University of Montreal

Role of the multidrug-based approach to control chronic pain and cognitive impairment in people with chronic refractory pain - literature review

By

Jabril Bashir Eldufani

Biomedical Sciences Program

Faculty of Medicine

Submission to the Faculty of Graduate and Postdoctoral Studies

In order to obtain the degree of Master of Science (MSc)

Biomedical Sciences Program

Experimental Medicine Division

November 2017

University of Montreal

Faculty of Graduate and Postdoctoral Studies

This thesis entitled:

Role of the multidrug-based approach to control chronic pain and cognitive impairment in people with chronic refractory pain - literature review

Presented by: Jabril Bashir Eldufani

Has been evaluated by a jury composed of the following persons:

Dr. Florina Moldovan, Chairperson-Rapporteur

Dr. Ana Míriam Velly, Member of the Jury

Dr. Gilbert Blaise, Research Director

Résumé

La douleur chronique est une complication de nombreuses pathologies, parmi celles-ci il faut mentionner, le diabète, le zona, les maladies de la colonne vertébrale, l'ostéoarthrose et de nombreuses maladies neurologiques dégénératives. Pour de nombreux cliniciens et algologues le traitement de la douleur chronique est devenu un défi grandissant. Parmi les multiples modalités du traitement de la douleur, l'utilisation de mélanges médicamenteux composés de substances dont le mécanisme d'action est différent et donc agissant sur différentes voies de génération et de transmission de la douleur, a beaucoup plus de chances d'être une thérapeutique efficace avec moins d'effets secondaires qu'une seule substance utilisée à des doses plus élevée, nous ne disposons pas de médicament miracle. Parmi les médicaments pouvant être utilisés en traitement de la douleur, il faut mentionner, les anesthésiques locaux. Les alpha-2 agonistes, les inhibiteurs du cholinestérase, les opiacés etc.

La combinaison de ces médicaments même à faible dose peut cependant entraîner des effets secondaires propres dus à la combinaison de plusieurs substances. La connaissance du mécanisme d'action spécifique de ces drogues, de leur profil pharmacologique et pharmacocinétique et de leur interaction médicamenteuse est une nécessité pour prévenir les effets secondaires tout en obtenant un effet thérapeutique intéressant. Dans ce travail notre intérêt a été porté notre attention sur les données scientifiques publiées pour chaque agent avec un intérêt pour les données expérimentales et cliniques. Notre intention et de porter plus d'intérêt sur les données cliniques, en particulier sur l'effet de mélanges thérapeutiques sur la douleur chronique, le système immunitaire et la fonction cognitive.

Mots clés : Morphine, bupivacaine, ketamine, clonidine, dexmedetomidine, neostigmine, naloxone, douleur chronique, cognition, Dépression.

Summary

Chronic pain is a debilitating clinical condition that is associated with a variety of disease entities, such as diabetic neuropathy, postherpetic neuralgia pain, low back pain, osteoarthritis and chronic neurological disorders. For many clinicians and specialists, management of chronic pain has become an intimidating challenge. As a modality of multidisciplinary pain management, different types of medications are often prescribed in combinations to provide fast and effective pain relief. However, many medications for pain treatment, including local anesthetics, α2-adrenergic agonist, cholinesterase inhibitors and opioid analgesics have significant adverse effects which could compound when drugs are administrated in combination.

Preventing or reducing the severity and frequency of the side effects mainly depend on understanding the mechanisms of actions, as well as physiological and pharmacological effects of these medications. In this project, we will focus on 1) the scientific basis of each agent with specific effects criteria regarding experimental and clinical aspects. 2) We need more to focus on clinical studies regarding the effects of medications on chronic pain, the immune system, and on cognitive function.

Keywords:

Morphine, bupivacaine, ketamine, clonidine, dexmedetomidine, neostigmine, naloxone, chronic pain, cognitive functions, depression.

Abstract

Chronic pain is a multifactorial clinical condition that has negative impacts on physical, social, and emotional states of the patients. Globally, it affects approximately 20% of the population, especially in developed countries, and continues to exist as a significant problem in the elderly. However, in last two decades, there have been advances in pain treatment regarding analgesic medications and technical procedures. This review will provide a mechanism- and evidence-based approach to enhance the outcome for the pharmacologic management of chronic refractory pain while minimizing the negative impact on cognitive function. Therefore, this approach will discuss different types of medications that affect chronic pain, as well as the cognitive function (morphine, ketamine, bupivacaine, naloxone, clonidine, and neostigmine).

Table of Contents

List of tables

List of figures

List of abbreviations:

- Ach — Acetylcholine
- AD — Alzheimer's disease
- ADHD — Attention-deficit hyperactivity disorder
- ESI — Epidural steroid injection
- CBT — Cognitive-behavioral therapy
- CCHS — Canadian community health survey
- CNS — Central nervous system.
- CRPS — Complex regional pain syndrome
- CSF — Cerebrospinal fluid
- ECT — Electroconvulsive therapy
- FM — Fibromyalgia
- GIT — Gastrointestinal tract
- GABA — Gamma-aminobutyric acid
- HMGB1 — High mobility group box 1
- IASP — International Association for the Study of Pain
- ICD — International Classification of Diseases
- IFN-y — Interferon gamma
- IL — Interleukin
- IM — Intramuscular
- IDDS — Intrathecal drug delivery systems
- IT — Intrathecal
- IV — Intravenous
- LA — Local anesthetics
- LPS — Lipopolysaccharide
- MDD — Major depressive disorder
- MMSE — Mini Mental State Examination
- MNTs — Mechanical nociceptive thresholds
- mTOR — Mammalian target of rapamycin
- mRNA. — Messenger Ribonucleic Acid.

- NIH National Institutes of Health
- NCBI National Center for Biotechnology Information
- NF-κB Nuclear factor κ-light-chain-enhancer of activated B cells
- NO Nitric oxide
- NMDA N-methyl-D-aspartate receptors
- NRS Numerical rating scale
- NSAID Non-steroidal anti-inflammatory drugs.
- PCA-IV Intravenous patient-controlled analgesia
- PCEA Patient-controlled epidural analgesia
- pCO2 Arterial partial pressure of carbon dioxide
- PD Parkinson disease
- PHA phytohaemagglutinin
- PO Per os
- POCD Postoperative cognitive dysfunction
- PVI Paravertebral infiltration
- PPAR-α Peroxisome proliferator-activated receptor-α
- RCTs randomized controlled trials
- S/C Subcutaneous
- SAH Subarachnoid hemorrhage
- TNF-α Tissue necrosis factor α
- VASI Visual Analogue Scale Index
- VD Vascular dementia

Thanks

I would like to thank Dr. Gilbert Blaise for his continuous help and support, which enabled me to complete this project in order to achieve my master's degree. Dr. Blaise's teams at the laboratory and the clinic, too, were very helpful and cooperative. I would also like to thank my parents, who have been waiting for over three years for me to come back to my home and country, Libya. Special thanks go to the Minister of Higher Education and Scientific Research who offered me the scholarship allowing me to pursue my academic degree.

I am very proud to be a graduate student with a master's degree who completed his academic courses under the tutelage of the distinguished professors at the University of Montréal.

Chapter I

1.1 Introduction

The International Association for the Study of Pain (IASP) has defined chronic pain as the pain that persists after the normal tissue healing time of approximately three months (1). However, there is no standard definition of chronic pain can be universally accepted (2). Most recent studies used 3 or 6 months as a pain duration to identify chronic pain, and also other studies include the intensity of pain and pain frequency criteria as well (3). The new International Classification of Diseases, Eleventh Revision (ICD 11), which is a slandered diagnostic method for health management and clinical purposes, has classified chronic pain based on the most common clinical disorders, namely chronic primary pain, chronic cancer pain, chronic posttraumatic and postsurgical pain, chronic neuropathic pain, chronic headache and orofacial pain, chronic visceral pain, and chronic musculoskeletal pain (4).

Chronic pain is identified as a common issue which affects people general health (5), psychological health (6), and socioeconomic well-being (7, 8). Chronic pain is recognized as one of the most common rationales for seeking medical care (9). In addition, people who suffer from chronic pain need health services five times more than others do (10), causing many workdays lost (11). Consequently, there has been increasing recognition of pain treatment as a fundamental human right (12, 13).

During the last decades, the prevalence of chronic pain has dramatically increased especially among adults (14). In a recent study review, chronic pain prevalence ranges from 2% to 40% (median value 15%) of the adult population (15). Female sex, middle age, and lower socioeconomic status are strongly related to chronic pain (14). Telephone surveys showed that overall chronic pain prevalence was 27% for Canadian men and 31% for Canadian women (14).

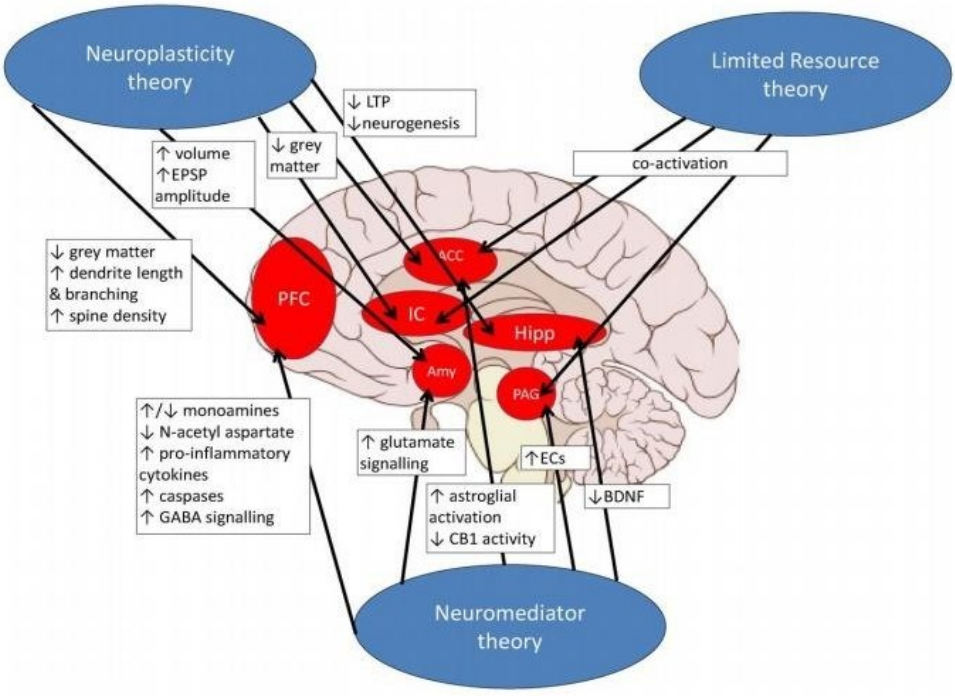
Significantly, chronic pain prevalence in Canada has reached an alarming rate, leading to more focusing on finding the treatment that is more effective to control the situation.

In 1983, $40 billion was spent annually in the United States to treat chronic pain (16). More recently, the New Institute of Medicine report in 2011 estimated the economic burden of chronic pain to society from health care costs to be over $600 billion annually in the United States (17). As seen, the annual cost of chronic pain management has increased over the years. According to the recent report from Canadian Community Health Survey (CCHS) (in a survey represented 2,072,691 Ontarians and 5,375,298 Canadians with chronic pain), the weighted annual for every person cost to order to manage chronic pain for survey respondents was $1334 (18). The total annual burden of chronic pain was estimated at $2.8 billion for Ontario and $7.2 billion for Canada (18).

Since the prevalence of chronic pain is rising in an aging population with increasing annual cost (19, 20), many people with chronic pain do not receive enough pain management contributing to disease burden (21, 22). Significantly, 36 % of primary care physicians in Canada estimated that chronic pain to be well controlled in 2001 while just 3% of chronic pain cases were well controlled (23). Similarly, 40% of primary care physicians assumed chronic pain to be managed in 2004 while just 1% of chronic pain cases were achieved (23). Poor chronic pain management in Canada was 67% in 2001 while it was 72% in 2004 (23). Poor chronic pain management has an impact on health care burden 85%, patients suffering 98%, physician burden 80%, economic productivity 80%, drug abuse 70%, and health care costs 83% (23). With all that cost, chronic pain management has not been fully appreciated (18).

Moreover, patients with chronic pain might suffer from impairment in their cognitive functioning (24). That might return to neural systems related to chronic pain and cognitive

processing is strictly linked, and they might modulate each other alternately (24). Cognition has been defined as the brain's information possession, processing, storage, and retrieval of knowledge (25). The exact mechanisms of the relationship between chronic pain and cognitive function have not to be clarified. Therefore, a literature review has provided support for some theories: chronic pain consumes cognitive resources, modifies neural plasticity, and impact on releasing of different cellular neuro-mediators and chemicals across a complex system of cognition-related brain regions to finally cause cognitive impairment (Fig. 1) (24).



Potential mechanisms of pain-related cognitive impairment, a theoretical model. Pain-induced changes in resource utilisation, neuromediators and neuroplasticity may affect cognition through a network of brain regions. PFC: prefrontal cortex, IC: insular cortex, Hipp: hippocampus, Amy: amygdala, PAG: periaqueductal grey, ACC: anterior cingulate cortex, LTP: long-term potentiation, EPSP: excitatory post-synaptic potential, BDNF: brain-derived neurotrophic factor, ECs: endocannabinoids.

Figure 1: potential mechanisms of pain-related cognitive impairment (24).

With all these negative impacts of chronic pain on patients' health and community, finding a new approach and alternative method to achieve an efficient, durable and safe chronic pain management is requisite. In 2015, a clinical report illustrated intrathecal (IT) infusion of an

analgesic medications mixture (26). That includes of bupivacaine 1 mg/mL, naloxone 0.02 ng/mL, morphine 0.01 mg/mL (with a dramatically reduced in the consumption), ketamine 100 µg/mL and clonidine 0.75 µg/mL controlled the chronic pain of three patients suffered from different kinds of chronic pain (26). Moreover, significant adverse effects such as muscle weakness, constipation, sphincter dysfunction, hypotension, and cognitive impairment were not noticed with this method of treatment (26). However, one patient had a urinary tract infection, which was treated with antibiotics (26). IT approach has less adverse effects due to fewer drug doses (26). In addition, IT rout gives better results comparing to epidural route for chronic cancer pain (27). Indeed, Food and Drug Administration establish morphine for IT use (26). Naloxone, morphine, ketamine, and clonidine were used successfully by IT route with a higher dose than used doses in this clinical study (Table 1) (26).

Comparison of recommended intrathecal daily drug doses and doses used in the present study

Drug	Recommended dose (9)	Dose used in the present study*
Morphine	1–20mg	0.08–0.24 mg
Bupivacaine	4–30 mg	8–24mg
Clonidine	30–1000 µg	6–18 µg
Naloxone	no data available	0.2–0.5 ng
Ketamine	1–50 mg	1–2.4 mg

**Calculated on the basis of ≤1 ml/h infusion rate*

Table: 1 Comparison of recommended IT dose and used dose in the study (26).

Significantly, IT infusion of this analgesic medications mixture has a variety of mechanisms of action and the synergistic effect that explain the analgesic effect of this combination over different kinds of chronic pain at lower concentrations (26). In addition, systemic side effects of this mixture were not significant due to the very low concentration of the drug combinations, particularly the ultra-low dose of naloxone (26). All these achievements of

this analgesic mixture could make this method to be viewed as an alternative to patients whose chronic pain is uncontrollable via conventional techniques. However, this study was done on just three patients, so other scientific research should be done to support this evidence. Consequently, based on this advanced clinical study, this literature review was conducted to come out with good knowledge about mechanisms of action of these analgesic medications and their effects on chronic pain and cognition impairment.

Intrathecal neostigmine analgesic effect on chronic pain was reported in experimental sheep (28) and humans (29). Moreover, two other medical reports have shown using of neostigmine combined with morphine to control different kinds of chronic pain in adults (30, 31). Further, low-dose neostigmine improves morphine analgesia in chronic pain management, without increasing the occurring of the side effects (31). As a result, neostigmine was added to the analgesic medications mixture in this literature to review the overall outcomes of each medication.

In order to improve patient outcomes, different mechanisms of pain, sensitization, and multi-mechanistic of analgesic medications should be addressed. Therefore, physicians and pain management specialties need to be familiarized with these areas (32). This review explains each analgesic medication regarding the efficacy and safety to use these specific medications as combinations over monotherapy for managing chronic pain with cognitive disorder. These synergistic combinations effect provides a reduction in the individual drug dose, and thus lower the incidence of drug-related adverse effects.

