



# GUIDELINES FOR USE OF ORAL MORPHINE TO MANAGE PAIN



CanSupport  
New Delhi, India

## A note from Harmala Gupta, Founder-President, CanSupport:

**A**s India finds its place in the sun, ironically, a large number of its people will find that the sun has set for them. It is estimated that almost 7 million Indians a year will need palliative care for life limiting conditions. Pain relief will be an important component of such care. The need to bring out a booklet on oral morphine has, therefore, never been greater.

I congratulate CanSupport doctors Ravinder Mohan, Mythily Shivkumar, Pratik Banerjee, Avinash Meshram, Reena Sharma and Pushpa Gaikwad for putting this handbook together. I also thank Dr. Sushma Bhatnagar, Head, Deptt of Anesthesia, Institute Rotary Cancer Hospital at AIIMS for her valuable inputs. Dr. Ambika Rajvanshi, Director of CanSupport's Home Care programme also deserves special mention for guiding this vital initiative every step of the way.

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**GOVERNMENT OF NATIONAL CAPITAL TERRITORY OF DELHI**  
**DRUGS CONTROL DEPARTMENT: F-17, KARKARDOOMA, DELHI-32**

**FOREWORD**

Millions of people are diagnosed with Cancer in India every year in which pain is often severe and sometimes excruciating. Unrelieved pain can not only adversely impact upon the quality of life of the patient, but also affect the family and the community, physically financially and emotionally.

Morphine is an essential drug for cancer pain management. Despite India's heavy cancer burden, it consumes far less morphine than most countries, reasons for which could be any or many. Before the turn of the century, the state licensing system for procurement and distribution morphine preparations was quite complex, making it difficult to procure the said drug leading to avoidable pain.

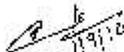
However, in 1998, after becoming aware of prevailing complex licensing procedures which were telling on patient's pain management, a simplified rule model for the medical use opioids was developed. Delhi became one of the 14 states and UTs in India, where simplified rules were adopted, and it has since helped to dramatically increase availability of oral morphine, as much that greater number of healthcare institutions in Delhi, including non-governmental palliative care providers like Can Support, are now licensed to stock and dispense the medication.

The Drugs Control Department, Govt. of NCT of Delhi, recognizes pain management as a human right and takes proactive steps to smoothen the licensing procedures for opioids particularly used by medical fraternity for pain management.

It is my strong belief that in almost every case, patient suffering is unnecessary and mostly preventable. Suffering is inflicted not only by the disease or medication but gets multiplied by medical ignorance, misconceptions and complacency. Opiophobia among Medical Practitioners is compounded by opioignorance. We need to urgently rectify this.

I congratulate CanSupport in developing this guide to remove these misconceptions and bringing out these guidelines in shape of handbook for medical professionals. I am sure this will serve as a power tool and will go a long way in guiding them to safely and effectively prescribe morphine.

It need not be emphasize that the ignorance of pain relief is at the core of the medical ethics and every physician has an obligation to relieve pain and suffering of the patient.

  
( DR. S.S. GHONKROKTA )  
DRUGS CONTROLLER

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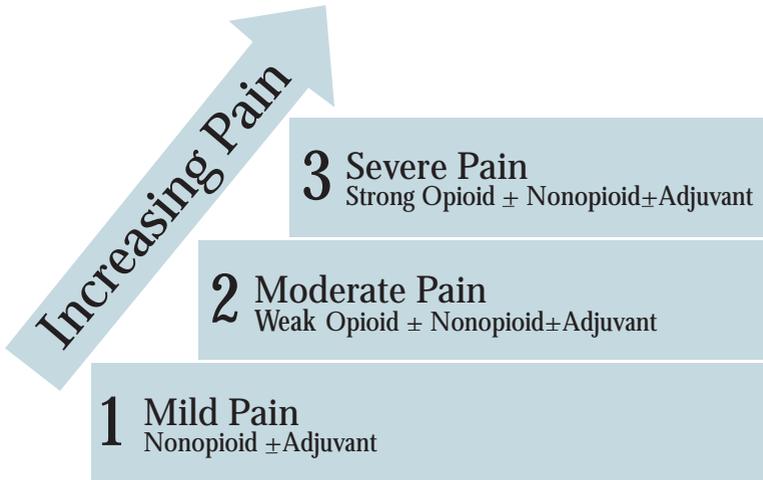
## Introduction

Morphine is the principal derivative of opium, which is found as a juice in the unripe seed pods of the poppy flower, *Papaver somniferum*. Morphine is a potent opiate analgesic psychoactive drug and is considered to be a prototypical opioid. In clinical medicine, morphine is regarded as the gold standard, or benchmark, of analgesics used to relieve moderate to severe pain and suffering. Like other opioids (oxycodone, hydromorphone and diacetylmorphine), morphine acts directly on the CNS to relieve pain.

