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The role of cannabinoids in pain management

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SUMMARY

Settings: In a wide number of diseases, the presence of pain is a frequent complains, and nowadays pain is considered a public health problem. During the last decade diverse drugs for pain control had been introduced in the Mexican market. In the last five years studies which evaluate the usefulness of cannabinoids in pain management had been performed. For that reason the objective of this document is to evaluate the available medical literature regarding the usefulness of cannabinoids for pain management. **Method:** A search of available medical literature of studies which evaluate the usefulness of cannabinoids in pain management was made using the Pubmed/Medline database. Studies which documented that association were considered for analysis. **Results:** 208 documents were identified and only 41 met the criteria for possible analysis. From those studies only 24 documented the administration of a cannabinoid and the presence or absence of analgesia or pain relief. In the 24 documents 31 interventions were identified, and 23 interventions showed a favorable analgesia. **Conclusions:** These results suggest that the administration of cannabinoids for pain relief might have a possible therapeutic benefice. However, more studies which document this association are needed.

Key words: Chronic pain, cannabinoids, magement, neuropathic.

RESUMEN

Marco situacional: *El dolor es una eventualidad en diversos tipos de enfermedades y es considerado actualmente como un problema de salud pública. En la última década se han introducido diversos fármacos en el mercado mexicano que han demostrado su utilidad en el manejo de diversos tipos de dolor. Durante los últimos cinco años se han realizado diversos estudios que evalúan la utilidad de los canabinoides en el manejo del dolor. Por ello, el objetivo del presente trabajo es evaluar la literatura médica disponible con respecto a la utilidad de los canabinoides para el alivio del dolor.* ***Método:*** *Se realizó una búsqueda de la literatura médica disponible en la base de datos Pubmed/Medline de documentos en los que se evaluó la utilidad de los canabinoides en el alivio del dolor. Se consideró para su análisis a aquellos documentos en los que se evidenciara dicha asociación.* ***Resultados:*** *De los 208 documentos identificados, sólo 41 eran susceptibles de análisis. De éstos sólo 24 documentaban la administración de canabinoides y la presencia o ausencia de alivio del dolor o analgesia. En estos 24 documentos se encontraron 31 intervenciones (administración de canabinoides), encontrando analgesia favorable en 23 de ellos.* ***Conclusiones:*** *Los resultados sugieren que la utilización de canabinoides en el alivio del dolor posiblemente presente algún beneficio terapéutico. Sin embargo, aún se requieren nuevos estudios que proporcionen más evidencia acerca de esta asociación.*

Palabras clave: *Dolor crónico, canabinoides, tratamiento, neuropático.*

INTRODUCTION

Statistical generalities about chronic pain in Mexico

Pain is a frequent event in diverse type of diseases, and its presence considerably affects life conditions of people suffering from it. Furthermore, pain alters people's social, family, economic and psycho-affective background.

We know that cancer is one of the main causes of death among Mexican population, and it has been identified that it is related to the 12.7% of the deaths in this country[1]. Along with its high incidence, it has been documented that about 80% of the patients with cancer will present hard pain before dying[2].

Diabetes mellitus[1] is another important cause of mortality in Mexican population. It has been estimated that its national prevalence in the general population is of a 8%[3], and international studies have reported that around the 24% of these patients will develop painful diabetic polyneuropathy[4]. In this reference context, two-million Mexican people suffer from neurogenic or neuropathic-type pain due to this cause[5].

On the other hand, it has been suggested that, currently, chronic pain is a public health problem at the international level[6]. It has been reported that it presents an international incidence of between the 8% to the 80%[7] and an average prevalence of the 15%[8] in the general population. With this information, we are able to express that almost 15.5 million Mexican people suffer from chronic pain.

