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Opioid Prescribing Trends by Croatian Dentists - Is there a Reason for Concern?

Trendovi u propisivanju opioida kod doktora dentalne medicine u Hrvatskoj – postoji li razlog za zabrinutost?

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Abstract

Objective: Prescription opioid abuse, associated with numerous opioids, is a well-established public health problem in developed countries such as the UK, US and Australia. Opioids have a limited role in general dental practice; hence the aim of this study was to assess prescribing rates of opioids in dentistry from 2013 to 2023 in Croatia. **Materials and Methods:** Data on opioid prescribing practices for this study were provided by the Croatian Health Insurance Fund. The analysis included the number of prescriptions, cost, and the number of packages prescribed. **Results:** Over the 11 years, dentists in Croatia have prescribed a total of 9132 opioid prescriptions, representing annually on average 1,1% of all analgesic prescriptions, and 0,2% of all dental prescriptions. The number of opioid prescriptions per 1,000 dental patients was on average 0, 19. Tramadol/paracetamol and tramadol were the most prescribed opioids, with average annual number of prescriptions amounting to 622, 7 (64% of opioids prescriptions) and 114, 5 (1, 1% of analgesic prescriptions), respectively. Trends in opioid prescription varied, especially during pandemic years (2020-2022), when tramadol rates decreased while fixed combination medications tramadol/paracetamol and tramadol/dexketoprofen increased. But an overall increasing trend was observed during that period. **Conclusion:** Dentists in Croatia are restrictive and conservative in prescribing opioids, and there is no need for intervention, but because of increasing trends, observing the prescribing pattern in the future is highly recommended.

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Introduction

Opioid analgesic medications can effectively reduce pain when taken as prescribed. Because of the possibility of abuse, addiction, or overuse, doctors must exercise extreme caution when administering opioids. Opioids have been prescribed more frequently globally in recent years, especially to treat persistent non-cancerous pain. (1). Opioids prescribed for dental pain are usually for indications such as the acute pain occurring with an infection, surgical removal of teeth, periodontal surgery and dental implants. There are also limited indications for chronic pain treatment such as long term dental pain associated with temporomandibular joint syndrome, but those do not represent a large number of opioid prescriptions (2). The use of opioids in general dentistry is limited. For dental pain management, NSAIDs alone (i.e. ibuprofen or naproxen) or in combination with paracetamol are more effective in reducing postoperative pain after dental procedures than opioid medications. For mild to moderate pain,

Uvod

Pravilnom primjenom opioidni analgetici mogu učinkovito ublažiti bol. Najveći oprez koji liječnici moraju primijeniti pri propisivanju tih lijekova proizlazi iz njihova potencijala za zlouporabu, razvoj ovisnosti ili nepravilnu upotrebu. U posljednjih nekoliko godina poraslo je propisivanje opioida diljem svijeta, posebno za liječenje kronične nekancerozene boli (1). Oni koji se propisuju za dentalnu bol obično su namijenjeni smirivanju akutne boli povezane s infekcijom, kirurškim vadenjem zuba, parodontološkim zahvatima i dentalnim implantatima. Postoje i ograničene indikacije za liječenje kronične boli, poput dugotrajne dentalne boli povezane s temporomandibularnim poremećajem, no takvi slučajevi nisu među značajnim dijelom propisanih opioida (2). Opioidi se ograničeno koriste u općoj dentalnoj praksi. Za upravljanje dentalnom boli nesteroidni protuupalni lijekovi (NSAID), poput ibuprofena ili naproksena, samostalno ili u kombinaciji s paracetamolom, učinkovitiji su od opioidnih

400 mg ibuprofen 4 times daily for 5 days provides effective analgesia, while for moderate to severe pain, 400 mg of ibuprofen plus 1,000 mg of paracetamol 4 times a day for 5 days. Those regimes provide pain relief as effective as, if not more effective as pain relief provided by opioids by the latest evidence based report (3-5). NSAIDs block the inflammatory mediators - prostaglandins, which cause postoperative pain, edema, and hyperalgesia following surgeries such as extractions. Opioids do not target inflammation; instead, they block the nociceptive pathway, which reduces pain perception. Nevertheless, in recent years, the rate of dental opioid prescriptions has risen globally (6).

Since there are no data available on utilization of opioids in dentistry in Croatia, the aim of this study was to evaluate the prescription patterns dispensed for opioid pain relievers among Croatian dentists.

Materials and Methods

This research included an analysis of issued prescriptions to the Croatian population from the Croatian Health Insurance Fund (CHIF), a nationally-representative database managed by the Ministry of Health of the Republic of Croatia. Data for analysis consisted of the number of prescriptions, the price of medicines expressed in the former national currency (Croatian Kuna [HRK]), and the number of prescribed packages. Since the legal regulations for prescribing opioids are strict to prevent their misuse, there are no private practice prescriptions. The dataset excluded also medicines dispensed to hospital patients' prescription (7).

In this study we analyzed the following opioid prescribed: morphine, oxycodone, oxycodone/naloxone, fentanyl, buprenorphine, tramadol, tapentadol, tramadol/paracetamol and tramadol/dexketoprofen which belong to N02AA, N02AB, N02AD, N02AE, N02AJ and N02AX anatomical therapeutic chemical code (ATC) groups.

For comparison of the rate of opioids in relation to all analgesic medication, we extracted data on ATC groups for M01AB, M01AC, M01AE and M01AH since there are no published data on analgesic prescriptions in Croatia.

In conducting the analysis of prescription data, we employed the ATC classification system established by the World Health Organization (WHO) to categorize medications accurately and the defined daily dose (DDD) (8). This unit was created to enable the comparison of drug consumption trends across different regions and time.

