EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2022,17 (24) 111-116
(*FORMERLY: CAPSULA EBURNEA*)

Review

PHARMACOLOGICAL MANAGEMENT OF THE POLYTRAUMA PATIENT. ON ANALGESIC THERAPY GUIDELINES

Daniele Lo Coco [1], Irene Mistretta [2], Arianna Rifiorito [3], Giuseppe Davide Albano [3], Leila Zummo [4], Ginevra Malta [3]

1. Complex Operative Unit of Neurology with Stroke Unit, A.O.O.R. "Villa Sofia – Cervello", Palermo, Italy.
2. Specialist in Pharmaceutical Science, Italy.
3. Department of Health Promotion Sciences Maternal and Child Care, Internal Medicine and Medical Specialties "Giuseppe D'Alessandro", University of Palermo, Via del Vespro 133, 90127 Palermo, Italy.
4. Complex Operative Unit of Neurology with Stroke Unit, ARNAS Civico – Di Cristina – Benfratelli, Palermo, Italy

ARTICLE INFO

Article history:
Received 27 Jul 2022
Accepted 31 Aug 2022
Published 16 Sep 2022

Keywords:
Analgesic, Guidelines, Polytrauma, Management, Pharmacology, Surveillance

ABSTRACT

In consideration of the constant, if not increasing number of polytrauma patients arriving in emergency rooms, the pharmacological treatment of pain is a topic that is always under observation and innovation. Even more important is the global management of pain in the polytrauma patient, i.e. its treatment in the phases even after hospitalisation. The existence of pharmacotherapeutic protocols is today an aid for the physician in order to act in the most appropriate way in the shortest possible time. This brief commentary is intended to be a practical guide to the analgesic treatment of the polytrauma patient, in the light of the most recent scientific evidence.

1. Introduction

The use of drugs in the treatment of different diseases has always been of enormous importance. Just think of the use of anti-SARS-CoV-2 vaccines that, together with the implementation of correct and appropriate prevention and protection procedures [1-4], were able to cope with the pandemic emergency by slowing its progression and reducing the number of hospitalizations [5-6].

In clinical practice, more often than not, the physician has the opportunity to take a careful anamnesis of the patient in order to establish a suitable drug therapy to resolve the disease and/or slow down its progression, as in the case of drugs prescribed for the treatment of neurodegenerative diseases [7]. However, there is not always the possibility of taking a detailed anamnesis of the patient due to the patient's particular emergency conditions.

In such cases, the physician has guidelines rather than treatment protocols at his disposal to ensure a prompt and appropriate drug therapy aimed at the recovery of the patient's vital functions [8].

This could be the case of a professional sportsman or worker who, following an injury, arrives at the hospital emergency room with two or more injuries simultaneously, often associated with the impairment of one or more vital functions [9-11]. In this case, there is little time to think, and useful drugs must be administered quickly to resuscitate the patient.

The presence of two or more traumas at the same time, 'polytrauma', is a clinical condition that can lead to physical, psychological, or other psychosocial damage. One of the most frequent manifestations of polytrauma is traumatic brain injury (TBI) [12,13]. It often occurs in polytrauma and disabling conditions, including amputations, hearing and visual impairments, spinal cord injuries, oxidative stress phenomena and post-traumatic stress disorder [14-21].

It is also interesting to recall how the frequency of work-related polytrauma is often related to stressful conditions caused by the working environment and modalities, rather than to the use of psychotropic substances such as alcohol, which can predispose to and increase the rate of injuries [22-26].

* *Corresponding author*: Ginevra Malta, *ginevra.malta@unipa.it*
DOI: 10.3269/1970-5492.2022.17.24
 ISSN: 2279-7165 - Available on-line at www.embj.org

From a pharmacological point of view, the approach to the polytrauma patient can be differentiated on a temporal basis into two different moments: pre-hospitalisation, an immediate pharmacological approach to the patient in order to stabilise his condition; post-hospitalisation, aimed mainly at treating and resolving the patient's pain condition. In these two moments, pharmacological therapy involves the administration of different drugs ranging from the most common crystalloids for volemic reintegration to the most recent molecules with antalgic activity.

