



Unintended consequences of COVID-19 safety measures on patients with chronic knee pain forced to defer joint replacement surgery

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Abstract

In recent months, with the emergence of the COVID-19 pandemic, the American College of Surgeons and the U.S. Centers for Disease Control and Prevention officially recommended the delay of nonemergency procedures until the public health crisis is resolved. Deferring elective joint replacement surgeries for an unknown period is likely to decrease the incidence of infection with SARS-CoV-2 but is likely to have detrimental effects in individuals suffering from chronic knee pain. These detrimental effects extend beyond the discomfort of osteoarthritis (OA) and the inconvenience of rescheduling surgery. Disabling pain is a driving factor for individuals to seek medical intervention, including pharmacological palliative treatment and surgical procedures. The need for surgical intervention due to chronic pain as for knee and hip replacement is now put on hold indefinitely because access to surgical care has been limited. Although a moderate delay in surgical intervention may not produce a significant progression of OA within the knee, it could lead to muscle wasting due to immobility and exacerbate comorbidities, making rehabilitation more challenging. Importantly, it will have an impact on comorbidities driven by OA severity, notably decreased quality of life and depression. These patients with unremitting pain become increasingly susceptible to substance use disorders including opioids, alcohol, as well as prescription and illegal drugs. Appreciation of this downstream crisis created by delayed surgical correction requires aggressive consideration of nonsurgical, nonopioid supported interventions to reduce the morbidity associated with these delays brought upon by the currently restricted access to joint repair.

Keywords: Total knee arthroplasty, Joint replacement, Joint pain, Elective surgery, Opioid, Chronic pain, Depression, Quality of life, COVID-19, Osteoarthritis

1. Introduction

The first case infected with the novel coronavirus SARS-CoV-2 was confirmed in the United States in mid-January, 2020,²³ nearly 2 months before the World Health Organization declared COVID-19, the disease caused by SARS-CoV-2, a global pandemic (March 11, 2020). As of the end of June 2020, more than 2.6 million cases have been reported across the country, with more than 10 million confirmed positive cases and 0.5 million deaths worldwide (Centers for Disease Control and Prevention [CDC]). The rapid dissemination of the virus, in addition to the

severity of the symptoms in vulnerable populations, has imposed great stress on the world economy and public systems. The effectiveness of the healthcare system, at the front line of this battle, is being tested every day.⁵⁵ The exponential number of severe COVID-19 cases in need of intensive care has produced a well-described shortage of medical resources ranging from essential supplies to qualified personnel.⁵⁵ For this and other reasons related to both the known and unknown epidemiology of the spread of the virus, the American College of Surgeons and the U.S. CDC officially recommended the delay of nonemergency procedures until the COVID-19 crisis is resolved.¹ This essential measure has potentially seeded a new problem for millions of patients who have been asked to defer elective surgeries as well as an inevitable future backlog challenge for a healthcare system under stress. Although some entities have made an effort to continue providing treatment for those suffering from more severe and acute conditions,² it seems certain that patients with chronic pain such as that of the knee and hip will be required to wait months, if not longer, to receive the recommended/elected care.

2. Modeling the impact of knee replacement surgeries deferment

Osteoarthritis (OA) in large joints is one of the major causes of chronic pain worldwide. The 2013 Global Burden of Disease

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study reported that approximately 242 million people were suffering from symptomatic and activity-limiting OA of the hip and/or knee.⁴⁴ The high prevalence of risk factors associated with OA, increased longevity, progressive nature of the disease, and limitations of effective long-term pain management therapeutic options have driven joint replacement surgeries, and in particular total knee arthroplasty (TKA), to become one of the most common orthopedic procedures worldwide.³³ More than one million procedures were reported in the United States alone in 2017, including 966,000 knee arthroplasties and more than 600,000 hip replacements.²⁷ Furthermore, projections of nearly 80% growth in the next 3 decades have been proposed.^{34,52}

The current guideline for prioritizing surgical procedures is not based solely on whether the disease is defined as “serious” with long-term impact, but on multiple parameters encompassing both immediate risk to patients and future severity of the condition.^{2,55} In that approach, a patient could anticipate a delay of at least 3 months for scheduled joint replacement surgeries,⁵⁵ and likely could be asked to wait longer.