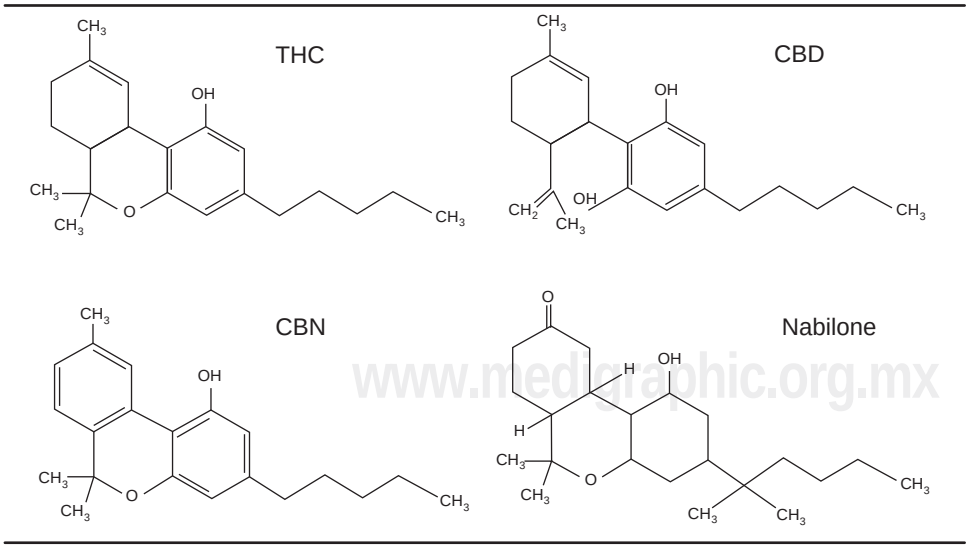
Furthermore, it is a well-known fact that around 4.3-million Mexican people were admitted to hospital during 2003[9]. In this sense, a national study revealed that the 96.3% of the patients presented acute pain[10]. In this context, 3.3-million Mexicans are believed to present this type of pain during their hospital stay.

This data suggests that pain presence is a national problem that requires attention at different levels. The aforementioned fact has been already reported by diverse national groups, which have proposed practice parameters or management guides that may orient the physician with regard to pain relief in different contexts[5,11,13].

On the another hand, and since that recently many medicines have been introduced in our country, it is necessary to evaluate different options with this purposed aim, because several drugs will be soon available in our country in the close future.

Generalities about cannabinoids and their use to relieve pain

It is called cannabinoid «every ligand of cannabinoid receptors and its related compounds, including receptor endogen ligands and synthetic analogues». There are over 60 cannabinoids in the leaves and the top flowers of the *Cannabis sativa* plant (marihuana). The compounds that present the highest identifiable activity are: (a) delta-9-tetrahydrocannabinol or THC, (b) canabinnol and (c) cannabidiol or CBD (Figure 1)[14].



Abreviations:
THC, delta-9-tetrahydrocannabinol. CBN, canabinnol. CBD, cannabidiol

Figure 1. Chemical structure of cannabinoids.

It has been proposed that the action of cannabinoid receptors type 1 (CBr1): (a) inhibits GABA receptors; (b) disinhibits dopominergic receptors type 2 (D2) and alfa2-adrenergics, (c) blocks serotoninergic receptors (5-HT) y (d) synergizes the activity of opiate receptors[14].

Because of that reason, it has been reported that cannabinoids probably present a place in pain treatment. However, the use of this set of drugs has been controversial due to diverse social and legal implications that have underestimated their clinical usefulness.

In spite of the possible controversy with regard to their use, this group of medicines has been approved for the treatment of pain caused by multiple sclerosis in the United Kingdom and Canada (Table I).. Moreover, a Canadian study has identified that from the 10% to the 15% of the patients with chronic pain use herbal cannabis to relieve their pain[15].

Recent studies about the use of cannabinoids in pain relief suggest that a possible benefic therapeutic effect after their administration.[16] In the same way, it has been reported that the employment of cannabinoids for the control of symptoms in patients suffering from AIDS[17] and cancer [18] might be very useful.

Despite the possible benefits associated to the use of these drugs, in Mexico we lack epidemiological studies documenting (a) herbal cannabis consumption for pain relief in patients suffering from chronic pain, (b) cannabinoids consumption for the control of symptoms in AIDS or cancer patients, and (c) the usefulness of these drugs for pain relief or symptom relief.

