Tramadol and Paracetamol Fixed Combination in a Portuguese Primary Care Unit: A Cross-Sectional Study

Combinação fixa de Tramadol e Paracetamol numa Unidade de Cuidados de Saúde Primários Portuguesa: Um Estudo Transversal

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RESUMO

INTRODUÇÃO: A combinação tramadol/paracetamol é um dos medicamentos mais prescritos para a dor em Portugal. Na Administração Regional de Saúde de Lisboa e Vale do Tejo, ao longo de 12 meses, foram prescritas 1 119 229 embalagens de tramadol/paracetamol, constituindo o segundo analgésico mais prescrito. Estes números fazem questionar se este fármaco é prescrito para dor aguda e dor crónica agudizada ou se é prescrito como tratamento prolongado para dor crónica.

MÉTODOS: Este é um estudo transversal que descreve a prescrição tramadol/paracetamol numa Unidade de Saúde Familiar portuguesa. A população em estudo corresponde aos 344 utentes a que foi prescrito tramadol/paracetamol no período compreendido entre Julho de 2020 e Junho de 2021.

RESULTADOS: Neste período foram emitidas 687 receitas que corresponderam a 2500 embalagens de tramadol/paracetamol, das quais 1874 foram dispensadas. Não houve diferença estatisticamente significativa entre o número de embalagens dispensadas ao longo dos 4 trimestres (p=0,275) e 35,3% dos utentes dispensaram receitas em mais do que um trimestre. Verificou-se que 16,5% dos utentes comprou esta combinação em quantidade que permite uma utilização superior a 90 dias.

CONCLUSÃO: Assim se demonstra que a combinação tramadol/paracetamol desempenha um papel central no tratamento da dor e que uma percentagem significativa dos utentes utiliza este medicamento de forma crónica, questionando-se a adequação da terapêutica nestes doentes. Contudo, são necessários estudos mais alargados e que avaliem o controlo da dor para suportar os resultados apresentados neste trabalho.

PALAVRAS-CHAVE: Acetaminofeno; Cuidados de Saúde Primários; Dor Crónica; Terapêutica Medicamentosa Combinada; Tramadol

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ABSTRACT

INTRODUCTION: Tramadol/paracetamol combination is one of the most prescribed pain medications in Portugal. At the Regional Health Administration of Lisbon and Tagus Valley, 1 119 229 packages of tramadol/paracetamol were prescribed for 12 months, corresponding to the second most prescribed analgesic. We ask whether this drug is prescribed for acute and irruptive pain or if it is prescribed as a long-term treatment for chronic pain.

METHODS: This cross-sectional study describes the prescription of tramadol/paracetamol in a Portuguese primary care unit. The population studied corresponds to the 344 patients who received a tramadol/paracetamol prescription between July 2020 and June 2021.

RESULTS: In this period, a total of 687 prescriptions were made, corresponding to 2500 packages of tramadol/paracetamol, of which 1874 were bought. There was no statistically significant difference between the number of packages bought over the 4 trimesters (p = 0.275) and 35.3% of the patients bought this medication in more than one trimester. We found that 16.5% bought tramadol/paracetamol in an amount that allows a use of more than 90 days.

CONCLUSION: This demonstrates that the tramadol/paracetamol combination plays a central role in the treatment of pain and that a significant percentage of patients use this medication chronically, questioning the adequacy of this therapy in these patients. However, larger studies that assess pain control are needed to support the results presented in this work.

