UTICAJ KOVID-19 PANDEMIJE NA LEČENJE PACIJENATA SA HRONIČNIM BOLOM

PO IZBORU UREDNIKA

EDITOR'S CHOICE

IMPACT OF THE COVID-19 PANDEMIC ON CHRONIC PAIN MANAGEMENT

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SAŽETAK

Uvod: Pandemija KOVID-19 oboljenja izazvala je velike potrese među svima koji su uključeni u interventnu terapiju bola (ITB). Kako je ITB kategorisana kao „neobavezna", brojne ordinacije za terapiju bola širom Sjedinjenih Američkih Država bile su prinuđene da zatvore svoja vrata tokom pandemije, ostavljajući pacijente sa hroničnim bolom bez terapije na neodređeno vreme, a lekare koji se bave ovom terapijom pod pojačanim stresom i sa sindromom „sagorevanja".

Rezultati: Kao odgovor na ove štetne posledice, stvoreni su različiti mehanizmi i tehnike za ponovno otvaranje, kako bi se, uz oprez, ponovo nastavila praksa interventne terapije bola uživo. Kako imaju mogućnost da neposredni lični kontakt svedu na minimum, telemedicina i farmakoterapija dobile su značajniju ulogu u interventnoj terapiji bola tokom pandemije, ali njihova povećana primena je takođe dovela do pogoršanja situacije, kada su u pitanju zloupotreba narkotika i epidemija upotrebe opioida. Sadejstvo upotrebe steroida i njihovog imunosupresivnog efekta u odnosu na KOVID-19 infekciju i KOVID-19 vakcinu se takođe nametnulo kao važno pitanje.

Zaključak: Kako ordinacije počinju, u bezbednim uslovima, da se ponovo otvaraju, širom Sjedinjenih Američkih Država, posledice koje su osetili pacijenti sa hroničnim bolom tokom pandemije moraju se naglasiti, a nikako zanemariti. Ovaj rad naglašava probleme sa kojima su se suočavali pacijenti sa bolom tokom pandemije, kao i potrebu da se ažuriraju i redefinišu propisi koji se tiču interventne i terapije hroničnog bola.

Ključne reči: hronični bol, interventna terapija bola, KOVID-19, telemedicina, opioidi, steroidi, vakcine

ABSTRACT

Introduction: The COVID-19 pandemic has generated considerable turmoil in the interventional pain management (IPM) community. Due to IPM being classified as 'elective', numerous pain practices across the United States were forced to close during the pandemic, leaving chronic pain patients untreated for indefinite periods, and IPM physicians with increased stress and burnout.

Results: In response to these detrimental effects, various re-opening tools and techniques have been created to facilitate a cautious resumption of in-person interventional pain practice. Due to their ability to minimize person-to-person contact, telehealth and pharmacotherapy played a more significant role in IPM during the pandemic, but their increased utilization has also led to the exacerbation of substance abuse and the opioid epidemic. The interplay between steroid use and its immunosuppressive effects, in relation to the COVID-19 infection and the COVID-19 vaccine, has also arisen as an issue of concern.

Conclusion: As practices begin to safely re-open throughout the United States, the effects felt by chronic pain patients during the pandemic must be emphasized and not ignored. This review emphasizes the struggles pain patients have had to face during the pandemic and the need to update and redefine regulations regarding interventional and chronic pain management.

Keywords: chronic pain, interventional pain management, COVID-19, telemedicine, opioids, steroids, vaccines

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UVOD

Tokom proteklih osamnaest meseci, pandemija bolesti izazvane koronavirusom 2019 (KOVID-19) prouzrokovala je dramatične društvene, ekonomske, kao i poremećaje u sistemu zdravstvene zaštite širom sveta. Zaključno sa 20. junom 2021. godine, samo u Sjedinjenim Američkim Državama, prijavljeno je ukupno 33.368.860 slučajeva KOVID-19 oboljenja, kao i 599.354 smrtnih slučajeva uzrokovanih oboljenjem KOVID-19 [1] (Tabela 1, Slika 1). Svi koji su uključeni u interventnu terapiju bola (ITB) posebno su osetili restrikcije koje nameće KOVID-19, a koje kategorišu interventne tehnike kao „neobavezne", čime je njihova primena, *de facto*, ukinuta tokom pandemije. Kao posledica ove situacije, pacijenti sa hroničnim bolom ostali su bez terapije na neodređeni vremenski period, što je pogoršalo njihove ishode i dovelo do toga da neki od njih potencijalno pribegnu neodgovarajućim alternativnim terapijskim rešenjima. Kada su u pitanju lekari koji se bave interventnom terapijom bola, pojačani stres i sindrom „sagorevanja", nastali usled pandemije, doveli su do toga da većina lekara iz ove oblasti medicine razvije negativan stav prema izgledima za budućnost.

Kako bi mogla da se bezbedno nastavi neposredna praksa sprovođenja interventne terapije bola, uvedeni su različiti protokoli skrininga, stratifikacije rizika, trijaže i korišćenja resursa, koji omogućavaju zdravstvenim rad-

INTRODUCTION

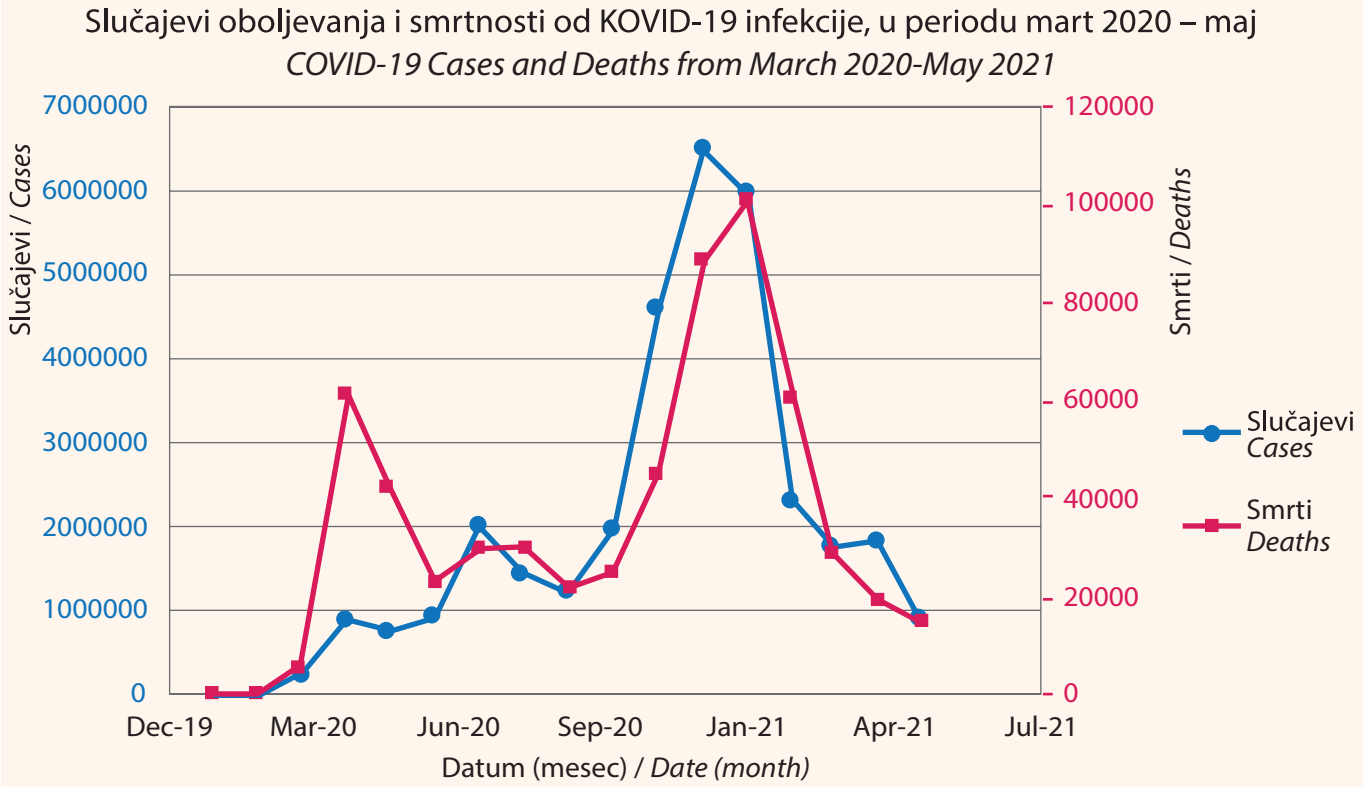
Over the past eighteen months, the coronavirus disease 2019 (COVID-19) pandemic has caused dramatic societal, economic, and healthcare disruptions across the world. As of June 20th, 2021, in the United States alone, a total of 33,368,860 cases of COVID-19 have been reported, along with 599,354 COVID-19 deaths [1] (Table 1, Figure 1). The interventional pain management (IPM) community has been especially impacted by COVID-19 restrictions, which classify interventional techniques as 'elective', effectively excluding their use during the pandemic. This has led to chronic pain patients being left untreated for indefinite periods of time, worsening their outcomes and causing some to potentially pursue inappropriate alternatives to treatment. As for interventional pain physicians, increased stress and burnout, derived from the pandemic, has led a majority of practitioners to develop a negative outlook of the future.

In order to safely resume in-person interventional pain practice, various screening, risk stratification, triaging, and resource utilization protocols were created, allowing practitioners to prioritize their most urgent cases while simultaneously limiting the spread of COVID-19. A significant shift towards telemedicine was also observed, as telehealth visits were utilized more

Tabela 1. Podaci američkog Centra za kontrolu bolesti (engl. *Centers for Disease Control - CDC*) o slučajevima oboljevanja od KOVID-19 infekcije i smrtnim slučajevima od ove bolesti, na mesečnom nivou, u periodu mart 2020 – maj 2021.

