ORIGINAL ARTICLE

AVAILABILITY OF INFORMATION TO THE POPULATION ON THE MAIN DRUGS USED FOR CHRONIC PAIN TREATMENT

DISPONIBILIDADE DE INFORMAÇÃO À POPULAÇÃO SOBRE OS PRINCIPAIS FÁRMACOS UTILIZADOS PARA O TRATAMENTO DA DOR CRÔNICA

Catarina Vidal de Moura, Sarah Silva Bezerra[1], Thais Milla Franco de Freitas[1], Joyce Ferreira Gomes de Oliveira[2], Raphaella Amanda Maria Leite Fernandes[3]

[1] Medical student at Centro Universitário Maurício de Nassau, [2] Student at Universidade de Pernambuco (UPE), Pernambuco, Brazil, [3] Academic coordinator of the Faculdade de Medicina de Olinda (FMO), Pernambuco, Brazil.

ABSTRACT

Introduction: Pain is defined as a sensory and emotional experience associated with actual or potential tissue damage or description of this damage. It is a common reason for seeking medical attention and negatively impacts daily activities. Also, pain is characterized as chronic when it persists for longer than three months, which does not require immediate tissue injury to trigger persistent painful stimuli. The lack of professional training and myths on pain management may lead to unwarranted fears, such as those related to the adverse effects of drugs. Therefore, adequate information is crucial for healthcare professionals and patients involved in managing chronic pain. **Objectives:** To evaluate the availability of information regarding pharmacological treatments of chronic pain for the general population, focusing on identifying limitations in patient information leaflets. **Methods:** Patient information leaflets were analyzed for indications related to chronic pain management, and four drug classes were included: anticonvulsants, tricyclic antidepressants, benzodiazepines, and selective serotonin reuptake inhibitors. **Results:** Of 62 drugs evaluated, 37 (59.68%) had publicly available information, whereas 25 (40.33%) did not. Among those with public information, 13 (35.14%) explicitly stated an indication for chronic pain management. **Conclusion:** A relevant knowledge gap exists among the general population due to limited or absent data on indications for chronic pain treatment in most patient information leaflets. Therefore, this topic requires further attention to enhance the understanding of health professionals and patients and improve chronic pain management.

Keywords: Chronic pain; Medicine package inserts; Access to information

RESUMO

Introdução: A dor é definida como uma experiência sensitiva e emocional, associada ao dano tecidual real ou potencial, ou à descrição desses danos. É uma causa frequente de busca ativa por atendimento médico, com impacto negativo nas atividades diárias. A dor é crônica quando tem duração maior que três meses e o seu mecanismo de ação não necessita de lesão instantânea para desencadear o estímulo álgico e contínuo. A falta de treinamento e os mitos podem levar, por exemplo, a medos descabidos dos efeitos adversos de medicações. Dessa forma, as informações adequadas são essenciais para todos os profissionais de saúde e pacientes envolvidos com o tratamento da dor crônica. **Objetivos:** Promover uma pesquisa da prevalência de informações disponíveis sobre o tratamento farmacológico das dores crônicas para a população em geral. Além disso, demonstrar a limitação dos dados contidos nas bulas medicamentosas e a disponibilidade de acesso da população a essas informações. **Métodos:** Foram analisadas bulas de medicamentos à procura de indicação para o tratamento da dor crônica. Foram consideradas 4 classes de fármacos utilizadas no tratamento da dor crônica, as quais são: anticonvulsivantes, antidepressivos tricíclicos, benzodiazepínicos e inibidores seletivos da recaptação de serotonina. **Resultados:** Dos 62 fármacos pesquisados, 37 (59,68%) estavam disponíveis para consulta gratuita, sendo 25 (40,33%) indisponíveis. Desses 37 disponíveis, 13 (35,14%) tinham indicação formal na bula para o tratamento de algum tipo de dor crônica. **Conclusão:** Existe um prejuízo para a população geral no conhecimento sobre condições dolorosas crônicas uma vez que as bulas, em sua maioria, têm restrição de dados ou a falta de indicações para o tratamento da dor crônica. Além disso, observa-se que é necessária uma melhor abordagem deste tema para os profissionais de saúde e pacientes, em especial, objetivando um manejo mais bem conduzido.