The aim of this review would be achieved via the implantation of an intrathecal drug delivery system (IDDS) that offers many advantages by improving analgesia with reduction of systemic or cerebral side effects compared to oral or parenteral routes (33). A product of

combination, including morphine, bupivacaine, ketamine with clonidine and the ultra-low dose of naloxone would be an appropriate as a mixture of combined medications via IT infusion (26). Moreover, neostigmine combined with bupivacaine (34) and morphine (31) produces superior analgesia comparing with using bupivacaine or morphine alone. This combination may give a positive outcome for patients who have suffered from chronic neuropathic pain and cognitive impairment (35). Based on pharmacological interactions, adverse effects of analgesic medications, as well as the complexity of chronic pain mechanisms that might suggest combinations drug therapy is justified and fundamentally necessary.

Therefore, the objective of this Master thesis is to review the existing literature to improve the supporting evidence of the analgesic medications mixture usage (bupivacaine, naloxone, morphine, ketamine, clonidine, and neostigmine) in term of achievement of safe and effective chronic pain management and decreasing the cognitive impairment. Also, to create a condensed version of current studies that can be used to benefit both physicians and their patients.

1.2 Study Method

This thesis is intended to review the effectiveness and safety of the analgesic medications mixture for treating chronic pain and improving cognitive function. The analgesic medications that are frequently used as pharmacological interventions including opioids (morphine), local anesthetics (bupivacaine), alpha-2 receptor agonists (clonidine), ketamine, naloxone, and neostigmine. The literatures that were focusing on the chronic pain, which is treated via these medications, were included in this review.

The used databases were Drug Bank, PubMed, Canadian Journal of Anesthesia, American Society of Anesthesiologists (ASA) and MEDLINE from 1983 to 2018, using the key words ‘chronic pain’, ‘morphine’, ‘bupivacaine’, ‘clonidine’, ‘ketamine’, ‘naloxone’, ‘cognitive function’, and ‘mechanisms of action’. Then, the traditional snowball method was used. However, due to the time limit of this Master thesis, Dr. Gilbert Blaise has selected the literatures that were the most relevant. This literature review identified 108 studies, which had assessed the chronic pain management of those analgesic medications. After reading each literature, determining the quality of the research, identifying the most related information, and summarizing all these information to get a helpful analysis, the following summary of the classified literature was written.

In addition, the systematic review articles summarize findings of clinical studies in which neurocognitive performance was measured in chronic pain samples. Clinical and non-clinical studies were related to some medications that essentially effect on chronic pain and cognitive function, as well as immune system. The abstracts for each of these articles are evaluated for their consistency with the intent of the review.

The parameters of this project are to: provide chemical and pharmacological comprehension for each medication, understand the mechanism of action and adverse effects of these medications to come out with a proper mixture of combined medications, identify the effectiveness and safety of cognitive function, and find out how various drugs interaction is essential to make a practical pharmacological decision to manage chronic pain and cognitive impairment. Therefore, this project will discuss these analgesic medications regarding their pharmacology, metabolism, toxicity, adverse effects, and their effects on the immune system, chronic pain, and cognitive function.

Chapter II

1.2.1 Morphine

Physical, chemical, pharmaceutical and formulation properties:

Common name: morphine sulfate, USP (pentahydrate), and the chemical name is 7, 8- dihydro-4, 5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2:1) (salt), pentahydrate (36).

Molecular formula: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

Molecular weight: 758.83

Structural formula:

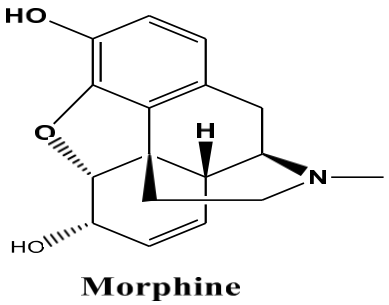


Figure 2: Morphine structural formula (36).

Morphine is a white, crystalline, odorless powder (36). It is freely soluble in water and in solutions of fixed alkali and alkaline earth hydroxides, as well as in phenol (36). It is moderately soluble in some mixtures with alcohol and slightly soluble in benzene and ammonia (36).

1.2.1.1 Pharmacology

Morphine is an opioid receptor agonist that mainly acts by binding to opioid receptors (36, 37). There are three major classes of opioid receptors (36, 37). Firstly, μ-receptor that has three subtypes, μ1, μ2, and μ3, existing in the brainstem and the thalamus (36, 37). Activation of these receptors could lead to pain suppression, hypnosis, constipation, and euphoria, as well as respiratory depression. Secondly, kappa receptors present in the limbic system, brainstem, and

spinal cord (36, 37). The stimulation of this receptor leads to pain relief, sedation, respiratory depression and addiction (36, 37). Thirdly, delta receptor δ has significant distribution in the brain, and it also presents in the spinal cord and gastrointestinal tract (36, 37). Activation of this receptor may result in analgesic and antidepressant effects and possibly respiratory depression (36, 37).

Understanding the mechanism of action and the role of morphine as a competitive agonist at opiate receptors in the CNS is crucially important, especially the μ receptors and, to a lesser extent, kappa receptors (36, 37). Activating the μ -1 subtype receptor has been considered to promote analgesia and dependence while stimulating the μ -2 receptor has been thought to be responsible for respiratory depression and inhibition of gut motility (36, 37). Additionally, exciting the kappa receptor might mediate spinal analgesia (36, 37). Indeed, the analgesic action of morphine is effective at many spinal and supra-spinal sites (36, 37).

1.2.1.2 Pharmacodynamics

Morphine has a very low lipid solubility, and it rapidly undergoes conjugation with glucuronic acid, ionizes at normal physiologic pH (36). Then, it becomes highly protein-bound after oral intake (36). Therefore, it takes approximately 30 minutes for the immediate-release morphine formulation to reach the central nervous system and about 90 minutes for the prolonged release formulation (36). The elimination of morphine occurs in approximately 120 minutes following systemic administration (36), so that is why the intrathecal approach of this drug is more supported due to providing onset of action and long duration of action (38) immediately. Around 40% of the administered dose reaches the central nervous system because of first-pass effect (metabolism in the liver) (36). Once absorbed, morphine is distributed to skeletal muscle, the kidneys, liver, intestinal tract, lungs, spleen, and brain (36). Morphine can

also cross the placental membrane in pregnant women, and it might be found in the breast milk of lactating women (36).

1.2.1.3 Pharmacokinetics

- Absorption: the rate of absorption depends on the route of administration. Absorption is approximately 30% following oral intake, whereas absorption increases with rectal, subcutaneous, intravenous (IV) and intramuscular (IM) administrations (38). Following epidural administration, the absorption of the intrathecal space occurs via the meninges (38). While morphine injected intrathecally spreads directly to the spinal nerves, which makes good advantage of relieving the pain immediately (38).
- Distribution: it is widely distributed to skeletal muscle, the liver and gastrointestinal tract, and can cross the placenta in pregnant women (38).
- Protein binding: usually <20% in premature infants and 35% in adults (38).
- Half-life: this typically depends on the age and body mass index of the subject. For example, premature neonates: 10–20 hours; neonates: 7.6 hours; infants 1–3 months of age: 6.2 hours; toddlers 1–2.5 years of age: 2.9 hours; children 3–6 years of age: 1–2 hours; adults: 2–4 hours (38). Its active metabolites are excreted by the kidneys (38).
- Table 2 shows the onset and the duration of action of morphine with different routes of administration (38).

Route	Onset (min)	Peak (hr)	Duration (hr)
PO	unknown	1	4–5
PO-ER	unknown	3–4	8–24
IM	10–30	0.5–1	4–5
S/C	20	0.83–1.5	4–5
Rectal	unknown	0.33–1	3–7
IV	rapid	0.33	4–5
Epidural	6–30	1	up to 24
IT	rapid	unknown	up to 24

Table 2: the duration of action of morphine with different routes of administration (38).

1.2.1.4 Metabolism

The metabolism of morphine is mainly hepatic (90%), and it transformed to morphine 3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in the liver, and also converted to dihydromorphinone and normorphine (36, 37).

1.2.1.5 Immune system

The activation of both central and peripheral μ receptors by administering morphine causes anti-hyperalgesia, as well as inhibition of edema formation (39). In fact, stimulation of receptors located in the CNS by systemic administration of morphine after block of the peripheral μ receptors using q-naltrexone results a significant reduction in edema (39). However, morphine has a direct and huge impact on the immune system, and it can decrease the effectiveness of several functions of both innate and adaptive immunity while reducing cellular immunity (40). Additionally, morphine has an inhibition activity on the reticuloendothelial

system and phagocyte count, killing properties, and superoxide anion production in polymorph nuclear leukocytes and macrophages (40).

1.2.1.6 Toxicity

Treatment with morphine has not been associated with increased serum enzymes (41). It appears to have hepatotoxicity (41). Morphine sulfate might irritate the respiratory system when it produces an anesthetic effect (41). Also, the inhalation of significant quantities of morphine could produce pulmonary edema and breathing difficulties (41). The most common targets of morphine toxicity are the central nervous system, respiratory system, and eyes (41).

1.2.1.7 Side effects of Morphine

Common side effects associated with morphine use affect different body systems, including:

- The effects on the central nervous system might lead to euphoria, but at higher doses could result in unpleasant symptoms such as a headache, delirium, dizziness, confusion, and seizure (42). Therefore, low dose of morphine is recommended.

- The effects of morphine on the gastrointestinal tract include nausea, vomiting, abdominal cramps, and constipation (43). Morphine receptors are present in the gastrointestinal tract; their stimulation might result in decreased intestinal motility, thereby leading to constipation (43, 44, 45).

- Dermatological effects of morphine could lead to the release of histamine in the skin, skin warmth, flushing, and urticarial eruptions with itching may occur (46). Additionally, the skin may become cool and clammy, which could lead to hypothermia (46).

- The respiratory mechanism could be suppressed in response to low blood oxygen supply (47). In healthy subjects, as blood oxygen level decreases and blood carbon dioxide increases, so the

drive for breathing rises (48). Morphine can inhibit this drive in the brain, and this could lead to a very dangerous side effect, respiratory depression, which is commonly associated with higher doses of morphine (47, 48).

- One of the prominent effects of morphine use is the development of physical or psychological dependence and withdrawal symptoms once the drug is stopped (49). Morphine is a highly addictive agent and withdrawal manifestations include pain, loss of sleep, goosebumps, hot and cold flashes and intense drug craving (49).

- Tolerance occurs when a person requires taking a drug in higher doses to achieve the same degree of euphoria or pain relief (50). Thus, developing a tolerance to morphine could lead to addiction as higher doses of the drug are required to obtain an analgesic effect (49, 50).

- The effects of morphine on the cardiovascular system, which may induce peripheral arteriolar and venous dilatation by activating histamine release and blunting reflex vasoconstriction, may lead to hypotension (51, 52).

Therefore, as mentioned before, IT morphine administrated with the other medications in the analgesic medications mixture is injected in low dose with dramatical reduction in the consumption that minimizes the side effects of morphine including the immune system disturbance and most of the mentioned systemic toxicity. This would consider the drug combination as a good chose for treating chronic pain (26).

1.2.1.8 The effects of morphine on pain

Historically, in 1803, Friedrich Serturner extracted morphine from opium as an opioid analgesic (53). In the 1850s, Charles Pravaz and Alexander Wood invented the hypodermic needle, and the latter used it to inject morphine to relieve pain from neuralgia (53). Since that

time, some diseases associated with acute or chronic pain were widely considered to be appropriate for morphine therapy (53). However, concern about addiction contributed to their under-treatment was occurred (53). The twentieth century saw much-advanced research and many changes in the way opioids were used for the management of pain in subjects with cognitive disorders (53). Nevertheless, during most of the twentieth century, the consensus among researchers in the United States was that the long-term use of morphine to treat chronic pain was contraindicated due to the increased risk of addiction, contributing disability and lacking efficacy over time (53). During the 1990s, a significant change in attitude occurred, driven by a variety of medical and nonmedical factors (53). The use of opioids for chronic pain began to increase, showing a substantial year-to-year rise that continues today (53).

Opiate analgesia typically involves at least three anatomical regions of the central nervous system: the periaqueductal-periventricular gray matter, the ventromedial medulla, and the spinal cord (54). Additionally, the analgesic effect of morphine is mainly dependent on μ-receptor saturation, so its efficacy depends on the type and severity of the pain (54). Significantly, morphine is necessarily the most common medication used in the treatment of chronic pain (54). Moreover, several studies have reported that specific doses of morphine have improved the quality of life for patients with chronic pain (55, 56).

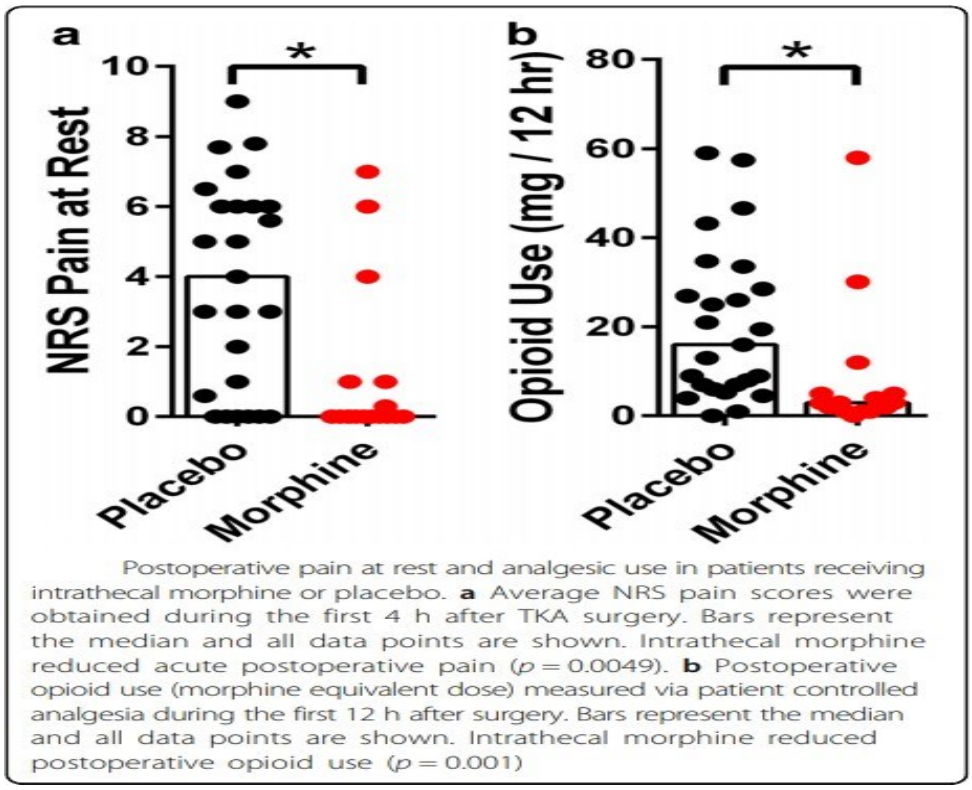
The management of chronic refractory pain and the decision to start morphine treatment should be very carefully considered regarding tolerance and adverse effects. Benefits and risks of the possible long-term management must be balanced, and patients must understand the responsibilities of morphine use (55). In conventional therapies, cancer patients with chronic pain start morphine therapy during their curative treatments, and if their chronic pain is developed, the morphine administration is continued (55). Typically, follow-up and monitoring

of patients should include regular evaluation of pain by visual analogue scale index (VASI), aim achievement, and quality of life to ensure decreasing the addictive and side effects of the drug (55). However, these precautions are difficult to adhere to which makes long-term morphine treatment in chronic pain is complicated. As a result, another advantage for the analgesic medications mixture can be considered as morphine consumption is dramatically reduced in this method of pain management, so it would not be used in long-term. Therefore, used morphine in this mixture does not cause side effects of the long-term use.

However, opioids should not be considered as the only treatment for chronic cancer pain, and pain management that includes only opioids is unlikely to be helpful in the long-term control (56). Therefore, it is always important to establish the opioid sensitivity of pain, especially chronic cancer pain, which is often neuropathic pain that has variable opioid sensitivity and might respond to a combination of other medications (56).