Table 1. Centers for Disease Control (CDC) data on monthly COVID-19 cases and deaths, from March 2020 - May 2021

Mesec / *Month*	Broj slučajeva na mesečnom nivou */Monthly cases*	Broj smrti na mesečnom nivou */ Monthly deaths*
January 2020	51	0
February 2020	1,020	214
March 2020	227,048	5,019
April 2020	882,003	60,702
May 2020	754,332	42,008
June 2020	920,641	22,691
July 2020	1,969,268	29,703
August 2020	1,425,924	29,912
September 2020	1,222,948	21,982
October 2020	1,947,482	24,667
November 2020	4,569,319	44,340
December 2020	6,480,794	88,316
January 2021	5,966,253	100,646
February 2021	2,281,405	60,194
March 2021	1,765,200	28,726
April 2021	1,819,244	18,991
May 2021	880,395	14,898



Grafikon 1. Podaci američkog Centra za kontrolu bolesti (CDC) o slučajevima oboljevanja od KOVID-19 infekcije i smrtnim slučajevima od ove bolesti, na mesečnom nivou, u periodu mart 2020 – maj 2021

Figure 1. Centers for Disease Control (CDC) data on monthly COVID-19 cases and deaths, from March 2020 - May 2021

nicima da odrede slučajeve sa najvišim prioritetom, a da istovremeno ograniče širenje KOVID-19 infekcije. U značajnoj meri je uočeno prebacivanje na telemedicinu, pošto su su lekarski telepregledi korišćeni češće, usled toga što pružaju mogućnost da se kontakti među ljudima svedu na minimum. Iz istog razloga, stavljen je akcenat na modalitete farmakoterapije koji premošćuju prazninu u terapiji, nastalu usled nedostatka primene interventnih tehnika. Međutim, veće oslanjanje na farmakoterapiju, sledstveno je dovelo do pogoršanja u zloupotrebi narkotika kao i do pogoršanja epidemije upotrebe opioida. Pojavila su se i pitanja u vezi sa potencijalnom vezom između upotrebe steroida i njihovog imunosupresivnog efekta na infekciju KOVID-19 kao i vakcinu protiv KOVID-19 oboljenja, zbog neizvesnih ishoda i nejasnih interakcija.

DEJSTVO KOVID-19 PANDEMIJE NA PACIJENTE SA HRONIČNIM BOLOM

Uticaj na ishode pacijenata

Primena restrikcija nastalih usled KOVID-19 pandemije, a koje su u vezi sa uvođenjem takozvane socijalne distance, imala je za rezultat zatvaranje pridruženih centara fizikalne terapije, ambulanti za kiropraktiku, i ostalih pomoćnih službi, čime je pacijentima drastično ograničen pristup različitim modalitetima za terapiju bola [2]. Štaviše, pokazalo se da je održavanje farmakoloških terapijskih režima

frequently due to their ability to minimize contact between individuals. For that same reason, an emphasis was also placed on pharmacotherapy modalities to replace the treatment gap left by interventional techniques. However, a greater reliance on pharmacotherapy has subsequently led to the exacerbation of substance abuse and the opioid epidemic as well. Concerns over a potential link between steroid use and its immunosuppressive effects on COVID-19 infection and the COVID-19 vaccine have also surfaced due to uncertain outcomes and interactions.

COVID-19 IMPACT ON CHRONIC PAIN PATIENTS

Effect on patient outcomes

The implementation of COVID-19 restrictions, associated with social distancing, has resulted in the closure of adjuvant physical therapy centers, chiropractic clinics, and other healthcare services, severely limiting a patient's access to various modalities for managing their chronic pain [2]. Moreover, maintaining pharmacological regimens with patients has proven challenging for pain physicians, as many have been forced to restrict their practices, both due to state-guided restrictions, as well as to the lack of support staff.

Individuals working virtually from home have also developed repetitive strain injuries, as a result of the

sa pacijentima postalo otežano za lekare koji se bave terapijom bola, pošto su mnogi bili prinuđeni da ograniče rad svojih ordinacija, i zbog restrikcija nametnutih od strane države, ali i zbog nedostatka pomoćnog osoblja.

Kod ljudi koji su obavljali rad od kuće, takođe je došlo do razvoja povreda nastalih usled ponavljanih naprezanja, što je bio rezultat loše ergonomičnosti mesta za rad, koja nisu zadovoljavala optimalne standarde [2]. Sa povećanjem količine vremena koje su porodice provodile zajedno kod kuće i povećanjem aktivnosti u prirodi, povezanim sa pandemijom, došlo je i do pojave novih povreda i akutnih pogoršanja hroničnih oboljenja kičme, nastalih usled aktivnosti kao što su popravke u kući, popravke na automobilu, pojačana rekreacija, ili igranje sa decom. Oni, kod kojih je došlo do ovih novih povreda ili do pogoršanja postojećih stanja u toku pandemije, prepušteni su da, uz minimalnu medicinsku pomoć, sami rešavaju svoje simptome, zato što nisu mogli da zakažu preglede kod svojih izabranih lekara ili fizioterapeuta, a nije im bilo ni omogućeno da se jave hitnim službama ili urgentnim centrima.

I mada je farmakološka terapija postala važna opcija, s obzirom da su ordinacije za terapiju bola bile ograničene u svom radu, u smislu opsega usluga koje su mogle da ponude, pandemija je, nažalost, usled ovog prelaza na farmakoterapiju, za posledicu imala porast u zloupotrebi narkotika, kao i u broju predoziranja opioidima i ne-opiodima [3].

Posledice odlaganja ITB-a

Pacijenti sa hroničnim bolom su često pod visokim rizikom od KOVID-19 infekcije, pošto je veliki broj njih, po pravilu, starijeg životnog doba i-ili ima neku hroničnu osnovnu bolest [4]. Ovi rizici se dalje usložnjavaju za one kojima je ograničen pristup zdravstvenoj zaštiti. Ovi faktori čine da su pacijenti sa hroničnim bolom skloni da izbegavaju lične posete lekaru kao i da odlažu interventne procedure za terapiju bola. Na primer, pacijenti sa ugrađenom intratekalnom pumpom za kontinuirano ubrizgavanje leka mogu da dožive bolne, teške, ili životno ugrožavajuće simptome apstinentske krize, koji nastaju ukoliko im se pumpa ne može napuniti na vreme ili ukoliko se baterije na pumpi isprazne pre nego što se izvrši zamena [5]. Sledstveno tome, pacijenti se mogu okrenuti drugim, škodljivijim tretmanima, kao što su povećane doze nesteroidnih antiinfalmatornih lekova (NSAIL), nelegalne supstance ili opioidi [4].

Dejstvo restrikcija uvedenih za neobavezne hirurške zahvate na ordinacije koje se bave interventnom terapijom hroničnog bola

Mnogi centri za ambulantno hirurško lečenje (engl. *ambulatory surgery centers – ASCs*) i uprave bolnica širom

poor ergonomics of suboptimal workstations [2]. With increased indoor family time and outdoor activity, associated with the pandemic, new injuries and acute exacerbations of chronic spinal conditions have also emerged from activities such as fixing one's house or car, increasing one's exercise routine, or playing with one's children. Those who developed these new injuries or aggravated existing conditions mid-pandemic were left to manage their symptoms with minimal assistance, as they were unable to schedule appointments with their primary care physicians or physical therapists and prohibited from going to the emergency room or urgent care center.

While pharmacological therapy has become an important option, with pain practices being restricted, in terms of the breadth of services they can offer, the pandemic has seen an unfortunate rise in substance abuse, as well as opioid and non-opioid overdoses, accompanying this shift towards pharmacological therapy [3].

Consequences of delaying IPM

Chronic pain patients are often at high risk of COVID-19, as many are characteristically older patients and/or have a chronic underlying disease [4]. These risks are compounded for those who have limited access to healthcare. Ultimately, these factors make chronic pain patients more likely to avoid in-person clinical visits and postpone interventional pain procedures. For instance, patients with intrathecal drug infusion systems may suffer painful, distressing or life-threatening withdrawal symptoms if their pump cannot be refilled on time or their pump's batteries die before replacement [5]. Consequently, patients may turn to other, more harmful treatments such as increased doses of non-steroidal anti-inflammatory drugs (NSAIDs), illicit drugs, or opioids [4].

Impact of elective surgery restrictions on interventional pain practices

Many ambulatory surgery centers (ASCs) and hospital administrators across the United States wrongly categorized most IPM services as 'elective' and closed their IPM services during the pandemic, as a result [2]. In these settings, interventional pain physicians or their representatives were often not consulted before these decisions were made. These actions were particularly deleterious for IPM practices, as only one-third of IPM physicians work in an office-based setting, thus leaving the larger proportion of IPM physicians, who rely on hospital suites or ASCs, without a facility to treat their patients [6]. Due to the unknown duration and severity of the COVID-19 pandemic and related societal

Sjedinjenih Američkih Država su pogrešno kategorisale većinu usluga interventne terapije bola kao „neobavezne", te su, sledstveno, svoje službe interventne terapije bola zatvorili tokom trajanja pandemije [2]. U ovim ustanovama, lekari koji se bave interventnom terapijom bola često nisu konsultovani pre donošenja ovakvih odluka. Ovi postupci su bili posebno štetni za ITB praksu, pošto svega jedna trećina lekara koja se bavi interventnom terapijom bola radi u nezavisnim ordinacijama. Na taj način je veći deo lekara koji se bavi ITB-om, a koji radi u okviru bolnica i centara za ambulantno hirurško lečenje, ostao bez prostorija gde bi mogao da leči svoje pacijente [6]. Usled toga što se nije moglo znati koliko će dugo trajati i koliko će ozbiljna biti pandemija KOVID-19 infekcije, a samim tim ni koliko će trajati zatvaranja, pacijenti sa bolom pripremili su se na to da će na neodređeno vreme morati da se nose sa nelečenim bolom, uz dodatnu brigu o dugoročnim posledicama koje će nelečeni bol ostaviti na njihovo zdravlje [2].

DEJSTVO KOVID-19 PANDEMIJE NA PRAKSU INTERVENTNOG LEČENJA BOLA

Pregled stanja i dejstvo na lekare koji se bave interventnom terapijom bola

Neobavezne procedure interventne terapije bola i posete ordinacijama za ITB stopirane su u Sjedinjenim Američkim Državama, usled pandemije KOVID-19 [2]. Kako je bol razlog za 45% poseta hitnim službama, odlaganje ITB-a je imalo značajan uticaj na praksu interventne terapije bola [7]. U anketi koju je sprovelo Američko društvo lekara koji se bave interventnom terapijom bola (engl. *American Society of Interventional Pain Physicians - ASIPP*), a koja se ticala dejstva KOVID-19 pandemije na sindrom „sagorevanja" kod lekara koji se bave interventnom terapijom bola, 98% ispitanika izjavilo je da je na njihovu praksu uticala KOVID-19 pandemija, pri čemu je 91% ispitanika izjavilo da je pretrpelo finansijske posledice, 54% je prijavilo pojavu sindroma „sagorevanja" nastalog usled KOVID-19 pandemije, 19,55% je prijavilo da nastoji da se povuče iz lekarske prakse, dok je 66% steklo negativan stav prema izgledima za budućnost [8].