Palavras-chave: Dor crônica; Bulas de medicamentos; Acesso à informação

INTRODUCTION

According to the International Association for the Study of Pain, pain is defined as a sensory and emotional experience associated with actual or potential tissue damage or description of this damage. It is a prevalent, subjective, and personal symptom that ranks among the most common reasons for seeking medical attention and negatively affects daily activities, including work and leisure.[1-5]

Severe pain demands substantial investment from healthcare systems and commitment from patients and society, being recognized as a public health priority.[5,6]

In this sense, untreated chronic pain or inadequate treatment becomes a critical health issue due to the impairment of the quality of life and worsening of patients diseases, compromising their functionality.[7] Therefore, effective chronic pain management requires the identification of underlying pathophysiological mechanisms of pain and accurate diagnosis to ensure appropriate pharmacological strategies.[4,8]

In addition to the conventional analgesics, benzodiazepines, tricyclic antidepressants, anticonvulsants, and selective serotonin reuptake inhibitors (SSRI) are often employed in the chronic pain management.[8] Despite substantial evidence supporting the efficacy of numerous drugs for chronic pain treatment, many of them do not list chronic pain among their formal indications in the patient information leaflets.[1]

In this context, the lack of formal indication in patient information leaflets may lead to treatment nonadherence since patients may infer that the drug should not have been prescribed, abandoning the recommended treatment. Also, the lack of health professional training on chronic pain treatment may lead to inadequate management due to insecurity in prescribing these drugs.[7,9]

The limited availability of patient information leaflets for public consultation may hinder treatment adherence. Also, some leaflets have incomplete information, without a formal indication for chronic pain treatment.

This study aimed to evaluate the availability of public information on pharmacological treatments for chronic pain.

METHODS

This review analyzed publicly available patient information leaflets of drugs for chronic pain treatment. Four pharmacological classes were analyzed: benzodiazepines, anticonvulsants, tricyclic antidepressants, and SSRI.

Data were collected by retrieving patient information leaflets in full text or summary, in English or Portuguese. Data were analyzed using direct counting, and results were presented as comparative graphs.

RESULTS

This study evaluated benzodiazepines, anticonvulsants, tricyclic antidepressants, and SSRI. A total of 62 drugs were investigated; 37 (59.68%) had publicly available patient information leaflets, whereas 25 (40.33%) did not. Of the 37 drugs with available patient information leaflets, only 13 (35.14%) presented a formal indication for chronic pain treatment.

A categorical analysis using pharmacological classes revealed that the SSRI had the highest availability of patient information leaflets (100%), followed by anticonvulsants (70.58%), tricyclic antidepressants (57.14%), and benzodiazepines (46.87%).

Most drugs (64.86%) across all pharmacological classes had no formal indication for chronic pain treatment in their patient information leaflets. Moreover, of the six (100%) SSRI, only one (16.6%) mentioned the formal indication for chronic pain treatment, and of the twelve (70.58%) anticonvulsants with publicly available patient information leaflets, only five (29.41%) presented this formal indication. Of the four (57.14%) tricyclic antidepressants with available information, two (50%) presented indication for chronic pain treatment, and of the fifteen (46.87%) benzodiazepines, six (40%) presented an indication.

Discrepancies were observed between the number of drugs with indications for chronic pain treatment in patient information leaflets and scientific literature. Although all six (100%) SSRI had literature support for chronic pain treatment, only one (16.6%) included this indication in its patient information leaflet. For anticonvulsants, eight (66.66%) of twelve (70.58%) available drugs presented support in the literature for chronic pain treatment, whereas only five (41.66%) had a formal indication

in patient information leaflets. All four tricyclic antidepressants with publicly available patient information leaflets (57.14%) had literature support for chronic pain, but only two (50%) presented this indication in the patient information leaflets. Of the 15 (46.87%) benzodiazepines, 9 (60%) had recommendations supported by literature, whereas six (40%) presented formal indication for chronic pain in patient information leaflets.

