

CNS Depressants:

General anaesthetics
Opioid analgesics
Ethyl alcohol
Sedative - hypnotics

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Sedatives: those drugs that decrease activity, moderate excitement & exert a calming effect

Hypnotic: produces drowsiness & facilitates a state of sleep (resembling natural sleep)

Alcohol: refers to ethyl alcohol (C_2H_5OH)

Inebriant poisons: produce intoxication \Rightarrow light-headedness, confusion, disorientation, & drowsiness

\rightarrow transparent, colourless, volatile liquid

\rightarrow Absolute alcohol \Rightarrow 99.95%

Rectified spirit \Rightarrow 90%

Denatured alcohol \Rightarrow 95% alcohol + 5% wood naphtha.

\rightarrow Ethanol is produced by fermentation of sugar by yeast.

\rightarrow Proof spirit: which at $10.5^{\circ}C$ weighs exactly $12/13$ part of an equal measure of distilled water.

\rightarrow 1 standard drink = 45 mL of distilled spirit (15 g of alcohol)

= 150 mL of wine (11 g of alcohol)

= 350 mL of beer (13 g of alcohol).

\rightarrow Safe limits for drinking per week (to avoid liver damage) \Rightarrow 210 g alcohol in men

\Rightarrow 140 g alcohol in women

\rightarrow Concentration of alcohol in common beverages:

Vodka 60-65%

Rum, liqueur 50-60%

Whisky, brandy, gin 40-45%

Port, Sherry 20%

Wine, Champagne 10-15%

Beers 4-8%

Absorption: alcohol requires no digestion prior to absorption.

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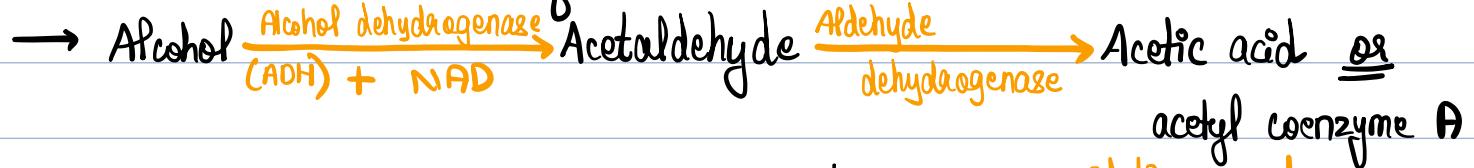
- maximum absorption from small intestine
- alcohol can be detected in blood within 2-3 minutes of swallowing.
- maximum concentration is reached within 45-90 minutes.
- carbonated drinks ↑ absorption (∴ bubbles greatly increase the surface area)
- Factors delaying alcohol absorption ⇒ food ingested with alcohol.
- Habituated heavy drinkers absorb alcohol more rapidly (due to ↑ in liver enzymes until liver damage develops)

Distribution:

Sample	Relative concentration
Whole blood	1
Plasma / serum	1.12 - 1.2
Brain	0.85
Spinal fluid	1.1 - 1.27
Vitreous	1.2
Urine	1.3
Liver	0.85
Alveolar air	0.0021

- alcohol passes easily through BBB to exert central effects
- alcohol also crosses the placenta & can be found in foetal circulation.

Metabolism: ~90% of alcohol absorbed is oxidised in the liver



→ Fructose $\Rightarrow \uparrow \uparrow$ alcohol metabolism

→ Alcohol disappears at the rate of 15 mg / 100 mL / hour from blood.

Activity: well-known stimulant ; selective depressant for higher nervous centres.

→ Order & dose required to affect CNS:

i) Frontal lobes (sensitive to low concentrations) \Rightarrow mood changes

ii) Occipital lobes \Rightarrow visual disturbances

iii) Cerebellum \Rightarrow loss of coordination of movements (gait instability)

→ self-inhibition \downarrow , self-confidence $\uparrow \uparrow$ \Rightarrow unrestrained behaviour

→ Increasingly fatal concentrations \longrightarrow depression of vital centres in mid-brain & medulla \longrightarrow cardiorespiratory failure \longrightarrow death

→ generalised vasodilatation (especially in the skin)

→ \uparrow sexual drive but poor performance \therefore not a true aphrodisiac

→ hypnotic, diaphoretic

→ low concentrations: \uparrow HR

concentration $\geq 300 \text{ mg \%}$: \downarrow HR

→ \uparrow appetite, \uparrow salivation, \uparrow secretion of gastric juice.

