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Original article

Comparative Pharmacoepidemiological Analysis on Analgesics Consumption in the Republic of Serbia and Nordic Countries in the period 2015-2018

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SUMMARY

Introduction/Aim. Analgesics are drugs used in the pain pharmacotherapy and are one of the most prescribed drugs in all countries. Modern pain pharmacotherapy involves the use of analgesic steps. The objective of this paper was to analyze the consumption of drugs used in the pain pharmacotherapy in the Republic of Serbia (RS), in the period from 2015 to 2018, and to compare the obtained results with the consumption of the mentioned drugs in the Kingdom of Norway (KN) and the Republic of Finland (RF) in the same time period interval.

Material and methods. Data on drug consumption were taken from the website of the Agency for Medicines and Medical Devices of Serbia, the official website of the Norwegian Institute of Public Health and from the official website of the Finnish Medicines Agency. The consumption of medicines is monitored using the defined daily dose (DDD) methodology.

Results. Paracetamol consumption was 13 to even 20 times lower in the RS compared to the KN and 10 to 15 times lower compared to the RF. The average consumption of diclofenac during the four observed years was about 30 DDD/1,000 inhabitants/day in the RS, about 7 in the KN and about 4 DDD/1,000 inhabitants/day in the RF.

Conclusion. In the pain pharmacotherapy in the RS, the consumption of non-steroidal anti-inflammatory drugs is dominated by diclofenac, while in the KN and the RF ibuprofen and paracetamol from non-opioids.

Keywords: **pain pharmacotherapy, analgesics, non-steroidal anti-inflammatory drugs, drug consumption.**

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INTRODUCTION

One of the primary goals of modern medicine is the relief of pain and suffering in patients. Pain is one of the most common symptoms among patients. The rate of pathological processes accompanied by degrees of pain ranging from mild, moderate to severe is high. Elimination of pain is symptomatic treatment that also significantly improves the quality of life of patients experiencing pain of any origin. However, it is of extreme importance to combine antidolorose therapy with causal therapy aimed at the underlying cause of the pain.

The International Association for the Study of Pain – IASP defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain is a subjective experience described by using several characteristics (quality, localization, intensity, emotional impact, behavioral changes, frequency) (1). Out of all the aforementioned characteristics, pain intensity has been recognized as a crucial characteristic for pharmacotherapy of pain.

Considering the fact that pain is a subjective experience, subjective sensation, there are no valid methods to measure its intensity. For this reason, single-dimensional and multidimensional tools for assessing pain intensity have been developed (2). Single-dimensional tools for measuring pain intensity are: the visual analogue scale – VAS, verbal rating scale – VRS, numerical rating scale – NRS. Apart from single-dimensional tools, there are also multidimensional tools for pain intensity assessment. The most common ones are: McGill Pain Questionnaire, the Brief Pain Questionnaire, the Pain Assessment Cards, Pain DETECT questionnaire, DN4 Questionnaire.

A modern approach to pain management means the application of the following means and procedures:

1. Pharmacotherapy, as the name suggests, involves the use of medications to alleviate pain. For this purpose, the following groups of drugs can be applied: analgesics, psychotropic drugs, amino acid precursors, corticosteroids.

2. Neurosurgical procedures are nerve ablation techniques that are used when other therapeutic options have failed.

3. Electrical neuromodulation refers to manipulation of painful sensation by using electrical impulses to stimulate nerve tissue.

4. Acupuncture is an ancient Chinese method for pain relief and for the treatment of certain conditions by using thin needles inserted at specific points on the skin. It is convenient for use in pain relief in arthritis, bursitis, tenosynovitis, trigeminal neuralgia and alike.

5. Physical therapy has a significant role in pain management. The scope of physical therapy includes heat and/or cold treatments, massage, therapeutic exercises, and transcutaneous electrical nerve stimulation.

6. Psychotherapy is necessary in some cases because the pain is often accompanied by anxiety and depression. Hypnosis as a method is also a significant part of psychotherapy (3).

A modern approach to pain management is based on the fact that pain treatment should be introduced gradually, first starting with weak and then stronger analgesics. This method of analgesia has been referred to as an "analgesic ladder", introduced and adopted by the World Health Organization. It allows gradual introduction of medications and monitoring the success and progress of the treatment. (2). These are the steps of the ladder (2): Step 1– mild pain, intensity 1 - 3/10, non-opioid analgesics recommended; Step 2 – moderate pain, intensity 4 - 6/10 – weak opioids, non-opioid analgesics and adjuvant therapy recommended; Step 3 – severe pain, intensity 7 - 10/10 – strong opioids, non-opioid analgesics, adjuvant therapy recommended.

Pharmacotherapy for pain management should be administered orally whenever possible, which is a fundamental principle in pain pharmacotherapy. Additionally, the therapy should be titrated individually to meet patient's needs using the "analgesic ladder" and multidisciplinary approach. Combination of drugs as well as adjuvant therapy utilization are recommended, with pain assessment

and therapy success evaluation performed more often, which is considered highly significant (4).

Analgesics are traditionally classified as non-opioid, opioid and adjuvant analgesics (4).

Non-opioid analgesics are paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Paracetamol has mild anti-inflammatory effects and belongs to antipyretic analgesics (5). These drugs are weak inhibitors of cyclo-oxygenase enzyme (COX) and they produce antipyretic and primary analgesic effects by acting upon the central nervous system (CNS). Non-steroidal anti-inflammatory drugs are widely used due to their analgesic, antipyretic and anti-inflammatory properties. The mechanism of action of these drugs is based on the inhibition of the COX enzyme. There are two types of COX enzymes, COX1 and COX2. Therapeutic effects of NSAIDs are explained by the inhibition of the enzyme COX2 that plays an important role in the production of mediators responsible for the development of inflammation and pain. The majority of these drugs non-selectively inhibit both enzymes and they are referred to as non-selective COX inhibitors (6). This group of drugs includes diclofenac, ibuprofen, naproxen, ketoprofen and others. On the other hand, NSAIDs that inhibit only COX2 are called selective COX inhibitors, including celecoxib, parecoxib and etoricoxib (7).

Opioid analgesics interact with opioid receptors and inhibit nociception at supraspinal, spinal and peripheral levels, altering emotional reaction to pain. Most of the opioid analgesics with clinical application are relatively selective μ–opioid receptor agonists with effects similar to those of morphine. Strong opioid analgesics are: morphine, hydromorphone, oxycodone, fentanyl, tapentadol. Weak opioid analgesics are: codeine, dihydrocodeine and tramadol (8).

Adjuvant analgesics are a diverse group of drugs with different primary indications (e.g. antidepressants, anticonvulsive drugs, local anesthetics, glucocorticoids, muscle relaxants, calcitonin, bisphosphonates and others). They are used in treating certain, mostly chronic painful conditions, when traditional analgesics failed to achieve satisfactory level, or cannot be administered. They are combined with traditional analgesics or other non-pharmacological procedures for pain relief, but they are sometimes used independently as monotherapy (e.g. neuropathic pain) (9).

AIMS

The aim of the paper was to analyze the use of drugs in the pain management in the Republic of Serbia in the period from 2015 to 2018.