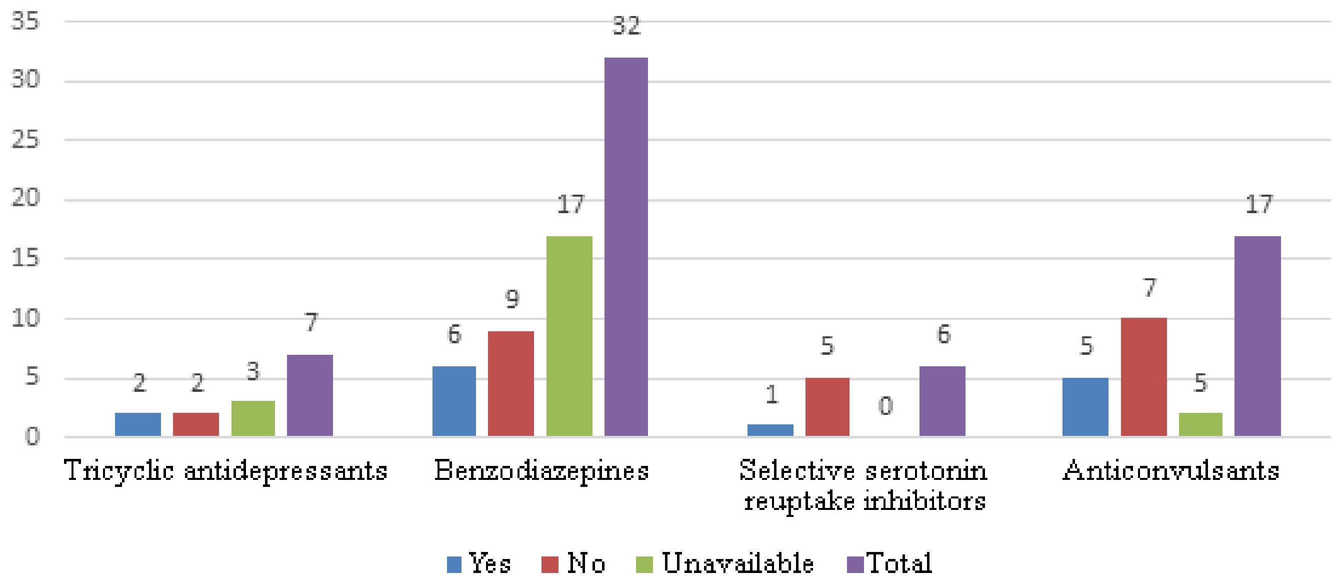

Figure 1. Prevalence of drugs with formal indication for chronic pain treatment. Blue: indication for chronic pain treatment stated in the patient information leaflet. Red: indication for chronic pain treatment supported by literature. Green: number of patient information leaflets unavailable for public consultation. Purple: total number of drugs in each pharmacological class.

