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REVIEW ARTICLE

Recommendations for the use of opioids in Brazil: Part I*

Recomendações para uso de opioides no Brasil: Parte I

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ABSTRACT

BACKGROUND AND OBJECTIVES: The adequate use of opioids is still a major challenge to date. There are several mismatches in the clinical practice although these agents have started to be used in the 1980s. Understanding the importance of such subject, the Brazilian Society for the Study of Pain has invited a number of professionals to develop recommendations, based on existing literature, to help the composition of a practical guide for patients' adequate treatment.
CONTENTS: This review has discussed the following recommendations: indication of opioid therapy, its titration and weaning; opioids rotation and monitoring of results, thus evidencing good clinical practice.
CONCLUSION: It is important to adequately elect patients to receive long-term opioids, by evaluating adverse effects and matching the dose to each clinical situation.

Keywords: Chronic pain, Long-term use, Opioid.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O emprego adequado de opioides ainda é um grande desafio no mundo contemporâneo. Diversas são as inadequações na prática clínica, apesar do uso desses agentes ter se iniciado desde a década de 1980. Compreendendo a importância desse tema, a Sociedade Brasileira de Estudo da Dor convidou vários profissionais para desenvolver recomendações que facilite; baseado na literatura médica existente, a composição de um guia prático para o tratamento adequado dos pacientes.
CONTEÚDO: Nessa revisão foram discutidas as seguintes recomendações: indicação de terapia com opioides, sua titulação e retirada; rotação de opioides, monitoração de resultados, evidenciando a boa prática clínica.
CONCLUSÃO: É importante eleger de maneira adequada os pacientes que utilizarão opioide em longo prazo, avaliando os efeitos adversos e adequando a dose a cada situação clínica.

Descritores: Dor crônica, Opioide, Uso prolongado.

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INTRODUCTION

Adequate and monitored use of opioids is still a challenge for health professionals. So, by initiative of a specialists group with institutional validation of the **Brazilian Society for the Study of Pain** (SBED), we have decided for a publication with the primary proposal of presenting recommendations to guide health professionals in the use of opioids to control acute and chronic pain. This program will progressively discuss: indication of opioid therapy, its titration and discontinuation; opioid rotation, monitoring of results; patients' clinical status and specific populations; addiction, abuse and dependence; adverse effects; in addition to all treatment pillars, aiming at optimizing therapeutic results with this class of drugs.
Recommendations presented here and in future publications in sequential manner aim at starting the composition of a practical guide for adequate patients' management, disclosing available information about the use of opioids in different clinical situations; encouraging studies related to opioids safety and effectiveness and demystifying the inadequate association between addiction/dependence and the use of opioids.

INDICATIONS OF OPIOID THERAPY

Before starting opioid therapy it is critical to have patient's complete documentation, which includes the following data: 1) pain evaluation; 2) general clinical status; 3) psychossocial history; 4) psychiatric conditions; 5) possible illegal drug abuse[1,2]; informed consent term for the use of opioids (directive 859 of the National Sanitation Surveillance Agency (ANVISA) from 11/12/2002) (Figure 1).

Observations:
- The complete filling of this Term and respective signature are mandatory for drugs supply.
- This term shall be filled out in two copies remaining one filed at the pharmacy in charge of delivering the drugs and the other in patient's medical chart.

PAIN HISTORY AND EVALUATION

Pain evaluation shall include patient's history which, in addition to baseline diseases, includes pain intensity scale (numerical or visual) as tool to evaluate patient's stage according to the three-steps pain evaluation proposed by the World Health Organization (WHO)[3,4]. A fourth step, called "interventionist" has been

INFORMED CONSENT TERM

Codeine, Morphine, Methadone

I_____ (patient's name), identified and signed below, hereby declare having been clearly informed about all indications contraindications and major adverse effects related to the use of Codeine, Morphine and Methadone for Chronic Pain relief.

All medical terms were explained and all my questions have been answered by the physician _____ (name of prescribing physician).

I also express my agreement and spontaneous will to be submitted to the above-mentioned treatment, taking the responsibility and the risks for possible undesirable effects.

So, I declare that:

I have been clearly informed that the drugs may have, as major benefit, pain relief and quality of life improvement.