KEYWORDS: Acetaminophen; Chronic Pain; Drug Therapy, Combination; Primary Health Care; Tramadol

INTRODUCTION

In Portuguese Primary Health Care (PHC), chronic pain (CP) is one of the most frequent medical problems, with a prevalence of 33.6%[1] and 37% of patients reporting uncontrolled pain.[2,3] The lumbar region is the most common pain location, representing 42% of cases.[2,4]

Oral Tramadol is available in Portugal in normal and prolonged-release formulations.[5–7] In addition to these formulations, there is the fixed-dose combination of tramadol and paracetamol (tramadol/paracetamol),[6] a fast-acting, effective multimodal combination with good tolerability and lower incidence of side effects when compared to other drugs (even when compared to its isolated components).[8] In several clinical studies, tramadol/paracetamol is effective, especially in situations of moderate to severe acute pain and in exacerbated CP.[8,9] Its administration should be performed every 6 to 8 hours.[8] In Portugal, there are combinations of 37.5 mg of tramadol with 325 mg of paracetamol and 75 mg of tramadol with 650 mg of paracetamol,[6] both available in packs of 20 tablets, which shows the optimal use of this combination for acute pain or exacerbated CP.

The fact that the tramadol/paracetamol combination is well tolerated,[8,9] associated with cultural factors inherent to the fear of opioids,[10,11] makes this drug one of the most prescribed for pain in PHC. According to the PHC Identity Card, at the Administração Regional de Saúde de Lisboa e Vale do Tejo (ARS-LVT), 1 119 229 packages of tramadol/ paracetamol were prescribed from July 2020 to June 2021.[12] The only analgesic with more prescriptions was paracetamol. On the other hand, the remaining opioid drugs have a much lower number of prescriptions. At the Unidade de Saúde Familiar Ramada (USF Ramada), the trend is similar, with 2975 prescribed packages in the same period.

Thus, tramadol/paracetamol is the most prescribed drug with an opioid component. We can ask if this drug is prescribed for acute pain and exacerbated chronic pain or if it is prescribed as a long-term treatment for CP. In addition to the lack of studies that define what can be considered chronic use of tramadol/paracetamol, most are not consistent in the definition of chronic use of opioids. The Centers for Disease Control and Prevention (CDC) Guidelines for the prescription of opioids for CP considers chronic use of these drugs as the prescription for at least 3 months.[13]

Although there are studies that characterize the use of opioids regarding patient characteristics and possible adverse effects,[14,15] there are no studies that describe the tramadol/paracetamol prescription characteristics and its adequacy in the PHC setting. This study aims to characterize the prescription of tramadol/paracetamol in a Portuguese primary care unit (USF Ramada), to understand the proportion of chronic users of this drug and its characteristics.

METHODS

This is a cross-sectional study, in which all patients who were prescribed tramadol/paracetamol from July 2020 to June 2021 at USF Ramada were selected, with a total of 361.

In this study, chronic and non-chronic users of tramadol/paracetamol were evaluated. According to the CDC definition,[13] chronic users were considered to be those who purchased tramadol/paracetamol, which dosages indicated by the family physician allowed an intake equal to or greater than 90 days. In cases in which it was not possible to identify the prescribed dosage, as in cases of omission and described as the "usual dosage" or as "SOS", we considered 3 pills per day and 1 pill per day, respectively.

Data was collected through the Functional Units Monitoring System (MiM@UF) to obtain the list of tramadol/paracetamol users, through the *SClinico* platform to determine the biosocial characteristics of the patients (gender and age) and the location and etiology (oncological and non-oncological) of pain associated with the prescription of tramadol/paracetamol. Data were also collected through the Electronic Prescription of Medicines platform to describe the prescribed dosage, date of prescription, number of packages prescribed and purchased by the user and to identify other analgesics prescribed simultaneously.

Data were analyzed using Microsoft Office Excel® 2019 and the Statistical Package for the Social Sciences (SPSS®) version 26.

A descriptive analysis of the data obtained was performed and the Chi-Square test was used to analyze differences in the proportion of prescriptions between trimesters.

This study was performed with the authorization of the Health Ethics Committee of ARS-LVT (n° 3170/CES/2022).

RESULTS

At USF Ramada from July 2020 to June 2021, tramadol/paracetamol was prescribed to 361 patients. We analyzed 344 patients since 17 were excluded due to death. The median age was 70 years [56-78] and 74.8% of the patients were female.