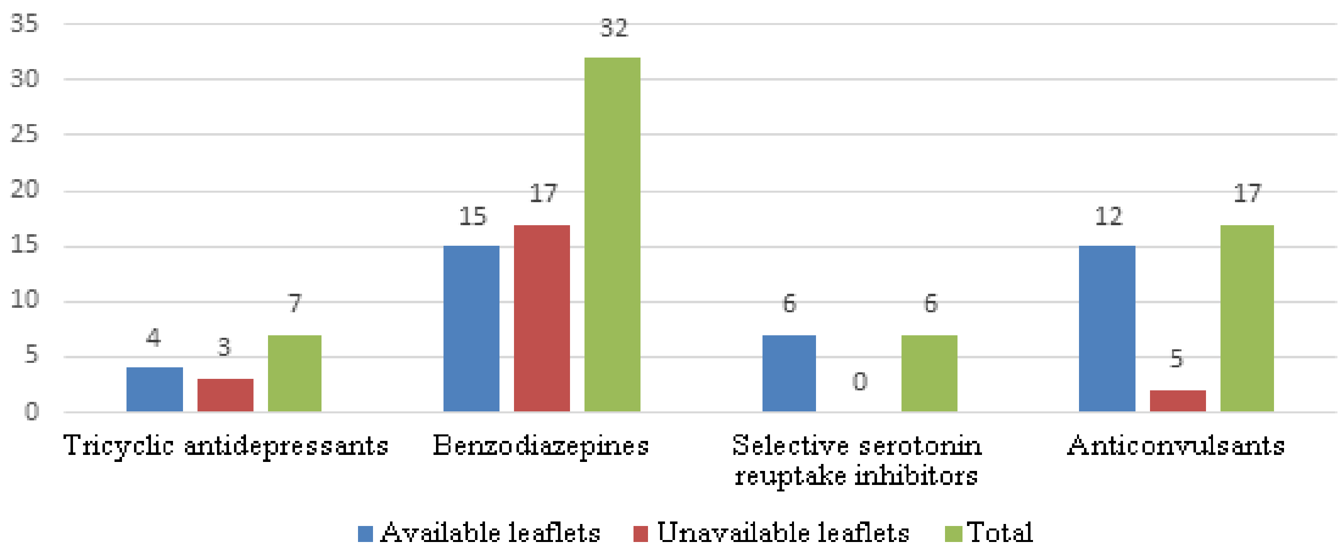

Figure 2. Public availability of patient information leaflets. Blue: number of drugs with publicly available patient information leaflets. Red: number of drugs without publicly available patient information leaflets. Green: total number of drugs per pharmacological class.

DISCUSSION

This study examined patient information leaflets from four major pharmacological classes commonly used in the treatment of chronic pain (i.e., benzodiazepines, anticonvulsants, tricyclic antidepressants, and SSRI). Also, a comparative analysis was conducted between the formal indications documented in the patient information leaflets and recommendations supported by scientific literature. Thus, this approach allowed a critical analysis of the importance of these drugs in chronic pain treatment and potential consequences of the lack of information and guidance for healthcare teams and the general population in managing this condition.

Adequate information regarding the mechanism of action of each drug is essential since many drugs used in chronic pain treatment require one or more weeks of continuous use to induce analgesic effects.[10] Thus, the absence of clear instructions may cause overdose or discontinuation of the treatment since patients may misinterpret a delayed therapeutic response as inefficacy. This issue is particularly exacerbated in countries or settings with limited resources, where health literacy levels are typically low.[11] Therefore, improved access to treatment indications in patient information leaflets is needed for understanding clinical management, nature of the disease, and adverse effects of the drugs, particularly tricyclic and tetracyclic antidepressants.

Tricyclic antidepressants

Tricyclic antidepressants are one of the most used adjuvant drugs in the chronic pain treatment. Also, amitriptyline, clomipramine, and nortriptyline at low doses exert direct analgesic effects in chronic pain and enhance the analgesia provided by other drugs.[3]

According to Hirsch and Birnbaum (2017)[10], the prescription of these drugs should consider their common adverse effects, the need to take them as prescribed rather than on an as-needed basis, and the expectation that a response or remission may not occur in less than four weeks after reaching the therapeutic dose. Amitriptyline, imipramine, desipramine, and nortriptyline are the most frequently prescribed tricyclic antidepressants in the United States, while clomipramine is commonly prescribed in Europe. Tricyclic antidepressants have different ranges of adverse effects, which are often considered when selecting the drug. Notably, nortriptyline and desipramine are generally better tolerated.[10]

The selection of a tricyclic antidepressant is generally guided by its adverse effects characteristics, which differ among the many available drugs. The tertiary tricycles, such as amitriptyline, clomipramine, doxepin, imipramine, and trimipramine, typically produce more adverse effects than other tricyclic antidepressants. Nortriptyline and desipramine generally have the best overall tolerability.[10]