I was also clearly informed about potential adverse effects, contraindications, risks and warnings about their use to relieve chronic pain:

Codeine

Analgesic drug, considered weak opioid, used to relieve moderate pain.

Contraindications: diarrhea associated to pseudomembranous colitis caused by the use of cephalosporins, lincomycin or penicillin; diarrhea caused by poisoning; hypersensitivity to codeine or other opioids; cases of drug dependence, including alcoholism.

Adverse effects: sleepiness; intestinal constipation; nausea and vomiting after first doses; allergic reactions; respiratory depression; mental confusion; blurred or double vision; dry mouth; appetite loss; urethral spasm.

Pharmacological interactions (interfering with codeine action): alcohol; sedatives; anti-histamines; monoamine-oxidase inhibitors (MAOI); tricyclic antidepressants.

Morphine

Strong opioid analgesic indicated for patients without adequate moderate, severe or very severe pain control. Its dosage may be gradually increased according to individual needs to reach analgesia.

Contraindications: hypersensitivity to morphine or some components of the formula; severe respiratory failure.

Adverse effects: sedation (may last 3 to 5 days, improving from then on); nausea and vomiting (tolerance is rapidly developed – 5 to 10 days); respiratory depression (cancer patients develop fast tolerance); intestinal constipation; mental confusion (may occur in the first days of treatment); urinary retention.

Less frequent adverse effects: weakness; headache; insomnia; anorexia; dry mouth; pruritus; palpitations.

Pharmacological interactions (interfering with morphine action): alcohol; sedatives; anti-histamines; monoamine-oxidase inhibitors (MAOI); phenothyazines, butyrophenones, tricyclic antidepressants.

Methadone

Synthetic opioid drug with high analgesic potency, indicated as alternative in cases of severe and difficult to treat pain.

Contraindications: hypersensitivity to methadone or any component of the formula; severe respiratory failure.

Adverse effects: respiratory depression; circulatory depression; delirium; dizziness; nausea and vomiting; excessive sweating.

Less frequent adverse effects: weakness; headache; euphoria; insomnia; dry mouth; anorexia; intestinal constipation; palpitations; urinary retention.

Pharmacological interactions (interfering with methadone action): alcohol, morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine); monoamine-oxidase inhibitors (MAOI); other morphine derivatives (analgesics or antitussives); H1 anti-histamines; sedatives; barbiturates; benzodiazepines; anxiolytics other than benzodiazepines; neuroleptics; clonidine and alike; fluoxetine and other serotoninergics; cimetidine, rifampicin, phenytoin and other hepatic enzymatic inducers.

The use of any above-related opioid requires further precautions and care in cases of pregnancy, breastfeeding, elderly patients and children.

Their use may impair motor abilities and physical capacity, needed to perform potentially hazardous tasks, such as drive cars or operate machines.

When impossible to prevent and treat adverse effects, the drug shall be discontinued, according to medical decision.

Demystification of opioid analgesics: they do not induce addiction; they do not cause clinically significant respiratory depression in cancer patients, even with chronic obstructive pulmonary disease (COPD); they do not accelerate death; they do not make patient a zombie.

I am aware that there might be the need to change doses as well as the type of drug which will be part of my treatment.

I am aware that I may discontinue this treatment at any time, without implying any type of embarrassment between me and my physician, who is willing to continue treating me under any circumstance.

I authorize the Ministry of Health and the Departments of Health to use information regarding my treatment, provided anonymity is assured.

Finally I declare having understood and agreed with all terms of this Informed Consent.

So, I do it by spontaneous will and by joint decision between me and my physician.

In addition, I was informed about the mandatory return of opioids which, for any reason, have not been used. This commitment is jointly undertaken by my relative or guardian who, together with me, signs this Informed Consent Term. Drugs shall preferably be returned to the same place where they were received.

My treatment will use **one** of the following drugs:

- Codeine
- Morphine
- Methadone

Model: patient's data

Patient:		
Patient's I.D.:		
Gender	Male ( ) Female ( )	Age:
Address:		
City and State:	ZIP code:	Telephone: ( )
Guardian (if appropriate):		
Guardian's I.D.:		
_____ Signature of patient and Relative or Guardian		

Observation: if the patient is disabled, this Informed Consent Term may be signed solely by duly identified relative or guardian.