Table I. Cannabinoids approved to use in medicine.

Pharmaco	Country	Approbation
THC (synthetic:	Canada	NVqt
dronabinol)	UK	NVqt
CN: Marinol	US	NVqt
THC + Cannabidiol	Canada	NVqt
CN: Sativex/Canador		Pain by MS
	UK	NVqt
		Pain by MS
Nabilone	Canada	NVqt
CN: Cesamet	UK	NVqt
	US	NVqt
	Mexico	NVqt
		Adjuvant chronic pain

Abreviations: (NVqt) nausea and/or vomit by chemotherapy. (MS) multiple sclerosis. (CN) commercial name.

Because of the facts mentioned above, the objective of the present study is to review the available medical literature regarding the usefulness of cannabinoids for pain relief.

METHOD

It was carried out a search in PubMed/Medline database, localizing those documents that in their title or abstract presented the following words: (a) the «cannab» root, and (b) pain.

The results were restricted to those articles with the following characteristics: (a) clinical studies, (b) controlled clinical studies, (c) meta-analysis, (d) management guides, and (e) review articles. Several articles from different languages and diverse publication dates were reviewed (Figure 2).

We analyzed those documents focused on the relationship between the intervention performing (administration of drugs with cannabinoid action) and the final result (pain relief/analgesia achievement). The final result was categorized through the four-point Likert Scale. (0 = analgesia absence, 1 = light analgesia, 2 = moderate analgesia, 3 = proper analgesia).

The obtained results were analyzed though descriptive statistics. The parametric variables were analyzed through the Student's «t» test, and the non-parametric variables through the Chi-square test. The analysis was carried out through a program for PC (personal computer) compatible with Windows (SPSS v.12.0, SPSS, Inc, Chicago, Illinois, USA).

RESULTS

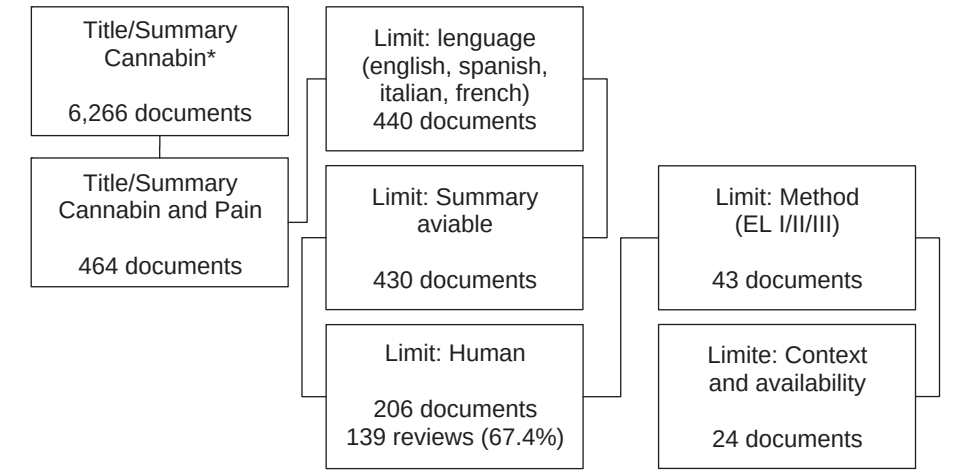
Results regarding the literature search

Two-hundred and eight papers were consulted. These articles included selection criteria and search limits. It is important to say that the 80.2% of them (167 out of 208) are review articles. In the same way, only 41 studies present the following methodology: (a) meta-analysis/ systematized reviews, (b) controlled clinical studies, (c) non-controlled, and (d) series of cases.

From the 41 studies whose methods presented the possibility of practicing analysis, only 24 of them were focused on the relationship between the intervention (administration of drugs with cannabinoid action) performing and final result (pain relief/analgesia achievement). The findings from these studies are resumed in table II, and their references are reported in **Appendix 1**.

Results with regard to the type of interventions

In the 24 analyzed papers, we found 31 interventions (drug administration with cannabinoid effect). From these publi-



Abbreviations:
EL: evidence level.

