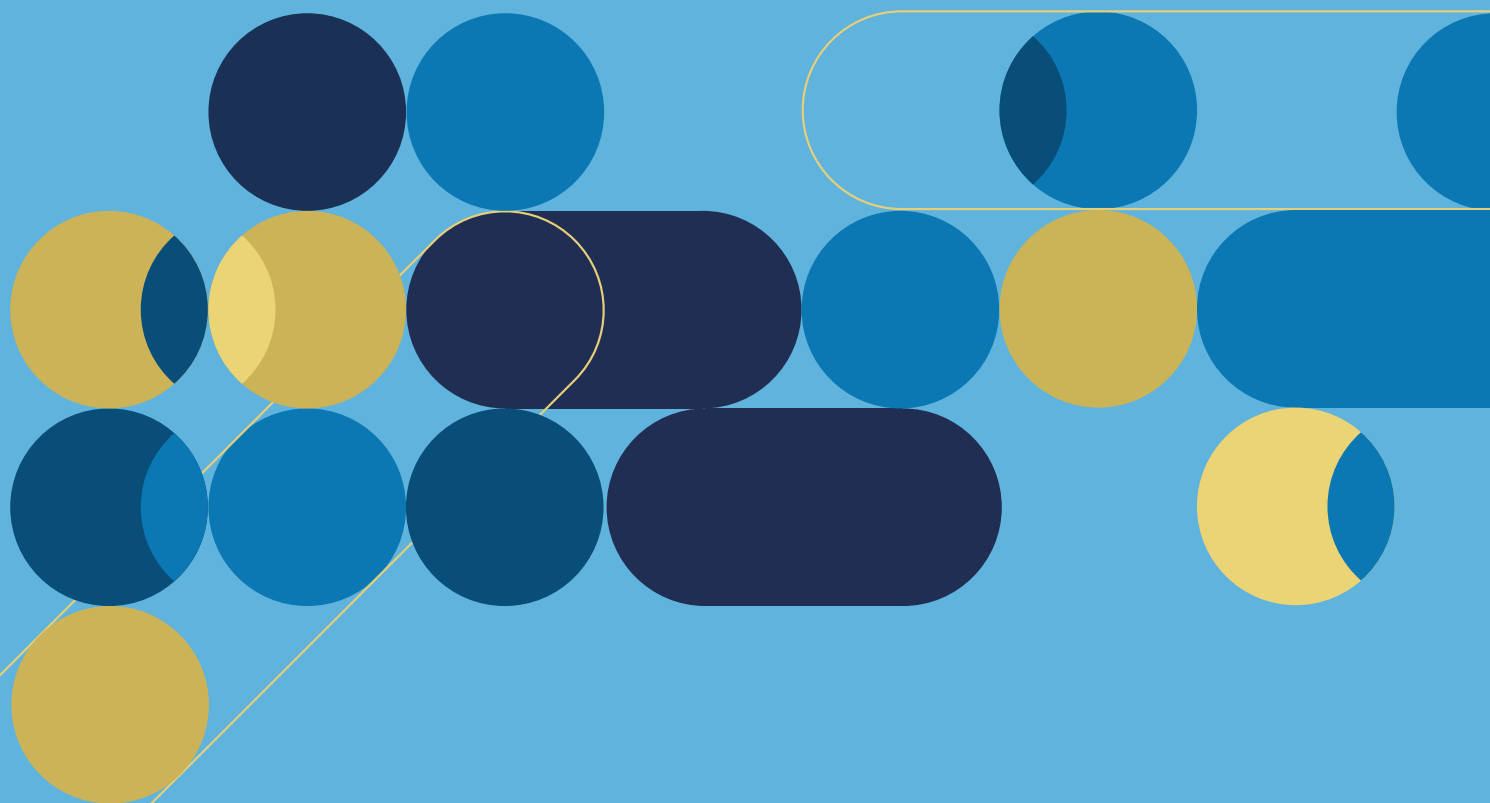




**L'Équipe de soutien  
clinique et organisationnel**  
en dépendance et itinérance

# Guide to Using Slow-Release Oral Morphine (Kadian®) in Opioid Agonist Therapy (OAT)

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**IUD** INSTITUT  
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DÉPENDANCES

Québec

## **Guide to Using Slow-Release Oral Morphine (Kadian®) in Opioid Agonist Therapy (OAT)**

is a publication of the Équipe de soutien clinique et organisationnel en dépendance et itinérance at the Institut universitaire sur les dépendances (IUD) of the CIUSSS du Centre-Sud-de-l'Île-de-Montréal.

This publication is a translation of the [Guide d'utilisation de la morphine à libération lente unquotidienne \(Kadian<sup>MC</sup>\) dans le cadre d'un traitement par agonistes opioïdes \(TAO\) \(Mars 2021\)](#).

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## DISCLAIMER

The content of this guide is based on scientific data and clinical guidelines. The content is the result of deliberations with a committee of Québec-based expert practitioners and organizations representing people who use opioids. This committee issued a recommendation on the use of slow-release oral morphine (SROM) in opioid agonist therapy (OAT) using the GRADE method. In addition, the document's content was verified with qualified experts to ensure that it would be as accurate as possible.

However, it should be noted that the guide is not prescriptive in nature, and its authors **cannot be held accountable** for the clinical practices of professionals. Clinicians are expected to assume responsibility for being appropriately qualified and trained. They must exercise clinical judgment when providing care and services, in compliance with the professional standards and codes of ethics to which they are subject.

