Clonidine, dexmedetomidine: alpha-2 adrenergic receptor agonists in neuroscience

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INTRODUCTION
In the past, there was a scientific theory of adrenergic mechanisms: it was thought that adrenergic receptors consisted of two classes and the actions of these groups resulted in either excitation or inhibition of effector cells.1 This theory was the accepted concept until Ahlquist demonstrated that there were subtypes of receptors in the class, which he termed α and β1. Researchers later discovered that one of α receptors inhibited neurotransmitter release from the presynaptic neuron (Figure 1).2

The α-2 adrenergic agonists were developed for their use in clinical practice, including as anesthesia and analgesic adjuncts. The administration of α-2 AR agonists as adjuncts gained popularity, as reported by Brodsky and Bravo in 1976.3

ABSTRACT
The alpha-2 adrenergic receptor (α-2 AR) agonists have a long history of use in treating different clinical conditions, such as hypertension, psychiatric entities (e.g., attention-deficit hyperactivity disorder), chronic pain, panic disorders, and, lately, for treating opioid withdrawal syndrome. In recent years, α-2 AR medications have been administered as adjuncts for managing inflammatory conditions, depression, chronic pain, sleep and cognitive disorders. This review will provide some clinical applications in neuroscience for this class of drugs. Understanding the pharmacological mechanisms is essential to obtaining neurochemical data that demonstrate that α-2 AR agonists have potential clinical significance in neuroscience.

Keywords: α-2 AR agonists, Cognitive, Depression, Immune system, Pain, Sleep
Moreover, it was shown that α-2 AR agonists were acting on both the central and peripheral nervous systems.\(^3\)
Centrally, within the locus coeruleus, for example, α-2 AR agonists can produce sedation, analgesia, and euphoric effects.\(^3\) More potent α-2 selective medications, such as dexmedetomidine, have been used as sole sedative agents or as adjuncts to drastically reduce a patient’s requirement for additional sedatives or general anesthetics.\(^4\)

Additionally, new agonists and antagonists with high selectivity for imidazoline receptor subtypes (I1, I2, and I3) have been recently developed. These pharmacological imidazole subtypes are more effective in the regulation of body fat, inflammation, neuroprotection, epilepsy, cell proliferation, stress, depression, and pain.\(^5\)

This review aims to elucidate the clinical effects of using α-2 AR agonists in some neurological conditions, including inflammatory conditions, cognitive disorders, chronic pain, depression, and sleep.

Dexmedetomidine is a highly selective α-2 receptor agonist, with a tenfold greater affinity and selectivity than clonidine. It produces clinical effects following binding to G protein-coupled α-2 AR, of which there are three subtypes (α2A, α2B, and α2C), with each providing different physiological functions and pharmacological actions.\(^6\) These pharmacological subtypes are present in the peripheral, central, and autonomic nervous systems (ANS), as well as blood vessels and vital organs. The pharmacokinetic properties of dexmedetomidine have not changed by age.\(^7\)

**REVIEW OF LITERATURE**

This review conducted by using PubMed, MENDS randomized controlled, systematic review and meta-analysis of randomized controlled trials and Cochrane database to identify studies that have shown the intervention of α-2 AR agonists for clinical use in neuroscience. Initially, we searched related studies for the efficacy of the α-2 AR agonists in specific clinical applications in neuroscience regarding the effectiveness of the immune system, cognitive function, pain, depression, and sleep. The literature selected was focused on clinical uses of α-2 AR agonists in medical conditions related to neurology and exclude other uses of α-2 AR agonists like the effect on cardiovascular system.

The aim of this paper has to be balanced with the need for clinical administration of α-2 AR agents on different neuroscience applications and to make their view relevant to a broad audience. We searched for the two medications of the α-2 adrenoceptors “Clonidine and Dexmedetomidine” and their clinical uses on different medical conditions. Studies are not meeting the inclusion criteria were excluded. These criteria are focused on the efficacy of these medications on the immune system, cognitive disorders, chronic pain, depression, and sleep. Therefore, the traditional snowball method was then used to select literature that the clinical research team deemed most relevant. Dr. Blaise, assessed for the quality of data and relevance, reviewed the literature, and our findings were summarized in this paper. All authors searched the Cochrane database by using the keywords α-2 AR agonists; immune system; depression; sleep; cognitive; pain from 1985 to 2018.