Promene u radu lekarskih praksi koje se bave interventnom terapijom bola

1. Preporuke Centra za kontrolu bolesti (CDC)

CDC preporučuje da se osobe koje se leče u ambulantnim centrima ili drugim ustanovama za ambulantno lečenje kontaktiraju pre dolaska u ustanovu kako bi se izvršio skrining pacijenta na KOVID-19 infekciju putem telefona [9]. Ukoliko pacijent sa sumnjom na KOVID-19 oboljenje ili potvrđenom KOVID-19 infekcijom treba da bude tretiran u ambulanti, od pacijenta treba zatražiti

shutdowns, pain patients braced themselves for dealing with untreated pain for an indeterminate length of time, which was coupled with worries about long-term effects of untreated pain [2].

COVID-19 IMPACT ON INTERVENTIONAL PAIN PRACTICE

Overview and impact on interventional pain physicians

Elective interventional pain management and office visits have been halted across the United States due to the COVID-19 pandemic [2]. With pain being the reason for 45% of visits to emergency departments, the postponement of IPM significantly impacted interventional pain practice [7]. In a survey conducted by the American Society of Interventional Pain Physicians (ASIPP) on the impact of COVID-19 on IPM physician burnout, 98% of respondents reported that their practices were affected by COVID-19, with 91% stating they were affected financially, 54% reporting new burnout secondary to COVID-19, 19.55% attempting to retire from medical practice, and 66% developing a negative outlook of the future [8].

Operational changes to interventional pain practices

1. Recommendations of the Centers for Disease Control (CDC)

The CDC recommends that individuals receiving treatment at an ambulatory care center or other outpatient institution be contacted prior to their visit and screened for COVID-19 risk over the phone [9]. If a patient with known or suspected COVID-19 needs to be treated in person, the patient should be requested to phone ahead of time so that personnel can be prepared (personal protective equipment - PPE, and infection control procedures) and the patient may be rapidly brought into the system and receive their care promptly. After surgical procedures, telephone follow-ups can be utilized to check on patients, confirm medication adherence, and answer any questions patients may have.

2. IPM resource utilization

A clinical team must evaluate a pain patient's COVID-19 history via methods such as antigen or antibody testing and/or a chest X-ray when considering an interventional pain procedure [10]. Procedures must also be carried out in accordance with federal, state, and local regulations, and all individuals who are in close proximity to the patient must have access to adequate PPE. Equipment should also be kept to a minimum in the exam room, and what is left should be protected with disposable covers [11].

da se najavi unapred telefonom, kako bi se osoblje pripremilo za njegov dolazak (lična zaštitna oprema – LZO, sprovođenje procedura za kontrolu infekcije), kao i da bi se pacijent mogao brzo uvesti u postupak i bez odlaganja sprovelo njegovo/njeno lečenje. Nakon hirurških intervencija, telefonskim putem se nadalje može pratiti pacijentovo stanje, kontrolisati da li se pacijent pridržava propisane terapije, kao i odgovarati na pitanja pacijenta.

2. Korišćenje resursa ITB-a

Kada razmatra proceduru za interventno lečenje bola, klinički tim mora da proceni istoriju KOVID-19 oboljenja kod pacijenta sa bolom, putem metoda kao što su testiranje na antigene odnosno antitela i/ili rentgenski snimak pluća [10]. Takođe, intervencije moraju da se sprovode u skladu sa propisima koji važe na federalnom, nivou pojedinačne savezne države, ali i na lokalnom nivou, a sve osobe u neposrednoj blizini pacijenta moraju imati na raspolaganju adekvatnu opremu za ličnu zaštitu. Takođe, u ordinaciji treba da bude minimalni broj aparata i druge opreme, dok oprema koja jeste u ordinaciji treba da bude zaštićena jednokratnim prekrivačima [11].

3. Definicija medicinske hitnosti slučaja

Stratifikacija medicinske hitnosti pacijenata može se izvršiti na osnovu njihovog kliničkog stanja i od slučaja do slučaja [2]. Neki slučajevi se mogu, bez opasnosti po pacijenta, odložiti na izvesno vreme, dok se drugi mogu odložiti na neograničeni period, bez negativnih posledica. Međutim, u mnogim situacijama je više rizika „u igri", usled međudejstva različitih faktora. Odmeravanje rizika između virusne infekcije, nelečenog bola i povećane doze lekova u odnosu na uobičajenu, jeste problem sa kojom se mnogi pacijenti sa hroničnim bolom suočavaju.

Vrsta bola od kojeg pacijent pati je takođe posebno važan činilac za utvrđivanje medicinske hitnosti. Akutan bol može biti simptom osnovne bolesti i može se tretirati kao medicinski hitno stanje. Subakutna ili hronična bolna stanja mogu biti povezana sa potencijalno ozbiljnim pridruženim funkcionalnim ograničenjima. Neodgovarajući tretman subakutnog ili hroničnog bola može imati kao posledicu porast pridruženih oboljenja i može nauditi pacijentu. U različitim studijama utvrđena je povezanost između nelečenog hroničnog bola i niza medicinskih stanja, kao što su: gubitak pamćenja, demencija, depresija, funkcionalni deficiti, anksioznost, nesanica, suicidnost, i rana smrtnost [12-18].

4. ITB skala za procenu statusa i potreba pacijenata

Da li je neka intervencija indikovana kao „hitna" ili „urgentna" ne može se utvrditi samo na osnovu toga da li je operacija „neobavezna" [19]. Specijalista za interventnu terapiju bola treba da bude odgovoran za procenu toga da li je neka intervencija medicinski neophodna,

3. Definition of medical urgency of a case

The medical urgency of a patient can be stratified based on their clinical situation and by case [2]. Certain cases can be safely postponed for a limited period of time, while others can be postponed indefinitely without harming the patient. However, in many circumstances, risks compete, due to an interplay of factors. Assessing the risks between viral infection, untreated pain, and higher-than-usual drug doses is a common predicament many chronic pain patients face.

The type of pain a patient experiences is also a particularly important component for determining medical urgency. Acute pain may be a symptom of underlying disease and may be addressed as an emergency. Subacute or chronic pain conditions can be associated with potentially severe concomitant functional limitations. Inadequate management of subacute or chronic pain may result in increased comorbidities and patient harm. Studies have linked untreated chronic pain with a myriad of medical issues such as memory loss, dementia, depression, functional deficits, anxiety, insomnia, suicidality, and early mortality [12-18].

4. IPM acuity scale

Whether or not a procedure is urgently or emergently indicated cannot be determined purely on the basis of whether or not the operation is 'elective' [19]. An interventional pain specialist should be responsible for assessing if a procedure is medically necessary, taking into account a variety of factors such as the patient's pain severity, physical incapacitation, underlying conditions, comorbidities, disease progression, mental health status, response to alternative treatments, visits to other healthcare professionals, extent of analgesic management (including opioid use), and likely outcomes, if a procedure is performed or delayed. The IPM environment is a dynamic one, as there are distinct differences between the types of pain patients and their accompanying functional impairments, regions from which these pain patients come from, and regional regulations. Hence, blanket decisions regarding procedures should be avoided.

5. Reopening interventional pain practices

Throughout the months of June and July 2020, 195 Spine Intervention Society members were surveyed regarding the demographics of their practices, perception of COVID-19 prevalence, financial impact of COVID-19 on their practices, and implementation of new re-opening tools and procedures [20]. Risk stratification tools and scheduling pattern changes were used by most respondents (71%). Initial assessments and follow-ups were conducted via telehealth by almost 70% and 87%, respectively. Upon a patient's

uzimajući u obzir niz činilaca kao što su: jačina bola koji trpi pacijent, fizička onesposobljenost, osnovne bolesti, pridružene bolesti, napredovanje bolesti, psihičko stanje pacijenta, reagovanje na druge vrste terapije, pregledi i terapije kod drugih zdravstvenih stručnjaka, stepen terapije analgeticima, (uključujući i primenu opioida), i mogući ishodi, u slučaju da se intervencija sprovede ili odloži. Kontekst interventne terapije bola je dinamičan, s obzirom da postoje jasne razlike između tipova pacijenata sa bolom i njihovih pridruženih funkcionalnih oštećenja, regiona odakle pacijenti dolaze, kao i regulative u različitim regionima. Stoga generalizovane odluke po pitanju intervencija treba izbegavati.

5. Ponovno otvaranje ordinacija za interventnu terapiju bola

Tokom juna i jula meseca 2020. godine, 195 članova Društva za spinalnu interventnu terapiju učestvovalo je u anketi o demografskoj strukturi njihovih lekarskih praksi, percepciji prevalencije KOVID-19 oboljenja, finansijskim posledicama KOVID-19 pandemije na njihove lekarske prakse/ordinacije, kao i o primeni novih alata i procedura za ponovno otvaranje ovih praksi/ordinacija [20]. Alate za stratifikaciju rizika i izmene u obrascima zakazivanja pacijenata primenjivala je većina ispitanika (71%). Prve procene pacijenata putem telemedicine primenjivalo je skoro 70% ispitanika, dok je kontrole putem telemedicine primenjivalo 87% njih. Prilikom lične posete pacijenta ordinaciji odnosno ustanovi, preko 80% ispitanika je vršilo provere simptoma odnosno temperature kod pacijenata, dok je 63% obavljalo skrining pacijenata telefonskim putem. Za posete ordinaciji pacijenti nisu testirani na KOVID-19 infekciju u više od polovine slučajeva (58%), ali je 38% njih testiralo one pacijente koji su imali simptome infekcije. Od ukupnog broja ispitanika, 43% njih nije testiralo pacijente na KOVID-19 pre epiduralnih injekcija, intraartikularnih injekcija, niti pre radiofrekventne neurotomije, ali je 36% ispitanika testiralo one pacijente koji su imali simptome infekcije. Nošenje maski je bio uslov za ulazak u ordinaciju, odnosno kliniku, koji je postavljao veći deo ispitanika (70%). Hirurške maske (85%), rukavice (35%), viziri odnosno zaštitne naočare (24%), N95 epidemiološke maske (15%), i hirurški mantili (6%) korišćeni su pri ne-intervencijskim susretima sa pacijentima. Manji deo ispitanika (26%) davao je pacijentima pisane informacije i uputstva o jedinstvenim rizicima i komplikacijama povezanim sa KOVID-19 infekcijom, dok je 66% ispitanika na ovu temu usmeno razgovaralo sa pacijentima. Doziranje steroida (67%) i preoperativna antikoagulantna terapija (97%), uglavnom nisu menjani. Velika većina (81%) procenila je da je pretrpela srednje težak ili težak finansijski gubitak u svojoj lekarskoj praksi usled KOVID-19 pandemije.

in-person entrance into a clinic or facility, over 80% performed symptom/temperature checks, and 63% screened patients over the phone. For office visits, patients were not tested for COVID-19 by more than half of the respondents (58%), but 38% did test patients, if they were symptomatic. Of the total number of respondents, 43% did not test patients for COVID-19 prior to epidural injections, intra-articular injections, and radiofrequency neurotomy procedures, but 36% did test patients, if they were symptomatic. Mask wearing was deemed a requirement for entering the clinic or facility by a majority of respondents (70%). Surgical masks (85%), gloves (35%), face shields/goggles (24%), N95 respirators (15%), and gowns (6%) were used for non-procedure encounters. A minority (26%) provided written information concerning unique COVID-19 risks and complications, while 66% discussed them verbally. Steroid dosage (67%) and peri-procedural anticoagulation management (97%) remained unchanged by most. A large majority (81%) estimated a moderate to severe financial impact on their practice due to COVID-19.

