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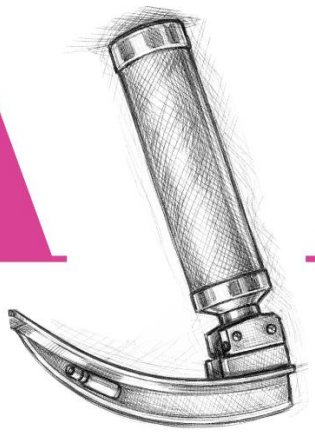

A Journal of
Anaesthesiology, Critical Care and Pain Medicine

Theme
Foundations First-Core Topics in Anaesthesiology, Critical care and pain Medicine

Editors
Dr.Jagadish Basumatary
Dr.Rupankar Nath

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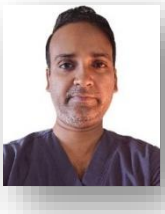

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Dr. Deepankar Sarma

MESSAGE FROM PRESIDENT ISA ASSAM

I am glad know that our E- Journal is going to be published under the able editorship of Dr. Jagadish Basumatary and Dr. Rupankar Nath. I request you all to participate in the journal actively and help us to grow and make our state branch more vibrant.

Thank you all once again!

Long Live ISA

Long live ISA Assam Chapter

Dr. Deepankar Sarma

President ISA Assam

Dr. Anil Koiry

MESSAGE FROM SECRETARY ISA ASSAM

Dear Esteemed members and Colleagues,

It is with immense pride and deep sense of accomplishment that I reach out to you today. On behalf of the Indian Society of Anaesthesiologists, Assam State Branch, I am thrilled to announce the official launch of the first ever edition of our E- journal.

As we transit further into the digital age the need for a dedicated platform to showcase the clinical excellence, research, and innovations emerging from our region is the need of the hour.

This E -Journal is not just a publication; it is a digital archive of our collective wisdom and a testament to the vibrant academic spirit of Anaesthesia community in Assam.

I look forward for original articles from leading practitioners and residents across the state, providing unique insights into challenging cases and innovative management techniques.

I am confident about the easy accessibility with a user-friendly designed format for easy reading on any device, ensuring our knowledge reaches every corner of the state and beyond.

This achievement would not have been possible without the visionary leadership of Dr Jagadish Basumatary and the meticulous efforts of Dr. Rupankar Nath and most importantly the contributors who shared their valuable work.

Let's use this platform to elevate the standards of our specialty and continue our journey of lifelong learning.

Thank you all once again.

Long Live ISA!

Dr Anil Koiry

Secretary ISA
Assam

PROF.(DR.) AJIT DEKA

GUEST EDITORIAL

It is heartening to witness the publication of the first issue of an e journal under the auspices of ISA, Assam. Anaesthesiology in Assam has travelled a long way from infancy since early seventies till today's fully matured position comprising significant numbers of young enthusiastic competent anaesthesiologists.

Over the past five decades, anesthesiology has undergone a paradigm shift, characterized by rapid advancements in pharmacology, monitoring technology, and neurophysiological understanding. Contemporary anaesthesiologists utilize a sophisticated array of safe agents and precise delivery systems, operating from workstations that rival the complexity of an aircraft cockpit. These technological and clinical strides have revolutionized the field, enabling the safe management of high-risk patients with severe comorbidities and facilitating intricate surgical interventions that were previously impossible.

Taking into account this excellent support system that we have today we should have no occurrence of major complications in the perioperative period. But unfortunately, even now we find reports of catastrophic incidents at regular intervals. Our obligatory responsibilities are to minimize complications to near zero level. One of the reasons of grave complications still occurring even in the best equipped hospitals may be due to

overdependence on machines. Of late many of the anaesthesiogists are losing clinical acumen because of total reliance on investigation reports and monitors. Clinical monitoring is often completely done away during peri-operative period. Due to this fact certain valuable pre warning signals are missed. This is even more vital during the pre anaesthetic phase.

Whatever great advancement we may have in the supporting armamentarium, we should never do away with clinical examination including history taking. A thorough pre-anaesthetic clinical evaluation is always a rightful due to our patients. This practice not only enhances patient's safety but also helps in creating a lasting rapport between the patient and the anaesthesiologist. It augments the confidence of the patients on the forthcoming event of anaesthesia and surgery.

We should always remember that in our specialty the man behind the machine is much more important than the machine. We should always remain alert in this regard otherwise in this age of Artificial Intelligence many of us may lose our jobs to machines in near future.

I wish all the best to our fraternity members to excel in their areas of work.

Thank you,

Long live ISA Assam!

Long live ISA National!

Prof (Dr) Ajit Deka
Former Professor & HOD,
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Past President, ISA Assam.

EDITORIAL

The Dawn of a New Era: The Inaugural Issue of the ISA Assam State Branch E- Journal

It is with immense pleasure and profound sense of accomplishment that we present the inaugural issue of the official e-journal of the ISA Assam State Branch. This launch marks a significant milestone, a culmination of vision, dedication, and tireless efforts of the executive committee and our editorial board. Our goal is to create a dynamic platform for dissemination of knowledge, research, and best practices in the field of anaesthesia, critical care, and pain medicine, tailored specifically to the unique challenges and advancements within our region and beyond.

Our Visions and Scopes

Anaesthesiology is a vibrant and ever evolving specialty, a cornerstone of healthcare that ensures patient safety and comfort across a spectrum of surgical and medical procedures. The scope of our practice is broad, encompassing not only the operation theatre but also intensive care units and chronic pain management clinics. The journal aims to cover all the areas offering a comprehensive resource for professionals in Assam and the wider medical community.

The journal is designed to be a forum for:

a) Original Research Articles
b) Review articles
c) Case Reports
d) Editorial and Commentaries

The Importance of Regional Platform:

Assam, with its unique geographical and demographic characteristics, faces specific healthcare challenges. A regional journal provides an essential platform for our members to publish what is locally relevant, ensuring that our collective experiences and findings contribute directly to improving local patient care and outcomes. It encourages academic writing and research among young anaesthesiogists who might otherwise find it challenging to publish in high-impact national or international journals. This e-journal will facilitate dissemination of information across the state and the nation.

A Call for Contribution

The success of this journal depends entirely on the active participation and contribution of our members. We encourage all our colleagues to share their works, insights and experiences. We are committed to fostering a culture of evidence - based practice and lifelong learning within ISA Assam State Branch.

Acknowledgements

We express our deepest gratitude to the executive committee of ISA Assam State Branch for their foresight and unwavering support in bringing this initiative to fruition. We also thank the authors whose contributions grace this inaugural issue and the reviewers who have ensured the quality of the content. We look forward to your support and active participation in making this e- journal a valuable source of knowledge in Anaesthesia, critical care and pain medicine.

Editors
Assam Journal of Anaesthesiology (AJA)
March 2026

REVIEW ARTICLE

MECHANISM OF UNCONSCIOUSNESS: WHAT WE KNOW FROM BASIC SCIENCE

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Abstract: *This review explores the mechanisms of unconsciousness from an anaesthesiology perspective, defining consciousness through clinical characteristics such as wakefulness and awareness. General anaesthesia induces a unique, reversible state distinct from natural sleep, where unresponsiveness does not necessarily equate to unconsciousness. This review article examines the Neural Correlates of Consciousness (NCC) and neurophysiological mechanisms, detailing how anaesthetics disrupt information integration across cortical and subcortical networks. Furthermore, it discusses neurochemical mechanisms, specifically the modulation of neurotransmitters like GABA and NMDA, and ion channels, which underpin the loss of consciousness.*

Keywords: *General Anaesthesia, Unconsciousness, Neural Correlates of Consciousness (NCC), Neurotransmitters, GABA Receptors, Cortical Connectivity, Neurophysiology.*

In this review, constrained by the permitted word limit, I will try to explore the essence of consciousness, defining a few of its characteristics, and then seek to understand unconsciousness from an anaesthesiology viewpoint followed by a brief examination of the mechanisms underlying its different attributes.

I. Consciousness and its perspective from Anaesthesiology

The exploration of consciousness spans multiple disciplines, including clinical medicine, philosophy, physics, psychology, neurobiology, mathematics, and computer science. These diverse engagements have advanced various viewpoints, complicating efforts to integrate and compare insights. Thus, there are various definitions of `consciousness` and a central challenge is the absence of a consistent definition.[1] Within my judgment capabilities, perhaps the perspective that consciousness is “the ability to maintain an alert state, attention, and awareness of self and environment” embodies most of the contributes from the perspective of medical science. [2]

The philosophical perspective distinguishes two aspects of consciousness. The phenomenal consciousness is the subjective "what it feels like" aspect, and access consciousness, the cognitive availability for reasoning and behaviour. [3]

From the perspective of a clinician, consciousness can be examined through its primary clinical characteristics—wakefulness, awareness, and responsiveness. [3] It is the practical framework that is used by us anaesthesiologists. Wakefulness, or the level of arousal, is the capacity to open one's eyes, either spontaneously or in response to a stimulus. [3] Awareness is divided into two aspects: internal awareness, which includes mental activities such as inner speech and mind wandering, and external awareness, which involves consciously perceiving the environment through sensory channels. These facets shape our overall conscious experience, balancing internal thoughts with external stimuli. [3] Conscious behaviour depends on sufficient arousal (i.e., being awake) and awareness of content (i.e., sensory, cognitive, and emotional experiences). [4] Global Neuronal Workspace Theory (GNWT), Higher-Order Theories (HOT), Integrated Information Theory (IIT), Recurrent Processing Theory (RPT), and Predictive Processing (PP) are prominent theories that seek to explain the nature of consciousness in the realms of neuroscience. [5] Discussions on consciousness, sleep, and anaesthesia are frequently complicated by a multitude of confusing, often tautological, and partially overlapping terms, such as “consciousness,” “awareness,” “responsiveness,” “wakefulness,” “arousal,” “hypnosis,” “sleep,” and “sedation” etc. [6] As a clinical correlate

of consciousness, awareness is frequently assessed in clinical anaesthesiology practice. [6] From a clinical standpoint consciousness is often divided into two components: arousal (wakefulness) and awareness (of self and environment). [7] In this context, "awareness" refers to both consciousness and the clear recall of events during surgery. [7]

II. Unconsciousness and its perspective from Anaesthesiology

Similar to consciousness, unconsciousness has been approached from various perspectives depending on the scientific field, each emphasizing different aspects such as neural mechanisms, clinical assessment, or cognitive processes. Unconsciousness is a pillar of anaesthesia. [4] General anaesthesia is a medically induced, reversible state characterized by unconsciousness, memory loss, pain relief, and muscle relaxation, while maintaining stable autonomic, cardiovascular, respiratory, and thermoregulatory functions. [8] The reversible nature of general anaesthesia induced unconsciousness distinguishes it as a unique state.

In the context of anaesthesiology, unconsciousness induced by general anaesthesia is not a singular state but encompasses distinct states that vary based on the presence or absence of subjective experience, environmental perception, and responsiveness. [3, 6] Unconsciousness in anaesthesia may manifest as complete unconsciousness (no subjective experience), disconnected consciousness (dream-like states without environmental perception), or connected consciousness (episodic awareness of self and environment). [3, 6] Connected consciousness may not be associated with its explicit recall. [3] Unresponsiveness is frequently equated with unconsciousness but unresponsiveness does not equate to unconsciousness. [6] Patients may be unresponsive due to muscle relaxants (e.g., succinylcholine) or subcortical suppression but still experience connected or disconnected consciousness. [6]

III. Mechanisms of unconsciousness during anaesthesia

The notion that consciousness arises from brain activity places neural correlates of consciousness (NCC) at the forefront of understanding the

mechanisms of both consciousness and unconsciousness. [3] NCC refers to a minimal set of neuronal mechanisms sufficient for any phenomenological aspect of consciousness to emerge. [3] Neurotransmitter systems play a critical role in modulating the brain's functional mechanisms that underpin conscious experience. [3] It is not surprising that distinct NCC and neurotransmitter systems are implicated in various attributes across the spectrum of anaesthesia-induced unconsciousness.

