## ABSTRACT

**Title:** Sublingual Sufentanil for Acute Pain on and off the Battlefield: A Narrative Overview



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**Introduction:** The sublingual sufentanil tablet system (SSTS) is an easily administered single dose potent analgesic that allows for quick pain relief in patients that do not have IV access or are unable to swallow pills. Pain needs to be adequately treated; however, the time and accessories IV medications require can be burdensome in austere settings and poor pain management leads to prolonged hospitalization, delayed wound healing, increase in health care costs, and psychological consequences. This narrative review analyzes existing literature discussing the current use of SSTS, along with the pharmacologic properties, limitations, research gaps, and potential future uses.

**Methods:** A literature search was conducted from January 2013 to December 2023, where articles published on PubMed and Medline were searched regarding use of sublingual sufentanil in acute pain settings as well as the pharmacokinetics, pharmacodynamics, and clinical applications. Search fields included key words such as “sublingual sufentanil,”"Dsuvia,”"battlefield pain,”"opioids in acute pain,”"prehospital acute pain,” and “sufentanil in acute pain.” Results from the main clinical trials and systematic reviews are discussed which included a total of 46 studies.

**Results:** In recent years, two SSTSs have been developed by AcelRx Pharmaceuticals, Inc, Dsuvia and Zalviso. We identified 46 studies that met inclusion criteria for our analysis, 6.5% (3) of which took place in emergency settings and 87% (40) in the post-operative setting. SSTS have shown to be efficacious with ease of use for both trained medical professionals and for patients as a PCA. There were significant reductions in pain intensity without dose-dependent increase in oxygen desaturation events and the most common adverse effect being nausea. Currently, there are no civilian post-marketing studies demonstrating the use of SSTS outside of research purposes in emergency medicine, prehospital, or wilderness medicine and there are no direct comparison studies of SSTS and the current standard of care for battlefield medicine.

**Conclusion:** The nature of battlefield pain requires easy to use and quickly accessible medications that can either be self or buddy administered with basic medical training to manage polytrauma efficiently and effectively in austere and hostile settings—a need that sublingual sufentanil tablets have the potential to fill. The key impact of this review is to provide an analysis of the current research and research gaps of SSTS.

**Introduction:**

The nature of physical trauma on the battlefield and in mass casualty events necessitates rapidly accessible and easy-to-administer analgesia, in contrast to typical hospital settings where a range of pain management resources are available (1). Inadequate pain control can impede recovery and contribute to long-term disability, potentially becoming as debilitating as the initial trauma. Despite its critical role, pain management remains underemphasized in mass casualty response protocols. For instance, the latest edition of the *Major Incident Medical Management and Support* manual references analgesia only seven times within its 216 pages (2). Poorly managed acute pain can lead to nervous system dysregulation, resulting in chronic pain syndromes, prolonged hospitalizations, increased healthcare costs, and worse overall patient outcomes (5-37). Additionally, numerous studies indicate that inadequate pain control during the peritraumatic period increases the risk of posttraumatic stress disorder, depression, and anxiety. Recognizing this, the U.S. military advocates for early and continuous analgesia from the point of injury through all stages of care, including battlefield stabilization, military medical facilities, Veterans Administration hospitals, and civilian rehabilitation centers (4).

Given the evolving medical challenges posed by current international conflicts, there is an urgent need to enhance the rapid, accessible, and effective management of acute traumatic pain in both civilians and military personnel. Existing pain control options remain insufficient, particularly in pre-definitive care settings and for patients with severe burns or polytrauma, where IV analgesia may be impractical due to time constraints and equipment requirements. The sublingual route offers a viable alternative, bypassing the limitations of intramuscular (IM) administration in acute trauma scenarios. In battlefield injuries, for example, hypovolemia frequently compromises muscle perfusion, reducing systemic absorption of IM medications such as morphine and rendering them ineffective. Sublingual administration mitigates these concerns, providing a more reliable and efficient method for pain control in austere environments (6).

Over the past decade, systematic reviews evaluating sublingual sufentanil and the sublingual sufentanil tablet system (SSTS) have highlighted the benefits of noninvasive administration, ease of accessibility without the need for IV placement or additional resources (e.g., tubing, ultrasound, flushes, antiseptics), and controlled dosing via the SSTS (7, 8). However, most studies have focused on its use in postoperative pain management, leaving a significant gap in research on its efficacy in acute traumatic battlefield pain—the original intent of its FDA approval—and in civilian prehospital settings (9-33). This narrative review will examine the existing literature on sublingual sufentanil, including its current applications, pharmacologic properties, limitations, research gaps, and potential future roles in acute pain management.

**Methods:**

A literature search was conducted from January 2013 to December 2023, where articles published on PubMed and Medline were searched regarding use of sublingual sufentanil in acute pain settings as well as the pharmacokinetics, pharmacodynamics, and clinical applications. Search fields included key words such as “sublingual sufentanil,"”Dsuvia,”"battlefield pain,"“opioids in acute pain,”“prehospital acute pain,” and

“sufentanil in acute pain.” Results from the main clinical trials and systematic reviews are discussed which included a total of 46 studies. Out of the studies analyzed, *** number of papers were observational trials, and *** number of papers were randomized control trials.

**?Body (results? Discussion? How do we name this?)**

**Sublingual Sufentanil Background**

Sublingual sufentanil is a synthetic opioid analgesic approved by the FDA for managing severe pain; however, it remains underutilized in most U.S. healthcare settings. Known for its high selectivity and strong affinity for mu-opioid receptors, sufentanil has been used for decades in clinical practice—administered intravenously as part of balanced general anesthesia and epidurally in combination with local anesthetics (10). It is among the most potent opioids available, with an estimated effect-site concentration approximately 12 times greater than fentanyl and a potency roughly 400 times that of morphine based on dosage (11).

