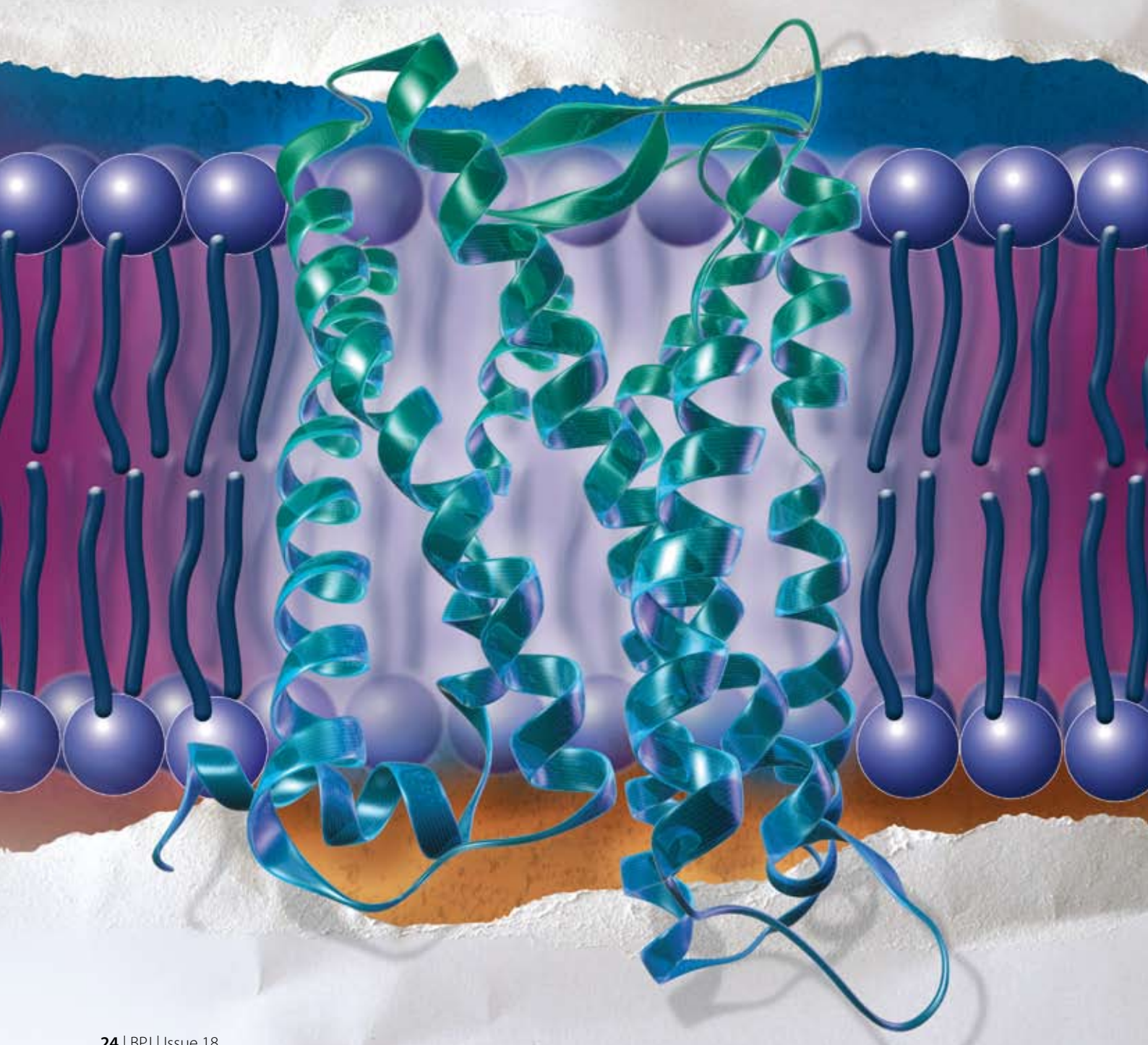
WHO Analgesic Ladder: Step 3

Methadone – safe and effective use for chronic pain



Methadone is a strong opioid

In BPJ 16 (September 2008), we provided guidance about the management of chronic pain. The three step pain ladder was recommended for managing pain; start with a non-opioid analgesic, add a weak opioid if pain is uncontrolled, and finally change to a strong opioid if pain continues to be uncontrolled.