The aim was also to compare the obtained results in the Republic of Serbia with the results of the same drugs consumption in two Nordic countries, the Kingdom of Norway and the Republic of Finland, countries with well-established pharmacotherapy practice.

MATERIAL AND METHODS

Data on the dispensation of drugs used in pain management in the Republic of Serbia in the period from 2015 to 2018 were retrieved from the official site of the Medicine and Medical Devices Agency of Serbia (ALIMS) (10 - 13).

Data on the utilization of drugs in the Kingdom of Norway for the same period were retrieved from the official website of the Norwegian Institute of Public Health (14) and the official website of the Finnish Medicines Agency Fimea (15).

The methodology used for the results was ATC/DDD methodology. This internationally recognized and widely accepted methodology on drug utilization is based on anatomical-therapeutic-chemical (ATC) classification system and the defined daily dose (DDD) (16).

Consumption of fixed combination of drugs is controlled by defined daily dose (DDD) methodology. Defined daily dose is a statistical measurement unit of drug consumption and it is an average daily dose for a drug used in adults independently of price, strength and package size. The DDD/1,000 inhabitants per day can provide the number of individuals per 1,000 inhabitants who are using certain drug(s) or who are exposed to its effects daily. The evaluation of drug consumption on the national and international level has been simplified and improved by utilization of DDD. DDD is the dose of active substances defined by the WHO Collaborating Center (16, 17).

Anatomical-therapeutic-chemical (ATC) classification is based on seven elements made up from the letters and numbers assigned for the International Nonproprietary Name (INN) of a drug or a combination of drugs. The ATC classification enables complete drug utilization statistics at five different levels, with numbers showing the total consumption

of all the products classified into major groups. Substances are classified into groups at five different levels (16, 17).

The first anatomical level is represented by a capital letter. Drugs are classified into 14 main groups according to the organ or system they primarily act upon. According to the ATC classification, the drugs acting on the central nervous system belong to the group N.

The second level is represented by two digits and indicates the main therapeutic group a certain drug belongs to.

The third level consists of one letter and closely describes the therapeutic-pharmacological subgroup.

The fourth level consists of one letter and indicates the pharmacological-chemical subgroup.

The fifth (chemical) level consists of two digits and indicates a specific drug.

The proportion of utilized drugs is represented as the number of defined daily doses per 1,000 inhabitants per day (DDD/1,000/inhabitants/daily) (17).

The results of this study on drug utilization in the Republic of Serbia, the Kingdom of Norway and the Republic of Finland are presented in tables.

RESULTS

Table 1 shows comparative illustration of drugs consumption in the groups M and N in the Republic of Serbia in the period 2015-2018. The same illustrations for the Kingdom of Norway and the Republic of Finland are shown in Table 2 and 3.

Table 4 illustrates drugs utilization that act upon the nervous system only (group N) in the Republic of Serbia for the studied period, and tables 4 and 5 illustrate drug utilization that act upon the nervous system only (group N) for the Kingdom of Norway and the Republic of Finland.

The illustration on analgesic utilization (N02 group) for the period observed in the Republic of Serbia is shown in Table 7, while the utilization of drugs from the same group for the Kingdom of Norway and the Republic of Finland are shown in Table 8 and 9.

Table 1. *Comparative illustration on drugs consumption in drug groups M and N in the Republic of Serbia in the period 2015-2018 represented in the number DDD/1,000 inhabitants/daily and percentage (%)*

Country	Republic of Serbia							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
A	**170.22**	10.58	**236.74**	14.63	**171.91**	11.32	**212.24**	13.02
B	**290.74**	18.07	**283.59**	17.53	**294.20**	19.37	**319.64**	19.61
C	**701.41**	43.59	**635.12**	39.25	**624.32**	41.09	**658.17**	40.38
D	**0.19**	0.01	**0.20**	0.01	**0.19**	0.01	**0.24**	0.01
G	**40.57**	2.52	**40.43**	2.50	**42.97**	2.83	**40.46**	2.48
H	**25.16**	1.56	**29.45**	1.82	**27.83**	1.83	**25.74**	1.58
J	**35.97**	2.24	**30.74**	1.90	**25.60**	1.69	**25.04**	1.54
L	**4.28**	0.27	**4.93**	0.30	**5.32**	0.35	**5.68**	0.35
M	**71.08**	4.42	**66.88**	4.13	**84.81**	5.58	**69.63**	4.27
N	**185.36**	11.52	**203.35**	12.57	**165.29**	10.88	**189.08**	11.60
P	**0.64**	0.04	**0.59**	0.04	**0.85**	0.06	**0.39**	0.02
R	**73.57**	4.57	**72.00**	4.45	**75.88**	4.99	**83.56**	5.13
S	**9.76**	0.61	**14.09**	0.87	**-**	-	**-**	-
V	**0.05**	0.00	**0.07**	0.00	**0.06**	0.00	**0.06**	0.00
TOTAL	**1.609.01**	100.00	**1.618.17**	100.00	**1.519.22**	100.00	**1.629.93**	100.00

A – Digestive tract and metabolism
B – Blood and blood-forming organs
C – Cardiovascular system
D - Dermatological drugs
G – Urogenital system and sex hormones
H – Systemic hormones without sex hormones
J - Systemic anti-infective drugs
L – Antineoplastics and immunosuppressants
M – Musculoskeletal system
N – Central nervous system
P – Medicines against parasitic infections
R – Respiratory system
S – Sense organs
V – Others
DDD – DDD/1,000 inhabitants/day

Table 2. *Comparative illustration on drugs utilization in groups M and N in the Kingdom of Norway in the period 2015-2018 presented as the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Kingdom of Norway							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
A	**164.26**	12.08	**171.35**	12.38	**177.99**	12.69	**181.57**	12.57
B	**139.87**	10.29	**143.33**	10.35	**144.44**	10.30	**163.63**	11.33
C	**417.84**	30.73	**421.17**	30.42	**424.57**	30.27	**432.87**	29.97
D	**2.44**	0.18	**2.62**	0.19	**2.75**	0.20	**3.00**	0.21
G	**25.42**	1.87	**27.06**	1.95	**28.19**	2.01	**29.71**	2.06
H	**47.64**	3.50	**48.88**	3.53	**48.15**	3.43	**49.17**	3.40
J	**20.81**	1.53	**20.14**	1.45	**19.42**	1.38	**19.14**	1.32
L	**19.06**	1.40	**20.17**	1.46	**21.11**	1.51	**21.72**	1.50
M	**62.30**	4.58	**62.25**	4.50	**63.37**	4.52	**63.15**	4.37
N	**239.10**	17.59	**241.32**	17.43	**242.58**	17.30	**242.04**	16.76
P	**0.97**	0.07	**0.97**	0.07	**0.97**	0.07	**0.97**	0.07
R	**200.08**	14.72	**205.6**	14.85	**209.7**	14.95	**217.86**	15.08
S	**19.57**	1.44	**19.42**	1.40	**19.02**	1.36	**19.37**	1.34
V	**0.28**	0.02	**0.29**	0.02	**0.3**	0.02	**0.33**	0.02
TOTAL	**1.359.64**	100.00	**1.384.57**	100.00	**1.402.56**	100.00	**1.444.53**	100.00