→ Diuretic (secondary to inhibition of ADH release from posterior pituitary)

→ Moderate consumption (15-30 g / day) \Rightarrow \uparrow HDL, \downarrow LDL

→ *In vino veritas* \Rightarrow In wine, there is truth.

Cause of Death: i) Direct depression of respiratory centre in the brainstem or
ii) Aspiration of vomit.

Symptoms (of Acute Alcohol Intoxication): 3 stages

I] Stage of Excitement: feeling of well-being & excitation

→ lowering of inhibition, ↑↑ confidence, ↓↓ self-control.

Blood Alcohol Concentration (BAC)	effect
0 - 50 mg %	Mild euphoria
50 - 100 mg %	↓ inhibition, ↑ self-confidence, ↓ attention-span, slurring of speech, mild incoordination, alcohol gaze nystagmus.
100 - 150 mg %	Mental confusion, emotional instability, loss of judgement, impaired memory, sleepiness
150 - 300 mg %	Loss of muscular coordination, staggering gait, mental confusion, decreased pain response, disorientation.
300 - 400 mg %	Stupor, marked incoordination, possibly coma.
≥ 400 mg %	Anaesthesia, depression of responses, respiratory failure, deep coma, death.

II] Stage of Incoordination: BAC = 150 - 250 mg %

→ sense perception & skilled movements are affected

→ incoordination in fine & more skilled movements.

→ nausea, vomiting

→ breath smells of alcohol.

→ flushing of face, pulse is rapid, ↑ HR.

III] Stage of Coma: slurring & thickening of speech

- patient is giddy, staggers & falls.
- stertorous breathing
- subnormal temperature
- pupils are contracted, but stimulation of the person (pinching/slapping) causes them to dilate with slow return \Rightarrow Mc Ewan Sign.
[Occurs $\geq 300 \text{ mg\%}$]

Micturition Syncope: usually occurs after heavy beer drinking

- when person rises from bed in the middle of the night \Rightarrow loss of consciousness during the act of urination

Munich beer heart: cardiac dilatation & hypertrophy

Recovery: coma gradually lightens into deep sleep

- patient usually recovers in 8-10 hours
- patient wakes up with acute depression, nausea, abdominal discomfort, irritability, lethargy, severe headache \Rightarrow hangover

Fatal Dose: 150-250 ml of absolute alcohol consumed in 1 hour

Fatal Period: 12-24 hours

Tolerance to alcohol: acquired phenomenon

- restricted by liver damage
- a person who is habituated to consuming alcohol daily can drink alcohol without getting 'drunk' in quantities which would seriously affect a person unaccustomed to taking it.

Treatment of Acute Alcohol Intoxication:

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- (i) Gastric lavage (only when patient is brought soon after ingesting alcohol, which is rare)
- (ii) Maintain patent airway.
- (iii) Prevent aspiration of vomitus.
- (iv) Tracheal intubation & positive pressure respiration if required.
- (v) Maintenance of fluid & electrolyte balance
- (vi) Correction of hypoglycemia by glucose infusion till alcohol is metabolized
- (vii) Thiamine (100 mg in 500 mL glucose solution infused i.v.).
- (viii) Haemodialysis hastens recovery.
- (ix) Insulin + fructose drip accelerates alcohol metabolism

Management of Addiction / withdrawal syndrome:

- Psychological & medical support
- Benzodiazepines are the preferred CNS depressant
- Naltrexone: - weakens reinforcing effects of alcohol
 - helps prevent relapse of alcoholism by reducing alcohol craving.
- In patients who sincerely desire to leave drinking habit ⇒ Disulfiram

aversion therapy:

- (i) Make sure that patient has not consumed alcohol in the last 12 hours
- (ii) Disulfiram 500 mg/day for 1 week followed by 250 mg/day
- (iii) Sensitization to alcohol develops 2-3 hours after 1st dose & lasts for 7-14 days after stopping it (∴ inhibition of aldehyde dehydrogenase with disulfiram is irreversible & fresh enzyme is required for return of activity)

(iv) Distressing symptoms that appear on drinking (Aldehyde Syndrome):

- Flushing, burning sensation, throbbing headache, perspiration, uneasiness, tightness in chest, dizziness, vomiting, visual disturbances, confusion, postural fainting, circulatory collapse.

