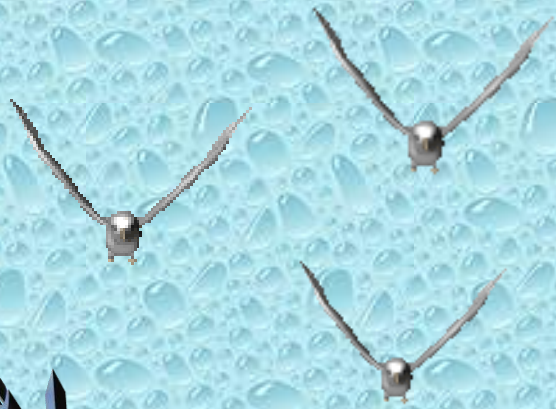

بسم الله الرحمن الرحيم

Opioid analgesics

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opioid

- All compounds related to opium
- Opium derived from opos, Greek word of juice, juice of opium poppy, Papaver somniferum

Opiates

- Drugs derived from opium.
- Included the natural products morphine, codeine and thebaine and semisynthetic derivatives.
- Narcotic derived from the Greek word of stupor, now became associated with opioids.

Source &composition of opium

- Papaver somniferum
- 20 alkaloids: phenantherenes morphine 10%, codeine 0.5%, thebaine 0.2% and benzylisoquinolines papaverine (smooth muscle relaxant) 1% and noscapine 6%.

History

- The first reference to opium is found in writing of Theophrastus 300BC.
- In 1680, Sydenham wrote “among remedies which it has pleased God to give to man to relieve his sufferings, none is so universal and so efficacious as opium”.

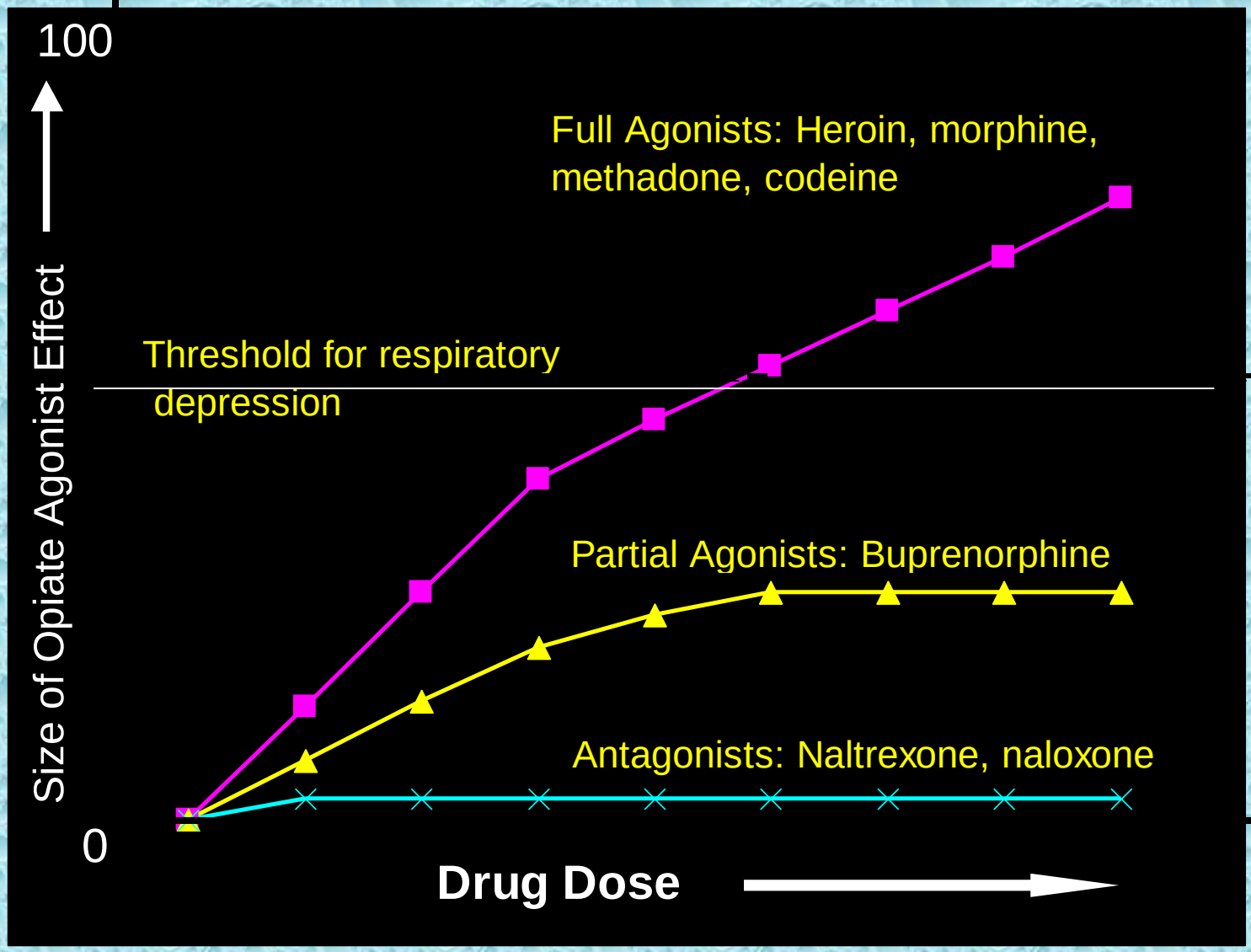
- Opium contains > 20 alkaloids.
- A pure substance from opium isolated in 1806 called morphine, after Morpheus (Greek god of dreams).
- Then codeine and papaverine were isolated.