Thus, the mechanisms underlying unconsciousness during anaesthesia are primarily explained through neurophysiological and neurochemical frameworks. The mechanisms of general anaesthesia have been studied using various animal models and cell lines. [9] Studies using in vitro sensitivity, in vivo sensitivity, direct binding (via photolabeling and structural studies), and in vivo regulation (genomic/proteomic techniques) have been used to elucidate the mechanism of action of these agents at molecular, cellular, and neuronal network levels. [9]

III.a Neurophysiological mechanisms

The neural correlates of anaesthesia have been studied using EEG, fMRI, and PET. [3,8] Cutting-edge neuroscience techniques, such as optogenetics, chemogenetics, and targeted genetic methods, have advanced understanding of these circuits.[9] General anaesthetics induce unconsciousness by acting on multiple neural circuits in both cortical subcortical brain regions. Studies reveal that anaesthesia alters brain communication, particularly in the prefrontal, parietal, and posterior regions to modulate consciousness states. [3] General anaesthetic agents generate agent-specific, unique and dose-dependent EEG, fMRI, and PET patterns. [3, 10, 11] Thus some anaesthetics tap into sleep-related neural pathways to cause unconsciousness. [3, 10, 11] Additionally, anaesthetics suppress wakefulness by directly inhibiting cortical neurons and subcortical arousal-promoting neurons. [3, 10, 11] Propofol alters cortical activity, particularly in the default mode network and frontoparietal networks, which are associated with self-awareness and attention. [12] Subcortical regions, including the brainstem, hypothalamus, and basal forebrain, play a role in regulating arousal and are targeted by anaesthetics. [13] Anaesthetics suppress subcortical arousal systems, contributing to the loss of

consciousness by reducing cortical activation. [13] Brown et al.` s review is an excellent source for those interested in neural corelates of general anaesthesia agents and the molecular pathway involved. [13] Apart from the dispersion of specific NCC, anaesthetics disrupt the brain's ability to integrate information across distributed networks, a process thought to be essential for consciousness. [3, 8, 14] General anaesthetics fragment neural networks, reducing the brain's capacity for integrated information processing. [3, 8, 14] This is reflected in decreased measures of brain complexity, such as entropy, reduce neural complexity and connectivity in large-scale brain networks correlated with unconsciousness. This loss of information integration sets it apart from natural sleep. [8, 14]There is evidence both supporting and challenging the theories of neural correlates (GNWT, IIT and RPT) of consciousness and anaesthesia. [3] Mashour and Hudetz propose that general anaesthetics modulate consciousness through two distinct mechanisms: bottom-up pathways, which suppress subcortical arousal systems and reduce the level of consciousness, and top-down mechanisms, which disrupt cortical connectivity and degrade the content of consciousness. [15] Different anaesthetics affect these dimensions to varying degrees. [15]

III.b Neurochemical mechanisms-

Brain cells communicate through a diverse array of chemical neurotransmitters, which are released into the synapse in response to electrical signals within the neural circuits. Neurotransmitters are broadly categorized as excitatory (glutamate and acetylcholine) or inhibitory [γ-aminobutyric acid (GABA) and glycine]. [16, 17] Excitatory neurotransmitters promote depolarization of the postsynaptic membrane, while inhibitory neurotransmitters suppress it. These neurotransmitters interact with ion channel receptors, regulating ion flow and, consequently, cellular electrical activity. Different types of receptors are associated with different aspects of reduced consciousness such as sedation, amnesia, nociception etc. [7, 16, 17]

The GABA type A ($GABA_A$) receptor is a primary target for many general anaesthetics, particularly inhalational agents (e.g., isoflurane, sevoflurane) and intravenous agents (e.g., propofol, etomidate). [16, 17] These drugs enhance GABA mediated inhibitory neurotransmission by binding to specific

sites on the $GABA_A$ receptor, increasing chloride ion conductance and hyperpolarizing neurons. This results in reduced neuronal excitability, contributing to sedation and unconsciousness. Propofol bind to a site in the transmembrane domain of the $GABA_A$ receptor, allosterically enhancing GABA binding affinity or prolonging channel open time. [16] Several anaesthetics have been found to decrease the desensitization of $GABA_A$ receptors. [16] At higher concentrations, they can directly activate the receptors even in the absence of GABA. [16] N-methyl-D-aspartate (NMDA) receptors, which mediate excitatory neurotransmission, are inhibited by certain anaesthetics, notably ketamine and nitrous oxide. By blocking glutamate binding or channel activity, these agents reduce excitatory signalling, contributing to dissociative anaesthesia and analgesia. [16, 17] Two-pore domain potassium (K2P) channels, such as TREK-1 and TASK-3, are activated by volatile anaesthetics, leading to neuronal hyperpolarization. This enhances potassium efflux, stabilizing the resting membrane potential and reducing excitability. [16,17] General anaesthetics also interact with additional ion channels and receptors, including glycine receptors, voltage-gated sodium channels, and HCN (hyperpolarization-activated cyclic nucleotide-gated) channels. [16,17] These interactions contribute to the multifaceted effects of anaesthetics, such as muscle relaxation and amnesia.

Conclusion

There is substantial evidence that general anaesthesia comprises multiple distinct pharmacological effects, likely involving different neural circuits and acting through separate molecular targets. Recent advances have elucidated anaesthetic binding sites at atomic resolution. [9] However, challenges remain, including understanding the synergy between multiple targets, the differential effects of anaesthetics across brain regions and different aspects of unconsciousness. It is worth noting that emergence from anaesthesia involves distinct arousal pathways (e.g., cholinergic, dopaminergic, histaminergic, and orexinergic), with evidence suggesting that activating these pathways (e.g., via nicotine or dopamine stimulation) can hasten recovery. [18] Despite their widespread use, the precise neural correlates and molecular mechanisms underlying their effects remain

incompletely understood. Understanding the detailed mechanism of action will hopefully provide strategies to separate desirable effects (e.g., amnesia) from adverse outcomes (e.g., postoperative delirium). Understanding anaesthetic mechanisms could advance broader neuroscience questions, such as the nature of consciousness and memory formation.

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REVIEW ARTICLE

ADVANCES IN NEUROMUSCULAR BLOCKING AGENTS AND REVERSAL AGENTS

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Abstract: *Neuromuscular blocking agents (NMBA) are the integral part of modern anaesthesia. It is used in both operation theatre and intensive care units, facilitating tracheal intubation, optimizing surgical conditions and aiding mechanical ventilation. The advent of newer generation NMBAs including Rocuronium, emerging ultra-short acting Gantacurium and CW002 promise rapid onset with spontaneous recovery and minimal cardiovascular effects. Novel reversal drugs like Calabadion and cysteine – based compounds are under development which aims for broader and faster antagonism of neuromuscular block. The advancement in these drugs would represent more safer, predictable perioperative neuromuscular management.*

Keywords: Neuromuscular blocking agents, Reversal agents, Gantacurium, CW002

Recent advancements in anaesthesia gives us knowledge about neuromuscular blocking agents (NMBAs), which cause muscle relaxation in addition to traditional narcosis and analgesia. This article highlights the indications, mechanism of action, administration methods, adverse effects, contraindications, monitoring, and toxicity of NMBAs, equipping healthcare professionals with the knowledge necessary for optimizing treatment through anaesthesia and other therapeutic

combinations. A clear understanding of NMBAs facilitates precise dosage adjustments and minimizes potential adverse reactions, contributing to safer, more effective patient care.

HISTORY

Harold Griffith and Enid Johnson published their famous paper on the use of curare in general anaesthesia. They administered curare to a young patient undergoing an appendectomy at the Homeopathic Hospital in Montreal.[1] This is considered the first major step towards using NMBA for muscle relaxation during anesthesia. The introduction of curare allowed adequate muscle relaxation at a lighter depth of general anaesthesia, yet well tolerated. Several new compounds were developed and used in clinical practice till date to maintain neuromuscular blockade.

FDA-APPROVED INDICATIONS

Indications for NMBA administration include [2]:

- Endotracheal intubation
- Therapeutic hypothermia after cardiac arrest
- Acute respiratory distress syndrome
- Elevated intraabdominal pressure
- Elevated intracranial pressure
- Status asthmaticus
- Prevention of patient-ventilator asynchrony in patients on mechanical ventilation
- Muscular relaxation for a surgical procedure
- Adjunct therapy for patients undergoing electroconvulsive therapy

MECHANISM OF ACTION

NMBAs act at the neuromuscular junction (NMJ), which consists of 3 parts [2]:

- Presynaptic nerve terminal
- Synaptic cleft
- Postsynaptic nicotinic receptors

Neuromuscular blocking agents (NMBA) are the compounds that act on acetylcholine receptors (Ach R) present at the neuromuscular junction to produce skeletal muscle paralysis without any effects on cardiac and smooth muscle. At the NMJ, motor neuron activity triggers the release of acetylcholine (ACh), which binds nicotinic acetylcholine receptors (nAChRs) densely expressed in the "motor endplate" area of muscle fibers. The nAChRs, pentameric ligand-gated ion channels, open to allow Na+ influx and depolarization when two ACh molecules are bound, thereby initiating muscle action potentials. Rapid breakdown of ACh by acetylcholinesterase ensures brief and controlled contraction. This molecular choreography underlies the clinical power and risk of neuromuscular blocking agents (NMBAs) and the critical importance of controlled blockade and reliable reversal.

Depolarizing Neuromuscular Blocking Agents: -

Depolarizing NMBAs (e.g., succinylcholine) act on receptors at the motor endplate of the neuromuscular junction (NMJ), causing depolarization of the membrane inducing a refractory period. These drugs have an onset of action of 1 minute and a duration of 6 minutes and are rapidly metabolized by plasma butyrylcholinesterase.[3] The continued disruption of ACh-mediated effects causes muscular fasciculation and twitching. Succinylcholine, or suxamethonium, is the only depolarizing NMBA used clinically.

Nondepolarizing Neuromuscular Blocking Agents: -

Nondepolarizing NMDAs prevent acetylcholine from binding to the motor plate at the NMJ by competing for the ACh binding site on the α subunit of nicotinic receptors. As the concentration of non-depolarizing NMBAs at the junction increases relative to ACh, a neuromuscular blockade becomes established.[4]

Ideal NMBAs should have properties like: rapid onset, provide adequate relaxation, predictable duration of action, minimal side effects and easily reversible.[5]

Classification and Pharmacology of Neuromuscular Blockers

Structural and Functional Classes

NMBAs are classified as:

Depolarizing: Succinylcholine, which mimics ACh, causes persistent depolarization, and is rapidly hydrolyzed by plasma cholinesterase for a brief, intense block.

Nondepolarizing: Subdivided into aminosteroidal (rocuronium, vecuronium, pancuronium) and benzylisoquinolinium (atracurium, cisatracurium, mivacurium) agents.

Pharmacokinetics/Dynamics and Clinical Profiles

- Aminosteroidal agents (rocuronium, vecuronium):
    - Metabolized renally/hepatically.
    - Rapid to intermediate onset, with duration adjustable by dose.
    - Minimal histamine release and cardiovascular effects but can accumulate in renal or hepatic failure.

- Benzylisoquinolinium agents (atracurium, cisatracurium):
    - Undergo Hofmann elimination or ester hydrolysis, independent of organ function.
    - Lower risk of accumulation in critical illness or organ dysfunction.
    - Atracurium can cause histamine release; cisatracurium is much less likely to do so.

But search for the ideal NMBA is still on as use of Succinylcholine, though met most of the criteria, is not without side effects that can be ignored. One important area of research is the development of a short-acting non-depolarizing neuromuscular blocking agent with a fast onset & short duration of action, not dependent of end-organ metabolism and rapid & complete reversal.

Recent drug development led to a new series of neuromuscular compounds, called the chlorofumarates such as Gantacurium, CW002, and CW011.[6]

GANTACURIUM

Gantacurium is an asymmetric enantiomeric isoquinolinium diester of chlorofumaric acid. It is available as a lyophylized powder as it is unstable in aqueous solution and reconstitution is required before administration. In amorphous state it is stable for up to 4 weeks at 25-40° C. [7] Gantacurium is an ultra-short acting non-depolarizing NMBA with a rapid onset and a wide safety margin. In human volunteers, the calculated ED_{95} of Gantacurium is 0.19 mg/kg [8] with onset of action less than 3 min and shortened to approximately 1.5 min by increasing the dose to 4× ED_{95}. At these doses, the duration of action of Gantacurium (recovery to train-of-four of ≥ 0.90) approximately 15 min.

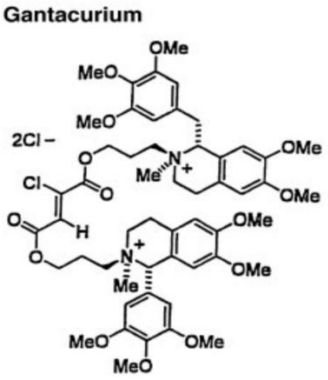

FIG 1: Chemical structure of Gantacurium

Transient(<5min) cardiovascular side effects (Hypotension, Tachycardia) were observed at doses of 3×ED_{95} or higher. Furthermore, humans showed significant histamine release when Gantacurium was administered in doses of 4× ED_{95}. [8] However, at lower doses (2.5× ED_{95}), there was no evidence of histamine release. In animals, no changes in peak inspiratory pressure were observed signifying no muscarinic receptors mediated smooth muscle constriction.

Metabolism of Gantacurium is by chemical degradation through cysteine adduction (fast process) and pH-sensitive hydrolysis (slow process). Cysteine adduction results in replacement of chlorine by cysteine forming a heterocyclic ring which lacks neuromuscular blocking property, can no longer interact with the postjunctional acetylcholine receptor. The elimination of Gantacurium is not renal and hepatic dependent.

