



# A Review of Sublingual Sufentanil Tablet (SST) and its Utility as an Analgesic Agent for Pain Procedures

Sarang S. Koushik<sup>1</sup> · Ruben H. Schwartz<sup>1</sup> · Denis Cherkalin<sup>2</sup> · Vignesh Sankar<sup>3</sup> · Naum Shaparin<sup>2</sup> · Omar Viswanath<sup>4,5</sup>

Accepted: 6 December 2021 / Published online: 25 January 2022

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

## Abstract

**Purpose of Review** Sedation for pain medicine procedures provides a unique challenge for proceduralists. Many patients dealing with pain are on chronic opioids and require higher doses of sedation for adequate procedural comfort. Chronic pain patients have various comorbidities including depression, neuropsychiatric disorders, peripheral vascular disease, and renal impairment, among others [1]. These confounding variables make the overall treatment of their pain condition much more challenging.

**Recent Findings** For patients requiring intravenous (IV) sedation for their pain procedures, the constant need for access may render them a “difficult stick” over time. Another factor to consider is the increasing requirements by the hospital system needing IV sedatives and analgesics in the intensive care unit and operating rooms during the coronavirus (COVID-19) pandemic.

**Summary** Sublingual sufentanil (SST) provides an excellent analgesic option for patients undergoing interventional pain procedures. The use of SST allows hospitals to preserve IV agents for more critical areas and mitigates the difficulty of obtaining IV access in patients.

**Keywords** Sublingual Sufentanil (SST) · Interventional Pain Management · Intravenous Sedation · Coronavirus (COVID-19)

## Introduction

The use of sedation for interventional pain procedures is controversial with many on the pro and con side of the argument. In addition to the clinical need for sedation related to

the actual procedure, other things to take into consideration include the time to obtain intravenous (IV) access and the necessity of prolonged post-sedation monitoring in the recovery unit. This is particularly important in a smaller procedure area with limited pre-procedure and post-procedure space to recover. In light of the coronavirus (COVID-19) pandemic, other things to take into consideration currently are minimizing patient contact with healthcare providers and accounting for periodic drug shortages of commonly used IV medications for sedation such as fentanyl and midazolam.

Although intravenous sufentanil has been used by anesthesiologists since its synthesis in the 1970s, the new sublingual formulation (SST) offers significant advantages in the ambulatory setting, especially in the midst of social distancing and drug shortages related to the COVID-19 pandemic. SST has been studied and used in multiple hospital departments including the emergency room and ambulatory surgery centers [2•]. This current formulation of the drug is a single-dose sublingual application. The benefits of the drug profile include a high bioavailability with avoidance of first-pass hepatic metabolism, rapid drug equilibration

---

This article is part of the Topical Collection on *Chronic Pain Medicine*

---

✉ Sarang S. Koushik  
Sarang.koushik@gmail.com

<sup>1</sup> Department of Anesthesiology & Pain Medicine, Keck School of Medicine of USC, 1520 San Pablo Street #3450, Los Angeles, CA 90033, USA

<sup>2</sup> Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, NY, USA

<sup>3</sup> Dr. Kiran C. Patel College of Osteopathic Medicine, Fort Lauderdale, FL, USA

<sup>4</sup> Department of Anesthesiology, University of Arizona College of Medicine, Phoenix, AZ, USA

<sup>5</sup> Department of Anesthesiology, Creighton University School of Medicine, Omaha, NE, USA

between central and peripheral compartments, the lack of active metabolites, and a high therapeutic index [3, 4]. SST is able to provide potent analgesia without an IV. As previously mentioned, an increased demand for mechanical ventilation has led to drug shortages of medications used for sedation. The American Society of Anesthesiologists has urged congress to address these shortages in a press briefing [5]. These same medications are commonly used to ensure comfort during outpatient interventional pain procedures. Even as restrictions have been lifted and outpatient medical care has begun to return, the drug shortages still may be an ongoing issue. The new formulation of sublingual sufentanil tablet (SST) may be an appropriate and useful alternative.