- Until early 1970s endogenous opioid system was unknown.
- Mechanisms of action of opioids as analgesic and addictive agents were related to monoaminergic and cholinergic systems.
- In 1973, opiate-binding sites demonstrated.
- In 1975, an endogenous opiate-like factor called enkephalin was found.
- Then endorphins and dynorphins.

Opioid receptor

- Three classical opioid receptor are:μ,δ and κ.
- Each receptor has a unique anatomical distribution in brain, spinal cord and priphery.
- Most opioids are relatively selective for μ receptor, reflecting their similarity to morphine.
- Morphine and most clinically used opioid agonists exert their effects through mu opioid receptors.

Classification of Opioids



Opioid agonist/antagonists

- Nalbuphine and butorphanol are competitive μ-receptor antagonists
- But exert their analgesic effects by acting as agonists at κ receptors.
- Pentazocine is the same as nalbuphine but is a weaker μ-receptor antagonist while retaining its κ-agonist activity.

Buprenorphine

- Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa opioid receptor.
- Naloxone is an antagonist at the mu-opioid receptor.
- Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

- **Buprenorphine tablets** intended for sublingual administration.
- It is available in two dosage strengths, 2mg buprenorphine and 8mg buprenorphine free base.
- Each tablet also contains lactose, mannitol, corn starch, citric acid, sodium citrate and magnesium stearate.

- Buprenorphine/naloxane **tablet** intended for sublingual administration.
- It is in two dosages , 2mg bupr. with 0.5mg naloxone, and 8mg Bupr. with 2mg naloxone free bases.
- Each tablet also contains lactose, mannitol, corn starch, citric acid, sodium citrate, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon flavor.

