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Considerations in methadone dosing for opioid addiction

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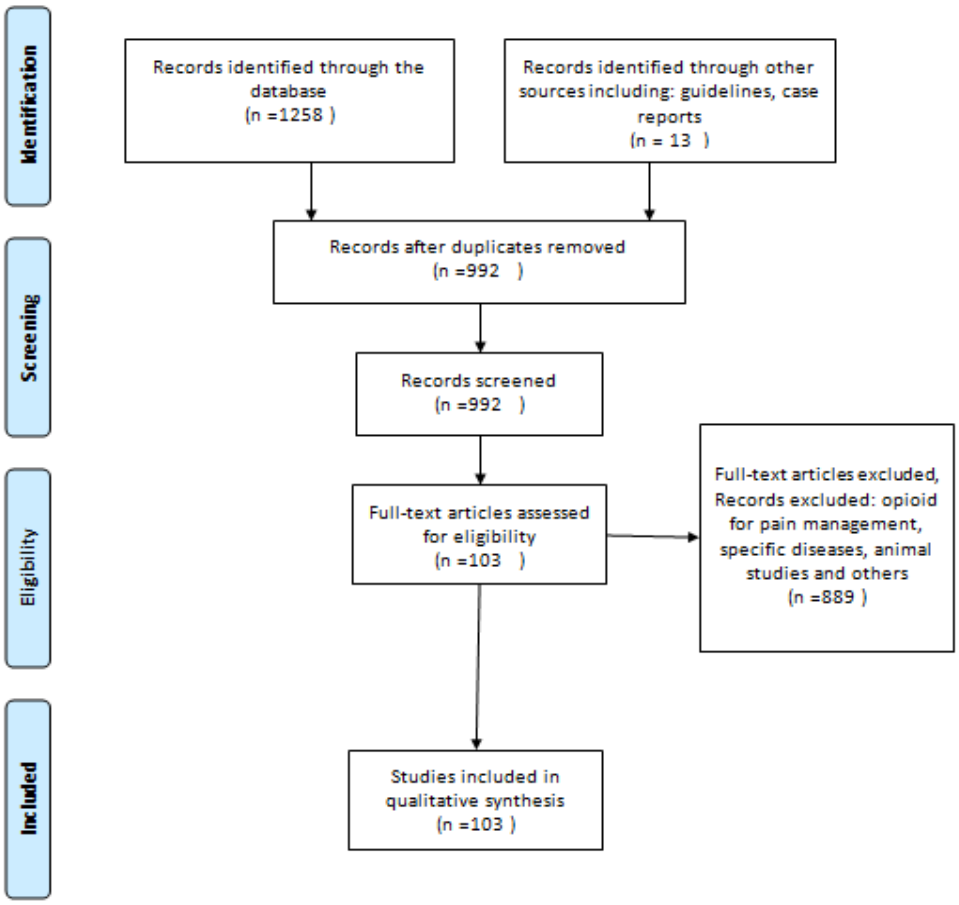
Abstract
Introduction: Methadone has been an essential medication in the treatment of opioid addiction worldwide.
Aim: To discuss dosing considerations related to different methadone programs.
Method: A search was performed the Ovid (all resources) including: Medline, Cochrane, and EMBASE databases using the following terms: methadone dose, methadone optimization, and methadone adequacy. We compared and assessed the eligible studies with respect to the global guidelines for methadone dosing.
Result: 103 different resources have been discussed and presented in the context of methadone dosing. Types of related concerns included: impact of dose on type of the program, dose induction, maintenance dose, dose in case of adverse events, doses in patients with different ethnicities, doses in males and females and dose and compliance.
Conclusion: Although there is no global consensus on methadone dosing, there is a good similarity amongst the guidelines and published data on the general practical dosing regimens. Go-Slow is the most commonly used technique, and described to be the safest, too.

Keywords: Methadone, Opioid, Dose, Optimize

1. Introduction
Methadone administration is an important aspect of the successful treatment of opioid addiction. Methadone administration should be personalized according to the patients' needs and ethnicity. This review compiles many of the key issues related to methadone dosing in a short and straightforward manner, in order to facilitate and optimize the process of treatment initiation and maintenance. In addition, this review considers the factors affecting methadone treatment under a range of conditions.