### Typical Medications Used for Interventional Pain Procedures

The use of conscious sedation in an outpatient setting allows physicians to perform minimally invasive procedures without having to go to a hospital or ambulatory surgery center. Within the field of interventional pain management, many procedures require some form of sedation. Some common procedures that do not require sedation and can be done under local anesthesia according to American Society of Anesthesiologists' Committee on Pain Medicine include epidural steroid injections, epidural blood patches, trigger point injections, injections into the elbow, thigh, knee, and sacroiliac joints [6]. Some interventional pain procedures require sedation due to procedural discomfort or patient factors. Additional procedures require patient feedback to ensure proper placement of a device (spinal cord stimulator), and therefore, patients cannot be over sedated.

Although procedural patients will require intravenous sedation, a short-acting oral benzodiazepine such as midazolam can suffice. For mild anxiolysis, practitioners utilize midazolam due to its short duration of action and rapid metabolism in the liver and renal excretion in 1 to 4 h [7]. Midazolam, although usually tolerated well by most patients, must be carefully administered in patients with renal disease as the metabolite alpha 1-hydroxy midazolam may accumulate causing increased sedation [8]. Short-acting intravenous opioids including fentanyl, morphine, and alfentanil also are commonly utilized due to their fast onset. Fentanyl's increased lipid solubility was compared to morphine attests to its rapid onset and greater potency [6]. Benzodiazepines and short-acting opioids may be combined, but the medical staff must be vigilant to watch for signs of respiratory distress.

Deep sedation and general anesthesia are rarely indicated for interventional pain procedures. Recently, the American Society of Interventional Pain Physicians (ASIPP) recently published an opinion that propofol should not be utilized for procedural sedation due to its "potency, rapid onset, capacity

for dose-dependent respiratory depression, as well as patient inability to communicate during a procedure" [9]. Propofol causes profound amnesia and respiratory depression even at low doses, especially in elderly patients. The use of other hypnotics including ketamine and dexmedetomidine has recently grown in favor but require the skills of qualified professionals including anesthesiologists or certified registered nurse anesthetists [10].

### Sublingual Sufentanil Tablet (SST) Literature Review

SST was initially developed for moderate-to-severe acute pain in an inpatient setting and for traumatic injuries in the emergency department (ED). A single 30 mcg dose dissolves sublingually within 5 min and showed an average bioavailability of 52% with plasma concentrations reaching therapeutic levels within 30 min, peaking by hour 1, and decreased below therapeutic levels by hour 3 [11]. Due to its properties such as ease of administration, high potency, and extended duration of action, SST has uses in all phases of perioperative medicine. Initial studies focusing on efficacy of analgesia showed promising results with high satisfaction in both patients and healthcare practitioners (HP). Phase III clinical studies comparing SST to placebo showed favorable analgesia in the postoperative state with reporting of adverse events similar to the placebo groups [12, 13]. Retrospective global assessment of SST as a new form of analgesia in patients and practitioners involved in the phase III studies showed SST as highly favorable across race, gender, BMI, and age, thus supporting its use as a new form of analgesia in all populations [14]. In addition, a multicenter study assessing patient and HP satisfaction was highly favorable toward SST with 88% of patients and 90% of healthcare practitioners giving scores of good or excellent [15]. When compared to IV morphine PCAs in patients postop from abdominal and orthopedic surgeries, SST showed a 78.5% successful patient global assessment scores vs 65.8% in the IV morphine PCA group and showed statistically superior analgesia at 24- and 72-h assessments with the incidence of adverse events similar in both groups [16]. A meta-analysis comparing SST vs IV morphine PCAs showed equivocal results in patient global assessment score; however, the onset of analgesia was earlier and rates of adverse events were lower in the SST group [17]. Pool analysis of 363 patients showed that SST 30 mcg was effective at managing both postoperative and traumatic pain across various demographics including age, gender, ethnicity, BMI, and ASA classification with statistically improved pain scores when compared to placebo [18••]. A comparison of studies with the use of SST vs studies with the use of transdermal fentanyl patches for noninvasive postoperative pain management showed more favorable

pain scores and patient satisfaction with SST at 24, 48, and 72 h [19]. Cost analysis in Ireland in 2017 showed that SST as a postoperative pain management therapy saved 39.57 euros per treatment when compared to IV opioids. Furthermore, SST use when compared to IV opioid administration decreased average nursing time spent on administration by 13 min per treatment per patient [20].