Authors summarized the data from literature reviews in order to find out the effect of the α-2 AR agonists on neurological conditions in terms of they could reduce cytokines in serum levels and boosting the immune system and can produce adequate analgesia to humans by spinal administrations. In addition, clonidine reduces PTSD trauma nightmares and enhances sleep physiology while dexmedetomidine can minimize the development of delirium and improve cognitive function. Also, dexmedetomidine has excellent analgesic and sympatholytic sedative effects in the central nervous system. There is no adequate data show dexmedetomidine efficacy and safety on depression; however, several studies

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**Figure 1: Synaptic influences of α-1 and α-2 receptors.** Post-junctional α-1 receptors mediate effects on target tissues whereas pre-junctional α-2 receptors inhibit neurotransmitter release and provide negative feedback.

**Pharmacology**

Clonidine is an imidazole derivative and is a centrally acting α-2 AR agonist.\(^6\) The stimulation of α-2 receptors has several effects, such as inhibition of adenyl cyclase, promotion of phospholipase D, stimulation of mitogen-activated protein kinases, stimulation of K+ currents and inhibition of Ca2+ currents.\(^7\) Clonidine acts specifically on α 2-receptors. These receptors regulate some signalling pathways promoted by multiple Gi proteins, Gαi1, Gαi2, and Gαi3.\(^3\) In addition, the hypotensive effect of clonidine centrally is attributed to both α-2 AR and non-adrenergic N1-imidazoline receptors; whereas their sedative action has only involved the activation α-2 AR located in the locus coeruleus.\(^9\)
have shown 1MeTIQ has completely antagonized the clonidine-induced depression and restored their levels to the control values. Therefore, this paper concluded that the α-2 adrenoreceptors would serve as useful pharmacological intervention for improving the neuronal stability and function when used in the long term.

**DISCUSSION**

Authors have reviewed the clinical effects of using α-2 AR agonists in some neurological conditions in terms of inflammatory conditions, cognitive disorders, chronic pain, depression, and sleep.

**Immune system**

An experimental study has shown that perineural injection of clonidine at the time of surgery delayed the onset of hypersensitivity for two weeks after partial sciatic nerve injury in rats. This study observed α-2 adrenoceptor immunoreactivity in macrophages and T cells in the injured nerve and it was suggested that clonidine changed immune cell function to produce the delayed onset of action and prolonged effect by normal stimulation lymphocytes and inhibition cytokines. Repeated perineural clonidine injection resulted in the delayed development of hypersensitivity and was associated with significant reductions in TNF-α and IL-1β concentrations in rats. Two observations support the presence of an immunomodulatory effect of clonidine: a similar time course of behavioral and immunologic influences, and the presence of α2-adrenergceptors on immune cells at the site of injuries.\(^{10}\)

Significantly, as clonidine decreases hypersensitivity reactions in animals with nerve injuries, it also provides analgesia in neuropathic pain patients after spinal injection. The effect of clonidine occurs rapidly and lasts for some time by reducing pro-inflammatory cytokines IL1, IL 6, and TNF as well as increasing anti-inflammatory cytokines stimulation, such as IL4 and IL10. If clonidine is injected at the area of nerve injury, it leads to reduced hypersensitivity. However, the onset will take a few days, but the duration of action will be more than a week.

This slow time route indicates the reflection of clonidine-induced changes in the recruitment and functions of immune cells at the site of inflammation. This process would support by the observations noted with perineural clonidine, which reduced pro-inflammatory cytokines content in the damaged nerve when used at the time of injury.\(^{11}\)

Dexmedetomidine is a highly selective α-2 adrenergic receptor agent. It produces anxiolytic, sedative, and analgesic actions, and it has been proven to attenuate delirium and postoperative cognitive dysfunction (POCD), particularly in the postsurgical period. Many experimental studies have indicated that dexmedetomidine has a neuroprotective effect during stress, as well as during the inflammatory response. In a rat tibial fracture model, dexmedetomidine pre-treatment significantly reduced inflammatory responses, as demonstrated by lower TNF-α and IL-1β levels, significantly inhibited nuclear factor-xB (NF-kB) activity, and alleviated overexpression of microglia and astrocytes in the hippocampus and is thus associated with activation of a cholinergic anti-inflammatory pathway.\(^{11}\)