2. Search Methodology
A search was performed in the Ovid (all resources) including: Medline, Cochrane, and EMBASE databases using the following terms: methadone dose, methadone optimization, and methadone adequacy. The main concern is to clarify the issue of: the best dosing regimen for methadone as an alternative strategy for opioid addiction and the factors that affect it. All full-text studies in the context of opioid dependence and therapy were included that directly discussed the issue of adult methadone dose, or the impact of the methadone dose on clinical outcome. Types of related concerns included: impact of dose on type of the program, dose induction, maintenance dose, dose in case of adverse events, doses in patients with different ethnicities, doses in males and females and dose and compliance.
We excluded studies that included pregnant women and children from this review. We further excluded all the animal-based, pain-related, and diseases-specific studies. We compared and assessed the eligible studies with respect to the global guidelines for methadone dosing.

3. Result
1258 different resources have been identified in all the databases. Duplicated references have been removed. All un-related references have been also excluded, mostly on pain management and related issues. Types of related concerns included: impact of dose on type of the program, dose induction, maintenance dose, dose in case of adverse events, doses in patients with different ethnicities, doses in males and females and dose and compliance.



Flow Chart 1 Data Synthesis

4. Mechanism of Action of Methadone

Methadone hydrochloride is fully synthetic strong opioid agonist which binds to μ-opioid receptors (OPRM1), N-methyl D-aspartic acid receptors (NMDA) and partially antagonizes the effects of glutamate [1]. Methadone's antagonist activity at the NMDA receptor, perhaps by disrupting memory circuitry, are likely to be the mechanism responsible for overcoming tolerance, and ameliorating withdrawal symptoms including craving [2]. Methadone can be administered orally or parenterally as several pharmaceutical preparations, including oral suspensions, traditional pills, sublingual tablets, dispersible tablets in water, and injections.

5. Dosing in Detoxification and Maintenance Programs

Generally, methadone dosing depends on the chosen program plan, which can include either detoxification or maintenance programs, whereby each can be short-term or long-term programs [3, 4]. For detoxification treatment, a program is considered to be short-term if it is intended to run for one month only and long-term if it is to run for more than one month. For maintenance therapy, a program is considered to be short-term if it is designed to run for six months or less. Regardless of the program employed, the patient's addiction to opiates must be established clinically and historically, and the drugs involved must also be identified [5, 6]. Methadone detoxifying program aims to eliminate withdrawal symptoms, while maintenance programs are intended to prevent relapse, and dose varies significantly depending on the choice of treatment program. Accordingly, dose titration mainly depends on the type of treatment program involved. In particular, the length and purpose of the treatment program represent the main determinants of methadone doses.

5.1 Conservative Dose Induction

Most guidelines advocate a conservative approach to the initial phase of managing withdrawal symptoms [7-9]. Dose initiation has been reported at 15-60 mg/day in studies conducted worldwide, with a mean of 30 mg/day [10]. The US, British, Australian, and Canadian guidelines on methadone induction recommend similar initiation doses. These guidelines advocate that the initial dose should range between 10 and 40 mg/day. If the patient's opioid tolerance is very high, 25-40 mg/day would be appropriate, whilst the initial dose should be lower if tolerance is low or unknown [11]. An initial dose of higher than 30-40 mg on the first day is discouraged, and dose estimation should be tolerance-based. Patients should be kept under surveillance for 2-4 hours in order to top-up the dose as required. Patients should also be seen daily during the first week to monitor and adjust their dosing scheme. Dose can be escalated by 20-30 mg during the first week, as a mean of 5-10 mg daily. Although rapid maintenance is essential for the success of treatment, safe induction is also a key concern as it can reduce the risk of death [8, 9, 12-17].

5.2 Rapid Dose Induction

This inpatient method for ultra-rapid high dose methadone detoxification is rarely used. The patients undergoing rapid dose induction are hospitalized for about 5 days and given 150-300 mg/day to eliminate their withdrawal symptoms rapidly. Several medications are coadministered to ameliorate the potential toxicity of methadone and to relieve the patients' withdrawal symptoms. These include clonidine, antibiotic(s), colloid solutions, naloxone, and a non-opioid pain killer [18].

An alternative approach uses rapid methadone induction to reach a dose of 120 mg/day within approximately six weeks, with multiple heroin challenges. Patient will start at 30 mg methadone, regardless of their tolerance, for three weeks. This is followed by 60 mg for three weeks, and then 120 mg for three weeks. Following the final dose of methadone, heroin challenges are scheduled at 4, 28, and 52 h [19].

