

# Hurdles in successful treatment of cancer pain caused by primary healthcare

Eržebet Patarica-Huber<sup>1</sup>, Nedeljka Boškov<sup>2</sup>

## SUMMARY

**Background:** *The aim of this study is to envisage the hurdles set by physicians in primary healthcare that can cause, or contribute to unsatisfactory cancer pain management.*

**Methods:** *The study has been carried out as a prospective open non-randomized one (based on a questionnaire). It comprised 283 physicians in primary healthcare from 21 institutions of primary healthcare in Serbia. The choice of physicians was done at random, and the completion of questionnaires was voluntary. The questionnaire comprised 12 questions. Among other issues the questions covered the most important characteristics of the analgesics in their opinion, the individual doses of drugs they most often prescribe, maximum daily doses of these drugs they prescribe (tramadol, fentanyl TD, hydromorphone, methadone, IR morphine); whether they introduce opioids and/or increase the dose autonomously or only upon a specialist's recommendation; and what is preventing them to successfully treat cancer pain; what side effects they fear and others.*

**Results:** *Tramadol was favored in the previous year (82.3%), in the last month the physicians prescribed NSAID as therapy in 63.4% of the cases, tramadol was given to 13.60%; fentanyl TD to 13.40%; hydromorphone to 2.7%; IR morphine to 3.80%. Efficiency was marked by 89.80% of physicians as the most important characteristic, tolerability by 82.3%, and duration of effects by 77.4%. Tramadol is most often the choice of therapy in their daily practice although they said it to be less efficient, less tolerable, with shorter analgesic effect, less user friendly, and more expensive compared to fentanyl TD and the other opioids. They said the side effects they fear the most were respiratory depression and sedation. 23.70% of the physicians in the primary healthcare introduce and/or increase the dose of opioids (34.6%) into the therapy autonomously, and 76.30% of them introduce these drugs and/or increase the dose (65.4%) only upon a specialist's recommendation.*

**Conclusion:** *Barriers have a great influence on successful treatment of cancer pain. There is a burning need for further education which has to encompass raising awareness of the current guidelines and recommendations in the cancer pain therapy, their acquisition and utilization in everyday practice through interactive workshops with case studies because there is still an alarming lack of knowledge, level of prejudice and apparent opiophobia.*

**Key words:** *Neoplasms; Pain; Drug Therapy; Primary Health Care; Serbia*

## INTRODUCTION

Malignant diseases have a permanent tendency of growth. According to the WHO projections, 15 million people will have become ill by 2020. About 32,000 new cases of malignant diseases are diagnosed annually in Serbia, while around 20,000 cancer patients die in a single year. Pain is one of the most usual symptoms of a malignant disease. Along with the advancement of the malignant disease, frequency and intensity of pain also increase. It appears in about 60% of patients in all phases of the diseases. About 30-40% of patients feel pain already when the disease is diagnosed. About 25-30% of patients feel severe pain. Pain is a symptom of a malignant disease, which terrifies the patient and their closest relatives the most. According to the WHO, cancer pain can be obviated in about 70-90% of patients. Our daily practice indicates that cancer pain treatment is not satisfactory. Statistics of the WHO say that treatment of cancer pain is successful only in 50% of patients. There is a large difference between the possibilities for successful treatment and the results of treatment in practice. There is a whole range of hurdles to successful cancer pain treatment. They can originate from medical staff, patients, healthcare system, and restrictive national policy in opiate control. One of the most important reasons for poor cancer pain management is opiophobia.

The aim of this study is to envisage the hurdles set by physicians in primary healthcare that can cause, or contribute to unsatisfactory cancer pain management.

## MATERIAL AND METHODS

The study has been carried out as a prospective open non-randomized one (based on a questionnaire). It was executed in the period of July/August in 2009. The study comprised 283 physicians in primary healthcare from 21 institutions of primary healthcare in Serbia (healthcare centers in Belgrade, Čačak, Užice, Novi Sad, Pančevo, Kragujevac and Niš). The study was done in cooperation with the Association of Pain Study and Treatment of Serbia. The choice of physicians was done at random, and the completion of questionnaires was voluntary. In the introductory segment of the questionnaire, the physicians were informed about the aim of the questionnaire, as well as about the importance of the thereby obtained and processed data, which will be used as basis for recognizing the hurdles that stand in the way of successful cancer pain treatment. What is more, to use them as basis for future planning of 'jumping over these hurdles'. (We deliberately call them hurdles and not obstacles because by definition hurdles are obstacles that we are expected to overcome.) The questionnaire comprised 12 questions. They covered the following issues: workload, (number of examinations per day), number of patients per month that report moderate and severe cancer pain, analgesics they use, the most important characteristics of the analgesics in their opinion (ranked from 1-10), the individual doses of drugs they most often prescribe, the maximum daily doses of these drugs