Conditioned Reflex Treatment: giving alcoholic beverages to the patient in surroundings that affect his visual & olfactory senses.

→ Various types of liquor + drugs causing immediate nausea & vomiting
given together.

→ After 5-8 days of daily treatment \Rightarrow symptoms are brought on just by sight of a bottle \longrightarrow patient mentally associates his painful sickness with alcohol.

Postmortem Appearances:

Acute Intoxication: alcoholic odour on opening of body cavities.

→ acute inflammation of stomach with a coating of mucus.

→ Brain, liver, lungs: congested

→ Smell of alcohol in viscera

→ blood is fluid & dark.

→ Brain & meninges \Rightarrow oedema & congestion

→ cloudy swelling of parenchymatous organs.

Chronic poisoning:

→ signs of malnutrition may be present.

→ gastric mucous membrane: deep reddish-brown with patches of congestion/effusion; hypertrophied

→ liver: congested, enlarged, shows fatty infiltration (weight may exceed 2 kg)

- surface is pale & greasy

- patchy yellowish areas may be seen within normal hepatic parenchyma.

- later \Rightarrow cirrhosis occurs with 5-10 mm nodules \longrightarrow liver becomes smaller

- contracted to a hard greyish-yellow block of 800-1200 g.

→ kidneys: granular degeneration

→ Heart: dilated, fatty degeneration, patchy fibrosis.

Drunkenness: condition produced in a person, who has taken alcohol in a quantity sufficient to cause him to lose control of his faculties to such an extent, that he is unable to execute safely, the occupation in which he was engaged at the particular time.

Examination:

1] Consent

2] Exclusion of Injuries & Pathological States: Exclusion of head injuries is important.

- Conditions simulating alcohol intoxication:
 - Severe head injuries
 - Hypoglycaemia, Hyperthyroidism, Uraemia
 - Drugs: insulin, barbiturates, morphine, atropine, antihistamines, tranquilizers
 - General paresis
 - High fever
 - Exposure to CO

3] History: related events, amount & type of liquor, ongoing medical treatment for any disease/disability.

4] General behaviour:

- i) General manners
- ii) State of dress
- iii) Speech: thick, slurred
- iv) Self-control

5] Memory & Mental Alertness: memory of recent events

6] Handwriting: ask the patient to copy a few lines of text

- Note - time taken
- ability to read his own writing.
- repetition/omission of words

→ Ask patient to sign & compare with that on his driving licence (if any)

7] Pulse: usually rapid, full & bounding

8] Temperature: surface temperature is usually raised

9] Skin: dry/moist, flushed/pale

10] Mouth: tongue is dry/bitter, smell of breath

11] Eyes:

i) General appearance

ii) Gross defects in visual acuity

iii) Pupils - dilated/contracted

- Reaction to light

iv) Extrinsic muscles - convergence - nystagmus - strabismus

12] Ears: - gross impairment of hearing

- abnormality of tympanic membrane

13] Gait: - manner of walking

- reaction time to turn in a particular direction

- manner of turning

14] Stance: Romberg's sign

15] Muscular coordination: - finger nose test

- finger to finger test

- unbuttoning & rebuttoning

16] Reflexes: - Knee } delayed/sluggish
 - Ankle }

17] Examination of Systems: - CVS

- RS

- GIT

18] Laboratory Investigations: concentration of alcohol in blood, wine, saliva, breath.

→ wine alcohol concentration about 25% higher than in blood collected at the same time \Rightarrow diagnostic.

→ Methods for determining Blood Alcohol Concentration (BAC):

- Kozelka & Hine test (macro-method)
- Cavett test (micro-method).

Widmark formula: $a = p \cdot c$

$$\left\{ \begin{array}{l} a = \text{weight of alcohol (in g.) in the body} \\ p = \text{body weight (in kg.)} \\ r = \text{constant (men: 0.68 ; women: 0.55)} \\ c = \text{blood alcohol concentration (in mg/kg)} \end{array} \right.$$

For urine: $a = \frac{3}{4} p \cdot q$.

→ Collection of Blood: alcohol (spirit) must not be used to clean the skin \Rightarrow

use mercuric chloride or soap & water.