Why Combining Buprenorphine and Naloxone Sublingually Works

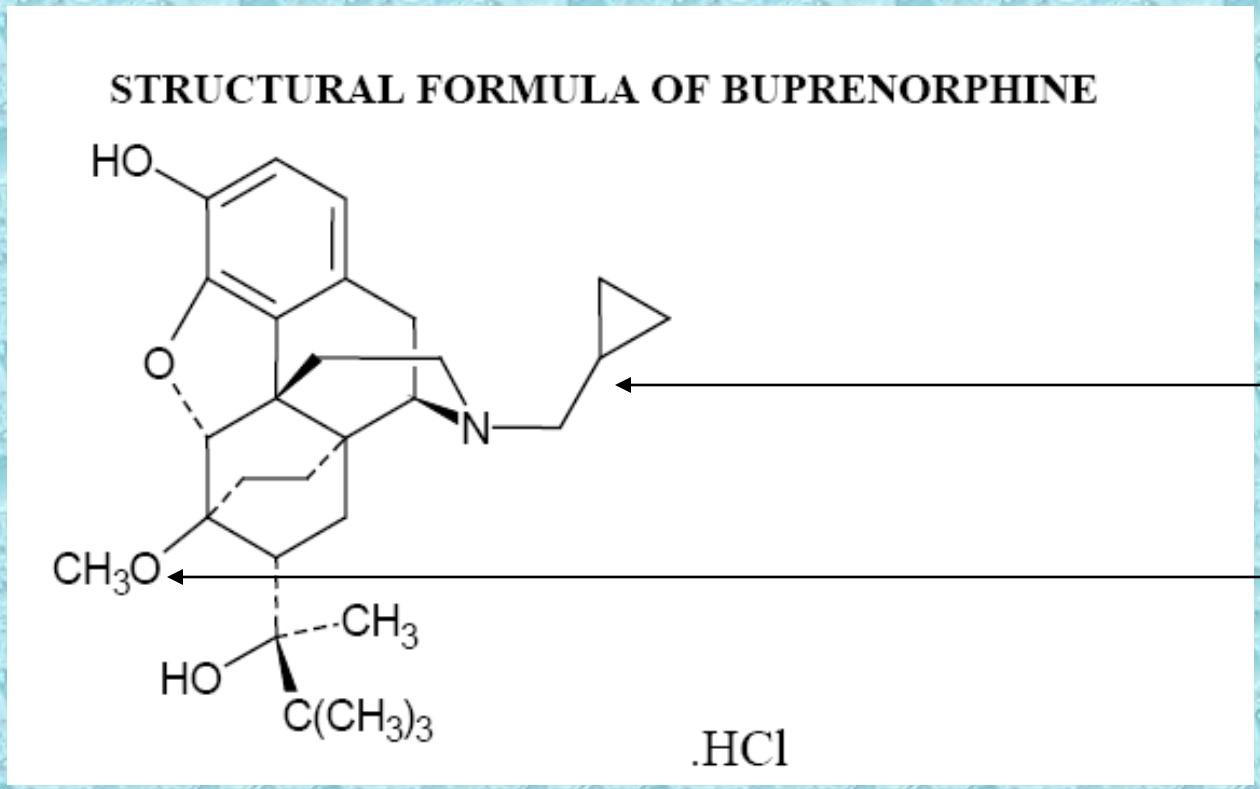
- Buprenorphine and naloxone have different sublingual (SL) to injection potency profiles that are optimal for use in a combination product.

SL Bioavailability	**Injection to Sublingual Potency**
Buprenorphine 40-60%	**Buprenorphine ≈ 2:1**
Naloxone 10% or less	**Naloxone ≈ 15:1**

- Semisynthetic highly lipophilic opioid derived from thebaine
- 25 to 50 times more potent than morphine. About 0.4 mg bupr. =10 mg morphine IM.
- It produces analgesia and other CNS effects qualitatively similar to morphine.
- Analgesia duration longer than morphine.

- Respiratory depressant effects are slower in onset and last longer than those of morphine.
- Bupr. Dissociates very slowly from opioid receptors. The dissociation half life from mu receptors is 166 minutes.

Molecular formula



- Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (17mg/mL).
- Chemically, buprenorphine is 17-(cyclopropylmethyl)-α -(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy- α -methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5α, 7α(S)]-.
- Buprenorphine hydrochloride has the molecular formula C29 H41 NO4 HCl and the molecular weight is 504.10.

Mode of administration

- High 1st pass metabolism
- Bioavailability: IV> SC > SL > oral
- Sublingual tablets
  - 0.4, 2 & 8 mg tablets available
  - tablets take 3 to 5 minutes to dissolve
  - only get ~ half effect if swallowed

Duration of effects

- Quick onset of action: 30–60 min
- Peak effects: 1 – 4 hours
- Duration of action is dose related
  - low dose (2 – 4 mg): 8 – 24 hrs
  - med dose (8 – 16 mg): ~ 24 hrs
  - high dose (16 – 32 mg): 2 – 3 days

  (alternate day dosing a possibility?)

pharmacokinetic

- **Absorption:**
- Plasma levels of buprenorphine increased with the sublingual dose of bupr.
- There was a wide inter-patient variability in the sublingual absorption of buprenorphine ,but within subjects the variability was low.
- Cmax of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

pharmacokinetic

- **Metabolism:**
- About 96% of the circulating drug is bound to protein. Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme.
- Norbuprenorphine, an active metabolite, can further undergo glucuronidation.
- Both N-dealkylated and conjugated metabolites are detected in the urine.
- But most of the drug is excreted unchanged in the feces.