A – Digestive tract and metabolism
B – Blood and blood-forming organs
C – Cardiovascular system
D - Dermatological drugs
G – Urogenital system and sex hormones
H – Systemic hormones without sex hormones
J - Systemic anti-infective drugs
L – Antineoplastics and immunosuppressants
M – Musculoskeletal system
N – Central nervous system
P – Medicines against parasitic infections
R – Respiratory system
S – Sense organs
V – Others
DDD – DDD/1,000 inhabitants/day

Table 3. *Comparative illustration on drug consumption in groups M and N in the Republic of Finland in the period 2015-2018 presented as the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Republic of Finland							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
A	**296.33**	16.65	**297.21**	16.75	**291.99**	16.34	**293.16**	15.99
B	**143.56**	8.07	**138.19**	7.79	**137.60**	7.70	**135.62**	7.40
C	**557.78**	31.34	**556.14**	31.35	**568.49**	31.81	**591.52**	32.26
D	**2.96**	0.17	**2.79**	0.16	**2.72**	0.15	**2.85**	0.16
G	**133.18**	7.48	**131.56**	7.42	**132.34**	7.40	**134.88**	7.36
H	**54.22**	3.05	**54.74**	3.09	**53.64**	3.00	**55.91**	3.05
J	**21.74**	1.22	**19.41**	1.09	**17.82**	1.00	**17.72**	0.97
L	**19.35**	1.09	**20.08**	1.13	**20.52**	1.15	**22.17**	1.21
M	**99.14**	5.57	**98.40**	5.55	**96.53**	5.40	**97.19**	5.30
N	**260.16**	14.62	**256.84**	14.48	**261.90**	14.65	**269.76**	14.71
P	**2.27**	0,13	**2.22**	0.13	**2.31**	0.13	**2.35**	0.13
R	**165.75**	9.31	**171.35**	9.66	**174.56**	9.77	**182.15**	9.93
S	**22.96**	1.29	**24.79**	1.40	**26.66**	1.49	**28.23**	1.54
V	**0.13**	0.01	**0.14**	0.01	**0.15**	0.01	**0.16**	0.01
TOTAL	**1.779.53**	100.00	**1.773.86**	100.00	**1.787.23**	100.00	**1.833.67**	100.00

A – Digestive tract and metabolism
B – Blood and blood-forming organs
C – Cardiovascular system
D - Dermatological drugs
G – Urogenital system and sex hormones
H – Systemic hormones without sex hormones
J - Systemic anti-infective drugs
L – Antineoplastics and immunosuppressants
M – Musculoskeletal system
N – Central nervous system
P – Medicines against parasitic infections
R – Respiratory system
S – Sense organs
V – Others
DDD – DDD/1,000 inhabitants/day

Table 4. *Comparative illustration on drugs utilization that act upon the nervous system only (group N) in the Republic of Serbia for the period 2015-2018 presented in the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Republic of Serbia							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
N	**185.36**	100.00	**203.35**	100.00	**165.29**	100.00	**189.08**	100.00
N02	**6.69**	3.61	**8.68**	4.27	**6.01**	3.64	**7.78**	4.11
N03	**10.09**	5.44	**12.05**	5.93	**13.61**	8.23	**13.25**	7.01
N04	**4.43**	2.39	**4.05**	1.99	**4.35**	2.63	**4.46**	2.36
N05	**120.71**	65.12	**131.65**	64.74	**97.42**	58.94	**107.51**	56.87
N06	**34.73**	18.74	**38.01**	18.69	**35.66**	21.57	**46.55**	24.62
N07	**8.71**	4.70	**8.91**	4.38	**8.24**	4.99	**9.52**	5.03

N – drugs that affect the nervous system
N02 – analgesics
N03 – antiepileptics
N04 – antiparkinsonian drugs
N05 – psycholeptics
N06 – psychoanaleptics
N07 – other drugs that act on the nervous system
DDD – DDD/1,000 inhabitants/day

Table 5. *Comparative illustration on drugs utilization that act upon the nervous system (group N) in the Kingdom of Norway for the period 2015-2018 presented in the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Kingdom of Norway							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
N	**239.10**	100.00	**241.32**	100.00	**242.58**	100.00	**242.04**	100.00
N02	**63.95**	26.75	**66.26**	27.46	**67.30**	27.74	**68.57**	28.33
N03	**16.66**	6.97	**16.87**	6.99	**17.50**	7.21	**17.91**	7.40
N04	**4.08**	1.71	**4.12**	1.71	**4.18**	1.72	**4.28**	1.77
N05	**71.80**	30.03	**71.02**	29.43	**69.47**	28.64	**68.16**	28.16
N06	**70.48**	29.48	**70.63**	29.27	**71.25**	29.37	**70.24**	29.02
N07	**12.13**	5.07	**12.42**	5.15	**12.88**	5.31	**12.88**	5.32

N – drugs that affect the nervous system
N02 – analgesics
N03 – antiepileptics
N04 – antiparkinsonian drugs
N05 – psycholeptics
N06 – psychoanaleptics
N07 – other drugs that act on the nervous system
DDD – DDD/1,000 inhabitants/day

Table 6. *Comparative illustration on drugs utilization that act upon the nervous system (group N) in the Republic of Finland for the period 2015-2018 presented in the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Republic of Finland							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
N	**260.16**	100.00	**256.84**	100.00	**261.04**	100.00	**269.76**	100.00
N02	**51.98**	19.98	**53.29**	20.75	**54.50**	20.81	**54.50**	20.20
N03	**20.13**	7.74	**20.59**	8.02	**21.46**	8.19	**22.23**	8.24
N04	**5.25**	2.02	**5.22**	2.03	**5.17**	1.97	**5.09**	1.89
N05	**78.97**	30.35	**73.44**	28.59	**72.78**	27.79	**73.18**	27.13
N06	**87.88**	33.78	**87.82**	34.19	**90.58**	34.59	**96.70**	35.85
N07	**15.95**	6.13	**16.48**	6.42	**17.41**	6.65	**18.06**	6.69

N – drugs that affect the nervous system
N02 – analgesics
N03 – antiepileptics
N04 – antiparkinsonian drugs
N05 – psycholeptics
N06 – psychoanaleptics
N07 – other drugs that act on the nervous system
DDD – DDD/1,000 inhabitants/day

Table 7. *Comparative illustration of analgesic utilization (group N02) in the Republic of Serbia in the period 2015-2018 presented by the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Republic of Serbia							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
N02	**6.69**	100.00	**8.68**	100.00	**6.01**	100.00	**7.78**	100.00
N02AA01	**0.06**	0.89	**0.05**	0.58	**0.05**	0.83	**0.05**	0.64
N02AA03	**0.05**	0.75	**0.05**	0.58	**0.03**	0.50	**0.03**	0.38
N02AA05	-	**-**	-	**-**	-	**-**	**0.01**	0.13
N02AB02	**0.01**	0.15	**0.01**	0.12	**0.01**	0.17	**0.01**	0.13