- Preserve 10 mL of blood with 100 mg sodium fluoride & 30 mg potassium oxalate.

Breath Test: Based on Henry's Law: when a volatile chemical (ethanol) is dissolved in a liquid (blood) & is brought to equilibrium with air (alveolar air), there is a fixed ratio between concentration of volatile compound (ethanol) in air (alveolar air) & its concentration in liquid (blood) [constant at a given temperature]

Urine Test:

[time for equilibrium: 25 mins]

→ urine: blood = 1.25 : 1 (when urine & blood are in equilibrium)

→ analysis of 2 samples is required (25-30 minutes apart)

→ if $p_m \text{ BAC} > p_m \text{ urine alcohol level} \Rightarrow$ subject is in absorptive phase.

Medical Terminology:

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$< 10 \text{ mg \%}$	Sober
$10-80 \text{ mg \%}$	Drinking
$80-150 \text{ mg \%}$	Under the influence
$150-300 \text{ mg \%}$	Drunk or Intoxicated
$300-400 \text{ mg \%}$	Stupor
$\geq 400 \text{ mg \%}$	Coma & death.

Alcohol Withdrawal:

- symptoms appear 12-48 hours after reduction in alcohol intake.
- most common symptom: tremors / shakes.
 - nausea & vomiting
 - malaise, weakness
 - hypertension, tachycardia, sweating
 - anxiety, depression, irritability
 - transient hallucinations
 - headache, insomnia
- 1/3 of these patients develop delirium tremens unless preventive measures are taken.

Treatment: 20mg chlordiazepoxide or 100mg diazepam, QID

Delirium Tremens: results from long-continued action of poison on brain.

- occurs in chronic alcoholics due to:
 - temporary excess
 - sudden withdrawal of alcohol
 - shock after injury
 - acute infection (pneumonia, influenza, erysipelas)

→ typically begins 72-96 hours after the last drink.

→ acute attack of insanity • coarse muscular tremors of face, tongue & hands

- insomnia
- restlessness
- loss of memory
- psychomotor agitation
- confusion
- disorientation
- uncontrollable fear
- homicidal / suicidal tendency
- diarrhoea
- dilated pupils
- fever
- tachycardia, tachypnoea
- disorientation to time, place & person

→ death occurs in 5-15% cases due to cerebral oedema / cardiac failure / shock.

→ diazepam is given to control agitation.

Hazards of Alcohol:

→ domestic violence, child abuse, suicide

→ d/e of exposure

→ pneumonia, choking

→ ↓ resistance to hypoxia

→ falls & injuries, fall in water

→ accidental poisoning

→ Saturday night palsy.

→ RTA ⇒ due to - ↑ reaction time

- false confidence

- impaired concentration

- poor judgement

- decreased muscular coordination

- blurring of vision.

- In India, according to sec. 185 Motor Vehicle Act 1988, statutory limit of BAC is 30 mg %.

- Punishment for 1st offence: ₹ 2000 ± 6 months imprisonment.

- Punishment for 2nd offence: ₹ 3000 ± 2 years imprisonment.

Methyl Alcohol: (wood alcohol)

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→ colourless, volatile liquid, odour similar to ethanol, burning taste.

Signs & Symptoms: (of drunkenness) inebriation is not prominent (unlike ethanol)

- nausea, vomiting
- dizziness
- marked muscular weakness
- hypothermia
- severe pain / cramps in abdomen
- neck stiffness
- delirium, coma
- confusion
- depressed cardiac function
- headache
- vertigo
- fixed, dilated pupils

→ urine is strongly acidic, may contain acetone & traces of albumin.

(due to inhibitory effect on oxidative enzyme system)

→ severe non-diabetic anion gap metabolic acidosis in unconscious person is suggestive of methanol poisoning.

- Optic effects:
- photophobia
 - central & peripheral scotomata
 - complete blindness (due to optic neuritis & atrophy by formic acid)
 - blurred/misty (snowfield) vision
 - ↓ light perception

10-20 mL of methanol can cause blindness.

Fatal Dose: 60-200 mL

Fatal Period: 24-36 hrs

Absorption: methanol is rapidly absorbed from stomach & intestine, lungs, skin

→ rate of oxidation of methanol is 1/5 that of ethanol.