Figure 2. Flowchart of bibliographical search.

cations, 23 presented favorable comments about analgesic effect, and eight of them referred effects against it ($p = 0.000$). From the interventions that presented analgesic action, 14 had a moderate effect, and nine had a proper analgesic action ($p = 0.05$).

Nine drugs with cannabinoid effect were identified in the 31 analyzed interventions. The results from each report were distributed in the following way (Figure 3):

(a) Delta-9-tetrahidrocanabinol (THC) was administered in 14 interventions and favorable results were observed in 11 (72.7%) of them. This difference had no statistical difference.
(b) The combination of THC plus cannabidiol was given in three cases and it presented proper results in the 100% of the interventions.
(c) Cannabis extract was used in two cases and it showed favorable results in the 100% of them.
(d) Nabilone was given in three interventions and it presented favorable results in three cases. It is important to remark that the study identifying analgesia absence is framed in the context of peri-operative pain.
(e) Dronabinol was used in two interventions and it presented favorable results in the 100% of the cases.
(f) Marihuana cigarette was used in two interventions, and it presented favorable results in only one of them.
(g) Benzopirene pyridine was given in three interventions and it presented favorable results in all of them.
(h) CT-3 (THC analog) was given in one intervention, achieving favorable results.
(i) Levonantradol (synthetic cannabinoid) was administered in one intervention, with favorable results.

Results regarding type of pain

From the 24 analyzed articles, the focus on pain was distributed in the following way: (a) 41.6% (10 out of 24) in neuropathic pain; (b) 29.1% (7 out of 24) in acute pain; (c) 12.5% (3 out of 24) in chronic pain; (d) 12.5% (3 out of 24) in pain caused by cancer; and (e) just one paper (4.1%) corresponded to a systematized review including articles about chronic and acute pain in its methodology. These differences had no statistical significance.

With respect to the 31 interventions and the studied type of pain, the results were distributed in the following form (Figure 4): (a) 35.5% (11 out of 31), in neuropathic pain; (b) 25.8% (8 out of 31) in acute pain; (c) 9.7% (3 out of 31) in chronic pain; (d) 19.4% (6 out of 31) in pain due to cancer; and (e) 9.7% (3 out of 31) in non-specific pain. These differences did not present any statistical significance.

Neuropathic (neurogenic) pain

Regarding cannabinoid administration and pain relief or analgesia achievement in the context of neurogenic pain, analgesia was observed in 10 out of the analyzed interventions. This difference was not statistically significant.

In the interventions that demonstrated analgesia, it was observed the following trend: (a) 6 cases with proper analgesia; (b) 4 interventions with moderate analgesia; and (c) one case with absence of analgesia. These differences were not statistically significant.

Table II. Summary of documents located in the literary search.

Author	Year	Tipe of study	Drug	Dose/day/route	Result
Noyes, et al.	1975	II	THC	10 mg O	Pain by cancer Moderate analgesia Important adverse effects
				20 mg O	Pain by cancer Moderate analgesia Less adverse effects
Noyes, et al.	1975	III	THC	15 mg O	Pain by cancer Moderate analgesia Important adverse effects
				20 mg O	Pain by cancer Moderate analgesia Important adverse effects
Raft, et al.	1977	II	THC	0.022 mg/kg IV	Acute pain (dental) Moderate analgesia Better tolerance
				0.044 mg/kg IV	Acute pain (dental) Moderate analgesia Less tolerance
Gottschalk, et al.	1977	III	Cigarette marijuana (THC)	0.05 mg INH	Acute pain (angor pectoris) No analgesia Contraindicated in case of coronary disease.
Jochimsen, et al.	1978	II	Benzopyranpyridine (analog THC)	2 mg O	Pain by cancer No analgesia Increase pain perception
				4 mg O	Pain by cancer No analgesia Increase pain perception
Maurer, et al.	1990	III	THC	5 mg O	Neuropathic pain (spinal cord injury and ME) Adequate analgesia No identified (AE)
Holdcroft, et al.	1997	III	THC	50 mg O	Acute pain (MF) Adequate analgesia It was used like adjuvant analgesic, was observed a decrease in analgesic base. No identified (AE)
Campbell, et al.	2001	I	THC	5-20 mg O	Acute and chonic pain Analgesia similar to codeine (50-120 mg) common AE
			Levonantradol	1.5-3 mg IM	Acute and chonic pain Analgesia similar to codeine (50-120 mg) common AE
			Benzopyranpyridine	2-4 mg	Acute and chonic pain Minor analgesia to codeine (60-120 mg) Analgesia similar to placebo, common AE
Ware, et al.	2002	IV	Cigarette marijuana (THC)	NR INH	Chronic pain Adequate analgesia Relief to the pain with low doses of inhaled cannabis No identified (AE)