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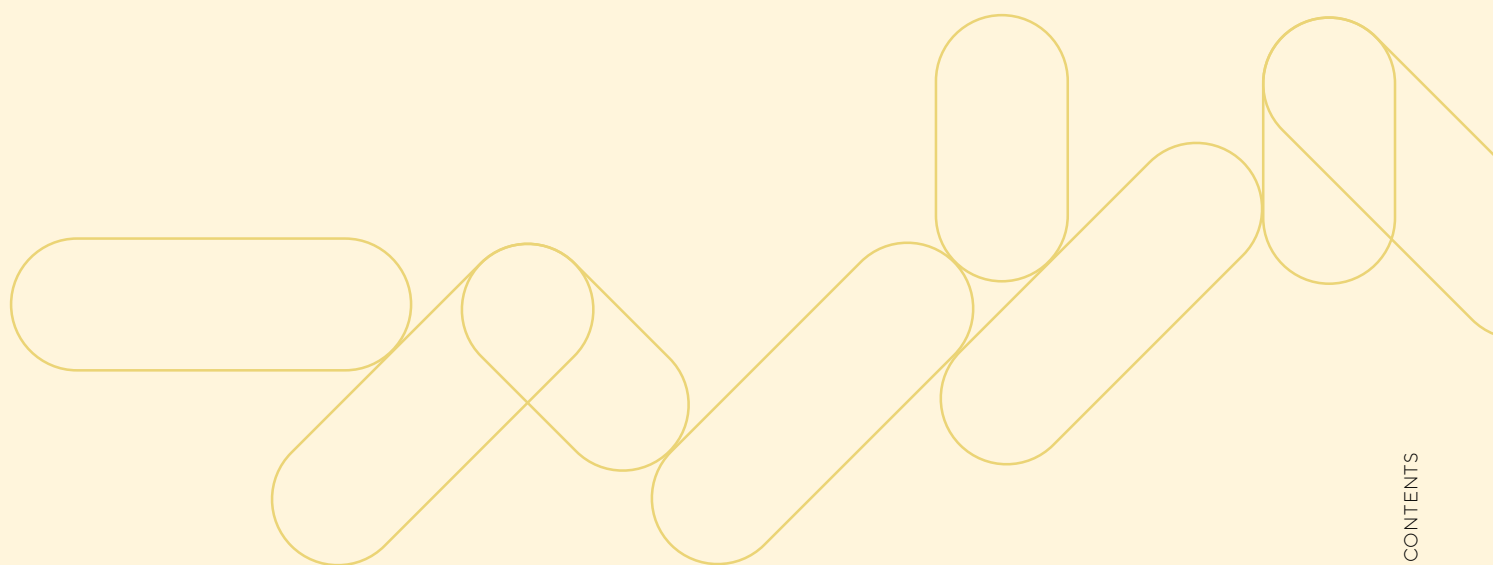
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# Guide to Using Slow-Release Oral Morphine (Kadian®) in Opioid Agonist Therapy (OAT)

## Québec recommendation developed using the GRADE method

In cases where opioid agonist therapies with methadone or buprenorphine-naloxone have been proven ineffective, are contraindicated or unacceptable, prescribers should consider using slow-release oral morphine (SROM).

Treatment with SROM should only be initiated by an experienced prescriber or after consulting with an expert.

Considering the lack of available data regarding misuse, overdose and diversion, and considering the risk of rapid loss of tolerance when doses have been missed, the expert committee recommends that:

- The prescription of unsupervised doses be allowed, based on the clinical judgment of the prescriber and the partner care team,<sup>A</sup>
- The prescription of unsupervised doses should be circumscribed by a decision support tool (see [Appendix 2](#)).

## 1. GENERAL PRINCIPLES

- SROM is a pure selective mu ( $\mu$ )<sup>1</sup> opioid receptor agonist.
- Kadian®, the only SROM formulation so far available in Québec, is covered by the province's public drug plan, although its use as an OAT is currently off-label.
- SROM is approved and covered by Health Canada as an OAT under the Non-Insured Health Benefits (NIHB) program for First Nations and Inuit.<sup>1</sup>
- It is administered orally, once daily, and is released over a period of 24 hours.<sup>2</sup>
- Its peak plasma level is reached after 8.5 to 10 hours. Its elimination half-life is approximately 11 to 13 hours.<sup>3</sup>
- SROM has a lesser impact on the QTc than methadone.<sup>4</sup>
- SROM seems to lead to fewer heroin cravings than methadone.<sup>5</sup>
- Treatment retention with SROM is thought to be similar to that of methadone.<sup>5,6</sup>

## 2. ELIGIBILITY

### To be eligible for the treatment, a patient must:

- Be 18 years of age or older (with some exceptions)
- Have a diagnosis of opioid use disorder (OUD) as described in the DSM-5

💡 Exceptionally, subject to compliance with the [rules regarding the consent of minors to treatment](#) (in French only), a person under the age of 18 may be eligible for OAT with SROM based on the clinical judgment of an experienced prescriber.

<sup>A</sup> Partner care team: This refers to the interdisciplinary team that closely supports the person in treatment for an opioid use disorder, i.e. a physician, a nurse, a psychosocial worker, a peer helper and a community pharmacist. The team members are part of the same unit or collaborate through formal partnerships.

### 3. CONTRAINDICATIONS

#### Main contraindications

- Hypersensitivity to morphine sulfate or one of the non-medicinal ingredients
- Acute respiratory depression, asthma with severe bronchospasm, severe chronic obstructive pulmonary disease
- Gastrointestinal obstruction (including paralytic ileus)
- Concomitant use, or use within the last 14 days, of a monoamine oxidase inhibitor (MAOI)
- Significant acute intoxication with a central nervous system depressant (an opioid, alcohol, benzodiazepine, etc.)

💡 For a full list of contraindications, see [Appendix 1](#) and the [Kadian® monograph](#).

### 4. TREATMENT PRINCIPLES

#### Pre-treatment assessment

- Since the use of SROM in OAT is an off-label practice, the prescriber is encouraged to document the individual's clinical history prior to initiation of treatment, including the following:
  - ⇒ Why this treatment was selected for this individual;
  - ⇒ The risks and benefits of this treatment compared to the risks and benefits of conventional therapies or no treatment;
  - ⇒ The person's free and informed consent.<sup>7</sup> (consult [Appendix 6](#)).

💡 For more information on the initial assessment required of an individual before prescribing an OAT, see the [CMQ guidelines](#) (in French only).

#### Administration

- The capsules are taken once daily, every 24 hours. They can be swallowed whole with a glass of water.<sup>2</sup>
- To minimize the risk of diversion, the capsules should be opened. In this case, the granules in the capsules should be sprinkled into fruit puree, yoghurt or pudding and consumed within 30 minutes.<sup>2,8</sup>
  - ⇒ In practice, the granules can also be diluted in water and consumed immediately.
- The contents of the capsules should never be chewed, crushed or dissolved, as this may alter the pharmacokinetics (morphine release and absorption rates, half-life, etc.) of SROM.

#### 💡 For pharmacists:

Snack-size fruit puree products (in a cup) are easy to use and store, and are readily available and inexpensive.

SROM doses can be prepared in advance in a pill dispenser, with the dates included on the prescription. This saves time and ensures that they are administered on the correct dates. If the patient is entitled to unsupervised doses, give them the pill dispenser compartments in a safe vial.