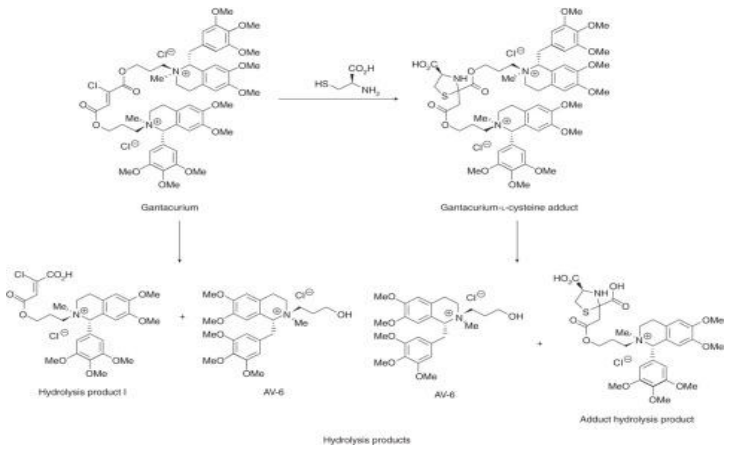

FIG 2: Metabolism of Gantacurium

As Gantacurium is a non-depolarizing NMBA so it can be reversed with cholinesterase inhibitors. Spontaneous recovery time is around 5.7 min without any reversal agent, so the most suitable drug for reversal is Edrophonium(0.5mg/kg), whose peak effect is in less than 2 min. In humans, edrophonium was able to decrease the reversal time of a Gantacurium-induced neuromuscular block at 10% recovery of T1 to a train-of-four ratio ≥ 0.90 to 3.8 min.

Gantacurium is, due to its unique metabolism, rapidly inactivated by cysteine adduction and alkaline hydrolysis. Therefore, Gantacurium can also be reversed by administration of L-Cysteine, commonly administered in humans as an essential component of parenteral nutrition. In animal study L-Cysteine given as a bolus dose of 10–50 mg/kg to reverse neuromuscular

block didn't cause any toxicity, yet clinical studies are still needed for further investigations.

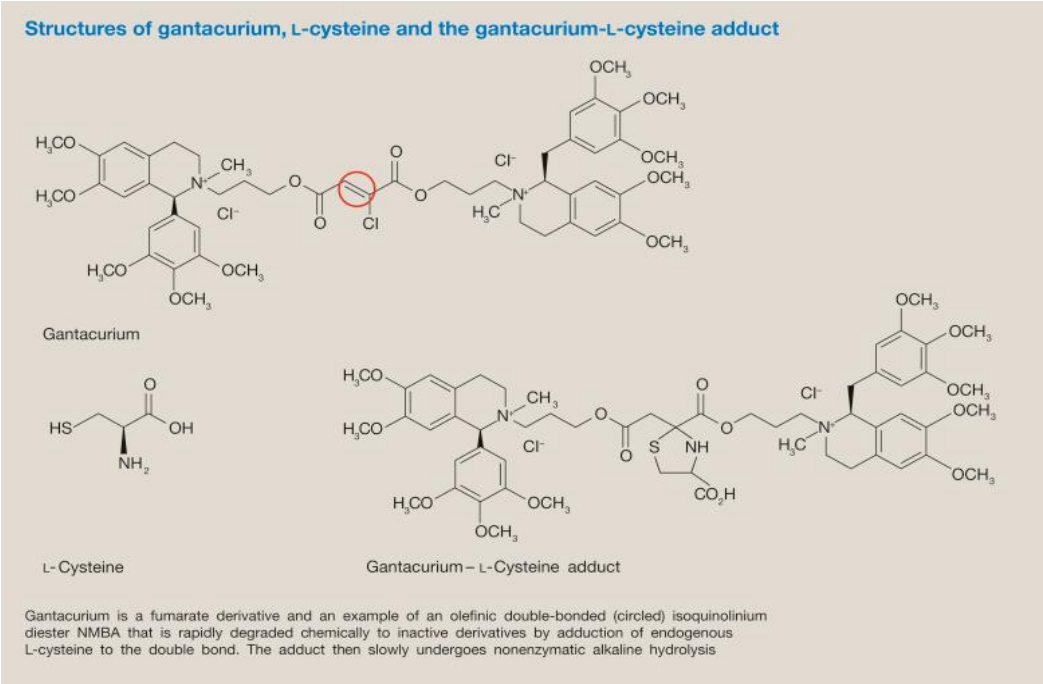

FIG 3: Structure of Gantacurium, L-Cysteine

CW002

CW002 is a new benzoquinolinium fumarate diester non-depolarizing NMBA, which belongs to the family of tetrahydroisoquinolinium compound. The molecular structure of CW002 has similarity with Gantacurium; the difference is that CW002 lacks a chlorine at the fumarate double bond and it is symmetrical unlike Gantacurium.

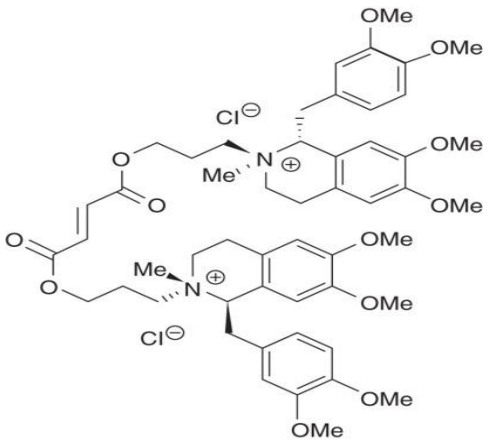

FIG: 4: The chemical structure of CW002

CW002 is also metabolised by endogenous L-Cysteine adduction and alkaline hydrolysis but unlike Gantacurium, cysteine adduction process is relatively slower in case of CW002, making it an intermediate-acting NMBA. The metabolites of CW002 have no clinically significant neuromuscular blocking property (0.01-0.001 times of CW002).

Human study with CW002 revealed its less potency in human than animals. The ED_{95} of CW002 in humans is 0.077 mg/kg. [9]

With a dose of 1.8× ED_{95} (0.14 mg/kg), the block onset time is approximately 90 seconds and the clinical duration is almost 33.8 min (range 28.8–36.1 min). Time from 25 to 75% recovery of T1 is 14 min whereas the spontaneous recovery to a train-of-four (TOF) ≥ 0.90 was 73 min.

CW002 with doses up to 0.14 mg/kg (1.8×ED_{95}) did not result in significant cardiopulmonary side effects or any signs of histamine release so far in limited human study. [9]

As CW002 is a nondepolarizing NMBA, so blockade can be reversed with cholinesterase inhibitors (Neostigmine at a dose of 50mcg/kg, is most suitable), but it only shortened the recovery time minimally. Whereas cysteine adduction to reverse the block in animals showed promising result, human study is yet to be done.

CW011

CW011 is a new asymmetrical benzoquinolinium maleate diester, like CW002 (a symmetrical fumarate), a non-halogenated olefinic diester analogue of Gantacurium.

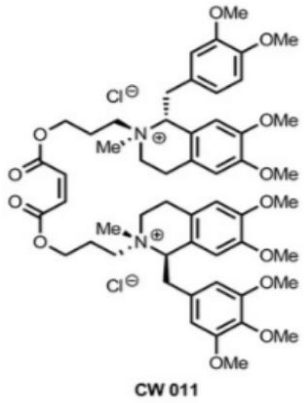

FIG 5: Chemical structure of CW 011 [10]

Animal study showed that CW011 has predictable slower L-Cysteine adduction, making its duration of action longer than that of Gantacurium.[10]

In animals calculated ED_{95} is 0.025 mg/kg (Potency is higher than Gantacurium) and duration of block at 4–5× ED_{95} is approximately 20.8 min (three times longer than that of Gantacurium).

Reversal of neuromuscular block can be achieved by both Cholinesterase inhibitors (Neostigmine) as well as exogenously administered L-Cysteine. L-Cysteine reversal showed full reversal from a neuromuscular block induced by CW011 5× ED_{95} within 2–3 min, proving its superiority over cholinesterase inhibitors in terms of speed and effectiveness of reversal.[10] Human studies are required to investigate and confirm the above-mentioned results in animals.

Reversal of Neuromuscular Block: Mechanisms and Modalities

Ideal characteristics of a reversal agent to antagonise neuromuscular block.[11]

- Can be used to reverse any neuromuscular blocking drug.
- Can be used to reverse any depth of neuromuscular block.
- A rapid onset of maximal effect (within a few minutes).
- No adverse cardiovascular effects.

- No adverse muscarinic effects (e.g. bradycardia, bronchospasm, abdominal pain, nausea and vomiting).
- No histamine release or risk of anaphylaxis.
- Not dependent on organ elimination.
- No ceiling effect.
- Does not produce depolarising block if given in excess.
- Low cost.

Conventional Reversal: Anticholinesterases

Neostigmine inhibits acetylcholinesterase, extending ACh half-life, and enabling competition with nondepolarizing agents. Yet, it has a "ceiling effect"—cannot reverse deep blockade (TOF count <2), and is associated with cholinergic side effects (bradycardia, bronchorrhea), requiring co-administration of antimuscarinics. Meta-analyses show unreliable reversal with neostigmine in deep blockades and high residual paralysis rates (up to 32% after moderate block, >95% after deep block within 60 min).

Sugammadex: **A Selective Relaxant Binding Agent**

Mechanism: Sugammadex, a modified γ-cyclodextrin, encapsulates aminosteroidal NMBAs in a 1:1 host-guest complex, rapidly reducing unbound drug concentration and driving gradient-mediated removal from the NMJ. [11]

Recovery to TOFR >0.9 occurs within 1–3 min even after deep block, without muscarinic side effects. Sugammadex does not require coadministration of an antimuscarinic agent. Sugammadex has a lipophilic core and eight outer tails with a negative charge at their tips (FIG 6). These negative charges attract the positively charged quaternary ammonium group on the aminosteroid molecule, drawing the neuromuscular blocking drug into the more lipophilic core of the toroid and holding it there irreversibly. The attraction of sugammadex for rocuronium is as strong as the attraction of acetylcholine to the postsynaptic nicotinic receptor.

The rocuronium–sugammadex complex is excreted in the urine with a plasma clearance similar to the glomerular filtration rate.

Comparative Clinical Data:

Multiple systematic reviews and meta-analyses found that Sugammadex produces more reliable, faster, and complete recovery than neostigmine, with a significant reduction in residual blockade and airway complications. rNMB incidence post-sugammadex: 2.8% at 6 min, <1% by 15 min. For neostigmine: 82% at 6 min, 14–32% at 10–60 min.

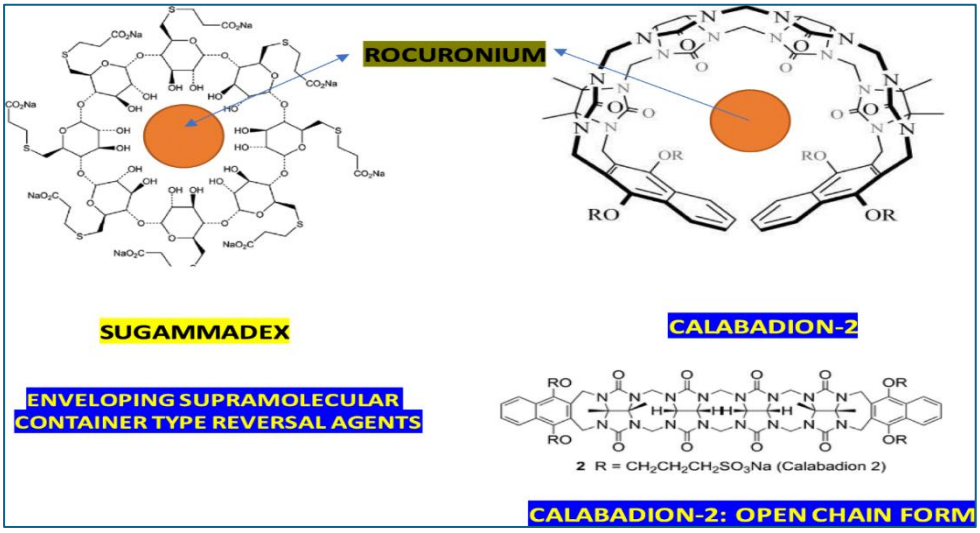

Fig 6: Structures of neuromuscular reversal agents

Agent	Reversal Time (TOFR ≥0.9)	Reversible NMBAs	Safety Profile	Special Notes
Sugammadex	1–3 minutes	Rocuronium, Vecuronium	Rare anaphylaxis	Not for benzylisoquinoliniums
Calabadion-2	<1 minute (preclinical)	Steroidal + benzylisoquinoliniums	High biocompatibility	Not yet available clinically
Adamgammadex	2.9–3 minutes	Rocuronium	Good tolerance	Comparable or superior to sugammadex
Neostigmine	7–10 minutes	Most non-depolarizing agents	Muscarinic side effects	Requires T2 return; antimuscarinic needed

Table 1: Comparative list of neuromuscular agent reversals.

Macrocyclic and Supramolecular Advances

Calabadion

Calabadion-1: Acyclic cucurbituril analog with fast reversal of both steroidal and benzylisoquinolinium NMBAs in rats. Time to TOFR >0.9: 84s for rocuronium, much shorter than neostigmine (4.6 min) and placebo (16.2 min). Binding constants similar to sugammadex for rocuronium; weaker for Cisatracurium.[12]

Calabadion-2: Second-generation with “naphthalene walls” and 89-fold increased affinity for rocuronium (Ka 3.4 × 10^9 M^-1), dose-dependent and faster reversal of all major nondepolarizing agents in animal studies. 49–62% renal excretion within one hour and high selectivity (18,900 times preference for rocuronium over Ach). Demonstrated to reverse deep blocks with “broad spectrum” efficacy in preclinical models, outperforming sugammadex in affinity and recovery times.[12]

Pillararenes

Sulfonated Pillararene (SPA): Experimental studies showed rapid in vivo reversal of succinylcholine-induced block with strong host–guest interactions and mitigation of hyperkalemia, arrhythmias, and rhabdomyolysis. High binding affinity (10^5 M^-1) and clinical promise for depolarizing block reversal, a unique advance not achieved with cyclodextrins or calabadion.[13]

Mechanism of reversal

Pillararenes, particularly those with sulfated modifications like Pillar MaxQ (P6AS), demonstrate high binding affinities for specific NMBAs, especially those with quaternary ammonium groups, such as rocuronium and vecuronium. [14]

By encapsulating these NMBAs within their cavity, pillararenes effectively sequester them, reducing their concentration at the neuromuscular junction and allowing acetylcholine (ACh) to bind to its receptors, thereby reversing the blockade and facilitating the return of muscle function.