Table II continuation.

Wade, et al.	2003	II	THC	2.5-120 mg INH (Spray)	Neuropathic pain Adequate analgesia AE common in ambulatory patients
Naef, et al.	2003	II	THC	20 mg O	Acute pain (experimental) No analgesia AE common and moderate
Karst, et al.	2003	II	CT-3 (analog THC)	40 mg O	Neuropathic pain Adequate analgesia AE absence majors
Buggy, et al.	2003	II	THC	5 mg O	Acute pain (perioperatory) No analgesia AE absence majors
Zajicek, et al.	2003	II	THC	NR O	Neuropathic pain (ME) Moderate analgesia AE absence majors
			Extract of Cannabis (Análogo THC)	10 mg O	Neuropathic pain (ME) Moderate analgesia AE absence majors
Attal, et al.	2004	II	THC	25 mg O	Neuropathic pain (refractory) No analgesia Retirement of 5 patients by AE
Svendsen, et al.	2004	II	Dronabinol	10 mg O	Neuropathic pain (ME) Adequate analgesia Presence of EA
Wade, et al.	2004	II	THC + Cannabidiol	2.5-120 mg O	Neuropathic pain (ME) Adequate analgesia AE absence majors
Svendsen, et al.	2005	II	Dronabinol	10 mg O	Neuropathic pain (ME) Moderate analgesia Moderate AE
Rog, et al.	2005	II	THC + Cannabidiol	2.7:2.5 mg INH (Spray)	Neuropathic pain (ME) Moderate analgesia Moderate AE
Blake, et al.	2006	II	THC + Cannabidiol	2.7:2.5 mg INH (Spray)	Chronic pain (RA) Moderate analgesia Moderate AE
Holdcroft, et al	2006	II	Extract of Cannabis (Análogo THC)	5-15 mg O In scaling	Acute pain (perioperative) Moderate analgesia Dependent AE of the dose, they forced the completion from the study when climbing to 15 mg/day
Pinsger, et al.	2006	II	Nabilone	1-4 mg O	Chronic pain Adequate analgesia AE absence majors
Beaulien P.	2006	II	Nabilone	10 mg O	Acute pain (postoperative) No analgesia Presence of EA
Wissel, et al.	2006	II	Nabilone	1 mg O	Neuropatic pain (ME) Adequate analgesia AE absence majors

Abbreviation: THC, delta-9-tetrahydrocannabinol. AE: adverse effects . NR, not reported. MF, mediterranean fever. NP, neuropathic pain. ME, multiple sclerosis . RA, rheumatoid arthritis. Routes of administration: O, oral. IV, Intravenous. INH, inhaled (smoke inhalation / nasal spray). Studies: Revised, N = 41/Eliminated, N = 17 (Total of analysed studies = 24). Type of studies: I, metaanalysis/systematic reviews. II, controlled clinical tests. III, no controlled clinical tests. IV, series of cases.