In a single-center prospective study, forty-two total knee arthroplasty (TKA) patients who suffer from chronic pain were enrolled in a double-blinded randomized clinical trial (57). Then, they were grouped into two groups (57). One group (intervention group) received intrathecal morphine to manage their chronic pain, and another group (control group) received placebo (57). Numerical rating scale NRS pain scores for each group were analyzed by t-test (57). The results of this study have shown that intrathecal morphine decreased postoperative pain in NRS pain score and the need for systemic opioids (Fig. 3). Thus, intrathecal morphine has shown a significant effect in chronic pain management with $p= 0.0049$ in a recent study (57), leading to

supporting evidence for intrathecal morphine use in the mixture analgesic medications.



Postoperative pain at rest and analgesic use in patients receiving intrathecal morphine or placebo. **a** Average NRS pain scores were obtained during the first 4 h after TKA surgery. Bars represent the median and all data points are shown. Intrathecal morphine reduced acute postoperative pain ($p = 0.0049$). **b** Postoperative opioid use (morphine equivalent dose) measured via patient controlled analgesia during the first 12 h after surgery. Bars represent the median and all data points are shown. Intrathecal morphine reduced postoperative opioid use ($p = 0.001$)

Figure 3: postoperative pain in patients receiving intrathecal morphine or placebo (57).

1.2.1.9 The effects of morphine on cognition

One of the main concerns associated with the long-term use of morphine in some patients is possible cognitive side effects and its impact on disabilities (58). These effects have been addressed after an acute administration in patients with intractable pain under morphine therapy comparing with healthy individuals (58). However, it is difficult to assess as regards the liability of the pain and treatments in the test results of mental functions (59). Also, a study has demonstrated that 12-month therapy with morphine did not disrupt cognitive functioning in patients with chronic refractory pain, and, in fact, some findings have shown a moderate improvement of some aspects of cognitive functioning as a consequence of the pain relief and concomitant increase in well-being (60). In addition, there is another study that has shown

cognitive functions, such as the ability to drive a car or operate a machine, is preserved in patients taking stable, moderate doses of opioids for chronic pain (60). However, cognitive function was impaired for up to a week after an increase in the dose of morphine (60).

In another clinical study, 20 patients with chronic pain who were received a stable dose of opioids (morphine) were compared with 20 patients with chronic pain who were on increasing dose of opioids (61). Increasing dose was related to impaired reasoning, memory, and reaction time while stable dose did not affect cognitive function (61). A study has revealed that patients who received chronic oral opiate treatment demonstrated no cognitive impairment, while parenteral opiates were more often associated with dose-related cognitive dysfunction (62, 63). Based on these findings, the analgesic medications mixture might not affect cognition due to low-dose of morphine in short time, and it might improve the cognition function in some aspects (63). Moreover, another study has demonstrated that morphine is a better chose of chronic pain management in term of preserving the cognition function than other medications, and also they approved that morphine is connected to cognition improvement (64).

Chapter III

1.2.2 Bupivacaine

Physical, chemical, pharmaceutical and formulation properties.

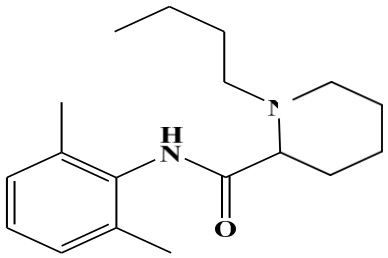
Common name: Bupivacaine hydrochloride

Chemical name: 1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamide (65)

Molecular formula: C18H28N2O (65).

Molecular weight: 288.43

Structural formula:



Bupivacaine

Figure 4: Bupivacaine structural formula (65).

1.2.2.1 Pharmacology

Bupivacaine is a local anesthetic of the amide type, and it is classified as a membrane-stabilizing agent (66). Pharmacologically, bupivacaine is like other local anesthetic medications, and it may cause a reversible blockade of impulse signals along nerve fibers by barring the inward movement of sodium ions through the nerve membrane (66). Additionally, it is thought to act within the sodium channels of the nerve membrane that might have similar effects on excitable membranes in the heart and brain (66). If large amounts of the agent have rapidly reached the systemic circulation, symptoms, and signs of toxicity would mainly be manifested in the central nervous system and the cardiovascular system (66).

Significantly, direct influences of local anesthetics on the myocardium include slow conduction and negative inotropic action might be occurred (67). Additionally, indirect cardiovascular effects, such as low blood pressure and decreased heart rate, may occur after epidural or spinal administration depending on the extent of the concomitant sympathetic block (67). Clinically, bupivacaine leads to loss of nerve function, which occurs in a particular order: pain, temperature, touch sensation, proprioception, and muscle tone (66). The analgesic effect of bupivacaine is essentially thought due to the block of sodium channel receptors, whereas the anti-inflammatory effect occurs by binding to the prostaglandin E2 receptors, and subtype EP1 that inhibit the production of prostaglandins, thereby reducing fever, inflammation, and hyperalgesia (66).

1.2.2.2 Pharmacodynamics

Bupivacaine is widely administered as a local anesthetic medication (68). It is commonly used for surgical wound sites to minimize pain for up to 20 hours after the surgical procedure (68). Compared with other types of local anesthetic agents, it has a long duration of action (68). It is thought the most toxic to the heart when given in excessive amounts (68). Therapeutic doses with specific concentrations in the blood may lead to minimal changes in cardiac conduction, excitability, contractility, and peripheral vascular resistance (68). However, toxic doses can elicit depressed cardiac conduction, decreased cardiac output, and hypotension, thereby leading to atrioventricular block, ventricular arrhythmias and, eventually, cardiac arrest (68). In the central nervous system, CNS stimulation and depression, or both can follow systemic absorption (68).

1.2.2.3 Pharmacokinetics

Following absorption into the blood, bupivacaine is more highly binding to plasma proteins than any other local anesthetic agents (68). Bupivacaine has a very low degree of placental transmission amongst parenteral local anesthetics, so it produces minimal fetal depression (68).

- The onset of action depends on the route of administration (68).
- Duration of action is approximately 2-9 hours (68).
- Half-life: 8.1 hours in infants and about 2-7 hours in adults (68).
- Time to peak plasma concentration (for peripheral nerves, epidural or caudal block) is about 30 – 45 minutes (68).
- Protein binding is approximately 95% (68).
- Excretion usually occurs through the kidneys (6% unchanged) (65, 69).

1.2.2.4 Metabolism

Local anesthetic medications of the amide type, such as bupivacaine are mostly metabolized in the liver by conjugation with glucuronic acid (65). Therefore, the major metabolite of bupivacaine is 2, 6-pipecololoxylidine, which is fundamentally catalyzed via cytochrome P450 (65).

1.2.2.5 Immune system

There are accumulating data that have shown local anesthetic (LA) agents have a wide range of anti-inflammatory actions through their direct influence on cells of the immune system (70). Also, they affect other cells, such as thrombocytes and red blood cells (70). Therefore, the potent anti-inflammatory features of local anesthetics are superior in many conditions to traditional anti-inflammatory medications of the NSAID and corticosteroid groups and produce fewer adverse effects (70). This aspect has prompted physicians to prescribe LAs in the

treatment of various inflammation-related conditions and diseases; LAs have proved successful agents in the treatment of interstitial cystitis, ulcerative colitis, osteoarthritis, and herpes simplex infections (70). However, the mechanisms of action of these drugs are not fully understood; they seem to involve reversible interactions with membrane proteins and fats that lead to regulating cell metabolic activity, exocytosis and phagocytosis (70).

Moreover, mechanisms suppressing the adherence of leukocytes to endothelial cells have been attributed to local anesthetics (70). This would occur when local anesthetic agents have induced a release of prostacyclin from the endothelium, which might be considered as a part of the mechanism for both LA and prostacyclin (70). Some studies have suggested that LAs may inhibit leukocyte adhesion to the endothelium by interfering with the actions of integrin's receptor on the platelets and leukocyte adhesion molecule-1(70).

1.2.2.6 Toxicity

In vivo studies have shown the mean toxic seizure dosage of bupivacaine in rhesus monkeys to be 4.4 mg/kg with a mean arterial plasma concentration of 4.5 mcg/mL (71). Recent clinical studies from patients who have received local anesthetic medications and developed convulsions demonstrated the rapid development of hypoxia and metabolic acidosis with bupivacaine within a minute of the onset of seizures (71). These observations suggest that oxygen consumption and carbon dioxide production are substantially increased during LA convulsions, so immediate and effective ventilation with oxygen is required to prevent cardiac arrest (69, 71). Also, injecting a high dose of bupivacaine by intravenous route or subcutaneous route in rats may lead to severe seizures and respiratory suppression as shown in the table 3 (68).

Animal	Route of administration	Loading dose 50mg/kg	Observation
Rat	I.V	7mg	At high intravenous doses in rats, toxicity symptoms included stimulation of the central nervous system followed by convulsions. Death is usually happened due to respiratory depression or cardiac arrest.
Rat	S/C	45mg	

Table 3: Bupivacaine toxicity loading dose (68).

1.2.2.7 Side Effects of Bupivacaine

The most common side effects that require immediate intervention are related to the central nervous and the cardiovascular systems (72). Nausea is one of the first symptoms and hypotension that are induced by spinal and epidural anesthesia (73). Significantly, people over 65 years of age, particularly those with hypertension, might be at a higher risk of developing hypotensive effects (73).

Bupivacaine is known to elicit a variety of side effects on different systems as follows:

- Central nervous system:

The neurological side effects of bupivacaine following epidural or caudal anesthesia have included spinal block, persistent anesthesia, generalized weakness, and fecal and urinary incontinence (73). Further CNS side effects include mood disturbance, depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, nausea, vomiting, and pupil constriction (72, 73).

- Cardiovascular system:

Cardiovascular side effects include slow heart rate, low blood pressure, decreased cardiac output, and ventricular arrhythmias (including ventricular tachycardia and ventricular fibrillation) and cardiac arrests (72).

- Respiratory system:

Respiratory side effects have involved respiratory paralysis or underventilation because of cephalad extension of the level of spinal anesthesia (72).

- Digestive system:

Gastrointestinal side effects include nausea and vomiting during the administration of spinal anesthesia (72).

- Hypersensitivity:

Allergic-type reactions, such as urticarial rash, itching, erythema, angioneurotic edema, increased heart rate, dizziness, syncope, excessive sweating, elevated temperature, and anaphylactic-like symptomatology have been reported (72).

These reactions are essentially dose-related and due to high plasma levels of the medication and loss of sympathetic tone (73). That is why low dose of bupivacaine is recommended in the analgesia medications mixture to minimize the side effect.

1.2.2.8 The effects of bupivacaine on pain

This medication is used as local infiltration, epidural injection, and spinal analgesia during some surgical procedures and continuous intrathecal infusion for the chronic refractory pain of cancer and non-cancer origins (73). Clinical findings have confirmed that bupivacaine in combination with opioids delivered by utilizing an implantable infusion pump has a significant

role in treating chronic pain, particularly when injected epidurally (73). In a retrospective study measuring pain relief with intrathecal treatment, patients who received a combination of bupivacaine and morphine experienced significantly better pain relief compared to those treated with morphine alone (73). Bupivacaine is commonly used with morphine in a continuous intrathecal infusion with relatively high intrathecal bupivacaine dose and concentration (74). Morphine: bupivacaine ratio of approximately 1:10 and concentrations of morphine of 0.5 mg/ml and bupivacaine of 4.75 mg/ml might significantly improve a patient with chronic pain, though not without a certain risk of adverse effects (74).

According to some clinical studies, bupivacaine is considered a safe and effective drug for treating chronic pain by using intrathecal procedure (75). It may be concluded that bupivacaine is a stable and compatible medication when used in an implantable drug infusion system (75). That has shown by chronic supplementation of intrathecal morphine with bupivacaine was a safe method for improving and providing continued treatment of chronic pain in cancer or non-cancer origin by getting better VAS score (75). A study of post-cesarean pain concluded that higher doses of local anesthetics and the use of anti-inflammatory drugs at the time of surgery reduced the incidence of chronic pain, as evaluated at three months post-op (76).

Recently, 17 patients had shown significant pain relief and improvement in functionality and quality of life when bupivacaine combined with morphine in a retrospective study (77). The dose of morphine was kept constant at 14.10 mg/day, and the treatment of bupivacaine was initiated at 2.08 mg/day to increase to 4.83 mg/day (77). No neurological adverse effects were observed (77). Also, a double-blind study had found no added analgesia or improving in quality of life in 24 patients with chronic pain when bupivacaine was added to the infusion solution to deliver 4, 6, or 8 mg/day (78). However, there is another study has shown that initiating

bupivacaine along with morphine from the outset of IT therapy reduces morphine dose escalation with the average daily dose of bupivacaine is over 10 mg/day in a retrospective study (79, 80).

Moreover, a study reported on the stability and tolerability of higher doses of bupivacaine as an adjunct to morphine by intrathecal injection (81). That shows excellent stability has reported and no nonreversible neurological complications were identified in patients receiving daily doses of bupivacaine up to 21.4 mg (81). However, tolerability varied with the patient's physical condition and the adverse effects of medication (81). Therefore, bupivacaine would be appropriate for the mixture of drug combination for managing chronic pain.

1.2.2.9 The effects bupivacaine on cognitive function

In vivo study assessed the effects of perinatal epidural bupivacaine on infant behavioral and cognitive development when administered to term-pregnant rhesus monkeys. No harmful effects of bupivacaine were detected for neonatal neurobehavioral and cognitive abilities or on the performance of cognitive tasks by older infant monkeys (71). Clinical studies have reported that local anesthetic agents, including bupivacaine, used in various pain management techniques provide efficient postoperative pain control with less cognitive function impairment (61). Typically, patient-controlled epidural analgesia (PCEA) produced better postoperative analgesia than intravenous patient-controlled analgesia (PCA-IV) (61). As a result, neurobehavioral function on the first postoperative day suggested that patients who felt less pain experienced a lesser decline in cognitive function (60, 61).

Following epidural and intrathecal administration of high-dose local anesthetic agents might have observed motor and sensory deficits (82). However, it is not clear if this is related to the local anesthetic (82). Therefore, preservative-free preparations might be added for neuraxial applications. However, neurotoxicity is rarely reported with nerve blocks except in some cases of intraneural injection (82). Paresthesias and hypoesthesias have been noticed following IT and

epidural blocks from LA, especially when vasoconstrictors added to the solution (83, 84). These conditions might lead to autonomic nervous system dysfunction, sensory and motor deficits, and potential neurotoxicity, although these complications are not naturally observed at doses of less than 15 mg per day (85, 86). Thus, these studies support this medication is essential as one of the analgesic mixture with a specific dose that positively effects on pain and cognitive function.

Chapter IV

1.2.3 Ketamine

Physical, chemical, pharmaceutical and formulation properties

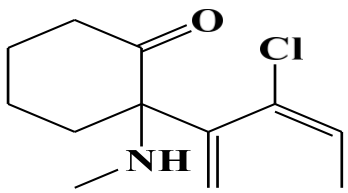
Common name: ketamine hydrochloride

Chemical name: 2-(2-chlorophenyl)-2-(methylamino) cyclohexane-1-one; hydrochloride (87).

Molecular formula: $C_{13}H_{16}ClNO.HCl$

Molecular weight: 237.727 g/mol

Structural formula:



Ketamine

Figure 5: Ketamine structural formula.

1.2.3.1 Pharmacology

Ketamine is considered as a dissociative anesthetic medication, and it is commonly administered by a parenteral route (87). It is widely used as a general anesthetic agent for short-term diagnostic and surgical techniques (87). Chemically, it is a cyclohexanone derivative used for induction of anesthesia. It's mechanism of action is not well understood, but it is thought that ketamine could block some important receptors, especially sigma receptors (87). Significantly, ketamine has many clinically useful properties; most notable is its ability to produce analgesia with less cardiorespiratory depression than other anesthetic medications (87). Additionally,

ketamine has been reported to produce general and local anesthesia by interacting with N-methyl-D-aspartate (NMDA) receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive calcium ion channels (87). However, ketamine does not interact with GABA receptors (87).

1.2.3.2 Pharmacodynamics

Ketamine is a rapidly-acting general anesthetic agent that is characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, slightly improved skeletal muscle tone, cardiovascular and respiratory stimulation, and minimal respiratory depression (87). Ketamine is indicated as the sole anesthetic medication for diagnostic and surgical procedures that do not require skeletal muscle relaxation (88). The anesthetic state provided by ketamine has been named "dissociative anesthesia" as ketamine appears to selectively interrupt association pathways of the brain before producing sensory blockade (88). Also, it might selectively depress the thalamocortical pathway before obtunding the more ancient cerebral centers, such as the reticular activating system and limbic system (88).