In the majority of pharmacoepidemiologic investigations, the DDD has become a standard dose unit because it offers a fixed unit of measurement that is unaffected by dosage form, package size, or cost. The DDD of every chemical substance administered by SIGAF was initially transformed into the same mass-milligram unit in accordance with the 2019 Guidelines for ATC categorization and DDD assignment as well as the list of DDD for combined goods. After

lijekova kad je riječ o smanjenju postoperativne boli poslije dentalnih zahvata. Za blagu do umjerenu bol, prema najnovijim izvješćima na temelju dokaza, 400 mg ibuprofena četiri puta na dan tijekom pet dana pruža učinkovitu analgeziju, a za umjerenu do jaku bol 400 mg ibuprofena i 1000 mg paracetamola četiri puta na dan tijekom pet dana omogućuje jednako, ako ne i učinkovitije olakšanje boli nego što se to postiže opioidnim lijekovima (3 – 5). NSAID-i inhibiraju prostaglandin koji je odgovoran za upalne medijatore koji uzrokuju postoperativnu bol, oticanje i hiperalgiju poslije zahvata poput vađenja zuba. Opioidi samo prekidaju nociceptivni put kako bi inhibirali percepciju boli, ali ne djeluju na upalu. Unatoč tomu, stopa propisivanja tih lijekova u dentalnoj medicini porasla je u posljednjih nekoliko godina diljem svijeta (6).

S obzirom na to da nema dostupnih podataka o korištenju opioida u dentalnoj medicini u Hrvatskoj, svrha je ovog istraživanja evaluirati obrasce propisivanja opioida za ublažavanje boli, tj. u kojem slučaju to čine doktori dentalne medicine u Hrvatskoj.

Materijali i metode

Ovo istraživanje obuhvatilo je analizu izdanih recepata hrvatskoj populaciji na temelju podataka Hrvatskoga zavoda za zdravstveno osiguranje (HZZO), nacionalno reprezentativne baze podataka kojom upravlja Ministarstvo zdravstva Republike Hrvatske. Podatci za analizu uključivali su broj recepata, cijenu lijekova izraženu u bivšoj nacionalnoj valuti (hrvatska kuna – HRK) i broj propisanih pakiranja. Budući da su zakonski propisi za propisivanje opioida strogi kako bi se spriječila njihova zloupotreba, ne postoje recepti iz privatne prakse. Također su isključeni lijekovi dani pacijentima u bolnicama na temelju bolničkih recepata (7).

U ovom istraživanju analizirani su sljedeći propisani opioidi: morfij, oksikodon, oksikodon/nalokson, fentanil, buprenorfin, tramadol, tapentadol, tramadol/paracetamol i tramadol/deksketoprofen koji pripadaju anatomskim terapijskim kemijskim skupinama (ATC) N02AA, N02AB, N02AD, N02AE, N02AJ i N02AX.

Za usporedbu stope propisivanja opioida u odnosu na sve analgetike, izdvojeni su podatci za ATC skupine M01AB, M01AC, M01AE i M01AH zato što ne postoje objavljeni podatci o propisivanju analgetika u Hrvatskoj.

U analizi podataka o receptima koristili smo se ATC sustavom klasifikacije koji je uspostavila Svjetska zdravstvena organizacija (WHO) za preciznu kategorizaciju lijekova te definiranu dnevnu dozu (DDD) (8). Ta jedinica omogućuje usporedbu trendova potrošnje lijekova u različitim regijama i vremenskim razdobljima.

DDD je postao standardna jedinica doziranja u većini farmakoepidemioloških istraživanja jer pruža fiksnu jedinicu mjerenja neovisnu o obliku doziranja, veličini pakiranja ili cijeni. Prema smjernicama za ATC klasifikaciju i dodjelu DDD-a iz 2019. godine, te popisu DDD-a za kombinirane proizvode, DDD svih kemijskih tvari koje je SIGAF distribuirao najprije je pretvoren u istu jedinicu mase – u miligrame. Zatim su izračunati ukupni DDD-i i DDD-i na 1000

that, the annual total DDD and DDD per 1,000 inhabitants were calculated. Each chemical substance's concentration in milligrams was multiplied by the number of pharmaceutical forms (such as tablets) to determine the overall DDD. The result was then divided by the drug-specific DDD. The number of DDD was multiplied by 1,000, and the result was then divided by the population to estimate the number of DDD per 1,000 inhabitants annually (8). This calculation was independently performed by two of the authors of this paper.

The official national population statistics were taken from the website of the Croatian Bureau of Statistics and the First Results publication for the number of inhabitants. These are short and concise statistical information sheets issued in accordance with the regular survey schedule (9). Data pertaining to the number of licensed dentists, patient demographics, and the array of dental procedures performed were gathered from the Croatian Institute for Public Health (CIPH) (10).

The data did not contain any personal or medical information, such as diagnosis, on either the practitioners or the patients, and the Ethics Committee of the School of Dental Medicine, University of Zagreb, independently reviewed and approved the study under the approval No. 05-PA-30-XI-11/2019. The data were analyzed using Microsoft Excel software, and the results are presented using descriptive statistics including means and percentages. A paired t-test was conducted to compare time periods and assess differences between specific means (prescribed drugs across time intervals). Two-year intervals were compared sequentially, spanning from 2013/2014 to 2022/2023. A quantitative analysis was undertaken using a methodology based on DID and ATC classification according to WHO standards.

Results

Between 2013 and 2023, the average number of opioid prescriptions per dentist was 0.19 prescriptions/1,000 patients, or 0.019 prescriptions/1000 populations. A single dentist prescribed 0.48 opioid prescriptions on average per year.

The average annual number of all prescriptions prescribed by dentists between 2013 and 2023 was 455, 152. Dental opioid analgesic utilization that includes the ATC groups N02AA, N02AB, N02AD, N02AE, N02AJ and N02AX in Croatia for observed period of the 11 years was a total of 9,132 prescriptions, representing on average 1.1% of all analgesic and anti-inflammatory prescriptions and 0.2% of all dental prescriptions. Data on the number of prescriptions are summarized in Table 1, and data analyzed as DDD/TDS are summarized in Table 2. An increase of 51 % in opioid prescription was registered over the 11 observed years. The increase wasn't steady, with 2015 and 2020 disturbing observed continuum.