Most antidepressants are dangerous in overdose, with toxicity generally linked to QT interval prolongation, which may lead to arrhythmia. An overdose of tricyclic antidepressants may also result in anticholinergic toxicity and seizures. In addition, these drugs are highly lipophilic and protein-bound; thus, they are not effectively removed by hemodialysis. Consequently, clinicians should avoid prescribing tricyclic antidepressants to outpatients at possible high risk for intentional overdose.[12]

In this context, tricyclic antidepressants provide actual therapeutic benefits for chronic pain conditions when properly prescribed (i.e., adequate treatment duration and dosage) since 100% of the drugs evaluated in the present study had indications documented in scientific literature. However, a relevant limitation was observed; only slightly over 50% of patient information leaflets were publicly available, distancing the information in literature from public access, especially for the affected population.

Selective serotonin reuptake inhibitors

SSRI are drugs that inhibit the serotonin reuptake, reducing the action of presynaptic serotonin reuptake transporter by 60% to 80%, which increases the availability of serotonin in the synaptic cleft and enhances the occupancy of postsynaptic serotonin receptors. Also, SSRI have little or no effect on the reuptake of other neurotransmitters, such as norepinephrine. The drug should not exert an effect on other reuptake mechanisms, receptors, or enzymes to be fully effective.[13] Escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are some examples of SSRI.[14]

In recent years, SSRI have emerged as potential alternative treatments for chronic pain due to their favorable profile and fewer adverse effects than other classes of antidepressants, particularly tricyclic antidepressants.[15]

Overall, SSRI have good tolerability, and

adverse effects include headache, nausea, gastrointestinal disturbances, fatigue, insomnia, anxiety, and depressive symptoms. The reviewed studies indicated that adverse effects occurred in 20% to 84% of patients; however, treatment was limited in only 0% to 41% of cases.[16]

This study analyzed patient information leaflets of six SSRI, revealing that only one (16.67%) had a formal indication for chronic pain. Although all SSRI are clinically used for chronic pain treatment, five (paroxetine, sertraline, escitalopram, fluvoxamine, and citalopram - 83.33%) lacked formal indications for this condition in the patient information leaflets. Thus, although all patient information leaflets of SSRI were publicly available, the findings underscored a critical need for alignment between scientific literature and regulatory documents since the absence of an indication for chronic pain treatment may contribute to patient nonadherence.

Anticonvulsants

Anticonvulsants act on ion channels, such as sodium and calcium, by blocking synaptic transmission involved in epileptic seizures and neuropathic pain since they have similar pathophysiological and biochemical mechanisms, such as N-methyl-D-aspartate receptor activation. Drugs that block sodium channels act by reducing the active phase of neuronal firing, inhibiting the rapid generation of action potentials during depolarization. In addition, the synaptic blockade limits fluctuations in neuronal ionic gradients. This class includes carbamazepine, phenytoin, and lamotrigine.[3]

Calcium channel blockers include gabapentin and pregabalin.[17] These drugs present specific therapeutic indications based on their mechanism of action. In this case, they play a key role by prolonging the refractory period between nerve impulses, limiting high-frequency firing induced by persistent depolarization that causes paroxysmal pain and enhancing central synaptic inhibition.[3]

According to Park and Moon (2010)[8], anticonvulsants have had an important role in pain management since the 1960s and remain one of the most clinically relevant classes in chronic pain treatment, along with antidepressants. Thus, neuropathic pain, trigeminal neuralgia, and postherpetic neuralgia can be adequately managed, particularly by alleviating intense, paroxysmal, and lancinating pain, such as that in cancer. This class of drugs tends to be more effective for these conditions than for pain related to paresthesia, such as burning sensations and allodynia.[8]

According to Longo et al. (2013)[18], carbamazepine and phenytoin were the first drugs shown to alleviate pain related to trigeminal neuralgia. Also, Alves Neto et al. (2009)[3] identified carbamazepine as the drug of choice for treating this condition and reported its use in managing neuralgic symptoms in diabetic neuropathy, especially when patients described electric shock-like pain. However, Goodman (2006)19 stated that this therapeutic effect is often limited to initial relief, with only 70% of patients achieving lasting symptom control.