Based on epidemiologic TKA data,²⁷ we modeled deferring knee replacement surgeries for 3 months (March to May 2020), assuming a progressive return to surgical capacity within the following 3 months (return to 100% capacity by September 2020) and then having the healthcare system generate 25% additional capacity by the end of the year (**Table 1**). We realize this is a very simplistic approach not taking into consideration that elective surgery deferment is not nationwide (currently), that patients can be redirected to other surgical centers, and that given the financial fallout associated with elective surgeries revenue that hospital systems are incentivized to reopen early and stay open as long as possible. However, the model allows for 25% over capacity, which might be difficult to achieve in an already efficient system limited in surgeons, anesthesiologists, and overall capacity, and does not take into account that TKA might be the lowest priority surgery among deferred elective surgeries (see below), hence any backlog effect might be compounded for this specific type of surgical intervention. The model only assumes a one-time shutdown of 3 months, whereas in reality, a second wave of COVID elective surgery slowdown or complete rolling local shutdowns is predictable as hotspots continue to emerge, and cases spike.

Taking into account the limitations of the model, we identified a likely backlog of approximately 300,000 procedures during 2020 created by a theoretical 3 months deferment of all TKA surgeries,

forcing the health system to work at overcapacity at the end of this year. Using this model, approximately 100,000 procedures would be delayed for 90 days or more, with some delayed in excess of 6 months. In the best-case scenario, it would likely take the U.S. surgical system 16 months (considering an average of 75,000 TKA per month) to clear the backlog of delayed surgeries. The concluded length of time that a patient’s procedure would be delayed and the time that it would take for the surgical system to recover from the backlog would be the result of several factors assumed in the model, such as a prompt return to normalcy, how much excess of surgical capacity can be implemented by December 2020, no other procedures taking precedence to joint replacements when surgeries resume, and that the first patients deferred would also be the first patients gaining access to surgery once it is again available.

In accord to our model (**Table 1**), a recent study on the impact of COVID-19 on hip and knee arthroplasty surgical volume in the United States reported the estimates of nonessential total primary TKA based on statistics from 2018 and 2019.⁷ For this analysis, they excluded primary surgeries related to fractures, infections, and other surgical revisions. The results predicted a delayed number of surgeries per week between 20,738 (100% cancellation) and 5,184 (25% cancellations).

In the context of COVID-19 measures, joint replacements have been classified within the lowest urgency among surgical procedures,⁵⁵ labeled as discretionary and for which deferment of longer than 3 months is judged to be acceptable. This stratification could put patients in need of joint replacement near the bottom of the waiting list for surgical access once routine hospital operations resume. Note that the wait times might be longer than that proposed in the model. Based on statistical models that consider surgical data from 1993 to 2017, Jain and colleagues (2020) projected a surgical orthopedic backlog (including total hip arthroplasty, TKA, cervical and thoracolumbar fusion) that could last for 2 years. The total cumulative number of cases contemplated in this calculation was approximately 500,000 by the month of July 2020 reaching more than 1 million by May 2022, considering the normal monthly surgical volume before the pandemic.²⁹

Thus, considering the impact of a widespread delay in joint replacement surgeries, it is critical to minimize the potential consequences to both the individual as well as the healthcare system. Our point here is that although a moderate delay in

Table 1
Total knee arthroplasty surgical backlog after a 3-month deferment order.

Months	#Patients	Surgical capacity	#TKR performed	#TKR delayed	0–30 d	30–60 d	60–90 d	90+ d	TKR backlog
20-March	75,000	0%	—	75,000	75,000	—	—	—	75,000
20-April	75,000	0%	—	75,000	75,000	75,000	—	—	150,000
20-May	75,000	0%	—	75,000	75,000	75,000	75,000	—	225,000
20-June	75,000	25%	18,750	56,250	75,000	75,000	75,000	56,250	281,250
20-July	75,000	50%	37,500	37,500	75,000	75,000	75,000	93,750	318,750
20-August	75,000	75%	56,250	18,750	75,000	75,000	75,000	<i>112,500</i>	<i>337,500</i>
20-September	75,000	100%	75,000	—	75,000	75,000	75,000	112,500	337,500
20-October	75,000	110%	82,500	–7,500	75,000	75,000	75,000	105,000	330,000
20-November	75,000	110%	82,500	–7,500	75,000	75,000	75,000	97,500	322,500
20-December	75,000	125%	93,750	–18,750	75,000	75,000	75,000	<i>78,750</i>	<i>303,750</i>

Model based on the estimation of 966,000 knee arthroplasties per year.²³ The model assumes (a) an even distribution of 75,000 procedures per month, (b) that the orthopedic surgical system full capacity equals 75,000 cases per month, (c) a progressive return to full capacity over 3 months (June-20 to September-20), (d) the procedures are rescheduled in chronological order to the initial presentation, (e) that other non-TKA surgeries do not affect the recovering surgical capacity, and (f) the ability to implement surgical overcapacity by the end of the year (increasing an excess of 25% of procedures). The bold numbers represent the total TKR surgeries delayed at the end of each period (#TKR delayed) as well as the size of the surgical backlog (TKR Backlog) that includes patients waiting for 1 month, 1 to 2 months, 2 to 3 months and more than 3 months. The italic text represents the backlog inflection point (highest backlog reached on August) and the final size of the backlog at the end of 2020 (20-Dec).