A study evaluated methadone dosing in two different groups. The first group of 18 patients was administered 28, 56, then 84 mg/day; the second group of 16 patients received escalating doses (28-84 mg on Days 1-6) which then tapered down to 56 mg/day. Both groups received 15 days of treatment, and emergency intervention was available. Craving and withdrawal symptoms were more optimized in the stepwise approach, whereas both exhibited positive mood enhancing effects. The stepwise approach significantly reduced craving and withdrawal symptoms and agonist impact and positive mood increased in both groups. Drug use and retention were not significantly different between the study arms [20], although a longer study duration would be required to evaluate retention appropriately.

Generally, there are few published studies employing rapid dose induction protocols. Therefore, if a rapid or intensive approach is chosen, hospitalization or inpatient protocols with contingency management should be employed, with co-administration of naloxone and clonidine [18-20]. Moreover, strict adverse event monitoring is warranted for these regimens. Monitoring may include electrocardiogram (ECG), liver function tests, and genetic testing to determine whether the patient is a rapid or slow metabolizer.

5.3 Maintenance Program Dosing

Methadone dose optimization is crucially important to control heroin addiction and to free the patient from craving and other withdrawal symptoms. However, craving may persist, even after stabilization [21]. The optimal dose during the maintenance phase has been debated by several studies since the establishment of the methadone maintenance therapy (MMT) principles. Evidence has indicated that the longer it takes to achieve the clinical endpoints, the more likely it is that patients will withdraw from the program [22]. The vast majority of guidelines and studies reported that maintenance doses range from 60-120 or higher in some sub-groups of the population [12-17, 23, 28, 30]. The exact dose employed depends on the clinical endpoints and is tailored to the patient's situation and symptoms [24-31].

For maintenance treatment, US government regulations emphasize that 40 mg is the highest starting dose [24]. However, the majority of patients can tolerate a range of 100-180 mg/day [26-34], and a threshold of 60 mg/day (35, 36). Some studies have reported doses of up to 250 mg/day where patients were adequately controlled, with no major adverse events [37]. Adequate individual doses range from as little as 10 mg/day up to, or even in excess of, 500 mg/day in rare situations [38, 39]. Many researchers recommend that patients should be stabilized on the most appropriate dose to their needs, based on a clinical assessment made after careful consideration of their symptoms. According to the manufacturing guidelines [40], most patients can tolerate between 80 and 120 mg/day [41].

A contingency approach may be of value if cocaine use is evident [42, 43]. Further loading doses may be scheduled for such patients to suppress their withdrawal symptoms. Several approaches have been used and standardization has not yet been achieved.

Surprisingly, it has been shown that patients tend to underdose themselves with methadone when they are allowed to control their own dosing. This may become more prominent when they take their medication home. Therefore, if physicians are not aware of the most appropriate dosing and the proper up-size dosing, the result also will be the same. Lack of knowledge and inadequate clinical training may also contribute to either sub- or supra- therapeutic dosing [37].

6. Treatment Duration

The goal of replacement therapy is not solely to replace heroin or to relieve the withdrawal symptoms. As long as all objectives and goals are being achieved in the chosen program, the length of the treatment should not be limited. The size of the dose required will determine the length of the treatment, as most of the guidelines advocate gradual ascending doses [12-17]. The patient may require approximately 2 months to reach a dose of 60-70 mg/day safely and gradually. Rapid dose escalation can be employed but this is discouraged. Ideally, once the patient has been stabilized on the appropriate dose, they will be maintained on that dose until the patient and their healthcare providers are satisfied with their stability and outcomes. Craving may persist independent of the dose and duration [44]. A definite consensus on the optimum duration of treatment is yet to be established.

Higher doses may take a long time to be achieved, if lower doses are not suitable. If the patient tolerates 60-180 mg/day poorly, for example, a longer period is required to increase the dose safely. Furthermore, if the patient's dose exceeds the suggested threshold for cardiac toxicity, they will require much closer monitoring. Thus, the treatment duration may need to increase significantly by several months in order to achieve the optimal dose to block craving and drug-seeking behavior.