1.2.3.3 Pharmacokinetics

Ketamine is widely absorbed after parenteral administration; peak plasma levels of this medication average 0.75μg/ml and CSF levels are about 0.2μg/ml, one hour after dosing administration (89). Thus, the range of plasma half-life is approximately 2 to 4 hours (89). Following IM administration (absorption half-life of 2-15 minutes) its bioavailability reached up to 93 % while intrarectal and intranasal ketamine bio-availabilities are approximately 25 and 50%, respectively (89). Ketamine is rapidly distributed throughout the body into widely perfused tissues including the brain and spinal cord (89). The mean volume of distribution is

reported to range from approximately 2 to 3 L/kg, and the distribution half-life is about 7 to 11 minutes (89). Also, ketamine is around 20-50% bound to plasma proteins (89).

This medication can cross the placenta in induction doses, but in a small amount that has no harmful effects on the fetus (89). Approximately 90% of ketamine is excreted in the urine as metabolites, and about 5% is recovered in the feces (89). Ketamine rapidly passes the blood-brain barrier (blood effect site equilibration half-life 1–10 minutes) ensuring a quick onset of acute analgesic effect (90). After an epidural injected the dose, ketamine is rapidly distributed to the systemic circulation (90). Concerning long-term management for chronic pain, the analgesic onset/offset of ketamine exceeds that of acute pain relief, and it is estimated as 11 days in patients with chronic pain treated with 100 h of 20–30 mg h−1 of ketamine (91).

1.2.3.4 Metabolism

Ketamine is mainly metabolized in the liver by CYP3A4, CYP2B6 and CYP2C9 to nor ketamine (via N-demethylation) with the subsequent metabolism of nor ketamine into 4-, 5-, and 6-hydroxynorketamine by CYP2A6 and CYP2B6 (87, 88).

1.2.3.5 Immune system

Ketamine reduces tissue necrosis factor α (TNF-α) and nitric oxide (NO) production, both of which play vital roles during the inflammatory process, and the inhibition of these activities could affect macrophage-mediated immunity (92). Evaluating the potential mechanism of ketamine-induced immunosuppression in macrophages, TNF-α, IL-1β, and IL-6 messenger RNA (mRNA) syntheses in murine macrophages were studied, and it was found that ketamine inhibited mRNA syntheses by lipopolysaccharide (LPS)-activated macrophages (92). More recently, ketamine has been used as an anti-inflammatory drug, which emphasizes the significance of research on its interactions with the immune system (92). Indeed, major surgery

or sepsis leads to the release of proinflammatory mediators, including large amounts of cytokines, which can lead to undesirable effects, such as low blood pressure and multiple organ failures (90, 92).

Moreover, ketamine has a double effect that connects both the analgesic and neuroprotective actions of its anti-inflammatory effects (91). As ketamine regulates the inhibition of tumor necrosis factor α (TNF-α), interleukin 6 and proinflammatory cytokine activities that would happen in both peripheral immune cells and glial cells in CNS (91). Therefore, the primary protective inflammatory mechanism in the CNS in defense of brain injury is often rapidly deregulated in a cerebrovascular accident, such as stroke (91). As a result, excessive microglial activation with release of TNF-α leads to stimulation of the extrinsic apoptotic pathway, as well as IL-1β, IL-8, and IL-6 (91). This might lead to enhance blood-brain barrier permeability (91, 92). This process allows inflammatory cells, such as monocytes, neutrophils, and lymphocytes to cross the blood-brain barrier into the CNS, therapy leading to more prostaglandin and cytokine. (91, 92, 93)

Recently, there is a novel anti-inflammatory mechanism of ketamine is inhibition of high mobility group box 1 (HMGB1) - induced activation of endothelial cells (93). This group HMGB1 is considered as the main prototype of the emerging injured-associated molecular proteins and signals for host tissue damage (93). This condition is started by release proinflammatory cytokine from endothelial cells, as well as leukocyte adhesion and transmigration (93). Thus, elevated HMGB1 levels predict non-survivors in subarachnoid hemorrhage (SAH) that would be indicated by improving neuroinflammation in (SAH) (93). Ketamine is also shown to have an excessive inhibitory effect of HMGB1-induced endothelial cell activation by a mechanism involving nuclear factor κB and toll-like receptor (93).

1.2.3.6 Toxicity

Studies have shown that ketamine at low dose concentrations can induce apoptosis in non-neuronal and neuronal cells, while higher dose concentrations could predominantly lead to tissue necrosis (94). Ketamine induces apoptosis by the mitochondrial pathway and independent of the death receptor signaling pathway (95). Additionally, the apoptosis-inducing effect of ketamine is not potentially stereospecific, and it is unlikely to be mediated via the NMDA receptor (94).

However, there is a possibility of neurotoxicity induced by ketamine after application close to neural structures; the preservative chlorobutanol was recognized as the primary toxic agent after a single application (95). Furthermore, it has been recently discovered that preservative-free S (+)-ketamine applied intrathecally in rabbits could lead to severe histopathological damage without any functional neurological deficit (94).

1.2.3.7 Side effects of ketamine

Short-term effects of ketamine usually manifest approximately 30 seconds after I.V injection (95). Initially, the user starts to feel an overwhelming of relaxation, sometimes described as a “full-body buzz.” Some individuals feel like they are floating and some have described it as feeling out of their bodies (95). Additionally, there is some reporting of hallucinations that could last longer than the anesthetic effects (95). Large doses might produce more severe adverse effects (95). These effects are the same as those described by people who have had near-death experiences; a sensation described as “being in the K-hole (95)."

- Short-term side effects include unpleasant hallucinations, as with neuropsychotropic medications. Other side effects include confusion, drowsiness, tachycardia, and hypertension (95).

• Long-term ketamine adverse effects can be dangerous or harmful to individuals, even for first-time users (96). According to the Center for Substance Abuse, the effects of ketamine include anterograde amnesia, delirium, lack of coordination, loss of touch with reality, brain toxicity, and muscle spasm (96). However, the long-term side effects of ketamine are not well defined because the drug affects subjects in different ways (96). Since ketamine leads to distortions of reality when used, it disrupts the normal function of a user's brain neurotransmitters (96). Thus, chronic abuse could increase the risk of permanent damage to the brain (96). Also, the adverse effects of ketamine depend on the drug dose and duration (95), the small dose of ketamine in the analgesic mixture provide positive outcomes for patients with chronic pain and fewer adverse effects.

1.2.3.8 The effects of ketamine on pain

The anesthetic ketamine is administered to treat various chronic refractory pain, particularly those that have a neuropathic component (97). It has recently been reported in a systematic review that a low dose of ketamine produces potent analgesia in neuropathic pain conditions, presumably by inhibition of the N-methyl-D-aspartate receptor (97). However, it appears that particular mechanisms are potentially involved, including enhancing of descending inhibition and anti-inflammatory effects (97). In chronic pain conditions, prolonged nociceptive stimulation leads to activation and upregulation of the NMDAR at the dorsal horn synapses resulting in enhancing and amplifying pain signals to the brain (97). This phenomenon would be a significant factor in the process of perseverance and eventually severity of pain (97).

More recently, the evidence that NMDAR antagonists, such as ketamine, that can block the NMDAR, can halt the excessive barrage of nociceptive input to the brain; therefore there are possible alternatives to existing therapies of chronic pain syndromes (98). Also, there are other

effects of ketamine that might contribute to its analgesic activity by enhancing descending inhibition pathway, especially patients with chronic neuropathic pain (98). Indeed, ketamine could prevent the occurrence of chronic pain conditions, such as that experienced in the postsurgical period after a lower limb amputation (98). To achieve effective management of chronic pain, it is preferred to use a multimodal approach to different medications (98). Several clinical studies have reported that using ketamine with morphine in the treatment of chronic cancer pain has reduced morphine consumption with less pain and fewer adverse effects (98).

Two reports have revealed on the clinical use of ketamine in pain in adult patients with cancer. The review has concluded that there is not enough evidence regarding the effect of ketamine as an adjuvant to morphine in for patients with cancer pain (97). However, a case study concluded that ketamine might be an option for the treatment of intractable chronic pain in cancer with other analgesic medications (98). A randomized controlled trial has shown approximately 10% ketamine to be effective in relieving the allodynia of patients with complex regional pain syndrome (CRPS) (99). Ketamine was noted to be significantly better regarding pain relief. A double-blind placebo controlled study has shown the superiority of ketamine infusion over placebo in relieving pain and reducing allodynia, as well as improving motor function (100).

Additionally, ketamine improves the efficacy of opioid treatment in chronic cancer pain (98). This is because ketamine's ability to reduce neuropathic pain is superior to that of opioids, but it can additively and synergistically interact with opioids, probably through the descending inhibitory pathway (98). However, relieving acute pain would also be achieved by the inhibitory pathway of presynaptic spinal dorsal neurons (98). This activation of NMDAR at these

presynaptic areas could lead to the release of excitatory substances, including glutamate and substance P (98).

Overall, an evidence-based review, patients who suffer from intractable chronic pain may accept the risk of ketamine treatment when the pain is sufficient relief (101). Also, ketamine has shown an effect on chronic pain of patients whose chronic pain did not treat with first and second the line of treatments (101).

1.2.3.9 The effects of ketamine on cognitive function

Analysis of cognitive and memory functions during short-term ketamine administration has demonstrated impairment of working memory and reduction in the encoding of information into episodic memory (102). In contrast to other amnestic medications, ketamine impairs semantic memory in some patients (102). After the termination of short duration and single ketamine infusions, memory function reverts to a healthy state, which possibly indicates ketamine-induced memory loss is self-resolving (102). However, the effects of the long-term use of low-dose ketamine for the treatment of chronic pain on memory function are poorly reported and, consequently, unknown. Nevertheless, a recent study that examined the safety of high-dose, long-term ketamine in complex regional pain syndrome (CRPS) patients who received anesthetic doses over 5 days demonstrated no severe cognitive defects (99, 102).

Clinically, using of ketamine for neuroprotection either intraoperatively or in the intensive care unit settings with adequate neurocognitive or neuroradiological follow-up for a few studies would support the hypothesis that ketamine may protect their cognitive functions (93). One group has been particularly interested in the potential of ketamine to alleviate postoperative cognitive dysfunction (POCD) in non-head traumatic patients by neuroprotection mechanism. Significantly, clinical investigators have proven by conducting several

investigations that a single dose of ketamine at induction (0.5 mg/kg) attenuated POCD in patients undergoing cardiac surgery (93). Also, they have demonstrated ketamine on induction to reduce the incidence of postoperative delirium from 31% to 3%. Thus, these the beneficial effects of ketamine have assigned to mitigation of the postoperative systemic inflammatory response (93).

In a clinical study, where patients reached a Ramsay Score 4–5 depth of anesthesia and had ketamine levels of 250–300 ug/dl for at least 4.5 days (in a medically-induced coma), reported that deep ketamine therapy was effective for relief of chronic pain and without harmful cognitive effects (97). Additionally, ketamine is associated with antidepressant outcomes in patients with the major depressive disorder (MDD), as it has reported in several studies for treatment-resistant depression (102). Preclinical studies have shown ketamine has antidepressant effects in some animal models of depression by expressing serine/threonine protein kinase (102). This is called the mammalian target of rapamycin (mTOR), which modulates cell growth, proliferation, motility, survival, and protein synthesis (102).

Some studies have suggested that glutamate and neurotrophic receptors mediate ketamine and other antidepressants (103). This leads to stimulation of the mTOR pathway in the prefrontal cortex (PFC), thereby resulting in transient activation of the downstream effectors, such as 4E-binding protein 1and protein S6 kinase (103). Significantly, the activation of mTOR after ketamine administration would potentially indicate an association between significant deficits in synaptic proteins and dysregulation of mTOR pathway in MDD patients (103). More recently, some studies have focused on neuroinflammation and oxidative stress mechanisms in major depression. For example, an agonist of peroxisome proliferator-activated receptor-α (PPAR-α) is reported to inhibit neuroinflammation and oxidative stress, and it possesses

antidepressant-like effects of ketamine by preventing neuroinflammation of many proteins that are involved in inflammation-related genes including chemokines, interferon-gamma-induced genes (102).

Ketamine administrated acutely might lead to cognitive impairment, especially, encoding into episodic memory and processing information in working memory (104,105). However, preliminary human data from retrospective and non-randomized studies were suggested that ketamine anesthesia improves reorientation state and word recall after electroconvulsive therapy (ECT) (106, 107, 108). Further, it might result in a more rapid clinical response (109). In contrast, in randomized controlled trials (RCTs) have produced mixed results with several studies suggesting reorientation impairment and improvement or unchanged according to Mini-Mental State Examination (MMSE) scale after ketamine administration (110, 111). Also, a study has reported that ketamine produced no reduction in cognitive impairment after ultra-short right unilateral stimulation on a range of tests; although this technique relatively associated with minimal cognitive impairment compared with standard bilateral (ECT) (111, 112).

More recently, meta-analyses were found at efficacy, and including the same four placebo-controlled (RCTs) in which ketamine combined with ECT that would have reached different results (113). When continuous measures were pooled a moderate to substantial benefit for using ketamine was early observed in the (ECT) treatment course; however, no benefit found when end-of-treatment response and remission were meta-analyzed (114). Additionally, meta-analysis has reported higher rates of confusion and disorientation with ketamine (115). Currently, the small heterogeneous research of ketamine augmentation of (ECT) emphasizes the need for further a larger scale of clinical trials to reach to a reliable data (115). Therefore, low dose of ketamine may have some multiple beneficial effects on patients with chronic pain

regarding enhancing cognitive functions, improving depression state, and anti-inflammatory effects. These all criteria have positive outcomes for patients who plan to receive the analgesic mixture.

Chapter V

1.2.4 Neostigmine

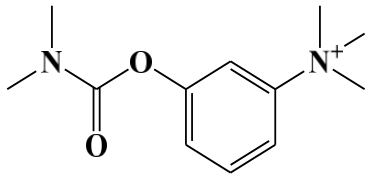
Physical, chemical, pharmaceutical and formulation properties.

Common name: Neostigmine methyl sulfate.

Molecular formula: C13H22N2O6S

Molecular weight: 334.387 g/mol

Structural formula:



Neostigmine

Figure 6: Neostigmine structural formula (116).

Neostigmine is a white, crystalline powder, moderately soluble in chloroform and ethanol (116).

1.2.4.1 Pharmacology

Neostigmine is a parasympathomimetic agent and is characterized as an analgesic agent (116). It primarily acts as a reversible inhibitor of the enzyme acetylcholinesterase (116). It works by inhibiting acetylcholinesterase, which is responsible for the degradation of acetylcholine (ACh) at sites of cholinergic transmission (116). Inhibiting acetylcholinesterase leads to more acetylcholine available in the synapse (116). By interfering with the degradation of acetylcholine, neostigmine indirectly promotes nicotinic and muscarinic receptors (116). Neostigmine does not cross the blood-brain barrier; therefore, the analgesic effect that results from spinal administration of neostigmine is due to increased ACh concentration (116). This

consequently leads to binding to muscarinic receptors M1, M3, M2 and M4 and to nicotinic receptors (116). Additionally, it enhances cholinergic action by facilitating the transmission of impulses and pathways across neuromuscular junctions (116). Further, it has a direct cholinomimetic effect on skeletal muscle and on autonomic ganglion cells and neurons of the CNS (116, 117).

1.2.4.2 Pharmacodynamics

Neostigmine is a cholinesterase inhibitor (118). It is used in the treatment of myasthenia gravis and to reverse some effects of muscle relaxants, such as vecuronium and atracurium (118). Therefore, more acetylcholine can bind to the fewer receptors found in myasthenia gravis and allow the better triggering of muscular contraction (118). It has functions that mimic the effects of parasympathetic nervous system activities by directly stimulating muscarinic receptors and potentiating cholinergic activity by slowing the breakdown of acetylcholine (118).

1.2.4.3 Pharmacokinetics

As neostigmine has been evaluated in humans after intravenous and oral administrations, the mean plasma T/2 for neostigmine after intravenous administration is 0.89 hours (118). The peak concentration occurred 1-2 hours following oral intake, although bioavailability is only 1-2% of the administered dose (118). The pharmacokinetics of neostigmine in patients with normal kidney function was determined and compared with those of patients with kidney transplants or a history of nephrectomy (118). In nephric patients, the elimination half-life is usually prolonged (118). Total serum clearance is 16.7 ml/kg/min in patients with normal kidney function and 7.8 ml/kg/min in nephric patients (118). However, neostigmine pharmacokinetics after kidney transplantation are not significantly different from those of patients with normal kidney function (118). Renal excretion accounts for 50% of neostigmine clearance (118, 119).