The primary focus of studies on sublingual sufentanil has been in postoperative pain management. A multicenter study of 342 postoperative patients using self-administered SST for pain control reported that 91.8% of patients were satisfied with the level of pain control and 95.9% were satisfied with the method of administration [21]. A hospital network in Netherlands incorporated SST as an option in their multimodal analgesia protocol (included Tylenol and NSAIDs three times daily) along with oral opioids, epidural analgesia, or IV morphine PCA; analysis of pain scores and satisfaction of SST group showed results that were equivocal to authors experience with the other options [22]. SST has also been tried in ERAS protocols in various centers. A study evaluating the use of SST in ERAS protocol of 111 orthopedic, spine, and thoracic surgical patients showed high satisfaction scores among patients and physical therapists with patients successfully achieving therapy goals [23]. When compared to oxycodone within ERAS protocol for post-total knee replacements, SST showed equivalent results in postoperative pain management score and early mobilization [24]. Another study in post-total knee replacement patients comparing SST to continuous femoral nerve block catheters showed that pain scores were lower for the nerve block group at rest; however, during mobility, the SST group had lower pain scores with improved ability to ambulate, less need for rescue doses, and shorter length of stay postoperatively making it a more viable option in surgical cases where early mobilization is a primary goal [25]. In postoperative cardiac patients starting from 24 h post-extubation, SST showed higher pain scores when compared to IV morphine PCAs; however, the morphine group had a significantly higher morphine milligram equivalents (MME) of 241.94 mg vs the SST MME of 39.84 mg [26]. In postoperative patients undergoing major lung resection surgery, SST compared to IV opioid analgesia showed more favorable mean pain scores at 24 h and significantly lower need for additional pain medication [27]. Another study showed that in addition to effectively reducing pain scores in thoracic surgery patients, 67.5% of patients resumed the original spirometric ability on postoperative day (POD) 1 [28]. SST was shown to be an effective analgesic in postoperative gynecologic patients as well with beneficial effects on early rehabilitation [29]. Sublingual sufentanil's pharmacologic properties of high potency and long duration make it a viable option as an oral alternative to induction opioids. A study compared the use of SST with intraoperative IV

opioids against only IV opioids in induction of general anesthesia in patients undergoing abdominal including bariatric, orthopedic, urologic, gynecologic, and ENT procedures. It showed that total opioid requirements in IV MME was similar in both groups; however, postoperatively in post-anesthesia care unit (PACU), the SST group's opioid requirement was less than half the control group with PACU times being reduced on average of 14 min [30].

Since approval, use has spread to other areas of the hospital for various purposes. A multicenter study of 76 patients presenting to the ED with moderate-to-severe pain secondary to trauma showed that single-dose SST 30 mcg was effective at significantly improving pain scores within 15 min and maintaining adequate analgesia at 2 h with no significant adverse events. In addition, the lack of need for IV placement, ease of administration, and faster analgesic onset of SST when compared to IV opioids make it a reasonable alternative to IV opioids in the ED setting [20]. Having a safe side-effect profile and low risk of respiratory depression, SST may have use in the ambulatory setting as well. A prospective study comparing the use of preoperative SST to a retrospective matched control in the ambulatory setting showed decreased opioid requirements of 10.9 mg MME for SST group vs 20.0 mg MME in control group, PACU opioid requirements of 0.9 mg MME in SST group vs 4.4 mg MME in control group, and a reduction of 34% in PACU stay in the SST group compared to control [31, 32]. In its sublingual form, sufentanil has a lower maximum plasma concentration but a prolonged action and with repeated dosing being able to mimic a continuous infusion possibly making it useful for sedation; however, further research into this use is needed [32, 33]. Another use for SST is on the battlefield. The US Department of Defense was closely involved in the development of SST to use in all aspects of care for its troops including combat [13]. It has since been approved for military use by medics, forward surgical teams, trauma platoons, and support medical companies as a new form of analgesia for acute trauma replacing fentanyl "lollipops" due to its fast onset, high potency, predictable offset, low risk of adverse events, ease of administration, and steady concentration, resulting in less euphoria and potential for abuse [15].