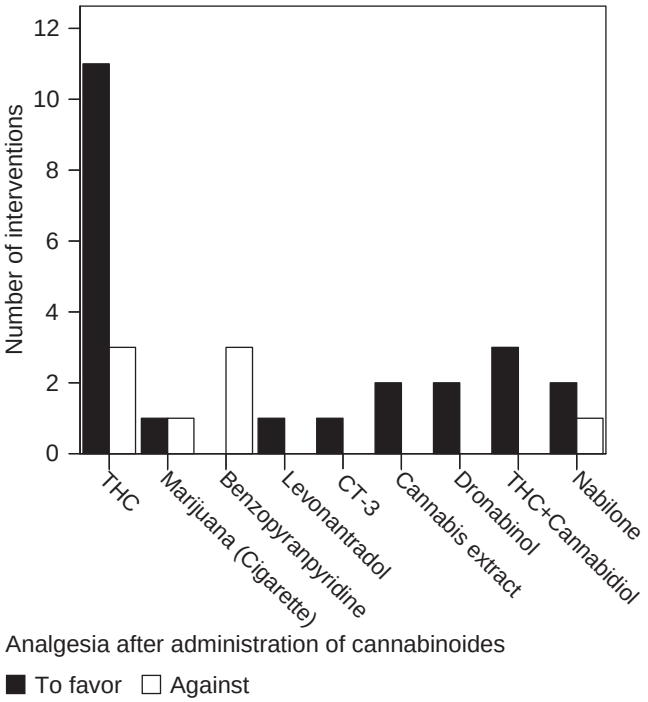


Figure 3. Absence or presence of analgesia with respect to the pain after the administration of a type of specific cannabinoide (N = 31).

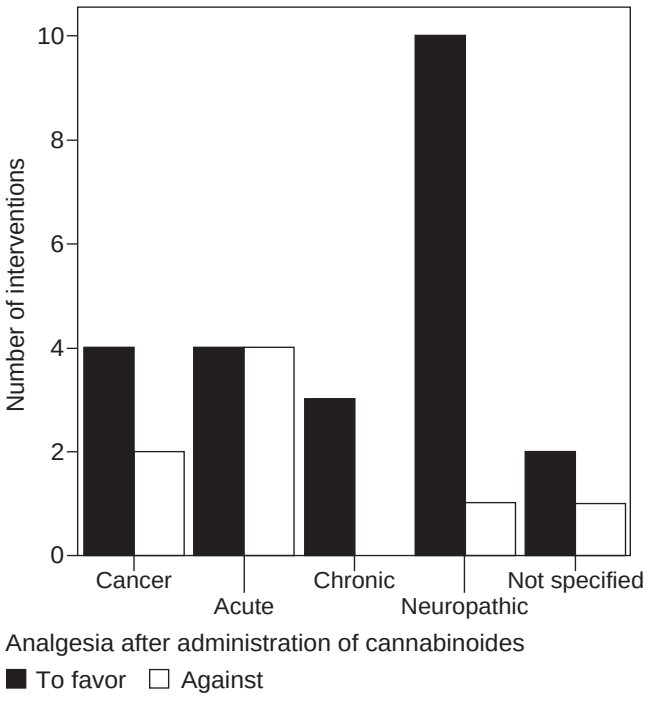


Figure 4. Absence or presence of analgesia with respect to the pain after the administration of cannabinoide (N = 31).

Acute pain

Regarding cannabinoid administration and pain relief or analgesia achievement in the context of acute pain, analgesia was observed in 4 out of 8 of the analyzed interventions.

In the interventions that demonstrated analgesia, it was observed the following trend: (a) only one case with proper analgesia; (b) 3 interventions with moderate analgesia; and (c) 4 cases without any analgesia. These differences were not statistically significant.

It is important to say that these studies place acute pain in different contexts: (a) dental (one study), (b) *angor pectoris* (one study), (c) Mediterranean fever (one study), (d) experimental study on healthy volunteers (one study), and (e) post-operative study (three studies).

From the three studies that evaluated post-operative pain, in two of them it was observed absence of analgesia; however, this difference was no statistically significant.

Pain caused by cancer

Regarding cannabinoid administration and pain relief or analgesia achievement in the context of pain caused by cancer, analgesia was observed in 4 out of 6 of the analyzed interventions.

In the interventions that demonstrated analgesia, it was observed the following trend: (a) six cases with proper analgesia; (b) 4 interventions with moderate analgesia; and (c) one case with no analgesia. These differences were not statistically significant.