Model: physician's data

Physician in Charge:		CRM:
Office address:		
City:	ZIP code:	Telephone: ( )
Physician's signature and stamp:		Place and date:

Figure 1. Informed consent term according to ANVISA directive 859 from 11/12/2002

proposed to be added to original WHO ladder because, although most cancer pains are effectively treated with opioids or by combining non-opioids and adjuvants, not all pains are relieved by this strategy[5,6]. (Figure 2).

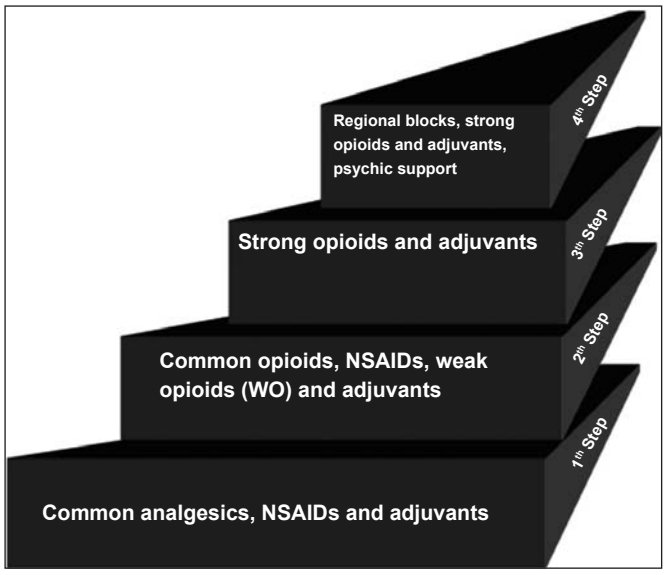

Figure 2. Modified pain ladder with four steps. Adapted[5,6].
NSAIDS: non-steroid anti-inflammatory drugs.

Personal background shall include possible use of drugs and/or procedures patient has been submitted to. It is also important to characterize the impact of pain on patient's daily activities: at work, school, at home and during leisure time, in addition to patient's psychossocial condition. In the history of use of psychoactive drugs involving abuse and/or dependence, try to identify whether patient or relatives have history of usage or are participating in treatment programs for substances with risk of addiction, including urine and blood test for some identifiable substances, such as alcohol, marijuana, tobacco, benzodiazepines, opioids, cocaine, amphetamine, barbiturates, hallucinogens and solvents[7]. For patients under benzodiazepines, especially the elderly, there is the need for special care; in such cases, opioids titration shall be slow and progressive.

OPIOIDS TITRATION AND WITHDRAWAL

Titration, method used to determine the optimal dose of a substance, consists in using the lowest recommended dose (Table 1) of a given opioid, and gradually increasing it until effective analgesia is achieved with tolerable adverse effects. Short-acting opioids shall be used during initial titration period and shall be replaced by long-acting formulations when the effective dose is reached and stabilized.

The objective of the treatment is to determine the opioid dose which improves function and/or decreases pain intensity in at least 30%[8]. So, opioids shall be titrated for patients who: 1) have never used these drugs and have to start treatment; 2) are being treated with weak or strong opioids and are presenting severe or intolerable adverse effects, or who need opioid rotation; 3) are no longer responding to weak opioids and require replacement by strong opioids; 4) are receiving strong opioids and require higher doses (due to increased pain intensity or to the development of tolerance) even when in association with adjuvant drugs; 5) are in severe distress and need fast and effective intervention due to previous and persistent undertreatment[9,10].

On the other hand, optimal opioid dose should be evaluated by the balance of three factors: a) **effectiveness:** 30% to 50% decrease in initial pain intensity or improvement of factors related to quality of life (level of activities at work or at home, dietary habits, level of autonomy, cognitive aspects, sleep quality; and level of social activities); b) **plateau dose**: when increasing dose does not improve analgesia. This is related to maximum effective dose; c) **adverse effects**: should be evaluated and controlled since the beginning of treatment. It has to be reminded that for patients at risk of abuse, there shall be strict monitoring of suspicious aberrant behaviors[11].