Analysis of pooled data from multiple phase III clinical studies showed mild adverse effects, mainly nausea, but no significant respiratory depression in 323 patients with administration of SST 30 mcg by healthcare professionals. However, in 323 patients given SST 15 mcg as a PCA, incidence of adverse events increased including three incidences of respiratory depression requiring naloxone administration [14]. Rates of adverse events were stable across various demographics including age, gender, and BMI. Due to sufentanil being a lipophilic medication with no active metabolites, it is safe to use in renal and hepatic impairment including the older population who are at higher risk of

postoperative renal injury. Incidences and types of adverse events in patients with hepatic or renal failure were similar when compared to patients with normal hepatic and renal function [11].

## Intravenous Drug Shortages During the Coronavirus (COVID-19) Pandemic

The existing supply of sedation strategies needed for the care of hospitalized and mechanically ventilated patients has become increasingly strenuous due to the surge of critically ill patients as a result of the COVID-19 pandemic. The most common complications of COVID-19 infection are pneumonia and respiratory failure. In up to 33% of patients, ICU admission and invasive mechanical ventilation develop [34, 35]. Pneumonia has been found to progress to acute respiratory distress syndrome (ARDS) in up to 42% of patients [36]. ARDS can often require the need for deep levels of sedation to lower respiratory effort and optimize long-term survival. The surge in critically ill patients requiring these treatment strategies has led to a shortage in many medications. According to the FDA and American Society of Health-System Pharmacists, there are ten sedative and analgesic agents that are currently in short supply, including propofol, midazolam, and dexmedetomidine [36, 37]. Additionally, the manufacturing of sedatives and analgesics, most of which are controlled substances, requires annual production quotas, which are tightly regulated by the Drug Enforcement Agency (DEA) [38]. Although quotas for these medications were increased in April 2020, the ability to upscale the manufacturing process in such short time was limited due to high operating costs. Nonetheless, there is a lack of incentive for manufacturers to produce less profitable drugs. Therefore, anesthesiologists must be flexible with using alternative medications to adapt in this shifting landscape.

Hospitals are putting forth contingency care protocols to provide adequate care while mediating for the unprecedented shortages. For example, in order to conserve intravenous analgesic supplies, patients may receive intermittent boluses of analgesics prior to continuous analgesic infusion. In addition, the use of opioids would be critical in conserving the supply of IV agents [39]. Unfortunately, IV sedation medication shortages are looming and will likely worsen as the pandemic continues with no end in sight, further stressing the need for utilization of alternative medications.

## Conclusion

SST is an excellent analgesic option for chronic pain patients presenting for interventional procedures in an outpatient setting. In the setting of COVID-19-related drug shortages

and social distancing, physicians must consider alternative options to increase patient comfort during interventional procedures. SST is a sublingual option offering analgesia without the need to obtain IV access. If anxiolysis is also required, the use of oral midazolam can also be considered. This strategy will allow hospitals to preserve the use of intravenous anesthetic and analgesic medications in other critical areas. In lieu of COVID-19 social distance requirement and drug shortages, SST is a safe and reliable option for patients requiring analgesia as an alternative to intravenous sedation.

## Compliance with Ethical Standards

**Conflict of Interest** Drs. Schwartz, Viswanath, Sankar, Cherkalin and Koushik declare no conflict of interest. Dr. Shaparin reports research and personal funding with Heron Therapeutics, Averitas Pharma, and AcelRX pharmaceuticals medical.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Dahan A, van Velzen M, Marieke Niesters; Comorbidities and the Complexities of Chronic Pain. *Anesthesiology*. 2014;121:675–7. <https://doi.org/10.1097/ALN.0000000000000402>.
- 2.● Miner JR, Rafique Z, Minkowitz HS, DiDonato KP, Palmer PP. Sufentanil sublingual tablet 30mcg for moderate-to-severe acute pain in the ED. Successfully demonstrated sufentanil as a potent and useful analgesic agent in the emergency room, outside of the typical operating room setting. *Am J Emerg Med*. 2018;36(6):954–961. Epub 2017 Oct 31.
3. Fisher DM, Chang P, Wada DR, Dahan A, Palmer PP. Pharmacokinetic Properties of a Sufentanil Sublingual Tablet Intended to Treat Acute Pain. *Anesthesiology*. 2018;128(5):943–952.
4. Niemegeers CJ, Schellekens KH, Van Bever WF, Janssen PA. Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs. *Arzneimittel-Forschung*. 1976;26(8):1551–6. PMID 12772.
5. <https://www.asahq.org/advocacy-and-asapac/fda-and-washington-alerts/washington-alerts/2020/03/asa-urges-congress-to-include-legislation-to-address-drug-shortages-in-covid-19-legislative-packages>. Accessed 8 Oct 2021.
6. Manzi JE, Jones MR, Cornett EM, Kaye AD. Moderate and deep procedural sedation—the role of proper monitoring and safe techniques in clinical practice. *Curr Opin Anaesthesiol*. 2021;34(4):497–501. <https://doi.org/10.1097/ACO.0000000000001011>.
7. Griffin CE, Kaye AM, Rivera Bueno F, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J*. 2013;13:214–23.