Studies have shown that P6AS binds to rocuronium and vecuronium with affinities significantly higher than that of sugammadex, a clinically used NMBA reversal agents. [15]

Advantages over existing reversal agents

- Higher Potency yet Reduced Side Effects
- Potential for Broader Spectrum: Pillararenes may hold potential for reversing the effects of a wider range of NMBAs, and could offer an alternative for patients who may not tolerate existing reversal agents.
- Decrease in postoperative pulmonary complications (hypoxemia, atelectasis, pneumonia)
- Lower rates of airway obstruction and reintubation
- Reduced PACU and hospital stay and Increased patient satisfaction.

Conclusion: A New Era of Individualized Neuromuscular Blockade

The advent of designer reversal agents (sugammadex, calabadion, pillararenes), coupled with quantitative monitoring, offers near-total precision in the induction and termination of neuromuscular blockade. While challenges remain—especially validation beyond animal models and translation to special populations—the broad-spectrum reversal, speed, safety, and selectivity of these agents herald a transformation in perioperative care. Continued research, adherence to international guidelines, and investment in robust monitoring will be critical for this new paradigm to realize its full patient safety potential.

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REVIEW ARTICLE

PHYSICS OF ANAESTHESIA CIRCUITS AND THEIR PRACTICAL APPLICATIONS

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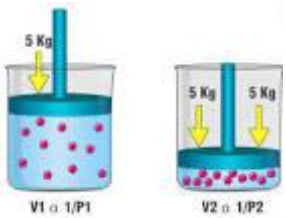
Abstract: *This overview elucidates the physical principles essential to anaesthesia breathing systems, connecting theory to clinical safety. It explores fundamental gas laws, including Boyle's, Dalton's, and Henry's, explaining their role in gas uptake and delivery. The text analyzes flow dynamics, resistance, and compliance, illustrating their impact on the work of breathing. Furthermore, it details the classification and mechanics of Mapleson circuits (A–F) and circle systems, addressing rebreathing, dead space, and fresh gas flow requirements. Finally, practical applications like the Venturi effect and CO2 absorption are discussed to optimize patient ventilation strategies.*

Keywords: *Anaesthesia breathing systems, Gas laws, Mapleson circuits, Flow dynamics, Compliance, Work of breathing, Circle system*.

Physics is deeply woven into Anesthesia—understanding it helps explain how gases move, how machines deliver anesthetics, and how the patient's lungs interact with circuits. Following is a structured overview of the physics in anesthesia.

Gas Laws and Anesthetic Gases: -

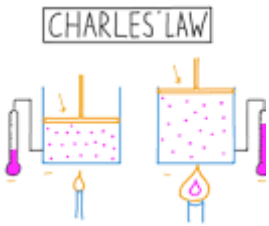
Boyle's Law ($P \times V$ = constant): Boyle's Law states that the pressure of a gas is inversely proportional to its volume when temperature and the amount of gas are kept constant. This means that if you increase the pressure on a gas, its volume will decrease, and vice versa, as long as the temperature and amount of gas remain unchanged. Mathematically, this relationship is expressed as $P_1V_1 = P_2V_2$, where P_1 and V_1 are the initial pressure and volume, and P_2 and V_2 are the final pressure and volume.



Here's a more detailed explanation:

Used in breathing circuits and mechanical ventilation—when pressure increases, volume decreases. For example, squeezing the reservoir bag delivers gas into the lungs.

Charles' Law ($V \propto T$): Charles's Law, also known as the Law of Volumes, it states that the volume of a gas is directly proportional to its absolute temperature (measured in Kelvin). This means that as the temperature of a gas increases, its volume also increases proportionally, and vice versa, provided the pressure remains constant.

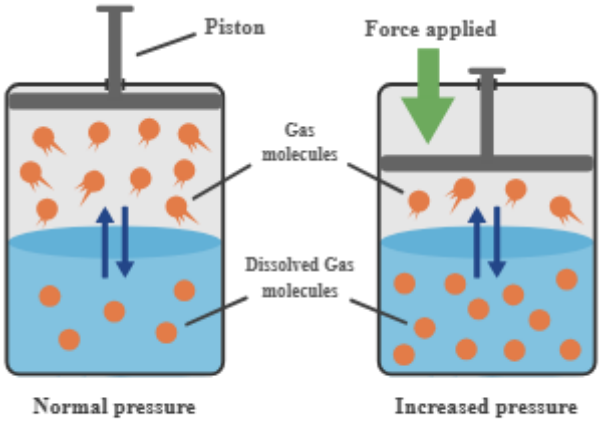


Gas volume changes with temperature; important in vaporizers.

Dalton's Law of Partial Pressures: Dalton's Law of Partial Pressures, also known as Dalton's Law, states that the total pressure exerted by a mixture of non-reacting gases is equal to the sum of the partial pressures of the individual gases in the mixture.

Total gas pressure = sum of individual gas pressures. Explains how oxygen, nitrous oxide, and anesthetic vapors mix.

Henry's Law: Henry's law describes the solubility of gases in liquids. It states that the amount of gas dissolved in a liquid is directly proportional to the partial pressure of that gas above the liquid, at a constant temperature. This means that if you increase the pressure of a gas above a liquid, more of that gas will dissolve in the liquid.



Henry's Law

Gas solubility in blood is proportional to its partial pressure—basis for uptake of volatile anesthetics.

Fick's Law of Diffusion: Fick's law of diffusion describes how substances move from areas of high concentration to areas of low concentration. It is expressed as $J = -D(dC/dx)$, where J is the diffusion flux, D is the diffusion coefficient, and dC/dx is the concentration gradient.

Elaboration:

Core Idea:
Substances diffuse from regions where they are more concentrated to regions where they are less concentrated, until the concentration evens out.

Flux:
The rate of this movement is called the diffusion flux (J), which is the amount of substance moving through a unit area per unit time.

Concentration Gradient:
The driving force for diffusion is the concentration gradient ($d\phi/dx$), which is the change in concentration (ϕ) over distance (x).

Mathematical Expression:
Fick's first law is often written as $J = -D(d\phi/dx)$, where D is the diffusion coefficient, a measure of how easily a substance diffuses. The negative sign indicates that diffusion occurs down the concentration gradient (from high to low).

Diffusion depends on surface area, thickness, and gradient—important in gas exchange in alveoli and across membranes (e.g., N_2O diffusion into air-filled cavities).

Flow Dynamics

Laminar vs. Turbulent Flow:

- Laminar flow: smooth, depends on viscosity (Poiseuille's law).
- Turbulent flow: chaotic, depends on gas density.

  Clinical: Heliox (helium + oxygen) reduces resistance in airway obstruction by lowering gas density.

Resistance in Airways/Circuits (Poiseuille's Law): Resistance $\propto 1/(\text{radius}^4)$.

Small decreases in tube radius (edema, kinked ETT) massively increase resistance.

Pressure & Ventilation

Compliance ($\Delta V/\Delta P$): In physics, compliance refers to a material's or structure's ability to deform or change shape in response to an applied force or pressure. It's essentially the inverse of stiffness, meaning that a compliant object deforms easily, while a stiff object resists deformation. Specifically, compliance is often defined as the change in volume per unit change in pressure.
Stiff lungs (ARDS) = low compliance; floppy lungs = high compliance.

Work of Breathing: Determined by compliance + resistance. Mechanical ventilation reduces patient effort.

Positive Pressure Ventilation: Opposite to normal breathing (negative pressure); has hemodynamic consequences.

In practice:

- Choosing tube sizes (Poiseuille's law).
- Adjusting ventilator settings (compliance, resistance).
- Preventing hypoxia (Dalton's law).
- Avoiding complications like N_2O expansion (Fick's law, diffusion).

Physics of Anesthesia Circuits and Their Practical Applications

The anesthesia breathing circuit is an essential component of modern anesthetic practice. It serves to deliver oxygen and anesthetic gases, remove carbon dioxide, and permit controlled or spontaneous ventilation while minimizing work of breathing. A clear understanding of the physics governing anesthesia circuits is necessary for safe and effective patient management.

Principles of Gas Flow

Gas flow within circuits may be **laminar** or **turbulent.**

- **Laminar flow** follows Poiseuille's Law:Flow is proportional to the fourth power of the radius and inversely proportional to viscosity and length.
- **Turbulent flow** occurs at high flow rates, sharp bends, or narrow connectors, and is governed by gas density rather than viscosity.

Application: In pediatric circuits, wide and short tubes minimize resistance. In conditions of airway obstruction, heliox (a low-density gas mixture) reduces turbulent resistance.

Resistance in Circuits

Resistance is defined as the pressure difference required to generate a given flow. It increases with smaller radius, greater length, moisture, and additional connectors.

Application: Narrow endotracheal tubes increase resistance, especially in children. Filters and heat-moisture exchangers add resistance and may cause CO_2 retention in neonates. Thus, circuit design must prioritize smooth walls and low resistance.

Compliance of Circuit Tubing

Compliance is the volume change per unit pressure. Highly compliant tubing can lead to volume loss before gas reaches the patient.

Application: In adult patients, compliance losses are negligible relative to tidal volume. However, in neonates with small tidal volumes, even minimal compliance can cause significant hypoventilation. Modern circuits use low-compliance tubing to prevent this problem.

Dead Space

Dead space is the portion of ventilation that does not participate in gas exchange. It can be anatomical (airway structures) or apparatus-related (circuit components).

Application: Additional connectors, long tubes, or bulky masks increase apparatus dead space, which is especially hazardous in neonates and infants. Circle systems limit dead space to the segment between the Y-piece and the patient.

Rebreathing and Fresh Gas Flow

Rebreathing depends on circuit design, fresh gas flow (FGF), and the presence of a CO_2 absorber.

Venturi Effect and Bernoulli's Principle

According to the Venturi effect, gas passing through a narrow orifice increases velocity, decreases pressure, and entrains ambient air.

Application: Venturi masks deliver a fixed FiO_2 independent of patient effort. Nebulizers use the same principle for drug delivery, and injector devices in anesthesia machines apply Bernoulli's principle for gas mixing.

Work of Breathing

The work of breathing is determined by resistance and compliance of the circuit. Increase in either parameter raises patient effort.

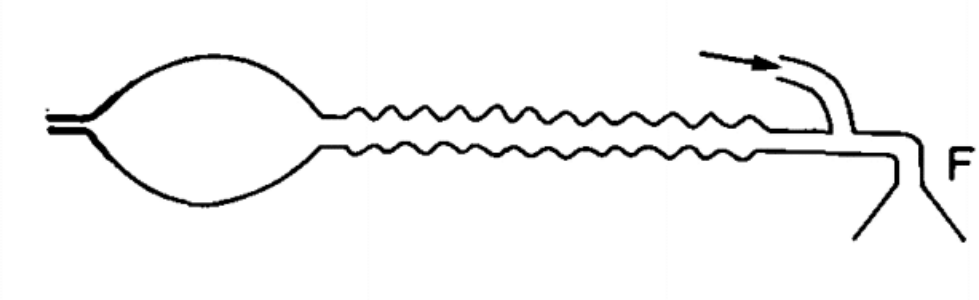
Application: Spontaneously breathing patients, especially children or those with respiratory disease, require low-resistance, lightweight circuits. The circle system with modern low-resistance valves is safe even in pediatric practice.

Mapleson circuits

History of the Mapleson Circuit Systems

1954 – Mapleson's landmark paper classified anaesthetic breathing circuits and gave rise to the nomenclature of Mapleson circuits A, B, C, D and E. This classic paper was initially regarded as a minor theoretical study by Mapleson who was awaiting volunteers for another neuromuscular relaxant study.

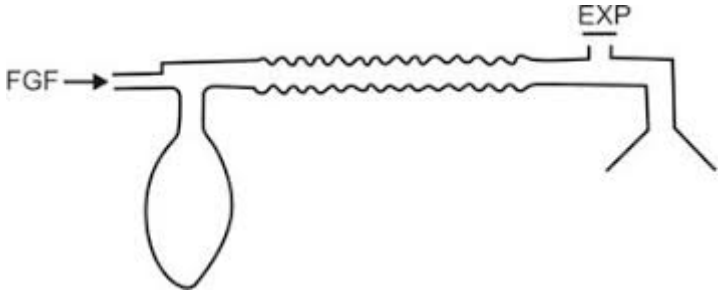
1975 – Willis, Pender and Mapleson described the Mapleson F, a modification of Mapleson E using the Jackson Rees modification of Ayres T-Piece during spontaneous respiration.