surgical intervention may not lead to a significant progression of knee OA, it would likely have a significant impact on some comorbidities associated with OA and overall patient quality of life, especially on those whose surgeries have or will be cancelled. Chronic pain is a critical driving factor for individuals seeking medical intervention due to OA, including pharmacological palliative treatment and surgical procedures.^{20,44} The constant and intractable chronic pain with which patients live before their scheduled orthopedic surgery, and for which they have elected to proceed with the surgery, is indefinitely put on hold because of the limited access to surgical care.

3. Health risks associated with deferring chronic pain relief

Primary TKA, as well as other total joint replacement surgeries, is reserved for patients suffering from debilitating and serious end-stage OA characterized by severe pain, sleep disturbance, mood alterations (depression, anxiety, and a sense of hopelessness), decreased functional ability (with deconditioning and muscle wasting), and failure to respond to conservative management.³⁵ These and other serious conditions are defined by the FDA as morbidities that produce a substantial impact on day-to-day functioning; are irreversible, persistent, or recurrent; and if left untreated, will progress from a less severe condition to a more serious one.¹³ Although a large population of patients suffering from orthopedic chronic pain, including severe knee OA, have developed coping mechanisms, delaying surgical treatment in these patients may overcome these mechanisms and increase the risk of symptom worsening and other poor outcomes.

4. Effects of delayed total knee arthroplasty repair on surgical outcome

Studies in patients with chronic pain have shown that prolonged wait time for elective orthopedic surgeries can affect postoperative clinical outcomes by delaying improvements in pain and function due to physiological variables such as muscle mass deterioration.^{16,48} Fortin et al. (2002) reported that patients with lower functionality scores before TKA have poor functional status up to 2 years after surgery, including a higher incidence in the need for assistance from other persons in activities of daily living. Another study by Rossi et al. also reported the negative effects of delaying access to TKA. The results show that patients with delayed surgeries performed a lower level (greater pain and difficulty with functional activities) than those with shorter waiting times.⁴⁹

The role of preoperative health-related quality of life (HRQOL) scores as a predictor of postoperative outcomes has also been described in other major joint replacement surgeries. Garbuz et al. studied the postoperative effect of short (less than 6 month) compared with long (greater than 6 month) waiting time on function and HRQOL scores in patients scheduled for total hip replacement.¹⁸ Although the results did not show a difference in postoperative stiffness and pain, there was a negative impact on functionality and HRQOL scores when surgery was delayed by more than 6 months. *Critically, the results suggested that each month of shortening waiting time decreases the odds of achieving a better than expected postoperative functional score by 8%. This difference was reflected as 50% greater odds of worse results when surgery was delayed more than 6 months.* Data suggest that shorter waiting time to surgery, higher functionality scores, and better quality of life during preoperative stages can have a positive impact on TKA outcomes.¹⁵ It is interesting that these comments are in accord with

a large body of preclinical work in which persistent joint inflammation may lead to the generation of chronic pain states that display a polyneuropathic phenotype.⁶⁰