Morphine was discovered as the first active alkaloid extracted from the opium poppy plant in December 1804 in Paderborn, Germany by Friedrich Strummer. A vast majority of morphine is derived from the poppy pod by traditional method of gathering latex from the scored unripe pods or by processes using poppy straw.

Internationally, morphine is a Schedule I drug under the Single Convention on Narcotic Drugs.

## WHO Analgesic Ladder



1. Non-opioids: Paracetamol, NSAIDs
2. Weak opioids: Codeine, Tramadol
3. Strong opioids: Morphine; Diamorphine/Fentanyl/Hydromorphone
4. Adjuvants: Anticonvulsants, Steroids, Tricyclic antidepressants, Gabapentin & Pregabalin, Muscle relaxants, Anxiolytics, etc.

Opioids exist to be given, not merely to be withheld; their use is dictated by therapeutic need and response, not by the brevity of prognosis.

## Morphine: A Gold Standard Analgesic

The efficacy and safety of oral morphine is well-established in clinical practice. It is indicated in patients with pain which does not respond to the optimized combined use of a non-opioid and a weak opioid (Step-2 of WHO Analgesic Ladder). It is a Step-3 analgesic that is easily titrated to achieve good pain control in combination with a non-opioid and an adjuvant, if required.

In India, oral morphine (Morphine sulphate) is available as:

	Immediate Release Tablets (IR)	Sustained Release Tablets (SR)
Dose	10/20/30/60 mg	10/20/30/60 mg
Onset	30 minutes	60 minutes
Peak	1 hour	3-6 hours
Duration	3-4 hours	12 hours
Dosage	4 hrly (q4h)	12 hrly (q12h)
When to use	-Starting morphine for 1st time -Breakthrough pain	-To reduce dosing frequency once pain control stabilizes on IR

### BRAND NAMES

- Vermor (Verma Pharmaceuticals)
- Duramor (Bio-E)
- MORF (Cipla)
- Morphi Troy (Troikkaa)
- Rumorf (Rusan HC)
- Morphigesic (West Coast Pharmaceuticals)

Remember: Morphine is NOT an over the counter medication and is not to be taken as SOS treatment for pain. Since most patients require medication chronically, it should be given by the clock, by the mouth, by the analgesic ladder and monitored regularly. It can be taken with or without food.

# Guidelines for Using Oral Morphine

## Abbreviations

IR: Immediate Release Morphine    q4h: every 4 hrs    prn: (pro re nata)  
SR: Sustained Release Morphine    q12h: every 12 hrs    as needed

## (A) Starting Oral Morphine

The starting dose of oral morphine is calculated to give a greater analgesic effect than the medication already in use:

- If patient was not on any weak opioid, start on a total daily dose of IR 15-30 mg divided in 4 hrly doses, ie, 2.5 mg to 5 mg q4h.
- If patient was previously receiving a weak opioid, give a total daily dose of IR 30-60mg divided in 4 hrly doses, ie, 5 mg to 10 mg q4h.
- If changing from an alternative weak or strong opioid, calculate the dose as given in the [Equianalgesic Table](#).
- In addition, provide patient with a supply of breakthrough or rescue dose (1/6th of total daily dose) of IR morphine at any time for pain that is not controlled by the regular doses. Encourage a patient to take a breakthrough dose as soon as s/he feels pain to stop it from building up. If patient has to take 2 or more prn doses in 24 hours, increase regular dose by 30-50%.
- Frequently assess pain relief during the opioid titration period. Titrate dose based on the patient's report of pain relief.
- Stop upwards titration of dose when pain is relieved or intolerable adverse effects supervene.
- The aim is to have the patient free of pain and mentally alert.

**Scheme-1: Immediate Release (IR) Morphine**

- Give 4hrly (q4h) regularly 'by the clock' and prn doses of equal amount.
- If pain is not relieved or patient has to take two or more prn doses per day, titrate the dose upwards (even daily, if required) gradually by 30-50% till there is adequate relief throughout each 4hr period.
- A double dose at bedtime obviates the need to wake the patient for a q4h dose during the night.