GUIDELINE METHODOLOGY

Numerous organizations have released their respective guidelines for the care of non-COVID-19 patients during the pandemic. The ASIPP has developed the COVID-ASIPP Risk Mitigation and Stratification (COVID-ARMS) Return to Practice Task Force, to provide interventional pain practices with a framework for cautious and strategic reopening [10].

The COVID-ARMS Return to Practice Task Force created a point-based system of risk stratification with regards to patients presenting for interventional pain procedures, for decreasing COVID-19 morbidity. Risk factors and comorbidities of interest for the risk stratification system were chosen based on their increased prevalence among overall COVID-19 hospitalizations. These included age, nursing home or long-term care residence, pulmonary disease, cardiovascular conditions, obesity, diabetes, renal dysfunction, hepatic dysfunction, and immunocompromised state. Each risk factor or comorbidity is assigned a point value depending on the severity of its manifestation in the respective individual. With increasing severity observed, a higher point value is assigned. Once points are assigned to all risk factors and comorbidities present in the individual, they are summed to produce a total value, which, in turn, can be used to classify the patient's overall risk as 'low', 'moderate', or 'high', with respect to pursuing an interventional pain procedure.

In addition to risk stratification, the ASIPP has also provided guidance for triaging pain interventions as 'emergent', 'urgent', or 'elective' based on descriptive

METODOLOGIJA IZRADE SMERNICA

Brojne organizacije objavile su svoje smernice zdravstvene zaštite i nege ne-KOVID-19 pacijenata tokom pandemije. Američko društvo lekara koji se bave interventnom terapijom bola (*ASIPP*) je oformilo KOVID-ASIPP radnu grupu za suzbijanje i stratifikaciju rizika sa ciljem povratka lekarskoj praksi (engl. *COVID-ASIPP Risk Mitigation and Stratification (COVID-ARMS) Return to Practice Task Force*), kako bi se ordinacijama/lekarskim praksama koje se bave interventnom terapijom bola pružio okvir za ponovno oprezno i strateško otvaranje [10].

Ova radna grupa sačinila je bodovni sistem stratifikacije rizika u pogledu prezentacije pacijenata za postupke interventne terapije bola, u cilju smanjenja KOVID-19 morbiditeta. Pridružene bolesti i faktori rizika, koji su značajni za sistem stratifikacije rizika, odabrani su na osnovu njihove povećane prevalencije među sveukupnim hospitalizacijama zbog KOVID-19 oboljenja. Ovi faktori i pridružene bolesti su: starost, smeštaj u domu za stara lica ili drugoj vrsti doma za dugotrajnu negu, plućno oboljenje, kardiovaskularna oboljenja, gojaznost, dijabetes, bubrežna disfunkcija, hepatična disfunkcija, i stanje imunokompromitovanosti. Svakom faktoru rizika ili pridruženoj bolesti dodeljuje se bodovna vrednost koja zavisi od težine njihove manifestacije kod datog pacijenta. Što je veća uočena težina te manifestacije to se dodeljuje veća bodovna vrednost. Kada se svim faktorima rizika i pridruženim bolestima uočenim kod osobe dodele bodovne vrednosti, bodovi se sabiraju kako bi se dobila ukupna vrednost, koja se zatim može upotrebiti kako bi se sveukupni rizik za pacijenta mogao klasifikovati kao „nizak", „umeren" ili „visok", u pogledu podvrgavanja interventnoj terapiji bola.

Uz stratifikaciju rizika, društvo *ASIPP* je takođe obezbedilo smernice za trijažu intervencija za tretiranje bola prema kategorijama „hitne", „urgentne" ili „neobavezne", na osnovu deskriptivnih indikatora, lokalizacije terapije, primera specifičnih za određenu situaciju, primera intervencija, i vremenskih faktora [2]. *COVID-ARMS* radna grupa je takođe sačinila i dijagram toka za suzbijanje rizika od KOVID-19 morbiditeta tokom poseta pacijenata zbog interventne terapije bola, koji je namenjen da se koristi zajedno sa stratifikacijom rizika i alatima za trijažu pacijenata [10].

Zakonski gledano, promene u smernicama i popuštanje različitih propisa omogućilo je pružaocima ovih usluga više fleksibilnosti u lečenju pacijenata, uz nastavak poštovanja mera sprečavanja širenja KOVID-19 infekcije. Uvođenje telemedicine, pre svega, pomoglo je da se proširi pokrivenost pacijenata na one koji se, u uslovima van pandemije, ne bi kvalifikovali za ovakvu vrstu usluge. Zakonske izmene, kao što su: Zakon [SAD] o dopunskim apropriacijama po pitanju pripremljenosti

indications, the location of treatment, situation specific examples, intervention examples, and timing factors [2]. The COVID-ARMS Return to Practice Task Force has also produced a flow chart for mitigating the risks of COVID-19 morbidity during interventional pain encounters, to be used in conjunction with risk stratification and triaging tools [10].

Legislatively, guideline changes and the relaxation of various regulations allowed providers more flexibility to treat patients, while still maintaining COVID-19 precautions. The introduction of telehealth, in particular, has helped expand coverage to those who would not have qualified under non-pandemic circumstances. Legal changes, such as the Coronavirus Preparedness and Response Supplemental Appropriations Act and 1135 Waiver, have allowed Medicare and Medicaid services to expand the offerings of telehealth appointments to "office, hospital, and other visits furnished via telehealth across the country including in patients' places of residence" [21]. Additionally, the United States Drug Enforcement Administration (DEA) also relaxed regulations, allowing DEA-registered physicians to "prescribe opioids via telehealth visits provided they are issued for a legitimate medical purpose by a practitioner acting in the usual course of his/her professional practice; the telemedicine communication is conducted using an audio-visual, real-time, two-way interactive communication system; and the practitioner is acting in accordance with applicable federal and state law" [21].

Efforts have also been made to combine classification systems from various organizations, such as the American Society of Regional Anesthesia and Pain Medicine (ASRA), European Society of Regional Anesthesia and Pain Therapy (ESRA), and American Society of Pain and Neuroscience (ASPN), to produce a new framework of guidelines aimed at providing a consensus and a streamlined reopening approach for interventional pain practices [22]. In the aforementioned combined classification system, the components of risk stratification, triaging, and PPE requirements continue to be emphasized.

TELEMEDICINE

An adaptation to the COVID-19 pandemic was the implementation of telehealth visits, in order to meet the needs of patient care, while limiting potential patient exposure to COVID-19. While, in theory, telehealth should be able to meet patient needs and demands related to care and pain management, subtleties in the patient-physician interaction related to communication and nonverbal cues, which are absent in telehealth visits, may affect treatment and the overall patient

i mogućnosti za odgovor na pandemiju koronavirusa (engl. *Coronavirus Preparedness and Response Supplemental Appropriations Act*) i Oslobođenje od obaveze na osnovu člana 1135. Zakona [SAD] o socijalnoj zaštiti (engl. *1135 Waiver*), omogućile su da se u okviru *Medicare*[1] i *Medicaid*[2] usluga proširi ponuda zakazanih termina za usluge telemedicine na „posete u ordinaciji, bolnici, i druge posete zakazane putem usluga telemedicine širom zemlje, uključujući i domove pacijenata" [21]. Uz to Američka uprava za borbu protiv droge (engl. *United States Drug Enforcement Agency - DEA*) je takođe izvršila popuštanje propisa, dozvolivši lekarima registrovanim kod *DEA*-e da „prepisuju opioide telemedicinskim putem pod uslovom da su lekovi prepisani iz medicinski opravdanog razloga od strane lekara u okviru njegove/njene uobičajene profesionalne prakse; da se telemedicinska komunikacija odvija putem audiovizuelnog, dvosmernog, interaktivnog komunikacionog sistema, u realnom vremenu; i da lekar postupa u skladu sa odgovarajućim federalnim i zakonom date savezne države" [21].

Takođe su učinjeni napori da se kombinuju sistemi klasifikacije različitih organizacija, kao što su: Američko društvo za regionalnu anesteziju i medicinu bola (engl. *American Society of Regional Anesthesia and Pain Medicine - ASRA*), Evropsko društvo za regionalnu anesteziju i terapiju bola (engl. *European Society of Regional Anesthesia and Pain Therapy - ESRA*) i Američko društvo za bol i neuronauku (engl. *American Society of Pain and Neuroscience - ASPN*), kako bi se sačinio novi okvir smernica usmerenih na postizanje konsenzusa i jedinstvenog pristupa ponovnom otvaranju lekarskih praksi koje se bave interventnom terapijom bola [22]. U gore spomenutom kombinovanom sistemu klasifikacije, komponente stratifikacije rizika, trijaže i neophodnih mera primene LZO-a zadržale su svoj značaj.