5. Effects of delayed surgical repair on comorbidities

The impact of chronic pain secondary to OA unmitigated pain in the patient whose surgical repair is delayed has multidimensional characteristics. It goes beyond a simple change in physical status, but is also associated with alterations in sleep, fatigue, and negative mood,^{39,44} driving other comorbidities such as depression.¹⁴ The prevalence of depression in patients presenting axial pain due to orthopedic conditions has been reported to be as high as 89%.⁶ More precisely, clinical depression in patients waiting for TKA has been reported as high as 60%.³⁷ As an aside, it is interesting to note that the coexpression of pain and depression reflects the spinofugal pathways activated during chronic pain, which project to higher-order systems responsible for not only the sensory discriminative but also the affective-motivational component of a chronic pain phenotype.^{24,40,51} Indeed, the negative impact of the synergistic effect of the pain-depression complex, as well as other psychological conditions, such as anxiety and pain catastrophizing (PC), during perioperative stages in patients waiting for TKA surgeries has been described.^{19,31,39,58} Lingard et al. (2004) reported that mental health status, among other preoperative variables, was associated with poor functional outcome and persistent pain after TKA. Poor (lower) preoperative emotional health (Mental Component Score <50) in patients undergoing TKR correlates with less significant improvement in physical function (when scored by Short Form 36 Physical Component Score (SF-36 PCS) and Western Ontario and McMaster Universities Osteoarthritis Index). Although only 6 of 165 patients included in this study had a mental health-related diagnosis (eg, anxiety and depression), one-third of the patients presented a preoperative Mental Component Score <50, suggesting that subclinical conditions related to depression, anxiety, and poor social support may be sufficient to produce suboptimal functional return after TKR.⁵ It should also be noted that the patients who receive surgery in the midst of the current pandemic could have further adverse implications. Total knee arthroplasty is the final refuge to many patients who would otherwise consider an alternative treatment if available, given the known potential risk/poor outcomes related to the joint replacement surgery.⁴¹ Patient dissatisfaction has been reported as high as 30% and is not always positively correlated with functional outcomes.⁹ Some of the physical complications associated with TKA as endorsed by the members of the knee society include postoperative bleeding, failure of wound healing, symptomatic thromboembolic event, neural deficits, and vascular injury.²¹ Moreover, satisfaction rates after TKA seem to be influenced not only by physical outcome but also by the overall quality of life, which is determined by variables such as behavioral and psychological factors. Therefore, given the additional stress and anxiety in the current pandemic scenario, opting for surgery could lead to greater levels of dissatisfaction and higher demand for postsurgical care. The latter could translate into additional visits to health providers for postsurgical follow-ups, which could further increase the risk of exposure to COVID-19, particularly in high-risk population (age and comorbidities).

Pain catastrophizing is described as an exaggerated and continuous negative mental status present during an actual or anticipated painful experience leading to an overvaluation of pain sensation.³⁸ Pain catastrophizing has been clinically associated with increases in pain perception, narcotic usage, depression, development of chronic pain, and poor quality of life postoperatively.^{38,47} The social effect of a health crisis such as the current

COVID-19 pandemic could potentially increase the prevalence of PC among patients waiting for surgical intervention by exacerbating the 3 cornerstones of PC: (1) magnification (feeling afraid that something serious will happen), (2) rumination (unable to stop thinking about the painful condition), and (3) helplessness (feeling that there is no intervention one can partake to reduce the intensity of pain).^{5,47} Although, under normal conditions, patients suffering from chronic pain may not be affected by short delays to surgical access, additional factors present during a pandemic (ie, sudden unemployment or under employment) and the intrinsic high levels of mental illness (approximately 20% prevalence in the adults) in the United States⁴³ can increase the susceptibility of this particular population. These psychological variables and their progression over time should be an additional factor to consider when postponing major joint replacement surgeries in a susceptible population.

6. Effects of delayed surgical repair on morbidities associated with opiates and illicit drug use

Another critical component that adds to the problem arising from delayed orthopedic repair is the use of opioids, commonly prescribed for pain relief in severe case of OA. Although opioids are not recommended as a first line of treatment for patients suffering from chronic pain conditions,⁶² their use is not uncommon in patients progressing to disease states requiring surgery. In a 34,000-patient cross-sectional study of preoperative use of opioids, it was noted that 23% of the patients scheduled for surgery and 21% of those scheduled for knee surgery reported preoperative use of opioids.²² Despite the evidence of negative effect of preoperative administration of opioids in postsurgical outcomes,^{17,45,46} an increase in opioid prescriptions has in fact been observed in the past decade,^{10,62} a trend with potentially deleterious consequences. Preoperative opioid users have higher rates of consumption after TKR as well as suboptimal improvement in pain and higher dissatisfaction rates with the surgical outcome than opioid-naïve users. The incidence of chronic postoperative opioid use, 2 years after TKA, among the preoperative opioid users has been reported as high as 35% vs 5% in the nonuser population.^{17,46} Chronic preoperative opioid consumption also seems to positively correlate with longer time to discharge, poor rehabilitation progression, and higher in-hospital complications and disability rates.^{32,62} In patients suffering from chronic pain, the prevalence of opioid use disorder has been reported as high as 43%.²⁴ Furthermore, on the multisite Prescription Opioid Addiction Treatment Study,⁵⁹ 83% of patients with opioid use disorder reported pain relief as the primary initial reason for use, and 56% of those reported withdrawal avoidance as the mean reason for current use followed by pain relief in 22.6%.