- **Elimination:**
- A mass balance study of buprenorphine showed complete recovery in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified
- buprenorphine metabolites.

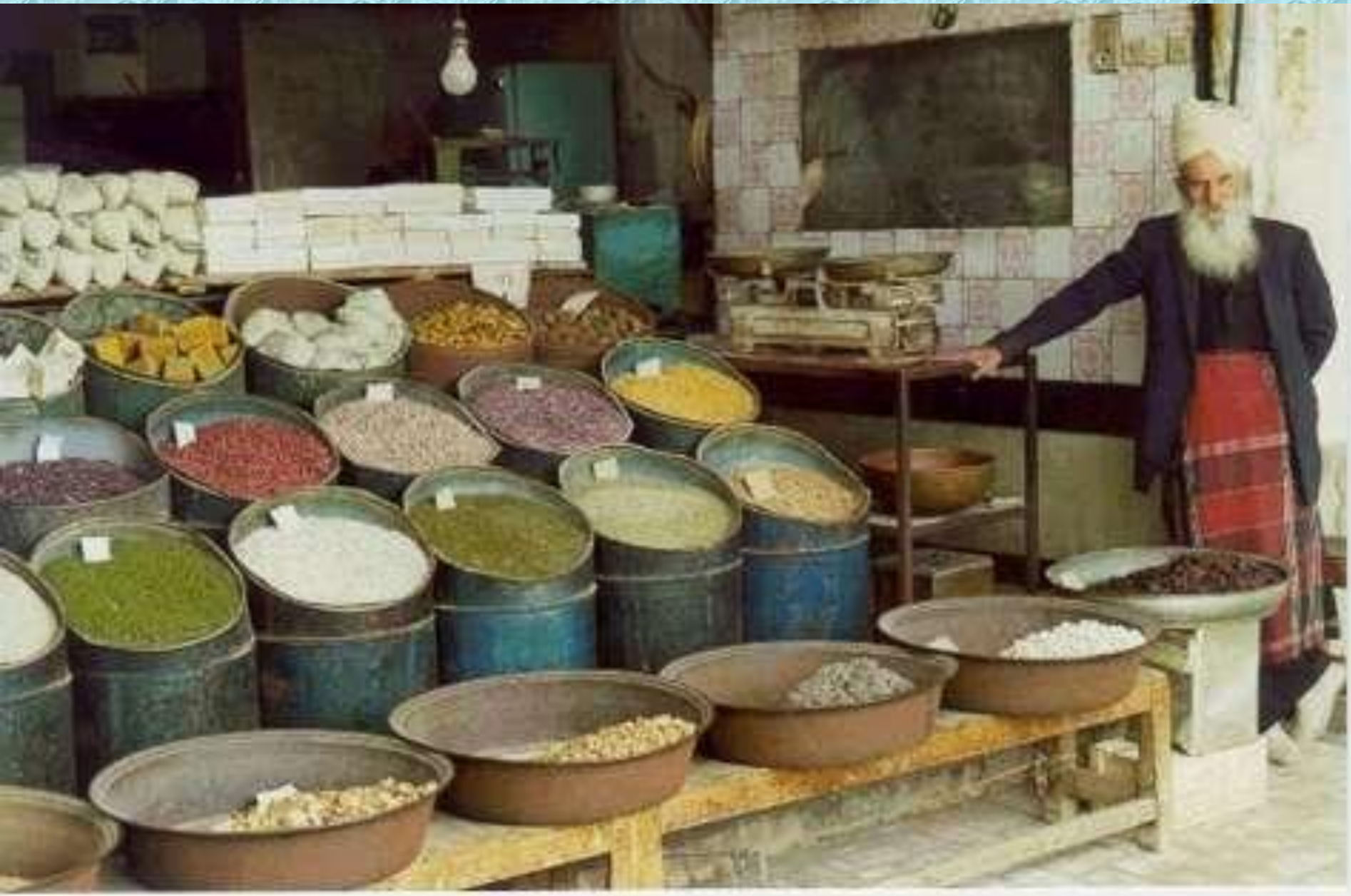
- In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).
- Buprenorphine has a mean elimination half-life from plasma of 37 h.

