Q14 Compare and contrast the mechanism of action, pharmacokinetics and central nervous system effects of morphine and tramadol (Sept 2013)

	Morphine	**Tramadol**
Mechanism of action	Binds primarily to inhibitory G-Protein coupled μ-opioid receptors, which results in an increase in adenylyl cyclase, a reduction in cAMP and hyperpolarization of the cell, hence reduced neurotransmitter release. The μ-receptor is located throughout the CNS. Also acts at kappa and delta receptors.	Racemic mixture of two enantiomers. It is a non selective agonist at μ, kappa and delta opioid receptors, with higher affinity for μ, producing potent analgesia. It also inhibits neuronal uptake of Nad/5HT and enhances 5HT release; inhibition of pain partly involves the activation of descending inhibitory pathways within the spinal cord. Compared to other opioids it produces less respiratory depression and constipation.
CNS effects	Analgesia (particularly effective for visceral pain), sedation, dysphoria or euphoria, confusion and psychomimetic effects, miosis (via excitation of Edinger-Westphal nucleus), nausea/vomiting (via stimulation of the CTZ). Reduces the sensitivity of the brainstem to CO2 causing respiratory depression. Reduces sympathetic tone causing mild bradycardia/hypotension.	Potent analgesia, sedation, dysphoria/euphoria, miosis (via excitation of Edinger-Westphal nucleus), nausea/vomiting (via stimulation of the CTZ, less so than morphine). May cause serotonin syndrome in combination with certain drugs.
Pharmacokinetics		
- Administration	Route – PO/IV/IM/SC/IT Dose – titrate to effect. Typically 2.5-5mg IV or 5-20mg PO to start with. Bioavailability – well absorbed but extensive first pass metabolism, bioavailability ~30%	Route - PO/IV Dose - 50-100mg QID for all routes (1/5th the potency of morphine) Bioavailability - 60-100% PO
- Distribution	Vd - 3-4L/kg Protein binding – 20-40% (mostly albumin) Lipid solubility – significantly less than fentanyl but does cross the BBB pKa – 8.0 (23% unionized at pH 7.4)	Vd - 4L/kg Protein binding - 20%. Crosses placenta.
- Metabolism	Mainly hepatic metabolism with some renal. 70% is metabolized to morphine-3-glucuronide and 10% to morphine-6-glucuronide, which is 13 times more potent than morphine. It has a similar duration to morphine and can accumulate in renal failure.	85% metabolised by demethylation in liver. O-desmethyltramadol is active.
- Elimination	Excreted mainly in urine as conjugates with 10% in faeces Half-life 1.5-2 hrs, large interpatient variability	90% excreted in urine, 10% in faeces. Half life 4-6 hours (doubled in renal or hepatic dysfunction)