#### Unsupervised doses

- Supervision of the patient's SROM intake is strongly recommended at the start of treatment.
- Supervision of intake is also recommended if the person is clinically and psychosocially unstable, or if you suspect potential misuse or diversion.
- The clinical judgment of the prescriber and the partner care team plays a key role in the prescription of unsupervised doses. They will need to assess the associated risks and benefits.<sup>8</sup>
- The rationale for granting unsupervised doses should be clearly documented in the patient's medical file and communicated to the community pharmacist with the prescription.

💡 For more information on unsupervised doses, see [Appendix 2](#).

## Prescription

- Kadian® is available in 10 mg, 20 mg, 50 mg and 100 mg sustained-release morphine sulfate capsules.
- When SROM is prescribed as part of OAT, it is important to state on the prescription: [Substitution treatment for opioid use disorder](#) (opioid agonist therapy) (in French only)
- For a model SROM prescription, see [Appendix 3](#).

### For pharmacists:

In order to obtain the fees associated with Service Code J of Rule 29, the pharmacist must contact RAMQ's pharmacist support centre for each new prescription prepared for the patient and fax a copy of the prescription to RAMQ.

## Induction, dosage and stabilization of treatment

- If the person is not receiving OAT, SROM can be initiated on the same day, as long as there are no signs of acute intoxication.<sup>9</sup>
- In order to reduce the risk of overdose associated with the introduction of a new opioid, the general rule is to start with SROM doses that are lower than those reported by the person and increase them as needed. The maximum starting dose is usually 200 mg (see [Table 1](#)).
- If the person is already being treated with opioid agonists (methadone or buprenorphine-naloxone), induction with SROM can begin on the day following the last dose of the previous treatment.<sup>7,10</sup>
- Safer supply can be provided as a complement to the SROM prescription, during both the induction and stabilization periods. For more information on safer supply, see: [Substance Replacement Therapy in the Context of the COVID-19 Pandemic in Québec](#).
- At the first assessment and at each subsequent follow-up appointment you should offer the naloxone kit and provide instructions on how to use it, as well as distribute essential harm reduction materials.



- There is no pre-established dosing protocol for the use of SROM in OAT. Due to variations in tolerance to opioids from one individual to the next and uncertainties around the composition of the substances sold on the illicit market, dosages administered in clinical practice may differ from those reported in the related literature.
- The person's treatment is maintained at a dose that relieves withdrawal symptoms for 24 hours and that suppresses cravings. This is called the stabilization dose.

**Table 1 : Indications from the literature by type of opioid used and type of OAT**

Induction and titration	Stabilization ratio	Stabilization dose	
<b>↓ Transfer from methadone (MTD)</b>			
<p>Start with an MTD:SRM ratio of <b>1:4</b> and gradually increase according to the severity of withdrawal symptoms and cravings.<sup>7,11</sup></p> <p>Example: 60 mg of MTD = 240 mg of SRM</p>	<p>The stabilization dose is usually equal to an MTD:SRM ratio of <b>1:6 to 1:8</b><sup>11-15</sup>. A recent study showed a higher ratio of <b>1:11,8</b><sup>10</sup>.</p> <p>Example: 60 mg of MTD = 480 mg of SRM</p>	<p>The stabilization dose usually varies between 60 and 1200 mg/day.<sup>1,9,12-17</sup> Upward or downward variations may be considered, depending on the clinical presentation.</p>	
<b>↓ Transfer from buprenorphine-naloxone (BUP)</b>			
<p>According to a recent study,<sup>10</sup> the initial ratio on the first day of BUP:SRM is <b>1:42.3</b>.</p> <p>Example: 6 mg of BUP = 254 mg of SRM</p>	<p>According to a recent study,<sup>10</sup> the average BUP:SRM ratio after 14 days of stabilization is <b>1:58</b>.</p> <p>Example: 6 mg of BUP = 348 mg of SRM</p>		
<p>💡 N.B.: This proposal is based on a single study, so actual practice may differ.</p>			
<b>↓ Induction for persons without OAT and using illicit opioids</b>			
<p>The initial dose for the first day is 30–60 mg.<sup>7</sup> The dose is adjusted by 50 mg to 100 mg every 48 hours, depending on the severity of withdrawal symptoms and cravings.<sup>16,17</sup></p> <p>According to the experts, the initial dose may be 200 mg.<sup>17</sup> <a href="#">Swiss protocols on Sevre-Long®</a> (in French only, a SRM available in Switzerland as part of OAT) suggest an initial dose of up to 200 mg, with the possibility of an additional 120 mg if withdrawal symptoms persist 6 hours after the first dose, followed by daily increases of 120 mg.<sup>18</sup></p>	<p>Given variations in the composition of substances sold on the illicit market, prescribers should exercise caution when converting any quantities reported by the person. As a result, no ratio can be presented.</p>		



## Missed doses

- Due to SROM's short half-life, a missed dose will lead to a faster loss of tolerance than what is observed with methadone or buprenorphine-naloxone.
- Once two consecutive doses have been missed, the pharmacist should refer to the prescriber for a readjustment.
  - ⇒ Example of dose adjustment after several consecutive missed doses (according to [guidelines published by the British Columbia Centre on Substance Use](#))<sup>7</sup> :

Number of consecutive missed doses	Dose Adjustment Schedule	
	Example of a prescribed dose: 200 mg	Example of a prescribed dose: 800 mg
1	200mg	800mg
2	120 mg (40% reduction)	480 mg (40% reduction)
3	80 mg (60% reduction)	320 mg (60% reduction)
4	40 mg or initial dose (e.g.: 60 mg) select the highest (80% reduction)	160 mg (80% reduction)
5	Initial dose (e.g.: 60 mg)	Initial dose (e.g.: 60 mg)

💡 N.B.: The criteria to be considered when determining a dosage adjustment after a missed dose are: the usual daily dose, the number of missed doses, the potential for diversion, and other opioid use on the days of missed doses.<sup>7</sup>

## 5. PRECAUTIONS

### Adverse effects

- The major (and relatively rare) adverse effects of SROM are the same as those associated with opioids: respiratory depression to respiratory arrest, severe bradycardia to cardiac arrest, altered consciousness to lethargy, and status epilepticus.<sup>2</sup>
- The most common adverse effects are constipation, nausea, vomiting, dyspepsia, abdominal pain, urinary retention, drowsiness, headache, dizziness, hypotension, diaphoresis, xerostomia, dental pain, dysphoria and insomnia.<sup>2-4,7,12,19</sup>
- SROM use, like the use of other opioids, can lead to opioid-induced hyperalgesia. If this occurs, the use of morphine should be tapered and an alternative opioid used.<sup>16</sup>
- Chronic use of SROM, much like chronic use of other opioids, may also be associated with endocrine disorders such as adrenal insufficiency and hypogonadism.<sup>2</sup>

### Metabolism and elimination

- The main route for metabolizing SROM is by glucuronidation in the liver.
- The main route of elimination is renal.
- See [Appendix 4](#) for the dosage adjustments required in the event of renal or hepatic impairment.
- Particular attention needs to be paid to geriatric population.