**Cognitive function**

In a study of the cognitive effects of clonidine, immediate memory recall declined after a sixty-minute infusion by 12, 25, 25 and 45% in four groups (placebo or clonidine 1, 2, or 4µg kg⁻¹ h⁻¹), respectively. The only notable difference was observed in the placebo versus clonidine 4µg kg comparison graph. The comprehensive memory test (CMEM), given at ninety-minute in the recovery period, indicated that the 4µg kg dose significantly impaired recall of word lists recited at three time points of the experiment: 33% recall after placebo versus 7% recall after clonidine 4µg kg. Recall of the list given at the 45-minute recovery period was not significantly impaired after clonidine infusion. With placebo, recall increased from the baseline so that the most words were recalled from the most recent list. This pattern was not noticed in the clonidine infusion groups. Therefore, there is no evidence of retrograde amnesia, as the recall of the baseline list was not different between the placebo and clonidine infusions groups.\(^{12}\)

Although nocardipine and clonidine were found to have comparable effects in a study in hypertensive patients, these medications are distinctly different with respect to cognitive function and psychomotor performance.\(^{13}\) Clonidine altered vigilance, attention, and body control, as was shown by the significant increase in the length of body sway during evaluations. This study confirmed the sedative effects of clonidine (drowsiness and tiredness), which are frequently reported by hypertensive patients, and are well-known side effects of clonidine.\(^{14}\) Dexmedetomidine has sedative and analgesic properties, inducing a degree of depth of sedation in which patients can respond to verbal stimulation and obey simple commands.\(^{15}\)

Dexmedetomidine does not affect intracranial pressure, but there are some concerns that it might reduce cerebral blood flow leading to ischemia. Several studies have revealed a matched correlation between cerebral blood perfusion and cerebral metabolic rate.\(^{16}\) In addition, dexmedetomidine does not affect motor-evoked or somatosensory-evoked potentials, so this would make it a useful anesthetic-sparing medication, as well as an analgesic supplement during surgery.\(^{16}\) Some experimental studies have shown dexmedetomidine has neuroprotective effects in hypoxic-ischemic and traumatic brain damage in animal models. This protection appears to be supported by the action of the agent on α-2 AR and imidazoline receptors. However, the clinical relevance of these findings needs more evaluation.\(^{17}\)
In the ICU, patients who received dexmedetomidine were found to be more cooperative, more active, and better able to communicate their pain than those who receive other kinds of sedatives. Additionally, dexmedetomidine has been thoroughly evaluated to assess its efficacy in decreasing the occurrence of emergence delirium. On the other hand, decreases in blood pressure and heart rate have been significantly observed with dexmedetomidine compared with midazolam.

A clinical study compared the effectiveness of dexmedetomidine with midazolam for the maintenance of ventilated patients and examined the incidence of delirium in those patients. The findings revealed that dexmedetomidine significantly reduced the rate of delirium: 54% compared to 76.6% for midazolam. Furthermore, the duration of delirium was reduced to 48% in the dexmedetomidine patients, and patients were treated with dexmedetomidine had a significantly greater ability to cooperate and communicate than those receiving midazolam. Therefore, although cognitive impairment has been negatively reported with α-2 adrenergic receptors agonists, they have a crucial role in preventing or controlling emergence delirium and maintaining cognitive function.

**Chronic pain**

Since clonidine produces strong analgesia during experimental studies on animals, it can also provide adequate analgesia to humans by the local and spinal routes of administration. Clonidine is also a useful analgesic agent when used in an epidural procedure. However, it gives inadequate analgesia when administered systemically. According to laboratory and clinical findings, intraspinal administered α-2 AR agonists might be useful in the management of neuropathic pain.

Following intrathecal (IT) injection, clonidine reduced autonomic behavior in an animal model with neuropathic pain, which suggests that it is a more potent analgesic agent than using morphine alone. Clinically, it was shown to suppress chronic pain in open-label clinical trials of patients with chronic neuropathic pain. When clonidine was given with morphine as a mixture for chronic pain relief by the intrathecal technique, the combination was found more potent and effective than either drug administered alone.

Clonidine has anti-nociceptive activity via different mechanisms, including peripheral, supraspinal, and primarily spinal cord, as well as the activation of descending noradrenergic pathways. Clonidine has been shown to prolong the duration of analgesia. More recently, systematic reviews evaluated clonidine as an analgesic drug in patients who underwent various surgeries and received IT clonidine infusion. These reviews reported that patients who received clonidine had a statistically significant prolongation in the time to first analgesia request compared with the placebo group.