7. The Impact of Adverse Effects of Dose

The medical safety of MMT has been monitored since 1964. However, methadone was reported to be the most frequent contributor to or cause of death at the Utah Medical Center from 2003 to 2005. This report did not exclude patients who intended suicide using methadone and did not discuss dosage as a contributing factor [45]. Furthermore, at that time, the medical examiner revealed that methadone distribution had increased sharply in the Utah area, suggesting a potential abuse situation. Recent studies have revealed that most methadone-related fatalities are due to illicit use of the drug [46], with a significantly lower mortality within well-supervised programs [47]. The non-suicide emergency hospital visits due to methadone were estimated to be 4.5% per 100,000 patients in 2004 in Utah. Generally, the study did not show any clear association or causative relationship

to the results reported. Therefore, adverse events may limit dose optimization and reduce the patient retention time.

The most common adverse drug event is constipation, especially during the induction phase. Several studies have also reported other dose-related adverse drug events including nausea, vomiting, dizziness, sedation, and sweating [48]. Other more serious adverse events include respiratory depression and, to a lesser degree, hypotension. When overdosing occurs, the most serious adverse events will be cardiological and include bradycardia, cardiomyopathy, and some arrhythmias. ECG may show some Q-T prolongation, T-wave inversion, and torsade de pointes. Cardiac changes are more likely to be seen at doses above 120 mg/day [8, 9, 49]. A recent study suggested that patients taking relatively low doses tended to have more Q-T changes than those taking higher doses [50]. This relationship could be U- or J-shaped, as the higher or lower dose may show greater effects or adverse events. However, these data are not conclusive or definitive enough to identify the patients at the greatest risk for cardiotoxicity [51]. Patients with a base QTC that is > 500 ms might need further evaluation prior to entering a methadone program and may require more cautious dose titration. In contrast, patients with a base QTC of < 450 ms may be titrated up safely [8, 9]. Other symptoms of methadone toxicity include digestive, neurological, hematologic and lymphatic, dermatologic, and urogenital abnormalities. However, it is frequently difficult to differentiate methadone side effects of the opiate withdrawal syndrome. Typically, the appearance of adverse events starts during the induction phase and depends on the patient's opioid tolerance, especially among those who have not ingested heroin for more than 7 days. Subsequently, the adverse events disappear gradually over 2-3 days, along with the withdrawal symptoms, with the exception of constipation and sweating which may persist for an indefinite period of time [52].

Cognitive and psychomotor function should also be monitored closely during maintenance dosing. Significant impairment of performance in these domains can be seen at high doses of 200 mg/day, especially on attention- and memory-related tasks [53]. This might not be seen at lower doses of ≤ 100 mg. Dose optimization and close monitoring for other illicit drug abuse are key factors for enhancing patient cognition [54]. It is unclear whether sexual dysfunction is dose-related. While doses of 60-120/day may induce some level of sexual dysfunction due to methadone-induced hyperprolactinemia [55, 56], a Chinese study reported improved male sexuality at relatively low doses, with no association between dose and testosterone levels [57].

Mild adverse events such as constipation, nausea, headaches, and sweating might not impact negatively on treatment success. However, severe side effects such as ECG changes may significantly influence the patient retention time and the amount of drug abuse. Further evaluation of the impact of such adverse events on methadone optimization is required. If the patient experiences adverse events on high doses and craving on low doses, another therapeutic modality may be warranted.

8. Cessation

The most important concern is the lack of a clear definition of methadone adequacy, and the lack of a consensus on the adequate dose size. Although physical dependence is one of the most challenging issues in MMT, it can be overcome when the MMT program is ended by a gradual and careful dose tapering under medical supervision and with adequate patient compliance (12-17). The most commonly-used approach is to reduce the dose by 5 mg/day per week, followed by stabilization of the patient for the following three weeks. Some clinicians advocate reducing the dose by ≤ 20 mg/day per month, followed by a sufficient stabilization period. If the dosage was high (> 120 mg/day), it can be reduced by 10 mg/day per month. A slower tapering of 5 mg/day may be considered at doses lower than 40 mg [58]. During the cessation period, the opiate abstinence score must be measured frequently and the patient's situation should be evaluated weekly [59].

If the patient experiences any withdrawal symptoms during methadone cessation, the clinician should consider reversing the process and reinstating the previous dose [12]. It is imperative that the patient cease the drug safely without triggering withdrawal symptoms to avoid them returning to drug addiction. This requirement to avoid the risk of addiction is more important that the need to cease methadone therapy.