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<sup>1</sup>Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, <sup>2</sup>General Hospital "Đ. Jovanović", Zrenjanin, Serbia

Correspondence to:  
Eržebet Patarica-Huber, M. Sc. Med.  
Department of Surgery, Intensive Care and Pain Therapy Unit,  
Oncology Institute of Vojvodina, Sremska Kamenica, Serbia

erzebet.pataricahuber@gmail.com

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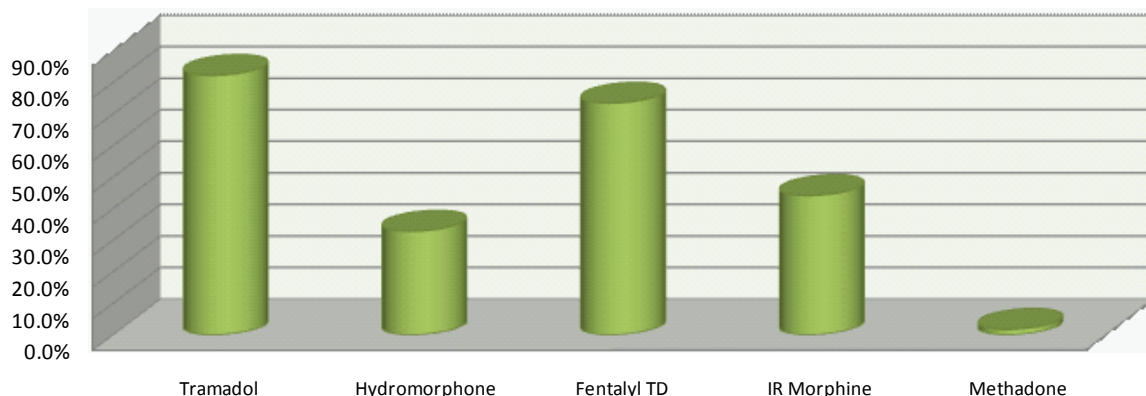


Figure 1. Did you, in the past year, give the following drugs?

they prescribe (the data referred to those drugs available for them at the time: tramadol, fentanyl TD, hydromorphone, methadone, IR morphine). The questionnaire also asked the interviewees whether they introduce opioids themselves or only upon a specialist's recommendation; whether they increase the opioid doses themselves or wait for the specialist's recommendation; also, what is preventing them from successfully treating cancer pain; what side effects they fear; as well as whether they are interested in further education and what it should look like. There was a possibility to comment, remark or make a suggestion.

### Statistical methods

The data were statistically processed through the following methods of descriptive statistics: rank, measures of central tendency (the mean and the median). The T-Test for Paired Sample was used for proving the significance of difference as well as the Wilcoxon Signed-Ranks Test.

### RESULTS

The study comprised 283 physicians of primary healthcare from 7 different cities in Serbia.

The median number of examinations per physician per month was 736 patients, Rank (30-1500 patients).

26.7% of patients that visit a physician in the primary healthcare suffer from chronic pain of moderate to severe intensity (12.6% malignant pain; 14.10% non-malignant pain).

One of the questions was: "Did you, in the last year, give the following drugs: tramadol, hydromorphone, fentanyl TD, IR morphine, methadone to your patients who suffer from chronic cancer pain?" and the result of the positive answers was as follows: tramadol was prescribed by 82.3% (233/283) of the physicians, hydromorphone by 32.9% (93/283), fentanyl TD by 73.5% (208/283), IR morphine by 44.2% (125/283), and methadone by 1.8% (5/283) of the physicians (Figure 1).

The following question was, unlike the others, not answered by all physicians. Actually, 74.9% (212/283) did answer the question: "What percent of patients with chronic cancer pain (of moderate and severe intensity) that you have treated in the last month have received the following drugs: NSAID; tramadol; hydromorphone; fentanyl TD; IR morphine; methadone?"