Based on the above premises, the aim of this mini-review will be to analyse the main molecules with antalgic activity to be used to treat the polytrauma patient in both the acute and chronic phases. Furthermore, the therapeutic approach useful for the stabilisation and resuscitation of the polytrauma patient will be briefly described.

2. Patient stabilisations

When trauma is generated, such as when using mechanical or high-pressure tools, road accidents, or accidental falls at work [27], our body goes from a state of motion to a state of rest. This transition results in the absorption of energy by the body, which is transmitted to the patient and his anatomical structures, compromising the functionality of those that are less resistant. The organs that better withstand energy changes are those rich in elastic fibres, as opposed to inelastic ones such as the liver and spleen, which, being incompressible, break very easily. In cases where trauma is caused by penetrating objects, the extent of the damage is directly related to the mass of the object and the speed with which it penetrated inside the patient.

Furthermore, the trauma may be visible from the outside, or it may be internal, and in the latter case, it is crucial to properly assess the patient and subject them to imaging procedures. It must also be remembered that most polytraumatised individuals have two or more skeletal injuries that further impair their vital functions [28].

The main conditions affecting a polytrauma patient are respiratory failure, circulatory compromise (haemorrhage), infection, neurological damage and intense pain [29-32]. Precisely for these reasons, the choice of drugs to be administered in the immediate future must be based on their ability to re-establish a correct circulation, avoid bacterial infections, and ensure a prompt and rapid neurological recovery of the patient.

Few drugs are needed to treat the patient in this acute phase. The most commonly used ones include: volemic replenishment drugs (crystalloids and/or plasma expanders); vasoconstrictors (ephedrine); vagolytics (atropine); antimicrobials (ampicillin + sulbactam); fibrinolysis inhibitors (tranexamic acid); drugs with analgesic activity (ketorolac, morphine, fentanyl, sulfentanil, buprenorphine, lidocaine) [33-37].

There are also emergencies in which the subject is in a particular critical condition, or in such a state of agitation that a correct diagnosis or administration of the drugs previously analysed is not possible. In these cases, it is necessary to intervene with the administration of molecules with anaesthetic/sedative activity, including the most commonly used ones such as: propofol, etomidate and ketamine.

These molecules, thanks to the sedation of the patient, allow the doctor to conduct a careful and in-depth diagnosis of the patient that is useful for defining the most suitable therapeutic strategy for treating the patient.

3. Medications with antalgic activity

The pain generated by polytrauma injuries poses numerous challenges from a pharmacological point of view. Generally, pain management in the polytrauma patient requires a thorough understanding of the patient's history as well as a comprehensive examination and consideration of the trajectory of care. Multimodal options for treatment include drugs, regional anesthesia and non-pharmacological treatments. Furthermore, it is crucial to remember that rapid pain management is of paramount importance in order to prevent the development of chronic pain. In this regard, it is possible to identify two different stages for pain therapy in the polytrauma patient: a first stage in which the administration of analgesic drugs is directly related to the patient's condition and is subordinate to the monitoring of vital functions and diagnosis; a second stage in which the choice of drug should be made after a careful and thorough assessment of the type of pain, site, degree of interference on the patient's autonomy and quality of life [38-40].

In the first stage, analgesic drugs are used, the administration of which requires the intervention of an anesthetist; in the second stage, drugs are mainly used only after identifying the site of the pain and quantifying its extent.