9. Compliance

Patients on methadone programs should have their compliance assessed thoroughly using several approaches, including assessment of their potential use of illicit drugs while on the treatment program [60]. MMT programs occur under medical supervision, as the patient must come to the clinic daily to receive methadone and any other oral fluids to ensure that optimal compliance has been achieved. The patient will not be given any take-home medications until compliance and stability have been established. Patients should be educated on issues related to compliance and encouraged to reveal the internal and external factors affecting their compliance [61]. Some patients knowingly become non-compliant, particularly when they are not convinced that the drug is working well, or feel that it is harming them more than benefiting them [62]. The majority were reluctant to reveal their non-compliance to their physicians, to avoid being removed from the treatment protocol.

Compliance is a critical factor that impacts on the whole therapeutic plan [22]. Since it is insidious in nature, a well-designed treatment program should include frequent assessment of compliance. Compliance is considered to be one of the most important issues in pharmaceutical care and pharmacists always believe that it can be overlooked by physicians. Typically, physicians frequently overlook its impact and hence do not pay particular attention to compliance. However, if the patient is non-compliant, physicians may waste medical resources, especially in government hospitals. In contrast, the private hospital physician may be less concerned about compliance, as it may generate greater revenue for them [63]. In either situation, non-compliance is a main contributor to drug-related hospitalizations and is an important confounder in studies of drug-related morbidity and mortality. One study has shown that 6% of hospital admissions resulted from non-compliance. Furthermore, 50% of the admissions of older patients due to progression of any disease were reported to be related to non-compliance [64].

Several approaches have been developed and utilized effectively by pharmacists to improve compliance, although there is no simple solution. The practitioner should utilize

the most appropriate approach and timing to obtain the required clinical goals. For example, clinicians may check the refill dates against the days of therapy supplied, or perform regular pill-counts. Verbal or written interviews may sometimes help to identify the cause(s) of non-adherence. The best approach to determining compliance is to combine pill checking with an interview, especially at the early stages of the treatment program. Another simple approach which has been used in pharmacokinetic studies of methadone is to assess the percentage of missed days over the entire month, and the blood drug concentrations. This approach was shown to be easy, fast, and reliable, especially in supervised therapies where the need for stringent compliance is reduced [65, 66]. Compliance is considered to be higher if the patient scores > 85% using this approach.

The most common reasons provided for missing medication were the practicality of daily visits and the cost, especially for self-funded patients, whereas the compliant patients tended to have good jobs and extensive history of addiction [67]. Other factors included the dose size, duration of treatment, and some other socioeconomic factors [68]. MMT programs should be designed to avoid any potential methadone misuse and to maintain regular stringent medical supervision. This usually entails daily visits, at least until the patient is judged reliable enough to be allowed take-home doses. As regards cost, there is a need for the government to control costs to make MMT more affordable to the average patient. The government should also consider increasing investment in this program so that more patients can benefit from fully-funded programs. They should also consider creating new subsidies for private clinics to reduce the direct costs to patients, enhancing accessibility and improving compliance.

10. Dosing and Ethnicity

Ethnicity can influence social and physiological factors that affect health [69]. Therefore, stratification of each patient population by ethnicity might contribute to more individualized therapy. However, most of the published data in this area have focused on other opioids, rather than methadone. It is unclear whether these data can be extrapolated to methadone.

Generally, the Chinese population differs substantially from the Malaysian and Indian populations in terms of particular single nucleotide polymorphisms (SNPs) that impact on drug response and metabolism [69,70]. The Chinese population showed the highest morphine consumption for analgesia and this associated with SNPs such as A118G, which was much more common in the Indian population than in Chinese study subjects.

Several other ethnicities have been investigated, including Korean, Japanese, Caucasian, South-African, American, and Ethiopian study subjects [71]. Significant differences have been identified with respect to the prevalence of alleles linked to drug dependency [72]. Unfortunately, the impacts of such variability on methadone responses and clinical outcomes have not been explored.

Allele *6 has been reported in Korean, Vietnamese, Chinese, and Japanese populations [73-76]. Alleles 4*, 5*, 6* and 7* have only been studied in some of these populations. In previous studies, the most common allele found was *6, found in 34% of Chinese, 27% of Vietnamese, 12% of Korean, and 16% of Japanese study subjects. In one pharmacogenetic study conducted in Switzerland, the impact of the Cytochrome P-4502B6 (CYP2B6) *6/*6 genotype was investigated in 209 MMT patients. The MMT patients who were *6/*6 carriers exhibited significantly higher trough levels of (S)-methadone (209 versus 105 ng/ml) and required lower doses (77-79) than those with the wild type. This group of patients may be at higher risk of methadone cardiotoxicity, as this toxicity was previously linked to (S)-methadone level. In terms of efficacy however, the main contributor to the pharmacological actions of methadone is the (R)-enantiomer.