## Drug interactions

- Prior to the introduction of SROM, it is important to consider certain drug interactions (see [Appendix 5](#) and the [Kadian® monograph](#) for more information):
  - ⇒ Central nervous system depressants
  - ⇒ Serotonergic drugs
  - ⇒ Naltrexone
  - ⇒ Monoamine oxidase inhibitors
  - ⇒ Diuretics
  - ⇒ Antihypertensives
  - ⇒ Efavirenz
  - ⇒ Ritonavir
  - ⇒ P-glycoprotein inhibitors
  - ⇒ Rifampicin

## Injection-related risks

- Injection of SROM can lead to a rapid increase in serum morphine levels, which is associated with an increased risk of lethal intoxication.
- Because SROM is less soluble than heroin and other fast-acting prescription opioids, its injection carries a greater risk of infection, embolism and vascular injury.<sup>9,20</sup>

## Pregnancy and breastfeeding

*This section is currently being prepared with the participation of the **Sainte-Justine Hospital's Centre IMAGE** and will be available shortly.*



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## REFERENCES

- Canadian Research Initiative in Substance Misuse (ICRAS-CRISM). CRISM National Guideline for the Clinical Management of Opioid Use Disorder [Internet]. Canadian Research Initiative in Substance Misuse (ICRAS-CRISM); 2018 [cited 2020 Jan 9]. Available from: [https://crism.ca/wp-content/uploads/2018/03/CRISM\\_NationalGuideline\\_OUD-ENG.pdf](https://crism.ca/wp-content/uploads/2018/03/CRISM_NationalGuideline_OUD-ENG.pdf)
- BGP Pharma ULC. Product monograph including patient medication information [Internet]. 2018 [cited 2020 Jun 16]. Available from: <https://www.mylan.ca/-/media/mylanca/documents/english/product-pdf/kadian-pm.pdf?la=en-ca>
- Morphine: Drug Information [Internet]. [cited 2021 Jan 26]. (UpToDate). Available from: <https://www.uptodate.com/contents/morphine-drug-information#F8776772>
- Hämmig R, Köhler W, Bonorden-Kleij K, Weber B, Lebentrau K, Berthel T, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat*. 2014 Oct;47(4):275-81.
- Klimas J, Gorfinkel L, Giacomuzzi SM, Ruckes C, Socias ME, Fairbairn N, et al. Slow release oral morphine versus methadone for the treatment of opioid use disorder. *BMJ Open*. 2019;9(4):e025799.
- Mosdol A, Ding KY, Hov L. NIPH Systematic Reviews. In: *Alternative Opioid Agonists in the Treatment of Opioid Dependence: A Systematic Review*. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH) Copyright (c) 2017 by The Norwegian Institute of Public Health (NIPH); 2017.
- British Columbia Center on Substance Use. A Guideline for the Clinical Management of Opioid Use Disorder [Internet]. 2017 Jun [cited 2020 Jun 16]. Available from: [https://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines\\_June2017.pdf](https://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines_June2017.pdf)
- Collège des médecins du Québec, Ordre des infirmières et infirmiers du Québec, Ordre des pharmaciens du Québec. Le traitement du trouble lié à l'utilisation d'opioïdes (TUO). Lignes directrices [Internet]. 2020 Mar. Available from: <http://www.cmq.org/publications-pdf/p-1-2020-03-20-fr-le-traitement-du-trouble-lie-a-l-utilisation-d-opioides-tuo.pdf>
- Barbeau D, Arbour P. Pour le trouble lié à l'usage des opioïdes. Morphine par voie orale à libération prolongée. *Le Médecin du Québec*. sept 2020;55(9):57-9.
- Baschiroto C, Lehmann K, Kuhn S, Reimer J, Verthein U. Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care. *J Pharmacol Sci*. 2020 Jun.
- Clark N, Khoo K, Lintzeris N, Ritter A, Whelan G. A randomised trial of once-daily slow-release oral morphine versus methadone for heroin dependence. *Drug and Alcohol Dependence*. 2002;6(1).
- Eder H, Jagsch R, Kraigher D, Primorac A, Ebner N, Fischer G. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction*. août 2005;100(8):1101-9.
- Beck T, Haasen C, Verthein U, Walcher S, Schuler C, Backmund M, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction*. avr 2014;109(4):617-26.
- Kastelic A, Dubajic G, Strbad E. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. *Addiction*. nov 2008;103(11):1837-46.
- Bond AJ, Reed KD, Beavan P, Strang J. After the randomised injectable opiate treatment trial: Post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug and Alcohol Review*. 2012;31(4):492-8.
- Mundipharma Medical Company. Sevre-Long [Internet]. [cited 2020 Aug 11]. Available from: <https://compendium.ch/product/61761-sevre-long-ret-kaps-30-mg/mpro#>
- Socias ME, Wood E, Dong H, Brar R, Bach P, Murphy SM, et al. Slow release oral morphine versus methadone for opioid use disorder in the fentanyl era (pRESTO): Protocol for a non-inferiority randomized clinical trial. *Contemporary Clinical Trials*. 2020;91:105993.
- Service d'addictologie des Hôpitaux universitaires de Genève. Prescription de morphine retard [Internet]. [cited 2020 Mar 8]. Available from: <https://pro.addictohug.ch/srom/>
- Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database of Systematic Reviews* [Internet]. 2013 [cited 2020 Jun 16];(6). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009879.pub2/full>
- Beer B, Rabl W, Libiseller K, Giacomuzzi S, Riemer Y, Pavlic M. [Impact of slow-release oral morphine on drug abusing habits in Austria]. *Neuropsychiatr*. 2010;24(2):108-17.
- Johnson F, Wagner G, Sun S, Stauffer J. Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended-Release) Capsules. *The Journal of Pain*. avr 2008;9(4):330-6.