→ dangerous level of methanol: 80 mg/dL.

→ methanol is oxidized in the liver to more toxic formaldehyde which is in turn oxidized to formic acid.

Cause of Death: — mainly due to: acidosis (due to production of organic acids)
— minor factor: CNS depression.

Treatment:

i] Gastric lavage using 5% bicarbonate solution

ii] Activated charcoal

iii] Antidote = Ethanol. (ethanol competes with methanol for oxidation by catalase \rightarrow reduced formation of formaldehyde) \Rightarrow competitive inhibition.

\rightarrow 10% solution i.v. starting with 500 mL

\rightarrow repeated as required until blood level falls below 25 mg %

\rightarrow serum ethanol levels must be checked frequently & maintained at 100-150 mg %.

iv] Haemodialysis \Rightarrow Treatment of choice in severe poisoning (no role of peritoneal dialysis)

v] Formipezole (4-methyl pyrazole/4MP): 15 mg/kg followed 12 hours later by 10 mg/kg 12th hourly for 4 doses

\rightarrow competitive inhibitor of alcohol dehydrogenase

vi] Folinic / folic acid: 50-75 mg every 4th hourly

vii] Blood sugar must be maintained since ethanol frequently causes hypoglycemia.

viii] Crystallloid therapy

ix] Dextrose

x] Thiamine

xi] Phosphate

xii] Sodium bicarbonate i.v. to correct metabolic acidosis.

xiii] Eyes should be kept covered to protect them from light.

xiv] Keep the airway clear.

Postmortem Appearances:

- marked cyanosis
- postmortem clotting of blood is absent.
- skin may be purple (due to pyridine)
- mucous membrane of stomach & duodenum ⇒ congested, inflamed.
- small &/or large intestine ⇒ contracted resembling a thick pipe with a very narrow lumen.
- lungs: congested, oedematous
- brain: oedematous, local haemorrhages. (haemorrhage in putamen)
- mucosa of bladder ⇒ congested.
- liver: fatty change, early necrosis.
- kidneys: tubular degeneration.

MLI:

- poisoning is mostly accidental.
- may be used to produce intoxication when ethyl alcohol is not available.

Opium: dried juice of poppy (*Papaver somniferum*).

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- flowers are white
- each plant bears 5-8 capsules → unripe capsule is incised & the white juice is collected & allowed to evaporate to obtain opium.
- Poppy seeds (khas khas) ⇒ white, harmless, demulcent, nutritive.
- Alkaloids in crude opium:
 - i) Phenanthrenes: • morphine • codeine • thebaine } ⇒ narcotic.
 - ii) Isoquinolines: • papaverine • narcotine } ⇒ mild analgesic.
- Morphine: white powder / white shining crystals
 - bitter taste
 - alkaline reaction

Classification of Opium:

- 1] Natural: • Morphine • Codeine
- 2] Semi-synthetic: • Heroin • Oxy codon
- 3] Synthetic: • Meperidine (pethidine) • Fentanyl • Methadone

Action: opiates are similar in action to natural substances ⇒ endorphine.

- opiates activate receptor sites normally occupied by the natural opiates or endorphine.
- depression of all centres except oculomotor, vomiting, sweating
- peripherally-acting analgesic.
- stimulates non-propulsive rhythmic contraction of small intestine.
- act synergistically with alcohol, barbiturates.

<u>Fatal dose</u> : Opium	2g	(fentanyl is 50-100 times more potent than morphine).
Morphine	0.2g	
Codeine	0.5g	

Fatal Period: 6-12 hours.

Signs & Symptoms:

- contact of morphine with the skin of sensitive people \Rightarrow erythema, urticaria,
- CNS: stimulation \longrightarrow depression \longrightarrow paralysis. itching dermatitis.

1] Stage of Excitement: short duration (may be absent if large doses are taken).

- ↑ sense of well-being
- talkativeness
- flushing of face
- ↑ mental activity
- restlessness
- excitement
- freedom from anxiety
- hallucinations
- maniacal condition

2] Stage of Stupor:

- headache
- nausea, vomiting
- sense of weight in the limbs
- giddiness, drowsiness
- incapacity for exertion

→ subject lies motionless with eyes closed (as if in a deep sleep)

→ contracted pupils, cyanosed face & lips.