The results of the answers to this question were as follows: NSAID was given to 63.40% of treated patients; tramadol was given to 13.60%; fentanyl TD to 13.40%; hydromorphone to 2.7%; IR morphine to 3.80%, methadone to 0.10% and other drugs to 0.10% of the treated patients (Figure 2).

The following results have been obtained for the question: "What were the most usual daily doses of tramadol, hydromorphone, fentanyl TD and IR morphine that you prescribed to your patients and what were the highest doses?" (Table 1).

Table 1. What were the most usual daily doses of tramadol, hydromorphone, fentanyl TD and IR morphine that you prescribed to your patients and what were the highest doses?

	Most usual daily dose mg/mcg		Highest daily dose mg/mcg	
	Median	Rank	Median	Rank
Tramadol	100	50-600	294	50-800
Hydromorphone	16	8-48	24	8-96
Fentanyl TD	50	25-375	100	25-500
IR Morphine	20	4-240	60	12.5-720

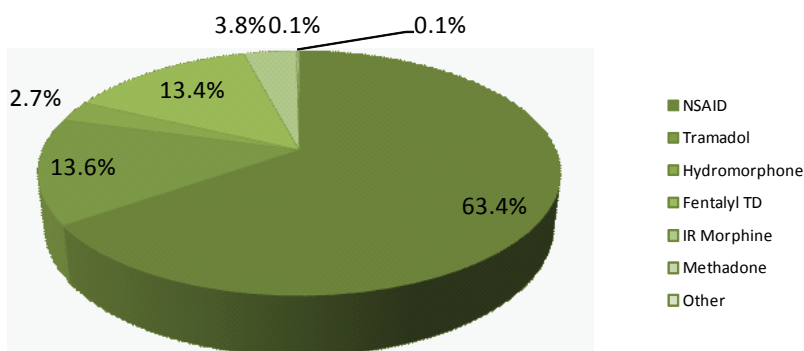


Figure 2. What therapies do you prescribe to patients with chronic cancer pain?

There was a question: "What are the most important characteristics for the usage of the available drugs: efficiency; tolerability; duration of effects; easy usage, price, availability, other characteristics?"

The results were the following: Efficiency was marked by 89.80% (254/283 physicians), tolerability by 82.3% (233/283), duration of effects by 77.4% (219/283), easy usage by

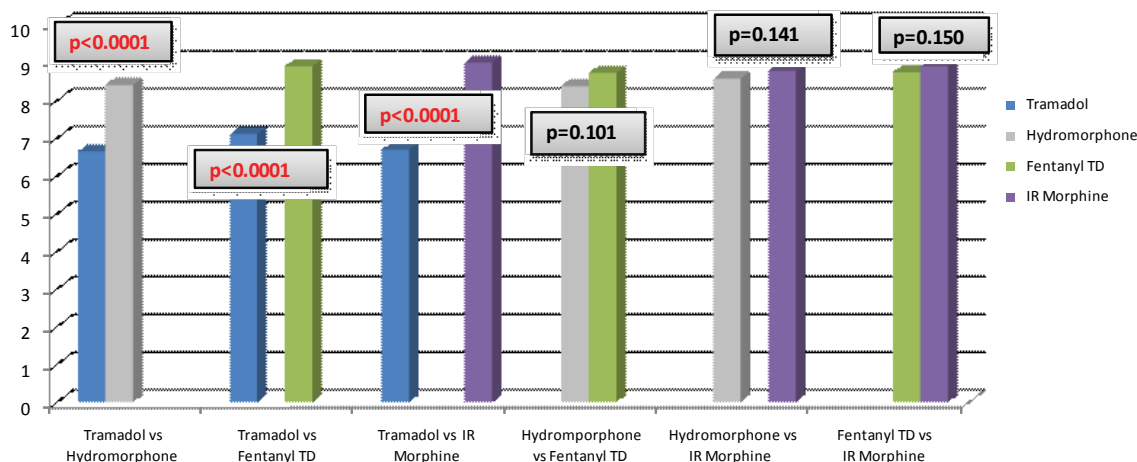


Figure 3. Drug efficiency assessment

25.80% (73/283), price by 12.70% (36/283), availability by 9.90% (28/293) of physicians.

The physicians assessed efficiency of the used opioids in cancer pain treatment: tramadol, hydromorphone, fentanyl TD and IR morphine. Methadone was not analyzed because of the very small sample. A 1-10 scale marked efficiency, where 1 meant least efficient and 10 meant most efficient. The drugs were compared to each other.