1.2.4.4 Metabolism

Neostigmine undergoes hydrolysis by cholinesterase, and microsomal enzymes mainly metabolize it in the liver (119, 120).

1.2.4.5 Immune system

Interleukin-1 (IL-1) is produced mainly by macrophages and monocytes, as well as some nerve cells within the brain (121). IL-1 has significant physiological effects on many different target cells that have been involved in inflammatory and immune responses (121). Therefore, excessive production and secretion of IL-1 might cause highly detrimental adverse effects on the immune system (121). Recently, results indicate that neural mechanisms also are involved in limiting inflammatory and immune responses (121). Significantly, it was found that acetylcholine (ACh) inhibits lipopolysaccharide (LPS)–induced production of proinflammatory cytokines, including IL-1 which is synthesized by macrophages and microglia (121). Therefore, the levels of ACh are possibly organized by the hydrolytic enzyme acetylcholinesterase (AChE), which promptly degrades ACh both in the periphery and central nervous systems (121). Thus, AChE inhibitors, such as neostigmine, are potent cholinergic agonists and are widely accepted as anti-Alzheimer's disease medications (121). Therefore, it has concluded that AChE inhibitors could diminish the production of IL-1β, which might have significant clinical implications (121). AChE inhibitors are considered beneficial and are frequently prescribed for patients with Alzheimer’s disease (121). According to recent findings, AChE inhibitors modulate IL-1β, IL-6, and tumor necrosis factor-α in peripheral blood mononuclear cells of patients with Alzheimer's disease (121). A study has reported that treatment with low doses of neostigmine attenuates the increase of inflammatory cytokines, such as TNFα in the heart, thereby improving cardiac hypertrophic responses to pressure overload (121). Thus, the evidence suggests that both the cholinesterase inhibitor “neostigmine” has elicited beneficial effects on the stressed heart by

enhancing cholinergic function (122). This might provide a new strategy for the treatment and prevention of heart failure in the future; however, the mechanisms of the beneficial cardiac effects of these treatments need to be clarified (122).

1.2.4.6 Toxicity

Over dosage of neostigmine would cause a cholinergic crisis, which is characterized by abdominal pain, diarrhea, miosis, increasing muscle weakness, increased sweating, and bronchial secretions (116). Extreme cases of paralysis of the respiratory muscles can result in death, as demonstrated in experimental studies in rats with different doses and various routes of administration (116).

1.2.4.7 Side effects of neostigmine

Side effects of anticholinesterases include

- Major side effects:

Cardiovascular: bradycardia, hypotension, and irregular heartbeats (123).

Respiratory: bronchospasm, hypoxia, and increased secretions (123).

Gastrointestinal tract (GIT): increased GI motility and secretions (123).

Eye: decreased intraocular pressure and double vision (123).

Neuromuscular: twitches of the muscle visible under the skin, unusual tiredness or weakness, puffiness around the eyes, face, lips, and tongue (123).

- Minor side effects:

GIT: diarrhea, nausea, vomiting, and excess gas in stomach or intestines (123).

CNS: a headache, drowsiness, and constricted pupils (miosis) (123).

Genitourinary system: increased need to urinate (123).

Endocrine system: a feeling of warmth, increased watering of the mouth, and increased sweating (123).

1.2.4.8 The effects of neostigmine on pain

Neostigmine belongs to the class of parasympathomimetic agents that produce cholinergic-mediated analgesia (124). It has been administered as an adjunct analgesic in the postoperative and peripartum period (124). The different routes of administration have been studied with various degrees of success. This includes the intrathecal route, which elicited some incidence of minor side effects, mainly nausea and vomiting (124). The epidural administration of neostigmine, both for postoperative analgesia and labor analgesia, is safe, efficient, and well tolerated (124). Moreover, caudal administration of neostigmine is a useful technique for an analgesic effect in the postoperative period; however, some studies have reported an increased rate of vomiting, whereas the intra-articular administration of neostigmine is effective in improving postoperative analgesia without any increase in side effects (124).

Neostigmine in combination with clonidine has shown common mechanisms of action mediated by the spinal release of acetylcholine, and beneficial interactions have been reported after concurrent neuraxial administration in volunteers, that is, enhancement of analgesia without noticeable adverse effects (125). An experimental study has found that neostigmine induced inhibition of the tail withdrawal reflex, which confirms its effectiveness and safety against chronic or recurrent pain (126). Also, these findings are similar to the clinical observation that neostigmine is effective against postoperative somatic pain but less efficient in controlling

visceral pain in humans (126). There is a suggestion that the use of a high intra-spinal dose of neostigmine could be an alternative in the management of postsurgical pain (126).

Using neostigmine as postoperative analgesic medication was better than magnesium sulfate (MgSO4) (127). Neostigmine offers some protection against hypotension during spinal anesthesia while MgSO4 protects against bradycardia (127). Some clinical studies have reported that administrating IT neostigmine with (MgSO4) is produced potential anti-nociception without neurotoxicity (127). Also, they augment analgesia of morphine and bupivacaine (128, 129, 130). Since the primary site of action of this medication is the spinal cord; therefore, direct IT infusion is preferable technique to get effective clinical analgesia (131, 132, 133). Thus, IT neostigmine and (MgSO4) in smaller doses may have become beneficial as adjunct analgesics to bupivacaine (133). Moreover, the ability of IT neostigmine to protect against hypotension and to augment GIT motility in the absence of respiratory suppression are distinctive positive features to conduct this study (134, 135).

1.2.4.9 The effects of neostigmine on cognitive function

Neostigmine has a crucial role as a cholinesterase inhibitor in the central nervous system by directly stimulating muscarinic receptors, which act post-synaptically to modulate neurotransmission that is mediated by other ionotropic and metabotropic receptors (136). Muscarinic receptors play a significant role in many brain functions including cognition, vigilance, mood, and sensorimotor gating (136). Additionally, muscarinic receptor dysfunction has been associated with some diseases of the CNS, such as Parkinson's disease and Alzheimer's disease (AD) (136). There is clear evidence from in vivo studies suggesting the role of muscarinic receptors in the pathophysiological mechanism of psychosis and cognitive

dysfunction (136). Individual molecules, acting as ligands to bind muscarinic receptor subtypes, would be sufficient as therapeutic targets for these diseases (136).

There are five distinct muscarinic acetylcholine receptors (M1–M5), which are characterized as belonging to the superfamily of G-protein-coupled receptors (136). However, M2 and M4 are coupled to Gi/o proteins, and they are mediated by inhibiting adenylyl cyclase activity (136). The lack of subtype-specific muscarinic molecules has made it difficult to determine the importance of the function of M1–M5 receptors with classical pharmacological studies (136). Furthermore, pharmacological, neuroanatomical, and clinical studies have suggested the significant role of muscarinic receptors in synaptic plasticity and cognitive function (136).

Cochrane reviews of cholinesterase inhibitors have concluded that treating patients with the AD for six months provide benefits and significant improvements in cognitive function, were observed (137). These measurements depend on daily life activities and psychological behavior; however, the failure of these medications effect was high (137). A double-blind randomized-controlled trial that was involved in the Cochrane review of cholinesterase inhibitors comparing donepezil with rivastigmine within two years; therefore, they have found no difference in improvement of cognitive function and behavior (138). However, it is difficult to decide about a time of stopping medications, which is debatable (138). More recently, there is evidence might be suggested a beneficial continuation of prescribing of AChE inhibitors, even during progressive stages of the disease (139).

Chapter VI

1.2.5 Clonidine

Physical, chemical, pharmaceutical and formulation properties.

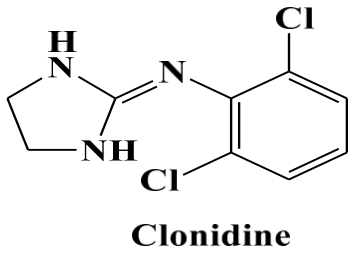
Common name: Clonidine hydrochloride

Chemical name: 2, 6-dichloro-N-2-imidazolidinylidenebenzenamine

Molecular formula: C9H9Cl2N3

Molecular weight: 230.09

Structural formula:



Clonidine

Figure 7: Clonidine structural formula (140).

Physical and chemical properties: white, odorless, crystalline powder with a bitter taste (140). Solubility: 1 in 13 of water, 1 in 25 of alcohol, 1 in 38 of dehydrated alcohol, and 1 in 240 of chloroform, practically insoluble in ether and chloroform (140).

1.2.5.1 Pharmacology

Clonidine is an imidazole derivative, and it is a centrally-acting α2-adrenergic agonist (141). It can cross the blood-brain barrier and works in the hypothalamus to induce a dropping of blood pressure (141). Further, it might be used as an adjunct medication by epidural infusion in the treatment of severe chronic refractory pains that it is not relieved by conventional therapy (141). It aids in the diagnosis of some tumors that are presented with high blood pressure, such as pheochromocytoma (141). Other clonidine uses include prevention of a vascular migraine, dysmenorrhea, and treatment of vasomotor symptoms associated with menopause, treatment of alcohol withdrawal used in conjunction with benzodiazepines, management of nicotine

dependence, as well as the management of psychological disorders, such as attention-deficit hyperactivity disorder (ADHD) (141).

1.2.5.2 Pharmacodynamics

Clonidine acts specifically on α2-receptors (141). These receptors regulate some signaling pathways promoted by multiple Gi proteins, Gαi1, Gαi2, and Gαi 3 (141). Therefore, the stimulation of α2-receptors could lead to mediate effects, such as inhibition of adenylyl cyclase, promotion of phospholipase D, stimulation of mitogen-activated protein kinases, stimulation of K+ currents and inhibition of Ca2+ currents (141). Further, three G-protein coupled α2-receptor subtypes have been recognized: α2A, α2B, and α2C (141). Each subtype has a particular pattern of tissue distribution in the brain and peripheral tissues (141).

The α2A-receptor is distributed mainly over the central nervous system tissue, and the α2C-receptor is primarily expressed in the central nervous system, including the striatum, olfactory tubercle, hippocampus and cerebral cortex (141). The α2A- and α2C-receptors are located pre-synaptically and inhibit the release of noradrenaline from sympathetic nerves (141). Thus, the stimulation of these receptors decreases sympathetic tone, thereby resulting in decreases in blood pressure and heart rate (141). Importantly, analgesia is mediated by centrally-located α2A-receptors, while peripheral α2B-receptors mediate the constriction of vascular smooth muscle (141). Also, α2A-receptors mediate essential components of the analgesic effect of nitrous oxide in the spinal cord (141). Clonidine's actions in the nervous system decrease sympathetic over-activity in patients undergoing opioid withdrawal (141). Indeed, clonidine is considered as a potent sedative and analgesic medication, and it could prevent post-surgical shivering in intensive and postoperative care (141).

1.2.5.3 Pharmacokinetics

Some experimental studies have indicated that clonidine is mostly distributed into body tissues in different concentrations (142). The concentration of the medication in tissues is higher than plasma concentrations (142). The mean volume of distribution of clonidine is reported to be about 2.1 L/kg following oral intake; the highest concentration of the drug is found in the kidneys, liver, and GIT (142). Additionally, high concentrations of the drug appear in the lacrimal and parotid glands (142). In contrast, the lowest concentration occurs in the brain (142). Clonidine is distributed into the cerebrospinal fluid (CSF); following epidural infusion, it is extensively and rapidly spread into the CSF, as well as into epidural blood vessels (142). However, as a result of higher CSF clonidine concentrations than epidural, early decrease in blood pressure occurs after intrathecal injection faster than epidural (143). In vitro, clonidine is about 20-40% bound to albumin and plasma proteins (142). In pregnant women, clonidine can cross the placenta, and it is distributed into the milk in lactating women (142).

After epidural administration of a single dose of clonidine to both healthy volunteers and patients with cancer pain, clonidine was widely absorbed into the systemic circulation (142). A mean peak plasma clonidine concentration at the range 3-5.8 ng/mL was reported, on average, 20 minutes following epidural administration of 700 micrograms of clonidine hydrochloride (given over 5 minutes in healthy people) (142). Following two weeks of continuous epidural infusion of clonidine hydrochloride and morphine sulfate (for patient-controlled analgesia in cancer patients), mean steady-state plasma concentrations were approximately 2.2 and 2.5 ng/mL on days 7 and 14 of dosing, respectively. Thus, the accumulation of clonidine does not occur after continuous epidural infusion of the drug in patients with chronic cancer pain (142).

1.2.5.4 Metabolism

Clonidine is mainly metabolized in the liver through minor pathways (144). The major metabolite, p-hydroxyclonidine, is found in concentrations less than 10% of those of unchanged clonidine in urine (144).

1.2.5.5 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 (145). This study observed α2-adrenoceptor immunoreactivity in macrophages and T cells in the injured nerve; it was suggested that clonidine changed immune cells functions to produce the delayed onset of action and prolonged effect (145). 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 clonidine-treated rats (145).

Two observations studies support the presence of an immunomodulatory effect of clonidine: a similar time course of behavioral and immunologic influences and the presence of α2-adrenoceptors on immune cells at the site of injuries (145).

Significantly, as clonidine decreases hypersensitivity reactions in animals with nerve injuries, it also provides analgesia in neuropathic pain patients after spinal injection (145). The effect of clonidine occurs rapidly and lasts for some time (145). If clonidine is injected at the area of nerve injury, it leads to reduced hypersensitivity (145). However, the onset will take a few days and duration of action will be more than a week (145). This slow time route indicates the reflection of clonidine-induced changes in the recruitment and functions of immune cells at the site of inflammation (145). This would be supported by the observations noted with perineural clonidine, which reduced pro-inflammatory cytokine content in the injured nerve when used at the time of injury (146).

There is another agent of α-2 adrenergic receptor agonist class, dexmedetomidine, which is a highly selective α-2 adrenergic receptor (147). 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 (147). Significantly, many experimental studies have indicated that dexmedetomidine has a neuroprotective effect during stress, as well as during the inflammatory response (147). The anti-inflammatory effect of dexmedetomidine is associated with increased activity of the vagus nerve in a murine model by inhibiting the release of proinflammatory cytokines and blocked NF-Kb, as well as astrocytic activity in the hippocampus of rats through the stimulation of cholinergic anti-inflammatory pathway (147).

Furthermore, intraoperative dexmedetomidine infusion has anti-hyperalgesic effects on remifentanil-induced postoperative hyperalgesia. Thus, pretreatment with dexmedetomidine has significantly reduced the enhancement of mechanical allodynia and thermal hyperalgesia (148). This effect depends on its ability to activate N-methyl-D-aspartate (NMDA) receptors in the spinal cord by suppression of phosphorylation NR2B subunit (148).

1.2.5.6 Toxicity

The symptoms of overdose include constriction of the pupils of the eyes, drowsiness; elevated blood pressure followed by dropping in pressure, agitation, hypothermia, slowed breathing, and generalized weakness (149). Also, clonidine may produce bradycardia and atrioventricular (AV) block, the possibility of additive effects should be considered if clonidine is given with other drugs that may affect sinoatrial node function or AV nodal conductions, such as beta-adrenergic blocking agents (e.g., propranolol) or calcium-channel blocking agents (1

1.2.5.7 Side effects of clonidine

The most common adverse effects of clonidine are dry mouth, dizziness, headache, sedation, constipation, feeling drowsy and tired (150). These effects are usually mild and decrease over time which might happen by oral administration (150). Also, other serious adverse effects are potentially life-threatening, including increased than reduced blood pressure, slower or faster heart rate (arrhythmia), pounding heart, slowed breathing, hallucinating state, nightmares, and sexual problems, such as erectile dysfunction and difficulty to pass urine (150). In contrast, when clonidine administrated by intrathecal infusion in combination with bupivacaine provides more satisfactory anesthesia and analgesia, and it has the benefit of not having pruritus, nausea, and vomiting as adverse effects (151). That supports the benefit of the analgesia medications mixture usage.

1.2.5.8 The effects of clonidine on pain

Since clonidine produces strong analgesia during experimental studies on animals, it can also provide adequate analgesia to humans by the local and spinal administration. Clonidine is also a useful analgesic agent when used in an epidural procedure (152). However, it gives inadequate analgesia when administered systemically (152). According to laboratory and clinical findings, intraspinal administered a 2-adrenergic agonist might be useful in the management of neuropathic pain (152). 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 (152). Clinically, it was shown to suppress chronic pain in open-label clinical trials of patients with chronic neuropathic pain. Also, 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 (152, 153).