In recent years, two sufentanil sublingual tablet delivery systems (SSTS), Dsuvia and Zalviso, have been developed by Talphera (formerly known as AcelRx Pharmaceuticals). Dsuvia is 30mcg dose of sublingual sufentanil that is distributed in a pre-packaged disposable single dose applicator device regulated to a minimum of 1 hour between doses and a max cumulative daily dose of 360 mcg (12 tablets/24 hour period). Additionally, a 15 mcg tablet for a patient-controlled analgesia device (Zalviso), has been produced, with a dosing interval of a minimum of 20 minutes and a treatment duration of up to 72 hours–currently only approved for use in Europe (12- 73).

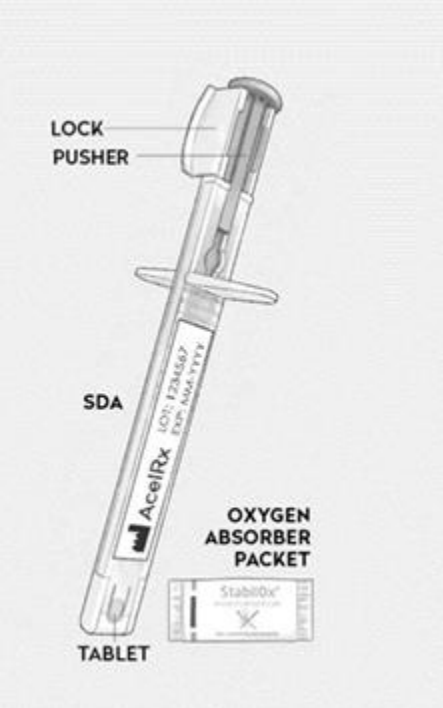
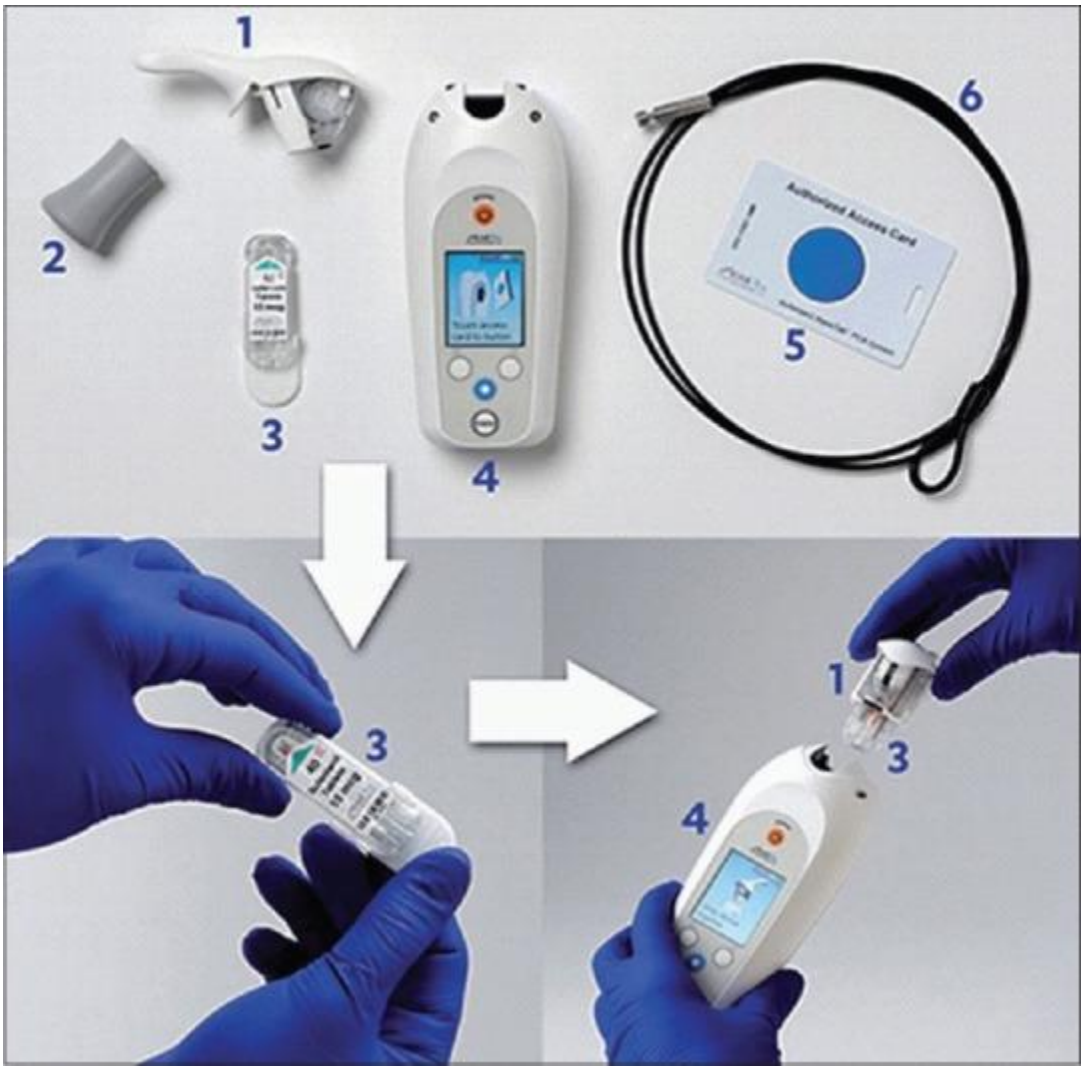



