68)	For ddom: Below 100 mg 3 : 1 100–300 mg 5 : 1 301–600 mg 10 : 1 601–800 mg 12 : 1 801–1000 mg 15 : 1 over 1000 mg 20 : 1

Methadone should not be administered regularly more often than every 6 h, because it has long plasma half-life and may accumulate (87). Italian (7,20,64), German (63) and American authors (66,69,73,75) indicate that methadone may be administered safely and efficiently every 8 h since the beginning of the therapy. In contrast to on demand administration (*ad libitum* schedule) (62) dosing every 8 h allows to fulfil rapidly the tissue reservoir by the drug (priming dose) at the start of treatment. This approach enables to achieve effective and stable plasma concentration of methadone within 1–2 days and in consequence renders satisfactory analgesia (70–72).

In patients switched from another opioid to methadone, most often its equianalgesic dose ratio calculation is based on Ripamonti et al. study (64). After 2–4 days of methadone treatment, a dose reduction

(67) or less frequent administration e.g. twice daily (62,68) may be considered because of tissue reservoir saturation. However in clinical practice, majority of patients with severe pain needs methadone dose increments. The increase in regular doses in most cases comes to 50% during 2 days (62) or 30% on the same day (63). In patients previously treated with opioids for weak to moderate pain, the initial methadone daily dose is usually 15 mg (5 mg tid) and in opioid-naive patients 9 mg (3 mg tid) (18,20). Careful methadone dosing and close monitoring are recommended especially to opioid-naive, elderly and cachectic patients, the latter have often decreased volume of distribution and drug clearance (18,32). Patients on high opioid doses before OR also require special attention because analgesic effect of methadone is stronger than in those treated with smaller opioid doses (44,64,74,76,88).

Table 3 (continued)

References	Conversion ratio of daily oral doses of morphine:methadone	
Soares – Brazilian model (69)	For ddom: < 100 mg	5 : 1
	100–300 mg	10 : 1
	Over 300 mg	12 : 1
Walker et al. (86)¶	ddomet:ddom	1 : 4.7
	ddimet:ddom	1 : 13.5

*After withdrawal of previous opioid completely, the initial, single, oral methadone dose is administered on demand (*ad libitum* schedule): the ratio of ddom to a single methadone oral dose is 10 : 1 (when ddom exceeds 300 mg an initial, single oral methadone dose is 30 mg). Methadone is administered on demand, but not more frequently than every 3 h. Steady dose is recommended after 5 days: the total amount of drug administered during the fourth and fifth day is divided by four, and fixed methadone dose is defined and administered twice a day. †The analgesic effect of levorotatory methadone (R-methadone) is approximately two times greater than racemic compound; doses of racemate should be twice as high. Doses apply to the first day of treatment. On days 2 and 3, the regular and p.r.n. doses can be increased by 30% when analgesia is insufficient without side effects. On day 4, the drug is administered every 8 h, additional doses are administered not more often than every 3 h in the same amount as on days 2 and 3. During the fifth and next days when analgesia is insufficient without adverse effects, the dose is increased by 30% every 8 h, or in case of pain every 3 h, until effective analgesia is achieved. Methadone doses administered every 8 h vary from 10 to 200 mg. ‡The conversion ratio applies to equivalent daily doses of subcutaneous morphine to daily doses of oral methadone. §With ddom below 100 mg, methadone 5 mg is administered every 8 h regularly and every 2 h if necessary. When ddom is over 100 mg, dose of previous opioid is reduced by 30–50% on day 1 and replaced by methadone in daily dose calculated by the ratio 10 : 1. On day 2, previous opioid dose is reduced by 30–50% and methadone dose is increased in case of moderate or severe pain. Breakthrough pain is relieved with short-acting opioid. On day 3, previous opioid is stopped, methadone is continued to be administered every 8h, 10% of methadone daily dose is administered in breakthrough pain and regular doses are titrated. ¶A conversion ratio of ddomet and ddimet to ddom when rotating from methadone to other opioids. Ratios relate to a stable ddom achieved after 2.5days of switch from intravenous and 2.6 days from oral methadone. Authors recommend in clinical practice a more careful approach with lower ratio than results of this retrospective study (86). Reports (7,20,61-63,67-69) recommend withdrawing previous opioid completely (stop-start approach) in the first day. Ripamonti et al. (64) withdrew morphine and substituted it with methadone gradually over 3days, reducing morphine dose by 30% on days 1 and 2 and remaining dose (40%) on day 3; ddomet was calculated as follows: ratio 4:1 for ddom of 30–90 mg, 8:1 for ddom of 91–300 mg and 12:1 for ddom above 300mg. In reports (65,66) switch to methadone was performed during 3 days with the ratio of daily dose of subcutaneous morphine to ddomet 5–7:1 (65) and ddom to ddomet 10:1 (66). ddom – equivalent daily dose of oral morphine i.e. calculated from morphine dose administered by other routes and from other opioids. ddomet – daily dose of oral methadone. ddimet – daily dose of intravenous methadone.