Mapleson F circuit. Jackson Rees modification of Ayres T-Piece. Br J Anaesth. 1975

MAPLESON A (also Magill system)

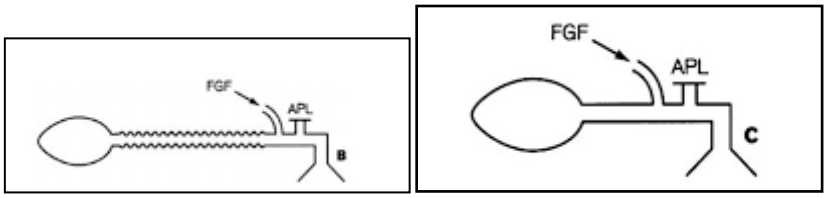
- Fresh gas flow enters near the reservoir bag at the machine end and the expiratory valve is positioned at the patient end
- The patient inhales fresh gas and the valve is closed during inspiration
- When the patient exhales, expired gas flows through the tubing and into the reservoir bag until the bag fills and the resultant pressure causes the expiratory valve to open
- The expired air is vented into the atmosphere which is further 'pushed' by the continuous fresh gas flow during the expiratory pause
- This minimises rebreathing of expired air
- This circuit functions best when the fresh gas flow equals the minute ventilation and dead space gas (free of CO_2 as does not take part in gas exchange) is allowed to be rebreathed
- It is the best circuit for the spontaneous breathing patient because of minimal rebreathing
- Main disadvantages include the proximity of the valve to the patient which makes it largely inaccessible during surgery and its constant evacuation of gases into the theatre environment
- Lacks modification added an expiratory limb which facilitated the scavenging of gas to prevent theatre pollution



MAPLESON B and C

- These are similar circuits with the fresh gas flow and expiratory valve located at the patient end and the reservoir bag at the machine end
- The corrugated tubing is absent in Mapleson C; it is a 'shortened' version of Mapleson B

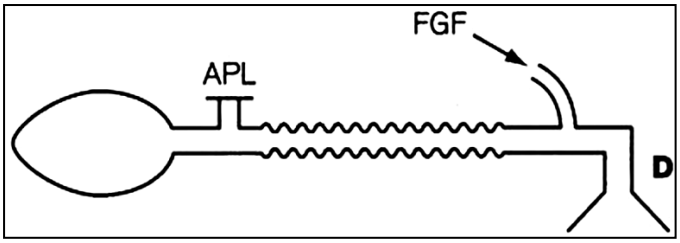
- Fresh gas flows and fills the reservoir bag and tubing.
- The patient inhales the fresh gas and expires into the reservoir tubing. During the expiratory pause, the fresh gas flow continues to fill the bag which now also contains the expired gas and as the pressure within the bag rises, the expiratory valve opens and these are vented into the atmosphere
- When the patient takes the next breath, it is both of mixed and fresh gas
- Fresh gas flow must be equal to peak inspiratory flow rate to prevent rebreathing as such, both these circuits require high gas flow and produce high theatre pollution

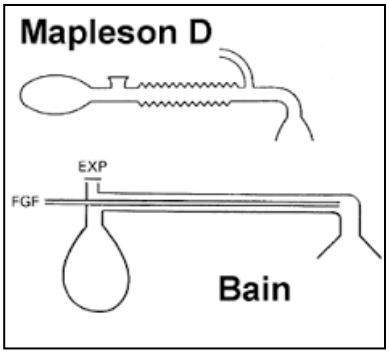


MAPLESON D

- Fresh gas flows from the machine end and connects to an Ayre T-piece at the patient end
- The T-piece has an extra limb of corrugated tubing which connects to the reservoir bag and the expiratory valve
- Patient inhales gas from the tubing and fresh gas flow
- Expired gas fills the tubing and fresh gas flow pushes this expired gas into the bag inflating it
- When the bag is sufficiently distended, the pressure causes the APL valve to open and the gas is vented into the atmosphere
- FGF needs to be 2-3 times the minute volume to prevent rebreathing
- The Bain modification of this circuit includes a ‘tube within a tube’
- Fresh gas flows in a tube that runs coaxially inside the corrugated tubing to the patient

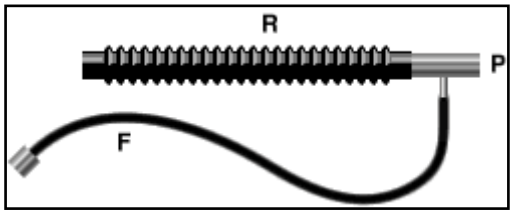
- When the patient exhales, the expired air flows back into the corrugated tubing and into the reservoir bag
- When the bag is full, the valve opens and excess gas is vented into the atmosphere
- During the expiratory pause, fresh gas flow continues and fills the proximal portion of the corrugated tube. This "pushes" the expired gas up the tube and into the bag
- On the next breath, the patient breaths fresh gas and the mixed gas in the corrugated tube
- If the fresh gas flow rate is high (1.5-2x minute volume) then the patient will inspire only fresh gas from the corrugated tube
- This is the most efficient system for controlled ventilation





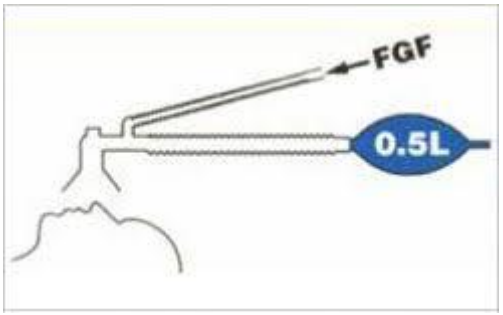
MAPLESON E

- Derived from the Ayre T-piece used in Mapleson D circuit and functions on the same principle as Mapleson D
- The primary difference is in the length of the tubing that is increased to be greater than the patient's tidal volume
- For spontaneous ventilation, the expiratory limb is open to the atmosphere
- It has no valves so there is no resistance to airflow nor points for possible mechanical failure

- Rebreathing is dependent on the fresh gas flow, patients minute volume and capacity of the expiratory limb
- Its main use is in pediatric patients
- 

MAPLESON F

- Jackson Rees modification of the Mapleson E system
- A 500ml bag is attached to the expiratory limb. A hole in the tail can be occluded by a finger to direct gas flow to the patients' lungs and provide pressure in controlled ventilation. The elasticity of the bag provides a 'pressure buffering effect' and prevents barotrauma; a problem often seen in Mapleson E due to overinflation
- The bag can also be fitted with a PEEP valve and converts the valveless system into one with a valve
- Observation of the bag during spontaneous ventilation helps in assessing and monitoring respiration.
- The system functions similar to a Mapleson E albeit with the added bag on the expiratory limb
- Fresh gas and expired gas mix in the bag during expiration
- FGF pushes the expired gas down the limb and into the bag during expiratory pause
- During the next inspiration, fresh gas is inhaled both from the FGF and from the expiratory limb of the circuit (now replaced with fresh gas)
- High fresh gas flows are required to prevent rebreathing (2.5-3x minute volume)
- Gases are vented into the atmosphere; scavenging is not possible



- Mapleson A is most efficient for spontaneous breathing.
- Mapleson D and Bain's modification are well suited for controlled ventilation.

Circle system

Uses unidirectional valves and soda lime absorber to allow low-flow anesthesia, conserving gases and heat.

Application: During patient transport, Mapleson circuits are preferred due to simplicity. For long surgeries, circle systems permit economical, low-flow anesthesia with reduced operating room pollution.

CO_2 Absorption

In circle systems, soda lime or calcium hydroxide lime absorbs CO_2. The reaction is exothermic, generating heat and water. Exhausted absorbent leads to rebreathing and hypercapnia.

Application: Clinicians must monitor for signs of exhausted absorbent such as increasing end-tidal CO_2, warm or color-changed canisters, and inadequate CO_2 elimination despite high FGF.

Conclusion

The function of anesthesia breathing circuits is grounded in basic physics principles, particularly gas flow dynamics, resistance, compliance, dead space, and rebreathing. These principles directly influence clinical practice: selection of circuits (Mapleson vs. circle), adjustment of fresh gas flows, and vigilance for potential hazards such as hypercapnia or increased work of

breathing. A sound grasp of circuit physics enables the anesthesiologists to optimize patient safety, conserve resources, and tailor ventilation strategies to the specific needs of each patient.

Further readings

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REVIEW ARTICLE

ANATOMICAL BASIS AND MECHANISM OF FASCIAL PLANE BLOCK

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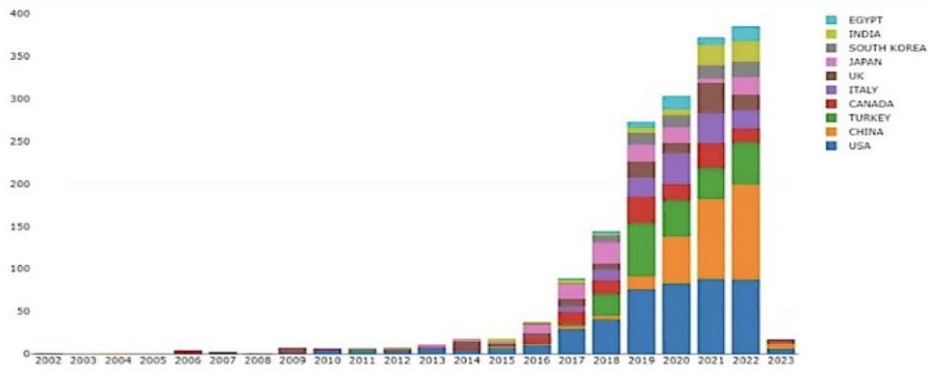
Abstract: *Fascial plane blocks (FPBs) have witnessed a surge in clinical practice as integral components of opioid-sparing multimodal analgesia. Unlike traditional techniques, FPBs deposit local anaesthetics into inter-fascial spaces, relying on complex mechanisms such as bulk flow, diffusion, and vascular uptake to modulate pain. While often effective, these blocks can be clinically unpredictable due to variables like fascial porosity, anatomical connectivity, and muscle dynamics. This review elucidates the anatomical basis and pharmacological behaviour of FPBs, underscoring their value when neuraxial blocks are contraindicated, while acknowledging significant knowledge gaps regarding their consistency and precise mechanisms.*

Keywords: *Fascial plane block, Regional anaesthesia, Multimodal analgesia, Fascial anatomy, Mechanism of action, Local anaesthetic pharmacokinetics*

Fascial plane blocks (FPB), including TAP, PECS, ESP, QL, SAP, RSB and many others, represent a growing and diverse group of regional anaesthesia techniques. These blocks leverage the anatomical spaces between fascial layers to deposit local anaesthetics (LA), providing analgesia without targeting nerves directly. While their popularity has surged, questions persist regarding their predictability, pharmacological behaviour, and precise mechanisms of action.

Over the last two decades, with the introduction of ultrasound in regional anesthesia practice, the fascia plane block has seen an unprecedented acceptance in clinical practice. It's easy to perform and in most situations, gives good post-operative pain relief making it a suitable component of multi modal analgesia technique. Easy to perform, rapid onset and part of ERAS make FPB an attractive component of opioid sparing post-operative MMA.



Explosive number of publications related to fascial plane block in the last decades

They are many in numbers namely TAP, PECS, ESP, QL, SAP, RSB, Clavipectoral, MTP, SSPP, SIFI, RISS, PIFB, SPEDI, ACB, IPACK, RLB, PIP, EOIC etc. but the question that comes frequently to our mind is, are they clinically relevant?

Over the last decade several large studies have shown the efficacy of these FPB as an integral part of multimodal analgesia postoperatively.

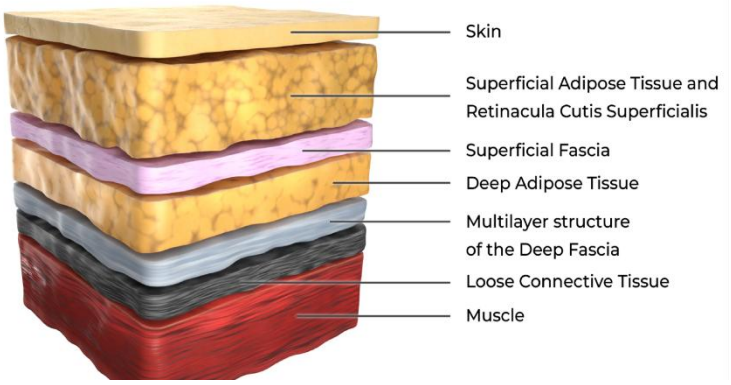
Few of the landmark studies published in recent years on FPB

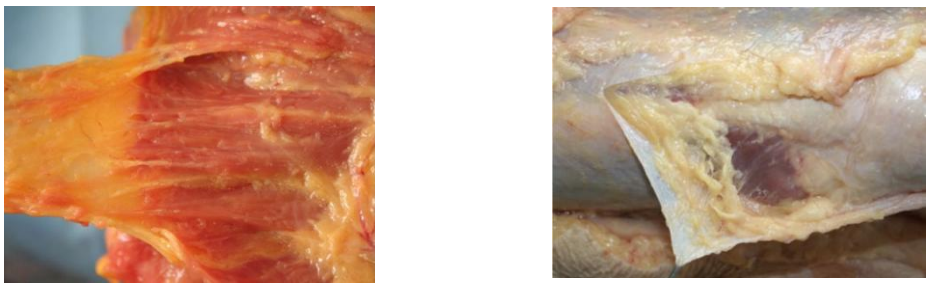
Fascia plane blocks are not always predictable, and the mechanism is not fully understood, they are heterogeneous in nature but useful in absence of neuraxial, paravertebral or plexus block.