Carbamazepine is also indicated for other types of neuropathic pain, including peripheral neuropathy, postherpetic neuralgia, myofascial pain, complex regional pain syndrome, central neuropathic pain, and idiopathic glossopharyngeal neuralgia.[18] However, the present study found that the patient information leaflet of carbamazepine has no indication for several conditions, such as peripheral neuropathy, myofascial pain, complex regional pain syndrome, and central neuropathic pain.

This study evaluated the patient information leaflets of 17 anticonvulsants, but only 12 (70.58%) were available for consultation. Of these, only 5 (41.66%) mentioned chronic pain. Thus, more than half of the available patient information leaflets have no indication for chronic pain, which may compromise the understanding of patients on the therapeutic purpose of their prescribed drugs.

None of the patient information leaflets distinguished dosage regimens for epilepsy and chronic pain treatment. Therefore, this lack of guidance may contribute to incorrect dosing since different pathologies require different dosages.

Anticonvulsants may require high doses to achieve efficacy, which may cause sedation if not appropriately dosed.[18] Older adults are particularly vulnerable to adverse effects due to their physical frailty and common comorbidities, which may interfere with drug metabolism. Therefore, the availability of comprehensive information through all communication channels is essential to properly inform about the risks and benefits of these drugs.

The lack of adequate information in patient information leaflets may add a further barrier to effective treatment: functional impairment from inad-

equate drug use due to inappropriate dosing intervals or high dosages. Despite these limitations, anticonvulsants remain one of the drug classes with the highest rates of publicly available patient information leaflets (70.58% of availability). However, more than half of the patient information leaflets (66.66%) had no formal indication for chronic pain treatment.

Benzodiazepines

Benzodiazepines are drugs that act on the central nervous system by modulating the GABA receptor complex, increasing presynaptic inhibition of afferent fibers from the spinal cord. Generally, they act as tranquilizers or anxiolytics and have muscle-relaxant activity. Thus, benzodiazepines have been mainly used as adjuvant therapy to enhance the effects of drugs for analgesia and manage emotional manifestations (common in patients with chronic pain) without causing excessive sedation. Currently, benzodiazepines are often prescribed for the treatment of some conditions, such as fibromyalgia syndrome.[2]

In this sense, a relevant obstacle was observed in providing information on the indications of benzodiazepines for chronic pain treatment. Of the 31 benzodiazepines analyzed, only 15 (46.87%) had publicly available patient information leaflets. Of these, only six (40%) had a formal indication for chronic pain treatment, whereas nine (60%) were supported by scientific literature.

A previous study indicated that patients using benzodiazepines should be warned about decreased attention, which may increase the risk of accidents involving vehicles and other psychomotor activities.[21] Thus, the importance of information related to chronic pain treatment in the patient information leaflets of benzodiazepines becomes evident since patients with chronic pain may consider the dose prescribed by the physician insufficient due to their prolonged suffering. Consequently, they may use increased doses or reduced administration intervals, leading to intense central nervous system or respiratory depression.

Another concern regarding the benzodiazepines includes the high number of drugs commercialized, but with the lowest rate of publicly available patient information leaflets. Moreover, this class may have difficult management due to the potential adverse effects in cases of overdose, tolerance, and serious harm to the health of patients if misused, especially by those poorly informed.

CONCLUSION

Access to information about treatment options for chronic pain conditions is currently limited since the main source of information is the patient information leaflet. The information available for the population is limited due to the lack of publicly available patient information leaflets and their limited content (usually incomplete) since more than half of those publicly available had no indication for chronic pain treatment.

In this context, the myths and lack of knowledge on drugs may foster unwarranted fears related to adverse effects and misconceptions about dependency risks.

The pharmaceutical industry must review its practices to improve disclosure related to the indication of drugs for chronic pain treatment and provide free access to patient information leaflets containing comprehensive information to achieve adequate therapeutic outcomes.

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