N02AB03	**0.11**	1.64	**0.11**	1.27	**0.12**	2.00	**0.13**	1.67
N02AX02	**0.34**	5.07	**0.36**	4.14	**0.32**	5.32	**0.34**	4.36
N02BA01	**1.24**	18.48	**0.80**	9.21	**1.00**	16.64	**0.78**	10.00
N02BB02	**1.85**	27.57	**2.35**	27.04	**1.88**	31.28	**1.56**	20.00
N02BE01	**2.95**	43.96	**3.03**	34.87	**2.04**	33.94	**3.64**	46.67
N02BE51	-	**-**	**1.77**	20.37	**0.38**	6.32	**1.09**	13.97
N02CA52	-	**-**	**0.03**	0.35	**0.05**	0.83	-	**-**
N02CC01	**0.08**	1.19	**0.11**	1.27	**0.11**	1.83	**0.13**	1.67
N02CC03	**0.01**	0.15	**0.01**	0.12	**0.01**	0.17	**0.02**	0.26
N02CC07	**0.01**	0.15	**0.01**	0.12	**0.01**	0.17	**0.01**	0.13

N02 – analgesics
N02AA01 – morphine
N02AA03 – hydromorphone
N02AA05 – oxycodone
N02AB02 – pethidine
N02AB03 – fentanyl
N02AX02 – tramadol
N02BA01 – acetylsalicylic acid
N02BB02 – metamizole-sodium
N02BE01 – paracetamol
N02BE51 – paracetamol, combinations excluding psycholeptics
N02CA52 – ergotamine, mecloxamine, camilofin, caffeine, propyphenazone
N02CC01 – sumatriptan
N02CC03 – zolmitriptan
N02CC07 – frovatriptan
DDD – DDD/1,000 inhabitants/day

Table 8. *Comparative illustration of analgesic utilization (group N02) in the Kingdom of Norway in the period 2015-2018 presented by the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Kingdom of Norway							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
N02	**63.95**	100.00	**66.26**	100.00	**67.30**	100.00	**68.57**	100.00
N02AA01	**1.05**	1.64	**1.11**	1.67	**1.08**	1.60	**1.06**	1.55
N02AA03	**0.19**	0.30	**0.24**	0.36	**0.19**	0.28	**0.18**	0.26
N02AA05	**2.05**	3.20	**2.20**	3.32	**2.40**	3.57	**2.42**	3.53
N02AA55	**0.27**	0.42	**0.28**	0.42	**0.30**	0.45	**0.32**	0.47
N02AB01	**0.14**	0.22	**0.11**	0.17	**0.08**	0.12	**0.08**	0.12
N02AB02	**0.03**	0.05	**0.03**	0.05	**0.02**	0.03	**0.02**	0.03
N02AB03	**1.37**	2.14	**1.43**	2.16	**1.40**	2.08	**1.36**	1.98
N02AE01	**0.70**	1.09	**0.73**	1.10	**0.78**	1.16	**0.77**	1.12
N02AJ06	**9.47**	14.80	**9.10**	13.73	**8.31**	12.35	**7.94**	11.58
N02AJ13	**0.13**	0.20	**0.14**	0.21	**0.09**	0.13	**0.10**	0.15
N02AX02	**4.18**	6.53	**4.30**	6.49	**4.40**	6.54	**4.27**	6.23
N02AX06	**0.08**	0.13	**0.11**	0.17	**0.16**	0.24	**0.19**	0.28
N02BA01	**0.18**	0.28	**0.16**	0.24	**0.13**	0.19	**0.13**	0.19
N02BB51	**1.54**	2.41	**1.45**	2.19	**1.35**	2.01	**1.27**	1.85
N02BE01	**38.07**	59.50	**39.98**	60.32	**41.80**	62.10	**43.60**	63.60
N02BE51	**0.47**	0.73	**0.46**	0.69	**0.45**	0.67	**0.40**	0.58
N02BG10	**0.03**	0.05	**0.32**	0.48	**0.04**	0.06	**0.04**	0.06
N02CC01	**1.64**	2.56	**1.58**	2.38	**1.70**	2.53	**1.72**	2.51
N02CC02	**0.06**	0.09	**0.07**	0.11	**0.07**	0.10	**0.09**	0.13
N02CC03	**0.70**	1.09	**0.78**	1.18	**0.81**	1.20	**0.79**	1.15

N02CC04	**0.67**	1.05	**0.71**	1.07	**0.73**	1.08	**0.75**	1.09
N02CC05	**0.07**	0.11	**0.07**	0.11	**0.07**	0.10	**0.08**	0.12
N02CC06	**0.45**	0.70	**0.48**	0.72	**0.48**	0.71	**0.48**	0.70
N02CX02	**0.38**	0.59	**0.39**	0.59	**0.41**	0.61	**0.43**	0.63

N02 – analgesics
N02AA01 – morphine
N02AA03 – hydromorphone
N02AA05 – oxycodone
N02AA55 – oxycodone, naloxone
N02AB01 – ketobemidone
N02AB02 – pethidine
N02AB03 – fentanyl
N02AE01 – buprenorphine
N02AJ06 – codeine, paracetamol
N02AJ13 – tramadol, paracetamol
N02AX02 – tramadol
N02AX06 – tapentadol
N02BA01 – acetylsalicylic acid
N02BB51 – acetylsalicylic acid, combinations excluding psycholeptics
N02BE01 – paracetamol
N02BE51 – paracetamol, combinations excluding psycholeptics
N02BG10 – cannabinoids
N02CC01 – sumatriptan
N02CC02 – naratriptan
N02CC03 – zolmitriptan
N02CC04 – rizatriptan
N02CC05 – almotriptan
N02CC06 – eletriptan
N02CX02 – clonidine
DDD – DDD/1,000 inhabitants/day

Table 9. *Comparative illustration of analgesic utilization (group N02) in the Republic of Finland in the period 2015-2018 presented by the number DDD/1,000 inhabitants/daily and in percentage (%)*

Country	Republic of Finland							
Year	2015.		2016.		2017.		2018.	
ATC group	**DDD**	%	**DDD**	%	**DDD**	%	**DDD**	%
N02	**51.98**	100.00	**53.29**	100.00	**54.50**	100.00	**54.50**	100.00
N02AA01	**0.30**	0.58	**0.31**	0.58	**0.31**	0.57	**0.29**	0.53
N02AA03	**0.03**	0.06	**0.05**	0.09	**0.08**	0.15	**0.09**	0.17
N02AA05	**1.58**	3.04	**1.59**	2.98	**1.63**	2.99	**1.68**	3.08
N02AA55	**0.21**	0.40	**0.24**	0.45	**0.27**	0.50	**0.27**	0.50
N02AB03	**1.00**	1.92	**0.95**	1.78	**0.89**	1.63	**0.83**	1.52
N02AE01	**0.98**	1.89	**1.15**	2.16	**1.29**	2.37	**1.38**	2.53
N02AJ06	**8.30**	15.97	**7.75**	14.55	**7.11**	13.04	**6.32**	11.60
N02AJ08	**0.24**	0.46	**0.22**	0.41	**0.10**	0.18	**0.14**	0.26
N02AJ13	**-**	-	**0.00**	0.00	**0.15**	0.28	**0.29**	0.53
N02AX02	**2.93**	5.64	**2.83**	5.31	**2.76**	5.06	**2.62**	4.81
N02BA01	**1.14**	2.19	**1.04**	1.95	**0.95**	1.74	**0.83**	1.52
N02BA51	**1.04**	2.00	**1.02**	1.91	**0.93**	1.71	**0.85**	1.56
N02BE01	**32.05**	61.66	**33.86**	63.55	**35.78**	65.63	**36.46**	66.91
N02BE51	**0.13**	0.25	**0.13**	0.24	**0.17**	0.31	**0.16**	0.29
N02CC01	**1.38**	2.65	**1.44**	2.70	**1.36**	2.49	**1.49**	2.73
N02CC02	**0.03**	0.06	**0.03**	0.06	**0.03**	0.06	**0.02**	0.04
N02CC03	**0.16**	0.31	**0.17**	0.32	**0.18**	0.33	**0.19**	0.35
N02CC04	**0.10**	0.19	**0.11**	0.21	**0.12**	0.22	**0.13**	0.24
N02CC05	**0.09**	0.17	**0.09**	0.17	**0.09**	0.17	**0.10**	0.18
N02CC06	**0.17**	0.33	**0.17**	0.32	**0.18**	0.33	**0.20**	0.37
N02CC07	**0.12**	0.23	**0.13**	0.24	**0.14**	0.26	**0.15**	0.28