→ itching sensation is felt all over the skin.

3] Stage of Coma: deep coma (patient cannot be aroused).

→ muscles: flaccid & relaxed

→ all reflexes are abolished.

→ pale face, congested conjunctivae, pin-point pupils (pupils do not react to light, but dilate during the agonal asphyxial phase caused by respiratory depression)

→ all secretions are suspended (except sweat \Rightarrow ↑ perspiration).

→ skin is cold, temperature is subnormal.

→ ↓ BP, ↓ pulse rate, ↓ respiratory rate

Differential Diagnosis:

- barbiturate poisoning
- carbonic acid poisoning
- carbon monoxide poisoning

- opium poisoning
- epileptic coma
- Uraemic coma
- cerebral haemorrhage
- acute alcohol poisoning
- brain trauma
- Encephalitis, meningitis
- Heat hyperpyrexia

Treatment:

- 1] Wash the stomach thoroughly with 1:5,000 KMnO₄ (leave some of the solution in the stomach)
- 2] Tablespoon suspension of charcoal
- 3] Intestines should be cleared out by enema BD for 2 days
- 4] Establish adequate airway.
- 5] Atropine is not recommended (it causes paralysis of sensory & motor nerves like morphine)
- 6] Naloxone hydrochloride \Rightarrow **specific opioid antagonist** (competes with opioids at receptor sites \Rightarrow reverses the actions of opioids)
 - 2 mg i.v. \Rightarrow if there is respiratory depression \rightarrow Repeat every $\frac{1}{2}$ - 1 min upto a total dose of 10-20 mg.
 - In opioid overdose \Rightarrow continuous infusion 0.4 - 0.8 mg / hour upto 48 hours.
- 7] Nalmefene (longer duration of action than naloxone) \Rightarrow 0.1 mg i.v.
- 8] Coma cocktail: in comatose patients where the identity of the poison is not known.
 - 100 mL 5% glucose
 - 100 mg thiamine
 - 2mg naloxone i.v
- 9] Dextrose 50 mL of 50% solution i.v. & thiamine 100 mg.
- 10] Physostigmine 0.04 mg/kg i.v. (to reverse respiratory depression \Rightarrow if naloxone is not available).
- 11] Amiphenazole 20-40 mg i.v.
- 12] Analgesics (amphetamine / caffeine / ephedrine) may be given.
- 13] Long-term management: Buprenorphine, LAAM.

PM Appearances: signs of asphyxia are prominent.

- cyanosed face, nails
- froth at mouth, nostrils
- smell of opium on opening the chest (disappears when putrefaction sets in).
- congested trachea & bronchi with froth
- lungs are oedematous & congested
- blood is usually dark & fluid.

Opium rapidly disappears from the cadaver.

Marquis' Test: 1 drop of mixture of (3 mL conc. H_2SO_4 + 3 drops of formalin) + fragment of the suspected residue \rightarrow purple-red colour \rightarrow violet \rightarrow blue.

Chronic Poisoning [Morphinism / Morphinomania]:

→ habit of morphine use is acquired by young adults as it is believed to be an aphrodisiac (produces a sense of euphoria).

→ opium addict can tolerate 3-6 g / day.

- dry skin
- tattooing from needles
- abscesses or scars of healed abscesses

→ initially \Rightarrow euphoria

repeated large doses \Rightarrow disinterest & recurring episodes of depression.

→ restlessness, irritability, disturbed sleep.

→ loss of memory, mental fatigue, gradual intellectual deterioration.

→ hallucinations may occur

→ constipation, anorexia, emaciation, weakness

→ impotence is frequent.

Treatment:

- 1] gradual withdrawal of drug
- 2] Methadone: 30-40 mg daily (tapered off gradually)
- 3] Dihydrocodeine / codeine
- 4] Propranolol 80 mg (to relieve anxiety & craving)
- 5] Tranquillizers / sedatives at bed time.
- 6] Psychiatric counselling.

Meperidine / Pethidine: colourless, crystalline powder, bitter taste.

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→ analgesic, antispasmodic, sedative properties.

Action: acts on the cerebrum → analgesia, sedation.

Fatal dose: ~ 2 gm.

Fatal period: 24 hours

Symptoms: similar to those of morphine.

→ greater elation than morphine.

Treatment: same as that for opium.