Analgesic and anti-inflammatory prescriptions that included ATC groups M01AB, M01AC, M01AE and M01AH, represent on average 14.2% of all prescriptions and the data in number of prescriptions are summarized in Table 3. Increase of 107% of overall analgesic prescriptions was registered for observed years, with ibuprofen as the most pre-

stanovnika na godinu. Za izračun ukupnoga DDD-a, broj farmaceutskih oblika (npr. broj tableta) svake kemijske tvari pomnožen je s njezinom koncentracijom u miligramima, a rezultat je podijeljen s DDD-om specifičnim za lijek. Za procjenu DDD-a na 1000 stanovnika na godinu, broj DDD-a pomnožen je s 1000, a zatim podijeljen s brojem stanovnika (8). Takav izračun neovisno su provela dva autora rada.

Službeni nacionalni statistički podatci o broju stanovnika preuzeti su s mrežnih stranica Državnoga zavoda za statistiku Republike Hrvatske i publikacije Prvi rezultati za broj stanovnika. To su kratki i sažeti informativni statistički listovi izdani u skladu s redovitim rasporedom istraživanja (9). Podatci o broju licenciranih doktora dentalne medicine, demografiji pacijenata i spektru obavljenih dentalnih zahvata dobiveni su od Hrvatskoga zavoda za javno zdravstvo (HZJZ) (10).

Podatci nisu sadržavali osobne i medicinske informacije, poput dijagnoza, o liječnicima ili pacijentima, a Etičko povjerenstvo Stomatološkog fakulteta Sveučilišta u Zagrebu neovisno je pregledalo i odobrilo studiju pod brojem 05-PA-30-XI-11/2019. Analiza podataka provedena je korištenjem softvera Microsoft Excel, a rezultati su prikazani deskriptivnom statistikom uključujući srednje vrijednosti i postotke. Usporedbe vremenskih razdoblja i razlike između specifičnih srednjih vrijednosti (propisanih lijekova tijekom vremenskih intervala) provedene su s pomoću t-testa za zavisne uzorke. Dvogodišnji intervali uspoređivani su sekvencijalno u razdoblju od 2013./2014. do 2022./2023. Kvantitativna analiza provedena je metodologijom temeljenom na DID i ATC klasifikaciji prema standardima WHO-a.

Rezultati

Između 2013. i 2023. godine prosječan broj recepata za opioide po doktoru dentalne medicine iznosio je 0,19 na 1000 pacijenata, odnosno 0,019 recepata/1000 stanovnika. Pojedini doktor dentalne medicine prosječno je na godinu propisivao 0,48 recepata za opioide.

Prosječan godišnji broj svih recepata koje su doktori dentalne medicine propisivali između 2013. i 2023. bio je 455.152. Korištenje dentalnih opioidnih analgetika, uključujući ATC skupine N02AA, N02AB, N02AD, N02AE, N02AJ i N02AX, u Hrvatskoj u promatranom razdoblju od 11 godina obuhvatilo je ukupno 9132 recepta, što je prosječno 1,1 % svih analgetskih i protuupalnih recepata te 0,2 % svih recepata u dentalnoj medicini. Podatci o broju recepata sažeti su u tablici 1., a podatci analizirani kao DDD/TDS nalaze se u tablici 2. Tijekom promatranih 11 godina zabilježen je porast propisivanja opioida od 51 %. Porast nije bio kontinuiran, a taj trend narušen je 2015. i 2020. godine. Recepte za analgetike i protuupalne lijekove, uključujući ATC skupine M01AB, M01AC, M01AE i M01AH, u prosjeku čini 14,2 % svih recepata, a podatci o broju recepata sažeti su u tablici 3. Tijekom promatranih godina zabilježen je porast ukupnoga broja recepata za analgetike od 107 %, pri čemu je ibuprofen bio najčešće propisivani lijek s najvećim porastom

Table 1 Utilization of opioid analgesics by the number of prescriptions
Tablica 1. Iskorištenost opioidnih analgetika prema broju recepata

| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 |
|------------------------|------|------|------|------|------|------|------|------|------|------|------|
| Tramadol/ Paracetamol | 549 | 552 | 648 | 597 | 661 | 634 | 787 | 382 | 687 | 730 | 746 |
| Tramadol/Dexketoprofen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 67 | 129 | 148 | 136 |
| Tramadol | 100 | 107 | 133 | 110 | 87 | 149 | 126 | 130 | 110 | 93 | 90 |
| Fentanyl | 7 | 11 | 16 | 9 | 13 | 8 | 16 | 21 | 9 | 6 | 11 |
| Tapentadol | 0 | 0 | 0 | 0 | 16 | 17 | 25 | 26 | 17 | 14 | 8 |
| Oxycodone/Naloxone | 0 | 0 | 2 | 13 | 9 | 8 | 17 | 20 | 4 | 4 | 4 |
| Oxycodone | 0 | 5 | 4 | 3 | 1 | 4 | 2 | 4 | 2 | 2 | 4 |
| Buprenorphine | 4 | 3 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 3 | 2 |
| Morphine | 0 | 4 | 3 | 3 | 3 | 4 | 5 | 3 | 2 | 1 | 1 |