When treating breakthrough pain, some authors prefer the next regular methadone dose to be administered earlier rather than an additional one (18). In case where breakthrough pain occurs often, it is recommended to increase the regular methadone dose (23). The amount of additional methadone dose is determined individually. When the drug is administered every 8 h, the extra dose most often equals 1/6th (half of the single regular dose) (7), 1/5th (69) or 10% of the daily dose (64). Nonsteroidal anti-inflammatory drugs (NSAIDs) may be administered to patients with bone pain (20,64) and ketamine in severe neuropathic pain (89,90). Preliminary clinical data indicate that oral methadone has a rapid onset of analgesic action and is equally effective as other opioids (morphine, fentanyl and hydromorphone) in breakthrough pain treatment in cancer patients (91). A significant pain relief with a median onset of 5 min without serious adverse effects was obtained

with sublingual methadone in a pilot study in four of seven patients with cancer related breakthrough pain (92). In another preliminary report, methadone proved to be effective and appeared to work faster than morphine ($p < 0.01$) but not faster than oxycodone or hydromorphone and slower than oral transmucosal fentanyl citrate ($p < 0.001$), in cancer breakthrough pain (93). The usefulness of methadone in breakthrough pain treatment may be limited by different time frame of pain flare (usually sudden onset and short duration) and long methadone half-life.

Routes of administration

Methadone as other opioids is preferably administered orally. Clinical experience indicates that methadone can also be administered rectally in the form of homemade micro-enemas (49,94) or suppositories

(87,95,96). Bioavailability after rectal administration (mean 76%) is similar to oral (mean 86%). Rectal administration causes faster onset of methadone analgesic effect: t_{max} (time to maximum plasma concentration) for rectal route is 1.4 h, for oral it is 2.8 h, duration of analgesia is 10 h (97). When rotating subcutaneous hydromorphone to methadone, different equianalgesic dose ratio of methadone to hydromorphone was observed depending on methadone administration route: ratio 1.2 ± 1.3 for oral and 2.1 ± 2 for rectal route ($p < 0.03$) (95), 1.07 ± 0.9 and 1.88 ± 1.27 respectively ($p < 0.01$) (96), which suggest greater oral bioavailability.

Subcutaneous administration is usually a substitute for the oral route. When switching from oral to parenteral route 50% reduction of a methadone dose is advisable (18,41,98). Methadone administered subcutaneously may cause local inflammatory reactions (pain and redness), which require frequent rotation of infusion site or an intravenous administration (99). Although some authors do not recommend the subcutaneous route (59) other reported positive experience (98,100–102). A daily rotation of infusion site and 1500 IU hyaluronidase addition to the 16 ml solution of methadone in 0.9% normal saline allowed avoiding local reactions (98). Addition of 1–2 mg of dexamethasone to methadone solution prolongs mean time without changing butterfly needle insertion site from 2.6 to 4.9 days (101). The solution can be also more diluted with normal saline in a syringe (103) or methadone may be administered through a normal saline hypodermoclysis site with no signs of skin irritation (100). Some authors indicate that methadone does not differ from other opioids with regard to skin irritation, and change of infusion site every 5 days is sufficient (104). Alternatively methadone administration intravenously (105) is effective both in adults (106) and in children (107), previously treated with morphine, fentanyl (108) and hydromorphone (109).

Methadone may be used locally as a mouthwash for the management of painful oral ulcers. A 5 ml solution (1 mg/ml concentration) was administered together with other drugs (diphenhydramine, nystatin, tetracycline and dexamethasone) and kept in mouth for 1 min. The solution containing methadone reduced pain by 75% (other drugs not containing methadone reduced it by 40%) (110). Methadone in powder was successfully used locally as an analgesic on an open, exudative wounds with little eschar (111).