Figure 1 - (5-37) Dsuvia tablet Administration system

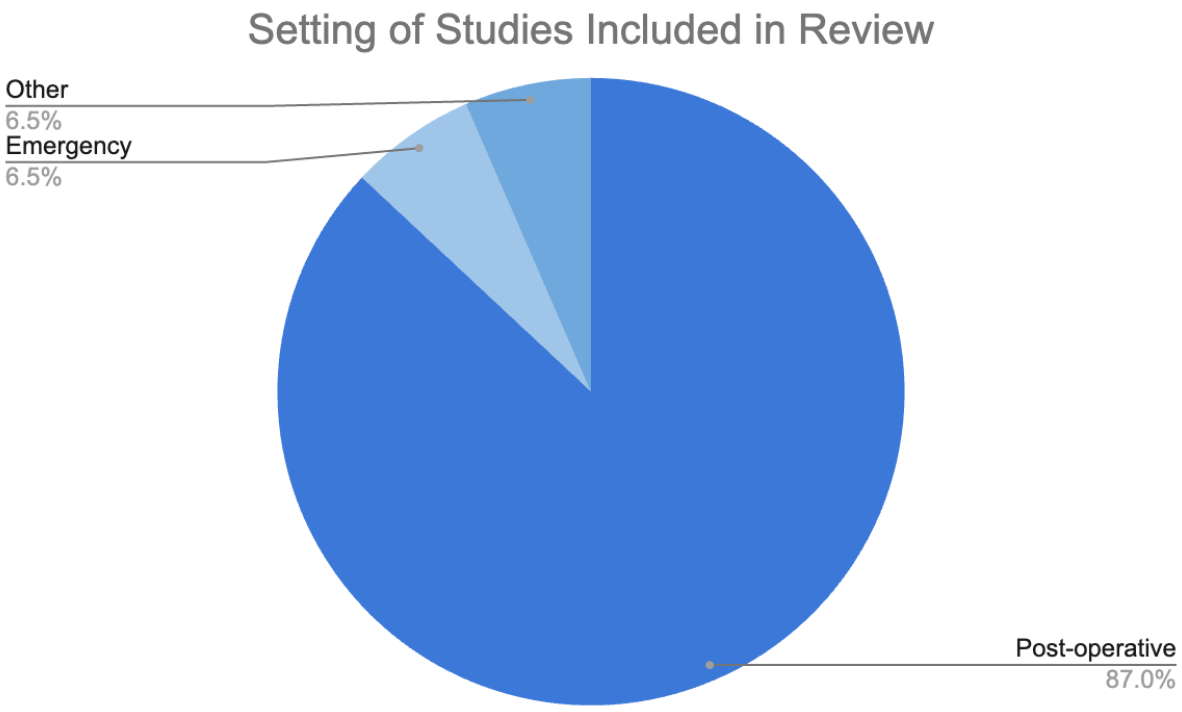

Figure 2 - (31) Zalviso System




**Fabio (38) - Zalviso System**

A single dose of sublingual sufentanil dissolves in approximately 5 minutes, with 53% of the drug entering the bloodstream, compared to a 1-minute intravenous infusion of 30 mcg sufentanil. The peak blood concentration of sublingual sufentanil is reached within 1 hour and is 17 times lower than the same dose administered intravenously. Steady-state concentration is achieved after seven consecutive sublingual doses (13- 79).

If any portion of the sublingual tablet is swallowed instead of absorbed under the tongue, only 9% of the swallowed dose reaches systemic circulation. Sufentanil is metabolized in the liver, and both sufentanil and its metabolites are eliminated via the kidneys (14- 71, 15 - 76).




*Graph 3: Of the 46 studies that met inclusion criteria for this review, 6.5% (3) took place in emergency settings and 87% (40) in the postoperative setting.*

| Analgesic Option | Oral Morphine Equivalent Multiplication Factor | Onset of Action | Duration |
|---|---|---|---|
| 30 mcg Sufentanil SL | Approx 1500 | 15 min | 2-3 hrs |
| 30 mcg Sufentanil IV | 3000 | 1-3 min | 2.3-3.8 hrs |
| 50 mcg Fentanyl IV/IO | 300 | < 1 min | 0.5-1hr |
| 100 mcg Fentanyl IN | 160 | 7 min | 1 hr |
| 800 mcg Oral transmucosal fentanyl citrate (OTFC) | 130 | 5-15 min | 1-2 hrs |

*Table 1 Comparing the Morphine Equivalent Factor, Onset of Action, and Duration of sublingual and IV Sufentanil to intranasal, IV, and transmucosal Fentanyl, the current opioid analgesic recommended for battlefield analgesia in the Tactical Combat Casualty Care guidelines.*

*(Data taken from Medscape and the FDA approval)*

## Post-Operative Setting

Since its approval, sublingual sufentanil has been studied most extensively in the postoperative setting. One of the primary conditions keeping patients in the hospital after operations is pain. With recent shift towards performing less invasive surgical procedures in an ambulatory setting, numerous studies have been undertaken to compare effective pain management methods that reduce post-operative time under care[16].

