INTRODUCTION
Clonidine is an imidazoline compound with the molecular formula C₉H₉Cl₂N₃. The structural formula¹ is as shown in figure 1. It is the prototype of alpha-2 adrenoceptor agonists that has been extensively studied with an alpha-2:alpha-1 ratio of 200:11. The drug is licensed for the treatment of hypertension, migraine and menopausal flushing.² It is also an analgesic, sedative and anxiolytic.¹,³ These properties along with its ability to maintain peri-operative haemodynamic stability make clonidine a useful agent in anaesthesia and intensive care.¹

We set out to perform a systematic review on the efficacy of clonidine as a sedative agent in adult patients on the intensive care unit. A comprehensive literature search was performed. Medline, Embase, AMED, British nursing index, CINAHL, PsychINFO, Bandolier, Cochrane Library, HTA database and the DARE was searched for the following terms "Clonidine", "Intensive care", "Critical care", "Sedation" from the period 1951 to January 2009. The references of the retrieved reviews and original articles were also manually searched. Only studies in English for adult patients were included in our review.

This literature search revealed 2 randomized controlled trials (1 unpublished), 1 single centre prospective interventional study, 1 observational study, 1 dose finding study and 4 case reports [Table 1, Fig. 2]. Since the paucity of studies precluded a systematic review, this is therefore a narrative review of the use of clonidine focussing on its role as a sedative agent on the intensive care unit.

Figure 2
The Flowchart of studies in the Review

Screened Citations (n= 1011)
Excluded (n= 782): Animal Studies
Studies not in English Duplication
Abstracts identified for analysis (n=229)
Excluded (n= 222): Non-ICU Studies Paediatric Studies
Relevant Full Text Articles retrieved (n=7)
2 further studies identified from manual searching of references
9 Studies included in the final review:
2 RCT’s (1 Unpublished)
1 Prospective Interventional study
1 Observational study
1 Dose finding study
4 Case reports

Drs. Sunil Jamadarkhana, Specialist Registrar, Shameer Gopal, Consultant, Department of Anaesthesia and Intensive Care Medicine Critical Care Services, New Cross Hospital, Wolverhampton, West Midlands, WV10 0QF, UK
Correspondence: Dr. Sunil Jamadarkhana, Email: sunilj_2004@yahoo.com
Table 1  
Characteristics of included studies in the Review