Methadone may be administered intrathecally although it is rapidly redistributed systemically from epidural and subarachnoid spaces. Few studies on this route of administration have been conducted

(112). In a large study during 5-year period, 3954 patients with chronic and postoperative pain were treated at an in-patient pain service in one hospital, 3442 (87%) received epidural and 512 (13%) oral methadone. Acceptable pain relief was achieved in over 90% and 85% patients treated with epidural and oral methadone respectively (113). Methadone may be also administered intranasally (114) and sublingually (92,115).

Adverse effects

Adverse effects attributed to methadone include constipation, nausea, drowsiness, confusion, hypotension, myosis and urinary retention (14,18). Methadone adverse effect profile is similar to morphine although it may become more prominent with repeated dosing (116). In cases of overdose, symptoms appear within 9 h of ingestion with a mean symptom onset of 3.2 h and include respiratory and CNS depression, constricted pupils, muscle flaccidity, bradycardia and hypotension. In severe overdose apnoea, cardiac arrest and death may occur. Treatment usually comprises naloxone administration in repeated injections or continuous infusion as it has short half-life (1 h). Airway and respiratory support, monitoring vitals and pulse-oximetry for 72 h may be needed (117).

It seems that methadone may cause fewer adverse effects in comparison to morphine as a result of its higher lipophilicity, fewer peripheral effects and the lack of active metabolites. In a large (196 patients), retrospective long-term study, 6.6% of patients withdrew because of methadone-related side effects (20). In a randomised, prospective study in patients previously not treated with strong opioids, there were more drop-outs in methadone than in morphine group (22% vs. 6%), but this could be connected with too high starting methadone dose (see below) (21). In two randomised studies (22,39) methadone and morphine adverse effects were similar with more intense dry mouth and less headache in morphine group observed in the first trial. In a prospective study after morphine to methadone switch, a significant improvement in nausea and vomiting, constipation and drowsiness was observed (7). In a randomised study, 108 patients no longer responsive to weak opioids received either sustained-release oral morphine, TF or oral methadone. No differences in adverse effects intensity between all three patients groups were observed (118). In an open study, 45 patients were treated with oral liquid preparation of methadone administered 2–3 times daily and followed up at home; methadone was well tolerated and did not cause serious adverse effects (119). In

another open study, oral methadone proved to be effective and well tolerated in 12 of 15 patients who continued long-term therapy without serious side effects; three patients withdrew because of nausea (2) and confusion (1) (120).

Although methadone is considered not to generate neurotoxic reactions because of lack of active metabolites, literature provides descriptions of patients with myoclonus (121,122), chorea movements (123), serotonin syndrome and mutism (124) caused by methadone. Mercadante et al. (125) described hyperalgesia appearing in spite of methadone switch from TF and morphine. Methadone was stopped and bupivacaine administration intrathecally alone or with morphine warranted analgesia.

Ventricular arrhythmia was observed in patients treated with high doses of methadone. Three patients treated with high oral methadone dose (over 600 mg a day) were diagnosed with ventricular arrhythmia, probably caused by drug interaction with CYP3A4. Two patients had been earlier diagnosed with cardiac muscle damage. Authors of the study recommend careful observation of patients treated with high doses of methadone (over 600 mg a day), especially when it is administered together with other drugs interacting with CYP3A4. Similar precautions need to be taken in patients with ventricular arrhythmia history (126). Ventricular arrhythmia was observed in 17 patients treated for pain or addiction, with the mean doses 400 mg a day. Among possible reasons, other drugs (gabapentin), cardiac diseases, drug interactions with methadone, hypo-potassium in blood serum and bradycardia are listed (127). These observations were confirmed in another study, which indicated prolonged QT interval in patients treated with intravenous methadone in comparison to patients treated with intravenous morphine (128). Cruciani et al. (129) reviewed 104 patients receiving oral methadone as treatment for chronic pain or addiction. Median daily dose was 110 (range 20–1200) mg, median number of months on methadone – 12.5 (range 1–144). QT prolongation appeared in 33% of patients, but it was no longer than 500 ms. Although methadone prolonged QT interval, there was little risk of serious prolongation. Chugh et al. (130) found that of patients who died as a result of sudden cardiac death and used methadone for therapeutic reasons (blood level < 1 mg/l), cardiac abnormalities were found in 23% in contrast to 60% ($p = 0.002$) of patients not treated with methadone.