What we definitely know about FPB is that nerves run through fascial plane, LA can spread out of FP to adjacent compartments, FPBs do not always result expected blockade like plexus block, FPBs produce peak plasma Lignocaine concentration equal to IV Lignocaine and Bupivacaine, Ropivacaine & Lidocaine have similar mechanism of action in FPB.

But what we still don't know for sure whether cadaver studies on FPB can replicate clinical effects, what determines the LA spread beyond the fascial plane and vascular absorption, what is the influence of volume, concentration and mass of LA on FPB and if additive improves FPB outcome.

Anatomy of a Fascia



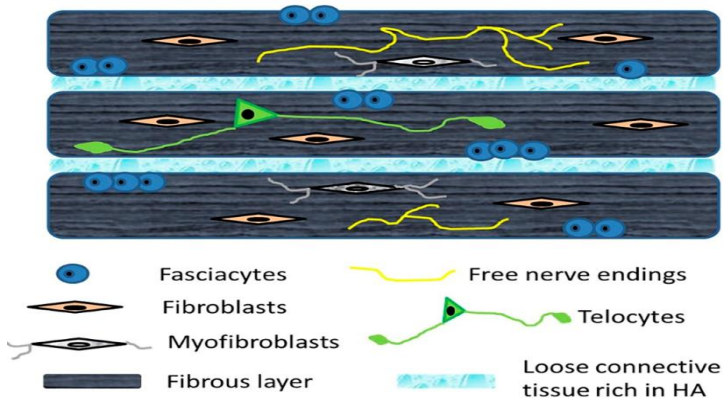


Epimysial (left) and aponeurotic fascia

There are 3 fundamental fascial connective layers in human Superficial fascia, Deep fascia, Muscle related fascia (Epimysium, Perimysium & Endomysium)

Grossly fasciae are classified into four layers - Superficial, Deep, Visceral and Parietal whereas some clinician classifies it functionally as

Linking, Fascicular, Compression and Separating. Fasciae are made up of collagen fibres; it is the richest sensory organ in our body. Fasciae attach, stabilise, impart strength, maintain vessel patency, separate muscles, and enclose different organs in our body. From a microscopic perspective, fasciae are composed of various cell types embedded within an extracellular matrix rich in collagen and hyaluronan.



Cellular component of a fascia

Fibroblasts- help produce collagen and other fibres that provide structural support.
Fasciacytes-specialized cells that are responsible for producing hyaluronan.
Myofibroblasts- are fibroblasts with contractile abilities, helping regulate the basal tone of fascial tissues.
Telocytes- are newly identified cells possess long, thin extensions called telopodes that form networks within the fascia.

Characteristic of a fascia

Fascia is a complex structure existing in superficial and deep fascia; deep fascia is classified as either epimysial or aponeurotic. Fascia is permeable

and perforated and the fasciae planes communicates with each other. Somatic and sympathetic nerves travel through the fascial layers.

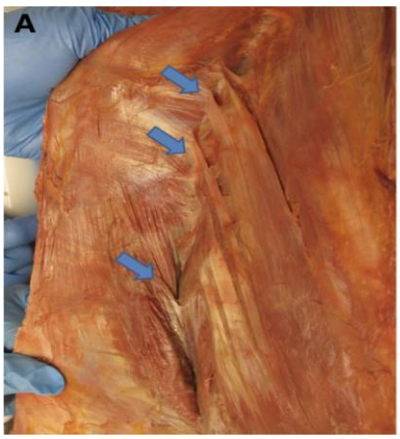
Table *1. Difference between Epimysial and Aponeurotic fascia*

	Epimysial	Aponeurotic
Thickness	Thinner (150–200 μm)	Thicker (600–1400 μm)
Grouping	Specific to each muscle	May envelop several muscles
Action	Localized	Transmits muscular forces over greater distance
Adherence	Usually adherent to muscles via fibrous septa	Easily separable from muscle
Anatomical location	Found in deep fascia of trunk muscles (eg, pectoralis major and latissimus dorsi) and the epimysium of limbs	Found in the thoracolumbar fascia, rectus sheath, and deep fascia of limbs (eg, fascia lata)
Block examples	PECS II, SAP, and TAP	Adductor canal, ESP, fascia iliaca, QL, and rectus sheath

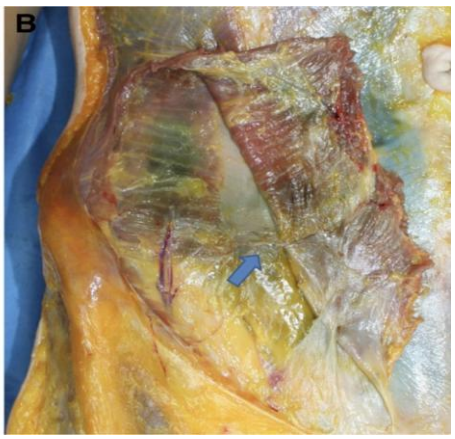
Biomechanical properties of Fascia & Fascia dynamic

When muscles contract, the related fascia get stretched leading to drug spread, fasciae may also have its own contractile element and behave like piezoelectric materials of second harmonic generation that converts mechanical force applied into energy.

Line of fusion either anatomical or post - operative creates compartments that may limit LA spread in a fascia plane block

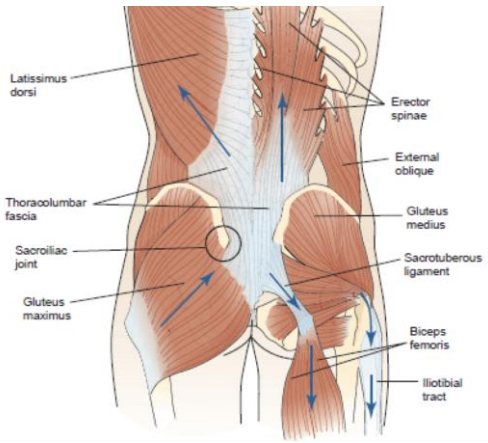


Linea alba



post-surgical adhesions

Interfacial connectivity



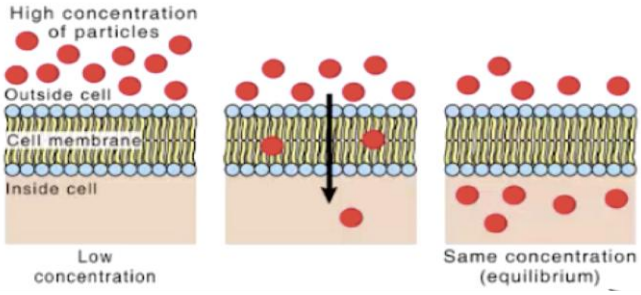
Connections between fasciae like thoracolumbar fascia, Endothoracic fascia and gluteal fascia allow drugs to spread without clear boundaries.

MECHANISM OF ACTION OF FASCIA PLANE BLOCK

The local anaesthetics blocks the nerve endings situated in the fascial plane or it may directly block the peripheral nerves running through the fascial plane like in RSB, PECS etc. or it may block the nerves/ root in the adjacent compartment like in ESP block.
The mechanism of fascial plane block can be broadly divided into 3
1. Bulk flow
2. Diffusion
3. Vascular uptake

Bulk flow allows rapid dispersion of local anaesthetics in the fascial plane after the injection and block the nerve endings, the extent of bulk flow depends on the force of injection, recoil of distended fascia and influenced by positioning of patient and gliding of fascia on muscle contractions.

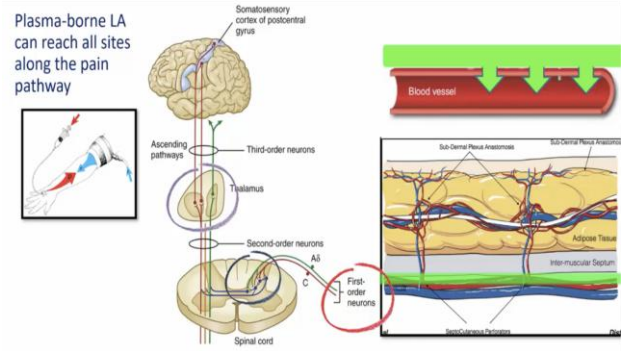
Whereas diffusion of anaesthetics happens slowly through all fascia to neighbouring structures through random walk of Brownian motion. Fascial layers are porous and perforated.



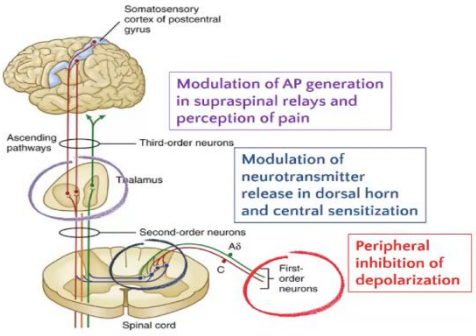
Diffusion of anaesthetics through fascia

Due to this slow process of anaesthetic dispersion, the fascial plane block can keep progressing beyond 45 minutes.

The vascular uptake of local anaesthetics from the site of injection brings the drug to the central circulation and probably behaves the same way as that of IV lignocaine or Bier's block, vascular uptake of anaesthetics may contribute to potential local anaesthetics toxicity.

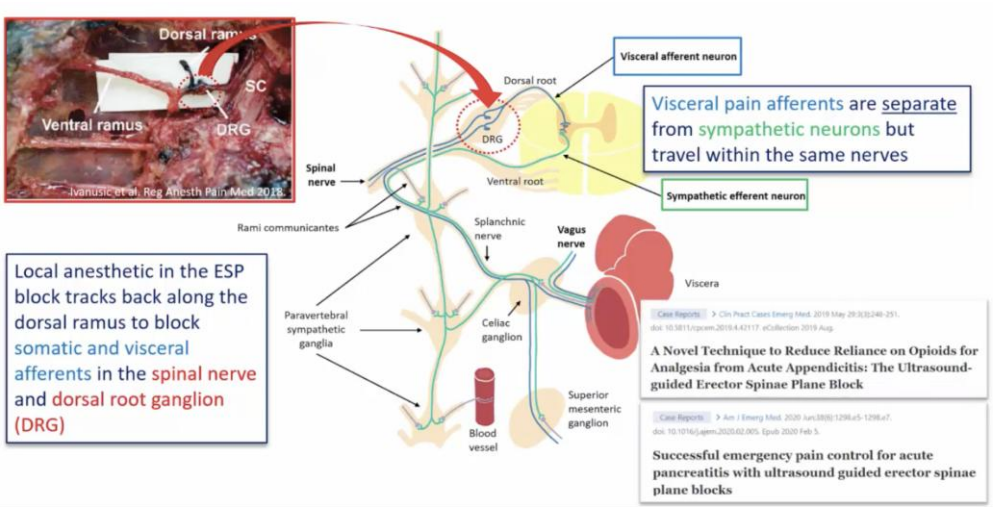


Vascular uptake of Local anaesthetic



Mechanism of IV lignocaine

Relevance of sympathetic innervation and control of visceral pain following fascial plane block like ESP where visceral afferent and somatic afferent converge in the dorsal root ganglia and can give visceral pain relief.



Variables affecting fascial plane block success

It is difficult to replicate same pattern of sensory block even when an FPB is performed by the same practitioner in the same subject, several factors contribute to the variability of the block.

Anatomical factors – Cutaneous innervations are more complex than described and multi segmental innervation and cross over innervation are common leading to a patchy or incomplete sensory block. Post-surgical adhesions, anatomical separation and interfacial connectivity influence LA spread in FPB.

Physiological factors – FPB are not same as plexus block as drug is deposited far away from the target in most situation. Age related muscle laxity and fascial contractility influence the bulk flow of LA leading to a variable block. Vigorous muscle contraction following FPB make the drug spread unpredictable.

Technical factors – Instead of fascia, intramuscular injections will lead to inadequate block. Volume, concentration and speed of injection also play a role in variability in FPB.

Challenges and Knowledge Gaps

- Lack of consistency in block outcomes.
- Difficult to replicate sensory block patterns in every individual.

- Influence of LA volume, concentration, and additives still under investigation.
- Cadaveric studies only partially replicate clinical effects.

Clinical Relevance

FPBs are particularly useful for post- operative pain management in settings where neuraxial or plexus blocks are contraindicated or not possible. However, they should not be expected to produce dense motor or sensory blockade as seen with traditional nerve blocks. Their role is increasingly valuable in multimodal analgesia (MMA) strategies, especially for postoperative pain control.

Conclusion

Fascia plane blocks represent an evolving area in regional anaesthesia. Despite promising results, their unpredictable efficacy, complex anatomy, and variable pharmacokinetics underscore the need for further research. Clinicians must approach FPBs with an understanding of their unique dynamics and limitations to optimize their utility in perioperative pain management.