Over the 12 months evaluated, 687 prescriptions of tramadol/paracetamol were made, in a total of 2500 prescribed packages (median of 4 [2-9], mode of 3, minimum of 1, and maximum of 49), and 1874 packages were bought (median of 3 [1-6], mode of 1, minimum of 0 and maximum of 49). There was no statistically significant difference between the number of packages bought over the 4 trimesters (p = 0.275). Also, 35.3% of the users received and bought tramadol/paracetamol in more than one trimester, with only 7.8% in adjacent trimesters.

The prescribed dosage varied. However, in 21.2% of the users, the prescriptions were delivered without identification of the dosage (13.4%) or described as "SOS" (7.8%) (Table 1).

CHRONIC USERS

In this study, 16.5% of users bought packages of tramadol/paracetamol which prescribed dosage allowed for more than 90 days of use. Of these, 71.9% were female. The median age was 77 [63-80] years. A total of 86% of chronic users obtained and purchased

TABLE 1. Prescribed dosages of Tramadol/Paracetamol to the 344 patients of USF Ramada according to clinical records (July 2020 – June 2021)

Dosage	Chronic users				Non-chronic users			
	37.5 mg + 325 mg		75 mg + 650 mg		37.5 mg + 325 mg		75 mg + 650 mg	
	%	(n)	%	(n)	%	(n)	%	(n)
1/2p every 12/12h			3.5%	2			1.0%	3
1p every 12/12h	26.3%	15	8.8%	5	30.7%	88	2.1%	6
1p every 24/24h	7.0%	4	3.5%	2	2.4%	7	0.0%	
1p every 8/8h	10.5%	6	8.8%	5	42.5%	122	1.4%	4
1p in the morning and 2p in the evening	1.8%	1	0.0%		0		0.0%	
2p every 8/8h	1.8%	1	0.0%		0		0.0%	
Omission	7.0%	4	3.5%	2	12.2%	35	1.7%	5
SOS	14.0%	8	3.5%	2	4.9%	14	1.0%	3
Total	68.4%	39	31.6%	18	92.7%	266	7.3%	21

p – pill; h – hour

prescriptions in multiple trimesters, with just one of these users receiving prescriptions in consecutive trimesters. The lumbar pain was the most prevalent (21%) (Table 2). However, in 57.8% of users, the clinical record did not allow them to identify the location of the pain. Oncological etiology was identified in only one user. The combination of 37.5 mg of tramadol and 325 mg of paracetamol represented 68.4% of these prescriptions, which dosage allowed for a use of 120 [110-210] days. The combination of 75 mg of tramadol and 650 mg of paracetamol represented 31.6% of these prescriptions, allowing the use of 410 [195-525] days. Regarding other analgesic therapy prescribed simultaneously, 33.3% of these users had no prescription other than tramadol/paracetamol, and 79% were not prescribed another opioid (Table 3).

NON-CHRONIC USERS

On the other hand, 83.5% of users bought packages of tramadol/paracetamol which prescribed dosage allowed for less than 90 days of use. Of these, 75.26% were female. The median age was 67 [54-77] years. Nearly a quarter (24.7%) of non-chronic users obtained and purchased prescriptions in more than one trimester, with just 9.1% of these users receiving prescriptions in consecutive trimesters. The lumbar pain was the most prevalent (30%) (Table 2). However, in 40.1% of these users, the clinical record did not allow them to identify the location of the pain. There were no reported cases of oncological etiology. The combination of 37.5 mg of tramadol and 325 mg of paracetamol represented 92.7% of the prescriptions whose dosage allowed for a use of 20 [6.7-40] days. The combination of 75 mg of tramadol and 650 mg

TABLE 2. Location of the pain of the 344 patients taking Tramadol/Paracetamol at the USF Ramada according to clinical records (July 2020 – June 2021)

Location of pain	Chronic users		Non-chronic users	
	%	(n)	%	(n)
Not identified	57.9%	33	40.1%	115
Lumbar region	21.1%	12	30.0%	86
Knee	8.8%	5	10.1%	29
Hip	8.8%	5	5.6%	16
Shoulder	1.8%	1	4.5%	13
Leg	1.8%	1	0.7%	2
Skin			1.7%	5
Head			1.7%	5
Cervical region			1.0%	3
Hand			1.0%	3
Foot			1.0%	3
Urinary tract			0.7%	2
Abdominal region			0.7%	2
Forearm			0.3%	1
Thigh			0.3%	1
Breast			0.3%	1