### Sublingual Sufentanil Tablet System (SSTS) vs IV Morphine

Morphine patient-controlled analgesia (PCA) is a widely used method for managing post-operative acute pain in many hospitals. To compare its effectiveness with the sufentanil sublingual tablet system (SSTS), a 2014 randomized, active-comparator trial evaluated the efficacy of the sufentanil sublingual tablet system (SSTS) in 357 patients undergoing open abdominal or orthopedic surgery. The study found no statistically significant difference in overall patient satisfaction between SSTS and IV PCA morphine. However, a greater proportion of patients rated SSTS as successful for pain control at 24, 48, and 72 hours postoperatively. Secondary outcomes, assessed using validated ease-of-care questionnaires, indicated that SSTS provided a faster onset of pain relief and resulted in higher satisfaction scores from both patients and nurses (17, 18). Additionally, patients using IV PCA morphine required approximately five times longer (7 hours vs. 1.3 hours) than those on SSTS to achieve clinically meaningful pain relief (18).

In contrast however, four years later, a 2018 retrospective analysis of 80 post-spinal surgery patients found a significant difference in pain intensity scores, with more patients favoring morphine PCA (19). At 48 hours postoperatively, the mean opioid consumption was 35 morphine milligram equivalents (MMEs) of IV morphine and 18.6 sufentanil tablets. The findings are not simple and straightforward however, as a 2022 study of 30 postoperative patients comparing SSTS and IV morphine PCA found no clinically significant difference in pain control between the two groups from postoperative day 0 to day 3 (20). Similarly, an open-label, non-inferiority, parallel-group randomized trial of 36 patients post-pancreatoduodenectomy compared 15 mcg SSTS with the hospital's standard-of-care analgesia (epidural ropivacaine/sufentanil or intravenous morphine) and the mean pain scores, number of patients reporting unacceptable pain, and patient satisfaction per postoperative day did not differ significantly between SSTS and standard care (22).

In 2023, another postoperative study comparing the efficacy of morphine PCA with 15 mcg SSTS found both to be equally effective in pain relief. However, in contrast to previous studies, patients in the SSTS group used a higher morphine milligram equivalent (MME) of opioids at 24 hours postoperatively. This outcome was attributed to the higher maximum hourly dose allowed in the sufentanil group (45 mcg, equivalent to 9 mg of morphine per hour) compared to morphine (6 mg per hour). Despite differences in opioid exposure, the incidence of side effects remained similar between both groups, aligning with previous findings (21).

In 2021, a prospective, open-label, randomized controlled trial of 64 patients post-cardiothoracic surgery found that the primary outcome—cumulative mean numerical rating scale (NRS) pain scores—was significantly lower in the nurse-controlled continuous morphine infusion group compared to the 15 mcg SSTS group (0.8 vs. 1.3; $p = 0.006$) (23). However, the SSTS group

had significantly lower overall opioid consumption. Secondary outcomes, including adverse effects such as postoperative nausea and vomiting, sedation, hypoventilation, bradycardia, and hypotension, showed no significant differences between the two groups.

| Citation, Journal | Authors | Study Design | Summary | Limitations |
|---|---|---|---|---|
| 17 - Current Medical Research and Opinion, 2018 | Morlion, B., Schäfer, M., Betteridge, N., & Kalso, E. | *Narrative Review* | Non-invasive PCA systems are easy to use and allow for earlier patient mobilization | Narrative Review discussing main clinical trials |
| 18 - Pain Practice, 2014 | Melson TI, Boyer DL, Minkowitz HS, Turan A, Chiang YK, Evashenk MA, Palmer PP. | Randomized, open label, non-inferiority study of 357 post operative patients | Demonstrated non-inferiority<br><br>SSTS - more rapid onset of analgesia, greater nurse ease of care, and higher patient satisfaction.<br><br>Similar adverse event rate though SSTS group had fewer O2 desats | Open abdominal and major orthopedic surgeries in same study |
| 19 *J Clin Anesth Pain Med.* 2018 | Dransart C, De Bue P, Jamart J, et al. | *Retrospective analysis of 80 patients undergoing spinal surgery* | Pain intensity scores better controlled with morphine PCA<br><br>Higher opioid exposure? | Different PACU analgesia used in each group prior to start of PCA |
| 20 - Perioper Med (Lond). 2022 | Rineau E, Dumartinet B, Samson E, Dollfus A, Aubourg C, Lasocki S. | Prospective observational case study | No clinically significant difference in pain control<br><br>No difference in recovery rate | Case study |
| 21 - Cureus. 2023 | Fernandes DL, Pereira AIG, Amorim A, Freitas J. | Open-label, parallel-group, randomized controlled trial with 54 patients | No clinically significant difference in pain control<br><br>SSTS used more mme of opioids<br><br>Incidence of side effects similar | Higher maximum dose per hour allowed in the sufentanil group compared to that of morphine |
| 22 - J Pain Res. 2022 | Groen JV, Boon SC, Minderhoud MW, Bonsing BA, Martini CH, Putter H, Vahrmeijer AL, van Velzen M, Vuijk J, Mieog JSD, Dahan A | open label non-inferiority parallel group randomized trial following 36 patients post pancreatoduoden ectomy | No significant difference in mean pain score, number of patients reporting unacceptable pain, and patient satisfaction per postoperative day | Standard of care had options of morphine or ropivicaine/epi |

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| 23 - J Cardiothorac Vasc Anesth. 2021 | Van Tittelboom V, Poelaert R, Malbrain MLNG, La Meir M, Staessens K, Poelaert J. | Prospective, open-label, randomized controlled trial of 64 patients post cardiothoracic surgery | pain scores significantly lower in the nurse-controlled continuous morphine infusion<br><br>SSTS group had reduced opioid consumption<br><br>No difference in incidence of side effects | Comparing patient directed SSTS vs nurse directed morphine infusion |

**Comparison of SST and Oral Oxycodone**

Morphine has not been the only opiod of interest, as multiple studies have also looked at the efficacy of SSTS in comparison to popular oral oxycodone. Specifically, Noel et al. compared 15 mcg SSTS with oral oxycodone extended-release (10 mg twice daily) plus oxycodone immediate-release (5 mg up to four times daily as needed) in patients undergoing total knee arthroplasty. The study found no clinically significant difference in pain control or time to mobilization between the two groups. However, the SSTS group experienced a higher incidence of postoperative nausea (33% vs. 9% in the oxycodone group) (24).