### Efficiency

The results of this study have shown a statistically significant difference in terms of efficiency: tramadol in combination with hydromorphone, fentanyl TD and IR morphine. In all three combinations, tramadol proved to be, statistically significantly ( $p < 0.0001$ ), less efficient. When the strong opioids are compared, though, such as hydromorphone, fentanyl TD and IR morphine, there is no statistically significant difference in their efficiency (Figure 3).

### Tolerance

Results have also shown that there is a statistically significant difference in terms of tolerance toward these drugs – tramadol vs. fentanyl TD ( $p < 0.0001$ ), and tramadol vs. IR morphine ( $p < 0.0001$ ). In both cases, tramadol is less tolerable. If we compare hydromorphone vs. fentanyl TD ( $p < 0.0001$ ) and hydromorphone vs. IR morphine ( $p < 0.0001$ ) the difference is statistically significant, hydromorphone is less tolerable. It is interesting to notice that there is no statistically significant difference in terms of tolerance when tramadol vs. hydromorphone is compared ( $p = 0.436$ ) neither is there difference between fentanyl TD vs. IR morphine ( $p = 0.068$ ).

### Length of analgesic effect

The interviewees confirmed a statistically significant difference ( $p < 0.0001$ ) in terms of length of effect of strong opioid preparations (hydromorphone, fentanyl TD and IR morphine) when compared to the weak tramadol. The already known difference in length of effect was only confirmed between fentanyl TD and hydromorphone as SR opioids and IR morphine.

### Simplicity of usage

Results have shown that there is a statistically significant difference in terms of simplicity of usage, i.e. “user friendliness” of certain analgesics. Hydromorphone, fentanyl TD and IR morphine are more simple for usage when compared to tramadol ( $p < 0.0001$ ). There is no statistically significant difference in the case of hydromorphone vs. IR morphine ( $p = 0.045$ ) neither in the case of fentanyl TD vs. IR morphine ( $p = 0.687$ ). There is an interesting fact that the difference between the simplicity of usage between hydromorphone and fentanyl TD is on the border of statistical significance ( $p = 0.048$ ).

### Price of the drugs

The tabular data undoubtedly show that there is a statistically significant difference in terms of the price of the drugs. Tramadol is more expensive than hydromorphone and fentanyl TD ( $p < 0.0001$ ). When compared, there is a significant difference in terms of price among strong opioids – fentanyl TD vs. hydromorphone ( $p < 0.0001$ ). Fentanyl TD is more expensive. IR morphine is statistically significantly more expensive than hydromorphone ( $p = 0.002$ ) more even than fentanyl TD ( $p = 0.001$ ) (Table 2).

Table 2. Price

		Paired Samples Statistics			
		Mean	N	Std. deviation	Std. Error Mean
Pair 1	Tramadol	8.5	58	1.657	0.218
	Hydromorphone	6.67	58	1.941	0.255
Pair 2	Tramadol	8.85	118	1.545	0.142
	Fentanyl TD	7.13	118	2.623	0.242
Pair 3	Hydromorphone	6.57	60	1.817	0.235
	Fentanyl TD	7.33	60	2.08	0.269
Pair 4	Hydromorphone	6.64	56	1.843	0.246
	IR Morphine	7.88	56	1.63	0.218
Pair 5	Fentanyl TD	6.98	77	2.571	0.293
	IR Morphine	8.16	77	1.71	0.195

### Availability of the drugs

The results have shown that tramadol, when compared to hydromorphone, fentanyl TD and IR morphine, is statistically significantly more easily available ( $p < 0.0001$ ) and that fentanyl TD is more readily available than hydromorphone ( $p < 0.0001$ ) and IR morphine ( $p = 0.001$ ). There is no statistically

significant difference in terms of availability between hydromorphone and IR morphine ( $p=0.874$ ).

The following results have been obtained to the question whether side effects (nausea, dizziness, vomiting, constipation, sedation, respiratory depression) represent an obstacle to prescribing opioids and what side effects they fear the most:

Tests have shown that there is a statistically significant difference ( $p<0.0001$ ) in the estimate that they mostly fear respiratory depression when compared to the other side effects. When all the other side effects were compared, the results showed no statistically significant differences among them. The only exception was the comparison: sedation vs. nausea ( $p=0.026$ ). They fear sedation more. When sedation vs. vomiting was compared ( $p=0.041$ ), results showed that they fear sedation more (Figure 4).