Table 1. Initial opioid doses and usage interval

Drugs	Initial dose	Interval (hours)
Codeine	15-30mg	4-6
Tramadol	50mg	4-6
Morphine	5-10mg	3-4
Methadone	5-10mg	8-12
Hydromorphone oros	8mg	24
Oxycodone	10-20mg	12
Transdermal fentanyl	12-24µg	72

Titration ends when: 1) optimal dose (effective and stable) is reached; 2) favorable results are not reached due to insufficient analgesia after increasing two or three doses; 3) there are intolerable adverse effects or other medical complications (undesired interactions, co-morbidities); 4) there are evidences of abuse or dependence. On the other hand, opioids should be discontinued when: 1) pain generating prescription is resolved; 2) patient does not respond to any drug even with opioid rotation; 3) high opioid doses were used and patient, even with partial pain relief, remains disabled; 4) there are aberrant behaviors (abusive use) and/or intolerable adverse effects[12].

Recommendations for withdrawal, based on specific evidences and guidelines, are conflicting. In general, if withdrawal is slow, there will be 10% total daily dose decrease every week, and for fast withdrawal, 25 to 50% every two or three days. More prolonged withdrawal is recommended for patients with anxiety disorders, opioid-dependent, those with cardiorespiratory co-morbidity and for those preferring slow withdrawal[13].

Dose should be maintained or increased if patient, during withdrawal, has withdrawal syndrome, significant pain increase or changes in quality of life. Withdrawal may take from two to three weeks to three to four months and it is necessary to avoid sedatives, especially benzodiazepines[14]. It is important to stress that during pregnancy its acute withdrawal has

been associated to premature birth and spontaneous abortion, in addition to risk to mother's health. Also, for psychiatric patients, withdrawal may significantly increase anxiety and insomnia, and special care shall be taken with patients with co-morbidities which may be worsened by anxiety. It is recommended that patients with aberrant behaviors are referred to a specialized rehabilitation program. One may conclude that the withdrawal process requires constant medical visits, pain, withdrawal symptoms and benefits evaluation[15].

OPIOIDS ROTATION

Implies changing from one opioid to the other when patients experience therapeutic efficacy decline, or when analgesia is associated to adverse effects impairing quality of life. The incidence of this practice varies from 15 to 40%[16].

Opioid rotation may adequately decrease adverse effects or relieve pain in 50% to 70% of cancer patients. Reasons for changing opioids are poorly studied and complex, involving pharmacokinetic and pharmacodynamic factors, such as increased drug metabolism or decreased sensitivity of the opioid receptor. When thinking about changing the opioid, it is necessary to understand that the efficacy of the technique is related to differences among potencies of such agents and to the variety of opioid actions on the receptor[17].

Reasons for opioid rotation

Increased pain or adverse effects intensity is normal due to disease progression, tolerance, genetic polymorphism and inadequate agent absorption (swallowing incapacity, hypotension – limiting transdermal transportation). In addition, females seem to have better response to opioids as compared to males[17]. Genetic polymorphism in genes coding catechol-O-methyltransferase may affect morphine requirements, density of μ receptors and severity of adverse effects on central nervous system. Genetic differences may also interfere with opioid metabolism, with ultrafast metabolizers, affecting response to treatment.

Gene CYP2D6 allele variants are present in 1 to 7% of the population and this helps metabolism of such drugs, increasing toxicity due to fast conversion to active (with metabolites build up) or more potent molecules. On the other hand, 7% of Caucasians are slow metabolizers. So, the use of polypharmacy with agents using the CYP isoenzymes route, decreases the clearance of each drug. Opioids using the glucoronidation metabolism route (hydromorphone) may be an alternative to decrease such complications[18].

Similarly, adverse effects are difficult to handle when there is interaction with other drugs, changes in protein binding (higher agent free fraction) and chronic renal failure. Tolerance to opioids should be considered, as well as cross tolerance for action on the receptor. However, it seems that cross tolerance is incomplete or asymmetric both for experimental animals and humans, favoring the hypothesis that rotating opioids may improve analgesia[19].