Chronic pain

Regarding cannabinoid administration and pain relief or analgesia achievement in the context of pain caused by cancer, analgesia was observed in all of the three analyzed interventions.

In the interventions that demonstrated analgesia, it was observed the following trend: (a) two cases with proper analgesia; (b) one intervention with moderate analgesia; and (c) no case with any analgesia. These differences were not statistically significant.

It is important to remark that the previous studies do not specify pain etiology, and one of them is framed inside pain conditioned by rheumatoid arthritis.

DISCUSSION

The present work does not intend to be a systematized literature review. The obtained data could not be analyzed ac-

cording to our standards proposed by the Cochrane Group for the performing of systematized reviews[19].

However, it is important to outline that the use of herbal cannabis for therapeutic aims has been documented since a long time ago[20], despite the fact that the clinical studies showing this usefulness are scarce.

In fact, the 80.2% of the evaluated papers during the literature search corresponds to review articles. This fact supposes that the usefulness of cannabinoids in the context of pain relief requires a higher number of studies in order to state stronger conclusions.

Along with the aforementioned fact, only 24 studies evaluated their analgesic efficiency. From them, 31 interventions were identified. It calls our attention that in 23 of these mentioned interventions, it was observed the analgesia presence.

The fact above matches to the situations observed in other similar study[15] and it establishes the possibility that this group of drugs might be useful for pain management. However, the evidence analysis leads us to be more cautious and meticulous about the obtained results.

It is necessary to remark that 10 out of the 23 performed interventions where analgesia was observed, are focused on neuropathic or neurogenic pain. In six of them proper analgesia was reported, while in four interventions, moderate analgesia was reported.

It calls our attention that from the interventions that identified analgesia, 8 of them are focused on pain caused by multiple sclerosis (8 out of 10), and from the cases that identify proper analgesia in this context, 6 interventions correspond to pain produced by multiple sclerosis.

Upon the base of this information, it might be possible that cannabinoids produce relief for neurogenic pain caused by multiple sclerosis. In such a sense, in countries as the United Kingdom and Canada, this association matches to a single prescription for cannabinoids for pain relief[15].

On the other hand, in acute pain, it was found an important number of interventions (8 out of 31). Nevertheless, just the 50% of them presents favorable results. This fact possibly implies that the use of this group of drugs may be controversial for pain relief.

However, it is important to remark that the studies carried out regarding cannabinoid usefulness for acute pain, evaluate a wide range of conditions that are able to present this type of pain. If we focused on the context of peri-operative pain, we can say that only three studies report this kind of association, and only three of them show analgesia absence.

With regard to chronic pain, three interventions were also identified. In all of them, analgesia presence was observed. Two of them reported the presence of proper analgesia. In a very interesting way, the studies evaluating pain have generated certain conceptual controversies related to their definition and the fact that chronic pain can embrace a number of causes. Therefore, it may be possible that the role of cannabinoids in this context require a more extensive evaluation.

Regarding pain caused by cancer, six interventions were identified. In four of them, THC was used and in these cases, a proper analgesia was identified. In the two interventions using benzopirene pyridine, analgesia absence was reported, the fact mentioned above suggests that not every cannabinoid presents analgesic effects, and this phenomenon may be probably related to its affinity with receptors[20]. The fact before makes it necessary to perform a higher number of studies in order to achieve firmer conclusions.

It is elementary that Mexican physicians be informed about the diverse available analgesic choices, as well as about the role of each of them in the control of this painful syndrome. The aforementioned fact is especially relevant because, during the last decade, diverse drugs have entered the Mexican market, and currently we have more and more therapeutic options for the proper care of our patients.

In several countries, the use of cannabinoids has been approved for the management of diverse situations, such as for the treatment of syndromes associated to AIDS or cancer. Nevertheless, in the context of pain, there are only few approved drugs.

Despite the previous facts, the evidence indicates that the use of these drugs for pain relief might present beneficial effects. However, we should consider the entire available evidence before making up our own prescriptions. Through these actions, we will be able to provide good and efficient treatments for our patients' pain control.

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