Table 2 Utilization of opioid analgesic by the DDD/1000 population/year (DID) by WHO
Tablica 2. Korištenje opioidnih analgetika prema DDD/1000 stanovnika/godini (DID) prema SZO-u

| | 2013 DID | 2014 DID | 2015 DID | 2016 DID | 2017 DID | 2018 DID | 2019 DID | 2020 DID | 2021 DID | 2022 DID | 2023 DID |
|-------------------------|----------|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Tramadol/ Paracetamol | 0,0044 | 0,0047 | 0,0057 | 0,0052 | 0,0059 | 0,0058 | 0,0077 | 0,0035 | 0,00667 | 0,0073 | 0,0075 |
| Tramadol/ Dexketoprofen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0,00025 | 0,0005 | 0,0007 | 0,0006 |
| Fentanyl | 0,0004 | 0,0005 | 0,0008 | 0,0004 | 0,00059 | 0,0005 | 0,0007 | 0,001 | 0,00026 | 0,00034 | 0,00053 |
| Tramadol | 0,0005 | 0,0004 | 0,0007 | 0,0006 | 0,00043 | 0,00076 | 0,001 | 0,0006 | 0,00056 | 0,00055 | 0,00047 |
| Oxycodone/ Naloxone | 0 | 0 | 0,000001 | 0,000009 | 0,0000047 | 0,0000042 | 0,0001 | 0,00012 | 0,0000039 | 0,0000028 | 0,0000051 |
| Tapentadol | 0 | 0 | 0 | 0 | 0,0000039 | 0,0000065 | 0,000008 | 0,0000065 | 0,0000066 | 0,0000055 | 0,0000023 |
| Buprenorphine | 0,00004 | 0,00004 | 0,00006 | 0,0000045 | 0,0000047 | 0,0000054 | 0,0000063 | 0,0000079 | 0,0000074 | 0,0000024 | 0,0000017 |
| Oxycodone | 0 | 0,000003 | 0,000002 | 0,0000015 | 0,0000005 | 0,0000021 | 0,000001 | 0,000002 | 0,0000016 | 0,0000011 | 0,0000011 |
| Morphine | 0 | 0,000003 | 0,000001 | 0,0000011 | 0,0000012 | 0,0000016 | 0,000002 | 0,0000012 | 0,0000008 | 0,0000004 | 0,0000004 |

Table 3 Utilization of non-opioid analgesics by the number of prescriptions
Tablica 3. Iskorištenost neopioidnih analgetika prema broju recepata

| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 |
|---------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Ibuprofen | 21167 | 27133 | 33084 | 38757 | 43477 | 47906 | 50166 | 54772 | 59652 | 62063 | 63267 |
| Ketoprofen | 8743 | 9491 | 10168 | 11834 | 11879 | 11667 | 11883 | 13269 | 13437 | 13073 | 12539 |
| Diclofenac | 10578 | 9791 | 8958 | 8241 | 7721 | 6985 | 6119 | 6481 | 5882 | 5109 | 4588 |
| Naproxen | 0 | 27 | 475 | 691 | 1116 | 1568 | 1572 | 2259 | 2450 | 2843 | 3348 |
| Dexketoprofen | 44 | 361 | 329 | 346 | 398 | 387 | 502 | 595 | 590 | 544 | 674 |
| Metamizole | 0 | 0 | 0 | 0 | 0 | 128 | 230 | 280 | 287 | 271 | 311 |
| Paracetamol | 183 | 145 | 125 | 123 | 161 | 136 | 128 | 131 | 129 | 124 | 115 |
| Indomethacin | 43 | 50 | 43 | 43 | 35 | 33 | 40 | 50 | 40 | 36 | 19 |
| Piroxicam | 43 | 59 | 48 | 52 | 40 | 24 | 20 | 23 | 17 | 10 | 13 |
| Etoricoxib | 0 | 3 | 9 | 14 | 10 | 8 | 19 | 43 | 13 | 7 | 10 |
| Meloxicam | 29 | 22 | 30 | 37 | 21 | 15 | 18 | 13 | 19 | 8 | 6 |
| Acemetacin | 0 | 0 | 0 | 0 | 2 | 2 | 3 | 0 | 3 | 5 | 2 |
| Celecoxib | 0 | 0 | 0 | 4 | 0 | 2 | 1 | 2 | 1 | 0 | 2 |
| Eletriptan | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Penicillamine | 4 | 0 | 1 | 4 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| Sumatriptan | 5 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Zolmitriptan | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 6 | 0 | 0 |
| Rizatriptan | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

scribed medication and with highest increase in prescribing frequency among them.

Over the period of 10 years, there were 6227 prescriptions for tramadol/paracetamol and 1145 prescriptions for tramadol, with dentists accounting for 0.03% of all nation-

učeštalosti propisivanja. Tijekom desetogodišnjeg razdoblja zabilježeno je 6227 recepata za kombinaciju tramadol/paracetamol i 1145 recepata za tramadol, pri čemu se na doktorske dentalne medicine odnosi 0,03 % svih nacionalno propisanih recepata za tramadol/paracetamol (11). Doktori dental-

ally prescribed tramadol/paracetamol (11). Croatian dentists preferentially prescribed the tramadol/paracetamol combination 37.5 mg/325 mg accounted for 622.7 (64%) of dental opioids prescriptions, followed by tramadol 50 mg accounted for 114, 5 (11%) of opioids prescriptions. No indication or diagnosis was available from data received from CHIF or CIPH.

Trends in opioid prescription varied, especially during pandemic years (2020-2022), when tramadol rates decreased, while fixed combination medications tramadol/paracetamol and tramadol/dexketoprofen increased. In 2023, the highest rate of opioid prescriptions was recorded (1 002), and the least amount of prescriptions was in 2020 (659). Compared years are presented in Figure 1 and 2.

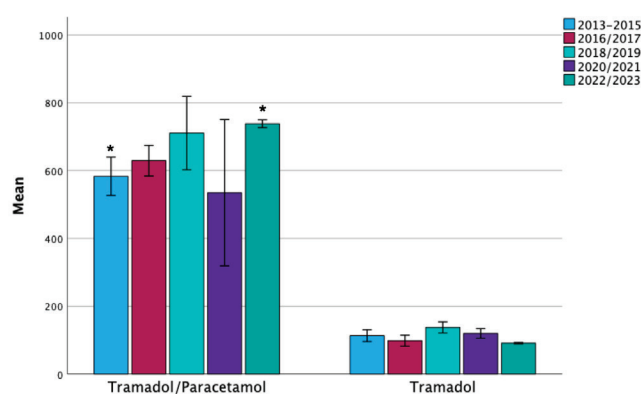


Figure 1 Paired t-test comparisons for most prescribed opioid analgesics tramadol and fixed combination tramadol/paracetamol prescriptions in time intervals (13//15, 16/17, 18/19, 20/21, 22/23)

* $p < 0.05$, present statistically significant difference among interval. Error bars denote ± 1 SD.