# APPENDICES

**Appendix 1 :** Contraindications

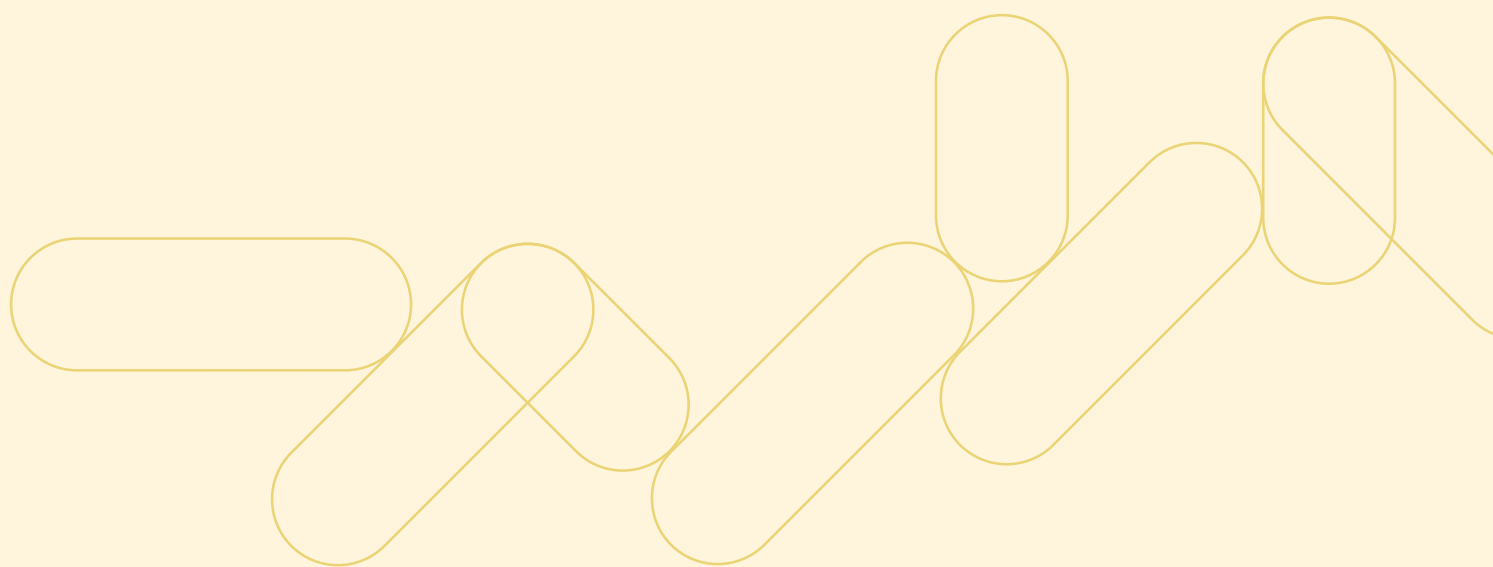
**Appendix 2 :** Decision Support Tool for Granting Unsupervised Doses

**Appendix 3 :** Model Prescription

**Appendix 4 :** Adjusting Doses in Response to Renal or Hepatic Impairment

**Appendix 5 :** Common SROM Drug Interactions

**Appendix 6 :** Making an Informed Choice of OAT Medication: Slow-Release Oral Morphine (Kadian®)



# APPENDIX 1

## Contraindications

### Absolute contraindications to the use of SROM

- Hypersensitivity to morphine sulfate or any of the non-medicinal ingredients
- Acute respiratory depression
- Asthma with severe bronchospasm
- Severe chronic obstructive pulmonary disease (COPD)
- Gastrointestinal obstruction (including paralytic ileus)
- Concomitant use or use within the last 14 days of a monoamine oxidase inhibitor (MOAI)
- Significant acute intoxication with a central nervous system depressant (an opioid, alcohol, benzodiazepine, etc.)

### Relative contraindications to the use of SROM

- Hypersensitivity to other opioid analgesics
- For pregnant or breastfeeding women or women in labour or delivery, refer to the [pregnancy and breastfeeding section](#) of the Guide to Using SROM in OAT
- Asthma or mild to moderate chronic obstructive pulmonary disease (COPD)
- An acute abdomen (e.g. appendicitis or acute pancreatitis)
- Delirium tremens and seizure disorders
- Concomitant use of a central nervous system depressant
  - ⇒ Before initiating SROM, it is essential to inform the patient of the risks associated with concomitant use of SROM and central nervous system depressants (alcohol, benzodiazepines, other opioids, certain psychiatric medications, etc.). Such combinations increase the risk of adverse effects as well as serious complications, including overdose and death from respiratory failure.
  - ⇒ Regarding alcohol use disorders, although the Kadian® product monograph mentions an increased risk associated with acute alcohol intoxication, other data show that alcohol does not significantly alter the pharmacokinetics of SROM.<sup>21</sup>
- Renal or hepatic impairment (for more information, see [Appendix 4: Dose Adjustment in the Event of Renal and Hepatic Impairment](#))
- Craniocerebral injury (mainly if associated with intracranial hypertension)
- Heart rhythm disorder

💡 In this document a distinction is made between absolute and relative contraindications, based on clinical judgment and pharmacological references. However, the [Kadian® monograph](#) makes no distinction between absolute and relative contraindications.

## APPENDIX 2

# Decision Support Tool for Granting Unsupervised Doses

Unsupervised doses should only be offered after weighing the benefits against the anticipated risks. This means that even in the presence of a certain level of risk, it may be deemed appropriate to offer unsupervised dosing if this can improve autonomy, quality of life, adherence and retention, given the logistics required by OAT (regular visits to a pharmacy and clinic, transportation time, etc.). This tool is intended to assist prescribers and members of the partner care team, but it should never replace their clinical judgment.

The following questions can guide deliberations over the decision of whether to grant unsupervised doses. These questions allow for an objective and person-centered view of the recovery process. We have provided real-world clinical examples for each question, although the list is not exhaustive:

### 1. What are the expected benefits of providing unsupervised doses?

- Less travel time and a reduction in the costs associated with travel to a pharmacy
- Enabling a return to or a continuation of school, work, family obligations, etc.
- Increased adherence to treatment
- Facilitating a stay in therapy, in a rehabilitation centre, etc.
- Facilitating a stay with relatives, holidays, travel outside Québec, etc.