Patients with poorly addressed chronic pain states are susceptible to other substance use disorders including abuse of alcohol and illegal drugs, with high prevalence in adults suffering from arthritic pain.^{24,56,57} A similar bidirectional prevalence as the one observed with chronic pain and depression is present between chronic pain and substance use disorders. Patients with chronic pain have been reported to use illicit drugs (51%) and alcohol (38%) as a self-medication for pain relief.⁴ Past health crises leading to quarantine or isolation have demonstrated that the psychological effect of diminished human interaction can be substantial and long-lasting.⁸ The social distancing that is so essential to the time course of the pandemic cannot be easily separated from feelings of isolation that have been identified as a potential trigger for an epidemic of clinical depression.³⁰ In the absence of the surgical alternative, the baseline of 20% patients using opioids before their knee replacement²² might significantly increase.

What is to be done? The above commentary regarding the issues posed by the practical need to halt and/or defer elective joint replacement surgeries because of the COVID-19 pandemic has the potential to create lasting negative effects for individuals and the health system. As mentioned, joint replacements are not exempt of complications, long recovery periods, and poor outcomes, and it is important that surgeons and specialty clinicians who frequently manage these orthopedic patients are aware of and attuned to the critical need for aggressive nonopioid management of these patients whose pain state will persist otherwise unabated or worsen in the absence of corrective surgery. For those suffering from orthopedic chronic pain, this is a real threat that could go beyond their present physical pain, impacting their long-term wellbeing and overall quality of life. If the current health conditions cannot be corrected soon, or if new wave of infected cases is presented forcing the additional cancellation of joint replacement surgeries for several months, the healthcare systems could be at risk of facing a new crisis where chronic pain, depression, and long surgical waiting lists would challenge its accountability and effectiveness again.

What is not needed is increased reliance on conventional opioid use for these severe pain patients. Addressing the needs of this patient population requires aggressive implementation of the full range of available pain management protocols, although those might currently be insufficient because surgery is generally the last resort option when other approaches have failed. These interventions include at least 3 components that should be considered/addressed by the clinicians:

- (1) Robust psychological support including counselling and an active implementation of mindfulness protocols. Certain self-regulation practices such as mindfulness meditation has shown to significantly attenuate pain, along with associated depression and anxiety can be considered for the chronic pain patients seeking narcotic-free, self-facilitated pain therapy.^{28,61} In a clinical trial, OA patients who completed the mindfulness training before surgery had greater improvements in pain and function 12 months after their surgery compared to the group with usual standard of care presurgery. In fact, a large proportion of patients who underwent the mindfulness training decided to not proceed with surgery based on the improvement observed.³
- (2) Aggressive engagement of minimally interventional therapeutic approaches using titrated dosing of nonopioids, including NSAIDs, acetaminophen, and gabapentin.^{11,12} Currently, CDC recommends intra-articular administration of hyaluronic acid and a limited number of glucocorticoid injections as a second-line treatment in chronic OA patients who fail to respond to acetaminophen and NSAIDs and are often used for transient symptom relief. Most of the OA patients choose TKA as their last resort, ie., after trying all the available above-mentioned existing drugs and hence very few may reconsider this approach, given that even best of these agents are beneficial only to half of the population taking these medications, not to mention the side effects and potential toxicities in patients with associated comorbidities.⁵³
- (3) Finally, implementing long-term therapeutic interventions focusing on peripheral changes in neural afferent activity arising from the inflamed joint including persistent periarticular delivery of local anesthetics¹¹ and ablating agents that target the peripheral nerve terminal^{25,26,50,54} should be considered. Selective neurotargeting of nociceptive nerve fibers can induce analgesia without compromising motor and sensory modalities unrelated to nociception. For example, targeting the TRPV1 channel or NaV 1.7/1.8 sodium channels that are

specifically expressed on sensory nerve fibers that transmit pain signals are some of the therapies in development that has gained attention in recent years. Resiniferatoxin (RTX), a potent TRPV1 agonist, that specifically targets and ablates the nociceptive nerve fibers is pending phase 3 trials for knee OA pain and shows promising outcome in terms of long-term efficacy.³⁶ If the drug lives up to its promise, it could become a viable alternative to surgery and supportive therapy for patients in need of a pain-controlled deferment of their surgical procedure. Similarly, NaV 1.8 blocker VX-150 has efficacy in treating acute pain in multiple pain conditions, with pending phase 2a results with OA in the knee.⁴²

It should be noted that one-time outpatient procedures that do not require frequent visits to the hospitals compared to traditional nonsurgical/surgical management, consisting of lifestyle modification consultations or physical therapy, for example, would be preferred as to limit possible exposure to pathogens during a pandemic, even if sanitation precautions are taken. To summarize, we emphatically wish to make the point that the patients suffering the enduring pain associated with a delay in joint repair cannot be simply placed in a holding mode without anticipating potential negative consequences of not managing their chronic pain. Also, given the additional risks associated with surgery under the current conditions, any alternative treatment allowing to comfortably delay surgery might be medically and psychologically welcomed by patients who would otherwise have to choose between living with the pain or pushing forward with their surgery and accept the inherent surgical risks in addition to SARS-CoV-2 exposure. Therefore, developing individual comprehensive minimally invasive pain management strategies and support for these patients is critically important to their long-term quality of life, well beyond the current short-term crisis.