The most common α2-receptor agonist for intrathecal administration is clonidine, as its combination with local anesthetics and morphine has a synergistic effect for relieving pain. Clonidine is mainly administered in combination with morphine for treating neuropathic pain. Furthermore, IT administration of clonidine with the average daily dose range of 50 to 200μg minimizes the risk of morphine tolerance, and thereby reduces the risk for opioid-related side effects. It is important to note that abruptly stopping long-term IT therapy might lead to rebound hypertension and psychotic behaviour.

A retrospective patient chart review was performed comparing IT clonidine alone or in combination with opioids for managing chronic pain conditions, i.e., complex regional pain syndrome (CRPS), neuropathic pain, and cancer pain. All 15 patients received a trial of a single-shot and/or short-term clonidine infusion. Ten of 15 patients reported a significant pain relief (over 50% decrease in visual analog scale (VAS) scores) with the initial trial and then received long-term therapy. Initially, 70% patients responded to clonidine alone before requiring a second medication. IT clonidine in combination with IT opioids provided a long-term benefit (from 6 months to ongoing at 29 months when the article was published) in patients who had previously failed IT opioid monotherapy. Thus, clonidine has a synergistic effect with other analgesic medications and prolongs their analgesic action, while decreasing the risk of morphine tolerance.

Dexmedetomidine has the same effect as clonidine, but it presents with a variety of more favorable pharmacokinetic properties. It exerts its effects on various areas in the pain pathway, but a central action area is at the level of the spinal cord in the substantia gelatinosa of the dorsal horn. This action reduces the release of nociceptive neurotransmitters, such as substance P. Additionally, dexmedetomidine might offer a novel paradigm in the pharmacologic therapy of symptoms of chronic pain and delirium at the end of life. The Food and Drug Administration has approved the use of dexmedetomidine in managing chronic intractable pain in patients with cancer. Dexmedetomidine has a significant opioid-sparing action, and it is useful in severe neuropathic pain. It is of particular benefit in specific patient populations where the respiratory-depressant impacts of opioids are deleterious and hazardous to patients. A randomized controlled trial in thoracic surgical patients found less supplemental opioid was needed in the group who also received an IV dexmedetomidine infusion.

**Depression**

For many years, depression was not generally accepted to be a side effect of clonidine, it seems that it could manifest as another central side effects. Some studies, though, have strongly suggested that clonidine is a contributing factor in depression. Therefore, it might be that the possibility of clonidine to cause depression is underestimated, as reported clonidine induced-depression is a universally rare
adverse effect. More recently, an experimental model of depression examined the behavioral (locomotor activity test and forced swim test FST]) and neurochemical (monoamines metabolism) effects of a low dose of clonidine (0.1mg/kg i.p.) in rats.27

Researchers investigated the antidepressant-like effect of an endogenous neuroprotective amine, 1-methyl-1, 2, 3, 4-tetrahydroisoquinoline (1MeTIQ) administered in a dose of 25mg/kg i.p. before clonidine. The behavioral test revealed that clonidine produced depression in the locomotor activity test, but it did not lead to pro-depressive effect in the FST. Significantly, 1MeTIQ produced an antidepressant-like effect in the FST, and its antagonized clonidine-induced sedation in the locomotor activity test. The neurochemical study demonstrated that clonidine produced a significant suppression of monoamine metabolism in the central nervous system. Thus, 1MeTIQ, as an endogenous neuroprotective structure with a distinct antidepressant-like activity, could play an important role in the efficiency of antidepressant medications in the future.28

Dexmedetomidine acts predominantly in the locus coeruleus, and it reduces central nervous system excitation by decreasing presynaptic norepinephrine release. It also works as a sedative medication and, to a lesser extent, as an analgesic, anxiolytic, and sympatholytic.29

Some psychological disorders, such as major depression and schizophrenia can be managed with electroconvulsive therapy (ECT), which is an effective and safe non-pharmacological intervention. However, ECT leads to postictal agitation (PIA) during the treatment course. A retrospective study was carried out on seven patients with major depressive disorder who underwent 178 ECT sessions over four years. In 101 sessions, patients received dexmedetomidine with ketamine as mono-anesthetic.30

The main finding of this research is the significant reduction (34% vs 62% prevalence without dexmedetomidine) of postictal agitation occurrence when adjunctive dexmedetomidine administration to ketamine in a selected individual with a very high intractable PIA rate.30 Additionally, multiple studies have reported the successful use of dexmedetomidine in the prevention and treatment of delirium and agitation, particularly in intensive care units. Based on these studies, it is concluded that dexmedetomidine as an adjunct is effective and safe for patients who suffer from major depression and are undergoing ECT after failing traditional antidepressant medications.31