### 2. What are the expected risks?


- Intravenous injection
- Severe intoxication or overdose
  - ⇒ Uncontrolled active use of a central nervous system depressant, whether prescribed or not (e.g. alcohol, benzodiazepines, GHB, etc.)
- Diversion or resale

### 3. How is this person able to stay safe?

- By understanding the risks and their ability to provide consent
- Through the stability of his or her doses and SROM intake in recent weeks
  - ⇒ By not missing appointments (at the clinic and the pharmacy)
  - ⇒ By not having missed doses at the pharmacy in recent weeks
- Through a lack of suicidal ideation, a psychotic disorder or cognitive impairment

### 4. How is this person able to ensure the safety of the community?

- By having a safe place to store unsupervised doses
  - ⇒ By paying particular attention to high-risk living environments: e.g. where young children or people who use psychoactive substances are present, etc.
- Through stable living arrangements
- Through no history of stolen or lost unsupervised doses

 For more information on unsupervised OAT dosing, see [Le traitement du trouble lié à l'utilisation d'opioïdes – lignes directrices](#) (CMQ, OIIQ, OPQ, 2020), Section 3.2.3 (in French only).

# APPENDIX 3

## Model Prescription

[ Patient contact information ]

### PHARMACEUTICAL PRESCRIPTION SLOW-RELEASE ORAL MORPHINE (KADIAN®)

Hospital <input type="checkbox"/>	Recovery Housing <input type="checkbox"/>	Rehabilitation <input type="checkbox"/>	Frontline <input type="checkbox"/>
Allergy/Allergies : _____ Aucune connue : <input type="checkbox"/> Adverse reactions to medications : _____			
<b>SLOW-RELEASE ORAL MORPHINE (KADIAN®)</b>			
<b>INDICATION</b>			
QHR notice: <b>Substitution treatment for opioid use disorder (opioid agonist therapy)</b>			
Period: _____ TO _____			
DD	MM	YYYY	DD MM YYYY
Slow-release oral morphine (Kadian®) _____ mg DIE			
<ul style="list-style-type: none"> <li>▪ Number of daily doses in the presence of the pharmacist _____ days/week.</li> <li>▪ The patient can never bring more than _____ doses home between supervised doses taken in the presence of the pharmacist.</li> <li>▪ <b>Once two consecutive doses have been missed, the pharmacist should refer to the prescriber for a readjustment.</b></li> <li>▪ Do not dispense if the patient is visibly under the influence of alcohol or intoxicated by medication or drugs.</li> <li>▪ As needed, check:               <ul style="list-style-type: none"> <li><input type="checkbox"/> The capsule should be opened during a supervised intake. Sprinkle the pellets into fruit puree, yoghurt, pudding or water and serve immediately. CAUTION: Do not chew, crush or dissolve the granules.</li> </ul> </li> </ul>			
<b>OTHER MEDICATIONS</b>			
<b>CONFIDENTIAL TRANSMISSION BY FAX</b>			
Pharmacy: _____			
Fax number: _____		Date/Time: _____	
[ Identification of the prescriber's location of practice ]			
Prescriber's name (block letters): _____		Permit n°: _____	
Prescriber's signature: _____		Date and time: _____	

### PHARMACEUTICAL PRESCRIPTION SLOW-RELEASE ORAL MORPHINE (KADIAN®)

## APPENDIX 4

# Dose Adjustment in the Event of Renal or Hepatic Impairment

### Mild to moderate hepatic impairment

Caution is suggested, but no specific recommendation is made for cases of mild to moderate hepatic impairment. This is because only a small amount of glucuronide metabolites are excreted in the bile, and the enterohepatic cycle of SROM is considered minor.

### Severe hepatic impairment

Downward dose adjustments are recommended. This includes considering dosing intervals that are 1.5 to 2 times longer. Hepatic cirrhosis may alter the morphine's pharmacokinetics, i.e. by extending the half-life and increasing the area under the curve, resulting in higher plasma concentrations.

### Renal impairment

The use of SROM and its impacts on renal impairment have not been formally studied. However, since it is known that active morphine metabolites are excreted in the urine and that there is a significant risk of accumulation in renal impairment, caution is recommended when using SROM in such a context. Precautionary strategies include slower titration, reduced dosing, and even a change of drug, if necessary. For information purposes only, here are some recommendations from experts based on current literature:

Creatine Clearance	Dose Adjustment
ClCr $\geq$ 60 ml/minute	No adjustment required.
ClCr from 30 ml to 60 ml/minute	Consider using an alternative treatment if possible. If necessary, administer 50% to 75% of the initial dose.
ClCr from 15 ml to 30 ml/minute	Avoid use if possible. If necessary, give 25% to 50% of the initial dose.
ClCr < 15 ml/minute	To be avoided.

### Geriatric population

Caution and lower doses are suggested, as aging may alter the pharmacokinetics of morphine. Geriatric population is therefore more likely to present with higher plasma morphine concentrations and develop adverse effects.



## APPENDIX 5

### Common Drug Interactions with SROM

**Central nervous system depressants** (benzodiazepines, barbiturates, sedative H1 antihistamines, pregabalin, gabapentin, etc.), **including alcohol and other opioids**

Increased cardiorespiratory risk, ranging from hypotension to life-threatening respiratory distress.

**Serotonergic drugs** (antidepressants including SSRIs, SNRIs, tricyclics and mirtazapine; some psychiatric drugs including buspirone, lithium and trazodone; antimigraine drugs including triptans; antiemetics including ondansetron; other serotonergic drugs including linezolid, dextromethorphan, cyclobenzaprine, St. John's wort and tryptophan; etc.)

Increased risk of serotonin syndrome (clinical triad of altered mental status, autonomic hyperactivity and neuromuscular abnormalities such as myoclonus and hyperreflexia).

#### **Naltrexone**

Risk of sudden opioid withdrawal. Naltrexone is an opioid antagonist and can therefore precipitate opioid withdrawal syndrome or reverse virtually all the therapeutic effects of opioids.

**Monoamine oxidase inhibitors** (MAOIs: moclobemide, selegiline, phenelzine, tranylcypromine)

Increased risk of serious drug interactions affecting the central nervous system and cardiorespiratory function (e.g. serotonin syndrome). The risk is present with concomitant use of MAOIs and for 14 days after discontinuation.

#### **Diuretics**

Morphine reduces the effectiveness of diuretics by inducing the release of antidiuretic hormone (ADH). Morphine can also lead to acute urinary retention by causing spasms in the bladder sphincter.