N02 – analgesics
N02AA01 – morphine
N02AA03 – hydromorphone
N02AA05 – oxycodone
N02AA55 – oxycodone, naloxone
N02AB03 – fentanyl
N02AE01 – buprenorphine
N02AJ06 – codeine, paracetamol
N02AJ08 – codeine, ibuprofen
N02AJ13 – tramadol, paracetamol
N02AX02 – tramadol
N02BA01 – acetylsalicylic acid
N02BA51 – acetylsalicylic acid, combinations excluding psycholeptics
N02BE01 – paracetamol
N02BE51 – paracetamol, combinations excluding psycholeptics
N02CC01 – sumatriptan
N02CC02 – naratriptan
N02CC03 – zolmitriptan
N02CC04 – rizatriptan
N02CC05 – almotriptan
N02CC06 – eletriptan
N02CC07 – frovatriptan
DDD – DDD/1,000 inhabitants/day

DISCUSSION

Drugs that are used for pain pharmacotherapy belong to the group M and group N according to ATC drug classification.

The utilization of drugs that act on the nervous system (group N) in the Republic of Serbia in the observational period was rather high. The overall consumption of drugs from the group N in 2015 was 185.36 DDD/1,000 inhabitants/daily or 11.52% of total consumption in the Republic of Serbia; in 2016, the utilization was 203.35 DDD/1,000 inhabitants/per day or 12.57%; in 2017 there were 165.29 DDD/1,000 inhabitants/daily or 10.88%, and in 2018 189.08 DDD/1,000 inhabitants/daily or 11.60%. By observing the total consumption of drugs in the Republic of Serbia, drugs from group N in the first year of the observational period were on the third place, while they shifted to the fourth place in the following three years.

In the Kingdom of Norway, the consumption of group N drugs in 2015 was 239.10 DDD/1,000 inhabitants/daily or 17.59%; in 2016, it was 241.32 DDD/1,000 inhabitants /daily or 17.43%; in 2017, the consumption was 242.58 DDD/1,000 inhabitants/daily or 17.30%, while in 2018 it was 242.04 DDD/1,000 inhabitants/daily or 16.76% out of total number of utilized drugs in the Kingdom of Norway, and that is more than in the Republic of Serbia in the same period. In the Kingdom of Norway, unlike in the Republic of Serbia, in the observed period, the consumption of drugs from the group N was rather consistent and was about 240 DDD/1,000 inhabitants/daily or about 17% out of the total consumption of drugs. Within the total drugs utilization, group N was on the fourth place during all the four years in the Kingdom of Norway.

Group N was in the Republic of Finland on the third place out of the total drug consumption during all the four years of the observational period. In the Republic of Finland, the consumption of drugs from the group N in 2015 was 260.16 DDD/1,000 inhabitants/daily or 14.62%; in 2016, it was 256.84 DDD/1,000 inhabitants/daily or 14.48%, in 2017 it was 261.90 DDD/1,000 inhabitants/daily or 14.65%, while in 2018 it was 269.76 DDD/1,000 inhabitants/daily or 14.71% out of the total consumption of drugs in this country. Similar to the Kingdom of Norway, group N drugs consumption in the observational period in the Republic of Finland was pretty consistent and was about 260 DDD/1,000 inhabitants/daily or about 14.5% out of the total consumption of drugs. Also, such a consumption of drugs in the Republic of Finland was higher both absolutely and relatively in comparison to the Republic of Serbia in the same period. In comparison to the Kingdom of Norway, the consumption of drugs from the group N in the Republic of Finland was relatively slightly lower and was about 14.5% out of the total consumption of drugs. In absolute numbers, the utilization in the Republic of Finland is by 20 DDD/1,000 inhabitants/daily higher than in the Kingdom of Norway.

By further analysis and by comparing drug utilization from the group N in the observational period, it can be seen that in the Republic of Serbia the consumption of analgesics (group N02) was in the range between 3.61% and 4.27% of the overall consumption of drugs that act upon the nervous system. During 2015, the total consumption of analgesics on the territory of the Republic of Serbia was 6.69 DDD/1,000 inhabitants/daily, in 2016, the consumption of these drugs was 8.68 DDD/1,000 inhabitants/daily; in 2017, it was 6.01 DDD/1,000

inhabitants/daily, while in 2018 the consumption was 7.78 DDD/1,000 inhabitants/daily. In the Republic of Serbia analgesics were on the fifth place regarding consumption out of a total of six subgroups in the group N during all four years of the observational period. Such a consumption of analgesics can be explained by the fact that patients do not commonly complain about pain, presuming that it is normal to endure pain within their underlying disease or in a postoperative period, or a practicing physician forgot to ask patients about their eventual pain and did not prescribe analgesic therapy.

In the Kingdom of Norway and in the Republic of Finland, analgesics are much more present in the overall consumption of drugs that act upon the nervous system in comparison to the Republic of Serbia. In the Kingdom of Norway, the percentage was from 26.75% to 28.33%, while in the Republic of Finland, it was in the range from 19.98% to 20.81% out of the overall consumption of drugs that act upon the nervous system. In the Kingdom of Norway in 2015, the consumption of analgesics was 63.95 DDD/1,000 inhabitants/daily, in 2016 it was 66.26 DDD/1,000 inhabitants/daily, in 2017 it was 67.30 DDD/1,000 inhabitants/daily, and in 2018 this consumption was 68.57 DDD/1,000 inhabitants/daily. In the first three observational years the utilization of analgesics in the Kingdom of Norway took the third place per N group drugs consumption, while it was ranked second place in the fourth year. The consumption of analgesics in the Republic of Finland in 2015 was 51.98 DDD/1,000 inhabitants/day, in 2016, it was 53.29 DDD/1,000 inhabitants/day, while in 2017 and 2018, it was 54.50 DDD/1,000 inhabitants/day. During all four years of observation, the consumption of analgesics was at the third place in the N group drugs consumption in the Republic of Finland. A higher utilization of analgesics in these countries in comparison to our country indicates a higher level of awareness among their population regarding the quality of life of persons suffering from pain, it also shows that their practicing physicians have more time dedicated to conversation and examination of patients, when information on painful conditions should be gathered, followed by analgesics prescriptions. In our country, due to the organization of healthcare system and services, practicing physicians are not always able to take enough time to devote to conversation with patients, so sometimes important anamnestic details about pain are lacking, resulting in underprescription of analgesics and lower consumption of these drugs in comparison to developed countries.