The allele frequencies for A118G have been investigated in two clinical studies and compared with the three major ethnic groups found in Malaysia, Chinese, and Indian. The A118G allele frequency in these three ethnic groups has been examined several times and shown to be stable in post-operative morphine analgesia [69, 70, 80]. The frequency of A118G was reported to be 34-39%, 45-49%, and 44-47% in the Chinese, Malay, and Indian groups, respectively. These frequencies were similar to other reported studies in Asian populations [81, 82], but were almost three times higher than the 7-20% reported for Caucasians, African-Americans, and Hispanic populations [83, 84].

Generally, comparison of the published western guidelines with the published Asian articles indicated that Chinese people may require lower methadone doses than Europeans or Americans. While western maintenance doses range from 60-120 mg/day [12-17], death rates may be increased in Chinese individuals receiving > 60 mg/day [85], although most patients tolerated 60 mg/day [86]. However, the same study reported higher drop-out rates in patients receiving < 60 mg/day. Most Chinese clinics rarely appear to exceed this dose and many use 50 mg/day as their maximum, while some believe that they should increase the dose to improve outcomes [87, 88]. The low dosage may not reflect the adequacy of the response but may instead relate to confounding factors such as lack of knowledge, fear of liability, risk of death, and others [89]. In Malaysia, the majority of patients require approximately 80 mg/day [90]. In Nepal and Bangladesh, patients may require lower doses and further assessment [91]. In summary, Asians may require relatively lower doses of methadone than those recommended by the published western guidelines, to avoid any potential adverse events.

11. Dosing and Gender

No studies have compared male and female dose requirements. However, the frequency of A118G may vary between male and female patients [92]. In non-Asians, females exhibited lower frequency of allele G than those of males (8% versus 12%). The C17T frequency also varied, with a higher T allele among females (9% versus 4%). However, no studies have been carried out with the specific aim of making these comparisons. The frequency of A118G in male patients was found to be lower than that reported by other Malaysian studies which recruited solely females [69]. This result was opposite to the information published for Hispanic, African-American, and Caucasian populations.

Some direct comparisons have revealed no differences in the methadone dose employed in male and female patients, regardless of their genetic predispositions [78]. A possible explanation for this is the reporting of more adverse cardiac events in males, as compared to females. The ECG changes or cardiovascular events may be more apparent in males than in females at low doses [93-95] or in the overall treatment

program [8, 9]. This may reflect the needs of men or their sensitivity toward methadone. Other studies have suggested that females have a higher risk of developing ECG changes [96, 97].

12. Methadone Formulations

There is a range of methadone formulations available worldwide. The oral dosage forms are considered to be the least expensive, and solid formulations are generally cheaper than liquid forms [98]. The type of formulation used may partially explain the huge variability and debate on methadone dosing requirements and blood concentrations. The bioavailability of methadone may also range from 40-95%; its pharmacokinetic profile is very complex, and varied substantially between similar formulations used in different studies [99]. The huge differences in bioavailability significantly influence the clinical application of MMT. One study compared tablets, effervescent tablets, and solutions in chronic patients and found them to be comparable [100]. However, the study only included 9 patients and is not consistent with more recent publications. Most of the published articles did not provide the brand name of the methadone formulation employed or the product bioavailability; this confounds the process of comparison, especially between different countries.

Several reports have raised the issue of increased toxicity using syrup formulations, as compared to other types [101]. This toxicity has been attributed to misuse, as tablets may exert more potent adverse effects than the same dose of syrup [102]. Furthermore, a few new formulations have been tested *in vitro* but not in clinical MMT programs to date [103]. In summary, different dosage formulations and brands may impact positively or negatively on the clinical response to methadone.

13. Conclusion

Methadone dosage is still a concern for most clinicians involved with methadone maintenance or detoxification programs. The 'dose-low and go-slow' approach was very common amongst the published data in all populations studied. Patients receiving higher dosing schemes must be monitored closely for any potential adverse events.

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