Sleep

Alpha-2 ARs are found in high concentrations in the prefrontal cortex (PFC), but at low level of concentrations in the nucleus accumbens. The most common subtype in the PFC is α-2 AR regulating hyperactivity, impulsivity, and inattentiveness. It seems that clonidine might work in a synergistic pattern with stimulants by the mediating of PFC. Thus; this enhancing of efficacy without compromising safety has been proven.32

Several studies have revealed that lower dose clonidine increases R sleep or REM sleep (the fourth stage of sleep, in which the brain waves are the same as in a wakened state - most dreams occur in this stage) and decrease non-rapid eye movement NREM sleep. N sleep or NREM sleep is identified in stages N1, N2, and N3 or deep sleep, and N sleep occupies about three-quarters of an adult’s sleeping time. Medium dose clonidine, however, significantly decreased R sleep and increased (second stage) N2 sleep and has been reported as effective in reducing the frequency of nightmares.33

Several studies support this indication, including an open-label case series to minimize PTSD-induced nightmares and enhance sleep in Cambodian refugees, as well as improve PTSD symptoms in veterans. Improved sleep in the open-label study was accompanied by improving sleep physiology as determined by the polysomnography test.34 Clonidine was effective in reducing sleep initiation latency, minimizing night awakening, and improving attention-deficit/hyperactivity disorder (ADHD) symptoms, mood instability, and aggressiveness in a cohort of 19 children with autism spectrum disorder (ASD).35

Dexmedetomidine has excellent analgesic effects and sympatholytic sedative effects in the central nervous system. Its pharmacological properties are regulated by agonism of α-2 AR mainly in the locus coeruleus of the pons where it results from suppression of norepinephrine release. Therefore, it has been postulated that these findings in disinhibition of the ventrolateral preoptic nucleus would lead to the release of inhibitory neurotransmitters. This pathway is a part of the complicated circuitry process of the natural sleep pattern, resulting in the good quality of sedation with dexmedetomidine, which more closely resembles regular physiological sleep than that of the familiar GABA-ergic sedatives agents, such as propofol and benzodiazepines.36

This sedation is positively characterized by the typical pattern of ventilation, which is preserved muscle tone, spontaneous movements, and awakening by external stimuli. When roused, most patients sedated with dexmedetomidine are cooperative and can obey simple instructions. Electroencephalograms have confirmed that the sedative effects of dexmedetomidine closely resemble stage 2 NREM sleep.37 However, experimental studies have explained that noradrenergic neurons in the locus coeruleus are active during vigilance, less vital during NREM sleep, and silent during REM sleep.38

Administration of dexmedetomidine (0.3mg/kg) leads to inhibition of noradrenergic neurons within the locus coeruleus, and systemic administration of dexmedetomidine may be predicted to prolong REM sleep in rats. However, findings show that dexmedetomidine led to a long-lasting elimination of REM sleep.39 The process
by which dexmedetomidine abolished REM sleep remains to be further elucidated (Figure 2). The study concluded that dexmedetomidine significantly changed normal sleep phenotypes, and its induced state would not compensate for sleep need. Therefore, dexmedetomidine-induced sedation was characterized by electrographic, immunohistochemical and behavioral phenotypes that are distinctly different from similar measures obtained during natural sleep in rats.

**CONCLUSION**

The α-2 adrenergic receptor medications have an established a place in the modern anesthetic clinical practice because of their ability to produce positive effects without causing harmful adverse effects. The α-2 AR agonists mainly promote neuronal stability while minimizing anesthetic requirements in some medical conditions. They serve as useful tools for managing chronic refractory pain due to their synergy with other analgesic medications. They have potent positive effects on the immune system and enhance cognitive function when used in the long term. The α-2 AR agonists have some antidepressant action and can improve sleep patterns. Dexmedetomidine, in particular, can provide an exceptional quality of conscious sedation, which resembles natural sleep.

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**Figure 2:** Dexmedetomidine disrupts the sleep/wakefulness cycle and increases electroencephalogram (EEG) delta power. Minutes per hour that rats spent in states of wakefulness (A): Non-rapid Eye Movement Sleep/sedation, (B): and Rapid Eye Movement Sleep, (C): are plotted as a function of time after systemic administration of saline or dexmedetomidine (0.3mg/kg), (D): shows average EEG power after systemic administration of saline or dexmedetomidine (0.3mg/kg).


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