One may, then, conclude that the following are reasons to rotate opioids:

- Pain ≥ 4 (pain numerical scale), in spite of dose increase;
- Development of tolerance;
- Poor response to first line opioid;
- Inability to tolerate effective dose;
- When maximum dose allowed for each drug is exceeded (for codeine it is 360mg and for tramadol 600mg);
- Presence of adverse effects (myoclonia, constipation, nausea, vomiting, dysphoria, delirium and excessive sedation);
- Inability to swallow (including patients in total parenteral nutrition);
- Need for alternative drug administration routes (patients with peripheral blood flow changes and with poor absorption of transdermal drugs);
- Decrease treatment costs;
- Non-acceptance of the drug by patient;
- Impossibility of reaching adequate blood concentration;
- Clinical presentation of hyperalgesia[20].

Problems with opioid rotation

Most common opioid rotation mistakes are related to incorrect conversion dose for the new administration route; difficult dose titration; and inadequate use of adjuvants[21]. Equianalgesic dose is defined as dose frequency of two agents to produce the same effect. For such, there are different empirical tables or based on old studies with cancer patients using low or single opioid dose in a short period of time in individuals with no co-morbidities. However, these tables in general supply higher doses than that of the previous agent and really should be used with caution.

So, the proposed opioid should be titrated and response should be adjusted and monitored according to clinical efficacy and patient's individual characteristics, such as age, renal function, adverse effects and type of painful syndrome. Opioid response for musculoskeletal, neuropathic and cancer pain varies widely and this is not considered by conversion tables[22].

It is important to stress that most severe adverse effects with opioids are seen in the first week after replacing the agent. So, it is necessary to: 1) treat patient, not the equivalence table; 2) choose only one conversion table; 3) start therapy conservatively, titrating the opioid and monitoring its effect[23].

Equianalgesia

The equianalgesia table (Table 2) allows the replacement of one drug by the other. When replacing administration route, morphine bioavailability shall be taken into consideration. It should be reminded that converting from oral or transdermal to parenteral route implies faster analgesia adjustment. To the systemic route, from oral to intravenous morphine, dose should be decreased three times; to subcutaneous, twice. This change might give good results in 75% to 90% of cancer patients. Many of those patients, however, use other drugs due to associated diseases. This should be seen with caution to prevent further adverse effects. So, patients under benzodiazepines, anti-histamines, antidepressant, anticonvulsant and antipsychotic drugs deserve strict surveillance. On the other

hand, intrathecal route may decrease morphine dose in up to 300 times. Implantable infusion pumps also help reaching satisfactory analgesia[23,24].

Table 2. Equivalence for opioids available in Brazil

Opioid	Approximately oral and/or transdermal equianalgesic dose
Morphine reference dose	30mg
Codeine	200mg
Transdermal fentanyl	12.5µg/hour
Methadone	4mg
Oxycodone	20mg
Tramadol	150mg
Hydromorphone	7.5mg

http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf

In Brazil, due to lack of immediate release opioid for oxycodone and hydromorphone, escapes are empirically done with morphine. However, the pharmacological association of agents acting on the same type of receptor is not recommended.

Methadone

For methadone, remember that there is inter-individual pharmacokinetic variation, as well as potential to induce late toxicity due to its half-life, which varies from eight to 59 hours. Methadone build-up during treatment days or weeks may be life threatening, due to respiratory depression, especially during sleep. We stress that for chronic non-cancer pain one should start methadone with doses below 30 mg and not exceed 40 mg/day. On the other hand, this initial dose may be hazardous for slow methadone acethylators or patients with sleep apnea. In addition, there are reports on cardiotoxicity (increased QT interval and *torsades de points* rhythm) with sudden death.

So, the equianalgesic ratio may vary from 16:1 to 2.5:1 depending on previous opioid extension or exposure, on total opioid dose, on the reason for rotation (pain or adverse effects), in addition to interaction with other drugs. Conversion rate of 5:1 for morphine doses below 300 mg and if the reason for rotation is pain, may be decreased to 3:1. On the other hand, 10:1 conversion rate for morphine doses above 300 mg shall be used for anxious or depressed patients, those with delirium or needing fast dose increase and for those with creatinine equal to or above 1.5 mg/dL.