4. Analgesics administered under the supervision of the anesthetist

Often, the polytraumatised person is in such a state of agitation that the doctor is unable to make a careful diagnosis. In such cases, sedative drugs are administered along with molecules with analgesic activity. Commonly used molecules include Ketamine, a parenteral anaesthetic agent with analgesic activity at sub-anaesthetic doses. It is a drug with antagonist activity on N-methyl-D-aspartate (NMDA) receptors with activity on opioid receptors [41-43]. This molecule, at a dose of 0.25-0.5 mg/kg i.v. is able to produce rapid and intense analgesia. Molecules such as the synthetic opiate fentanyl, which is about 75 times more potent than morphine, can be decisive if the patient does not present a state of intense agitation. In this case, it is desirable to combine analgesic therapy with drugs with anxiolytic or sedative activity as an adjuvant. Among these molecules we can mention midazolam, a centrally acting benzodiazepine capable of inducing drowsiness, muscle relaxation and short-term memory loss, and propofol useful both for sedation and for inducing deep anaesthesia [44-46]. As an alternative to these drugs, drugs capable of inducing loco-regional anaesthesia may be considered [47-49].

5. Analgesics administered chronically

The choice of analgesic drugs involves a thorough knowledge of the pharmacokinetic and pharmacodynamic properties of the molecules of interest.

These properties allow us to determine both the most suitable routes of administration and the possible occurrence of side effects. Furthermore, in the case of subjects taking one or more drugs, due to concomitant pathologies, knowledge of the properties of the analgesic drug allows us to avoid the possible occurrence of drug interactions.

Medications usually used for pain management include non-narcotic analgesics, non-steroidal anti-inflammatory drugs and paracetamol, or narcotics, opioids.

Non-steroidal anti-inflammatory drugs provide excellent pain relief due to their analgesic and anti-inflammatory action. These molecules inhibit cyclooxygenases (COX), enzymes necessary for the transformation of arachidonic acid into prostaglandin H (PGH2) and subsequently into other endogenous regulators: prostaglandins D (PGD2), E (PGE2), F (PGF2), prostacyclin and thromboxanes (TXA2 and TXB2) [50-51]. NSAIDs can be divided into different classes: salicylates (e.g. aspirin); acetic acid derivatives (e.g. diclofen and ketorolac); propionic acid derivatives (e.g. ibuprofen, ketoprofen); enolic acid derivatives (e.g. piroxicam and meloxizam); selective COX-2 inhibitors (coxibs) (e.g. celecoxib, etoricoxib); other NSAIDs (e.g. nimesulide). Among these molecules, Ketorolac seems to be endowed with good antalgic activity, such that the drug is useful in the treatment of post-operative pain [52,53].

Among molecules with analgesic activity, paracetamol remains one of the most widely used. The analgesic action of the drug seems to be linked to different mechanisms of action including, the inhibition of the centrally expressed COX-3 enzyme [54,55] and the activation of spinal 5-hydroxytryptamine type 3 (5HT3) receptors that occurs through an interference of the drug with the serotonergic descending pathways of pain [56,57]. In addition, some research groups have recently demonstrated the presence of an active metabolite of paracetamol (the fatty acid amide N-arachidonoylphenolamine; AM404) capable of activating the vanilloid receptor subtype 1 (TRPV1) and inhibiting cellular uptake of anandamide. All this promotes an increase in endogenous cannabinoid (CB) levels, resulting in a potentiation of their antalgic action that occurs through spinal descending inhibition mediated by CB1 receptor activation [58-64].

Opioids are among the best known drugs with analgesic activity. Their biological effect is due to neuronal inhibition by blocking the release of excitatory neurotransmitters [65]. This effect is a consequence of the activation of a well-defined number of receptors, predominantly μ receptors (μ_1 and μ_2), involved in the modulation of pain perception.

Opioids are commonly classified according to their analgesic potency: weak opioids (codeine and tramadol) and strong opioids (buprenorphine, morphine, methadone, fentanyl, oxycodone, hydromorphone, tapentadol). The former have a limited potency and possess a threshold dose above which the pain-relieving efficacy does not improve but, on the contrary, the occurrence of adverse effects increases. The drugs belonging to this group are mainly found in pharmaceutical formulations for oral use, in combination with paracetamol (codeine-paracetamol; tramadol-paracetamol).