8. Richter JJ. Current theories about the mechanisms of benzodiazepines and neuroleptic drugs. *Anesthesiology*. 1981;54(1):66–72.
9. Wehrmann T, Riphaut A. Sedation with propofol for interventional endoscopic procedures: a risk factor analysis. *Scand J Gastroenterol*. 2008;43:368–74. <https://doi.org/10.1080/00365520701679181>.
10. Tran T, Beutler S, Urman R. Moderate and deep sedation training and pharmacology for nonanesthesiologists. *Curr Opin Anaesthesiol*. 2019;32(4):457–63. <https://doi.org/10.1097/ACO.0000000000000758>.
11. Fisher DM, et al. Pharmacokinetic Properties of a Sufentanil Sublingual Tablet Intended to Treat Acute Pain. *Anesthesiology*. 2018;128(5):943–952. <https://doi.org/10.1097/ALN.0000000000002145>
12. Minkowitz HS, et al. Sufentanil Sublingual Tablet 30 mcg for the Management of Pain Following Abdominal Surgery: A Randomized, Placebo-Controlled, Phase-3 Study. *Pain Practice : Official J World Institute Pain* 2017;17(7):848–858. <https://doi.org/10.1111/papr.12531>
13. Miner JR, et al. Pooled Phase III safety analysis of sufentanil sublingual tablets for short-term treatment of moderate-to-severe acute pain. *Pain Manag* 2019;9(3):259–271. <https://doi.org/10.2217/pmt-2018-0090>
14. Leiman D, et al. Patient and Healthcare Professional Satisfaction Ratings and Safety Profile of Sufentanil Sublingual Tablets for Treatment of Acute Pain: A Pooled Demographic Analysis. *J Pain Res* 2021;14:805–813. 25. <https://doi.org/10.2147/JPR.S291359>
15. Hutchins JL, et al. An Open-Label Study of Sufentanil Sublingual Tablet 30 Mcg in Patients with Postoperative Pain. *Pain medicine (Malden, Mass.)* 2018;19(10):2058–2068. <https://doi.org/10.1093/pm/pxn248>
16. Melson TI, et al. Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, active-comparator trial. *Pain Practice : Official J World Institute Pain* 2014;14(8):679–88. <https://doi.org/10.1111/papr.12238>
17. Katz P, et al. Sublingual, transdermal and intravenous patient-controlled analgesia for acute post-operative pain: systematic literature review and mixed treatment comparison. *Current Med Res Opinion* 2017;33(5):899–910. <https://doi.org/10.1080/03007995.2017.1294559>
- 18.●● Hutchins JL, et al. Pooled Dosing and Efficacy Analysis of the Sufentanil Sublingual Tablet 30 mcg Across Demographic Subgroups for the Management of Moderate-to-Severe Acute Pain. *J Perianesthesia Nursing : Official J Am Soc Perianesthesia Nurse*. 2020;35(1): 22–28. <https://doi.org/10.1016/j.jopan.2019.08.009>. This study showed efficacy of sufentanil in reducing pain scores compared to placebo across numerous subgroups deeming the medication safe and reliable.
19. Katz P, et al. Indirect treatment comparison of two non-invasive patient-controlled analgesia treatments for acute post-operative pain management. *Curr Med Res Opinion*. 2017;33(5):911–918. <https://doi.org/10.1080/03007995.2017.1294560>
20. Meuser T, et al. Staff time requirements for postoperative pain management: Comparison of sufentanil sublingual tablet system and intravenous patient-controlled analgesia. *J Opioid Manag*. 2019;16,1 (2019):33–39. <https://doi.org/10.5055/jom.2020.0548>
21. Pogatzki-Zahn E, et al. Real-world use of the sufentanil sublingual tablet system for patient-controlled management of acute postoperative pain: a prospective noninterventional study. *Curr Med Res Opinion* 2020;6(2):277–284. <https://doi.org/10.1080/03007995.2019.1681133>