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REVIEW ARTICLE

ANTIBIOTIC STEWARDSHIP IN THE ICU- CHALLENGES AND STRATEGIES

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Abstract: *Antibiotic stewardship in the Intensive Care Unit (ICU) is a pivotal challenge for intensivists, particularly within India's semi-open ICU systems. Inappropriate antibiotic use accelerates drug resistance, increases mortality, and raises treatment costs. This document summarizes core elements for successful stewardship programs, which rely on strong leadership, accountability, and multidisciplinary collaboration. Essential strategies involve antibiotic "time outs" after 48-hours, reassessment, prospective audits, and pharmacy-driven interventions such as dose optimization based on pharmacokinetic principles. Ultimately, these measures protect public health and ensure financial viability through reduced expenditures.*

Keywords: *Antibiotic Stewardship, ICU (Intensive Care Unit), Antibiotic Resistance, Pharmacokinetics (PK/PD), Multidisciplinary Approach, Infection Control*

Antibiotic stewardship in the intensive care unit is of paramount importance and constitutes a major challenge for intensivists. Mostly ICUs in India are semi open systems, where antibiotic prescription authority is in multiple hands, right from primary consultants, anesthesiologists and physicians. An anesthesiologist–intensivist working in the ICU should possess sound knowledge of antimicrobial stewardship and awareness of local hospital infection patterns, with ready access to consultation from microbiologists and pharmacologists. Effective leadership in antibiotic management is essential and should be led by the

intensivist in charge of the ICU, supported by a multidisciplinary team comprising members from various specialties.

Patients who are unnecessarily exposed to antibiotics are placed at risk for serious adverse events with no clinical benefit. The misuse of antibiotics has also contributed to the growing problem of antibiotic resistance, which has become one of the most serious and growing threats to public health. Unlike other medications, the potential for spread of resistant organisms means that the misuse of antibiotics can adversely impact the health of patients who are not even exposed to them. The Centers for Disease Control and Prevention (CDC) estimates more than two million people are infected with antibiotic-resistant organisms.

Consequences of resistance

- Longer duration of illness
- Increased HAI
- Increased mortality
- Increased expense of treatment in ICU
- Patients act as reservoir of infection.

Improving the use of antibiotics is an important patient safety and public health issue as well as a national priority. The 2006 CDC guideline “Management of Multi-Drug Resistant Organisms in Healthcare Settings” stated that control of multi-drug resistant organisms in healthcare “must include attention to judicious antimicrobial use”. In 2009, CDC launched the “Get Smart for Healthcare Campaign” to promote improved use of antibiotics in acute care hospitals and in 2013, the CDC highlighted the need to improve antibiotic use as one of four key strategies required to address the problem of antibiotic resistance in the US.

This document summarizes core elements of successful hospital Antibiotic Stewardship Programs. It complements existing guidelines on ASPs from organizations including the Infectious Diseases. There is no single template for a program to optimize antibiotic prescribing in hospitals. The complexity of medical decision-making surrounding antibiotic use and the variability in the size and types of hospitals require flexibility in implementation.

However, experience demonstrates that antibiotic stewardship programs can be implemented effectively in a wide variety of hospitals and that success is dependent on defined leadership and a coordinated multidisciplinary approach.

Core Elements of Hospital Antibiotic Stewardship Programs

Leadership Commitment: Leadership support is critical to the success of antibiotic stewardship programs and can take a number of forms, including:

- Formal statements that the facility supports efforts to improve and monitor antibiotic use.
- Including stewardship-related duties in job descriptions and annual performance reviews.
- Ensuring staff from relevant departments are given sufficient time to contribute to stewardship activities.
- Supporting training and education.
- Ensuring participation from the many groups that can support stewardship activities.

Financial support greatly augments the capacity and impact of a stewardship program and stewardship programs will often pay for themselves, both through savings in both antibiotic expenditures and indirect costs.

Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician/intensivist leader is effective.

Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.

Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours).

Tracking: Monitoring antibiotic prescribing and resistance patterns.

Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff.

Education: Educating clinicians about resistance and optimal prescribing.

Broad interventions

Antibiotic Time-outs:- Antibiotics are often started empirically in hospitalized patients while diagnostic information is being obtained. However, providers often do not revisit the selection of the antibiotic after more clinical and laboratory data (including culture results) become available. An antibiotic "time out" prompts a reassessment of the continuing need and choice of antibiotics when the clinical picture is clearer and more diagnostic information is available.

Two blood culture samples from both hand is always preferable before putting iv access that is to be followed by all staffs in ICU.

Review: -All clinicians should perform a review of antibiotics 48 hours after antibiotics are initiated to answer these key questions:

1.Does this patient have an infection that will respond to antibiotics?
2.If so, is the patient on the right antibiotic(s), dose, and route of administration?
3.Can a more targeted antibiotic be used to treat the infection (de-escalate)?
4.How long should the patient receive the antibiotic(s)?

Prior authorization: - Some facilities restrict the use of certain antibiotics based on the spectrum of activity, cost, or associated toxicities to ensure that use is reviewed with an antibiotic expert before therapy is initiated. This intervention requires the availability of expertise in antibiotic use and infectious diseases and authorization needs to be completed in a timely manner.

Prospective audit and feedback: - External reviews of antibiotic therapy by an expert in antibiotic use have been highly effective in optimizing antibiotics in critically ill patients and in cases where broad spectrum or multiple antibiotics are being used. Prospective audit and feedback are different from an antibiotic" time out" because the audits are conducted by staff other than the treating team. Audit and feedback requires the availability of experts and some smaller facilities have shown success by engaging external experts to advise on case reviews.

Pharmacy-driven Interventions:- Automatic changes from intravenous to oral antibiotic therapy in appropriate situations and for antibiotics with good absorption (e.g., fluoroquinolones, trimethoprim-sulfamethoxazole, linezolid, etc.) which improves patient safety by reducing the need for intravenous access.

Dose adjustments in cases of organ dysfunction (e.g. renal adjustment).

Dose optimization including dose adjustments based on therapeutic drug monitoring, optimizing therapy for highly drug-resistant bacteria, achieving central nervous system penetration, extended-infusion administration of beta-lactams, etc

Automatic alerts in situations where therapy might be unnecessarily duplicative including simultaneous use of multiple agents with overlapping spectra e.g. anaerobic activity, atypical activity, Gram-negative activity and resistant Gram-positive activity.

Time-sensitive automatic stop orders for specified antibiotic prescriptions, especially antibiotics administered for surgical prophylaxis.

Detection and prevention of antibiotic-related drug-drug interactions e.g. interactions between some orally administered fluoroquinolones and certain vitamins.

*PK/PD:-*Knowledge of pk/pd has an important role in prescribing antibiotics in an ICU.

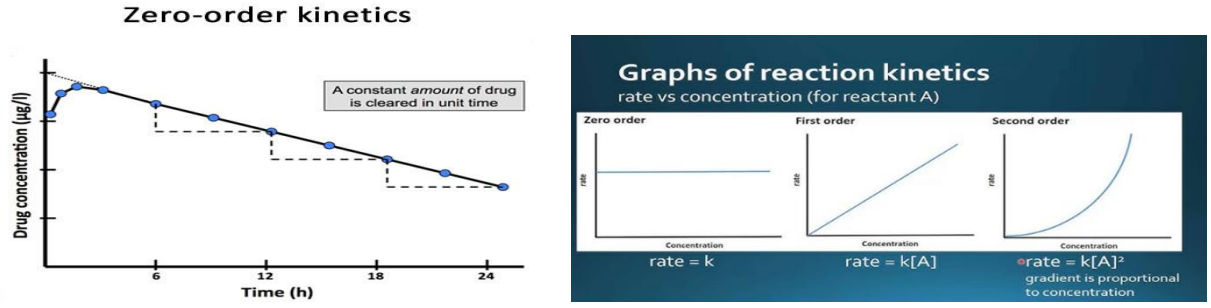

Fig: Different kinetics of drugs

Most antibiotics follows first order kinetics except few. Drugs which follow zero order kinetic are suitable for infusion whereas drugs following first order kinetics are suitable for interval doses.

Half-life and elimination:- Antibiotics those have long elimination half-life are suitable for single daily doses e.g, amikacin, fluoroqinolones etc. Other antibiotics are prescribed as intermittent bolus doses according to elimination half life's.

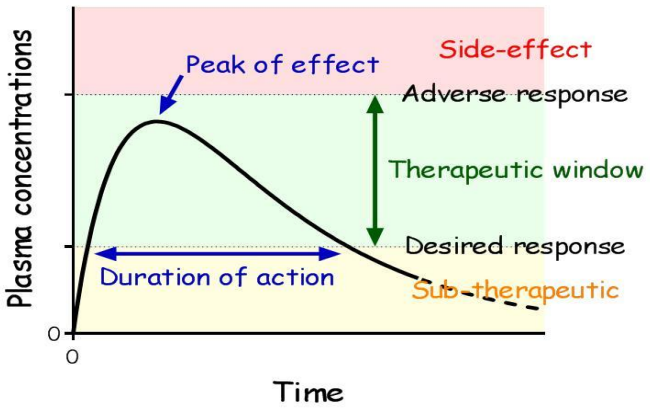

Fig- Dose response relationship

Piperacillin–tazobactam administered at 8-hourly intervals may result in subtherapeutic drug levels, as tazobactam has a shorter elimination half-life. Such inadequate concentrations fail to effectively eradicate target pathogens and may contribute to the development of antimicrobial resistance. A similar concern exists with imipenem–cilastatin; therefore, these antibiotics are preferably administered at 6-hourly intervals to maintain optimal therapeutic levels. Conversely, excessively high drug concentrations may exceed the therapeutic range and lead to toxicity, as seen with vancomycin in patients with renal impairment.

Infection and syndrome specific interventions

The interventions below are intended to improve prescribing for specific syndromes; however, these should not interfere with prompt and effective treatment for severe infection or sepsis.

Community-acquired pneumonia:- Interventions for community-acquired pneumonia have focused on correcting recognized problems in therapy, including: improving diagnostic accuracy, tailoring of therapy to culture results and optimizing the duration of treatment to ensure compliance with guidelines.

Urinary tract infections (UTIs):- Many patients who get antibiotics for UTIs actually have asymptomatic bacteriuria and not infections. Interventions for UTIs focus on avoiding unnecessary urine cultures and treatment of patients who are asymptomatic and ensuring that patients receive appropriate therapy based on local susceptibilities and for the recommended duration.

Skin and soft tissue infections:- Interventions for skin and soft tissue infections have focused on ensuring patients do not get antibiotics with overly broad spectra and ensuring the correct duration of treatment.

Empiric coverage of Methicillin-resistant Staphylococcus aureus (MRSA) infections: - In many cases, therapy for MRSA can be stopped if the patient does not have an MRSA infection or changed to a beta-lactam if the cause is methicillin-sensitive *Staphylococcus aureus*.

Clostridium difficile infections: - Treatment guidelines for CDI urge providers to stop unnecessary antibiotics in all patients diagnosed with CDI, but this often does not occur. Reviewing antibiotics in patients with new diagnoses of CDI can identify opportunities to stop unnecessary antibiotics which improve the clinical response of CDI to treatment and reduces the risk of recurrence.

Treatment of culture proven invasive infections:- Invasive infections (e.g. blood stream infections) present good opportunities for interventions to improve antibiotic use because they are easily identified from microbiology results. The culture and susceptibility testing often provides information needed to tailor antibiotics or discontinue them due to growth of contaminants.

Checklist for Core Elements of Hospital Antibiotic Stewardship Programs

The following checklist is a companion to Core Elements of Hospital Antibiotic Stewardship Programs. This checklist should be used to systematically assess key elements and actions to ensure optimal antibiotic prescribing and limit overuse and misuse of antibiotics in hospitals. CDC recommends that all hospitals implement an Antibiotic Stewardship Program.

Facilities using this checklist should involve one or more knowledgeable staff to determine if the following principles and actions to improve antibiotic use are in place. The elements in this checklist have been shown

in previous studies to be helpful in improving antibiotic use though not all of the elements might be feasible in all hospitals.

LEADERSHIP SUPPORT	ESTABLISHED AT FACILITY	
A. Does your facility have a formal, written statement of support from leadership that supports efforts to improve antibiotic use (antibiotic stewardship)?	❑ Yes	❑ No
B. Does your facility receive any budgeted financial support for antibiotic stewardship activities (e.g., support for salary, training, or IT support)?	❑ Yes	❑ No
ACCOUNTABILITY		
A. Is there a physician leader responsible for program outcomes of stewardship activities at your facility?	❑ Yes	❑ No
DRUG EXPERTISE		
A. Is there a pharmacist leader responsible for working to improve antibiotic use at your facility?	❑ Yes	❑ No

KEY SUPPORT FOR THE ANTIBIOTIC STEWARDSHIP PROGRAM

Does any of the staff below work with the stewardship leaders to improve antibiotic use?

B. Clinicians	❑ Yes	❑ No
C. Infection Prevention and Healthcare Epidemiology	❑ Yes	❑ No
D. Quality Improvement	❑ Yes	❑ No
E. Microbiology (Laboratory)	❑ Yes	❑ No
F. Information Technology (IT)	❑ Yes	❑ No
G. Nursing	❑ Yes	❑ No

ACTIONS TO SUPPORT OPTIMAL ANTIBIOTIC USE

POLICIES	POLICY ESTABLISHED	
A. Does your facility have a policy that requires prescribers to document in the medical record or during order entry a dose, duration, and indication for all antibiotic prescriptions?	❑ Yes	❑ No
B. Does your facility have facility-specific treatment recommendations, based on national guidelines and local susceptibility, to	❑ Yes	❑ No

assist with antibiotic selection for common clinical conditions?