**Scheme-2: Slow Release (SR) Morphine**

- Begin as for scheme-1.
- When the q4h dose is stable, replace with SR morphine q12h.
- The q12h dose will be three times the previous q4h dose; rounded to a convenient number of tablets.
- Continue to provide IR morphine tablets for prn use; give equivalent of a q4H dose, ie, 1/6 of total daily dose. SR morphine is never used for breakthrough pain.

**Equianalgesic Table**

Dose Comparison with and Conversion from other opioids

Drug	Route	Typical Dose	Total 24hrs dose	Relative potency to oral morphine	Equivalent Morphine 24 hrs dose	4 hrly oral morphine dose
Codeine	Oral		240 mg	1/10	24 mg	4mg
Tramadol	Oral	60mg qd	200 mg	1/5	40mg	6.6 mg
Fentanyl	Patch	50mg qd	-----	150	60 mg	10 mg

## (B) Dealing with Side Effects and Adverse Reactions

It is important to regularly review and assure patients with regard to morphine side effects. The patient should not stop the medicines due to these side effects as they are treatable.

- **Constipation** A chronic side effect which may be more difficult to manage than pain itself. Prescribe laxative and stool softeners to all patients right at the start of morphine therapy unless patient also has diarrhoea.
- **Nausea and Vomiting** - Occurs in about 50% patients on commencing morphine but generally resolves in 5-7 days. Prescribe antiemetic.
- **Sedation/Dizziness/Lightheadedness** - Commonly occurs on commencing morphine or when dose is increased. This usually improves after 3-4 days. If it does not improve, it may be a sign that the morphine dose is too high.
- **Sweating & Itching** Less common side effects.
- **Adverse reactions are rarely encountered, but patient should be aware of:**
  - Slow, shallow or irregular breathing
  - Blue or purple color to skin
  - Fast or slow heart beat
  - Seizures
  - Hallucinations
  - Blurring vision
  - Fainting
  - Hives, rashes, swelling of arms, hands, feet or ankles

### (C) Important Messages for Patients & Family

- Teach the patient and family about the purpose and benefits of opioids. Remove all myths and misconceptions they might have.
- Explain that morphine needs to be continued and taken by the clock even if there is no pain. They should not stop or adjust the dosage of morphine without consulting their treating doctor.
- They should not chew, crush or dissolve SR morphine as it will then behave like an IR preparation.
- The patient should not drive or operate heavy machinery, especially at the start of morphine.
- The patient should not consume alcoholic beverages or preparations containing alcohol while using morphine. Dangerous side effects or death can occur when alcohol is combined with morphine.
- They should not combine morphine with other CNS depressants (e.g., sleep medications, tranquilizers).
- They should keep these medicines in a secure location away from reach of children and mentally retarded people as they may be harmful to those not requiring them.
- They should not give these medicines to any other patients for any other types of pain. It is illegal unless it is prescribed by a doctor.

# Contraindications & Drug Interactions

## When is morphine contraindicated?

### 1. Absolute contraindication

Head injury is the only absolute contraindication to use of morphine. A history of head injury should be asked about.

### 2. Relative contraindications

Before using morphine, ask the patient if he is allergic to any drugs or has:

- Bronchial asthma, COPD, sleep apnea, or other breathing disorders (respiratory insufficiency);
- Liver or kidney disease;
- Urinary retention; enlarged prostate;
- Undiagnosed abdominal pain;
- Epilepsy or other seizure disorder;
- Mental illness (unstable personality);
- Hypothyroidism;
- Addison's disease or other adrenal gland disorders;
- A history of drug or alcohol addiction.

## Which other drugs can affect morphine?

Drug Group	Interaction with Opioids
Sedatives/ hypnotics	Increased central nervous system depression, particularly respiratory depression.
Antipsychotic tranquilizers	Increased sedation. Variable effects on respiratory depression.
MAO inhibitors	Relative contraindication to all opioid analgesics because of the high incidence of hyperpyrexia and hypertension.

## Frequently Asked Questions

### What is a breakthrough or rescue dose of morphine?

The rescue dose is equivalent to a single q4h dose of IR morphine taken in case the patient has pain between 2 regular q4h doses. At the end of the day, the total morphine consumed in 24 hours is divided by six to calculate fresh q4h dosage for adequate pain control.