Slika 1. Usporedbe parova t-testa za većinu propisanih opioidnih analgetika – tramadola i fiksne kombinacije tramadol/paracetamol u vremenskim intervalima (13./15., 16./17., 18./19., 20./21., 22./23.)

* $p < 0,05$, prisutna je statistički značajna razlika između intervala; trake pogrešaka označavaju ± 1 SD

Discussion

The study aimed to describe the patterns of dental opioid prescription in Croatia. To our knowledge this is the first assessment of the opioid prescribing trends on the national level. We noted that the prevalence of opioid analgesic use among the adult population in Croatia has increased, primarily due to a rise in prescriptions for tramadol combinations. Despite the observed increase, the number of prescribed opioids is not a constant cause of concern. It is low, thus representing the good prescribing practice.

The main result of our study is the low utilization of opioids on a national level. Our results demonstrated that, even if the total number of opioid prescriptions has increased, there has not been an epidemic spread of opioids in Croatia in recent years. The reason for such a good result lies probably in the fact that there are strict rules for prescribing opioid analgesic from a medicine formulary. Legislation for pre-

ne medicine u Hrvatskoj preferencijalno su propisivali kombinaciju tramadola/paracetamola od 37,5 mg/325 mg, što je 622,7 (64 %) receptata za dentalne opioide, a tramadol od 50 mg činio je 114,5 (11 %) receptata za opioide. Među podatcima dobivenima od HZZO-a i HZJZ-a nije bilo onih o indikacijama za propisivanje opioida, ili o dijagnozama zbog kojih su propisivani opioidi.

Trendovi u propisivanju opioida varirali su, osobito tijekom pandemijskih godina (2020. – 2022.) kada je zabilježen pad u propisivanju tramadola, a kombinirani lijekovi tramadol/paracetamol i tramadol/dexketoprofen zabilježili su porast. U 2023. godini zabilježen je najveći broj receptata za opioide (1002), a najmanji broj zabilježen je 2020. godine (659). Usporedbe među godinama prikazane su na slikama 1. i 2.

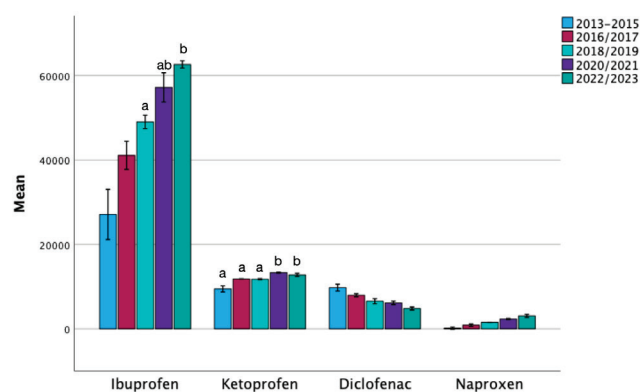


Figure 2 Paired t-test comparisons most prescribed non-steroid analgesics prescriptions in time intervals (13/15, 16/17, 18/19, 20/21, 22/23) Small letters indicate statistical homogeneity for comparisons among year intervals.

Slika 2. Usporedbe uparenih t-testa za većinu propisanih nesteroidnih analgetika u vremenskim intervalima (13./15., 16./17., 18./19., 20./21., 22./23.); mala slova označavaju statističku homogenost za usporedbe među godišnjim intervalima

Rasprava

Svrha ove studije bila je opisati obrasce dentalnog propisivanja opioida u Hrvatskoj, a prema našim saznanjima, ovo je prva procjena trendova u propisivanju opioida na nacionalnoj razini. Uočeno je da je prevalencija korištenja opioidnih analgetika među odraslom populacijom u Hrvatskoj porasla, uglavnom zbog povećanja broja receptata za kombinacije tramadola. Unatoč zabilježenom porastu broj propisanih opioida ne zabrinjava, nizak je i odražava dobru praksu u propisivanju lijekova.

Glavni rezultat naše studije jest niska uporaba opioida na nacionalnoj razini. Naši rezultati pokazali su da, unatoč povećanju ukupnoga broja receptata za opioide, ne možemo govoriti o epidemiji opioida u Hrvatskoj posljednjih godina. Razlog za takve pozitivne rezultate vjerojatno je u strogim pravilima propisivanja opioidnih analgetika prema popisu lijekova. Zakonodavac za propisivanje opioida nameće stroga

scribing opioids imposes strict limitations on the amount of medication that healthcare providers can prescribe. Moreover, prescriptions for opioids are issued in duplicate, with the second copy clearly marked as "copy" and containing the serial number of the record book pertaining to the issued prescription. Additionally, the doctors are mandated to maintain a specialized record book documenting narcotic drugs and psychotropic substances prescribed by prescription.

The share of dental opioid prescriptions among all dental medications in our study represents 0.2%. A comparison with available results from various studies in this field demonstrate that Croatian dentists prescribe significantly less opioids than dentists from the USA and Australia (12). In the United States, a country where the opioid crisis is a great concern, 22.3% of all dental prescriptions stand for opioids. Australia has also raised a concern lately. The results from their research showed 8.6 prescription/1000 populations, with 98% being paracetamol and codeine combinations (12). In contrast to their results, our study showed only 0,019 prescription/1000 population indicating more rational practice in opioid prescribing. Even when comparing our results with good practice results from an English dental prescription study with opioids accounted for 0.6% rate of all prescriptions, the prescribing trend by our results was 5 times more rational. Also results from latest studies in Europe, Asia and Africa show no or low opioid prescribing in general by dentists or by both dentists and general practitioners (12-17). The majority of European nations do not seem to have any indications of an opioid crisis comparable to the USA, where the number of deaths from opioid-analgesic poisoning has almost quadrupled in the last 20 years as a result of prescription opioid analgesic overuse and abuse (17-19). While this issue was most severe in the United States, opioid-analgesic poisoning death rates have increased in Canada, Sweden, Norway, Ireland, and the United Kingdom in recent years, thus indicating a growing opioid addiction and misuse-related health concern (20). This increase may be explained by a number of factors, including pharmaceutical corporations' aggressive marketing, easy availability to opioids that have been illegally or fraudulently given, and improper prescribing practices (21). Croatia does not appear to be affected by these factors.