Clonidine has anti-nociceptive activity via different mechanisms, including peripheral, supraspinal, and primarily spinal cord, as well as activating of descending noradrenergic pathways (154). Clonidine has shown to prolong the duration of analgesia (155). More recently, systematic reviews have evaluated clonidine as an analgesic drug that included patients who had underwent different surgeries and received IT clonidine infusion (155). These reviews have reported that patients who received clonidine had a statistically significant prolong in the time to first analgesia request compared with the placebo group (155, 156). Moreover, a study has demonstrated that patients receiving clonidine used less morphine compared to those who received placebo (156). α-2 adrenoreceptor agonists (clonidine and dexmedetomidine) have been evaluated as a class demonstrated a significant pain reduction scores for the first two hours postoperatively (157).

The most common α2-receptor agonist for intrathecal administration is clonidine, as it combines with local anesthetics and morphine is shown to have a synergetic effect for relieving pain (134). Therefore, clonidine mainly administrated in combination with morphine for treating neuropathic pain (158, 159). Furthermore, IT administration of clonidine with the average daily dose range from 50 to 200 μg minimizes the risk of morphine tolerance and thereby reducing the risk for opioid-related side effects (159, 160). Significantly, immediate stopping of long-term IT therapy might lead to rebound hypertension and psychotic behavior (161). In clinical study, using IT clonidine alone or in combination for managing chronic pain conditions, such as complex regional pain syndrome (CRPS) and neuropathic pain for 15 patients with cancer pain retrospectively reviewed (162). All patients have received a trial of short-term infusion of

clonidine and following initial response to clonidine treatment was shown seven patients required additional morphine (162). Also, the duration of relieving pain is typically shorter than 18 months in this group of patients (162). Therefore, clonidine has the synergistic effect with other analgesic medications and prolonged the analgesic section, as well as decreases the risk of morphine tolerance.

1.2.5.9 The effects clonidine on cognitive function

Although clonidine has direct and immediate decreased memory recall after one-hour infusion in the four groups to compare with placebo, the only notable difference is observed in the placebo versus clonidine in comparison memory recalls of the list given at the 45 min recovery period was not impaired after clonidine administrated (163). Additionally, during placebo recall has increased from baseline, thereby resulting the most words are recalled from the most recent list (163). Significantly, there is no evidence of retrograde amnesia as a result; the recall of the baseline list is not different between the clonidine and placebo infusions groups (163). Thus, clonidine infusion has led to significant and progressive sedation; however, all subjects are easily awoken to perform tests and assessments without effect on memory function (163).

Although nicardipine and clonidine were found to have comparable effects in a study in hypertensive patients, these medications are distinctly different concerning the cognitive function and psychomotor performance (164). Clonidine altered vigilance, attention, and body control, as was shown by the significant increase in the length of body sway during evaluations (164). This study confirmed the sedative effects of clonidine regarding drowsiness and tiredness, which are frequently reported by hypertensive patients, and are well-known side-effects of clonidine (164).

Chapter VII

1.2.6 Naloxone

Physical, chemical, pharmaceutical and formulation properties.

Common name: Naloxone hydrochloride

Chemical name: 17-Allyl-4, 5 α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride

Molecular formula: C19H21NO4

Molecular Weight: 327.38 g/mol

Structural Formula:

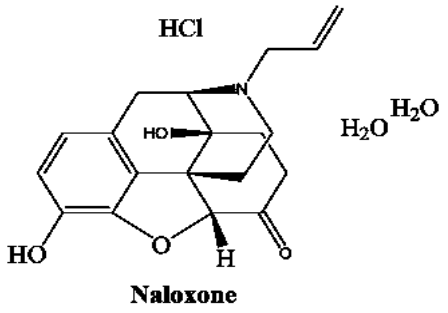


Figure 8: Naloxone structural formula (165).

Naloxone is a slightly off-white powder, soluble in water, dilute with acids and alkali (165). Naloxone is soluble in alcohol and melts at approximately 178°C (165). The pH of aqueous solutions is usually acidic (165).

1.2.6.1 Pharmacology

Naloxone is an opioid antagonist drug. It reverses and prevents the complications of opioid administration, including respiratory depression, sedation, and hypotension (165). It acts by binding to the opioid receptors in the CNS (165). Additionally, naloxone is mostly a pure narcotic antagonist medication and does not possess the morphine-like characteristic properties of other narcotic antagonists (165). Naloxone does not elicit respiratory suppression,

psychotomimetic adverse effects, or pupillary constriction (165). Indeed, in the absence of narcotics, it shows no pharmacologic activities (165). When naloxone is administrated intravenously, the onset of action appears within 2 minutes (165). However, the start of action is slower when given subcutaneously or intramuscularly (165). Also, the duration of action differs with the site of injection and the dose of concentration (165).

1.2.6.2 Pharmacodynamics

Naloxone hydrochloride is a semisynthetic drug (N-allyl-noroxymorphone hydrochloride), which is derived from thebaine (166). When is given in standard doses to subjects who have not recently taken opioids, naloxone does not exert any pharmacologic effects (166). However, high doses of the medication (10 times higher than usual therapeutic dose) may produce insignificant analgesia (166). The only adverse effect is a slight feeling of drowsiness, without respiratory depression or cardiovascular changes (166).

Naloxone acts efficiently in patients who have taken large doses of morphine or other medications that have the same effect as morphine - naloxone antagonizes most of the consequences of morphine-like actions (167). Since the duration of action of naloxone is shorter than that of the opioids, the effects of the opioid might return as the effects of naloxone dissipate (167). Significantly, naloxone has not been shown to produce tolerance, physical, or psychological dependence (167).

However, the dose 0.4 mg of subcutaneous naloxone would precipitate possibly severe withdrawal manifestations in patients who are physically dependent on morphine or pentazocine (167). The precise mechanism of action of the opioid antagonist effects of naloxone is not fully understood (167). Naloxone is believed to act as a competitive antagonist at μ, K, or σ opioid

receptors in the brain (167). However, it is thought this medication might have the highest affinity for the μ receptor (167).

1.2.6.3 Pharmacokinetics

Naloxone has an onset of action of two minutes after intravenous administration and approximately four minutes following SC and IM administration (168). The duration of action depends on the dose and route of administration; it is long after IM administration than IV administration (168). A study has shown that the length of action was 45 minutes following intravenous administration (168). The plasma half-life of this medication has been reported to be 60 to 90 minutes in adults and approximately three hours in the neonate (168).

In addition, naloxone is widely distributed into body tissues and fluids following parenteral administration (168). In an experimental study in animals, the highest concentrations were observed in the brain, kidney, spleen, lungs, heart and skeletal muscles. In humans, naloxone can readily cross the placenta in a pregnant woman, but it is still not known whether the medication is distributed into breast milk (168).

1.2.6.4 Metabolism

Naloxone is extensively metabolized in the liver by conjugation with glucuronic acid. The primary metabolite is naloxone-3-glucuronide (169). It also undergoes N-DE alkylation and reduction of the 6-keto group followed by conjugation (169). Some studies with radiolabeled naloxone have indicated that about 35% of intravenous doses of the drug are excreted as metabolites in urine within six hours, approximately 50% in one day and 65% within three days (169).

1.2.6.5 Immune system

In researching a new anti-inflammatory drug for Parkinson's disease (PD), a study has recently discovered that naloxone is widely effective in preventing dopaminergic neurodegeneration in different rodent PD models by inhibiting inflammatory responses (167). The inhibitory effects of naloxone on inflammatory pathways have been proven in some experimental studies (167).

Following systemic infusion of 1 mg/kg naloxone, intranigral LPS-induced microglial activation and neurotoxicity are significantly decreased (167). Furthermore, in midbrain and cortical neuronglia cultures, microglial activations and related proinflammatory cytokine productions including nitrite oxide, TNFα, and IL-1β, in response to LPS stimulation, were also attenuated by naloxone at 0.1-1 micromolar concentrations (167). Also, this study provided substantial evidence indicating that NOX2 is a novel non-opioid binding site for naloxone, which is essential in mediating its inhibitory effects on microglia over-activation and superoxide production (167).

In vitro, naloxone further induced inhibition of the phytohaemagglutinin (PHA) proliferative responses and IL-2 production, as well as a significant suppression interferon gamma (IFNγ) levels in human blood lymphocytes of these addicts (169). This significant suppression of (IFNγ) production is demonstrated in the presence of naloxone (169).

1.2.6.6 Toxicity

Naloxone hydrochloride is used for the complete or partial reversal of natural and synthetic opioid-related complications, such as respiratory depression (170). Naloxone might be useful as an adjunctive medication to elevate blood pressure in the treatment of septic shock (170). In humans, toxicity is associated with seizures, severe hypertension, hypotension, and

decreased heart rate (170). Naloxone-induced acute pulmonary edema, which can be fatal, is an infrequent complication (170).

Naloxone is weakly positive in the in vitro human lymphocyte chromosome aberration test (170). Also, naloxone might affect some functions of the immune system in humans, but its action is fast and transient (170). Experimental studies have observed that the injection of naloxone into the medial septal nucleus of rats produced a considerable increase in hippocampal acetylcholine release in a dose-dependent manner (171). In addition, it was found that rats showed a significant increase in motor activity and exhibited behavioral fits (171). By loading dose, 50 mg/kg toxicity is associated with irritability, tremors, and seizures as summarized below in table: 4 (170, 171).

Animal	Route	LD 50 (mg/kg)	Observations
Rat	S/C	240-260	Naloxone was twice as toxic in the newborn as in the six-week-old rat. At toxic doses, naloxone produces excitation, hyperactivity, salivation, tremors and tonic-clonic convulsions.
Rat	I.V	130-150	

Table 4: Naloxone loading dose (170, 171).

1.2.6.7 Side effects of naloxone

The most common adverse effects of naloxone are the following:

- Disturbance in blood pressure.
- Nausea or vomiting.
- Shaking and sweating.

- Generalized weakness (172).

The most severe adverse effects are:

- Irregular heartbeat (arrhythmia).
- Heart block.
- Seizures.
- Shortness of breath.
- Pulmonary edema (very rare) (172).

1.2.6.8 The effects of naloxone on pain

Naloxone has an essential function in the treatment of chronic refractory pain, mainly when administered with opioids (173). Naloxone at ultra-low doses is administered in combination with opioids to increase the opioid analgesic effect, and it can reduce the development of opioid tolerance in animals (173). Thus, ultra-low doses of naloxone have been shown to improve the antinociceptive effect of methadone, as well as it has produced an opioid-sparing impact on patients administered morphine for postoperative pain (173). In fact, there is an oral opioid agent that combines a therapeutic amount of oxycodone with a small dose of the antagonist naloxone for the treatment of moderate to severe chronic pain (173).

A study has theorized that ultra-low doses of naloxone might prevent the observed increase in sevoflurane needs during remifentanil infusion that is related to tolerance, as well as reduce mechanical nociceptive thresholds (MNTs), which are associated with hyperalgesia (173). Additionally, research has conducted by Younger et al. had performed a randomized crossover placebo-controlled study in which 31 women with fibromyalgia (FM) are placed on either low-

dose naloxone (4.5 mg/d) or placebo (174). They were followed for 16 weeks at the end of the study; therefore, the results were shown a significant reduction in pain in the low dose naloxone group in comparison to those taking placebo (174).

In retrospective study, naloxone plays a vital role in the management of chronic pain by retrolaminar paravertebral infiltration (PVI) for 31 patients compared with epidural steroid injection (ESI) when combined with other analgesic medications, such as morphine, bupivacaine, neostigmine, and ketamine (175). Both approaches were shown to be superior to the others in relieving pain and treatment satisfaction after six months (175). However, multiple PVIs might have further reduced pain (175). Additionally, study findings have indicated that the addition of naloxone to oxycodone in an extended release combination tablet might enhance the acceptability of opioid management for patients with chronic pain; therefore, this represents as a new therapeutic approach for the treatment of chronic refractory pain (176). To conclude, adding ultra-low-dose naloxone to the analgesic mixture as a drug combination has a beneficial impact on patients who suffering from chronic pain.

1.2.6.9 The effects of naloxone on cognitive function

A report published in 1985 suggested that naloxone 1-10 mg IV might improve clinical and psychometric evaluations in patients with dementia of the Alzheimer's type (177). Efforts to enhance cognitive functioning with naloxone in humans have been conflicting (177). Scientists have found no effect of 0.8 or 1.6 mg IV naloxone on performance in specific tests (symbol copying, digit-symbol substitution, and verbal learning) in healthy volunteers (177). Further, some studies have shown no effect of 10 or 20 mg intravenous naloxone on immediate or delayed recognition in normal subjects (177).

However, one study reported a detrimental effect of naloxone on memory recall in healthy humans is associated when given at a high intravenous dose (2 mg/kg) (177). More recently, findings demonstrate that naloxone may facilitate spatial learning and memory function and augment long-term potentiation of Schaffer collateral-CA1 synapse in the hippocampal slice preparations of vascular dementia (VD) in rats (178). Therefore, naloxone might have beneficial effects on cognitive function in VD rats by modulating and promoting the synaptic plasticity in the hippocampal neuronal network (178).

Chapter VIII

1.3 Discussion

What would happen if we mix these medications to eliminate chronic refractory pain?

As most of the reviewed non-clinical and clinical studies have proven the efficacy of combination drug treatment over monotherapy in chronic pain treatment with improved cognitive function at the same time. Therefore, the advantages of combination drug therapy for the management chronic pain include potential analgesic synergism with different classes of medications. Further, the efficacy of the drug combination approach is significantly higher than treatment with a single drug with less adverse effects as many studies have reported that.

The number of medications in this research has proven to be effective and safe in chronic pain with cognitive disorders, especially in old people. A combination of morphine, bupivacaine, ketamine with clonidine and the ultra-low-dose of naloxone is an appropriate mixture of combined medications to be intrathecally infused (26). Thus, this would have a positive result in patients who have suffered from chronic neuropathic pain and cognitive impairment as well. The mechanism of actions of different medications is substantially needed to improve patient`s outcomes. Therefore, a new combination treatment approach will be required in the future.

Although conventional treatment of chronic pain is still prescribed by some clinicians and pain specialists, avoiding ineffective management's approaches and maximizing the treatments that may have a better clinical trial with less adverse effects is still required. More importantly, physicians and pain specialists should be acknowledged and identified comorbidities that are related to managing pain regarding enhancing physical and psychological activities. Furthermore, the multi-modality management of chronic refractory pain approaches not just

associated with pharmacological interventions, but also there are some non-pharmacological strategies, such as chronic pain rehabilitation, physiotherapy, and psychotherapy.

What are non-pharmacological therapies can be used in the management of chronic pain?

Management of chronic pain usually involves medications and therapies. Many types of treatment can help ease the pain. Physical therapy plays a significant role in assisting patients to manage and overcome chronic pain, such as strengthening and stretching activities and low-impact exercise, such as walking, swimming and biking may help to minimize the pain. However, too much exercising or not at all can hurt patient with chronic pain. Occupational therapists would be appropriate to teach how to do ordinary tasks differently and how to pace yourself, so you will not hurt yourself. Behavioral therapy can reduce pain through methods, such as meditation and yoga that help you relax and decrease stress.

Biofeedback is a method of consciously controlling a physiological body function, and it is normally regulated automatically by the body physiology, such as skin temperature, muscle tension, heart rate and blood pressure. Additionally, lifestyle changes such as getting daily exercise, eating a healthy diet, getting enough sleep, and trying complementary therapies. Further, cognitive-behavioral therapy may help you to reduce the pain and to prevent it from getting worse. Cognitive-behavioral therapy (CBT) provides relaxation techniques, as well as stress management, and other ways to help you cope with pain physical, psychological, and social factors all play a vital role in chronic pain management. However, all these approaches could help, but it is difficult to adhere with, leading to a necessity of medication therapy, especially in chronic pain management.