One of the questions was also: "Do you introduce opioid analgesics into the therapy autonomously or only following the suggestion of a specialist?" and the following results have been obtained:

23.70% (67/283) of the physicians in the primary healthcare introduce opioids into the therapy autonomously, and 76.30% (216/283) of the physicians introduce these drugs only after a specialist's suggestion.

The following question: "Do you autonomously increase the dose of opioid analgesics depending on the intensity of pain, or do you require a specialist report?" resulted as follows: 34.6% (98/283) of the physicians increase the

dose autonomously, while 65.40% (185/283) of the physicians act exclusively upon a specialist's request.

When we asked what prevented physicians in the primary healthcare from prescribing opioids in the treatment of cancer pain, we obtained the following results:

34.6% (98/283) said that nothing prevented them from doing so; 26.10% (74/283) of the physicians stated personal trouble with regulators; 11.70% (33/283) of the physicians said they had not enough information about opioids; 8.80% (25/283) of them does not think a physician in the primary healthcare should be dealing with the treatment of cancer pain; 7.80% (22/283) of the physicians stated fear of side effects as a reason that prevents them from prescribing opioids (Figure 5).

### DISCUSSION

Malignancy in Serbia has a rising tendency and it represents the second most usual cause of death (after cardiovascular diseases). Of the 12.5 million newly diagnosed cases all over the world, more than 6.6 million die. Cancer pain often represents the first symptom that refers a patient to seek medical help. 20-40% of the patients complain about pain when diagnosed, in 40-70% of the cases, pain appears during the treatment, and in 70-90% of the patients with advanced, terminal stage of the disease, it is inevitably present. The tumor invasion itself causes pain in 77-80% of the cases, and although modern antineoplastic treatments successfully influence the course of the malignant disease, in 15-25% of the cases they contribute to early or delayed painful states. Cancer pain represents a great medical problem, although it is successfully treated in up to 90% of the cases. Tony O'Brien claims that pain can be treated more easily if you approach it correctly, than other accompanying symptoms, which he supports by experience acquired in institutions of palliative medicine worldwide, where good pain management has been achieved in 95% of the cases. It is a disturbing fact that this percentage in developed countries increases not higher than 50%, and in developing countries, the statistical data show even more devastating results (1-5).

Barriers to a correct treatment of cancer pain have been identified in recent years, and the US Agency for Health Care Policy and Research, in its 'First National Clinical Practice Guidelines on Cancer Pain', classified these barriers into three categories: system, professional, and patient barriers (6).

Low priority given to cancer pain and regulatory obstacles to the use of opioids for cancer pain can be placed among system barriers. Consequently, physicians may have personal worries about regulatory scrutiny and may opt not to use opioid therapy for this reason. System barriers can also be divided into internal or external – the former being represented by inadequate or late start-up of palliative care programs, and the latter by regulatory complications. Additionally, in developing countries, system barriers may also be represented by high cost of opioids, problems of availability of treatment or access to it, or by 'opiophobia' (7-9).

In the case of patient barriers, trust in health-care professionals was reported by Reid et al. as an important factor in helping patients to decide about opioid therapy. This can be deduced from the four categories of difficulty in accepting strong opioid therapy they defined: patients are reminded of their imminent death when strong opioids are prescribed and some even fear that