The opioid most frequently prescribed by dentists in our study was the fixed combination tramadol/paracetamol, followed by tramadol/dexketoprofen and tramadol, respectively. Tramadol/paracetamol 37.5 mg/325 mg prescriptions represented 64% of opioids, 0.87% of all analgesics and 0.16% of all dental medication prescriptions. We also analyzed the most frequently prescribed opioid and its usage ratio compared to non-steroidal anti-inflammatory drugs (NSAIDs). When discussing the most frequently prescribed analgesic, it is important to mention that the first choice of analgesic for dentists in Croatia is by far ibuprofen, the prescription rate of which has increased by 300% in the last decade. Ibuprofen prescriptions in the last analyzed year represent 14% of all prescriptions. Availability, convenience, costs and product marketing are likely to impact this trend. The develop-

ograničenja kad je riječ o količini lijekova koje liječnici mogu ordinirati. Uz to, recepti za opioide izdaju se u dva primjerka, pri čemu je drugi primjerak označen kao „kopija” i sadržava serijski broj knjige za evidenciju izdanih recepata. Liječnici su također obvezni voditi posebnu evidenciju o propisanim narkoticima i psihotropnim tvarima.

Udio recepata za dentalne opioide među svim dentalnim lijekovima u našoj studiji iznosi 0,2 %. Usporedba s dostupnim rezultatima iz drugih studija pokazuje da doktori dentalne medicine u Hrvatskoj propisuju znatno manje opioida nego doktori dentalne medicine u SAD-u i Australiji (12). U SAD-u, gdje je kriza opioida velik problem, 22,3 % svih stomatoloških recepata odnosi se na opioide. U Australiji je također zabrinutost sve veća jer njihova istraživanja pokazuju 8,6 recepata na 1000 stanovnika, pri čemu 98 % čine kombinacije paracetamola i kodeina (12). Suprotno njihovim rezultatima, naša studija pokazala je samo 0,019 recepta na 1000 stanovnika, što upućuje na racionalniju praksu propisivanja. Čak i uspoređujući naše rezultate s dobrim praksama iz Engleske, gdje opioidi čine 0,6 % svih recepata, naši rezultati pokazuju pet puta racionalniju praksu propisivanja. Najnovije studije u Europi, Aziji i Africi također pokazuju nisku ili nikakvu razinu propisivanja opioida općenito kad je riječ o doktorima dentalne medicine ili kombinaciji s liječnicima opće prakse (12 – 17). Većina europskih zemalja nema dokaza o opioidnoj krizi poput one u SAD-u gdje je stopa smrtnosti od trovanja opioidnim analgeticima tijekom posljednjih 20 godina gotovo četverostruko porasla zbog zlorabe i prekomjernog propisivanja (17 – 19). Iako je taj problem najizraženiji u SAD-u, i druge zemlje poput Kanade, Švedske, Norveške, Irske i Ujedinjenog Kraljevstva posljednjih su godina zabilježile porast smrtnih slučajeva povezanih s trovanjem opioidnim analgeticima, što upozorava na sve veću zdravstvenu krizu prouzročenu ovisnošću i zlorabom opioida (20). Nekoliko razloga može objasniti taj porast, uključujući agresivni marketing farmaceutskih tvrtki, jednostavan pristup ilegalno ili lažno propisanim opioidima te nepromišljenost u vezi s propisivanjem opioida (21). Te okolnosti, čini se, ne odnose se na Hrvatsku.

Najčešće propisivani opioid u našoj studiji bila je fiksna kombinacija tramadol/paracetamol, zatim tramadol/deksketoprofen i tramadol. Recepti za tramadol/paracetamol od 37,5 mg/325 mg činili su 64 % svih recepata za opioide, 0,87 % svih analgetika i 0,16 % svih dentalnih recepata. Također smo analizirali najčešće propisivani opioid i njegov omjer primjene u usporedbi s NSAID-ima. Ibuprofen se pokazao kao najčešće propisivani analgetik među doktorima dentalne medicine u Hrvatskoj – učestalost propisivanja porasla je za 300 % u posljednjem desetljeću, što čini 14 % svih recepata u posljednjoj analiziranoj godini. Na taj trend vjerojatno utječu dostupnost, praktičnost, troškovi i marketinške aktivnosti. Tijekom proteklog desetljeća razvoj propisivanja analgetika pokazuje da ibuprofen s tržišta potiskuje većinu drugih analgetika. Nastavljen je i trend povećanja propisivanja ibuprofena koji je uočen u ranijim studijama (22). Sve veća uporaba analgetika vjerojatno je posljedica njihove dostupnosti i razmjerno rijetkih nuspojava, a taj se trend nastavio i intenzivirao tijekom pandemije (23 – 26). Dokazi snažno

ment of analgesic prescriptions over the past ten years indicates that ibuprofen pushes the majority of other analgesics off the market. The trend of rising prescriptions for ibuprofen seen in earlier research has persisted (22). Due to their accessibility and very moderate adverse effects, analgesics are becoming more and more widely used; this tendency remained and grew during the pandemic (23-26). NSAIDs should be used as first-line therapy for acute pain management (3, 27), either alone or in combination with other medications, such as benzodiazepines (28). The evidence strongly supports the use of NSAIDs for all types of orofacial pain, with the exception of situations in which they are contraindicated. Opioids should only be used in clinical settings where nonsteroidal anti-inflammatory medications are contraindicated or when first-line therapy is not effective in reducing pain. The role of a dentist is to prescribe analgesics at the minimum effective dosage to minimize adverse effects and avoid routine delayed usage (29).