TELEMEDICINA

Jedan od načina prilagođavanja pandemiji KOVID-19 oboljenja bila je i primena telemedicinskih lekarskih konsultacija, kako bi se zadovoljile potrebe pacijenata za zdravstvenom zaštitom i negom uz istovremeno smanjivanje mogućnosti da pacijenti budu i izloženi KOVID-19 infekciji. Dok bi, teoretski, telemedicina trebalo da bude u stanju da zadovolji potrebe i zahteve pacijenata koji se odnose na zdravstvenu zaštitu i terapiju bola, nijanse u odnosu lekar-pacijent, a koje se odnose na komunikaciju i neverbalnu interakciju, i koje

1 Federalni program zdravstvenog osiguranja u SAD kojim su pokrivena lica starija od 65 godina, lica mlađa od 65 godina sa određenim invaliditetima, kao i lica sa terminalnom insuficijencijom bubrega. (Prim. prev.)

2 Program zdravstvenog osiguranja u SAD koji savezne države sprovode na osnovu federalnih propisa, a koji pokriva određene kategorije socijalno ugroženih porodica, trudnice, decu, starija lica i lica sa invaliditetom. (Prim. prev.)

experience. In a survey conducted by Berwick et al., the researchers retrospectively evaluated the service of a remote telehealth follow-up clinic, on themes including communication, self-help advice, and understanding [23]. Of the 30 chronic pain patients involved in the survey, 25 were on long-term follow-up. Pain etiology included musculoskeletal, neuropathic, chronic primary pain, and chronic postsurgical pain. Anatomically related pain included: back, shoulder, leg, arm, and generalized pain. From this survey, the researchers found that 19/30 patients reported the consultation had met their needs and 21/30 had been able to say all that they were required to. Despite these findings, however, 25/30 patients would still prefer to have a face-to-face appointment, while 17/30 patients would prefer video conferencing over telehealth appointments [23]. These results demonstrate that patients prefer traditional clinic visits over telehealth appointments, if given the opportunity, despite the reported satisfaction with telehealth appointments. Explanations for this finding include a significant reduction in the patient experience ratings regarding communication and missed symptom validation from the physician, due to the lack of a physical examination. Overall, these findings suggest that patients do not prefer telehealth to conventional consultations. This conclusion, combined with the fact that telehealth is no more efficacious than face-to-face consultations, should be taken into consideration when determining future standards of care and training related to pain management [24].

PHARMACOTHERAPY

Chronic pain had been severely affecting individuals and society alike, long before the COVID-19 pandemic emerged. However, it has been severely exacerbated in patients since the onset of the pandemic, due to the decimation of most conventional medical services, with the exception of virtual care and telehealth. In addition to worsening and untreated pain symptoms, many chronic pain patients have also been impacted in numerous other ways, with increases in cardiovascular disease, mental health problems, cognitive dysfunction, and early death [25]. Many different modalities have been utilized to manage and treat chronic pain throughout the years, including surgical and interventional techniques, physical therapy, and pharmacotherapy [25]. Due to the decline in interventional techniques and elective surgical procedures during the pandemic, treatment has been focused on commonly used pharmacological agents, including opioids, NSAIDs, local anesthetics, and steroids [26,27]. Use of these pharmacological agents, however, generates concern due to their immunosuppressive effects and

nedostaju u telemedicinskim konsultacijama, mogu uticati na terapiju, kao i na celokupno iskustvo pacijenta. U anketi koju su sproveli Bervik i saradnici, istraživači su retrospektivno ocenjivali usluge ambulante za praćenje bolesnika udaljenim telemedicinskim putem, po pitanju tema kao što su komunikacija, saveti za samopomoć i razumevanje [23]. Od 30 pacijenata uključenih u anketu, 25 njih je bilo na dugoročnom praćenju. Etiologija bola uključivala je muskulo-skeletni, neuropatski, hronični primarni bol, i hronični posthirurški bol. Anatomski gledano, bol kod pacijenata je bio: bol u leđima, ramenu, nozi, ruci, i generalizovani bol. Na osnovu ove ankete, istraživači su utvrdili da je 19 od 30 pacijenata izjavilo da je konsultacija zadovoljila njihove potrebe, te da je 21 od 30 pacijenata smatralo da su imali priliku da kažu sve što je bilo potrebno. Međutim, uprkos ovakvim rezultatima ankete, 25 od 30 pacijenata je izjavilo da bi se ipak radije opredelili za posetu lekaru uživo, dok je 17 od 30 pacijenata reklo da bi im više odgovarala video-konferencijska konsultacija od telemedicinske [23]. Ovi rezultati govore da će se pacijenti, ako im se pruži izbor, radije opredeliti za uobičajenu kliničku posetu lekaru nego za telemedicinsku konsultaciju, uprkos iskazanom zadovoljstvu po pitanju telemedicinskih konsultacija koje su imali. Među objašnjenja za ovakav rezultat spada i značajan pad u oceni iskustava pacijenata po pitanju komunikacije i propuštene validacije simptoma od strane lekara, usled neobavljenog fizičkog lekarskog pregleda. Sve u svemu, ovi nalazi ukazuju na to da se pacijenti neće pre opredeliti za telemedicinsku konsultaciju već za klasičnu lekarsku konsultaciju. Ovaj zaključak, kao i činjenica da se telemedicina nije pokazala ništa efikasnijom od konsultacija uživo, treba da budu uzeti u obzir kada se utvrđuju budući standardi zdravstvene zaštite i obuke u domenu terapije bola [24].

FARMAKOTERAPIJA

Hronični bol je ozbiljno pogađao i pojedince i društvo daleko pre pojave KOVID-19 pandemije. Ipak, od početka pandemije, došlo je do drastičnog pogoršanja ovog problema kod pacijenata, usled desetkovanja većine uobičajenih zdravstvenih službi, s izuzetkom virtuelne zdravstvene zaštite i telemedicine. Osim pogoršanja stanja i nelečenih simptoma bola, pacijenti su pretrpeli i druge brojne posledice, kao što je porast kardiovaskularnih oboljenja, psihičkih problema, kognitivne disfunkcije, i rane smrti [25]. Tokom godina, mnogo različitih modaliteta primenjivano je u terapiji bola, uključujući hirurške i interventne tehnike, fizikalnu terapiju i farmakoterapiju [25]. Usled pada u primeni interventnih tehnika i neobaveznih hirurških intervencija, tokom pandemije, terapija se svela na uobičajeno primenjivana farmakološka sredstva, uključujući

consequently susceptibility to COVID-19, as chronic pain itself may already be a risk factor, due to immunosuppression.

Opioids have been well-documented to suppress the immune system [28]. NSAIDs generated concern when non-peer-reviewed case reports emerged of several young patients infected with COVID-19 deteriorating after taking ibuprofen. However, neither the United States Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) are aware of any evidence linking the use of ibuprofen or other NSAIDs to worsening COVID-19, though the agencies do caution that "the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections" [29]. Acetaminophen is an alternative to NSAIDs, but has been shown in clinical trials to have weaker antipyretic and analgesic effects [30]. Nociceptive selective block of local anesthetics is valuable in chronic pain injections, especially in maintaining a patient's well-being and avoiding respiratory depression [27]. Finally, because of the pandemic, the multiple side effects of steroids, such as immunosuppression, have raised concerns, and recommendations have been made to utilize local anesthetic alone or limited doses of steroids [31,32]. In fact, systematic and focused review of local anesthetics and steroids utilized in interventional pain management for epidural injections, peripheral nerve blocks, and intraarticular injections, have shown that no significant difference was identified, based on whether or not steroids are added to local anesthetic, for epidural as well as facet joint injections [31,33,34]. Thus, steroids may be omitted in certain procedures, if fear of immunosuppression is a concern. Additionally, although steroids have been linked to infections caused by immunosuppression in the past, in a position paper from the Spine Intervention Society, the Patient Safety Committee concluded "there is no clear evidence of a causative effect between spinal injections and periprocedural infections and complications in immunosuppressed patients" [35]. Most are linked to contaminated solutions or poor infection control practice.

As the pandemic continues to afflict nations worldwide, it is concurrently worsening a public health crisis in the United States that had slowly been on the decline in the past few years: the opioid epidemic [25]. With the onset of the pandemic, many chronic pain patients' conditions have worsened due to delay of treatment from the decline in conventional health services. Correspondingly, chronic pain management has been significantly affected, causing

opioide, nesteroidne antiinflamatorne lekove (NSAIL), lokalne anestetike i steroide [26,27]. Upotreba ovih farmakoloških sredstava, međutim, izaziva brigu, usled njihovih imunosupresivnih efekata, a sledstveno tome i podložnosti KOVID-19 infekciji, pošto hronični bol, sam po sebi, može biti faktor rizika, usled imunosupresije.

Postoje brojni dokazi da opioidi vrše supresiju imunog sistema [28]. Zabrinutost u vezi sa dejstvom NSAIL-a pojavila se nakon pojave prvih nerecenziranih prikaza slučajeva o pogoršanju stanja kod nekoliko mladih pacijenata zaraženih KOVID-19 infekcijom nakon uzimanja ibuprofena. Međutim, ni Američka uprava za hranu i lekove (engl. *United States Food and Drug Administration - FDA*) niti Evropska agencija za lekove (engl. *European Medicines Agency* - EMA) ne raspolažu podacima koji dokazuju vezu između primene ibuprofena ili drugih NSAIL-a i pogoršanja stanja kod KOVID-19 oboljenja, mada ove agencije upozoravaju da „farmakološka aktivnost NSAIL-a u ublažavanju zapaljenskog procesa, a možda i povišene temperature, može umanjiti korisnost dijagnostičkih znakova u otkrivanju infekcija" [29]. Acetaminofen je alternativa za NSAIL-e, ali je u kliničkim probama pokazao slabije antipiretičko i analgetsko dejstvo [30]. Nociceptivni selektivni blok lokalnih anestetika je značajan kod injekcija za terapiju hroničnog bola, naročito u održavanju pacijenta u dobrom stanju i sprečavanju respiratorne depresije [27]. Najzad, zbog pandemije, brojna neželjena dejstva steroida, kao što je imunosupresija, uzrokovala su oprez u vezi sa njihovom primenom, te su date preporuke da se primenjuju samo lokalni anestetici ili ograničene doze steroida [31,32]. Zapravo, sistematski i ciljani pregled lokalnih anestetika i steroida koji se koriste u interventnoj terapiji bola za epiduralne injekcije, periferne nervne blokade i intraartikularne injekcije, pokazao je da ne postoji značajna razlika između toga da li se sterioidi dodaju ili ne dodaju u lokalne anestetike, bilo kod epiduralnih bilo kod injekcija za fasetne zglobove [31,33,34]. Stoga se steroidi mogu izostaviti u određenim intervencijama, ukoliko postoji bojazan od imunosupresije. Takođe, iako su u prošlosti steroidi povezivani sa infekcijama uzrokovanim imunosupresijom, u jednom dokumentu o stavu koji je izdala Komisija za bezbednost pacijenata (engl. *Patient Safety Committee*) Društva za spinalnu interventnu terapiju (engl. *Spine Intervention Society*), zaključeno je da „ne postoje jasni dokazi o uzročno-posledičnom odnosu između spinalnih injekcija i periproceduralnih infekcija i komplikacija kod imunosuprimiranih pacijenata" [35]. Većina infekcija se povezuje sa kontaminiranim rastvorima ili lošom praksom sprečavanja infekcije.