| Participants                                                                 | Interventions                                                                                                                                  | Outcomes                                                                                                                         | Study quality                                                                 |
|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Multiple-injured alcohol-dependent patients transferred to ICU after admission to emergency room and operative management (n=180). | 54 patients received flunitrazepam/clonidine, 50 patients chlorpromazine/haloperidol and 55 patients flunitrazepam/haloperidol. Duration of mechanical ventilation and major intercurrent complications (Pneumonia, sepsis, cardiac and bleeding disorders and death) were documented. | Advantage in the flunitrazepam/clonidine group. With respect to pneumonia and the necessity of mechanical ventilation. Symptom oriented treatment approach rather than a standard therapy for alcohol withdrawal syndrome should be considered. | Prospective, randomized, blinded, controlled clinical trial. Confounding minimized by randomization. Study was not double blinded because there were no controlled studies available for study subjects and no recommended dosage schedules were available. Power of 80%. (Two-tailed p of 0.05) 21 patients were excluded after assignment. 4 patients were excluded during therapy. |
| 40 consecutive polytraumatized patients on long-term ventilation with symptoms of sympathetic hyperactivity. | Primary aim of study was the control of cardio-vascular parameters and agitation. 150 microgram of clonidine bolus followed by an infusion. | Supplemetnal clonidine improved clinical symptoms of sympathetic hyperactivity in 95% of patients. | Non-randomized dose finding study. No blinding. Clonidine discontinued in two patients due to side effects. |
| 20 trauma patients mechanically ventilated for at least 7 days.               | Clonidine was compared with fentanyl-midazolam infusion.                                                                                       | Patients in the clonidine group did not develop sympathetic hyperactivity symptoms compared to 50% in the control group. Also, the control group required 34% higher amount of midazolam than the clonidine group for the whole study period. | Prospective, randomised study. Limited information available on the study design and methodology. |
| 30 ventilated ICU patients. (Head and multiple trauma, drug abuse patients requiring sedation for more than 7 days). | Clonidine was administered in a dose of 0.9 mg followed by an infusion of 1.8-2.5 mg / 24 hours when withdrawal symptoms developed. | Clonidine decreased haemodynamic, metabolic and respiratory demands in patients with withdrawal syndrome after sedation interruption. | Prospective, interventional, single-centre study. Not randomized and clonidine was not compared to standard therapy. 5 non-responders to clonidine treatment were excluded from the study. |
| Critically ill ventilator dependent patients with extended stays in the ICU (n=160). | Primary analyses investigated prescribing practices for oral clonidine (dose, duration, patient population, indications and adverse effects.) Secondary analyses evaluated the response to the drug in terms of requirements for other medications for analgesia and sedation. | Clonidine decreases pain and sedation requirements in ICU. Higher dose than routinely prescribed is needed to achieve desired effect. | Retrospective study. Observational chart review. Only 13 patients evaluated in secondary analysis. Overstrict exclusion criteria. |
| 63-year-old man who underwent distal oesophagectomy and partial gastrectomy and admitted to ICU. | Clonidine used as a sedative adjunct to fentanyl and midazolam in a dose of 1.44mg/70kg/24 hours. | Clonidine was very useful as a sedative adjunct on ICU but cardiovascular depre-ssion and withdrawal syndrome after abrupt discontinuation were the potential risks. | Isolated case report. |
| 2 patients (Multiple trauma, subtotal colectomy) with a past history of alcohol abuse admitted to ICU for treatment of respiratory problems. | Clonidine was used in a dose of 60-120 microgram/hour to control alcohol withdrawal symptoms. | Clonidine may be safely and effectively used in the management of acute alcohol withdrawal symptoms on ICU. | Isolated case report |
| 58-year-old woman with a penetrating hand injury who developed severe tetanus and treated on ICU. | Clonidine in a dose of 50 microgram / hour was used to control autonomic crises along with other agents. | Clonidine resulted in easier control of crises though it did not attenuate it. There was no appreciable difference in catecholamine levels with clonidine. | Isolated case report. |
| 45-year-old man involved in a road traffic accident with a compound fracture of the elbow who developed severe tetanus treated on ICU. | Clonidine was used to control autonomic crises along with magnesium, paralysis and sedation. | A logical place for clonidine in the treatment of autonomic crises in patients with severe tetanus. | First published evidence of clonidine to control sympathetic overactivity in the form of a case report. |
PHARMACOLOGY

Mechanism of action
Clonidine acts by stimulating the pre-synaptic alpha 2 adrenoceptors, thereby decreasing noradrenaline release from both central and peripheral sympathetic nerve terminals. The effects of clonidine occur due to its action both at spinal and supraspinal sites, including depression of thalamic transmission of impulses to the cerebral cortex as well as enhancement of descending inhibitory pathways to the dorsal horn. Supraspinally, the locus coeruleus in the floor of the fourth ventricle is the major site for the sedative and analgesic actions as revealed by radioligand studies. Clonidine markedly decreases noradrenaline concentrations in the locus coeruleus. The efferents from the locus coeruleus act on the descending fibres of the reticulospinal tracts that inhibit pain transmission at the spinal level. The dorsal nucleus of vagus has high densities of alpha 2 receptors responsible for the bradycardic and hypotensive effects. Alpha 2 adrenoceptors are found postjunctionally on the dorsal horn neurons of the spinal cord and acts by inhibiting the release of substance P. Clonidine also acts on the cholinergic, purinergic and serotonergic pain systems causing analgesia. Clinical and experimental studies have shown that alpha 2 agonists given together with opioids into the spinal cord act synergistically to reduce pain.