Strong opioids include tapentadol. This drug, in addition to acting on its own receptor sites, has the ability to inhibit the norepinephrine transporter [66], this makes it a particularly useful drug in the treatment of chronic pain such as neuropathic or mixed pain [67,68].

Should the above-mentioned molecules fail to resolve the problem, one can consider administering so-called adjuvant drugs. These are compounds that, although not classic painkillers, contribute in some way to the efficacy of the analgesic treatment.

These molecules include (i) tricyclic antidepressants (e.g., amitriptyline and nortriptyline), serotonin and norepinephrine re-uptake inhibitors (venlafaxine, duloxetine) and serotonin re-uptake inhibitors (fluoxetine); (ii) antiepileptics (e.g. carbamazepine, pregabalin, gabapentin); (iii) steroids (e.g., prednisone, dexamethasone).

6. Conclusions

The evaluation of the type of pain and the underlying pathogenetic mechanism, as well as the location of any irradiation, the qualitative and temporal characteristics, the degree of interference on the patient's autonomy and quality of life, are necessary to establish a suitable and careful pharmacological therapy aimed at resolving the pain sensation.

Today, thanks to the different therapeutic protocols, updated on the basis of the most recent scientific discoveries, the doctor has at his disposal all the tools useful in identifying the most suitable drug for the treatment of pain in all its forms. The possibility of choosing the drug in the shortest possible time is of great importance, especially in polytrauma patients in whom the timing between the identification of the best active ingredient and its administration is sometimes 'vital'.

References

1. Cirrincione L, Rapisarda V, Mazzucco W, Provenzano R, Cannizzaro E. SARS-CoV-2 and the Risk Assessment Document in Italian Work; Specific or Generic Risk Even If Aggravated?. Int J Environ Res Public Health. 2021a;18(7):3729. doi:10.3390/ijerph18073729.
2. Cirrincione L, Rapisarda V, Ledda C, Vitale E, Provenzano R, Cannizzaro E. Considerations on the Update of the Risk Assessment Document During the Pandemic State by COVID-19 in Italy. Front Public Health. 2021b;9:655927. doi:10.3389/fpubh.2021.655927.
3. Cirrincione L, Plescia F., Ledda C, Rapisarda V, Martonrana D, Moldovan EE, Theodoridou K, Cannizzaro E. COVID-19 Pandemic: Prevention and Protection Measures To be adopted at the workplace. Sustainibility. 2020, 12(9), 3603.
4. Cirrincione L, Plescia F, Ledda C, Rapisarda V, Martorana D, Lacca G, Argo A, Zerbo S, Vitale E, Vinnikov D, Cannizzaro E. COVID-19 Pandemic: New Prevention and Protection Measures. Sustainability. 2022, 14(8), 1-10. https://doi.org/10.3390/su14084766
5. Deplanque D, Launay O. Efficacy of COVID-19 vaccines: From clinical trials to real life. Therapie. 2021;76(4):277-283. doi:10.1016/j.therap.2021.05.004
6. Fathizadeh H, Afshar S, Masoudi MR, et al. SARS-CoV-2 (Covid-19) vaccines structure, mechanisms and effectiveness: A review. Int J Biol Macromol. 2021;188:740-750. doi:10.1016/j.ijbiomac.2021.08.076
7. Van der Schyf CJ. The use of multi-target drugs in the treatment of neurodegenerative diseases. Expert Rev Clin Pharmacol. 2011;4(3):293-8. doi: 10.1586/ecp.11.13.
8. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care. 2013; 19:17(2):R76. doi: 10.1186/cc12685.