Kako pandemija nastavlja da pogađa nacije širom sveta, ona istovremeno produbljuje jednu javno-zdravstvenu

severe restrictions in non-opioid therapy. According to health tracker data, there was a near 88% decline in elective surgeries and 15.1% in pain-related prescriptions [25]. As a result, many chronic pain patients are seeking out alternate and potentially harmful remedies to alleviate their symptoms, such as elevated doses of NSAIDs, illicit drugs, or opioids [4]. Drug deaths, which decreased for the first time in 25 years, in 2018, rose to record numbers in 2019 and are continuing to climb, worsened by the pandemic. Although the opioid epidemic was "already resurfacing with a 5% increase in overall deaths from 2018, the preliminary data show that prescription opioid deaths continued to decline, while at the same time deaths due to fentanyl, methamphetamine, and cocaine climbed, with some reductions in heroin deaths" [25]. It is crucial to develop appropriate regulations that will provide proper opioid therapy while containing the opioid epidemic, without limiting access to therapeutic opioids for chronic pain patients.

CHRONIC PAIN MANAGEMENT AND THE COVID-19 VACCINE

As the development and approval of vaccines for the COVID-19 pandemic progress worldwide, questions regarding the potential effects of pain treatments utilizing steroids on vaccine efficacy have started to arise. Corticosteroid injections often have systemic effects, two of which are systemic immune depression and hypothalamic-pituitary-adrenal (HPA) axis depression [36]. According to studies, the humoral immune response may be disrupted in immunocompromised people, resulting in a reduced immune response to vaccination. For example, in a large retrospective study, influenza-vaccinated patients who had undergone joint corticosteroid injections were 52% more likely to develop influenza than non-injection control patients, with women younger than 65 years being at the highest risk [37]. As a result, guidelines developed at the Institute for Pain Medicine, Tel Aviv state that patients are warned of the immunosuppression risks and are advised not to receive steroid injections during the 5-week period beginning one week prior to the first dose of the vaccine and ending one week after the second dose. However, if the patient insists on receiving an injection, dexamethasone is used due to a shorter duration of systemic effects [38].

The primary concern regarding COVID-19 vaccines in the setting of steroid use is efficacy, given the immunosuppressive hallmarks of corticosteroids. Regarding the clinical trials of specific vaccines, patients with systemic immunosuppression were excluded from participating in all except the *Johnson & Johnson*

krizu u Sjedinjenim Američkim Državama, koja je, prethodnih godina, bila počela polako da opada, a to je epidemija upotrebe opioida [25]. Sa početkom pandemije, kod mnogih pacijenata sa hroničnim bolom došlo je do pogoršanja njihovog stanja usled odlaganja terapije, do kojeg je došlo zbog slabljenja u pružanju uobičajenih zdravstvenih usluga. Isto tako, i terapija hroničnog bola je značajno pogođena, što je prouzrokovalo ozbiljna ograničenja u sprovođenju ne-opioidne terapije. Prema podacima praćenja zdravlja, došlo je do pada od skoro 88% u broju izvedenih neobaveznih hirurških intervencija i pada od 15,1% u izdavanju recepata za terapiju bola [25]. Posledica ovakve situacije jeste da mnogi pacijenti sa hroničnim bolom traže druge, potencijalno opasne alternative kako bi olakšali sebi simptome, kao što su povećane doze NSAIL-a, nelegalne supstance ili opioidi [4]. Smrtni slučajevi uzrokovani drogama, koji su, 2018. godine, bili u padu po prvi put nakon 25 godina, dostigli su rekordne brojeve 2019. godine, i nastavljaju da rastu, pod uticajem pandemije. Iako je epidemija upotrebe opioida „već bila počela da se ponovo pogoršava sa porastom od 5% u sveukupnom broju smrtnih slučajeva u 2018. godini, preliminarni podaci pokazuju da je broj smrtnih slučajeva uzrokovan prepisanim opioidima nastavio da opada, dok je istovremeno broj smrti uzrokovanih fentanilom, metamfetaminom i kokainom porastao, uz izvestan pad u broju smrti uzrokovanih heroinom“ [25]. Od ključnog je značaja da se uvedu odgovarajući propisi koji bi omogućili obezbeđivanje adekvatne terapije opioidima i istovremeno držali pod kontrolom epidemiju upotrebe opioida, bez ograničavanja pristupa terapiji opioidima pacijentima sa hroničnim bolom.

TERAPIJA HRONIČNOG BOLA I KOVID-19 VAKCINA

Kako napreduje razvoj vakcina protiv KOVID-19 oboljenja i počinje njihovo odobravanje za upotrebu širom sveta, javljaju se pitanja u vezi sa potencijalnim dejstvom različitih terapija bola koje sadrže steroide na delotvornost vakcine. Injekcije kortikosteroida često imaju sistemske posledice, među kojima su i sistemska imunska depresija i depresija hipotalamusno-hipofizno-nadbubrežne osovine (engl. *hypothalamic-pituitary-adrenal* (*HPA*) *axis*) [36]. Prema objavljenim studijama, humoralni imunski odgovor može biti poremećen kod imunokompromitovanih osoba, što dovodi do smanjenog imunskog odgovora na vakcinaciju. Na primer, u jednoj velikoj retrospektivnoj studiji, pacijenti vakcinisani protiv gripa, koji su prethodno primili injekcije kortikosteroida, imali su 52% veću verovatnoću da obole od gripa nego kontrolni pacijenti koji nisu primali ovakve injekcije, pri čemu su najveći rizik imale žene mlađe od 65 godina [37]. Usled toga, vaccine trial [39]. In the *Moderna* trial, for example, systemic treatment of corticosteroids was limited to ≥20 mg/day. Thus, lots of uncertainty surrounds the efficacy of vaccines administered concurrently with systemic corticosteroid use. With respect to efficacy, previous studies have demonstrated evidence of delayed response to hepatitis B vaccination in children receiving high-dose steroid therapy for nephrotic syndrome, as well as delayed response to the influenza vaccine in cancer patients receiving systemic steroids [40,41]. The effect on efficacy in these studies, however, was not statistically significant and cannot be used to confirm that chronic high dose steroids may impair vaccine-based immunity. Furthermore, while epidural steroids may be absorbed systemically, they are unlikely to have the immunosuppressive effects seen with chronic high-dose systemic steroid usage, based on current dosage regimens and the pharmacodynamics of these injections [39]. Additionally, short-term systemic bolus steroids have not been demonstrated to impact vaccine responsiveness. With respect to safety, corticosteroid use is a concern in the setting of live immunization and at systemic dosages equivalent to 2 mg/kg or a dose of 20 mg/day of prednisone equivalents for two or more weeks. However, all of the adenovirus vector vaccines approved by the FDA so far are considered appropriate for use in immunocompromised hosts, because there is no risk for reversion to a virulent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain, as may be the case with a traditional live vaccine [39].

In addition to concerns regarding the efficacy of COVID-19 vaccines in relation to corticosteroids, NSAIDs and cyclooxygenase (COX) inhibitors have also been under consideration. When used in pharmacological quantities, acetaminophen, aspirin, and naproxen have shown similar results in inhibiting antibody formation, with studies revealing a direct proportional association between greater NSAID dosages and decreased immunoglobulin synthesis [39]. In addition to their anti-inflammatory effect, NSAIDs exert immunomodulatory effects by interfering with human monocyte and T-lymphocyte activation, proliferation, and cytokine synthesis. However, previous research has found that low-dose aspirin had no effect on the efficacy of the H1N1 influenza vaccine in elderly people and that acetaminophen-associated antibody blunting still resulted in protective antibody levels [42,43]. Thus, data on the effect of NSAIDs and COX inhibitors on immunity and vaccine efficiency is often inconclusive or insufficient to determine if they are an appropriate substitute for corticosteroid injections.

smernice Instituta za medicinu bola u Tel Avivu navode da pacijente treba upozoravati na postojanje rizika od imunosupresije, te da im se savetuje da ne primaju injekcije steroida, tokom perioda od pet sedmica, počevši od jedne sedmice pre prve doze vakcine, zaključno sa jednom sedmicom nakon druge doze vakcine. No, ako pacijent insistira da primi injekciju, koristi se deksametazon, pošto je trajanje njegovih sistemskih efekata kraće [38].

Od primarnog značaja za KOVID-19 vakcinu, u kontekstu korišćenja steroida, jeste delotvornost vakcine, imajući u vidu imunosupresivna svojstva kortikosteroida. Kada su u pitanju kliničke probe konkretnih vakcina, pacijenti sa sistemskom imunosupresijom bili su isključeni iz svih kliničkih proba vakcina, sa izuzetkom proba *Johnson & Johnson* vakcina [39]. Kod ispitivanja vakcine *Moderna*, na primer, sistemska terapija kortikosteroidima bila je ograničena na ≥20 mg na dan. Stoga, postoji dosta nejasnoća kada je u pitanju delotvornost vakcina primenjenih istovremeno sa sistemskom upotrebom kortikosteroida. Što se tiče delotvornosti, prethodne studije su objavile dokaze o odloženom odgovoru na vakcinu protiv hepatitisa B kod dece koja su primala visoke doze steroida u okviru terapije za nefrotični sindrom, kao i odloženi odgovor na vakcinu protiv gripa kod pacijenata obolelih od raka koji su primali sistemske steroide [40,41]. Uticaj na delotvornost vakcine, u ovim studijama, međutim, nije bio statistički značajan, te ne može biti upotrebljen da potvrdi da hronična upotreba visokih doza steroida može negativno uticati na imunitet koji se razvija vakcinom. Štaviše, dok steroidi dati epiduralno mogu biti sistemski apsorbovani, nije verovatno da će oni imati imunosupresivne efekte viđene kod hronične sistemske primene visokih doza steroida, na osnovu sadašnjih režima doziranja i farmakodinamike ovih injekcija [39]. Uz to, nije se pokazalo da kratkoročno davanje sistemskih bolus injekcija steroida ima uticaja na odgovor na vakcinu. Kada je u pitanju bezbednost, upotreba kortikosteroida jeste nešto o čemu treba voditi računa u kontekstu imunizacije živom vakcinom i pri sistemskim dozama ekvivalentnim sa 2 mg/kg ili dozom od 20 mg na dan ekvivalenata prednizona, na preiod od dve ili više sedmica. Međutim, sve adenovirusne vektorske vakcine odobrene od strane *FDA* do sada, smatraju se podesnim za primenu kod imunokompromitovanih primalaca, zato što nema rizika da će doći do reverzije u virulentni soj - ozbiljni akutni respiratorni sindrom korona virus 2 (SARS-KoV-2), što može biti slučaj sa klasičnom živom vakcinom [39].