1.4 Conclusion

The ultimate goal of using different medications for the treatment of chronic pain is not only relieving that pain, but also improving and to managing the associated physical, emotional, and social issues of those who suffer. Different classes of monotherapies are used for the chronic pain treatment, which may elicit significant adverse effects. This can negatively affect the effectiveness of treatment regarding the physiological and pharmacological aspects of long-term management. Therefore, the idea of combination therapy is to provide better results for patients with fewer side effects. It is essential to find out a proper mixture of the drug combination, as well as to understand safety, efficacy, and adverse reactions of the individual medications, to know how various drug interactions are essential in making the most effective pharmacological decisions to manage chronic pain and cognitive disorders. The time limit might be counted as a limitation of this literature review, and also further clinical studies with the adequate sample are needed to confirm the positive impact of the analgesic medications mixture. Although this limitation might exist in this thesis, this scientific literature review has provided a condense knowledge for chronic pain management and decreasing cognitive disorder.

Chapter IX

Bibliography

1. Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. The Journal of Pain. 2010 Nov 1;11(11):1230-9.

2. Harstall C, Ospina M. How prevalent is chronic pain. Pain clinical updates. 2003 Jun;11(2):1-4.

3. Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. The Journal of Pain. 2010 Nov 1;11(11):1230-9.

4. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA. A classification of chronic pain for ICD-11. Pain. 2015 Jun;156(6):1003.

5. Becker N, Thomsen AB, Olsen AK, Sjøgren P, Bech P, Eriksen J. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. Pain. 1997 Dec 1;73(3):393-400.

6. Magni G, Marchetti M, Moreschi C, Merskey H, Luchini SR. Chronic musculoskeletal pain and depressive symptoms in the National Health and Nutrition Examination I. Epidemiologic follow-up study. Pain. 1993 May 1;53(2):163-8.

7. Latham J, Davis BD. The socioeconomic impact of chronic pain. Disability and rehabilitation. 1994 Jan 1;16(1):39-44.

8. Locker D. Disability and disadvantage: the consequences of chronic illness. Routledge; 1983.

9. Von Korff M, Dworkin SF, Le Resche L. Graded chronic pain status: an epidemiologic evaluation. Pain. 1990 Mar 1;40(3):279-91.

10. Von Korff M, Wagner EH, Dworkin SF, Saunders KW. Chronic pain and use of ambulatory health care. Psychosomatic Medicine. 1991 Jan.

11. Bowsher D, Rigge M, Sopp L. Prevalence of chronic pain in the British population: a telephone survey of 1037 households. Pain Clinic. 1991;4(4):223-30.

12. Brennan F, Carr DB, Cousins M. Pain management: A fundamental human right. Anesth Analg 2007; 105:205-21.

13. Lohman D, Schleifer R, Amon JJ. Access to pain treatment as a human right. BMC medicine. 2010 Dec;8(1):8.

14. Moulin DE, Clark AJ, Speechley M, Morley-Forster PK. Chronic pain in Canada-prevalence, treatment, impact and the role of opioid analgesia. Pain Research and Management. 2002;7(4):179-84.

15. Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain. 1998 Sep 1;77(3):231-9.

16. Aronoff GM, Evans WO, Enders PL. A review of follow-up studies of multidisciplinary pain units. Pain. 1983 May 1;16(1):1-1.

17. Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM. The economic costs of chronic pain among a cohort of treatment-seeking adolescents in the United States. The Journal of Pain. 2014;15(9):925-33.

18. Hogan ME, Taddio A, Katz J, Shah V, Krahn M. Incremental health care costs for chronic pain in Ontario, Canada: A population-based matched cohort study of adolescents and adults using administrative data. Pain. 2016 Aug 1; 157(

19. McVinnie DS. Obesity and pain. Br J Pain 2013; 7:163–70.

20. Narouze S, Souzdalnitski D. Obesity and chronic pain: systematic review of prevalence and implications for pain practice. Reg Anesth Pain Med 2015; 40:91–111.

21. Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press, 2011.

22. Karttunen NM, Turunen J, Ahonen R, Hartikainen S. More attention to pain management in community-dwelling older persons with chronic musculoskeletal pain. Age Ageing 2014; 43:845–50.

23. Boulanger A, Clark AJ, Squire P, Cui E, Horbay GL. Chronic pain in Canada: have we improved our management of chronic noncancer pain?. Pain Research and Management. 2007;12(1):39-47.

24. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Progress in neurobiology. 2011 Mar 1;93(3):385-404.

25. Lawlor PG. The panorama of opioid-related cognitive dysfunction in patients with cancer. Cancer. 2002 Mar 15;94(6):1836-53.

26. Abdolmohammadi S, Hétu PO, Néron A, Blaise G. efficacy of an intrathecal multidrug infusion for pain control in older adults and in end-stage malignancies: a report of three cases. Pain Research and Management. 2015;20(3):118-22.

27. Vissers KC, Besse K, Wagemans M, Zuurmond W, Giezeman MJ, Lataster A, Mekhail N, Burton AW, van Kleef M, Huygen F. 23. Pain in patients with cancer. Pain Practice. 2011 Sep 1;11(5):453-75.

28. Hood DD, Eisenach JC, Tong C, Tommasi E, Yaksh TL. Cardiorespiratory and spinal cord blood flow effects of intrathecal neostigmine methylsulfate, clonidine, and their combination in sheep. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1995 Feb 1;82(2):428-35.

29. Lauretti GR, Reis MP, Prado WA, Klamt JG. Dose-response study of intrathecal morphine versus intrathecal neostigmine, their combination, or placebo for postoperative analgesia in patients undergoing anterior and posterior vaginoplasty. Anesthesia & Analgesia. 1996 Jun 1;82(6):1182-7.

30. Lauretti GR, de Oliveira R, Reis MP, Maria-do-Carmo CJ, Pereira NL. Study of three different doses of epidural neostigmine coadministered with lidocaine for postoperative analgesia. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1999 Jun 1;90(6):1534-8.

31. Lauretti GR, Gomes JM, Reis MP, Pereira NL. Low doses of epidural ketamine or neostigmine, but not midazolam, improve morphine analgesia in epidural terminal cancer pain therapy. Journal of clinical anesthesia. 1999 Dec 1;11(8):663-8.

32. Stein C, Clark JD, Oh U, Vasko MR, Wilcox GL, Overland AC, Vanderah TW, Spencer RH. Peripheral mechanisms of pain and analgesia. Brain research reviews. 2009 Apr 1;60(1):90-113.

33. Mastenbroek TC, Kramp-Hendriks BJ, Kallewaard JW, Vonk JM. Multimodal intrathecal analgesia in refractory cancer pain. Scandinavian journal of pain. 2017 Jan 1; 14:39-43.

34. Abdulatif M, El-Sanabary M. Caudal neostigmine, bupivacaine, and their combination for postoperative pain management after hypospadias surgery in children. Anesthesia & Analgesia. 2002 Nov 1;95(5):1215-8.

35. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Progress in neurobiology. 2011 Mar 1; 93(3):385-404.

36. Morphine: Wishart Research Group; [Available from: https://www.drugbank.ca/drugs/DB00295.

37. Morphine Sulfate: National Center for Biotechnology Information; 217 [Available from: https://pubchem.ncbi.nlm.nih.gov/compound/5464280.

38. Morphine: Pharmacokinetics; http://www.drugguide.com/ddo/view/Davis-Drug-Guide/51518/all/morphine#3

39. Whiteside GT, Boulet JM, Walker K. The role of central and peripheral μ opioid receptors in inflammatory pain and edema: a study using morphine and DiPOA ([8-(3, 3-diphenyl-propyl)-4-oxo-1-phenyl-1, 3, 8-triaza-spiro [4.5] dec-3-yl]-acetic acid). Journal of Pharmacology and Experimental Therapeutics. 2005;314(3):1234-40.

40. Sacerdote P.Opioids and the immune system. Palliative medicine. 2006; 20(8_suppl):9-15.

41. Morphine: Toxicity; https://pubchem.ncbi.nlm.nih.gov/compound/morphine#section=Toxicity.

42. Slatkin N, Rhiner M. Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: a case report. Journal of pain and symptom management. 2004 Mar 1;27(3):268-73.

43. Kurz A, Sessler DI. Opioid-induced bowel dysfunction. Drugs. 2003 Apr 1;63(7):649-71.

44. De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. Pharmacology & therapeutics. 1996 Jan 1;69(2):103-15.

45. Aronoff GM. Complications of opioid therapy. InControlled Substance Management in Chronic Pain 2016 (pp. 135-161). Springer, Cham.

46. Yuan CS, Wei G, Foss JF, O'Connor M, Karrison T, Osinski J. Effects of subcutaneous methylnaltrexone on morphine-induced peripherally mediated side effects: a double-blind randomized placebo-controlled trial. Journal of Pharmacology and Experimental Therapeutics. 2002 Jan 1;300(1):118-23.

47. Borgbjerg FM, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. Pain. 1996 Jan 1;64(1):123-8.

48. Da Silva AT, Souza JD, Quest JA, Pagani FD, Moerschbaecher JM, Buller A, Hamosh P, Gillis RA. Central nervous system site of action for the respiratory depressant effect of diacetylmorphine (heroin) in the cat. The Journal of clinical investigation. 1983 Oct 1;72(4):1209-17.

49. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. European Journal of Pain. 2007 Jul 1;11(5):490-518.

50. Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Medicine. 2003 Dec 1;4(4):340-51.

51. Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine the peripheral capacitance and resistance vessels in human subjects. The Journal of clinical investigation. 1974 Dec 1;54(6):1247-58.

52. Joseph D. Tobias, 2002. Controlled Hypotension in Children. Department of Anesthesiology 3W40HThe University of Missouri Columbia USA. Retrieved by https://link.springer.com/article/10.2165/00128072-

53. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Experimental and clinical psychopharmacology. 2008; 16(5):405.

54. Nersesyan H, Slavin KV. Current approach to cancer pain management: Availability and implications of different treatment options. Therapeutics and clinical risk management. 2007; 3(3):381.

55. Ballantyne JC, Mao J. Opioid therapy for chronic pain. New England Journal of Medicine. 2003;349(20):1943-53.

56. Ballantyne JC. Chronic pain following treatment for cancer: the role of opioids. The oncologist. 2003; 8(6):567-75.

57. Sjogren P, Christrup LL, Petersen MA, et al. Neuropsychological assessment of chronic non-malignant pain patients treated in a multidisciplinary pain centre. Eur J Pain. 2005;9: 453–462.

58. Kaczocha M, Azim S, Nicholson J, Rebecchi MJ, Lu Y, Feng T, Romeiser JL, Reinsel R, Rizwan S, Shodhan S, Volkow ND. Intrathecal morphine administration reduces postoperative pain and peripheral endocannabinoid levels in total knee arthroplasty patients: a randomized clinical trial. BMC anesthesiology. 2018 Dec;18(1):27.

59. Banning A, Sjøgren P, Kaiser F. Reaction time in cancer patients receiving peripherally acting analgesics alone or in combination with opioids. Acta anaesthesiologica scandinavica. 1992 Jul 1;36(5):480-2.

60. Tassain V, Attal N, Fletcher D, Brasseur L, Degieux P, Chauvin M, et al. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. Pain. 2003; 104(1):389-400.

61. Beilin B, Hoofien D, Poran R, Gral I, Grinevich G, Butin B, et al. Comparison of two patient-controlled analgesia techniques on neuropsychological functioning in the immediate postoperative period. Journal of clinical and experimental neuropsychology. 2008; 30(6):674-82.

62. Clemons M, Regnard C, Appleton T. Alertness, cognition and morphine in patients with advanced cancer. Cancer treatment reviews. 1996 Nov 1;22(6):451-68.

63. Ersek M, Cherrier MM, Overman SS, et al. The cognitive effects of opioids. Pain Manag Nurs. 2004; 5:75–93.

64. O'Neill, W. M., Hanks, G. W., Simpson, P., Fallon, M. T., Jenkins, E., & Wesnes, K. (2000). The cognitive and psychomotor effects of morphine in healthy subjects: A randomized controlled trial of repeated (four) oral doses of dextropropoxyphene, morphine, lorazepam and placebo. Pain, 85, 209-215

65. Bupivacaine: Compound structure; https://pubchem.ncbi.nlm.nih.gov/compound/bupivacaine#section=Top.

66. Bupivacaine: National Center for Biotechnology Information; [Available from: https://pubchem.ncbi.nlm.nih.gov/compound/2474

67. Bupivacaine: Pfizer Australia Pty Ltd. (2012). Bupivacaine Injection BP. Retrieved by file:///C:/Users/aabdur2/Downloads/BUPIVACAINE_INJECTION-PI.pdf.

68. Bupivacaine: Pharmacodynamics [Available from: "https://www.drugbank.ca/drugs/DB00297"

69. Bupivacaine: [https://pubchem.ncbi.nlm.nih.gov/compound/bupivacaine#section=ATC-Code]

70. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. Acta Anaesthesiologica Scandinavica. 2006; 50(3):265-82.

71. Golub MS, Germann SL. Perinatal bupivacaine and infant behavior in rhesus monkeys. Neurotoxicology and teratology. 1998; 20(1):29-41.

72. Bupivacaine: https://www.drugs.com/sfx/bupivacaine-side-effects.html

73. Verlinde M, Hollmann MW, Stevens MF, Hermanns H, Werdehausen R, Lirk P. Local anesthetic-induced neurotoxicity. International journal of molecular sciences. 2016 Mar 4;17(3):339.

74. Deer TR, Caraway DL, Kim CK, Dempsey CD, Stewart CD, McNeil KF. Clinical experience with intrathecal bupivacaine in combination with opioid for the treatment of chronic pain related to failed back surgery syndrome and metastatic cancer pain of the spine. The Spine Journal. 2002;2(4):274-8.

75. Sjöberg M, Nitescu P, Appelgren L, Curelaru I. Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain. Results from a morphine: bupivacaine dose regimen of 0.5: 4.75 mg/ml. Anesthesiology. 1994; 80(2):284-97.

76. Hildebrand KR, Elsberry DD, Deer TR. Stability, compatibility, and safety of intrathecal bupivacaine administered chronically via an implantable delivery system. The Clinical journal of pain. 2001; 17(3):239-44.

77. de Brito Cançado TO, Omais M, Ashmawi HA, Torres MLA. Chronic pain after cesarean section. Influence of anesthetic/surgical technique and postoperative analgesia. Brazilian Journal of Anesthesiology. 2012; 62(6):762-74.

78. Kumar K, Bodani V, Bishop S, Tracey S. Use of intrathecal bupivacaine in refractory chronic nonmalignant pain. Pain Med. 2009;10:819–828.

79. Mironer Y, Haasis J, Chapple I, Brown C, Satterthwaite J. Efficacy and safety of intrathecal opioid/bupivacaine mixture in chronic nonmalignant pain: a double blind, randomized, crossover, multicenter study by the National Forum of Independent Pain Clinicians (NFIPC). *Neuromodulation.*2002;**5**:2008–2213.

80. Veizi IE, Hayek SM, Narouze S, Pope JE, Mekhail N. Combination of intrathecal opioids with bupivacaine attenuates opioid dose escalation in chronic noncancer pain patients. Pain Med. 2011; 12:1481–1489.

81. Goucke CR, Dusci LJ, Van Leeuwen S, Fairclough D, Ilett KF. Stability and tolerability of high concentrations of intrathecal bupivacaine and opioid mixtures in chronic noncancer pain: an open-label pilot study. Pain Medicine. 2010; 11(11):1612-8.

82. Kanazi GE, Aouad MT, Jabbour‐ Khoury SI, Al Jazzar MD, Alameddine MM, Al‐ Yaman R, Bulbul M, Baraka AS. Effect of low‐ dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiologica Scandinavica. 2006 Feb 1;50(2):222-7.

83. Lee SC, Moll V. Continuous Epidural Analgesia Using an Ester-Linked Local Anesthetic Agent, 2-Chloroprocaine, During Labor: A Case Report. A&A Case Reports. 2017 Jun 1; 8(11):297-9.

84. Tarkkila P. Spinal Anesthesia: Safe Practice and Management of Adverse Events. InComplications of Regional Anesthesia 2017 (pp. 245-258). Springer, Cham.

85. Murinova N, Krashin D, Kaye AD. Pharmacology and Clinical Relevance of Commonly Used Drugs. InEssentials of Interventional Techniques in Managing Chronic Pain 2018 (pp. 27-34). Springer, Cham.

86. Bottros MM, Christo PJ. Current perspectives on intrathecal drug delivery. Journal of pain research. 2014; 7:615.

87. Ketamine: Structure Compound; https://pubchem.ncbi.nlm.nih.gov/compound/ketamine#section=2D-Structure

88. Ketamine: Wishart Research Group; 2017 [Available from: https://www.drugbank.ca/drugs/DB01221

89. Ketalar, ketamine hydrochloride; Date of Preparation (2015). Retrieved by file:///C:/Users/jelduf/Downloads/213-1281-1-PB.pdf.

90. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. British journal of clinical pharmacology. 2014; 77(2):357-67.

91. Liu F-L, Chen T-L, Chen R-M. Mechanisms of ketamine-induced immunosuppression. Acta Anaesthesiologica Taiwanica. 2012; 50(4):172-7.

92. Beilin B, Rusabrov Y, Shapira Y, Roytblat L, Greemberg L, Yardeni I, et al. Low-dose ketamine affects immune responses in humans during the early postoperative period. British journal of anaesthesia. 2007; 99(4):522-7.

93. Bell, J. D. "In vogue: ketamine for neuroprotection in acute neurologic injury." Anesthesia & Analgesia. 2017; 124(4): 1237-1243.

94. Braun S, Gaza N, Werdehausen R, Hermanns H, Bauer I, Durieux ME, et al. Ketamine induces apoptosis via the mitochondrial pathway in human lymphocytes and neuronal cells. British journal of anaesthesia. 2010; 105(3):347-54.

95. Ketamine: Side Effects; http://drugabuse.com/library/the-effects-of-ketamine-use/

96. ketamine: http://ketamine.com/ketamine-effects/long-term-ketamine-effects/

97. Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev. 2012; 11:CD003351.

98. Bredlau AL, Thakur R, Korones DN, Dworkin RH. Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. Pain Med. 2013; 14:1505–1517.

99. Koffler SP, Hampstead BM, Irani F, Tinker J, Kiefer R-T, Rohr P, et al. The neurocognitive effects of 5 day anesthetic ketamine for the treatment of refractory complex regional pain syndrome. Archives of Clinical Neuropsychology. 2007; 22(6):719-29.

100. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. 2009; 147:107–115.

101. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. Anesthesia & Analgesia. 2003 Dec 1;97(6):1730-9.

102. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. Pain. 2009; 146:18–25.

103. Yang R, Wang P, Chen Z, Hu W, Gong Y, Zhang W, et al. WY-14643, a selective agonist of peroxisome proliferator-activated receptor-α, ameliorates lipopolysaccharide-induced depressive-like behaviors by preventing neuroinflammation and oxido-nitrosative stress in mice. Pharmacology Biochemistry and Behavior. 2017; 153:97-104.

104. Abelaira HM, Réus GZ, Ignácio ZM, dos Santos MAB, de Moura AB, Matos D, et al. Effects of ketamine administration on mTOR and reticulum stress signaling pathways in the brain after the infusion of rapamycin into prefrontal cortex. Journal of psychiatric research. 2017; 87:81-7.

105. Morgan CJ, Curran HV. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology (Berl) 2006; 188:408–424. doi: 10.1007/s00213-006-0572-3.

106. Krystal AD, Weiner RD, Dean MD, Lindahl VH, Tramontozzi LA, Falcone G, et al. Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT. J Neuropsychiatry Clin Neurosci. 2003; 15:27–34. doi: 10.1176/jnp.15.1.27.

107. Kranaster L, Kammerer-Ciernioch J, Hoyer C, Sartorius A. Clinically favourable effects of ketamine as an anaesthetic for electroconvulsive therapy: a retrospective study. Eur Arch Psychiatry Clin Neurosci. 2011.

108. McDaniel WW, Sahota AK, Vyas BV, Laguerta N, Hategan L, Oswald J. Ketamine appears associated with better word recall than etomidate after a course of 6 electroconvulsive therapies. J ECT. 2006; 22:103–106. doi: 10.1097/00124509-200606000-00005.

109. Okamoto N, Nakai T, Sakamoto K, Nagafusa Y, Higuchi T, Nishikawa T. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression: comparing ketamine and propofol anesthesia. J ECT. 2010; 26:223–227. doi: 10.1097/YCT.0b013e3181c3b0aa.

110. Rasmussen KG, Kung S, Lapid MI, Oesterle TS, Geske JR, Nuttall GA, et al. A randomized comparison of ketamine versus methohexital anesthesia in electroconvulsive therapy. Psychiatry Res. 2014;215:362–365. doi: 10.1016/j.psychres.2013.12.027.

111. Yen T, Khafaja M, Lam N, Crumbacher J, Schrader R, Rask J, et al. Post-Electroconvulsive Therapy Recovery and Reorientation Time With Methohexital and Ketamine: A Randomized, Longitudinal, Crossover Design Trial. J ECT. 2015;31:20–25. doi: 10.1097/YCT.0000000000000132.

112. Yoosefi A, Sepehri AS, Kargar M, Akhondzadeh S, Sadeghi M, Rafei A, et al. Comparing effects of ketamine and thiopental administration during electroconvulsive therapy in patients with major depressive disorder: a randomized, double-blind study. J ECT. 2014;30:15–21. doi: 10.1097/YCT.0b013e3182a4b4c6.

113. Loo CK, Katalinic N, Garfield JB, Sainsbury K, Hadzi-Pavlovic D, Mac-Pherson R. Neuropsychological and mood effects of ketamine in electroconvulsive therapy: a randomised controlled trial. J Affect Disord. 2012;142:233–240. doi: 10.1016/j.jad.2012.04.032.

114. Fond G, Loundou A, Rabu C, Macgregor A, Lancon C, Brittner M, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology. 2014;231:3663–3676. doi: 10.1007/s00213-014-3664-5.

115. McGirr A, Berlim MT, Bond DJ, Neufeld NH, Chan PY, Yatham LN, et al. A systematic review and meta-analysis of randomized controlled trials of adjunctive ketamine in electroconvulsive therapy: efficacy and tolerability. J Psychiatr Res. 2015;62:23–30. doi: 10.1016/j.jpsychires.2015.01.003.

116. Neostigmine Methyl Sulfate: National Center for Biotechnology Information; 2017 [Available from: https://pubchem.ncbi.nlm.nih.gov/compound/5824

117. Neostigmine: http://www.rxlist.com/neostigmine-drug/clinical-pharmacology.htm

118. Neostigmine: https://pubchem.ncbi.nlm.nih.gov/compound/neostigmine#section=Pharmacology-and-Biochemistry

119. Neostigmine: Metabolism; https://pubchem.ncbi.nlm.nih.gov/compound/neostigmine#section=Absorption-Distribution-and-Excretion

120. Neostigmine: Wishart Research Group; 2017 [Available from: https://www.drugbank.ca/drugs/DB01400.

121. Pollak Y, Gilboa A, Ben-Menachem O, Ben-Hur T, Soreq H, Yirmiya R. Acetylcholinesterase inhibitors reduce brain and blood interleukin-1β production. Annals of neurology. 2005; 57(5):741-5.

122. Freeling J, Wattier K, LaCroix C, Li YF. Neostigmine and pilocarpine attenuated tumour necrosis factor α expression and cardiac hypertrophy in the heart with pressure overload. Experimental physiology. 2008; 93(1):75-82.

123. Neostigmine: Side Effects; https://www.drugs.com/sfx/neostigmine-side-effects.html

124. Habib AS, Gan TJ. Use of neostigmine in the management of acute postoperative pain and labour pain. CNS drugs. 2006; 20(10):821-39.

125. Roelants F, Lavand'homme PM, Mercier-Fuzier V. Epidural Administration of Neostigmine and Clonidine to Induce Labor AnalgesiaEvaluation of Efficacy and Local Anesthetic–sparing Effect. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2005; 102(6):1205-10.

126. Prado W, Goncalves A. Antinociceptive effect of intrathecal neostigmine evaluated in rats by two different pain models. Brazilian journal of medical and biological research. 1997; 30(10):1225-31.

127. Joshi-Khadke S, Khadke VV, Patel SJ, Borse YM, Kelkar KV, Dighe JP, Subhedar RD. Efficacy of spinal additives neostigmine and magnesium sulfate on characteristics of subarachnoid block, hemodynamic stability and postoperative pain relief: A randomized clinical trial. Anesthesia, essays and researches. 2015 Jan; 9(1):63.

128. Malleeswaran S, Panda N, Mathew P, Bagga R. A randomised study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in patients with mild preeclampsia undergoing caesarean section. Int J Obstet Anesth. 2010; 19:161–6.

129. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. Anesth Analg. 2005; 101:S30–43.

130. Saxena AK, Arava S. Current concepts in neuraxial administration of opioid and non-opioid: An overview and future perspectives. Indian J Anaesth. 2004;48:13–24.

131. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal) Anesth Analg. 1999; 88:797–809.

132. Yaksh TL, Grafe MR, Malkmus S, Rathbun ML, Eisenach JC. Studies on the safety of chronically administered intrathecal neostigmine methylsulfate in rats and dogs. Anesthesiology. 1995; 82:412–27.

133. Chanimov M, Cohen ML, Grinspun Y, Herbert M, Reif R, Kaufman I, et al. Neurotoxicity after spinal anaesthesia induced by serial intrathecal injections of magnesium sulphate. An experimental study in a rat model. Anaesthesia. 1997; 52:223–8.

134. Chung CJ, Kim JS, Park HS, Chin YJ. The efficacy of intrathecal neostigmine, intrathecal morphine, and their combination for post-cesarean section analgesia. Anesth Analg. 1998; 87:341–6.

135. Klamt JG, Slullitel A, Garcia IV, Prado WA. Postoperative analgesic effect of intrathecal neostigmine and its influence on spinal anaesthesia. Anaesthesia. 1997; 52:547–51.

136. Tzavara E, Bymaster F, Felder C, Wade M, Gomeza J, Wess J, et al. Dysregulated hippocampal acetylcholine neurotransmission and impaired cognition in M2, M4 and M2/M4 muscarinic receptor knockout mice. Molecular psychiatry. 2003; 8(7):673.

137. Birks J. Cholinesterase inhibitors for Alzheimer's disease. The Cochrane database of systematic reviews 2006: CD005593.

138. Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin 2005;21:1317–27.

139. Bishara D, Sauer J, Taylor D. The pharmacological management of Alzheimer's disease. Progress in Neurology and Psychiatry. 2015 Jul 1;19(4):9-16.

140. Clonidine: https://pubchem.ncbi.nlm.nih.gov/compound/clonidine#section=2D-Structure
141. Clonidine: Wishart Research Group; [Available from: https://www.drugbank.ca/drugs/DB00575
142. Clonidine: https://pubchem.ncbi.nlm.nih.gov/compound/clonidine#section=Absorption-Distribution-and-Excretion
143. Castro MI, Eisenach JC. Pharmacokinetics and dynamics of intravenous, intrathecal, and epidural clonidine in sheep. Anesthesiology. 1989 Sep;71(3):418-25.
144. Clonidine: Metabolism; https://www.drugbank.ca/drugs/DB00575

145. Romero-Sandoval A, Eisenach JC. Perineural clonidine reduces mechanical hypersensitivity and cytokine production in established nerve injury. The Journal of the American Society of Anesthesiologists. 2006; 104(2):351-5.

146. Romero-Sandoval EA, McCall C, Eisenach JC. A2-Adrenoceptor stimulation transforms immune responses in neuritis and blocks neuritis-induced pain. Journal of Neuroscience. 2005; 25(39):8988-94.

147. Zhu Y-J, Peng K, Meng X-W, Ji F-H. Attenuation of neuroinflammation by dexmedetomidine is associated with activation of a cholinergic anti-inflammatory pathway in a rat tibial fracture model. Brain research. 2016; 1644:1-8.

148. Zheng Y, Cui S, Liu Y, Zhang J, Zhang W, Zhang J, et al. Dexmedetomidine prevents remifentanil-induced postoperative hyperalgesia and decreases spinal tyrosine phosphorylation of N-methyl-d-aspartate receptor 2B subunit. Brain research bulletin. 2012; 87(4):427-31

149. Clonidine: https://pubchem.ncbi.nlm.nih.gov/compound/clonidine#section=Interactions

150. Clonidine: https://www.peoplespharmacy.com/2013/02/18/clonidine-catapres-side-effects-complications/

151. Singh, G., et al. (2016). "Effect of intrathecal clonidine versus fentanyl on bupivacaine spinal block in transurethral resection of prostate surgeries." Anesthesia, essays and researches **10**(1): 65.

152. Eisenach JC, DuPen S, Dubois M, Miguel R, Allin D, Group ECS. Epidural clonidine analgesia for intractable cancer pain. Pain. 1995; 61(3):391-9.

153. Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. Anesthesia & Analgesia. 2000; 91(6):1493-8.

154. Pyati S, Gan TJ. Perioperative pain management. CNS Drugs. 2007;21(3):185–211.

155. Elia N, Culebras X, Mazza C, Schiffer E, Tramer MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. Reg Anesth Pain Med. 2008;33(2):159–67.

156. Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. Br J Anaesth. 2013;110(1):21–7.

157. Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology.2012; 116(6):1312–22.

158. Cohen SP, Dragovich A. Intrathecal analgesia. Med Clin North Am. 2007; 91:251–270.

159. Uhle EI, Becker R, Gatscher S, Bertalanffy H. Continuous intrathecal clonidine administration for the treatment of neuropathic pain. Stereotact Funct Neurosurg. 2000; 75:167–175.

160. Hassenbusch S, Burchiel K, Coffey RJ, et al. Management of intrathecal catheter-tip inflammatory masses: a consensus statement. Pain Med. 2002; 3:313–323.

161. Ghafoor VL, Epshteyn M, Carlson GH, Terhaar DM, Charry O, Phelps PK. Intrathecal drug therapy for long-term pain management. Am J Health Syst Pharm. 2007; 64:2447–2461.

162. Ackerman LL, Follett KA, Rosenquist RW. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. J Pain Symptom Manage. 2003; 26:668–677.

163. Hall JE, Uhrich TD, Ebert T. Sedative, analgesic and cognitive effects of clonidine infusions in humans. British journal of anaesthesia. 2001; 86(1):5-11.

164. Denolle T, Sassano P, Allain H, Bentué-Ferrer D, Breton S, Cimarosti I, et al. Effects of nicardipine and clonidine on cognitive functions and electroencephalography in hypertensive patients. Fundamental & clinical pharmacology. 2002; 16(6):527-35.

165. Naloxone: Chemical Structure; https://pubchem.ncbi.nlm.nih.gov/compound/5284596#section=Formulations-Preparations
166. Naloxone: https://pubchem.ncbi.nlm.nih.gov/compound/5284596#section=Pharmacology-and-Biochemistry

167. Naloxone: https://www.medicines.org.uk/emc/medicine/4900

168. Wang Q, Zhou H, Gao H, Chen S-H, Chu C-H, Wilson B, et al. Naloxone inhibits immune cell function by suppressing superoxide production through a direct interaction with gp91 phox subunit of NADPH oxidase. Journal of neuroinflammation. 2012;9(1):32.

169. Zaki N, Osman A, Moustafa H, Saad A. Alterations of immune functions in heroin addicts. The Egyptian journal of immunology/Egyptian Association of Immunologists. 2005;13(1):153-71.

170. Naloxone: Toxicity; https://pubchem.ncbi.nlm.nih.gov/compound/5284596#section=Toxicity-Summary
171. Naloxone: http://www.everydayhealth.com/drugs/naloxone
172. Naloxone Hydrochloride: National Center for Biotechnology Information; 2017 [cited 2017 Jan. 02, 2017]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/5464092.

173. Aguado D, Abreu M, Benito J, Garcia-Fernandez J, de Segura IAG. Effects of naloxone on opioid-induced hyperalgesia and tolerance to remifentanil under sevoflurane anesthesia in rats. The Journal of the American Society of Anesthesiologists. 2013; 118(5):1160-9.

174. Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Arthritis Rheum. 2013; 65:529–538.

175. Abdolmohammadi S, Nekoui A, Blaise G. Comparison of retrolaminar paravertebral infiltration of a non-steroid mixture with conventional epidural steroid infiltration in patients suffering from chronic radicular Pain-a retrospective study. Journal of Cellular & Molecular Anesthesia. 2017 May 12;2(2):43-9.

176. Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain.The Journal of Pain. 2008; 9-12:1144-54.

177. Wolkowitz OM, Tinklenberg JR. Naloxone's effect on cognitive functioning in drug-free and diazepam-treated normal humans. Psychopharmacology. 1985; 85(2):221-3.

178. Shi-Lei S, Xiao-Hu X, Guang-Yu M. Effect of naloxone on cognitive function in vascular dementia in rats. Indian Journal of Medical Research. 2002; 115:265.