Methadone is a strong opioid and may be suitable for people whose pain is uncontrolled with morphine (e.g. neuropathic pain) or who are unable to tolerate morphine (e.g. idiosyncratic reactions, or in renal failure).

Methadone has complex pharmacokinetics and pharmacodynamics

Methadone has a long half-life (30 hours) and displays wide variations between individuals. The duration of analgesic effect is much shorter. Methadone takes five to seven days to reach steady state and so is a difficult analgesic to titrate. If the dose is titrated too rapidly, accumulation and toxicity can occur. In the community, there is a high risk of unobserved respiratory depression and death if doses are escalated too quickly.

Because of the potential for fatal respiratory depression, it is recommended to never use methadone for breakthrough pain.

Key concepts

- Methadone may be suitable for people whose pain is uncontrolled with, or who are unable to tolerate, morphine
- Methadone has complex pharmacokinetics and pharmacodynamics and requires careful dosing and monitoring
- The general rule for dosing methadone in opioid naïve patients is “start low, go slow”
- Methadone interacts with other drugs, be especially aware of a change in therapeutic effect that may indicate an interacting drug is being used concurrently
- Monitor for adverse effects, especially respiratory depression
- Educate patients about the safe and effective use of methadone

Despite these issues, methadone is an excellent analgesic for complex pain and is increasingly being used as a first, rather than second or third-line opioid. With precautions methadone can be safely introduced in the community.

Methadone is a NMDA antagonist

Aside from its agonist activity at the mu opioid receptor, methadone has other actions that are believed to contribute to its unique analgesic activity.

Compared to morphine it is an agonist to a broader spectrum of opioid receptors and is also an antagonist at the N-methyl-D-aspartate (NMDA) receptor and inhibits the re-uptake of both noradrenaline and serotonin. These actions are believed to contribute to its increased analgesic efficacy for patients with chronic pain syndromes, hyperalgesia and neuropathic pain.

Example of methadone titration

Week 1	2.5 mg twice daily
Week 2	5 mg twice daily
Week 3	7.5 mg twice daily
Week 4	10 mg twice daily
Week 5	10 mg three times daily or 15mg twice daily
Week 6	20 mg twice daily or 10 mg four times daily

Many patients gain good analgesic control with once daily or twice daily regimens especially once a steady state is achieved. In situations where patients develop pain prior to their next dose, methadone given three or four times daily may be more effective.

Rapid titration

Quicker titration regimens are available but because of the risk of respiratory depression are not recommended in the community and inpatient admission is required. There are conversion regimens that can fully titrate methadone doses in about a week. Specialist advice/input is recommended.

Other opioids for breakthrough pain may be required

Patients who require extra analgesia outside of their methadone regimen can be initially prescribed either, codeine 30–60 mg as required, maximum four times per day, or morphine 2.5–5 mg as required (doses depend on clinical factors such as age, renal function and previous response to codeine).

Safe methadone dosing in the community

Methadone for opioid naïve patients – start low, go slow

When therapy with methadone is started, patients need to be carefully monitored for signs of toxicity, especially respiratory depression. This will require daily monitoring in the first days of treatment. Home visits may not be necessary and telephone calls may be adequate if the health professional can talk to a reliable adult. Ask about confusion, excessive drowsiness and control of pain. The patient should not be left home alone for the first five to seven days.

For patients who have not been taking regular opioids, a safe starting dose is 2.5 mg every 12 hours or 5 mg once daily. If pain is not controlled, and methadone is tolerated, doses can be increased slowly every five to seven days (see sidebar for an example).[1]

Methadone for opioid tolerant patients – ratios change based on current opioid dose

Because the analgesic effect of methadone is a result of more than its opioid effects, the conversion ratios with morphine are not linear but change with increasing doses. Various conversion ratios for morphine to methadone have been developed (see Table 2 for an example).