- **Hepatic Disease:**
- The effect of hepatic impairment on the pharmacokinetics of buprenorphine is unknown. Since the drug is extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment.
- Therefore, in patients with hepatic impairment dosage should be adjusted and patients should be observed for symptoms of precipitated opioid withdrawal.

- **Renal Disease:**
- No differences in buprenorphine pharmacokinetics were observed between 9 dialysis dependent and 6 normal patients following intravenous administration of 0.3mg buprenorphine.

Drug-drug interactions:

- *CYP 3A4 Inhibitors and Inducers:* A pharmacokinetic interaction study of ketoconazole (400 mg/day), a potent inhibitor of CYP 3A4, in 12 patients resulted in increases in buprenorphine mean Cmax values (from 4.3 to 9.8, 6.3 to 14.4 and 9.0 to 17.1).



- Subjects receiving buprenorphine should be closely monitored and may require dose-reduction if inhibitors of CYP 3A4 such as azole antifungal agents (e.g. ketoconazole), macrolide antibiotics (e.g., erythromycin) and HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir) are co-administered.

- The interaction of buprenorphine with CYP 3A4 inducers has not been investigated; therefore it is recommended that patients receiving buprenorphine should be closely monitored if inducers of CYP 3A4 (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered

CONTRAINDICATIONS

- buprenorphine should not be administered to patients who have been shown to be hypersensitive to buprenorphine.

WARNINGS

- ***Respiratory Depression:***
- Significant respiratory depression with buprenorphine, particularly intravenous route.
- A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines.
- Deaths have also been reported with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with buprenorphine.

- buprenorphine should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depress).

CNS Depression:

- Patients receiving buprenorphine with other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. With such combined therapy, reduction of the dose should be considered.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

- Buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m2 basis).

- was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli.*

- Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose) or up to 5mg/kg/day *im* or *sc* (estimated exposure was approximately 3 times the recommended human daily sublingual dose.

Buprenorphine is in the FDA pregnancy category C. This means that it is not known whether buprenorphine will be harmful to an unborn baby. Use of buprenorphine during pregnancy may cause withdrawal symptoms in a newborn baby.
Do not prescribe buprenorphine if your patient is pregnant or could become pregnant during treatment.

Category C

- Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

- Buprenorphine passes into breast milk and may be harmful to a nursing baby.
- **Do not** prescribe buprenorphine if your patient is breast-feeding a baby.

- Buprenorphine can cause constipation. Drink plenty of water (six to eight full glasses a day) to lessen this side effect.
- Increasing the amount of fiber in your diet can also help to alleviate constipation.

- Use caution when driving, operating machinery, or performing other hazardous activities.
- Buprenorphine may cause drowsiness, dizziness, or impaired thinking. If you experience drowsiness, dizziness, or impaired thinking, avoid these activities.

What are the possible side effects of buprenorphine?

- an allergic reaction (difficulty breathing; closing of the throat, swelling of the lips, tongue, or face; or hives);
- slow breathing;
- dizziness or confusion; or
- liver problems such as yellowing of the skin or eyes, dark colored urine, light colored stools (bowel movements), decreased appetite for several days or longer, nausea, or lower stomach pain.

Buprenorphine may cause liver problems.

- Call your doctor right away if:
- • Your skin or the white part of your eyes turns yellow (jaundice).
- • Your urine turns dark.
- • Your bowel movements (stools) turn light in color.
- • You don’t feel like eating much food for several days or longer.
- • You feel sick to your stomach (nausea).
- • You have lower stomach pain.

- Other less serious side effects may be more likely to occur. Continue to take buprenorphine and talk to your doctor if you experience
- headache;
- pain;
- problems sleeping;
- nausea;
- sweating;
- stomach pain; or
- constipation.

Dependence:

- Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper.
- The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset.

Thank you