Disclosures

The authors A. F. Cisternas, R. Ramachandran, and A. Nahama are employees of Sorrento Therapeutics, a company currently developing resiniferatoxin (RTX) for management of painful condition. A. F. Cisternas is the Medical Director of ARK Animal Health, a subsidiary of Sorrento Therapeutics Inc, R. Ramachandran is the Senior Translational Scientist at Sorrento Therapeutics Inc, and A. Nahama is the SVP Corporate Development at Sorrento Therapeutics Inc. T. L. Yaksh has previously undertaken preclinical work funded by Sorrento but has not had any current interactions.

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References

- [1] American College of Surgeons. COVID19 surgical patient guide. 2020. Available at: https://www.facs.org/-/media/files/covid19/covid19_surgical_patient_guide.ashx.
- [2] American College of Surgeons. Guidance for triage of nonemergent surgical procedures 2020. 2020. Available at: https://www.facs.org/-/media/files/covid19/guidance_for_triage_of_nonemergent_surgical_procedures.ashx.
- [3] ACTRN12611001184965. Available at: <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=347705>. 2012-2016. Accessed May 1, 2020.
- [4] Alford DP, German JS, Samet JH, Cheng DM, Lloyd-Travaglini CA, Saitz R. Primary care patients with drug use report chronic pain and self-medicate with alcohol and other drugs. *J Gen Intern Med* 2016;31:486–91.
- [5] Ayers DC, Franklin PD, Ploutz-Snyder R, Boisvert CB. Total knee replacement outcome and coexisting physical and emotional illness. *Clin Orthop Relat Res* 2005;440:157–61.
- [6] Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163:2433–45.
- [7] Bedard NA, Elkins JM, Brown TS. Effect of COVID-19 on hip and knee arthroplasty surgical volume in the United States. *J Arthroplasty* 2020;35: S45–8.
- [8] Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, Rubin GJ. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 2020;395:912–20.
- [9] Canovas F, Dagneaux L. Quality of life after total knee arthroplasty. *Orthop Traumatol Surg Res* 2018;104:S41–6.
- [10] Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *PAIN* 2004;109:514–19.
- [11] CDC. NonOpioid treatments for chronic pain. 2016. Available at: https://www.cdc.gov/drugoverdose/pdf/nonopioid_treatments-a.pdf.
- [12] Dowell D. CDC guideline for prescribing opioids for chronic pain—United States, 2016. Recommendations and Reports, March 18, 2016;65:1–49. Available at: <https://www.cdc.gov/mmwr/volumes/65/rr/r6501e1.htm>
- [13] FDA. CFR—code of federal regulations title 21. 2019. Available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.300#:~:text=312.300%20General.,a%20patient%27s%20disease%20or%20condition>.
- [14] Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain* 1997;13:116–37.
- [15] Fortin PR, Clarke AE, Joseph L, Liang MH, Tanzer M, Ferland D, Phillips C, Partridge AJ, Blisle P, Fossel AH, Mahomed N, Sledge CB, Katz JN. Outcomes of total hip and knee replacement: preoperative functional status predicts outcomes at six months after surgery. *Arthritis Rheum* 1999;42:1722–8.
- [16] Fortin PR, Penrod JR, Clarke AE, St-Pierre Y, Joseph L, Belisle P, Liang MH, Ferland D, Phillips CB, Mahomed N, Tanzer M, Sledge C, Fossel AH, Katz JN. Timing of total joint replacement affects clinical outcomes among patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2002;46:3327–30.
- [17] Franklin PD, Karbassi JA, Li W, Yang W, Ayers DC. Reduction in narcotic use after primary total knee arthroplasty and association with patient pain relief and satisfaction. *J Arthroplasty* 2010;25(6 suppl):12–16.
- [18] Garbus DS, Xu M, Duncan CP, Masri BA, Sobolev B. Delays worsen quality of life outcome of primary total hip arthroplasty. *Clin Orthop Relat Res* 2006;447:79–84.
- [19] Harden RN, Bruehl S, Stanos S, Brander V, Chung OY, Saltz S, Adams A, Stulberg SD. Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. *PAIN* 2003;106:393–400.
- [20] Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, Suarez-Almazor M, Gooberman-Hill R. Understanding the pain experience in hip and knee osteoarthritis—an OARS/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:415–22.
- [21] Healy WL, Della Valle CJ, Iorio R, Berend KR, Cushner FD, Dalury DF, Lonner JH. Complications of total knee arthroplasty: standardized list and definitions of the Knee Society. *Clin Orthop Relat Res* 2013;471:215–20.
- [22] Hilliard PE, Waljee J, Moser S, Metz L, Mathis M, Goesling J, Cron D, Clauw DJ, Englesbe M, Abecasis G, Brummett CM. Prevalence of preoperative opioid use and characteristics associated with opioid use among patients presenting for surgery. *JAMA Surg* 2018;153: 929–37.
- [23] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK, Washington State-nCoV-2019. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020;382: 929–36.
- [24] Hooten WM. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. *Mayo Clin Proc* 2016;91: 955–70.