By observing the consumption of certain drugs within N02 group in the Republic of Serbia, the greatest consumption in the observational period was recorded for paracetamol (N02BE01). Its consumption in 2015 was 2.95 DDD/1,000 inhabitants/day or 43.96%; in 2016, it was 3.03 DDD/1,000 inhabitants/day or 34.87%; in 2017, it was 2.04 DDD/1,000 inhabitants/day or 33.94%, while in 2018 it was 3.64 DDD/1,000 inhabitants/day or 46.67% out of the overall consumption of drugs from N02 group. The second highest consumed drug in the Republic of Serbia is metamizole - sodium (N02BB02). Its consumption in 2015 was 1.85 DDD/1,000 inhabitants/day or 27.57%; in 2016, it was 2.35 DDD/1,000 inhabitants/day or 27.04%; in 2017, it was 1.88 DDD/1,000 inhabitants/day or 31.28%, while in 2018 it was 1.56 DDD/1,000 inhabitants/day or 20.00% out of the overall consumption of N02 group drugs. The third highest consumed drug in the Republic of Serbia was shared between acetylsalicylic acid (N02BA01) and paracetamol, excluding combinations with psycholeptics (N02BE51). The third highest consumed drug in the Republic of Serbia in 2015 and 2017 was acetylsalicylic acid (N02BA01). Its consumption in 2015 was 1.24 DDD/1,000 inhabitants/day or 18.48%, while in 2017 it was 1.00 DDD/1,000 inhabitants/day or 16.64% out of the overall consumption of group N02 drugs. The consumption of paracetamol, excluding combinations with psycholeptics (N02BE51) in the Republic of Serbia in 2016 was 1.77 DDD/1,000 inhabitants/day or 20.37%, while in 2018 it was 1.09 DDD/1,000 inhabitants/day or 13.97% out of the overall consumption of drugs from the group N02.

In the Kingdom of Norway and the Republic of Finland, paracetamol (N02BE01) was the highest ranked consumed drug. Consumption of this drug in the observational period was about fifteen times higher in the Kingdom of Norway in comparison to the Republic of Serbia. Similar situation is about the Republic of Finland. The consumption of this drug was about ten times higher in the Republic of Finland in comparison to the Republic of Serbia.

The consumption of paracetamol in the Kingdom of Norway in 2015 was 38.07 DDD/1,000 inhabitants/day or 59.50%; in 2016, it was 39.98 DDD/1,000 inhabitants/day or 60.32%; in 2017, it was 41.80 DDD/1,000 inhabitants/day or 62.10%, while in 2018 it was 43.60 DDD/1,000 inhabitants/day or 63.60%

out of the overall consumption of group N02 drugs. The consumption of paracetamol showed a positive trend in the observed period in the Kingdom of Norway. The second highest consumed drug in the Kingdom of Norway was a fixed combination of codeine and paracetamol (N02AJ06). The consumption of this fixed combination in the Kingdom of Norway in 2015 was 9.47 DDD/1,000 inhabitants/day or 14.80%; in 2016, it was 9.10 DDD/1,000 inhabitants/day or 13.73%; in 2017, it was 8.31 DDD/1,000 inhabitants/day or 12.35%, while in 2018 it was 7.94 DDD/1,000 inhabitants/day or 11.58% out of the overall drug consumption in the group N02. The third highest consumed drug in the Kingdom of Norway was tramadol (N02AX02) and its consumption in 2015 was 4.18 DDD/1,000 inhabitants/day or 6.53%; in 2016, it was 4.30 DDD/1,000 inhabitants/day or 6.49%; in 2017, it was 4.40 DDD/1,000 inhabitants/day or 6.54%, while in 2018 it was 4.27 DDD/1,000 inhabitants/day or 6.23% out of the overall consumption of N02 group drugs.

In the Republic of Finland, similar to the Kingdom of Norway, the first highest consumed drug was paracetamol (N02BE01), the second one was the fixed combination of codeine and paracetamol (N02AJ06), and the third highest consumed drug was tramadol (N02AX02). Paracetamol consumption in the Republic of Finland in 2015 was 32.05 DDD/1,000 inhabitants/day or 61.66%; in 2016, it was 3.86 DDD/1,000 inhabitants/day or 63.55%; in 2017, it was 35.78 DDD/1,000 inhabitants/day or 65.63%, while in 2018 it was 36.46 DDD/1,000 inhabitants/day or 66.91% out of the overall consumption of N02 group drugs. This drug showed a constant increase in the observed period. The second highest consumed drug in the Republic of Finland was a fixed combination codeine and paracetamol (N02AJ06). The consumption of this combination in 2015 was 8.30 DDD/1,000 inhabitants/day or 15.97%; in 2016, it was 7.75 DDD/1,000 inhabitants/day or 14.55%; in 2017, it was 7.11 DDD/1,000 inhabitants/day or 13.04 %, while in 2018 it was 6.32 DDD/1,000 inhabitants/day or 11.60% out of the overall consumption of N02 group drugs. Unlike paracetamol, this fixed combination showed a negative trend in the observed period. The third highest consumed drug in the Republic of Finland was tramadol (N02AX02). Its consumption in 2015 was 2.93 DDD/1,000 inhabitants/day or 5.64%; in 2016, it was 2.83 DDD/1,000 inhabitants/day or 5.31%; in 2017, it was 2.76 DDD/1,000 inhabitants/day or 5.06%, while in 2018 it was 2.62 DDD/1,000 inhabitants/day or 4.81% out of the overall consumption of group N02 drugs. The use of this drug decreases slightly every year.

A consequence of higher consumption of non-opioid vs opioid analgesics is explained by the fact that opiophobia – excessive fear of prescribing opioid analgesics even in cases when they are indicated (e.g. cancer pain and other types of chronic non-malignant pain) – is widespread across the world. Irrational fear of prescribing this group of drugs, especially strong opioids, is associated with potential harmful effects, not only in healthcare professionals, but it is also present in patients who are afraid of using opioids although they are at the end of life and they should be on opioid therapy, but despite being aware that NSAIDs do not provide an adequate analgesic response and quality of life, they are still against opioid therapy (18).

The results of this study are based on the facts and thus they are logical, showing that opioid analgesics consumption is significantly lower than the consumption of non-steroidal anti-inflammatory drugs and non-opioids. Also, paracetamol is the most commonly prescribed drug as it is safe in all population groups, and consequently its consumption is greatest, as well as fixed combinations of this drug with another analgesic.

Tramadol is the best-selling opioid analgesic. It is the oldest opioid on the market, a weak opioid indicated to treat moderate pain, so it is most commonly prescribed drug from this group of analgesics. It is the third most consumed drug from this group in developed countries, probably due to its well-known safety profile regarding potential interactions with other co-medications in patients, adverse events profile and many years of experience (19).

The consumption of drugs acting upon the musculoskeletal system (group M) in the Republic of Serbia in 2015 was 71.08 DDD/1,000 inhabitants/day or 4.42%; in 2016, it was 66.88 DDD/1,000 inhabitants/day or 4.13%; in 2017, it was 84.81 DDD/1,000 inhabitants/day or 5.58%, while in 2018 it was 69.63 DDD/1,000 inhabitants/day or 4.27% out of the overall consumption of drugs.