By the results of our study there was a rise in the rate of tramadol/paracetamol combinations prescriptions. Prescribing rate for tramadol/paracetamol continuously increased for 73% in 11 years, while other opioids trends varied. This raise can be explained by the fact that tramadol showed positive effects on pain management after oral surgery and an improvement in local anesthetics (30). For Croatia, according to the latest published data from the The Agency for Medicinal Products and Medical Devices of Croatia (HALMED) database on the consumption of medicines in Croatia, the national consumption of opioid analgesics in total for the period 2017 - 2020 is mostly stable (11). The majority of opioid analgesics prescription in Croatia stands for tramadol in combinations, which represent 78% of all opioid analgesics (11), and dentists account for 0.03% of it. Monitoring the trends in opioid prescribing needs to be continued for timely interventions to prevent misuse and ensure patient safety.

In this study, neither CHIF nor CIPH provided us with diagnosis or indications for the use of prescription opioids. A small number of studies provide broad indications for the prescription of opioids following dental procedures, such as the prescription of opioids to patients following the extraction of impacted third molars (31). Implants, periodontal, root canal, and surgical procedures are the four dental procedures that are typically followed by the administration of opioids, according to Steinmetz et al. (32). Dana et al. (33) noted that, as we have already stated, opioids should only be used in cases of severe pain when NSAIDs are either contraindicated or not likely to be sufficient to treat the acute pain.

Understanding the annual impact of opioid-related fatalities in Croatia is crucial for evaluating the effectiveness of current healthcare interventions and policies. A slight increase in opioid prescriptions in Europe has been noted over two decades, but without a rise in mortality rates (17). In Croatia, the number of individuals treated for opioid addiction has fluctuated by the reports from CIPH over the last 5 years, peaking in 2018 (5434) and again rising in 2021. Tramadol was most used until 2020, when a shift occurred with fentanyl abuse. In 2021 and 2022, opioid-related deaths accounted for about 7% of all fatalities in Croatia (10). Den-

podupiru primjenu NSAID-a za sve vrste dentalne boli, osim u slučajevima kada su kontraindicirani i također bi trebali biti prva linija terapije za akutno upravljanje bolovima (3, 27), samostalno ili u kombinaciji s drugim lijekovima kao što su benzodiazepini (28). Upotreba opioida trebala bi biti rezervirana za kliničke situacije kada prva linija terapije nije dovoljna za ublažavanje boli, ili ako postoje kontraindikacije za nesteroidne protuupalne lijekove. Zadatak doktora dentalne medicine jest propisati analgetike u minimalno učinkovitoj dozi kako bi se smanjile nuspojave i izbjegla rutinska odgođena primjena (29).

Rezultati naše studije pokazuju da je stopa propisivanja kombinacije tramadol/paracetamol kontinuirano rasla za 73 % tijekom 11 godina, dok su trendovi drugih opioida varirali. Taj porast može se objasniti pozitivnim učinkom tramadola na upravljanje boli poslije kirurških zahvata u usnoj šupljini i poboljšanja lokalne anestezije (30).

Prema najnovijim podacima Agencije za lijekove i medicinske proizvode (HALMED) o potrošnji lijekova u Hrvatskoj, nacionalna potrošnja opioida za razdoblje od 2017. do 2020. uglavnom je stabilna (11). Većina recepata za opioide u Hrvatskoj odnosi se na kombinacije tramadola koje čine 78 % svih opioida (11), a doktori dentalne medicine sudjeluju s 0,03 % u ukupnom broju recepata. Praćenje trendova u propisivanju opioida mora se nastaviti kako bi se pravodobno interveniralo u sprječavanju zlouporabe i očuvala sigurnost pacijenata.

U ovoj studiji nisu analizirane indikacije i dijagnoze za primjenu opioida jer ti podatci nisu bili dostupni. Autori nekoliko studija analizirali su općenite indikacije za propisivanje opioida poslije stomatoloških zahvata, poput propisivanja opioida pacijentima nakon vađenja impaktiranih trećih kutnjaka (31). Prema Steinmetzu i suradnicima (32), četiri zahvata u usnoj šupljini poslije kojih se obično propisuju opioidi jesu kirurško postavljanje dentalnih implantata, drugi oralno-kirurški zahvati, parodontološki zahvati te endodontsko liječenje zuba. Dana i suradnici (33) istaknuli su, kao što smo već naveli, da se opioidi trebaju koristiti samo u slučaju jake boli kada NSAID-i nisu dovoljni ili su kontraindicirani za liječenje akutne boli.

Razumijevanje godišnjeg utjecaja smrtnih slučajeva povezanih s opioidima u Hrvatskoj ključno je za procjenu učinkovitosti postojećih zdravstvenih intervencija i politika. Tijekom posljednja dva desetljeća zabilježen je blagi porast propisivanja opioida u Europi, ali bez porasta stope smrtnosti (17). U Hrvatskoj je broj osoba liječenih zbog ovisnosti o opioidima, prema izvješćima HZJZ-a u posljednjih pet godina, varirao, s vrhuncem u 2018. godini (5434) i ponovnim porastom u 2021.. Tramadol je bio najčešće korišten do 2020. godine kada je zabilježen prelazak na zlouporabu fentanila. U 2021. i 2022. godini smrtni slučajevi povezani s opioidima činili su oko 7 % svih smrtnih slučajeva u Hrvatskoj (10). Doktori dentalne medicine trebali bi postupati oprezno kako bi spriječili da pacijenti potencijalno zlouporabljavaju opioidne recepte.

Ova studija ima određena ograničenja i potrebno ih je istaknuti. Prvo: s obzirom na to da podatci o lijekovima koji se izdaju bez recepta (OTC) nisu dostupni, mogli smo istra-

tists should exercise caution to prevent potential patient abuse of opioid prescriptions.