- [25] Iadarola MJ, Gonnella GL. Resiniferatoxin for pain treatment: an interventional approach to personalized pain medicine. *Open Pain J* 2013;6:95–107.
- [26] Iadarola MJ, Sapio MR, Raithel SJ, Mannes AJ, Brown DC. Long-term pain relief in canine osteoarthritis by a single intra-articular injection of resiniferatoxin, a potent TRPV1 agonist. *PAIN* 2018;159:2105–14.
- [27] iDataResearch. Total knee replacement statistics 2017: Younger patients driving growth. 2018. Available at: <https://idataresearch.com/total-knee-replacement-statistics-2017-younger-patients-driving-growth/>
- [28] Jacob JA. As opioid prescribing guidelines tighten, mindfulness meditation holds promise for pain relief. *JAMA* 2016;315:2385–7.
- [29] Jain A, Jain P, Aggarwal S. SARS-CoV-2 impact on elective orthopaedic surgery: implications for post-pandemic recovery. *J Bone Joint Surg Am* 2020.
- [30] Kanter J COVID-19 could lead to an epidemic of clinical depression, and the health care. 2020.
- [31] Khan RS, Ahmed K, Blakeway E, Skapinakis P, Nihoyannopoulos L, Macleod K, Sevdalis N, Ashrafian H, Platt M, Darzi A, Athanasiou T. Catastrophizing: a predictive factor for postoperative pain. *Am J Surg* 2011;201:122–31.
- [32] Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am* 2009;91:919–27.
- [33] Kulshrestha V, Datta B, Mittal G, Kumar S. Epidemiology of revision total knee arthroplasty: a single center's experience. *Indian J Orthop* 2019;53:282–8.
- [34] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am* 2007;89:780–5.
- [35] Lavernia C, D'Apuzzo M, Rossi MD, Lee D. Is postoperative function after hip or knee arthroplasty influenced by preoperative functional levels? *J Arthroplasty* 2009;24:1033–43.
- [36] Leiman D, Minkowitz H, Levitt RC, Solanki D, Horn D, Janfaza D, Sarno D, Albores-Ibarra N, Bai X, Takeshita K, Zhao T, Lu CW, Bharathi P, Ahern J, Klincewicz S, Nedeljkovic S. #197: preliminary results from a phase 1b double-blind study to assess the safety, tolerability and efficacy of intraarticular administration of resiniferatoxin or placebo for the treatment of moderate to severe pain due to osteoarthritis of the knee. Proceedings of the OARSI Vol. 28: Osteoarthritis and Cartilage 2020. Available at: [https://www.oarsijournal.com/article/S1063-4584\(20\)30295-8/pdf](https://www.oarsijournal.com/article/S1063-4584(20)30295-8/pdf).
- [37] Leite AA, Costa AJ, Lima Bde A, Padilha AV, Albuquerque EC, Marques CD. Comorbidities in patients with osteoarthritis: frequency and impact on pain and physical function. *Rev Bras Reumatol* 2011;51:118–23.
- [38] Leung L. Pain catastrophizing: an updated review. *Indian J Psychol Med* 2012;34:204–17.
- [39] Lingard EA, Katz JN, Wright EA, Sledge CB, Kinemax Outcomes G. Predicting the outcome of total knee arthroplasty. *J Bone Joint Surg Am* 2004;86:2179–86.
- [40] Meerwijk EL, Ford JM, Weiss SJ. Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. *Brain Imaging Behav* 2013;7:1–14.
- [41] Mulcahy H, Chew FS. Current concepts in knee replacement: features and imaging assessment. *AJR Am J Roentgenol* 2013;201:W828–842.
- [42] NCT02660424. A study of the efficacy and safety of VX-150 in subjects with osteoarthritis of the knee. Available at: <https://clinicaltrials.gov/ct2/show/NCT02660424>. Accessed April 14, 2020.
- [43] NIH. Available at: <https://www.nlm.nih.gov/health/statistics/mental-illness.shtml>. Accessed April 14, 2020.