22. Meijer F, et al. Sublingual sufentanil for postoperative pain relief: first clinical experiences. *J Pain Res*. 2018;11:987–992. <https://doi.org/10.2147/JPR.S160091>
23. Amson H, et al. Usability evaluation of sufentanil sublingual tablet analgesia in patients following Enhanced Recovery After Surgery. *J Comp Eff Res*. 2021;10(9):743–750. <https://doi.org/10.2217/ceer-2020-0239>
24. Noel E, et al. Sufentanil sublingual tablet system versus oral oxycodone for management of postoperative pain in enhanced recovery after surgery pathway for total knee arthroplasty: a randomized controlled study. *J Exp. Orthop*. 2020;7(1):92. <https://doi.org/10.1186/s40634-020-00306-x>
25. Scardino M, et al. Sublingual sufentanil tablet system Zalviso® for postoperative analgesia after knee replacement in fast track surgery: a pilot observational study. *J Exp Orthop*. 2018;5(1):8. <https://doi.org/10.1186/s40634-018-0123-y>
26. Van Tittelboom V, et al. Sublingual Sufentanil Tablet System Versus Continuous Morphine Infusion for Postoperative Analgesia in Cardiac Surgery Patients. *J Cardiothorac Vasc Anesthesia*. 2021;35(4):1125–1133. <https://doi.org/10.1053/j.jvca.2020.08.030>
27. Lomangino I, et al. Sublingual sufentanil in pain management after pulmonary resection: a randomized prospective study. *Ann Thoracic Surg*. 2020;S0003–4975(21):01294–7. <https://doi.org/10.1016/j.athoracsur.2021.06.063>
28. Fabio C, et al. Sufentanil sublingual tablet system (Zalviso®) as an effective analgesic option after thoracic surgery: An observational study. *Saudi J Anaesthesia*. 2019;13(3):222–226. [https://doi.org/10.4103/sja.SJA\\_109\\_19](https://doi.org/10.4103/sja.SJA_109_19)
29. Leykin Y, et al. Sublingual sufentanil tablet system for postoperative analgesia after gynecological surgery. *Minerva Medica*. 2019;110(3):209–215. <https://doi.org/10.23736/S0026-4806.19.05992-5>
30. Koth MC, Shannon MH, James CS, Mark DC. A Medication Use Evaluation of Sufentanil Sublingual Tablet 30 mcg for the Perioperative Management of Surgical Pain. 2020;8(5):6.
31. Tvetenstrand CD, Wolff ME. Reduced Opioid Use and Reduced Time in the Postanesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting. *J Clin Anesth Pain Manag*. 2020;4(2):123–8.
32. van de Donk T, et al. Pharmacokinetics and pharmacodynamics of sublingual sufentanil for postoperative pain management. *Anaesthesia*. 2018;73(2):231–7. <https://doi.org/10.1111/anae.14132>.
33. Kim SY, Buckenmaier CC, Howe EG, Choi KH. The Newest Battlefield Opioid, Sublingual Sufentanil: A Proposal to Refine Opioid Usage in the U.S. Military. *Military Med*. 2021;usab395. <https://doi.org/10.1093/milmed/usab395>
34. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China Lancet*. 2020;395(10223):497–506.
35. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–13.
36. FDA Drug Shortages [online]. Accessed October 1, 2021. <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>
37. ASHP Drug Shortages [online]. Accessed October 1, 2021. <https://www.ashp.org/Drug-Shortages>.
38. Agency DE. DEA takes additional steps to allow increased production of controlled substances used in COVID-19 care. <https://www.dea.gov/press-releases/2020/04/07/dea-takes-additional-steps-allow-increased-production-controlled>. Accessed October 1, 2021.
39. Narayanan M, Venkataraju A, Jennings J. Analgesia in intensive care: part 1. *BJA Education*. 2015;16(2):72–8.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.