#### **Antihypertensives**

Morphine may exacerbate the hypotensive effect of antihypertensive drugs. Caution should therefore be exercised when combining these two types of agents.

#### **Efavirenz**

Efavirenz can potentially increase plasma morphine concentrations through competition for the UGT2B7 enzyme binding site and therefore cause morphine toxicity. Close monitoring is recommended.

**Ritonavir** (including atazanavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir and fosamprenavir/ritonavir)

Ritonavir can increase hepatic metabolism (UGT) and decrease plasma morphine concentration. In addition, ritonavir can inhibit P-glycoprotein and increase plasma morphine concentration. Close monitoring is essential when antiretrovirals containing ritonavir are prescribed for a patient stabilized on SROM.

**P-glycoprotein inhibiting agents** (amiodarone, macrolide antibiotics, some antifungals, some antiretrovirals, etc.)

Greater risk of increased plasma SROM concentrations. Since morphine is a substrate of P-glycoprotein, a PGP inhibiting agent could have a major impact on morphine plasma concentrations, mainly in patients stabilized on high doses of SROM. Although there is a paucity of data on the pharmacokinetics of this type of combination, extreme caution and close monitoring would appear essential.

**Rifampicin**

Greater risk of decreased plasma morphine concentrations, which may lead to withdrawal symptoms. Combining SROM with rifampicin should therefore be avoided whenever possible. If rifampicin must be used, consider monitoring the patient closely and escalating the doses as needed.

## Making an Informed Choice of OAT Medication SLOW-RELEASE ORAL MORPHINE (Kadian®)

To make an informed choice of opioid agonist therapy (OAT) medication, it is recommended that you discuss the different options with a member of your partner care team.

### Slow-release oral morphine in OAT

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- For someone with an opioid addiction (now called opioid use disorder—OUD) whose drug use results in impaired functioning or considerable suffering, the scientific evidence shows that the most effective and safest treatment is long-term opioid agonist therapy (OAT).
- OAT is recognized as a “maintenance” treatment and is supported by medication that reduce withdrawal symptoms, decreases cravings, and causes minimal drowsiness or euphoria.
- Methadone and buprenorphine-naloxone (Suboxone®) are the most widely used medication for this purpose, but there is now a third option for people for whom they are ineffective, contraindicated, or unacceptable: slow-release oral morphine, better known by its brand name: Kadian®.
- In addition, psychosocial support is offered and encouraged when someone begins OAT. This tailored support provides the person with assistance in reorganizing certain facets of daily life where changes may be required.

### What is slow-release oral morphine (SROM)?

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- It is an opioid, like methadone, hydromorphone (Dilaudid®), heroin and fentanyl.
- Kadian® was developed to treat chronic pain, but it is also used in the treatment of opioid addiction. This option has been available in various European countries for several years.<sup>1</sup>

1 European Monitoring Centre for Drugs and Drug Addiction. Table HSR-1. Year of introduction of methadone maintenance treatment (MMT), high-dosage buprenorphine treatment (HDBT), heroin-assisted treatment, slow-release morphine and Suboxone®. Available at: <https://www.emcdda.europa.eu/stats09/hsrtab1>

## How the drug works

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- This drug is in fact a capsule of morphine taken orally and which is released into the body over a 24-hour period.
- The capsule contains the medication in granular form and is taken once daily. The capsule is either swallowed whole with a glass of water or it is opened and the granules are sprinkled into a fruit puree, yoghurt or pudding, or mixed with water.
- At the induction of the therapy, when the person has not reached their comfort dose, SROM (Kadian®) dosage can be increased every 2 days.
- SROM (Kadian®) side effects are similar to those for other opioids, e.g. constipation, nausea and vomiting, drowsiness, and headache.
- SROM (Kadian®) may be a good option for individuals with certain heart problems (QTc prolongation).<sup>2</sup> In addition, some data suggest that the drug reduces cravings.<sup>3</sup>
- In general, SROM (Kadian®) should be taken daily at a pharmacy. Unsupervised doses may be provided on a case-by-case basis, depending on the individual's personal situation.

## Advisory notice

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- The granules in the capsules should never be chewed, crushed or dissolved, as this may cause the sudden release of a large dose of morphine, potentially leading to an overdose.
- The use of opioids in combination with alcohol and other depressants, such as benzodiazepines (Ativan®, Xanax®, Rivotril®, etc.) or GHB, can be particularly dangerous and in some cases lead to death.
- Because SROM (Kadian®) is less soluble than heroin and other opioids such as Dilaudid®, injecting it carries a greater risk of infection, embolism and vein damage.
- If the daily doses are missed for more than 2 consecutive days, it will be necessary to drop back to a lower dose, since tolerance to SROM (Kadian®) decreases more rapidly than is the case with methadone or buprenorphine-naloxone.