- [44] OARSI. Osteoarthritis: a serious disease, submitted to the U.S. Food and Drug Administration. 2016. Available at: https://www.oarsi.org/sites/default/files/library/2018/pdf/oarsi_white_paper_oa_serious_disease121416_1.pdf
- [45] Pivec R, Issa K, Naziri Q, Kapadia BH, Bonutti PM, Mont MA. Opioid use prior to total hip arthroplasty leads to worse clinical outcomes. *Int Orthop* 2014;38:1159–65.
- [46] Politzer CS, Kildow BJ, Goltz DE, Green CL, Bolognesi MP, Seyler TM. Trends in opioid utilization before and after total knee arthroplasty. *J Arthroplasty* 2018;33:S147–53 e141.
- [47] Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. *Expert Rev Neurother* 2009;9:745–58.
- [48] Quon JA, Sobolev BG, Levy AR, Fisher CG, Bishop PB, Kopec JA, Dvorak MF, Schechter MT. The effect of waiting time on pain intensity after elective surgical lumbar discectomy. *Spine J* 2013;13:1736–48.
- [49] Rossi MD, Eberle T, Roche M, Waggoner M, Blake R, Burwell B, Baxter A. Delaying knee replacement and implications on early postoperative outcomes: a pilot study. *Orthopedics* 2009;32:885.
- [50] Sapio MR, Neubert JK, LaPaglia DM, Maric D, Keller JM, Raithel SJ, Rohrs EL, Anderson EM, Butman JA, Caudle RM, Brown DC, Heiss JD, Mannes AJ, Iadarola MJ. Pain control through selective chemo-ablation of centrally projecting TRPV1+ sensory neurons. *J Clin Invest* 2018;128:1657–70.
- [51] 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.
- [52] Sloan M, Premkumar A, Sheth NP. Projected volume of primary total joint arthroplasty in the U.S., 2014 to 2030. *J Bone Joint Surg Am* 2018;100:1455–60.
- [53] Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. *Osteoarthritis Cartilage* 2016;24:962–72.
- [54] Sorrento Therapeutics Inc. Sorrento therapeutics announces interim results in osteoarthritis knee pain phase 1b trial of resiniferatoxin with positive therapeutic signal and absence of dose limiting toxicities; pivotal trials targeted to start later 2019. 2019. Available at: <https://www.globenewswire.com/news-release/2019/01/22/1703244/0/en/Sorrento-Therapeutics-Announces-Interim-Results-In-Osteoarthritis-Knee-Pain-Phase-1b-Trial-of-Resiniferatoxin-With-Positive-Therapeutic-Signal-and-Absence-of-Dose-Limiting-Toxicity.html>
- [55] Stahel PF. How to risk-stratify elective surgery during the COVID-19 pandemic? *Patient Saf Surg* 2020;14:8.
- [56] Stang PE, Brandenburg NA, Lane MC, Merikangas KR, Von Korff MR, Kessler RC. Mental and physical comorbid conditions and days in role among persons with arthritis. *Psychosom Med* 2006;68:152–8.
- [57] Sullivan MD. Depression effects on long-term prescription opioid use, abuse, and addiction. *Clin J Pain* 2018;34:878–84.
- [58] Vissers MM, Bussmann JB, Verhaar JA, Busschbach JJ, Bierma-Zeinstra SM, Reijnen M. Psychological factors affecting the outcome of total hip and knee arthroplasty: a systematic review. *Semin Arthritis Rheum* 2012;41:576–88.
- [59] Weiss RD, Potter JS, Griffin ML, McHugh RK, Haller D, Jacobs P, Gardin J II, Fischer D, Rosen KD. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat* 2014;47:140–5.
- [60] Woller SA, Eddinger KA, Corr M, Yaksh TL. An overview of pathways encoding nociception. *Clin Exp Rheumatol* 2017;35(suppl 107):40–6.
- [61] Zeidan F, Vago DR. Mindfulness meditation-based pain relief: a mechanistic account. *Ann N Y Acad Sci* 2016;1373:114–27.
- [62] Zywiol MG, Stroh DA, Lee SY, Bonutti PM, Mont MA. Chronic opioid use prior to total knee arthroplasty. *J Bone Joint Surg Am* 2011;93:1988–93.