This study has some limitations that should be addressed at this point. First, since no data on OTC drugs are available, we were only able to investigate prescriptions entered to the centralized healthcare system, which represent all of opioid prescriptions but not all of other analgesics. Second, no information regarding diagnosis or indications for prescription of opioids was provided in the database. Lastly, we were unable to examine the influence of socioeconomic level on the prescription of opioid painkillers due to the lack of sociodemographic data. However, this study also has a number of advantages. The first strength of this study is that it offers thorough assessments of opioid analgesic prescriptions in Croatia over an 11-year period for the first time. The thorough coverage of the CHIPH prescription data is the strongest point of the study. The third strength is the nature of the available data, which made it possible to estimate objectively the number of analgesic prescriptions in Croatian general practices.

Conclusion

Opioid prescribing trends in Croatia are positive, with a low and stable rate of opioid prescriptions, despite an observed increase. The average annual number of opioid prescriptions prescribed by dentists between 2013 and 2023 was 830 prescriptions, representing on average 1.1% of all analgesic and anti-inflammatory prescriptions and 0.2% of all dental prescriptions. Tramadol, particularly in fixed combination forms, was the most commonly prescribed opioid. It accounted for 64% of all prescribed dental opioids. These trends indicate a responsible approach to opioid prescribing, suggesting no immediate cause for concern. Continued monitoring and adherence to strict regulatory guidelines are essential to maintain these good practices and prevent misuse.

Dentists should apply “universal precautions” when prescribing opioids, similar to infection control practices. It is necessary to prescribe medications only for dental treatments, as required by state laws; otherwise it can result in disciplinary actions. In addition, dentists should inform patients about expected pain and ensure that analgesics are appropriately taken. They should discuss past experiences and medical histories to avoid overdoses and interactions.

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žiti samo recepte unesene u centralizirani zdravstveni sustav, a to su svi recepti za opioide, ali ne i svi za druge analgetike. Drugo: baza podataka nije pružala informacije o razlozima za propisivanje tih lijekova. Konačno, sociodemografski čimbenici nisu bili dostupni, pa nismo mogli istražiti utjecaj socijalno-ekonomskog statusa na propisivanje opioidnih lijekova protiv bolova.

Unatoč ovim ograničenjima, studija ima nekoliko značajnih prednosti. Prva je to što se ovom studijom prvi put sveobuhvatno analiziraju recepti za opioidne analgetike u Hrvatskoj tijekom razdoblja od 11 godina. Druga je prednost u potpunoj pokrivenosti podataka o receptima iz HZZO-a. Treća prednost je sama priroda podataka koja je omogućila nepristranu procjenu propisivanja lijekova protiv bolova u općoj praksi u Hrvatskoj.

Zaključak

Trendovi propisivanja opioida u Hrvatskoj pokazuju pozitivan smjer, uz nisku i stabilnu stopu propisivanja unatoč zabilježenom povećanju. Prosječan godišnji broj recepata za opioide koje su propisivali doktori dentalne medicine između 2013. i 2023. godine iznosio je 830 recepata, što čini prosječno 1,1 % svih recepata za analgetike i protuupalne lijekove te 0,2 % svih stomatoloških recepata. Tramadol, osobito u obliku fiksnih kombinacija, bio je najčešće propisivani opioid i činio je 64 % svih propisanih stomatoloških opioida. Ti trendovi pokazuju odgovoran pristup u propisivanju opioida i sugeriraju da nema neposrednog razloga za zabrinutost. Kontinuirano praćenje i poštovanje strogih regulatornih smjernica ključni su za održavanje tih dobrih praksi i sprječavanje zlouporabe.

Doktori dentalne medicine trebali bi primjenjivati univerzalne mjere opreza u propisivanju opioida, slično praksama kontrole infekcija. Potrebno je propisivati lijekove samo za stomatološke zahvate, u skladu s državnim zakonima, jer u suprotnome mogu biti podložni disciplinskim mjerama. Trebaju informirati pacijente o očekivanoj boli i osigurati odgovarajuću analgeziju, raspravljajući o prethodnim iskustvima i medicinskoj povijesti kako bi se izbjegla predoziranja i interakcije lijekova.

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Sažetak

Cilj: Propisivanje opioida s lošom namjerom, povezano s mnogim opioidima, obilježava dobro poznatu javnozdravstvenu krizu u razvijenim zemljama poput Ujedinjenog Kraljevstva, SAD-a i Australije. Budući da se opioidi ograničeno koriste u općoj stomatološkoj praksi, cilj ovog istraživanja bio je procijeniti u Hrvatskoj stopu propisivanja opioida u dentalnoj medicini od 2013. do 2023. godine. **Matrijali i metode:** Podatci o praksama propisivanja opioida za ovo istraživanje dobiveni su od Hrvatskoga zavoda za zdravstveno osiguranje (HZZO). Analiza je obuhvaćala broj recepata, troškove i broj propisanih pakiranja. **Rezultati:** Tijekom 11 godina doktori dentalne medicine u Hrvatskoj ispitali su ukupno 9132 recepta za opioide, što prosječno na godinu čini 1,1 % svih recepata za analgetike i 0,2 % svih stomatoloških recepata. Broj recepata za opioide na 1000 stomatoloških pacijenata iznosio je u prosjeku 0,19. Najčešće propisivani bili su tramadol/paracetamol i tramadol, s prosječnim brojem recepata na godinu od 622,7 (64 % recepata za opioide) i 114,5 (1,1 % recepata za analgetike). Trendovi u propisivanju opioida varirali su, osobito tijekom pandemijskih godina (2020. – 2022.) kada je zabilježen pad u propisivanju tramadola, a kombinirani lijekovi poput tramadola/paracetamola i tramadola/deksketoprofena bilježili su rast. Ukupni trend pokazuje porast u promatranom razdoblju. **Zaključak:** Doktori dentalne medicine u Hrvatskoj konzervativni su i restriktivni u propisivanju opioida te nema potrebe za intervencijama. No zbog zabilježenog porasta preporučuje se daljnje praćenje obrazaca propisivanja.

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