Similarly, a 2018 retrospective study examining postoperative pain management in 227 patients undergoing total knee arthroplasty (68 receiving oxycodone, 87 receiving dexamethasone + oxycodone, and 72 receiving 15 mcg SSTS) found that SSTS did not provide superior pain control. Additionally, patients in the SSTS group reported increased nausea compared to the oxycodone-dexamethasone group, a commonly observed adverse effect consistent with previous literature (26). Pain scores among the three groups were comparable after postoperative day 0.

Study limitations included eight patients who dropped out due to Zalviso PCA malfunction (n=3), delirium (n=2), language barriers (n=1), and unknown reasons (n=2). These patients were subsequently treated with oxycodone but remained in the Zalviso group for analysis.

| Citation #, Journal | Authors | Study Design | Summary | Limitations |
|---|---|---|---|---|
| 24 - Journal of Experimental Orthopaedics 2020 | Noel E, Miglionico L, Leclercq M, Jennart H, Fils JF, Van Rompaey N. | Open label, randomized controlled trial of 72 patients undergoing TKA | No clinically significant difference in pain control at 24hrs post-op<br><br>No difference in time to first mobilization<br><br>83.9% of patients reported good/excellent pain control compartd to 52.9% of oxy<br><br>33% of SSTS patients reported nausea compared to 9% of Oxy | SSTS group received one 15mg dose and Oxy group had extended 10mg scheduled and immediate 5mg on demand release options<br><br>MME not calculated between groups |

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|---|---|---|---|---|
| | | | group | |
| 25 - Journal of Pain Research 2018 | Van Veen DE, Verhelst CC, van Dellen RT, Koopman | Retrospective, single center cohort study of 227 patients undergoing TKA | No clinically significant difference in pain control after day 0.<br><br>Zalviso group experienced more nausea at Day 0 and 1. | 8 patients dropped out of Zalviso group and were treated with Oxy but still analyzed in Zalviso group |

**Comparison of SSTS vs Nerve Block**

Additionally, there have so far been two studies comparing SSTS to continuous femoral nerve block (cFNB) for postoperative pain management. A 2018 observational study analyzing 95 patients on SSTS and 87 on cFNB after total knee arthroplasty (TKA) in a fast-track setting found that the SSTS group experienced less pain both at rest and during movement at all measured time points. Additionally, SSTS patients required significantly fewer rescue doses, with only 5% needing additional analgesia compared to 60% in the cFNB group (27).

A 2022 retrospective study of 71 TKA patients comparing the same treatments reported similar findings; however, after the first 24 hours, pain intensity differences between the groups were no longer statistically significant (28).

| Citation #, Journal | Authors | Study Design | Summary | Limitations |
|---|---|---|---|---|
| 27 - Journal of Experimental Orthopaedics, 2018 | Scardino M, D'Amato T, Martorelli F, Fenocchio G, Simili V, Di Matteo B, Bugada D, Kon E. | Retrospective observational study of 182 (95 SSTS, 87 cFNB) patients undergoing TKA | Pain intensity score lower at rest and during movement in SSTS group<br><br>Fewer rescue doses needed in SSTS group (5% vs 60% of cFNB)<br><br>Adverse effects in SSTS group 6% compared to 74% of cFNB<br><br>100% of SSTS patients released per protocol at 4 days of stay vs 36% of cFNB<br><br>SSTS rated easier to use by nursing staff | Study conducted in country with universal healthcare (Italy)<br><br>Patients with chronic pain, alcohol/drug addiction, and cognitive/psychiatric conditions excluded from study |
| 28 - Journal of Clinical Medicine 2022 | Angelini A, Parise GM, Cerchiaro M, Ambrosio F, Navalesi P, Ruggieri P. | Retrospective Observational Monocentric Study of 71 patients (50 | After first 24 hrs, no significant difference in pain intensity<br><br>SSTS group required less rescue doses (5% vs 60% cFNB group) | Small number of patients<br><br>Patients with chronic pain excluded from study |

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| | | SSTS, 21 cFNB) undergoing TKA | SSTS group reported adverse event of nausea<br><br>Mean hospital stay for SSTS group was significantly less<br><br>Significant reduction in nurse calls by patients in SSTS group | Seven patients dropped out of Zalviso arm due to ineffective pain relief (3) and malfunctioning of device (4) - Excluded from analysis after point they dropped out |

**Non-Comparative Analgesic Effect**

When looking at sublingual sufentanil next to a placebo, sublingual sufentanil has demonstrated significant analgesic efficacy, with studies showing greater reductions in pain intensity and lower requirements for rescue medication. Patients receiving sublingual sufentanil reported improved pain control at multiple time points, reinforcing its effectiveness as a non-invasive opioid analgesic (29, 30, 31).