9. Nguyen-Thanh Q, Trésallet C, Langeron O, Riou B, Menegaux F. Les polytraumatismes sont plus graves après chute d'une grande hauteur qu'après accident de la voie publique [Polytrauma is more severe after a free fall from a height than after a motor vehicle accident]. Ann Chir. 2003;128(8):526-9. doi: 10.1016/s0003-3944(03)00208-6. PMID: 14559303.
10. Cannizzaro, E., Plescia, F., Cirrincione, L., Lo Pinto, E., Plescia, F. Sport for job. Differences in cortisol levels in a water polo team at different times of workout. EuroMediterranean Biomedical Journal, 2018, 13(41), pp. 181–184
11. Soleo, L., Cannizzaro, E., Lovreglio, P., ...D'Errico, M.N., Pira, E. Protocols for the health surveillance | Protocolli per la sorveglianza sanitaria dei lavoratori della pesca. Giornale Italiano di Medicina del Lavoro ed Ergonomia, 2013, 35(4), pp. 222–226
12. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017;1:80(1):6-15. doi: 10.1227/NEU.0000000000001432.
13. Groswasser Z, Cohen M, Blankstein E. Polytrauma associated with traumatic brain injury: incidence, nature and impact on rehabilitation outcome. Brain Inj. 1990;4(2):161-6. doi: 10.3109/02699059009026161.
14. Ledda C, Cannizzaro E, Cinà D, Filetti V, Vitale E, Paravizzini G, Di Naso C, Iavicoli I, Rapisarda V. Oxidative stress and DNA damage in agricultural workers after exposure to pesticides. J Occup Med Toxicol. 2021 Jan 7;16(1):1. doi: 10.1186/s12995-020-00290-z. PMID: 33413467; PMCID: PMC7791774.
15. Greenwald BD, Kapoor N, Singh AD. Visual impairments in the first year after traumatic brain injury. Brain Inj. 2012;26(11):1338-59. doi: 10.3109/02699052.2012.706356. Epub 2012 Aug 16. PMID: 22897509.
16. Hackenberg K, Unterberg A. Schädel-Hirn-Trauma [Traumatic brain injury]. Nervenarzt. 2016 Feb;87(2):203-14; quiz 215-6. German. doi: 10.1007/s00115-015-0051-3.
17. Gallun FJ, Papesh MA, Lewis MS. Hearing complaints among veterans following traumatic brain injury. Brain Inj. 2017;31(9):1183-1187. doi: 10.1080/02699052.2016.1274781.
18. Plescia F, Salvago P, Dispenza F, Messina G, Cannizzaro E, Martines F. Efficacy and Pharmacological Appropriateness of Cinnarizine and Dimenhydrinate in the Treatment of Vertigo and Related Symptoms. Int J Environ Res Public Health. 2021;18(9):4787. doi: 10.3390/ijerph18094787.
19. Roup CM, Ross C, Whitelaw G. Hearing Difficulties as a Result of Traumatic Brain Injury. J Am Acad Audiol. 2020;31(2):137-146. doi: 10.3766/jaaa.18084.
20. Das M, Tang X, Mohapatra SS, Mohapatra S. Vision impairment after traumatic brain injury: present knowledge and future directions. Rev Neurosci. 2019;30(3):305-315. doi: 10.1515/revneuro-2018-0015.
21. Plescia F, Cannizzaro C, Plescia F, Lavanco G, Salvago P, Martines F, Brancato A, Cavallaro A. Pharmacological treatment of sensorineural hearing loss. Sensorineural Hearing Loss: Pathophysiology, Diagnosis and Treatment. 2019; 281-297. ISBN 978-153615049-0, 978-153615048-3
22. Brancato A, Lavanco G, Cavallaro A, Plescia F, Cannizzaro C. Acetaldehyde, Motivation and Stress: Behavioral Evidence of an Addictive ménage à trois. Front Behav Neurosci. 2017;11:23. doi: 10.3389/fnbeh.2017.00023.