## Naloxone, safe drug use equipment and personal protection equipment: everywhere, all the time, for everyone!

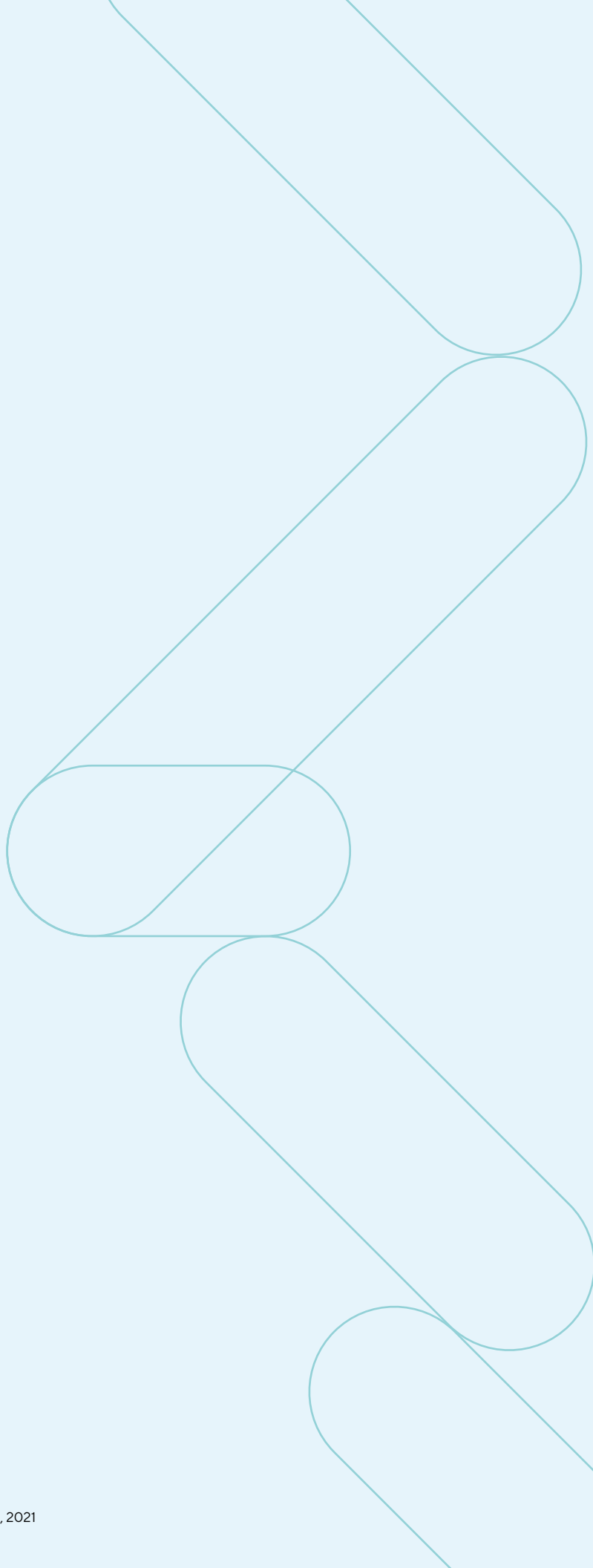
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- Regardless of which medication is chosen for OAT, always provide naloxone and instructions on how to use it, as well as safe drug use equipment and personal protection equipment. Do this at the first assessment as well as at each follow-up appointment.
- Naloxone, which is sometimes referred to as the “opioid overdose antidote”, saves lives by reversing the effects of an opioid overdose. This is why it is important to include the person's family and friends when distributing naloxone and giving instructions on its use. In addition, the distribution of safe drug use equipment and personal protective equipment helps reduce the risk of infection.
- As part of the services they offer, health and social service institutions can now distribute naloxone to certain specific populations. People undergoing treatment and their family and friends can also obtain it from pharmacies and certain community organizations.

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2 Hämmig R, Köhler W, Bonorden-Kleij K, Weber B, Lebentrau K, Berthel T, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat.* oct 2014;47(4):275-81.

3 Klimas J, Gorfinkel L, Giacomuzzi SM, Ruckes C, Socias ME, Fairbairn N, et al. Slow release oral morphine versus methadone for the treatment of opioid use disorder. *BMJ Open.* 2019;9(4):e025799.



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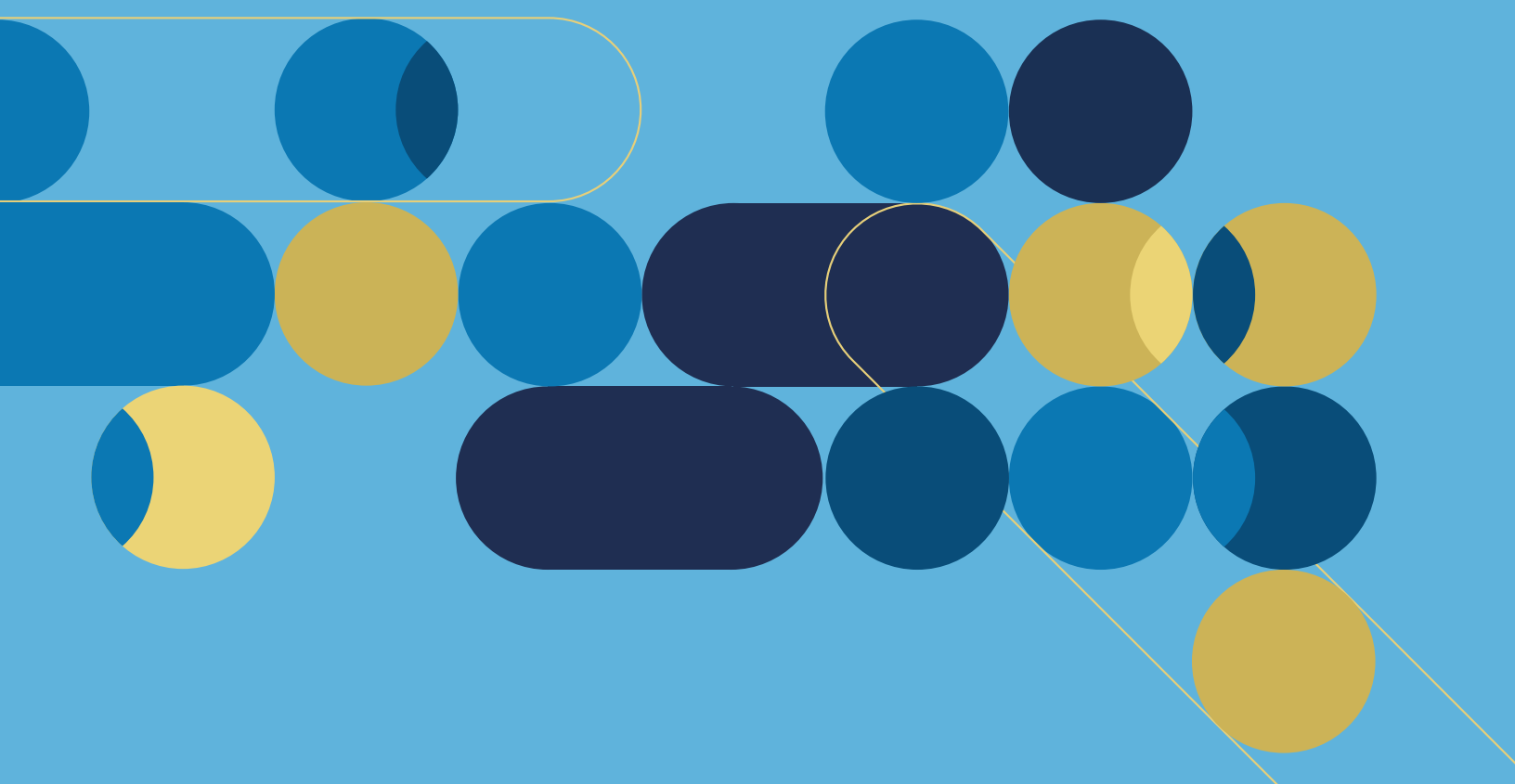
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