Pharmacokinetic actions
Clonidine is rapidly and well absorbed orally with a bioavailability of 100%. It is very lipid soluble and penetrates the central nervous system. It is 20% protein bound in the plasma with a volume of distribution of 1.7 -2.5 l kg-1. It is metabolised in the liver to inactive metabolites and 65% of the dose is excreted unchanged in the urine, 20% is excreted in the faeces. The clearance is 1.9-4.3ml kg-1 min-1 and the elimination half-life is 6-23 hours (average 7.7 hours). The half-life is markedly increased in renal impairment requiring a dose reduction. The peak action occurs in 10 minutes and lasts for 3-7 hours after single intravenous dose. On oral administration, it reaches a peak plasma level within 60-90 minutes.

Pharmacodynamic actions
Central nervous system: Clonidine produces dose-related sedation, analgesia, anxiolysis and a reduction in the requirements of other anaesthetic agents and opioids. It also reduces cerebral blood flow, cerebral metabolic rate of oxygen consumption and intraocular pressure. It also exerts a depressant effect on both spontaneous sympathetic outflow and afferent A delta and C fibre mediated somatosympathetic reflexes.

Cardio respiratory systems: Clonidine causes an initial short lived increase in blood pressure and systemic vascular resistance and a decrease in cardiac output due to activation of post junctional alpha 2 receptors on the peripheral vasculature. This is accompanied by a longer lasting decrease in heart rate and blood pressure resulting from a centrally mediated decrease in sympathetic tone and an increase in vagal activity. It has no effect on cardiac contractility and cardiac output is well maintained. There is a decrease in coronary and systemic vascular resistance. Clonidine causes very minimal respiratory depression along with good sedation. There is no change in respiratory rate, PaCO2, SpO2 on administration.

Renal, Metabolic and Endocrine: Clonidine decreases renovascular resistance and produces diuresis. It causes a decrease in plasma catecholamine concentrations and plasma renin activity. Blood sugar concentrations may increase secondary to alpha-adrenergic stimulation.

Dosage and administration
It is presented as a clear colourless solution for injection containing 150 micrograms in 1 ml ampoule. Clonidine is administered intravenously in boluses (50-150 microgram 8-hourly) or by continuous infusion. The dose may be extremely variable when given by infusion. However, the usual dose is in the order of 100-microgram hour -1. The oral dose is 50-600 microgram 8-hourly. The onset of action after an intravenous dose is within 10 minutes and lasts for 3-7 hours. It is also administered by extradural, intrathecal, intramuscular, transdermal and by nebulised routes.

Side effects
Dryness of mouth (50% of patients), dose related sedation, depression, fluid retention and constipation has been reported. Rapid withdrawal of the drug leads to life-threatening rebound hypertension and tachycardia. Clonic Pseudoostruction (Ogliive’s syndrome), an unusual complication of high dose clonidine infusion for the treatment of delirium tremens has been reported.

Clinical applications
Clonidine was introduced into clinical practice in the 1966 as a centrally acting anti hypertensive agent. It was first used for neuroptanalgesia in 1978. It is used for the treatment of migraine and menopausal flushing and also as an anaesthetic adjuvant (sedation, analgesia, anxiolysis, premedication).