If the previous dose of morphine is much higher than 300 mg/day the ratio increases even further. When converting at these doses it may be more suitable to do this in an inpatient setting where the patient can be monitored more closely.

Table 1: Morphine equivalent doses

Opioid	Equivalent to 10 mg morphine (oral)	Conversion factor
Codeine	100 mg	0.1
Dihydrocodeine	100 mg	0.1
Tramadol	50 mg	0.2
Oxycodone	5 – 7.5 mg	1.5 – 2

Table 2: Suggested safe and effective starting doses when changing patients from oral morphine to oral methadone[3]

Morphine dose (mg/ day)	Morphine to methadone equianalgesic dose ratio	Methadone starting dose
30–90	4:1	e.g. 90 mg morphine per day = 22.5 mg methadone per day
90–300	8:1	e.g. 200 mg morphine per day = 25 mg methadone per day
>300	12:1	maximum = 30 mg methadone per day as outpatient

It is recommended to not start higher than 30 mg of methadone per day unless the patient is in hospital.

To convert a patient from another opioid to methadone:[1]

Step 1. Assess current daily opioid dose – add up all long-acting and short-acting doses.

Step 2. If the current opioid is not morphine, convert this to a daily morphine equivalent dose.

Step 3. Based on this estimated daily equivalent morphine dose, work out the recommended methadone dose using the ratio.

Clinical scenario 1. Patient currently taking morphine for musculoskeletal pain associated with hemiplegia. Appears to be suffering thalamic pain. Plan change of opioid to methadone.

Step 1. Current opioid use: morphine 90 mg per day

Step 2. Not required

Step 3. Methadone dose: Divide the total daily morphine dose by the appropriate equianalgesic dose ratio (Table 2). In this case the equianalgesic dose ratio is 4:1.

90 mg morphine divided by 4 = 22.5 mg methadone per day given as 7.5 mg three times daily or rounded down to 10 mg twice daily.

Breakthrough analgesia is usually 1/6th of the total daily opioid dose. For this example, continue with previous breakthrough analgesia – morphine 90 mg/6 = 15 mg (morphine syrup) as required.

Clinical scenario 2. Patient currently taking oxycodone for pain from spinal stenosis. On increasing dose has developed severe itch. Plan change of opioid to methadone.

Step 1. Current opioid use: oxycodone 150 mg per day

Step 2. Morphine equivalent dose: Convert to a daily morphine equivalent dose (see Table 1 for morphine equivalent ratios). Equivalent morphine dose 150 mg x 2 = 300 mg morphine per day. Practitioners may be surprised at this equivalency.

Step 3. Methadone dose: Divide the total daily morphine dose by the appropriate equianalgesic dose ratio (Table 2). In this case the equianalgesic dose ratio is 8:1.

300 mg morphine equivalent divided by 8 = 37.5 mg methadone per day. As the maximum starting dose recommended is 30 mg methadone per day, start at 15 mg twice a day or 10 mg three times a day.

Breakthrough – continue with previous breakthrough analgesia e.g oxycodone 150 mg/6 = 25 mg as required.

In all cases review daily to check the effects until a stable dose is reached. Doses may be adjusted depending on the effect e.g. with signs of toxicity (drowsiness/