### What if a dose of morphine is missed?

If the patient misses his dose, he must take the missed dose as soon as he remembers. If it is almost time for the next dose, the missed dose is skipped. Do not use extra medicine to make up for the missed dose.

### Can oral morphine be used in children?

Yes, oral morphine can be safely and effectively used in pain management in children. The doses have to be calculated proportionate to body weight.

### What precautions should be taken in the elderly?

If the patient is frail and elderly, an initial lower and/or less frequent regular dose, eg, 5-10 mg 6 hrly, may be preferable. Thereafter, regularly monitor and titrate until there is adequate relief throughout each 4hr period.

### What if the patient has impaired renal / liver functions?

Due to accumulation of an active metabolite, a lower and/or less frequent regular dose may be preferable in patients with renal/liver function impairment, eg, 5-10 mg 6 hrly.

### Morphine Pregnancy Warnings

Morphine has been assigned to pregnancy category C by the FDA. Morphine may be harmful to an unborn baby, and could cause addiction or withdrawal symptoms in a newborn. No increased risk of congenital malformations has been associated with use of morphine in pregnancy. Morphine should only be given during pregnancy when benefits outweigh risk.

## Morphine Breastfeeding Warnings

Morphine is excreted into human milk in trace amounts and may harm a nursing baby. Morphine should only be given during breastfeeding when benefit outweighs risk.

## What is the maximum dosage of oral morphine?

There is no ceiling or upper limit to the amount of morphine that can be used safely. The more pain a patient has, the more morphine he will usually be able to tolerate. The correct dose for each patient is the dose that takes away the pain without giving unacceptable side effects or toxicity. However, if the patient is taking more than an adequate dose of morphine, he will have drowsiness that does not improve. In such a case, decrease the dose of morphine by 50% and titrate after review.

## Can/How do we wean off a patient from oral morphine?

Yes, we can. The WHO pain management ladder allows us to go both UP and DOWN the ladder. A reduction in dose may be required if the patient's pain ameliorates, for e.g., as a result of cancer treatment. Just as the dose was built up slowly, it must be reduced gradually. However, if the dose is reduced quickly, withdrawal symptoms can develop: the patient may suffer from anxiety, perspiration, yawning, crying, running nose, muscle twitching, cold flashes, loss of appetite, intestinal cramps, insomnia, vomiting, diarrhoea, involuntary urination and ejaculation and increased sensitivity to pain.

## What to do in case of accidental overdose of morphine?

This can be fatal. The patient is to be admitted to a hospital setting and treated with naloxone (antidote) and supportive measures.

## Are there limitations of morphine in pain relief?

Morphine is not the panacea for pain. Inadequate pain response to morphine occurs in bone pain, neuropathic pain, muscle spasms, abdominal cramps, etc. Adjuvant analgesics improve the management of the above mentioned pains with the inclusion of morphine. Interventional management (blocks, spinal medications, surgery, etc.) may be required. However, even combined use does not guarantee success, particularly if the psychosocial dimensions of suffering are ignored.

# Morphine Myths

## *Myth # 1*

### Morphine causes addiction

Cancer patients taking oral morphine for pain control are NOT psychologically dependent on the drug.

## *Myth No. 2*

### Morphine causes harmful respiratory depression

Pain is a physiological antagonist of the central depressant effects of opioids. Morphine does not cause clinically significant respiratory depression in patients in pain, if titrated properly.

## *Myth No. 3*

### Morphine causes excessive sedation

Morphine, if titrated properly, will not cause over sedation. An initial drowsiness can occur that almost always resolves after a few days.

## *Myth No. 4*

### Dose of morphine cannot be increased beyond a certain level

There is no ceiling or upper limit to the amount of morphine that can be used safely. The titration of morphine is done according to the severity of pain.

## *Myth No. 5*

### Morphine should only be started when pain is very severe

There is no need to wait until pain is severe to start morphine. It is generally indicated in patients with pain that does not respond to the optimized combined use of a non-opioid and a weak opioid.

## *Myth No. 6*

### Starting morphine means that the end is near

It is not the stage of a terminal illness but the degree of pain which dictates when morphine should be started.

## *Myth No.7*

### Morphine has a lot of side effects

All opioids cause nausea, drowsiness and constipation. However, these side effects disappear after 4-5 days except for constipation which can be easily managed through stool-softeners and laxatives.