Peri-operatively it obtunds hypertensive reflexes during endotracheal intubation and results in the decreased incidence of myocardial ischaemia. Along with local anaesthetic agents, it is an adjunct in regional anaesthesia.
and in the treatment of chronic pain.\textsuperscript{21}

The efficacy of clonidine as a sedative agent on the intensive care unit

In recent years, clonidine, the prototype of alpha 2 agonists has been used as an analgesosedative in intensive care both in ventilated and spontaneously breathing patients.\textsuperscript{12,14} The first reported use of clonidine for sympathetic overactivity on the ICU was for the treatment of autonomic dysfunction in tetanus in 1989\textsuperscript{22} [Table 1]. It plays a significant role in the treatment of a variety of conditions such as hypertension, delirious syndromes and withdrawal syndromes (opioid, alcohol and nicotine addiction).\textsuperscript{23-32} It is also used as an agent to facilitate weaning from long-term mechanical ventilation and in the prevention of resistance to opioids and benzodiazepines.\textsuperscript{33-36}

Mechanically ventilated patients on the ICU experience stress, agitation, anxiety and pain. The goals of ICU sedation are to provide analgesia and anxiolyis. It should also prevent cardiorespiratory and metabolic stress produced by catecholamines and achieve a state where a patient cooperates with interventions and health care providers.\textsuperscript{37} Propofol, opioids, benzodiazepines and neurolept agents are used to achieve sedation but are associated with significant side effects and cause global unconsciousness. A survey of sedation practices on ICU in Britain suggested that most units are driven towards achieving a lightly sedated and cooperative patient and at the same time fulfilling sedation goals. This national postal survey revealed that alfentanil, midazolam, morphine and propofol were the most commonly used sedative agents. Also, the sedation regimes changed depending on the length of stay on the ICU.\textsuperscript{38} Alpha-2 adrenoreceptor agonists may achieve this state without significant side effects.\textsuperscript{37}

A prospective, randomized, blinded, controlled clinical trial by Spies CD et al in a university hospital ICU assessed three different therapeutic regimens for the treatment of withdrawal syndromes in traumatized chronic alcoholic patients\textsuperscript{39} [Table 1]. The authors studied the treatment with regards to duration of mechanical ventilation, frequency of pneumonia and cardiac disorders during their ICU stay. They randomised patients who developed actual alcohol withdrawal syndrome to one of the following treatment regimens: flunitrazepam-clonidine (n=54); chlormethiazole-haloperidol (n=50) or flunitrazepam-haloperidol (n=55). A validated measure of the severity of alcohol withdrawal (Revised Clinical Institute Withdrawal Assessment for Alcohol Scale) was used to determine the need for administration of medication. Four patients in the Flunitrazepam-clonidine group were excluded from the study as they continued to hallucinate. Though there was no difference in the length of ICU stay between the three groups, the authors found that mechanical ventilation was significantly prolonged in the chlormethiazole/haloperidol group due to an increased frequency of pneumonia and cardiac complications were significantly increased in the flunitrazepam-clonidine group. The authors concluded that a symptom oriented treatment approach rather than a standard therapy should be considered. However, 21 patients were excluded from the study after assignment and a further 4 patients during therapy. The results are therefore subject to exclusion bias. Furthmore the study was not double-blinded and therefore is prone to observer bias. The study is also limited in that no predetermined dosage schedules were available.

The only other randomised prospective study involving the use of clonidine in ICU is unpublished\textsuperscript{35} [Table 1]. This study is described in an article on the use of clonidine for the prevention and treatment of withdrawal. We could not find any formal publication of this study even in abstract form. The efficacy of clonidine was assessed in reducing withdrawal symptoms in patients who were mechanically ventilated for more than 7 days. Clonidine was compared to Fentanyl-midazolam infusion. Patients in the treatment group received clonidine in addition to a fentanyl-midazolam infusion as compared to a fentanyl -midazolam infusion only in the control group. 20 patients were included in the study. The total amount of midazolam administered during the whole study period was 34\% higher in the control group than in the clonidine group. No sympathetic hyperactivity symptoms were seen in the clonidine group compared to 60\% in the control group. A systematic appraisal of this study could not be undertaken because of the limited information available on study design and methodology.