23. Cannizzaro E, Ramaci T, Cirrincione L, Plescia F. Work-Related Stress, Physio-Pathological Mechanisms, and the Influence of Environmental Genetic Factors. Int J Environ Res Public Health. 2019;16(20):4031. doi: 10.3390/ijerph16204031.
24. Cannizzaro E, Cirrincione L, Mazzucco W, Scorciapino A, Catalano C, Ramaci T, Ledda C, Plescia F. Night-Time Shift Work and Related Stress Responses: A Study on Security Guards. Int J Environ Res Public Health. 2020; 17(2):562. doi: 10.3390/ijerph17020562..
25. Castelli V, Lavanco G, Brancato A, Plescia F. Targeting the Stress System During Gestation: Is Early Handling a Protective Strategy for the Offspring? Front Behav Neurosci. 2020;14:9. doi: 10.3389/fnbeh.2020.00009.
26. Plescia F, Cirrincione L, Martorana D, Ledda C, Rapisarda V, Castelli V, Martines F, Vinnikov D, Cannizzaro E. Alcohol Abuse and Insomnia Disorder: Focus on a Group of Night and Day Workers. Int J Environ Res Public Health. 2021;18(24):13196. doi: 10.3390/ijerph182413196.
27. Vitale E, Ledda C, Adani R, Lando M, Bracci M, Cannizzaro E, Tarallo L, Rapisarda V. Management of High-Pressure Injection Hand Injuries: A Multicentric, Retrospective, Observational Study. J Clin Med. 2019;8(11):2000. doi: 10.3390/jcm8112000.
28. Nauth A, Hildebrand F, Vallier H, Moore T, Leenen L, Mckinley T, Pape HC. Polytrauma: update on basic science and clinical evidence. OTA Int. 2021;4(1):e116. doi: 10.1097/OI9.0000000000000116.
29. Della Torre V, Badenes R, Corradi F, Racca F, Lavinio A, Matta B, Bilotta F, Robba C. Acute respiratory distress syndrome in traumatic brain injury: how do we manage it? J Thorac Dis. 2017;9(12):5368-5381. doi: 10.21037/jtd.2017.11.03..
30. Morrison JJ, Ross JD, Markov NP, Scott DJ, Spencer JR, Rasmussen TE. The inflammatory sequelae of aortic balloon occlusion in hemorrhagic shock. J Surg Res. 2014 Oct;191(2):423-31. doi: 10.1016/j.jss.2014.04.012. Epub 2014 Apr 13. PMID: 24836421
31. Jungner M, Grände PO, Mattiasson G, Bentzer P. Effects on brain edema of crystalloid and albumin fluid resuscitation after brain trauma and hemorrhage in the rat. Anesthesiology. 2010;112(5):1194-203. doi: 10.1097/ALN.0b013e3181d94d6e..
32. Dobscha SK, Campbell R, Morasco BJ, Freeman M, Helfand M. Pain in Patients with Polytrauma: A Systematic Review [Internet]. Washington (DC): Department of Veterans Affairs (US); 2008 Sep. PMID: 21155208.
33. Lee GG, Park JS, Kim HS, Yoon DS, Lim JH. Clinical effect of preoperative intravenous non-steroidal anti-inflammatory drugs on relief of postoperative pain in patients after laparoscopic cholecystectomy: Intravenous ibuprofen vs. intravenous ketorolac. Ann Hepatobiliary Pancreat Surg. 2022 Mar 10. doi: 10.14701/ahbps.21-151. Epub ahead of print.
34. Koenig KL, Hodgson L, Kozak R, Jordan K, Sexton TR, Leiken AM. Ketorolac vs meperidine for the management of pain in the emergency department. Acad Emerg Med. 1994;1(6):544-9. doi: 10.1111/j.1553-2712.1994.tb02550.x.