## *Myth No. 8*

### Morphine hastens death

There is no evidence that morphine hastens death when properly titrated to the patient's pain. If death does occur soon after a dose of morphine is given, death would most likely have come anyway, and morphine allowed the patient to experience death with more comfort.

## *Appendix 1a*

### MORPHINE PHARMACOKINETICS

#### Absorption:

Morphine is absorbed through the subcutaneous, intramuscular and oral routes. There is a first pass effect of morphine which may be the reason for the drug not reaching satisfactory serum levels.

#### Distribution:

The drug rapidly leaves the blood compartment and enter highly vascular organs in very high concentrations such as the brain, lungs, liver, kidney and spleen. The muscles usually have a lower level of concentration of morphine but they act as the main reservoir.

#### Metabolism:

Morphine is metabolised in the liver by glucuronide conjugation. Most of the morphine metabolites are polar in nature and hardly cross the blood-brain barrier. Morphine-3-glucuronide (M3G) compound is neuro-excitatory which is not mediated through the mu receptors. The morphine-6-glucuronide has a 4-6 times analgesic potency compared to morphine. Plasma  $t_{1/2}$  life of morphine is 2-3 hours approximately. The withdrawal signs are within 6-10 hours after the last dose and usually peak within 36-48 hours. After 5 days, most of the withdrawal symptoms rebate but some may linger for months.

#### Excretion:

Glucuronide conjugates are excreted though the urine. Elimination is almost complete in 24hrs and is non- accumulative.

## Appendix 1b

### MORPHINE PHARMACODYNAMICS

Opioid receptor subtypes; their functions, and their endogenous peptide affinities:

Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
$\mu$ (mu)	Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed GI transit; modulation of hormone and neurotransmitter release	Endorphins; enkephalins and dynorphins
(delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins; endorphins and dynorphins
(kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed GI transit	Dynorphins; endorphins and enkephalins

- All the three receptors are present in the dorsal horn of the spinal cord.
- In the ascending pathway, morphine has a direct inhibitory effect on the excitatory neurons.
- Systemic action of morphine acts in the brain also. This is partly due to the release of endogenous opioid peptides that in themselves lead to partial analgesia. The other action may be due to the direct action of morphine on the  $\mu$  receptors which stimulate the release of endogenous opioids that may act on the  $\delta$  and  $\kappa$  receptors in the brain.
- Peripheral actions of morphine may be observed through the  $\mu$  receptors present outside the inflammation.

## Appendix 2

### PROCURING ORAL MORPHINE IN DELHI

- (A) CanSupport (for Cancer Pain Management) 011-2671 1212  
(B) Pain Clinic, Institute Rotary Cancer Hospital, AIIMS 011-26588500  
(C) Chemist Shops (use Form DD-12 in Appendix 3 to prescribe morphine)

#### Chemist Shops with License for Storing & Selling Morphine in Delhi



The map shows the outline of Delhi with several callout boxes pointing to specific locations. The callouts are arranged around the map, with some on the left side and others on the right side. Each callout box contains the name of a chemist shop, its address, and its phone number.