Gillison M and colleagues performed a retrospective study where clonidine-prescribing practices (dose, duration, patient population, indications and adverse effects) were analysed\textsuperscript{40} [Table 1]. The charts of 160 critically ill ventilator dependent patients with extended stays on the medical-surgical ICU who received clonidine were reviewed. Primary analyses of this review investigated prescribing practices for oral clonidine and the secondary analyses evaluated the response to the drug in terms of requirements of other medications for analgesia and sedation. The mean dose was 0.26mg and opioid and benzodiazepine requirements were decreased. The authors concluded that clonidine decreases pain and sedation requirements and also suggested that a higher dose than routinely prescribed is required to achieve the desired effect. Other case reports have also suggested clonidine to be a useful analgo-sedative that potentiates the effects of fentanyl and midazolam. They also conclude that clonidine is safe and effective in the treatment of established delirium
tremens and that it facilitates weaning from mechanical ventilation\textsuperscript{41-42} [Table 1].

The dose of clonidine is very variable when administered as an intravenous infusion. Tryba and colleagues conducted a dose-finding study to investigate the feasibility and dosage requirement of clonidine for the treatment of sympathetic symptoms in ventilated polytraumatized patients (18-70 years) with chronic alcohol intake\textsuperscript{35}. Forty consecutive polytraumatized patients on long-term mechanical ventilation with symptoms of sympathetic hyperactivity receiving sedation with fentanyl and midazolam were included in the study. A bolus of clonidine followed by infusion was administered to control the cardiovascular parameters (HR< 120/min and systolic BP<130 mmHg). Haloperidol was supplemented up to a maximum dose of 100 mg per day if agitation was not controlled with clonidine. The dose administered to control cardiovascular parameters varied extremely with the lowest effective dosage of 0.45 mg and the highest dosage of 15.45 mg. Sweating improved in most patients within 2-3 hours and disappeared within a maximum of 13 hours after start of clonidine. A reduction in HR to less than 120/min occurred in 90% of patients within 24 hours. After initiation of clonidine treatment, sedation became adequate in 24 patients and fentanyl-midazolam requirement could be reduced by 38 (+/-19) \% within 24 hours. The authors concluded that supplemental clonidine improved clinical symptoms of sympathetic hyperactivity in 95\% of patients.

Abrupt sedation interruption on ICU can result in the development of withdrawal symptoms (agitation, sweating, hyperventilation, hypertension and tachycardia) with a surge of catecholamines resulting in haemodynamic instability and increased metabolic demand. Domniki Liatsi and colleagues conducted a prospective, interventional study on 30 ventilated ICU patients with withdrawal symptoms treated with clonidine following sedation interruption. The authors state that clonidine significantly decreased haemodynamic, metabolic and respiratory demands and facilitated patient coordination with the ventilator and early weaning along with inducing mild sedation in patients with withdrawal syndrome. Clonidine also significantly lowered Ramsay sedation scores and patients were extubated 24-48 hours after starting treatment. However this was an interventional cohort study. There was no randomisation; no blinding and the 5 non-responders to clonidine treatment were excluded from the analyses\textsuperscript{36} [Table 1].

The treatment of autonomic dysfunction in tetanus consists of heavy sedation, paralysis, adrenergic blockade and magnesium sulphate\textsuperscript{43,44} [Table 1]. Clonidine has been successfully used to treat severe autonomic dysfunction in a 45-year-old patient with severe tetanus who was refractory to magnesium sulphate.\textsuperscript{42} Turner and colleagues also describe that the use of clonidine resulted in easier control of autonomic crises in a patient with severe tetanus when used along with other agents.\textsuperscript{43}

