Use of Clonidine in Acute Medicine to reduce Sedation induced Morbidity & Mortality.

Case 1:
- A 50 year old morbidly obese man who had fallen whilst drunk and dislocated his right shoulder.
- He had no other significant past medical history.
- On examination, he was morbidly obese and had a beard and a difficult airway.
- Despite conscious sedation with titration of morphine 10mg, midazolam 10mg and fentanyl 200mcg, he remained tachycardic, hypertensive, distressed and diaphoretic, and it was not possible to reduce his shoulder dislocation
- Clonidine 250mcg IV was infused over ten minutes which gave adequate pain relief and the dislocated shoulder was easily relocated.

This avoided the need for a GA in a high risk patient.

Case 2:
- A 55 year old obese lady with COPD Gold stage 4, on home O2 and BIPAP who presented with an IE of COPD.
- She was Hcp C positive from IDVA in the past.
- She was in respiratory distress but was unable to tolerate BIPAP
- She did not wish to be admitted to ICU, or to be mechanically ventilated
- She was drowsy, acidic, and her PaCO2 was 12 (baseline 8).
- We wished to avoid giving her opiates / benzodiazepines
- Clonidine 150mcg IV was titrated over 30mins and resulted in anxioylysis and analgesia sufficient to allow her to tolerate BIPAP.
- She was admitted to a ward and was discharged home ten days later.

Mechanism of Action
- Stimulates pre-synaptic alpha 2 receptors decreasing noradrenaline release from both central and peripheral sympathetic nerve terminals.
- Acts at spinal and supraspinal sites
- Depresses thalamic transmission of impulses to the cerebral cortex
- Enhances descending inhibitory pathways to the dorsal horn.
- Supraspinally, it acts in the locus coeruleus in the floor of the fourth ventricle where it reduces noradrenaline concentrations.
- Efferents from the locus coeruleus act on the descending fibres of the reticulospinal tracts which inhibit pain transmission at the spinal level 1.
- Dorsal nucleus of the vagus has a high density of alpha 2 receptors responsible for bradycardic and hypotensive effects.
- Alpha 2 receptors are found postjunctionally on the dorsal horn neurons of the spinal cord and inhibit release of substance P.
- Clonidine also acts on cholinergic, purinergic and serotonergic systems.
- Extrathalamic opioids given with alpha 2 agonists act synergistically to reduce pain.

Pharmacodynamics
- CNS: Dose related sedation, ataxia, analgesia, and a decrease in the requirements of opioids. It reduces CBF, CMRO2, and IOP. It depresses spontaneous sympathetic outflow and afferent A delta and C fibre mediated somato-sympathetic reflexes.
- CVS: May cause an initial increase in BP and SVR due to activation of postjunctional alpha 2 receptors on the peripheral vasculature. There is then a decrease in HR and BP due to central decrease in sympathetic tone and increase in vagal activity. It has no effect on contractility and CO is well maintained. There is a decrease in coronary and systemic vascular resistance.
- Respiratory: No change in RR, PaO2, or SpO2.

Dose and administration
- It is presented as a clear colourless solution for injection containing 150mcg in 1ml amp.
- It is given in IV boluses 50-150mcg 8 hourly, or 100mcg / hr as an infusion. Oral dose 50-600 mcg 8 hourly.
- Onset of action after an IV dose is within 10mins and lasts 3-7 hrs.
- It is also given by extradural, intrathecal, IM, transdermal and by nebulised routes.

Side Effects
- Dry mouth, sedation, depression, fluid retention, constipation, rebound hypertension, tachycardia.
- Colonic pseudo-obstruction (Ogilvie's syndrome) is an unusual complication of high dose clonidine infusion for treatment of DT's.

Clinical applications
- Sedative in Intensive Care Units,
- Ondards hypertensive reflexes during endotracheal intubation decreasing the incidence of myocardial ischemia,
- autonomic dysfunction in tetanus,
- hypotension,
- DTF's,
- weaning from mechanical ventilation
- prevention of resistance to opioids and benzodiazepines
- sedation and analgesia without global unconsciousness.

Available evidence
- Spies et al: prospective blinded RCT - assessed three different regimen (flumazenil-clonidine / clonidine + haloperidol / flumazenil- haloperidol) to treat alcohol withdrawal in trauma ICU patients. The Revised Clinical Institute Withdrawal Assessment for Alcohol Scale was used to determine the need for medication. Mechanical ventilation was significantly prolonged in the Haloperidol-Clomethiazole group, and cardiac complications were increased in the Flumazenil-clonidine group.
- Gillison et al: retrospective study where oral clonidine-prescribing practices were analysed. The charts of 160 critically ill ventilated patients who received clonidine were reviewed. The mean dose was 0.26mg and opioid and benzodiazepine requirements were decreased.
- Tryba et al: clonidine improved sympathetic overactivity in 95% of ventilated polytrauma patients.
- Domini et al: 30 ventilated patients, an interventional cohort study. Clonidine lowered sedation scores and facilitated earlier weaning.
- Desmedetomidine is a newer alpha-2 agonist which shares similar pharmacodynamic actions to clonidine. Two multicentre blinded RCT's found that desmedetomidine compared favourably to lorazepam and midazolam with a reduced incidence of delirium / coma and reduced duration of mechanical ventilation

Conclusion
- Further studies are required to establish the efficacy of clonidine as a sedative in critically ill patients or in patients in whom sedation poses a high risk.
- We describe two cases in which patient risk was reduced using clonidine to reduce or avoid the need for opiates, benzodiazepines or General Anaesthesia.
- We propose to carry out a RCT in Emergency Dept and Acute Medical Unit patients who require sedation/analgesia for acute painful procedures or for mechanical ventilation to compare opiate / benzodiazepines / general anaesthesia with and without use of supplemental clonidine.
- We anticipate that use of clonidine will reduce the need for opiates / benzodiazepines / general anaesthesia which will improve patient satisfaction and reduce morbidity and mortality.