Uz pitanja koja se tiču delotvornosti vakcine protiv KOVID-19 infekcije, u odnosu na kortikosteroide, takođe su se pojavila i pitanja u vezi sa NSAIL-ima i inhibitorima ciklooksigenaze. Kada se primenjuju u

Overall, there is currently no direct evidence to suggest that a corticosteroid injection, before or after the administration of an adenovirus vector-based COVID-19 vaccine, decreases the efficacy of the vaccine. However, based on the known timeline of HPA axis suppression following epidural and intraarticular corticosteroid injections, and the timeline of the reported peak efficacy of the *Johnson & Johnson* and *AstraZeneca* vaccines, physicians should consider timing an elective corticosteroid injection in such a way that it is administered no less than two weeks prior to and no less than two weeks following a COVID-19 adenovirus vector-based vaccine dose, whenever possible [44]. Given these facts, it is still recommended that physicians determine each individual patient's level of acuity and weigh out specific risks/benefits before considering the treatment plan.

CONCLUSION

It is clear that the COVID-19 pandemic has caused significant disruptions in all aspects of life within the past year. At the start of the pandemic, with the exception of emergency care, most conventional health services were put on hold as a transition to online and telehealth appointments was observed. This transition was particularly deleterious for chronic pain patients, as it severely limited the different treatment options and modalities available. As a result, guidelines concerning the definition of elective procedures were forced to be reexamined with respect to IPM. Many IPM physicians argued that patients must be considered holistically with respect to factors such as daily function, pharmacological drug use, comorbidities, other risk factors, mental health, social risk factors, and prognosis, when determining whether certain surgeries or procedures were classified as elective. Urgent and emergency acuity classification for IPM patients may be carried out when the clinician assesses that a delay would result in unacceptable disease progression, intractable pain, disability, or suffering. Additionally, with the transition to online and telehealth services, treatment shifted towards other pharmacotherapy methods, including opioids and other non-illicit drugs, further exacerbating the opioid epidemic. Steroids, another common pharmacotherapy used in pain management, were also heavily scrutinized due to the concern of their immunosuppressive effects on susceptibility to contract COVID-19, as well as effects on vaccine efficacy. Steroid distancing is recommended in response to inconclusive evidence regarding the effect of steroids on COVID-19 infection or vaccination. Physicians should consider timing an elective corticosteroid injection in such a way that it

farmakološkim količinama, acetaminofen, aspirin i naproksen su pokazali slične rezultate u inhibiciji formiranja antitela, gde su studije pokazale direktnu proporcionalnu povezanost između većih doza NSAIL-a i smanjene sinteze imunoglobulina [39]. Osim što imaju antiinflamatorno dejstvo, NSAIL-i imaju i imunomodulatorne efekte jer ometaju aktivaciju humanih monocita i T-limfocita, proliferaciju i sintezu citokina. Međutim, prethodna istraživanja su utvrdila da aspirin u niskim dozama nema uticaja na delotvornost vakcine protiv virusa gripa H1N1 kod starijih osoba, te da slabljenje antitela (engl. *blunting*) koje se povezuje sa acetaminofenom i dalje za rezultat ima zaštitne nivoe antitela [42,43]. Stoga se na osnovu podataka o dejstvu NSAIL-a i *COX* inhibitora na imunitet i delotvornost vakcina obično ne mogu doneti definitivni i pouzdani zaključci koji bi omogućili da se utvrdi da li su ovi lekovi odgovarajuća zamena za injekcije kortikosteroida.

Sve u svemu, trenutno nema direktnih dokaza koji bi ukazivali na to da injekcija kortikosteroida data pre ili posle davanja adenovirusne vektorske vakcine protiv KOVID-19 oboljenja umanjuje delotvornost ove vakcine. Međutim, na osnovu poznatog vremenskog toka supresije *HPA* osovine nakon epiduralnih i intraaurikularnih injekcija kortikosteroida, i vremenskog toka prijavljene najveće efikasnosti vakcina *Johnson & Johnson* i *AstraZeneca*, lekari bi trebalo da razmotre vremensko planiranje neobavezne injekcije kortikosteroida tako da se ona daje ne manje od dve sedmice pre i ne manje od dve sedmice nakon primanja doze adenovirusne vektorske vakcine protiv KOVID-19 infekcije, kad god je to moguće [44]. Imajući u vidu ove činjenice, i dalje se preporučuje da lekari utvrde status i potrebe za terapijom svakog pacijenta ponaosob, te da odmere konkretne rizike i dobiti, pre nego što razmotre i naprave plan terapije.

ZAKLJUČAK

Jasno je da je pandemija KOVID-19 infekcije izazvala značajne poremećaje u svim aspektima života, tokom protekle godine. Na početku pandemije, sa izuzetkom hitne zdravstvene zaštite, većina uobičajenih zdravstvenih usluga je stopirana i izvršen je prelaz na telemedicinske i lekarske konsultacije putem interneta. Ovaj prelazak je bio posebno težak za pacijente sa hroničnim bolom, pošto je ozbiljno ograničilo dostupnost različitih terapijskih opcija i modaliteta. Zbog toga je moralo doći do preispitivanja smernica koje se odnose na neobavezne intervencije, kada je u pitanju ITB. Mnogi lekari koji se bave interventnom terapijom bola zastupali su stav da se pacijenti moraju posmatrati holistički, kada su u pitanju faktori kao što su svakodnevno funkcionisanje, upotreba farmakoloških sredstava, pridružene bolesti, drugi faktori rizika, psihičko zdravlje,

is administered no less than two weeks prior to and no less than two weeks following a COVID-19 adenovirus vector-based vaccine dose. The findings discussed and observed in this review should be taken into consideration when evaluating the guidelines of IPM practices in the future.

LIST OF ABBREVIATIONS

COVID-19 - Coronavirus Disease 2019
NSAIDs - non-steroidal anti-inflammatory drugs
ASCs - ambulatory surgery centers
IPM - interventional pain management
ASIPP - American Society of Interventional Pain Physicians
CDC - Centers for Disease Control
PPE - personal protective equipment
COVID-ARMS - COVID-ASIPP Risk Mitigation and Stratification
DEA - United States Drug Enforcement Agency
ASRA - American Society of Regional Anesthesia and Pain Medicine
ESRA - European Society of Regional Anesthesia and Pain Therapy
ASPN - American Society of Pain and Neuroscience
FDA - United States Food and Drug Administration
HPA - hypothalamic-pituitary-adrenal
SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2
COX - cyclooxygenase

Conflict of interest: None declared.

socijalni faktori rizika, i prognoza, prilikom klasifikacije određenih intervencija kao neobaveznih. Urgentna odnosno hitna klasifikacija statusa i potreba pacijenata, za pacijente koji su indikovani za interventnu terapiju bola, može se sprovesti kada kliničar proceni da bi odlaganje intervencije imalo za posledicu neprihvatljiv stepen progresije bolesti, neprestani bol, invaliditet ili patnju kod pacijenta. Takođe, prelaskom na usluge telemedicine i konsultacije putem interneta, terapija je prebačena na druge farmakoterapijske metode, uključujući opioide i nelegalne supstance, čime se još više pogoršala epidemija upotrebe opioida. Steroidi, još jedan vid uobičajene farmakoterapije koji se primenjuje u terapiji bola, su takođe bili pod lupom zbog sumnje da njihov imunosupresivni efekat može uticati na podložnost KOVID-19 infekciji, kao i na delotvornost vakcine protiv ove bolesti. Preporučuje se da se davanje steroida vremenski udalji u odnosu na vakcinaciju, s obzirom na nedovoljno jasne dokaze o dejstvu steroida na zaražavanje KOVID-19 infekcijom ili na vakcinaciju. Preporučuje se da lekari vremenski planiraju davanje neobavezne injekcije kortikosteroida na takav način da je pacijent primi ne manje od dve sedmice pre i ne manje od dve sedmice nakon primanja doze adenovirusne vektorske vakcine protiv KOVID-19 infekcije. Rezultati koji su predstavljeni i o kojima se diskutuje u ovom radu trebalo bi da budu uzeti u obzir prilikom procene smernica za rad ITB praksi, u budućnosti.

Sukob interesa: Ne postoji.