| Citation #, Journal | Authors | Study Design | Summary | Limitations |
|---|---|---|---|---|
| 29 - Regional Anesthesia Pain Medicine, 2015 | Ringold FG, Minkowitz HS, Gan TJ, Aqua KA, Chiang YK, Evashenk MA, Palmer PP | Phase 3, Randomized Placebo Controlled, double blind study of 13 hospitals in US with total of 172 patients undergoing open abdominal surgery | SSTS patients and healthcare professionals reported significant difference of higher pain intensity difference (improved pain control) than placebo group<br><br>SSTS group required significantly less rescue doses of Morphine<br><br>Adverse events and vital signs similar between groups | AcelRx funded study<br><br>17% of SSTS group dropped out due to inadequate analgesia though they did so later and in lower numbers than placebo group<br><br>Patients excluded if they experienced chronic pain, alcohol or drug abuse, or opioid tolerance<br><br>Of 172 patients that started study, 105 (61%) completed through 48hrs, and 40 (23.2%) completed 72 hrs. |
| 30 - Anesthesiology. 2015 | Jove M, Griffin DW, Minkowitz HS, Ben-David B, Evashenk MA, Palmer PP | Prospective randomized parallel arm double blind placebo-controlled study of 426 patients in 34 different hospitals undergoing | SSTS group (315) reported significant difference of higher summed pain intensity difference (improved pain control) than placebo group (104).<br><br>SSTS group had a significant | AcelRx funded study<br><br>Patients with chronic pain, opioid tolerance, previous hip or knee arthroplasty were excluded<br><br>Of 419 patients that |

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|---|---|---|---|---|
| | | hip and knee arthroplasty | difference of increased number of nurses and patients rating “good” or “excellent” on global assessments<br><br>Higher incidence of nausea and pruritis in SSTS group | started study, 258 (61.6%) completed 48hrs study period, 150 continued beyond 48 hrs, and 85 (56.7%) completed 72 hr study period. |
| 31 - Journal of Trauma Acute Care Surgery, 2014 | Singla NK, Muse DD, Evashenk MA, Palmer PP. | Randomized, double-blind, placebo-controlled trial of 100 patients undergoing bunionectomy alone or with hammertoe repair | 30 mcg sufentanil dose group reported significant difference of higher summed pain intensity difference at 12 hours (improved pain control)<br><br>20 mcg SL sufentanil dose group not superior to placebo<br><br>Dose dependent increase of nausea, vomiting, and somnolence noted | 2:2:1 ratio to treatment assignment with SSM 20 µg, SSM 30 µg, or placebo resulting in small sample sizes |

**SSTS Favorability Among Patients and Providers**

Another area to consider is the subjectivity of the medication, which has lucikly been given attention as well. Throughout the past several years, mulitple studies have examined satisfaction related to SSTS use. An analysis of one phase II and three phase III studies found high satisfaction rates, with 88% of patients and 90% of healthcare practitioners rating SSTS as good or excellent (41- 87). Additionally, in a direct comparison of SSTS to IV PCA morphine, SSTS demonstrated a statistically significant advantage on the Nurse Ease of Care endpoint for both Total Score and Overall Satisfaction Score (42- 82)

A 2021 observational study of 298 postoperative patients using SSTS reported high patient and nursing ease-of-care scores, with 93.5% of patients being "extremely satisfied/satisfied" with pain control and 93.2% expressing the same level of satisfaction with the mode of administration (43- 105). Similarly, a 2019 non-interventional prospective study by Pogatzki-Zahn et al., involving 341 patients, mirrored these findings (44 – 106).

A 2021 prospective observational study assessed the usability of SSTS in 111 patients undergoing spine, orthopedic, and thoracic procedures (47- 90). After 72 hours, the median system usability score (SUS) was 90 for patients and 72.5 for nurses. According to SUS criteria, scores above 50 indicate acceptable usability, scores above 70 are considered good, and scores exceeding 85 are classified as excellent (47 – 90).

A study of 280 postoperative patients in the Netherlands demonstrated similar findings, supporting the success of SSTS as part of a multimodal approach, with effective pain control and high patient satisfaction. Regarding medication usage, the study reported an average

consumption of 18.6 tablets (279 mcg), with the majority taken within the first 24 hours post-surgery (48 -91).

Additionally, postoperative pain management with SSTS was found to be more effective in terms of pain control and patient/provider satisfaction when indirectly compared to the fentanyl iontophoretic patient-controlled transdermal system (33- 89).

**Economics of SSTS**

A 2019 German study across four hospitals compared staff time requirements for SSTS versus IV morphine PCA. On average, staff spent 36 minutes managing SSTS compared to 49 minutes for PCA ($p < 0.0001$). Across all stages of the process, SSTS consistently required less staff time (45 -119).

A 2020 prospective study evaluated whether preoperative administration of a sublingual sufentanil tablet could reduce overall opioid use and PACU time compared to historical controls in 127 patients. Contrary to prior studies, a smaller proportion of patients receiving sublingual sufentanil required postoperative opioids (10.5% vs. 63.0%; $p < 0.001$), and overall opioid consumption was reduced by more than 50% throughout the perioperative period (11.8 MME vs. 24.6 MME; $p < 0.001$). Additionally, significantly fewer SSTS patients required intraoperative adrenergic agonists, and PACU discharge was 34% faster than in the control group (52- 100).

A prospective study at Auburn Community Hospital (June 2019–March 2020) evaluated 140 patients requiring opioid-level analgesia for surgery. When matched to 158 patients undergoing similar procedures with the same surgeon, 90% of SSTS patients required only a single sublingual sufentanil tablet, while 10% required one additional dose in the PACU. Compared to traditional intraoperative IV opioid administration, sublingual sufentanil tablets reduced PACU opioid use by more than 50%, leading to a 14-minute reduction in recovery discharge time ($p < 0.001$) (53 – 102).

Notably, this study led to the discontinuation of the Zalviso sublingual sufentanil tablet system at a Brussels medical center due to cost concerns. The total cost per patient was $125, with an additional $1,750 for the device when treating 300 patients per year. In contrast, oxycodone cost approximately $0.75 per tablet (27 - 74). However, a 2017 cost analysis in Ireland indicated that sublingual sufentanil tablets for postoperative pain management resulted in $42.67 savings per treatment compared to IV opioids (30 - 83).