TABLE 3. Number of users who were prescribed another analgesic or adjuvant in addition to Tramadol/Paracetamol at the USF Ramada (July 2020 – June 2021)

Other analgesic therapy prescribed simultaneously		Chronic users		Non-chronic users	
		%	(n)	%	(n)
Opioids	Tramadol	4.6%	4	1.8%	6
	Tapentadol	8.0%	7	1.5%	5
	Tramadol + Dexketoprofen			2.1%	7
	Codeine + Paracetamol			0.9%	3
	Fentanyl	1.1%	1	0.3%	1
	Codeine	1.1%	1		
	Hydromorphone	1.1%	1		
Anti-inflammatories	Naproxen	2.3%	2	12.7%	42
	Ibuprofen	3.4%	3	9.7%	32
	Diclofenac	5.7%	5	8.8%	29
	Etoricoxib	6.9%	6	4.2%	14
	Meloxicam	3.4%	3	2.4%	8
	Acemethacin	0.0%		2.4%	8
	Flurbiprofen	1.1%	1	1.5%	5
	Nimesulida			1.2%	4
	Ketoprofen	1.1%	1	0.9%	3
	Clonixin	0		0.9%	3
	Indomethacin	1.1%	1	0.6%	2
	Celecoxib	0		0.6%	2
	Etodolac	0		0.6%	2
	Piketoprofen	0		0.6%	2
	Dexibuprofen	0		0.3%	1
	Piroxicam	0		0.3%	1
	Aceclofenac	3.4%	3	0.3%	1
	Lysine Acetylsalicylate	1.1%	1		
	Dexketoprofen	1.1%	1		
Other analgesics and adjuvants	Cyclobenzaprine	8.0%	7	13.0%	43
	Metamizole	4.6%	4	10.9%	36
	Pregabalin	19.5%	17	9.7%	32
	Paracetamol	13.8%	12	4.2%	14
	Thiocolchicoside	1.1%	1	3.6%	12
	Amitriptyline	3.4%	3	1.8%	6
	Duloxetine	1.1%	1	1.2%	4
	Topiramate	0		0.6%	2
	Methylprednisolone	0		0.3%	1
	Baclofen	1.1%	1		
Total		100%	87	100%	331

of paracetamol represented 7.3% of the prescriptions, allowing an average use of 38.6 ± 22.7 days (range: 0-86.67). Regarding other analgesic therapies prescribed simultaneously, 27.18% of the users had no prescription other than tramadol/paracetamol, and 93% were not prescribed another opioid (Table 3).

DISCUSSION

The tramadol/paracetamol combination represents a high proportion of analgesic prescriptions in Portuguese PHC, which demonstrates its importance in the treatment of pain. Although there are no studies that describe how adequately tramadol/paracetamol is prescribed, the data presented, associated with the increasingly frequent use of opioids,[14] demonstrates the importance of its characterization.

We found that 16.5% of tramadol/paracetamol users bought packages which posology prescribed by the doctor allows use for more than 90 days, that is, chronic use of this drug.[13] Chronic use is also seen when analyzing the prescription over the 12 months, since 35.3% of users received and bought tramadol/paracetamol in more than one trimester, including 24.7% of non-chronic users, which indicates a repeated need for the drug in this period.

In 13.9% of the non-chronic users, it was not possible to identify the prescribed posology, which may indicate repeated prescriptions by the family doctor for a drug already familiar to the patient. Again, this could suggest a repeated and chronic prescription of tramadol/paracetamol. In addition, 137 users were instructed to take tramadol/paracetamol every 8 hours, where 132 users were prescribed less frequent use (every 12 hours or just once daily). These data may suggest that these patients might achieve good pain control with lower daily doses than recommended or, on the other hand, that they are taking suboptimal doses (for example, for fear of the doctor prescribing higher daily doses[16]) resulting in uncontrolled pain.