SPECIFIC INTERVENTIONS TO IMPROVE ANTIBIOTIC USE

Are the following actions to improve antibiotic prescribing conducted in your facility?

BROAD INTERVENTIONS	ACTION PERFORMED	
C. Is there a formal procedure for all clinicians to review the appropriateness of all antibiotics 48 hours after the initial orders (e.g. antibiotic time out)?	❑ Yes	❑ No
D. Do specified antibiotic agents need to be approved by a physician or pharmacist prior to dispensing (i.e., pre-authorization) at your facility?	❑ Yes	❑ No
E. Does a physician or pharmacist review courses of therapy for specified antibiotic agents (i.e., prospective audit with feedback) at your facility?	❑ Yes	❑ No
PHARMACY-DRIVEN INTERVENTIONS Are the following actions implemented in your facility?	ACTION PERFORMED	
F. Automatic changes from intravenous to oral antibiotic therapy in appropriate situations?	❑ Yes	❑ No
G. Dose adjustments in cases of organ dysfunction?	❑ Yes	❑ No
H. Dose optimization (pharmacokinetics/pharmacodynamics) to optimize the treatment of organisms with reduced susceptibility?	❑ Yes	❑ No
I. Automatic alerts in situations where therapy might be unnecessarily duplicative?	❑ Yes	❑ No
J. Time-sensitive automatic stop orders for specified antibiotic prescriptions?	❑ Yes	❑ No
DIAGNOSIS AND INFECTIONS SPECIFIC INTERVENTIONS Does your facility have specific interventions in place to ensure optimal use of antibiotics to treat the following common infections?	ACTION PERFORMED	
K. Community-acquired pneumonia	❑ Yes	❑ No
L. Urinary tract infection	❑ Yes	❑ No
M. Skin and soft tissue infections	❑ Yes	❑ No
N. Surgical prophylaxis	❑ Yes	❑ No

O. Empiric treatment of Methicillin-resistant Staphylococcus aureus (MRSA)	❑ Yes	❑ No
P. Non-C. Difficile infection (CDI) antibiotics in new cases of CDI	❑ Yes	❑ No
Q. Culture-proven invasive (e.g., blood stream) infections	❑ Yes	❑ No

TRACKING: MONITORING ANTIBIOTIC PRESCRIBING, USE, AND RESISTANCE

PROCESS MEASURES	MEASURE PERFORMED	
A. Does your stewardship program monitor adherence to a documentation policy (dose, duration, and indication)?	❑ Yes	❑ No
B. Does your stewardship program monitor adherence to facility-specific treatment recommendations?	❑ Yes	❑ No
C. Does your stewardship program monitor compliance with one of more of the specific interventions in place?	❑ Yes	❑ No

ANTIBIOTIC USE AND OUTCOME MEASURES	MEASURE PERFORMED	
D. Does your facility track rates of C. difficile infection?	❑ Yes	❑ No
E. Does your facility produce an antibiogram (cumulative antibiotic susceptibility report?	❑ Yes	❑ No
Does your facility monitor antibiotic use (consumption) at the unit and/or facility wide level by one of the following metrics:	MEASURE PERFORMED	
F. By counts of antibiotic(s) administered to patients per day (Days of Therapy; DOT)?	❑ Yes	❑ No
G. By number of grams of antibiotics used (Defined Daily Dose, DDD)?	❑ Yes	❑ No
H. By direct expenditure for antibiotics (purchasing costs)?	❑ Yes	❑ No

REPORTING INFORMATION TO STAFF ON IMPROVING ANTIBIOTIC USE AND RESISTANCE

A. Does your stewardship program share facility-specific reports on antibiotic use with prescribers?	❑ Yes	❑ No
B. Has a current antibiogram been distributed to prescribers at your facility?	❑ Yes	❑ No
C. Do prescribers ever receive direct, personalized communication about how they can improve their antibiotic prescribing?	❑ Yes	❑ No

EDUCATION		
A. Does your stewardship program provide education to clinicians and other relevant staff on improving antibiotic prescribing?	❑ Yes	❑ No

Conclusion

Antimicrobial stewardship programs (ASPs) adopt a multidisciplinary approach with strong leadership and continuous monitoring, aimed at safeguarding public health. Education and training of support staff form a cornerstone of these programs. Adequate financial support significantly enhances the capacity and effectiveness of stewardship initiatives, and such programs often prove to be cost-effective by reducing antibiotic expenditure as well as indirect healthcare costs.

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REVIEW ARTICLE

PAIN PATHWAYS AND MODULATION: UNDERSTANDING THE BODY'S ALARM SYSTEM

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Abstract: *Pain is a complex, multidimensional protective mechanism involving sensory, emotional, and cognitive components, rather than a simple stimulus-response phenomenon. This overview delineates the ascending pain pathway, spanning transduction by nociceptors and transmission via afferent fibers to conscious perception in the brain. It further explores the nervous system's capacity to modulate signals through peripheral sensitization, spinal mechanisms like the Gate Control Theory, and descending inhibitory pathways involving endogenous opioids. Understanding these dynamic interactions is essential for developing multimodal clinical strategies that effectively target specific pathway levels to manage acute and chronic pain.*

Keywords: *Pain Pathway, Nociception, Pain Modulation, Gate Control Theory, Chronic Pain, Multimodal Management, Analgesia*.

Pain is a universal human experience, serving as the body's protective alarm system. While often perceived as an unpleasant sensation, pain plays a crucial role in warning us of injury and prompting protective action. The scientific understanding of pain has evolved from the idea of it being a simple stimulus–response phenomenon to a complex, multidimensional process involving sensory, emotional, and cognitive components.

I. The Pain Pathway – From Periphery to Perception

The journey of a painful stimulus from the site of injury to conscious awareness involves a series of well-orchestrated steps:

1. Transduction

This is the conversion of a noxious stimulus (thermal, mechanical, or chemical) into an electrical signal by specialized nerve endings called nociceptors. Located in skin, muscles, joints, and viscera, nociceptors are activated by tissue injury, which releases chemical mediators such as prostaglandins, bradykinin, and substance P.

2. Transmission

Once generated, the electrical signal travels along afferent nerve fibers to the spinal cord. Two main types of fibers are involved:

- A-delta fibers – myelinated, fast-conducting, responsible for sharp, well-localized pain.
- C fibers – unmyelinated, slow-conducting, responsible for dull, aching, and poorly localized pain.

The primary afferent neurons enter the dorsal horn of the spinal cord, where they synapse with second-order neurons. These neurons then cross to the opposite side and ascend via the spinothalamic tract to higher centers.

3. Perception

Pain perception occurs in the brain, primarily in the thalamus and somatosensory cortex, but is also influenced by the limbic system (emotions) and prefrontal cortex (cognitive evaluation). This explains why pain is not just a physical sensation but also has emotional and psychological dimensions.

4. Projection Pathways

While the spinothalamic tract is the primary route, other ascending tracts such as the Spino reticular and Spino mesencephalic tracts play roles in alertness and activating descending modulation systems.

II. Pain Modulation – Turning the Volume Up or Down

Pain perception is not fixed. The nervous system has built-in mechanisms to enhance or suppress pain signals at various levels of the pathway.

1. Peripheral Modulation

At the injury site, inflammatory mediators sensitize nociceptors, lowering their activation threshold. This results in hyperalgesia (increased sensitivity to pain) or allodynia (pain from non-painful stimuli). Anti-inflammatory drugs (NSAIDs) target this stage by blocking prostaglandin synthesis.

2. Spinal Modulation

Within the dorsal horn, interneurons release neurotransmitters such as enkephalins and dynorphins, which inhibit pain transmission by acting on presynaptic and postsynaptic opioid receptors.
The Gate Control Theory (Melzack & Wall, 1965) proposes that non-painful input (e.g., touch, vibration) activates inhibitory interneurons that "close the gate" to painful input — explaining why rubbing a painful area can reduce discomfort.

3. Descending Modulation

Descending pathways from the brainstem exert powerful inhibitory effects on pain transmission. Key structures include:

- Periaqueductal gray (PAG) in the midbrain – activates pain-inhibiting neurons.
- Rostral ventromedial medulla (RVM) – releases serotonin and norepinephrine to suppress dorsal horn activity.

Endogenous opioids (endorphins, enkephalins) and monoamines are key players in this descending inhibition.

4. Central Sensitization

Repeated or intense pain stimuli can lead to increased excitability of spinal neurons, amplifying pain perception. This phenomenon contributes to

chronic pain syndromes and underscores why early and effective pain management is important.

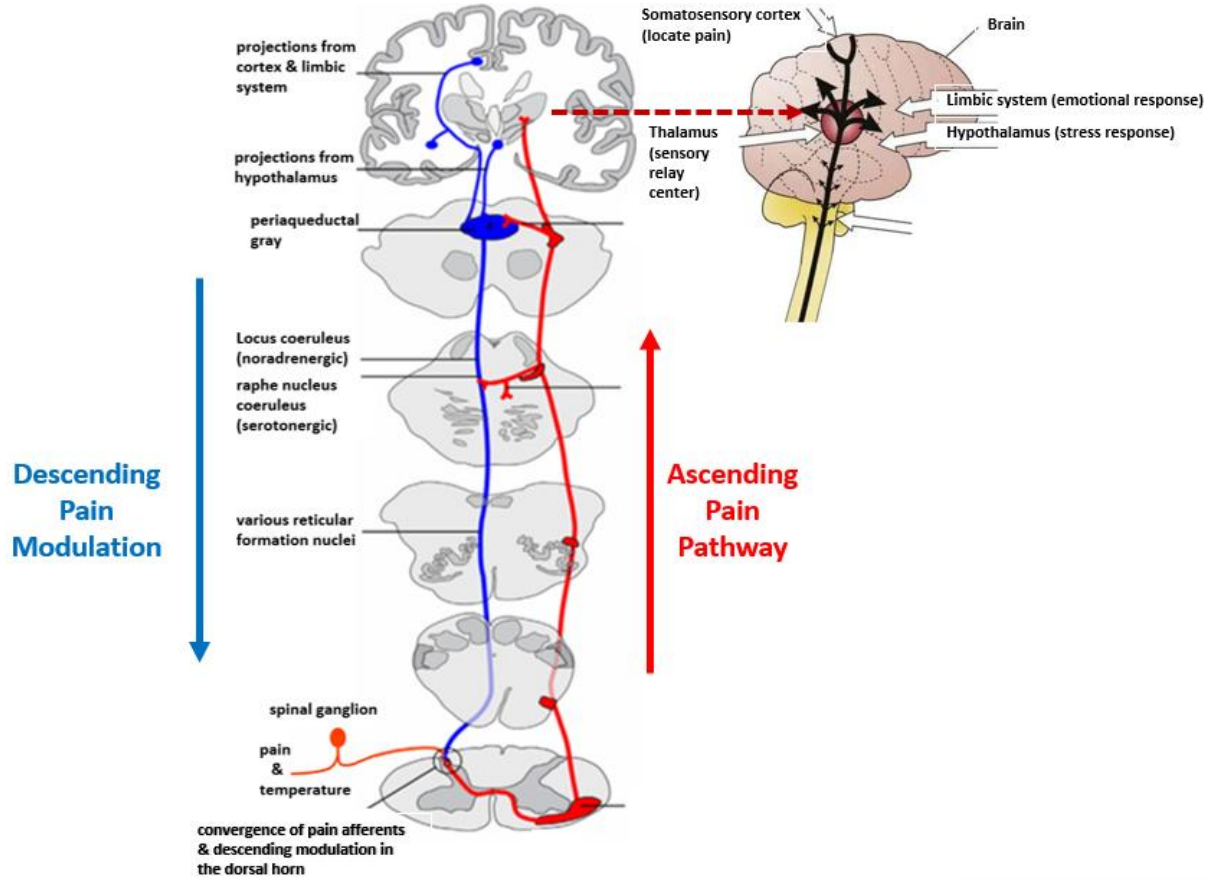

Figure: Ascending Pain Pathway & Descending Pain Modulation Pathway

III. Clinical Implications

Understanding pain pathways and modulation has shaped modern pain management strategies:

- Pharmacological approaches target specific levels — NSAIDs act peripherally, opioids work at spinal and supraspinal levels, and antidepressants enhance descending inhibition.
- Regional anesthesia interrupts transmission at the nerve or spinal level.
- Non-pharmacological methods like transcutaneous electrical nerve stimulation (TENS), physiotherapy, and mindfulness leverage endogenous modulation systems.

Chronic pain, in particular, requires a multimodal approach, addressing not just nociception but also psychological and social dimensions.

IV. Conclusion

Pain is not a simple “wiring problem” but a dynamic interaction between sensory input, spinal processing, brain interpretation, and modulatory influences. The body’s pain pathways ensure we are alerted to potential harm, while modulation mechanisms protect us from being overwhelmed by persistent nociception. A deep understanding of these mechanisms not only guides effective pain relief but also opens avenues for innovative therapies — aiming for the ideal balance between protection and comfort.

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