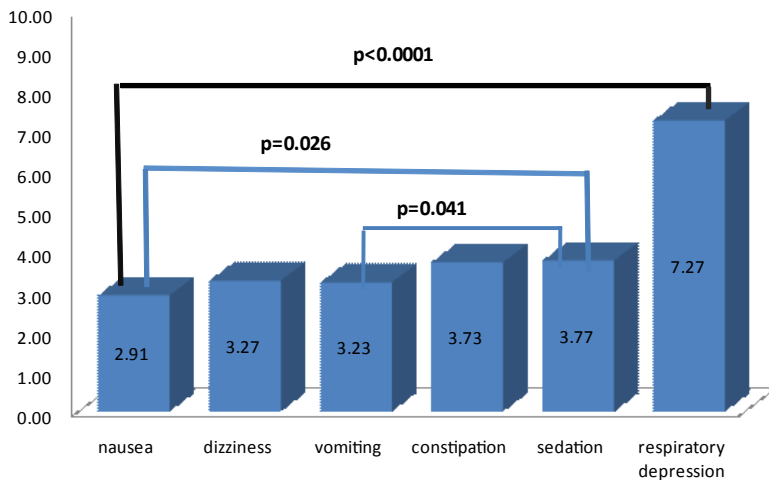


Figure 4. Side effects

### 2 out of 3 interviewees have a reason not to prescribe opioids!

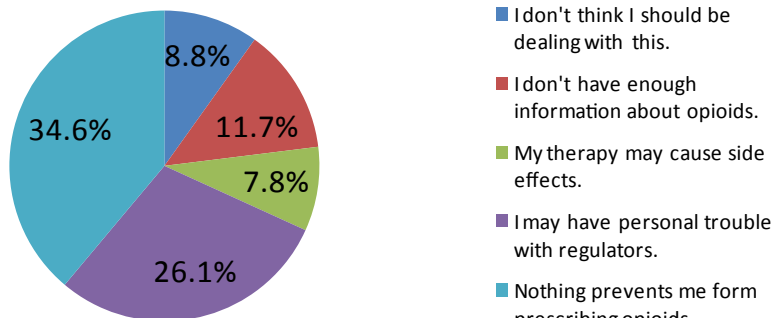


Figure 5. What prevents you from prescribing opioids?

these drugs will hasten their death; morphine is considered as a last resort; the feeling of having no choice but to start treatment with strong opioids; the role of health-care professionals in dealing with these situations (10).

A number of common physician barriers to correct cancer pain management may be mentioned: use of a 'disease-based' rather than a 'symptom-based' model of care; lack of physician education and failure to follow existing guidelines; lack of priority given to symptom management; analgesia level on the basis of prognosis rather than severity of pain; fear of patient addiction and analgesic tolerance; poor assessment of pain and lack of proactive questioning about the symptom; insufficient experience of pain management (7, 8).

Our study has shown that a physician in primary health-care receives 736 patients a month (up to 33 patients a day). 26.7% of the patients complain about chronic pain of moderate (VAS 4-7/10) or severe intensity (VAS 7-10/10) and in 12.6% of the cases it is a cancer pain.

It can be observed that the most favored is tramadol, a weak opioid analgesic. The results have also shown that NSAID are unquestionably the most usual choice in treatment of moderate and severe cancer pain. Furthermore, it is a fact that NSAID, tramadol and fentanyl TD have been present on the market the longest and that they have been always available in their everyday practice, however, although the efficiency and the toxicity of these drugs is well known to health-care professionals, it does not justify the neglect towards and/or insufficient use of hydromorphone and IR morphine and it definitely does not justify the high preference in the usage if NSAID in the treatment of cancer pain.

There is an apparent discrepancy between the obtained data in the previous two questions. One is telling us that 82.3% of physicians said they had prescribed tramadol in the last year and the other that they actually treated 13.60% of their patients with the same drug. The same observation can be ascribed to the data obtained about fentanyl TD, where the discrepancy is even more drastic (73.5% of the health-care professionals said to have prescribed it, but only 13.40% of the patients with cancer pain are said to have been treated with this opioid).

The data obtained about the most usual/largest prescribed daily dose of opioids (tramadol 100/294mg, hydromorphone 16/24mg, fentanyl TD 50/100mcg, IR morphine 20/60mg) empirically speak in favor of the apparent underdosage. The concept of this study did not cover comparative evaluation of pain intensity and the prescribed dosage; otherwise, the above presumption would have its factual support. The implications for this discrepancy may be diverse.

When talking about the characteristics of these analgesics, most of the physicians said that efficiency comes first (89.9%), then tolerability (82.3%), duration of effects (77.4%), easy usage (25.8%), price (12.7%) and availability (9.9%). When appraising and comparing the above-mentioned characteristics among these drugs, the health-care professionals stated that strong opioids (fentanyl TD, hydromorphone and IR morphine) are statistically significantly ( $p < 0.0001$ ) more efficient than tramadol, which is completely in accordance with the data provided in literature. Furthermore, in terms of tolerability, their experience also supported the statistically significantly ( $p < 0.0001$ ) lower tolerance of tramadol than fentanyl TD and IR morphine, just as is the case with hydromorphone when compared to fentanyl TD and IR morphine. The results have also shown that tramadol

was also statistically significantly rated as less adequate in terms of duration of effects, easy usage, and price. Only its availability has been marked higher than other opioids in this study. A significant disagreement can be observed here as well. Tramadol is most often the choice of therapy in their daily practice although they said it to be less efficient, less tolerable, with shorter analgesic effect, less user friendly, and more expensive compared to fentanyl TD and the other opioids. The legitimate question that arises here is what the reason behind it may be: ignorance, fear of side effects, habits, or plain indifference.