35. Kettler E, Brennan J, Coyne CJ. The effects of a morphine shortage on emergency department pain control. Am J Emerg Med. 2021;43:229-234. doi: 10.1016/j.ajem.2020.03.010.
36. Clattenburg EJ, Nguyen A, Yoo T, Flores S, Hailozian C, Louie D, Herring AA. Intravenous Lidocaine Provides Similar Analgesia to Intravenous Morphine for Undifferentiated Severe Pain in the Emergency Department: A Pilot, Unblinded Randomized Controlled Trial. Pain Med. 2019;20(4):834-839. doi: 10.1093/pm/pny031.
37. Goett R, Todd KH, Nelson LS. Addressing the Challenge of Emergency Department Analgesia: Innovation in the Use of Opioid Alternatives. J Pain Palliat Care Pharmacother. 2016;30(3):225-7. doi: 10.1080/15360288.2016.1209612.
38. Hui D, Bruera E. A personalized approach to assessing and managing pain in patients with cancer. J Clin Oncol 2014;32:1640-6.
39. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: a clinical review. JAMA. 2014;312(8):825-36. doi: 10.1001/jama.2014.9405.
40. Dobscha SK, Campbell R, Morasco BJ, et al. Pain in Patients with Polytrauma: A Systematic Review [Internet]. Washington (DC): Department of Veterans Affairs (US); 2008 Sep. EXECUTIVE SUMMARY. Available from: https://www.ncbi.nlm.nih.gov/books/NBK49095/
41. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. J Pain Palliat Care Pharmacother. 2002;16(3):27-35. doi: 10.1080/j354v16n03_03.
42. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: a systematic review. Acta Anaesthesiol Scand. 201;55(6):638-43. doi: 10.1111/j.1399-6576.2011.02446.x.
43. Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol. 2008;(182):313-33. doi: 10.1007/978-3-540-74806-9_15.
44. Nordt SP, Clark RF. Midazolam: a review of therapeutic uses and toxicity. J Emerg Med. 1997;15(3):357-65. doi: 10.1016/s0736-4679(97)00022-x.
45. Sahinovic MM, Struys MMRF, Absalom AR. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. Clin Pharmacokinet. 2018;57(12):1539-1558. doi: 10.1007/s40262-018-0672-3.
46. Chidambaran V, Costandi A, D'Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. CNS Drugs. 2015;29(7):543-63. doi: 10.1007/s40263-015-0259-6. Erratum in: CNS Drugs. 2018;32(9):873.
47. Häusler G, van der Vet PCR, Beeres FJP, Kaufman T, Kusen JQ, Poblete B. The impact of loco-regional anaesthesia on postoperative opioid use in elderly hip fracture patients: an observational study. Eur J Trauma Emerg Surg. 2021 May 7. doi: 10.1007/s00068-021-01674-4. Epub ahead of print.
48. Chaudet A, Bouhours G, Rineau E, Hamel JF, Leblanc D, Steiger V, Lasocki S. Impact of preoperative continuous femoral blockades on morphine consumption and morphine side effects in hip-fracture patients: a randomized, placebo-controlled study. Anaesthesia, critical care & pain medicine. 2016;35(1):37–43. https://doi.org/10.1016/j.accpm.2015.07.004.
49. Riddell M, Ospina M, Holroyd-Leduc JM. Use of femoral nerve blocks to manage hip fracture pain among older adults in the emergency department: a systematic review. CJEM. 2016;18(4):245–52. https://doi.org/10.1017/cem.2015.94.
50. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232-5.
51. Chaiamnuay S, Allison JJ, Curtis JR. Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. Am J Health Syst Pharm. 2006;63(19):1837-51.
52. Maslin B, Lipana L, Roth B, Kodumudi G, Vadivelu N. Safety Considerations in the Use of Ketorolac for Postoperative Pain. Curr Drug Saf. 2017;12(1):67-73. doi: 10.2174/1574886311666160719154420.
53. DeAndrade JR, Maslanka M, Maneatis T, Bynum L, Burchmore M. The use of ketorolac in the management of postoperative pain. Orthopedics. 1994;17(2):157-66. doi: 10.3928/0147-7447-19940201-11.
54. Chandrasekharan NV, Dai H, Roos KL et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci USA 2002;99: 13926–13931.
55. Warner TD, Mitchell JA. Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum? Proc Natl Acad Sci USA 2002;99: 13371–13373.
56. Pickering G, Loriot MA, Libert F et al. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther 2006; 79: 371–378.
57. Sutera FM, De Caro V, Cannizzaro C, Giannola LI, Lavanco G, Plescia F. Effects of DA-Phen, a dopamine-aminoacidic conjugate, on alcohol intake and forced abstinence. Behav Brain Res. 2016;310:109-18. doi: 10.1016/j.bbr.2016.05.006.
58. Bisogno T. Endogenous cannabinoids: structure and metabolism. J Neuroendocrinol. 2008;20 Suppl 1:1-9. doi: 10.1111/j.1365-2826.2008.01676.x.
59. Gühring H, Hamza M, Sergejeva M, Ates M, Kotalla CE, Ledent C, Brune K. A role for endocannabinoids in indomethacin-induced spinal antinociception. Eur J Pharmacol. 2002;454(2-3):153-63. doi: 10.1016/s0014-2999(02)02485-8.
60. Plescia F, Sardo P, Rizzo V, Cacace S, Marino RA, Brancato A, Ferraro G, Carletti F, Cannizzaro C. Pregnenolone sulphate enhances spatial orientation and object discrimination in adult male rats: evidence from a behavioural and electrophysiological study. Behav Brain Res. 2014;258:193-201. doi: 10.1016/j.bbr.2013.10.026.
61. Kelley BG, Thayer SA. Anandamide transport inhibitor AM404 and structurally related compounds inhibit synaptic transmission between rat hippocampal neurons in culture independent of cannabinoid CB1 receptors. Eur J Pharmacol. 2004;496(1-3):33-9. doi: 10.1016/j.ejphar.2004.06.011.
62. Zygmunt PM, Chuang H, Movahed P, Julius D, Högestätt ED. The anandamide transport inhibitor AM404 activates vanilloid receptors. Eur J Pharmacol. 2000;396(1):39-42. doi: 10.1016/s0014-2999(00)00207-7.