A 2022 study at an ambulatory surgery center compared 75 patients receiving either a 30 mcg sublingual sufentanil tablet or a 50 mcg intravenous fentanyl dose for postoperative pain management. The study found no significant differences between the two groups in readiness for discharge, additional opioid requirements (measured in morphine equivalents), or patient-reported outcomes regarding pain relief and rescue analgesia needs (26- 103).

**Current Uses in Emergency Medicine**

Currently, no studies have evaluated SSTS use on the battlefield, and the closest available data comes from its use in emergency departments (EDs). However, even this information remains limited, as few studies have specifically examined sublingual sufentanil in the ED setting.

A 2018 single-arm, multicenter, open-label trial conducted at three U.S. hospitals assessed the feasibility of using 30 mcg SST for moderate-to-severe pain management in 76 ED patients presenting with fractures, sprains/strains, soft tissue contusions/hematomas, lacerations, joint dislocations, burns, and infections. After a single dose, pain intensity decreased by an average of three points within one hour (29 - 80).

Although the study drug was available every hour, 75% of patients required only one dose, experiencing consistent pain relief at both one-hour and two-hour time points. Adverse events were analyzed across both treatment cohorts, revealing that 79% of patients experienced no adverse effects. Among those with adverse effects, the most common were nausea (9%), somnolence (5%), vomiting (4%), and oxygen desaturation (3%) (29- 80).

This study also uniquely evaluated cognitive function, assessing six-item screener (SIS) cognitive scores pre- and post-dosing in 75 patients. 97% of patients had either no change or improved SIS scores at one hour post-dosing, while 3% experienced a single-point decline, which coincided with the time of peak plasma concentration (29 -80). Unlike IV bolus administration, which causes a rapid plasma concentration spike, sublingual sufentanil is gradually absorbed, potentially explaining the lack of cognitive impairment. This is a notable finding, as IV morphine use has been associated with diminished recall, delayed reaction time, and impaired memory (57 - 118).

| Authors | Origin, Date | Purpose | Type of Source | Research Design | Target Population/ Limitations | Summary Points |
|---|---|---|---|---|---|---|
| Miner JR, Rafique Z, Minkowitz HS, DiDonato KP, Palmer PP. | Am J Emerg Med. 2018 | Sufentanil sublingual tablet 30mcg for moderate-to-severe acute pain in the ED | | | | |
| Leiman D, Jové M, Spahn GR, Palmer P. | J Pain Res. 2021 | Patient and Healthcare Professional Satisfaction Ratings and Safety Profile of Sufentanil | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Sublingual Tablets for Treatment of Acute Pain: A Pooled Demographic Analysis. | | | | |

**Potential for Battlefield use**

One of the main focus points of the DOD's Stepped Care Model for pain management Plan is the appropriate management of acute pain during initial injury as to prevent development of chronic pain syndromes that may lead to opioid addiction later. Physiologically inadequate pain control after traumatic injury can prompt a potent stress inflammatory response that has the ability to affect all organ systems and leads to downstream effects both psychiatric and neurologic that can lead to development of chronic pain conditions thus, seeking quality improvement of pain management of acute trauma is directly in line with the DOD's vision of reducing opioid reliance. It is possible that SSTs could fill a critical role in managing acute conditions in deployed military populations that without appropriate management could lead to downstream chronic pain effects. The DOD and AcelRx wanted to focus on sublingual delivery because on the battlefield IV access is not always practical or easily attainable and oral swallowed opioids have slower erratic onset if a patient even has the ability to swallow.

When looking at the benefits of sublingual sufentanil, studies have shown it to be a potent, highly lipophilic substance, with rapid plasma to CNS equilibration and appropriate physicochemical properties for rapid mucosal absorption of approximately 6.2 minutes. The relatively lower volume of distribution and rapid half life blunts the drug plasma peak concentration theoretically resulting in less euphoric potential than other synthetic opioid preparations. The sublingual dosing route creates an absorption delay that allows for more consistent plasma concentration than IV administration of sufentanil, resulting in approximately 2.3 hours of analgesia in the sublingual form, making constant dosing not a concern in intense battle environments. Additionally, its onset time is predictable, leaving less room for accidental compounded dosing and its potency at 5-10 times the strength of fentanyl allows for proper control of acute pain. Additionally, adverse effects have proven to be overall mild with nausea and vomiting being the most common, though not to ignore that somnolence and oxygen desaturation are a real possibility and have been seen in above mentioned studies at the peak plasma concentration of the SST.

A common theme in the current research showed that the sublingual sufentanil tablet is an easily administered single dose analgesic that has had high satisfaction scores with both patients and hospital staff–patient and nurse scoring on ease of use scales were significantly higher in patients using the SSTS than in those using standard IV morphine PCAs. In addition, in non-comparative studies (in both the post-operative setting and in the ED), SST provided great pain relief in patients as compared to the placebo, proving its ability to serve as an effective pain control method in patients that do not have IV access or are unable to swallow pills.

In the most current comparative studies, SSTS has been found to be non-inferior when it comes to post-operative pain control, offering equal reduction in pain scores to other standard of care medications and when looking at transdermal fentanyl and nerve blocks post-procedure, the SSTS did prove to reduce pain scores more significantly. Overall, it is a medication that works just as well, if not better than current medication standards that are currently used post-operatively.