Drugs acting on musculoskeletal system (group M) in the Kingdom of Norway are slightly less consumed in comparison to the Republic of Serbia. It can be noted that their utilization in the Kingdom of Norway was constant, within the range from 62.25 to 63.37 DDD/1,000 inhabitants/day. The

consumption of these drugs in 2015 was 4.58%; in 2016, it was 4.50%; in 2017, it was 4.52%, while in 2018 it was 4.37% out of the overall consumption of drugs in the Kingdom of Norway.

The highest consumption rate of drugs acting upon the musculoskeletal system (group M) was recorded in the Republic of Finland. The consumption of this group drugs in the Republic of Finland in 2015 was 99.14 DDD/1,000 inhabitants/day or 5.57%; in 2016, it was 98.40 DDD/1,000 inhabitants/day or 5.55%; in 2017, it was 96.53 DDD/1,000 inhabitants/day or 5.40%, while in 2018, it was 97.19 DDD/1,000 inhabitants/day or 5.30% out of the overall consumption of drugs.

By further analysis and comparison of group M drugs consumption, it can be seen that in all three countries, the first place undoubtedly belongs to anti-inflammatory drugs and antirheumatic drugs (group M01).

The consumption of anti-inflammatory and antirheumatic drugs (group M01) in the Republic of Serbia was in the range from 85.38% to 90.46% out of the overall consumption of drugs for the musculoskeletal system diseases (group M). In 2015, the overall consumption of anti- inflammatory and antirheumatic drugs on the territory of the Republic of Serbia was 63.09 DDD/1,000 inhabitants/day; in 2016, the consumption of these drugs was 58.55 DDD/1,000 inhabitants/day; in 2017, it was 76.72 DDD/1,000 inhabitants/day, while in 2018 it was 59.45 DDD/1,000 inhabitants/day.

The consumption of anti-inflammatory and antirheumatic drugs in the Kingdom of Norway in 2025 was 47.24 DDD/1,000 inhabitants/day or 75.32 %; in 2016, it was 47.48 DDD/1,000 inhabitants/day or 75.88%; in 2017, it was 48.50 DDD/1,000 inhabitants/day or 75.98%, while in 2018 it was 47.32 DDD/1,000 inhabitants/day or 75.76% out of the overall consumption drugs from group M. The consumption of drugs from this group in the Kingdom of Norway was constant in the observed years.

The consumption of anti-inflammatory and antirheumatic drugs in the Republic of Finland is also constant, similar to the Kingdom of Norway, but the consumption is somewhat higher. Therefore, in 2015 it was 78.66 DDD/1,000 inhabitants/day or 79.33%, in 2016; it was 78.81 DDD/1,000 inhabitants/day or 80.10%; in 2017, it was 76.73 DDD/1,000 inhabitants/day or 79.50%, while in 2018 it was 77.40 DDD/1,000 inhabitants/day or 79.67% out of the overall consumption of group M drugs.

As for the consumption of individual drugs within M01 group in the Republic of Serbia, the highest consumption rate in the observed period was registered for diclofenac (M01AB05). Its consumption in 2015 was 31.09 DDD/1,000 inhabitants/day or 49.28%; in 2016, it was 25.23 DDD/1,000 inhabitants/day or 43.09%; in 2017, it was 40.44 DDD/1,000 inhabitants/day or 72%, while in 2018 it was 20.99 DDD/1,000 inhabitants/day or 35.31% out of the overall consumption of drugs from M01 group. Diclofenac had the highest rate of consumption and that can be explained by general practitioners' prescriptions, pharmacists' recommendation in pharmacies, recommendations by patients themselves, what is pretty common in our country, because of the lack of awareness among population about its (and other NSAIDs) safety profile in long-term use, in terms of gastrointestinal and cardiovascular side effects (20, 21). The second highest place for consumption in the Republic of Serbia is taken by ibuprofen (M01AE01). Its consumption in 2015 was 15.50 DDD/1,000 inhabitants/day or 24.57%; in 2016, it was 16.01 DDD/1,000 inhabitants/day or 27.34%; in 2017, it was 18.22 DDD/1,000 inhabitants/day or 23.75%, while in 2018 it was 19.43 DDD/1,000 inhabitants/day or 32.68% out of the overall consumption of drugs from M01 group. As for ibuprofen, it is also used in everyday practice of general practitioners in our country, however, nowadays, its safety profile is much better understood in terms of gastrointestinal side effects in comparison to diclofenac (22). The third place regarding consumption in the Republic of Serbia belongs to nimesulide (M01AX17). The consumption of nimesulide in 2015 was 6.26 DDD/1,000 inhabitants/day or 9.92%; in 2016, it was 6.75 DDD/1,000 inhabitants/day or 11.53%; in 2017, it was 7.72 DDD/1,000 inhabitants/day or 10.06%, while in 2018 it was 7.58 DDD/1,000 inhabitants/day or 12.75% out of the overall consumption of drugs from M01 group. This drug, just as ibuprofen, has a significant place in the overall consumption of analgesics in our country, but also in a suppository form to partially avoid its inadequate safety profile and to achieve adequate analgesia at the same time (23).

In the Kingdom of Norway, the most consumed drug was ibuprofen (M01AE01). Its consumption in 2015 was 17.05 DDD/1,000 inhabitants/day or 36.09%; in 2016, it was 16.87 DDD/1,000 inhabitants/day or 35.53%; in 2017, it was 17.16 DDD/1,000 inhabitants/day or 35.38%, while in 2018 it was

16.24 DDD/1,000 inhabitants/day or 34.31% out of the overall consumption of drugs from M01 group.

As for diclofenac, (M01AB05), it can be seen that this drug was the second highest consumed drug in the Kingdom of Norway only in the first observed year. During the other three years, it was at the third place. On the other hand, a fixed combination of naproxen and esomeprazole (M01AE52) in the first year of the observed period it was third, while it took the second place in the following three years.

Diclofenac consumption (M01AB05) in the Kingdom of Norway in 2015 was 7.97 DDD/1,000 inhabitants/day or 16.87%; in 2016, it was 7.25 DDD/1,000 inhabitants/day or 15.27%; in 2017, it was 6.85 DDD/1,000 inhabitants/day or 14.12%, while in 2018 it was 6.31 DDD/1,000 inhabitants/day or 13.33% out of the overall consumption of drugs from M01 group. As it can be seen, diclofenac consumption in the Kingdom of Norway declined every year, both in absolute and relative figures. On the other hand, constant increase of fixed combination of naproxen and esomeprazole consumption was recorded during all four observed years. The consumption of fixed combination of naproxen and esomeprazole in the Kingdom of Norway in 2015 was 6.50 DDD/1,000 inhabitants/day or 13.76%; in 2016, it was 7.93 DDD/1,000 inhabitants/day or 16.70%; in 2017, it was 9.17 DDD/1,000 inhabitants/day or 18.91%, while in 2018 it was 9.96 DDD/1,000 inhabitants/day or 21.04% out of the total consumption of drugs in the M01 group. It is obvious that naproxen shows the safest profile in terms of least harmful cardiovascular events in long-term use, which may be a reason for its presence in drug consumption in the Kingdom of Norway (24).