Critically ill patients with alcohol and opiate withdrawal symptoms present significant treatment difficulties especially following sedation interruption. Several studies\textsuperscript{23-32} performed outside of the ICU setting indicate that oral clonidine may be effective in controlling autonomic and psychologic manifestations of alcohol and opiate withdrawal symptoms. In a double blind, placebo-controlled, crossover trial, clonidine eliminated signs and symptoms of opiate withdrawal for 240-360 minutes in eleven addicts in a hospital setting.\textsuperscript{25} In another prospective, randomised, double blind study involving 50 patients over a 4-day study period, the efficacy of transdermal clonidine was compared with that of chlorziazepoxide in the treatment of severe acute alcohol withdrawal syndrome.\textsuperscript{31} The group receiving transdermal clonidine had a more significant response globally for the signs and symptoms of alcohol withdrawal, as measured by the Alcohol Withdrawal Assessment Scale. The authors concluded that transdermal clonidine is effective treatment for the treatment of acute alcohol withdrawal syndrome. Although the above studies have been conducted in the hospital setting rather than in an ICU setting, they give an indication that clonidine may be safe and efficacious for the treatment of withdrawal syndromes.

Dexmedetomidine is a newer Alpha-2 adrenoceptor agonist.\textsuperscript{45-49} The drug shares similar pharmacodymanic actions to that of its predecessor clonidine. Two recent multicentre randomised controlled clinical trials have assessed the efficacy of dexmedetomidine as a sedative agent in adult ICU patients.\textsuperscript{48,49} These studies are of a robust methodological design; adequately powered, randomised, and blinded thereby reducing the potential for bias. Dexmedetomidine compared favourably to the control drugs (lorazepam and midazolam) with a lower incidence of delirium or coma and a reduced duration of mechanical ventilation.

CONCLUSION
The efficacy of clonidine as a sedative agent for adult patients in the ICU is yet to be established. The paucity of studies evaluating the efficacy of clonidine as a sedative agent on the intensive care unit precluded a systematic review. Whilst clonidine is used as a sedative agent on the ICU, the evidence underpinning this practice is of a relatively poor quality. In this era of clinical governance and evidence based medicine the continued use of clonidine as a sedative...
agent in adult patients on the ICU cannot be justified. If the
drug is to establish its place as a safe and effective sedative
agent in adult ICU patients then it should be subjected to
the rigors of well designed randomised controlled clinical
trials first. However it is much more likely that the newer
alpha-2 adrenoceptor agonist dexmeditomidine will replace
clonidine as a sedative agent having already shown promise
in two recent multicentre randomised controlled clinical
trials.18-49