Regarding other analgesic therapies prescribed simultaneously, 4.4% (n=15) of the patients were also prescribed a strong opioid (tapentadol in 12 patients, fentanyl in 2, and hydromorphone in only 1 patient). In these users, tramadol/paracetamol may be indicated for CP to control breakthrough pain. However, the control of pain in 60% (n=9) of these users may be questionable, since the prescribed dosage allows for chronic use of this drug. In addition, Table 3 shows that the 344 users evaluated were prescribed 418 drugs with analgesic purposes in addition to tramadol/paracetamol (87 in the case of chronic users). This could be interpreted as a multimodal intervention or as evidence of difficulty in pain control in these patients.

Regarding the location of pain, the data obtained in this study are comparable to the studies available in the literature that identify low back pain as the most prevalent in PHC.[2,4]

One of the limitations of our study is that it is a single-centered cross-sectional study of clinical record analysis. The description of the chronic use of tramadol/paracetamol is based on the posology prescribed by the family physician and not on the actual daily dosage that the patient takes, which may underestimate the proportion of chronic users. Furthermore, only prescriptions made by family physicians from USF Ramada were evaluated, and any other prescriptions (from hospital consultations or private clinics) were not included, which could translate into a higher percentage of chronic users. In addition, the characterization of pain was challenging, since many of the clinical records were incomplete or lacking information, which is demonstrated by the 148 patients in which it was not possible to characterize the etiology or characteristics of the pain. Furthermore, it was not possible to assess pain control through clinical records, so users with uncontrolled pain were not identified (even in cases of non-chronic users in which it was unclear whether they were patients with controlled CP or patients with acute pain). These data suggest that rigorous and methodical pain assessment by family physicians is still infrequent. This could be explained by the lack of awareness among doctors and other health professionals in this area, as well as the lack of organizational algorithms for the approach and treatment of these patients. This can be associated with the fact that pain assessment and treatment are not yet considered a priority, or by the limited time available in PHC consultations for the evaluation of these patients.[16] The need for more complete clinical records in PHC is also paramount, since it could result in a better quality of care and consequent pain relief.

However, the data presented are not to be underestimated, as it shows that there is a high number of patients with uncontrolled pain. This is demonstrated not only by the need for chronic use of tramadol/paracetamol but also by the fact that 31.6% of these patients take the formulation of 75 mg of tramadol and 650 mg of paracetamol, with some patients having purchased prescriptions that allow for use for more than one year.

The tramadol/paracetamol combination plays an important role in pain management. However, as the lit-

erature shows that 37% of CP patients do not obtain pain relief,[3] it cannot be excluded that a percentage of these are chronic users of tramadol/paracetamol.

The chronic prescription of tramadol/paracetamol can be justified by multiple factors, of which we highlight those associated with the physician, such as inadequate pain assessment, fear of possible adverse effects of other analgesics (including other opioids), or the need for more training, and those associated with the patient, such as fears and myths related to opioids or related to adverse effects of these drugs.[10,16] These barriers to the adequate treatment of patients with CP must be studied to provide the best approach to these patients.

CONCLUSION

This study demonstrates that the tramadol/paracetamol combination plays a central role in the treatment of pain and that a significant percentage of patients use this medication chronically, questioning the adequacy of this therapy in these patients. To the best of our knowledge, to date, this is the first work that studies this topic, which demonstrates the importance of the data presented. However, larger studies that assess pain control are needed to support the results presented in this work.

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BP, CS E MM: Desenho, análise e interpretação, escrita, revisão e aprovação final

FB: Análise e interpretação, escrita, revisão e aprovação final

MV: Análise e interpretação, revisão e aprovação final

FF E JN: Desenho, revisão e aprovação final.

BP, CS AND MM: Design, analysis and interpretation, writing, review and final approval

FB: Analysis and interpretation, writing, review and final approval

MV: Analysis and interpretation, review and final approval

FF AND JN: Design, review and final approval

RESPONSABILIDADES ÉTICAS

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