In the Republic of Finland, similar to the Kingdom of Norway, the first most consumed drug was ibuprofen (M01AE01). Its share was over 60% out of the total consumption of all drugs from the group M01. Its consumption in the Republic of Finland in 2015 was 49.19 DDD/1,000 inhabitants/day or 62.67 %; in 2016, it was 50.48 DDD/1,000 inhabitants/day or 64.17%; in 2017, it was 49.14 DDD/1,000 inhabitants/day or 64.13%, while in 2018 it was 49.77 DDD/1,000 inhabitants/day or 64.40% out of the total consumption of drugs from the group M01. It can be observed that the consumption of this drug was pretty constant over the period of the observed four years. The second most consumed drug in the Republic of Finland was etoricoxib (M01AH05). Its consumption in 2015 was 6.48 DDD/1,000 inhabitants/day or 8.26%; in 2016, it was 6.73 DDD/1,000 inhabitants/day or 8.56%; in 2017, it was 7.47 DDD/1,000 inhabitants/day or 9.75%, while in 2018 it was 8.89 DDD/1,000 inhabitants/day or 11.50% out of the total consumption of drugs in the group M01. Etoricoxib is a selective inhibitor of COX2 enzyme. The application this drug registered a rise in the Republic of Finland, both absolute and relative. The third most consumed drug in the Republic of Finland was naproxen (M01AE02). Its consumption in 2015 was 6.21 DDD/1,000 inhabitants/day or 7.91 %; in 2016, it was 6.27 DDD/1,000 inhabitants/day or 7.97%; in 2017, it was 6.04 DDD/1,000 inhabitants/day or 7.88%, while in 2018 it was 5.90 DDD/1,000 inhabitants/day or 7.63% out of total consumption of drugs in the M01 group. This drug showed mild decrease in consumption in each of the observed years. Coxibs are analgesics with high gastrointestinal safety and they are highly selective for the COX2 isoenzyme, so these properties may explain etoricoxib consumption in the Republic of Finland (25).

Diclofenac and ibuprofen are the most common and among the oldest prescribed drugs in the NSAIDs group prescribed by different specialists (from general practitioners to neurologists and neurosurgeons) for pain of different etiology. Apart from this, pharmacists also mostly recommend these two drugs in pharmacies, thus it is expected that their consumption is the highest. Diclofenac can also be found in the Republic of Serbia in the fixed combination with proton pump inhibitors (e.g. omeprazole). These drugs are still the most prescribed ones although they do not have an adequate safety profile, especially in long-term use, and this is probably due to their good analgesic potential for mild to moderate pain intensity. The most common side effects of their use are gastrointestinal problems in terms of ulcerogenic potential and possibility of gastrointestinal bleeding during a long-term use (21).

Unlike these two drugs, naproxen has been on the market in the Republic of Serbia only recently and there is a tendency of its active prescribing, primarily to elderly patients to alleviate pain of different etiology, it also has a good safety profile, primarily in terms of cardiovascular safety. In the Republic of Serbia it is not available in fixed combinations with proton pump inhibitors.

A significantly higher consumption of non-opioid analgesics in the Republic of Serbia is also ex-

plained by the fact that they are available in pharmacies as over-the-counter drugs without doctor's prescription, and very often patients buy them without consultations with doctors or pharmacists and without doctor's prescription. Perhaps the limitations of buying OTC drugs and better control by the physicians, prescriptions for drugs in this group would probably decrease and be more rational and maybe result in an increase for prescribing opioid analgesics for adequate conditions for which non-opioids are greatly prescribed or patients buy them on their own.

Unlike other countries, prescription use and consumption of selective COX2 inhibitors is rather low in our country, partially because of the limited number of agents in this group that are registered in our country, and partially because of limited indications due to safety risk in terms of cardiovascular toxicity.

CONCLUSION

The most consumed drug from the analgesics group (N02) in the Republic of Serbia was paracetamol. However, depending on the observed years, the consumption of this drug was from 13 to even 20 times less in the Republic of Serbia in comparison to the Kingdom of Norway and 10 to 15 times less in comparison to the Republic of Finland.

The consumption of metamizole – sodium in the Republic of Serbia was significant and was in the range between 20% and 30%out of total consumption of drugs in analgesics group (N02), depending on the year that was observed. The consumption of this drug was not registered in the same period in the Kingdom of Norway and the Republic of Finland.

As for anti-inflammatory and antirheumatic drugs in the Republic of Serbia, the highest consumption was registered for diclofenac. In the Kingdom of Norway and the Republic of Finland, ibuprofen was rated first in this group of drugs. A fixed combination of naproxen and esomeprazole is not present on the market in the Republic of Serbia, while the consumption of this drug in the Kingdom of Norway increased from initial 13% to over 21% out of the total consumption of drugs in this group of analgesics (N02) at the end of the observational period. The consumption of this fixed combination of drugs in the Republic of Finland was about 2 % out of total consumption of drugs in this group of analgesics (N02) throughout all four years of the observation period.

The consumption of selective COX2 inhibitors in the Republic of Serbia was about 0.5%, while, on the other hand, in the Kingdom of Norway and in the Republic of Finland the consumption of these drugs was about 10% out of the total consumption of drugs in this group of analgesics (N02) during the observational period.

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Uporedna farmakoepidemiološka analiza potrošnje analgetika u Republici Srbiji i nordijskim zemljama u periodu od 2015. do 2018. godine

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SAŽETAK

Uvod/Cilj. Analgetici su lekovi koji se koriste u farmakoterapiji bola i nalaze se među najpropisivanijim lekovima u svim zemljama. Savremena farmakoterapija bola podrazumeva upotrebu analgetskih stepenica. Cilj ovog rada bio je da se analizira potrošnja lekova korišćenih u farmakoterapiji bola u Republici Srbiji (RS) u periodu od 2015. do 2018. godine i da se dobijeni rezultati uporede sa potrošnjom navedenih lekova u Kraljevini Norveškoj (KN) i Republici Finskoj (RF) u istom vremenskom intervalu.

Materijal i metode. Podaci o potrošnji lekova preuzeti su sa sajta Agencije za lekove i medicinska sredstva Srbije, sa zvaničnog sajta Norveškog instituta za javno zdravlje i sa zvaničnog sajta Agencije za lekove Finske. Potrošnja lekova praćena je primenom metodologije definisane dnevne doze (DDD).

Rezultati. Potrošnja paracetamola bila je od 13 do čak 20 puta manja u RS nego u KN i od 10 do 15 puta manja nego u RF. Prosečna potrošnja diklofenaka tokom četiri posmatrane godine bila je oko 30 DDD/1000 stanovnika/dan u RS, odnosno oko 7 DDD/1000 stanovnika/dan u KN i oko 4 DDD/1000 stanovnika/dan u RF.

Zaključak. U farmakoterapiji bola u RS u potrošnji nesteroidnih antiinflamatornih lekova dominira diklofenak; u KN i RF od neopioidnih analgetika najčešće se koriste ibuprofen i paracetamol.

Ključne reči: **farmakoterapija bola, analgetici, nesteroidni antiinflamatorni lekovi, potrošnja lekova**