REFERENCES
1. Peden CJ, Prys-Roberts C. The alpha-2 adrenoceptors
and anaesthesia. In: Cedric Prys-Roberts and Burnell
R. Brown. International Practice of Anaesthesia, 6th ed.
Oxford (UK): Butterworth-Heinemann 1996.
2. Joint Formulary Committee. British National Formulary,
57th ed. London: British Medical Association and Royal
Pharmaceutical Society of Great Britain, September
2008.
3. Calvey T.N, Williams N.E. Principles and Practice of
Pharmacology for Anaesthetists, 4th ed. Oxford (UK):
Blackwell Science Ltd 2003.
4. Martin Sasada, Susan Smith. Drugs in Anaesthesia
and Intensive care, 3rd ed. Oxford (UK): Oxford
University Press 2003. p. 76-77
5. Scheinin M, Schwinn D. The Locus Coeruleus: Site of
hypnotic actions of alpha 2 adrenoceptor agonists?
Anesthesiology 1992; 76: 873-875.
6. Quintin L, Gonon F, Buda M, Ghignone M, Hilaire G,
Pujog J F. Clonidine modulates metabolic hyperactivity
induced by stress in behaving rats. Brain Res; 362:
366-369.
7. Kuraishi Y, Hirot a N, Sato Y, Kaneko S, Satoh M, Takagi
H. Noradrenergic inhibition of the release of substance
P from the primary afferents in the rabbit spinal dorsal
horn. Brain Res 1985; 359: 177-182.
8. Maze M, Tranquilli W. Alpha 2 adrenoceptor agonists:
defining the role in clinical anaesthesia. Anesthesiology
1991; 74: 581-605.
9. Aantaa R, Scheinin M. Alpha 2 adrenergic agents in
Anaesthesia. Acta Anaesthesiol Scand 1993; 37: 433-
438.
10. Flacke JW, FlackeWE. The use of alpha 2 adrenergic
agonists during general anaesthesia. Anaesth
Pharmacol Rev 1993; 1: 268-283.
11. Hayashi Y, Maze M. Alpha 2 adrenoceptor agonists
and Anaesthesia. Br J Anaesth 1993; 71: 108-118.
12. Kerenan A, Nykanen S, Taskinen J. Pharmacokinetics
and side effects of clonidine. Eur J Clin Pharmacol
1978; 13: 97-101.
13. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and
cognitive effects of clonidine infusions in humans. Br J
Anaesth 2001; 86: 5-11.
14. Tetsuya Ise, Mikiko Yamashiro, Hideki Furuya. Clonidine
as a drug for intravenous conscious sedation. Odontology
2002; 90: 57-63.
15. Ooi R, Pattison J, Feldman SA. The effects of
Intravenous clonidine on ventilation. Anaesthesia 1991;
46: 632 633.
16. Bailey PL, Sperry RJ, Johnson GK et al. Respiratory
effects of clonidine alone and combined with morphine
in humans. Anesthesiology 1991; 74: 43-8.
17. Stieger DS, Cantieni R, Frutiger A. Acute colonic
pseudoobstruction (Ogilvie's syndrome) in two patients
receiving high dose clonidine for delirium tremens.
Intensive Care Med 1997; 23: 70-782.
18. Helmut Stahle. A historical perspective: development of
clonidine. Baillieres Clin Anaesthesiol 2000; 14: 237-
246.
19. Kaukinen S, Kaukinen L, Eerola R. Preoperative and
postoperative use of clonidine with neurolept
anaesthesia. Acta Anaesthesiol Scand 1978; 23: 113-
120.
20. Talke PO, Mangano DT. Alpha 2 adrenergic agonists
and perioperative ischaemia. Anaesth Pharmacol Rev
1993; 1: 310-315.
21. Tamsen A, Gordh T. Epidural Clonidine produces
analgesia. Lancet II 1984; 231-232.
22. Sutton DN, Tremlett MR, Woodcock TE, Nielsen MS.
Management of autonomic dysfunction in severe
tetanus: the use of magnesium sulphate and clonidine
[review]. Intensive Care Med 1990; 16: 75-80.
23. Gold MS, Pottash AC, Sweeney DR, Kleber HD. Opiate
withdrawal using clonidine. A safe, effective, and rapid
nonopiate treatment. JAMA 1980; 243: 343-348.
24. Gupta AK, Jha BK. Clonidine in heroin withdrawal
syndrome: a controlled study in India. Br J Addict 1988;
83: 1079-1084.
25. Gold MS, Redmond DE Jr, Kleber HD (1978) Clonidine
blocks acute opiate withdrawal symptoms. Lancet 1978;
2: 599-602.
26. Kahn A, Mumford JP, Rogers GA, Beckford H. Double-
blind study of lofexidine and clonidine in the
detoxification of opiate addicts in hospital. Drug Alcohol
Depend 1997; 44: 57-61.
27. Taschner KL. A controlled comparison of clonidine and
doxepin in the treatment of the opiate withdrawal
syndrome. Pharmacopsychiatry 1986; 19: 91-5.
28. Lin SK, Strang J, Su LW, Tsai CJ, Hu WH. Double-blind
randomised controlled trial of lofexidine versus clonidine
in the treatment of heroin withdrawal. Drug Alcohol
Depend 1997; 48: 127-133.
29. Manhem P, Nilsson LH, Moberg AL, Wadstein J, Hokfelt B. Alcohol withdrawal: Effects of Clonidine on sympathetic activity, the renin aldosterone system, and clinical symptoms. Alcohol Clin Exp Res 1985; 9: 238-243.