If the reason for rotation is pain, this rate may be decreased to 5:1. Methadone should be up- or down-titrated every 48 or 72 hours, approximately 30 to 50%, evaluating clinical criteria, level of patient's satisfaction and the need for escape dose. Other studies suggest the slow withdrawal of the opioid to be replaced by methadone in three days, with 1/3 decrease per day of the agent and addition of 1/3 per day of total methadone dose. Morphine requisition is inversely proportional to age, but for methadone this relationship is independent.

Some authors have also not correlated dose equivalence in the conversion of morphine to methadone to gender, cancer and its treatment features, biochemical or hematological parameters. On the other hand, there are few studies on the transition of methadone to a different opioid. Other authors suggest that 10mg methadone would be equivalent to 20, 33 or 77.5mg morphine, to 4, 5 or 50mg hydromorphone, to 200, 400 or 2000µg fentanyl. This broad variation in the literature, in addition to methadone pharmacokinetic and pharmacodynamic characteristics, suggests that methadone should be gradually withdrawn until the complete introduction of the new agent[25,26].

MONITORING OF LONG TERM USE OF OPIOIDS

To monitor patients under long term opioids it is necessary to: 1) stratify patient's risk for adverse effects; 2) carefully monitor patient with adequate tools; 3) use the informed consent; 4) follow rules for substances control; 5) obtain clinical history and physical evaluation; 6) define the diagnosis; 7) evaluate risk-benefit ratio; 8) establish therapeutic objectives, dose titration and the use of adjuvants; 9) discontinue or rotate opioids, if indicated; 10) adequately monitor and manage adverse effects; 11) evaluate tolerance, hyperalgesia, dependence and abuse; 12) explain to patient that the probability of opioid dependence is a questionable and difficult to determine subject; 13) stratify the risk, considering: (a) low risk: no history of substance abuse or psychiatric co-morbidity (use Statistical Manual and Mental Disorders Diagnostic [DSM-V]); (b) medium risk: history of dependence or psychiatric co-morbidity (DSM-V); 3) high risk: history of dependence and aberrant behavior (theft of prescription, forging prescription, injectable use of oral formulations, alcohol abuse, obtaining prescription by illegal means, loss of prescription, multiple visits to emergency centers, loss of job, family and social life position); 14) consider that most severe adverse effects are related to dose, inadequate patient selection, drug interaction or polypharmacy; 15) treat common adverse effects, such as constipation, nausea and dizziness, the prevalence of which is around 30% in the first month of treatment. Sleepiness, vomiting, headache, pruritus, fatigue, insomnia, sweating, dry mouth and postural hypotension have prevalence below 15%, but may also be adequately treated. Remember that 10 to 20% of patients do not adhere to treatment in the first month due to adverse effects; 16) monitor endocrine effects, such as loss of insulin response in patients who gain weight or are at risk for *diabetes mellitus*; in cases of decreased libido, sexual dysfunction or fatigue, gonadotrophic hormones, especially testosterone, shall be evaluated; 17) evaluate opioid-induced sedation and sleepiness, which may be related to agent's anticholinergic activity. Treatment includes opioid rotation, decrease the dose and use psychic stimulants. For cancer patients under chronic opioid use, metylphenidate (in doses from 10 to 15mg/day) may improve psychomotor activity indices in up to 35% and significantly decrease sleepiness in up to 61% as compared to placebo. On the other hand, opioids may alter sleep and wake ratio, decreasing total sleep time, sleep efficiency, delta waves and REM sleep, and may cause fatigue along time; 18) consider that the ability to handle heavy pieces of equipment or drive cars may be impaired. Remember that driving under the influence of any psychoactive substance is considered very severe violation according to the

Brazilian Traffic Code, Law 11705, Art. 165. This fact should be evaluated by the physician during opioid titration period; 19) understand that inadequate pain evaluation and measurement, low expectation with regard to treatment, lack of communication with the health team, fear of adverse effects and dependence may interfere with the results of analgesia and that continuous education of the health team and of patients is needed, explaining any pending issues (includes informed consent).

CONCLUSION

It is important to adequately select patients who will use opioids in the long term; start titration and maintenance evaluating adverse effects and adjusting the dose to each clinical situation; observe when opioid should be withdrawn or rotated, as well as monitor patients in the long term.

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