Manfredi and Houde (131) perform electrocardiogram (ECG) before, after 24 and 72 h of starting an intravenous infusion and additionally after 24 and 72 h of increasing methadone dose; electrolytes level (potassium, magnesium and calcium) is also moni-

tored. Drugs prolonging QT interval and CYP3A4 inhibitors should be avoided and underlying cardiac and liver abnormalities identified. Authors do not recommend these procedures for oral administration. Ventricular arrhythmia risk may be decreased by using chlorobutanol-free parenteral methadone formulations and change to oral route (132). Ower et al. (133) recommend serial ECG in all patients treated with methadone even when dose remains stable because of possible QT interval fluctuation. Cruciani (134) recommends caution and ECG in patients who are or will be treated with drugs that are substrates of CYP3A4/CYP2D6 and have the potential to block rapid rectifying channel currents or in patients who are medically frail and have other risk factors for QTc prolongation (e.g. hypokalemia). Patients started on methadone during hospitalisation should get a baseline ECG, which should be repeated after dose escalation and when drugs that can increase the risk of arrhythmia are added. The lowest methadone dose at which ECG should be performed was not clearly established.

Respiratory depression was observed during switch from hydromorphone to methadone (135,136) and because of interaction of methadone with omeprazole and fluconazole (137) resolved by naloxone. In one report, a risk of 'delayed' respiratory depression was observed as a result of carbamazepine interaction in a 61-year-old patient treated with increasing doses of methadone up to 210 mg/day to control cancer bone and neuropathic pain, 11 days after carbamazepine withdrawal (the drug was gradually decreased from daily doses 1200 mg and eventually stopped). The patient recovered after two 0.2 mg injections and intravenous naloxone infusion, oxygen therapy and methadone cessation; the last one was reinstated 24 h later rendering good analgesia but at dose 75 mg/day (138). In Shir et al. (113) study, three (0.09%) patients with postoperative pain treated with epidural methadone developed clinically significant respiratory depression because of an overdose caused in all cases by epidural pump failure or pump misprogramming. All patients recovered completely once methadone was discontinued. Respiratory depression appeared in one of 21 patients after morphine to methadone switch because of alprazolam interaction, who recovered after naloxone infusion and methadone discontinuation (139).

Summary of methadone studies in cancer pain

A number of open studies assessed methadone as the second strong opioid in cancer patients rotated from

morphine (7,11,17,25,26,37,38,61–68,70,76,78,89,94, 95,106,107,109,139–141), hydromorphone (7,11,37, 75,77,95,96,109), fentanyl (8–10,17,68,72,108,139, 142) and other opioids (7,11,77,142). Although no randomised studies were performed (143,144), methadone improves analgesia and adverse effects profile in 46–89% (81), 75–100% of treated patients (60). Several randomised studies in patients with cancer pain demonstrated similar analgesia and adverse effects profile of methadone to morphine (21,22,39,43,105), to sustained release morphine and TF (118). In a meta-analysis of randomised, comparative studies methadone analgesia in cancer pain is similar to morphine, also in neuropathic pain (116).

In a double-blind, parallel study, 103 patients treated with non-opioids or weak opioids were randomised to receive either oral methadone (49 patients) 7.5 mg twice daily (5 mg every 4 h for breakthrough pain) or sustained release oral morphine (54 patients) 15 mg bid (5 mg every 4 h for breakthrough pain) for 4 weeks. The opioid escalation index at days 14 and 28 was similar for both groups. Similar proportion of patients with 20% or more improvement in pain at 4 weeks was observed in methadone (0.49) and morphine (0.56) group. More drop-outs caused by adverse effects were observed in methadone (11 of 49; 22%) than in morphine group (three of 54; 6%; $p = 0.019$) (21).

In an open study, 54 patients were randomised to receive either oral morphine or oral methadone after non-opioids or weak opioids. In both groups, satisfactory analgesia was achieved, however morphine doses increased by 63% and methadone doses remained stable over 14 days of study period. Adverse effects were similar, more intense dry mouth in morphine ($p < 0.001$) and headache in methadone group ($p < 0.001$) (22).

In a randomised study, 18 patients received either methadone or morphine. All patients had only brief and intermittent exposure to opioids before the study. Patients received given opioid first intravenously and then orally. Apart from clinical data (analgesia, adverse effects) pharmacokinetic assessment was performed. Terminal half-life was 30.4 ± 16.3 and 2.7 ± 1.2 h for methadone and morphine respectively. Methadone long half-life was associated with prolonged pain relief but also with dose adjustments in individual patients. There were pronounced differences in oral bioavailability: $79 \pm 11.7\%$ and $26 \pm 13\%$ for methadone and morphine respectively with the coefficient of variation of 15% for methadone compared with 50% for morphine. The initial dose of oral morphine varied from 15 mg every 4 h to 150 mg every 3 h, while the initial dose of methadone varied from 15 mg on alter-

nate nights to 20 mg twice daily. Both opioids provided satisfactory pain relief, and adverse effects were similar (43).