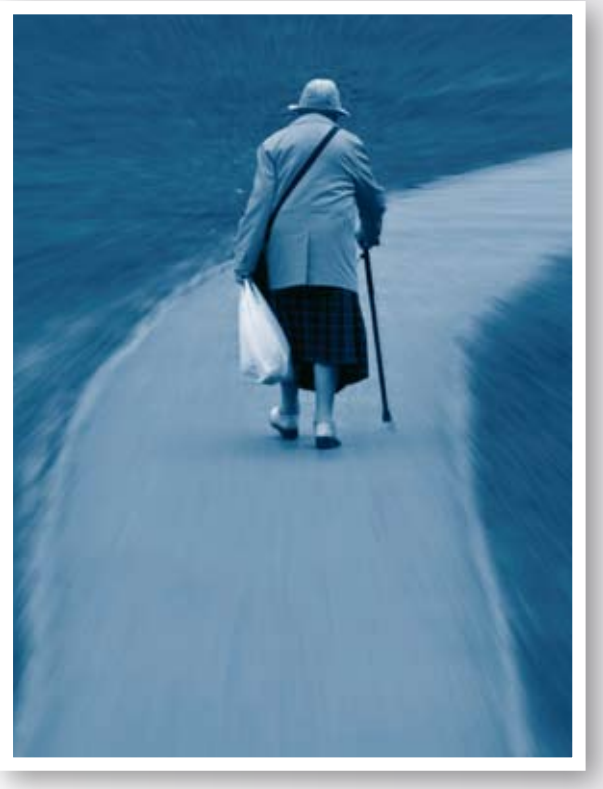
Methadone dosing in special populations

Liver disease and renal dysfunction

The dose of methadone does not need to be adjusted in stable liver disease and does not accumulate in people with renal dysfunction, although dosage adjustment may be required in end-stage renal disease.

Elderly people

Elderly people are more susceptible to the side effects of confusion, drowsiness and respiratory depression. It is recommended to start with once daily dosing in this population e.g. 2.5 mg once daily. For frail elderly people an even smaller starting dose can be used e.g. 1 mg once daily (0.5 mL of methadone oral liquid 2 mg/mL).[2] Dose changes should not occur faster than once weekly in this group.



respiratory depression) reduce dose. If pain is poorly controlled, increase the dose by 30-50% with extreme caution. Monitor for drowsiness and confusion.

Drug interactions

Methadone has a number of interactions that are not seen with morphine. It is mainly metabolised by CYP3A4 along with other CYP enzymes. Drugs that inhibit or induce these enzymes will affect the plasma concentration and therapeutic effect of methadone. Azole antifungals (e.g. fluconazole) inhibit CYP3A4 and may increase the concentration of methadone and increase the likelihood of adverse effects and overdose. Drugs that induce these enzymes, e.g. St John's Wort and some anticonvulsants (e.g. phenytoin, carbamazepine), may reduce the plasma concentration of methadone decreasing its therapeutic effect.[4]

Concomitant use of drugs that affect the CNS, for example, alcohol, benzodiazepines, or other opioids, may increase the likelihood of adverse effects such as sedation and respiratory depression.[4]

Methadone can cause QT prolongation which may lead to the development of potentially fatal arrhythmias. This is particularly associated with higher doses (e.g. >150 mg/day). Other risk factors include concomitant use of drugs that also prolong the QT interval, and use in patients with cardiac disease. ECG monitoring is recommended for these patients.[5, 6]

Large dose changes of methadone are not often required after initial titration unless the clinical picture changes. If therapeutic effect changes during treatment, consider whether the potential addition of another drug has altered the plasma concentration of methadone and therefore its therapeutic effect.[1]

Adverse effects – monitoring for respiratory depression is especially important

Constipation, drowsiness and respiratory depression are potential adverse effects. Respiratory depression is a

particular concern and patients should be monitored on a daily basis during the initial titration period. Consider hospital admission for a patient with a respiratory rate of less than 12 breaths per minute.

Methadone causes significant constipation as do other opioids. A stimulant/softener laxative should always be prescribed concurrently.

Patient education

Educate patients about the safe and effective use of methadone:

- Effective pain relief can take several days.[1] Advise that the initial dose may not provide adequate pain relief but reduces the chance of adverse effects, and the dose will be titrated to an effective level.[2]
- Use of methadone in combination with other opioids, other drugs or alcohol can be fatal.
- Frequent monitoring is required during initiation and maintenance of treatment. Patients should be instructed to immediately report any increasing or intolerable adverse effects.
- Constipation is a common adverse effect so advise patients to take laxatives as prescribed, eat a well-balanced diet containing plenty of fibre and drink adequate fluids.
- Patients may be aware that methadone is used to treat opioid addiction and may be concerned about the social stigma. Reassure them that this is an accepted pain medication and explain the difference between dependence and addiction.

References:

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