SPISAK SKRAĆENICA

KOVID-19 – bolest izazvana koronavirusom 2019
NSAIL - nesteroidni antiinflamatorni lekovi
ASC - centar za ambulantno hirurško lečenje (engl. *ambulatory surgery center*)
ITB - interventna terapija bola
ASIPP - Američko društvo lekara koji se bave interventnom terapijom bola (engl. *American Society of Interventional Pain Physicians*)
CDC - Centar za kontrolu bolesti (engl. *Centers for Disease Control*)
LZO - lična zaštitna oprema
COVID-ARMS - KOVID-ASIPP radna grupa za suzbijanje i stratifikaciju rizika (engl. *COVID-ASIPP Risk Mitigation and Stratification*)
DEA - Američka uprava za borbu protiv droge (engl. *United States Drug Enforcement Agency*)
ASRA - Američko društvo za regionalnu anesteziju i medicinu bola (engl. *American Society of Regional Anesthesia and Pain Medicine*)
ESRA - Evropsko društvo za regionalnu anesteziju i terapiju bola (engl. *European Society of Regional Anesthesia and Pain Therapy*)
ASPN - Američko društvo za bol i neuronauku (engl. *American Society of Pain and Neuroscience*)
FDA - Američka uprava za hranu i lekove (engl. *United States Food and Drug Administration*)
HPA - hipotalamusno-hipofizno-nadbubrežni (engl. *hypothalamic-pituitary-adrenal*)
SARS-KoV-2 – ozbiljni akutni respiratorni sindrom korona virus 2 (engl. *severe acute respiratory syndrome coronavirus 2 - SARS-CoV-2*)
COX – ciklooksigenaza (engl. *cyclooxygenase*)

LITERATURA / *REFERENCES*

1. Centers for Disease Control. COVID Data Tracker. [citirano 2021 06/22], dostupno na: https://covid.cdc.gov/covid-data-tracker/#datatracker-home.
2. Gharibo C, Sharma A, Soin A, Shah S, Diwan S, Buenaventura R, et al. Triaging Interventional Pain Procedures During COVID-19 or Related Elective Surgery Restrictions: Evidence-Informed Guidance from the American Society of Interventional Pain Physicians (ASIPP). Pain Physician. 2020 Aug;23(4S):S183-204.
3. Wan W, Long H. "Cries for help": Drug overdoses are soaring during the coronavirus pandemic. The Washington Post. 2020.
4. Eccleston C, Blyth FM, Dear BF, Fisher EA, Keefe FJ, Lynch ME, et al. Managing patients with chronic pain during the COVID-19 outbreak: considerations for the rapid introduction of remotely supported (eHealth) pain management services. Pain. 2020 May;161(5):889-93.
5. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol. 2002 Oct 1;20(19):4040-9.
6. Manchikanti L, Sanapati MR, Pampati V, Boswell MV, Kaye AD, Hirsch JA. Update on Reversal and Decline of Growth of Utilization of Interventional Techniques In Managing Chronic Pain in the Medicare Population from 2000 to 2018. Pain Physician. 2019 Nov;22(6):521-36.
7. Chang HY, Daubresse M, Kruszewski SP, Alexander GC. Prevalence and treatment of pain in EDs in the United States, 2000 to 2010. Am J Emerg Med. 2014 May;32(5):421-31.
8. Jha SS, Shah S, Calderon MD, Soin A, Manchikanti L. The Effect of COVID-19 on Interventional Pain Management Practices: A Physician Burnout Survey. Pain Physician. 2020 Aug;23(4S):S271-S82.
9. Centers for Disease Control. Managing Healthcare Operations During COVID-19. [citirano 2021 06/22], dostupno na: https://www.cdc.gov/coronavirus/2019-ncov/hcp/facility-planning-operations.html.
10. Shah S, Diwan S, Soin A, Rajput K, Mahajan A, Manchikanti L, et al. Evidence-Based Risk Mitigation and Stratification During COVID-19 for Return to Interventional Pain Practice: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2020 Aug;23(4S):S161-S82.
11. Uppal V, Sondekoppam RV, Landau R, El-Boghdadly K, Narouze S, Kalagara HKP. Neuraxial anaesthesia and peripheral nerve blocks during the COVID-19 pandemic: a literature review and practice recommendations. Anaesthesia. 2020 Oct;75(10):1350-63.
12. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association Between Persistent Pain and Memory Decline and Dementia in a Longitudinal Cohort of Elders. JAMA Intern Med. 2017 Aug 1;177(8):1146-53.
13. IsHak WW, Wen RY, Naghdechi L, Vanle B, Dang J, Knosp M, et al. Pain and Depression: A Systematic Review. Harv Rev Psychiatry. 2018 Nov/Dec;26(6):352-63.
14. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plast. 2017;2017:9724371.
15. Elbinoune I, Amine B, Shyen S, Gueddari S, Abouqal R, Hajjaj-Hassouni N. Chronic neck pain and anxiety-depression: prevalence and associated risk factors. Pan Afr Med J. 2016 May 27;24:89.
16. Nijs J, Mairesse O, Neu D, Leysen L, Danneels L, Cagnie B, et al. Sleep Disturbances in Chronic Pain: Neurobiology, Assessment, and Treatment in Physical Therapist Practice. Phys Ther. 2018 May 1;98(5):325-35.
17. Racine M. Chronic pain and suicide risk: A comprehensive review. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Dec 20;87(Pt B):269-80.

18. Da Silva JAP, Geenen R, Jacobs JWG. Chronic widespread pain and increased mortality: biopsychosocial interconnections. Ann Rheum Dis. 2018 Jun;77(6):790-2.
19. American College of Surgeons. COVID-19: Guidance for Triage of Non-Emergent Surgical Procedures. [citirano 2021 06/22], dostupno na: https://www.facs.org/covid-19/clinical-guidance/triage.
20. Huynh L, Chang RG, Chhatre A, Sayeed Y, MacVicar J, McCormick ZL. Reopening Interventional Pain Practices during the Early Phase of the COVID-19 Global Pandemic. Pain Med. 2021 Jul 25;22(7):1496-502.
21. Cohen SP, Baber ZB, Buvanendran A, McLean BC, Chen Y, Hooten WM, et al. Pain Management Best Practices from Multispecialty Organizations During the COVID-19 Pandemic and Public Health Crises. Pain Med. 2020 Nov 7;21(7):1331-46.
22. Murphy MT, Latif U. Pain During COVID-19: A Comprehensive Review and Guide for the Interventionalist. Pain Pract. 2021 Jan;21(1):132-43.
23. Berwick RJ, Herron K, Kee Tsang H. A survey of chronic pain telephone consultations during COVID-19 at an inner-city secondary care center. Pain Pract. 2021 Jul;21(6):731-2.
24. O'Brien KM, Hodder RK, Wiggers J, Williams A, Campbell E, Wolfenden L, et al. Effectiveness of telephone-based interventions for managing osteoarthritis and spinal pain: a systematic review and meta-analysis. PeerJ. 2018 Oct 30;6:e5846.
25. Manchikanti L, Vanaparthy R, Atluri S, Sachdeva H, Kaye AD, Hirsch JA. COVID-19 and the Opioid Epidemic: Two Public Health Emergencies That Intersect With Chronic Pain. Pain Ther. 2021 Jun;10(1):269-86.
26. Coluzzi F, Marinangeli F, Pergolizzi J. Managing chronic pain patients at the time of COVID-19 pandemic. Minerva Anestesiol. 2020 Aug;86(8):797-9.
27. Gharaei H, Diwan S. COVID-19 Pandemic: Implications on Interventional Pain Practice-a Narrative Review. Pain Physician. 2020 Aug;23(4S):S311-8.
28. Wei G, Moss J, Yuan CS. Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated? Biochem Pharmacol. 2003 Jun 1;65(11):1761-6.
29. Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020 [citirano 2021 6/24], dostupno na: fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19.
30. Olive G. Traitement analgésique/antipyretique: ibuprofène ou paracétamol? Mise au point [Analgesic/Antipyretic treatment: ibuprofen or acetaminophen? An update]. Therapie. 2006 Mar-Apr;61(2):151-60. French.
31. Manchikanti L, Kosanovic R, Vanaparthy R, Vangala BP, Soin A, Sachdeva H, et al. Steroid Distancing in Interventional Pain Management During COVID-19 and Beyond: Safe, Effective and Practical Approach. Pain Physician. 2020 Aug;23(4S):S319-50.
32. Helm Ii S, Harmon PC, Noe C, Calodney AK, Abd-Elsayed A, Knezevic NN, et al. Transforaminal Epidural Steroid Injections: A Systematic Review and Meta-Analysis of Efficacy and Safety. Pain Physician. 2021 Jan;24(S1):S209-32.
33. Knezevic NN, Manchikanti L, Urits I, Orhurhu V, Vangala BP, Vanaparthy R, et al. Lack of Superiority of Epidural Injections with Lidocaine with Steroids Compared to Without Steroids in Spinal Pain: A Systematic Review and Meta-Analysis. Pain Physician. 2020 Aug;23(4S):S239-70.
34. Manchikanti L, Knezevic NN, Parr A, Kaye AD, Sanapati M, Hirsch JA. Does Epidural Bupivacaine with or Without Steroids Provide Long-Term Relief? A Systematic Review and Meta-analysis. Curr Pain Headache Rep. 2020 Apr 25;24(6):26.
35. Popescu A, Patel J, Smith CC; Spine Intervention Society's Patient Safety Committee. Spinal Injections in Immunosuppressed Patients and the Risks Associated with Procedural Care: To Inject or Not to Inject? Pain Med. 2019 Jun 1;20(6):1248-9.
36. Miller DC, Patel J, Gill J, Mattie R, Saffarian M, Schneider BJ, et al. Corticosteroid Injections and COVID-19 Infection Risk. Pain Med. 2020 Aug 1;21(8):1703-6.
37. Sytsma TT, Greenlund LK, Greenlund LS. Joint Corticosteroid Injection Associated With Increased Influenza Risk. Mayo Clin Proc Innov Qual Outcomes. 2018 Mar 20;2(2):194-8.
38. Brill S, Hochberg U, Goor-Aryeh I. Neuro-axial steroid injection in pain management and COVID-19 vaccine. Eur J Pain. 2021 Apr;25(4):945-6.
39. Chakravarthy K, Strand N, Frosch A, Sayed D, Narra LR, Chaturvedi R, et al. Recommendations and Guidance for Steroid Injection Therapy and COVID-19 Vaccine Administration from the American Society of Pain and Neuroscience (ASPN). J Pain Res. 2021 Mar 5;14:623-9.
40. Yıldız N, Sever L, Kasapçopur Ö, Çullu F, Arısoy N, Çalışkan S. Hepatitis B virus vaccination in children with steroid sensitive nephrotic syndrome: immunogenicity and safety? Vaccine. 2013 Jul 18;31(33):3309-12.
41. Hottinger AF, George AC, Bel M, Favet L, Combescure C, Meier S, et al. A prospective study of the factors shaping antibody responses to the AS03-adjuvanted influenza A/H1N1 vaccine in cancer outpatients. Oncologist. 2012;17(3):436-45.
42. Jackson ML, Bellamy A, Wolff M, Hill H, Jackson LA. Low-dose aspirin use does not diminish the immune response to monovalent H1N1 influenza vaccine in older adults. Epidemiol Infect. 2016 Mar;144(4):768-71.
43. Saleh E, Moody MA, Walter EB. Effect of antipyretic analgesics on immune responses to vaccination. Hum Vaccin Immunother. 2016 Sep;12(9):2391-402.
44. Lee H, Punt JA, Patel J, Stojanovic MP, Duszynski B, McCormick ZL; Spine Intervention Society's Patient Safety Committee. Do Corticosteroid Injections for the Treatment of Pain Influence the Efficacy of Adenovirus Vector-Based COVID-19 Vaccines? Pain Med. 2021 Jun 4;22(6):1441-64.