**SUPER MEDICOS**  
3446, Delhi Gate  
Behind Telephone Exchange  
Ph: 23266332, 20212796

**SHUBHAM MEDICOS**  
402, Laxmi Tower, 4th Floor,  
Azadpur, Delhi-110 033  
Phone: 92124 09004

**SANYOG ENTERPRISES**  
2/3 & 4, Roop Nagar, Delhi-07  
Ph: 42821374

**SANYOG ENTERPRISES**  
9810, 2nd Floor, Express Plaza  
LSC Derawal Nagar

**SUDESH KUMAR & BROS**  
F-25/8, Old Rajinder Nagar

**GEMINI THERAPUTICS**  
J-3/188-B, Nehru Market  
Rajouri Garden  
Ph : 25417501, 9811211309

**BHATIA MEDICARE**  
Shop #26, A-5, DDA Market,  
Paschim Vihar  
Ph 25252752, 9810655645

**RAM MEDICOS**  
RZ-109, Indra Park, Uttam  
Nagar Ph: 9911331093

**DHIITI BIOTEC**  
SC 08, Jeewan Jyoti Complex, 3A  
Main Road, Madanpur Khadar

**PSRI DRUG STORE**  
PH-2, Press Enclave Marg  
Sheikh Sarai  
Ph: 30611700, 30611900, 30611999

**NEW DELHI MEDICOS**  
Shop 12-15, Old RK Ashram Marg  
Behind RML Hospital  
Ph: 98101 23218

**KRISHNA CHEMIST**  
Shop 5, Old R K Ashram Marg,  
Behind RML Hospital,  
Ph: 23365588, 9811736671

**ALBINO**  
Shop 8, CSC Market, Pocket-E,  
Opp GTB Hospital  
9810363890

**MITTAL MEDICOS**  
383/11-C, East Azad Nagar  
Ph: 22094448

**TRIVENI MEDICOS**  
C-39, Opp Swaran Cinema,  
East Krishna Nagar  
Ph: 22090518, 9811335339

**BATRA MEDICAL CENTRE**  
F5/10, Mandir Marg, Krishna  
Nagar  
Ph: 65637930, 9891379996

**VIMHANS PHARMACY**  
1, Institutional Area, Nehru  
Nagar Ph: 29832999, 29841389

**IMPEX INDIA**  
E-182, Krishna Market, Lajpat  
Nagar-I

**IMPEX INDIA**  
8/3, 1st Floor, Yusuf Sarai  
Ph: 28866058, 9910486274

**SOUTH DELHI MEDICOS**  
Shop# 26, Safdarjung Hospital  
Gate  
Ph: 26164570, 9313198637

**CGHS Dispensary Zonal  
Office, Sector 8 RK Puram**  
Ph: 26176205, 26175306



## *Appendix 4*

### INTERESTING FACTS ABOUT MORPHINE

- Morphine originates from the word Morpheus, The Roman God of Dreams and the son of Somnus, the God of sleep.
- The poppy flower has been cultivated in India from the 10th century onwards. After independence, the government of India began to check and monitor its production and usage. It is now cultivated in Rajasthan, UP MP, Punjab and HP.
- India is the only country authorized by the UN Single convention on Narcotic drugs to produce gum opium.
- India produces about half the opium utilized by the world's pharmaceutical industry to produce codeine, morphine, narcotine, thebaine, papaverine and other medical products.
- The US buys 80% of legal opium from India.
- Morphine is cheap but people in poorer countries often do not have access to it.
- With the projected rise in cancer patients in India in the coming years the need for the drug is going to be huge.

### LICENSING PROCEDURES

At present, in the majority of India states, procedures to get a license for morphine are cumbersome and require medical institutions and palliative care units to obtain import, export and transport licenses as well as to interact with at least two departments of the state government Health and Excise. Usually by the time one license is granted, the other has expired. A few states and union territories have adopted simplified licensing procedures, reducing the number of licenses that are required and transferring the authority for issuing licenses from the State Excise Department to the Drugs Controller in the Department of Health. These are Delhi, Haryana, Kerala, Madhya Pradesh, Orissa, Sikkim, Tamil Nadu and Tripura. Licenses, once procured, must be kept active and valid.

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- Robert Twycross, Introducing Palliative Care.
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# Notes

According to a 2005 estimate by the International Narcotics Control Board, six countries (Australia, Britain, Canada, France, Germany and the US) consume 80% of the world's morphine. The less affluent countries accounting for 80 % of the world's population (including India), consume only about 6 percent of the global morphine supply despite their heavy cancer burden.

India supplies much of the opium to make morphine for increasing use in the rest of the world, but produces very little for domestic use, due to lack of demand. Experts in pain management attribute the under-distribution of morphine to an unwarranted fear of the drug's potential for addiction and abuse. Lakhs of patients in India die in severe pain because doctors lack the competence and confidence in prescribing morphine.

This handbook has been written to empower physicians to manage moderate to severe pain not responding to an optimal combination of non-opioids and weak opioids. We hope it will guide your hand to choose to prescribe morphine confidently and relieve a person from physical suffering.

Please contact us if you require any further information or training in pain management and palliative care.

Central Resource Team  
CanSupport

**Among the remedies which Almighty God has given to man to relieve his sufferings, none is as universal and efficacious as opium.....**

**Thomas Sydenham**



## **CANSUPPORT**

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email: [info@cansupport.org](mailto:info@cansupport.org)

CanSupport is a Delhi-based organization that has been providing free home based palliative care services to cancer patients and their families in Delhi and the NCR since 1996. Our mission is to enable people with advanced cancer and their families to make informed choices and decisions and to receive appropriate physical, emotional, social and spiritual support.

Cover Credit: Poppy pods painting by Lorrie Herman



**CanSupport Helpline**

**011-26711212**

**Monday to Friday 9.30am to 5.30pm**