30. Wilkins AJ, Jenkins WJ, Steiner JA. Efficacy of clonidine in treatment of alcohol withdrawal state. Psychopharmacology 1983; 81: 78-80.

31. Walinder J, Balldin J, Bokstrom K, Karlsson I, Lundström B, Svensson TH. Clonidine suppression of the alcohol withdrawal syndrome. Drug Alcohol Depend 1981; 8: 345-348.

32. Baumgartner GR, Rowen RC. Transdermal clonidine versus chloralhydrateoxide in alcohol withdrawal: a randomized controlled clinical trial. South Med J 1991; 84: 312-321.

33. Zalunardo M, Zollinger A, Heinzelmann M et al. Restlessness during weaning from mechanical ventilation: successful use of clonidine [abstract]. Eur J Anaesthesiol 1993; 10: 67.

34. J. P. Kress, A. S. Pohlman, M. F. O'Connor, J. B. Hall. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342: 1471-1477.

35. Michael Tryba. Alpha 2-adrenoceptor agonists in intensive care medicine: prevention and treatment of withdrawal. Baillieres Clin Anaesthesiol 2000; 14/2: 459-470.

36. Domniki Liatsi, Basilis Tsapias, Smaro Pampori, Matthew Tsagourias, Ioannis Pneumatikos, Dimitrios Matamis. Respiratory, metabolic and hemodynamic effects of clonidine in ventilated patients presenting with withdrawal syndrome. Intensive Care Med 2009; 35: 275-281.

37. Maze M, Scarfino C, Cavaliere F. New agents for sedation in the intensive care unit. Crit Care Clin 2001; 17: 881-897.

38. Murdoch S, Cohen A. Intensive care sedation: A review of current British practice. Intensive Care Med 2000; 26: 922-928.

39. Spies CD, Dubisz N, Neumann T, et al. Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma. Results of a prospective randomised trial. Crit Care Med 1996; 24: 414-422.

40. Gillison M, Fairbairn J, McDonald K., Zvonar R, Cardinal P. Clonidine use in the intensive care unit of a tertiary care hospital: Retrospective analysis. Can J Hosp Pharm 2004; 57: 83-89.

41. Bohrer H, Bach A, Layer M, Wernig P. Clonidine as a sedative adjunct in intensive care. Intensive Care Med 1990; 16/4: 265-6.

42. IP Yam PC, Forbes A, Kox WJ. Clonidine in the treatment of alcohol withdrawal in the intensive care unit. Br J Anaesth 1992; 68/1: 106-8.

43. Freshwater-Turner D, Udy A, Lipman J, et al. Autonomic dysfunction in tetanus - what lessons can be learnt with specific reference to alpha-2 agonists? Anaesthesia 2007; 62: 1066-70.

44. Esslinger P, Kistler W, Berger T.M. Severe autonomic dysfunction in an 11-year-old girl with generalised tetanus. Eur J Pediatr Surg 2003; 13: 209-212.

45. Bachand R, Scholz J, Pinaud M et al. The effects of dexmedetomidine on patients in intensive care settings [abstract 622] Intensive Care Med 1999; 25 (suppl I): S 160.

46. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs 2000; 59: 263-268.

47. Dexmedetomidine: A novel agent for patients in intensive care settings [abstract 683]. Intensive Care Med 1999; 25 (suppl I): 623.

48. Richard R. Riker, Yahya Shehabi, Paula M Bokesch et al. Dexmedetomidine vs Midazolam for the sedation of Critically ill patients: A Randomized Trial. JAMA 2009; 301(5), 489-499.

49. Pratik P. Pandharipande, Brenda T. Pun, Daniel L. Herr et al. Effect of sedation with Dexmedetomidine vs Lorazepam on Acute brain dysfunction in mechanically ventilated patients: The MENDS randomized Trial. JAMA 2007; 298 (22): 2644-2653.