In a prospective, randomised, double-blind trial, analgesia produced by intravenous morphine and methadone for the period of 5–6 days was compared. One-eighth of the patient's daily opioid requirements was supplied as an intravenous infusion of either morphine or methadone over a period of 15 min, when initiated by a patient-controlled analgesia device. Twenty-three patients were randomised; 18 were fully evaluable: 10 received morphine, eight methadone. Dosing intervals did not change over the 5 days for either group. The mean dosing interval for the last 10 doses was 3.9 ± 0.85 h for morphine and 3.9 ± 1.6 h for methadone group ($p = \text{ns}$). Pain intensity and pain relief were similar for both groups. All patients had adequate analgesia as determined by at least a 50% difference in pain intensity at peak relief. Pain relief duration was similar during the entire study period although morphine and methadone have different plasma half-lives (3 vs. 25 h) (105).

In a randomised study, 40 patients received either sustained release morphine or methadone orally two to three times daily. The doses of both analgesics were titrated and kept as low as possible to render effective analgesia with minimal adverse effects. Both opioids were effective in terms of analgesia although treatment with methadone was connected with fewer gaps in effective analgesia scale. The opioid starting and maximal doses were higher for morphine ($p < 0.0005$ and $p < 0.005$ respectively), and the opioid escalating index for methadone was significantly lower in mg and in percentage ($p < 0.001$). No differences in adverse effects between patients groups were observed (39).

In another trial, 108 patients no longer responsive to opioids for moderate pain were randomly allocated to receive initial daily doses of 60 mg of oral sustained-release morphine, 15 mg of methadone or 0.6 mg (25 $\mu\text{g}/\text{h}$) of TF. Oral morphine was used as breakthrough pain medication during opioid titration. Patients were assessed for 4 weeks; 70 patients completed the study period (five, five and four patients treated with morphine, TF and methadone respectively required opioid switching). No differences in pain and symptom intensity were observed. Opioid escalating index was significantly lower ($p < 0.001$) in patients treated with methadone although it required up and down changes in doses. At the doses used, methadone was significantly less expensive ($p < 0.0001$), while the use and costs of supportive drugs and other analgesics were the same in all groups (118).

Methadone and morphine display similar analgesic and adverse effects profile when administered as the first strong opioid. However, more clinical experience is accumulated with morphine, which is also easier to titrate and has less risk of drug interaction (145). Opioid escalating index is significantly lower ($p < 0.001$) in patients treated with methadone than with morphine (39). Methadone is significantly less expensive (1.04 USD) than sustained release morphine (10.15 USD) and TF (24.3 USD) ($p < 0.0001$) (118). Methadone treatment with custom-made capsules or suppositories is more than 10-fold less expensive than hydromorphone in parenteral solution or in powder ($p < 0.0001$) (95,96). Hydromorphone may cause less occurrence of some adverse effects (pruritus, nausea and vomiting, constipation) in comparison to morphine (146). Another opioid for moderate to severe pain is oxycodone, which may also induce less CNS adverse effects than morphine and hydromorphone with similar analgesia probably because of lack of active metabolites (147). The role of buprenorphine in cancer pain treatment is less clear as it is a partial μ opioid agonist (148). However, development of transdermal preparation and lack of 'ceiling analgesic effect' in doses used for patients with cancer pain increased interest with a possible application in neuropathic pain and renal impairment (149). Another option is TF, which is usually indicated for patients with severe constipation (150).

Conclusions

Methadone is usually administered to patients with cancer pain refractory to morphine or other opioids and with intractable opioid-induced adverse effects. It may be also considered as the first strong opioid although other opioids are easier to use. Methadone similarly as fentanyl might be administered to patients with renal impairment; it is claimed to be indicated in neuropathic pain although this indication is based on methadone multimode analgesic activity rather than limited data supporting its superiority over other opioids.

When rotating from other opioids to methadone, a stop-start approach is suggested with its administration every 8 h and strict patient monitoring. Equianalgesic dose ratio should be individualised and take into account previous opioid dose, drug interactions and detailed clinical evaluation. If methadone is to be administered by parenteral route or to patients with a possible QT prolongation, the risk of arrhythmia should be carefully assessed. Future studies in cancer pain may focus on dose ratio when rotating from methadone to other opioids and

opposite way; comparative studies with other opioids (especially oxycodone and hydromorphone) would assess analgesia, adverse effects and quality of life.

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