The data obtained about the side effects that may be the reason for refraining from prescribing opioids suggest that physicians in the primary health-care statistically significantly ( $p < 0.0001$ ) fear respiratory depression the most, although it is a known fact that it does not represent a barrier when strong opioids are correctly administered in cases of moderate and severe cancer pain.

Bearing in mind all the results so far, it does not surprise to observe the finding that more than 2/3 of the interviewees (76.3%) introduce opioids exclusively upon specialist's recommendation and that only 34.6% of them increase the dosage autonomously depending on the intensity of pain their patients complain about. Consequently, a large number of patients go a very long and arduous way to reach good pain management and how winding this road is largely depends on the decision and the expertise of the health-care professional in primary health-care.

This study has also shown that nothing prevented 34.6% of the physicians interviewed in prescribing opioids, while the others mentioned regulatory barriers (26.13%) or lack of information (11.7%). Some are sure they should not be dealing with cancer pain (8.8%), while the rest (7.8%) are afraid of side effects. All the above-mentioned leads us to conclude that professional competence, correct communication, and a relationship based on trust are the three pillars patients rely on when deciding whether to start opioid treatment. The importance for patients of having their pain acknowledged and, in a certain sense, 'legitimized' within the doctor-patient relationship, during any stage of the disease, cannot be stressed enough. The perception of incredulity of the pain reported, of an underestimation of its severity, and of inadequate social support can thus lead to an increase in the level of suffering and of its expression (11).

If the study of Reid et al. (10), which originates from the birthplace of palliative care, is somewhat disturbing in the messages it conveys because it indicates that a great many years of health education have not produced the results that might have been hoped for in terms of opiophobia, then what can be hoped for in a medical environment such as ours? The problem remains that a number of health-care professionals today are still prejudiced against strong opioids and tend to reserve the use of opioids for the final stages of the disease. A vision of pain management that is not solely linked to the end-of-life but rather seen as a positive option, in the less advanced stage of disease as well needs to be promoted.

## CONCLUSION

Health-care professionals in the primary health-care are overloaded with work, which prevents them from allocating more time to individual patients. Physicians have insight and knowledge regarding the efficiency of opioids, but they use them insufficiently and inadequately in their daily practice.



A large number of patients gain pain relief with fentanyl TD, and it is known that a SR opioid hydromorphone has a wider therapeutic distribution. IR morphine is insufficiently used although it is a medication of choice for breakthrough pain. These observations can be justified by the fact that at the time of this study, hydromorphone and IR morphine were available at the market for a very short time and the physicians had no experience with them. Underdosage has been confirmed by the data on the average daily dose and the highest dose. Opiophobia is also hidden behind these data. Only 34.6% of the physicians have no hurdles regarding cancer pain therapy. There is a statistically significant fear of side effects. Fears of respiratory depression and sedation are the leading hurdles in prescribing and titration of opioids. Besides this, 26.13% of the interviewees state regulatory barriers, and 11.7% of them confirm being uninformed and lack of knowledge. Two out of 3 physicians introduce the therapy and/or increase the dose of analgesics in accordance with the intensity of pain only upon specialist's recommendation. The fact that 7.8% of them stated that a physician in the primary health-care should not be dealing with cancer pain is surprising, when it is well known that the team of palliative and supportive care also comprises physicians from the primary health-care where they may take a significant role. There is a burning need for further education. It has to encompass raising awareness of the current guidelines and recommendations in the cancer pain therapy, their acquisition, and utilization in everyday practice through interactive workshops with case studies.

The recognition of pain as the fifth vital sign has caused changes in the attitudes towards pain management. Pain is no longer considered to be merely a symptom and this supports the need for changing the use of a 'disease-based' rather than a 'symptom-based' model of care and give both their equally due relevance and importance and recognize pain as a condition that needs to be managed and treated just like the disease itself. It is a moral imperative to help people living with pain fulfill their wish for a life worth living — one that permits them to work and support themselves and enjoy their family members and friends. All people in pain have a right to timely, appropriate and effective pain care.

### Conflict of interest

We declare no conflicts of interest.

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