63. Cavallaro A, Martines F, Cannizzaro C, Lavanco G, Brancato A, Carollo G, Plescia F, Salvago P, Cannizzaro E, Mucia M, Rizzo S, Martini A, Plescia F. Role of cannabinoids in the treatment of Tinnitus. Acta Medica Mediterranea. 2016; 32(4), Pages 903 – 909. DOI:10.19193/0393-6384_2016_4_108
64. Plescia F, Plescia F, Raffa D, Cavallaro A, Lavanco G, Maggio B, Raimondi MV, Daidone G, Brancato A, Cannizzaro C. The role of (E)-6-chloro-3-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-2-styrylquinazolin-4(3H)-one in the modulation of cannabinoidergic system. A pilot study. Pharmacol Rep. 2018;70(6):1124-1132. doi: 10.1016/j.pharep.2018.06.004.
65. Freye E, Levy JV. Mechanism of Action of Opioids and Clinical Effects. Opioids in Medicine. 2008:85–187. doi: 10.1007/978-1-4020-5947-6_2.
66. Singh DR, Nag K, Shetti AN, Krishnaveni N. Tapentadol hydrochloride: A novel analgesic. Saudi J Anaesth. 2013;7(3):322-6. doi: 10.4103/1658-354X.115319.
67. Freo U, Romualdi P, Kress HG. Tapentadol for neuropathic pain: a review of clinical studies. J Pain Res. 2019 ;12:1537-1551. doi: 10.2147/JPR.S190162.
68. Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. Br J Anaesth. 2014;113(1):148-56. doi: 10.1093/bja/aeu056.