Current contraindications to SSTS include respiratory depression, severe bronchial asthma, and suspected gastrointestinal obstruction, as well as anaphylactic reaction to a component of Dsuvia, specifically. There is risk of developing serotonin syndrome, adrenal insufficiency, severe hypotension, in addition to risks of using it in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness. There are warnings and extra precautions that must be taken for use in special populations such as the elderly or those with hepatic and/or renal impairment (FDA Data Sheet). Like all opioids, SSTs do not come without risks of addiction as well. The more commonly used oral transmucosal fentanyl citrate (OTFC) lollipops for acute pain management on the battlefield has similar concerns. Originally this medication is meant for chronic pain in cancer patients and misusing it can lead to addiction, overdose, and other serious problems. Without a lock-out period, like the SSTS, overuse becomes a much bigger concern with OFTC and can be combated by this sublingual sufentanil tablet system that has been developed.

The unique formulation and delivery device of sublingual sufentanil can allow it to fill an important need on the battlefield however, as the FDA commissioner highlighted, the introduction of new opioid class medications should be compared with those already on the market to ensure that there is benefit derived that is clinically significant and separate from those already on the market. Although promising, with current studies showing non-inferiority of SSTS, we cannot yet say that this criteria has been met without first having further comparative studies taking place.

## Limitations

Several limitations were identified in this review. Variability among clinical trials remains a concern, including differences in surgical procedures, study designs, and endpoints examined. Additionally, this analysis was restricted to English-language studies, which may limit generalizability.

## Future Directions

One of the most significant research gaps is the lack of studies on SST use in prehospital settings, which would be most relevant for battlefield applications. The optimal dosing strategy for this setting also remains undetermined. Future research should consider the nature of injuries likely to be treated with SST, including blast injuries, gunshot wounds, motor vehicle collisions (MVCs), and amputations.

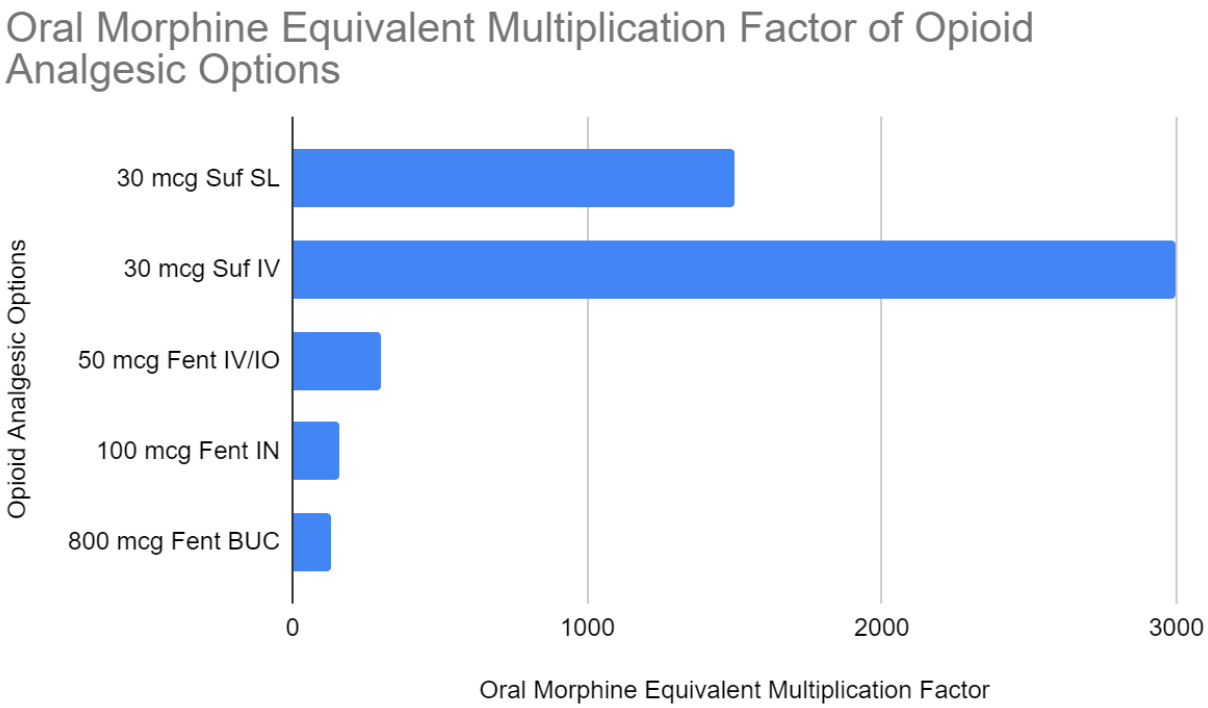
Additionally, traumatic brain injury (TBI) is a major concern in battlefield casualties, with 19.5% of previously deployed personnel in the Iraq and Afghanistan wars suffering probable TBI (7). Among casualties who die from TBI, uncontrolled intracranial pressure (ICP) within the first 48 hours post-injury is the primary cause of death (8). Sufentanil has been shown to increase ICP in patients with head trauma, even at modest doses, raising safety concerns regarding its use in polytrauma cases with suspected TBI (10). This presents a critical avenue for future investigation.

Another major gap is the lack of direct comparisons between SSTS and oral transmucosal fentanyl citrate (OTFC), the current preferred battlefield analgesic. Comparative studies are needed to establish SSTS's role in the stepped treatment approach, particularly given that OTFC is affordable, widely used, and readily available. Continued monitoring of abuse and diversion potential is also essential.

Several regulatory committee members have raised concerns about the lack of comparative efficacy studies between SSTS and existing opioid and non-opioid pain management standards. Future research should address this by expanding beyond immediate postoperative pain outcomes to include:

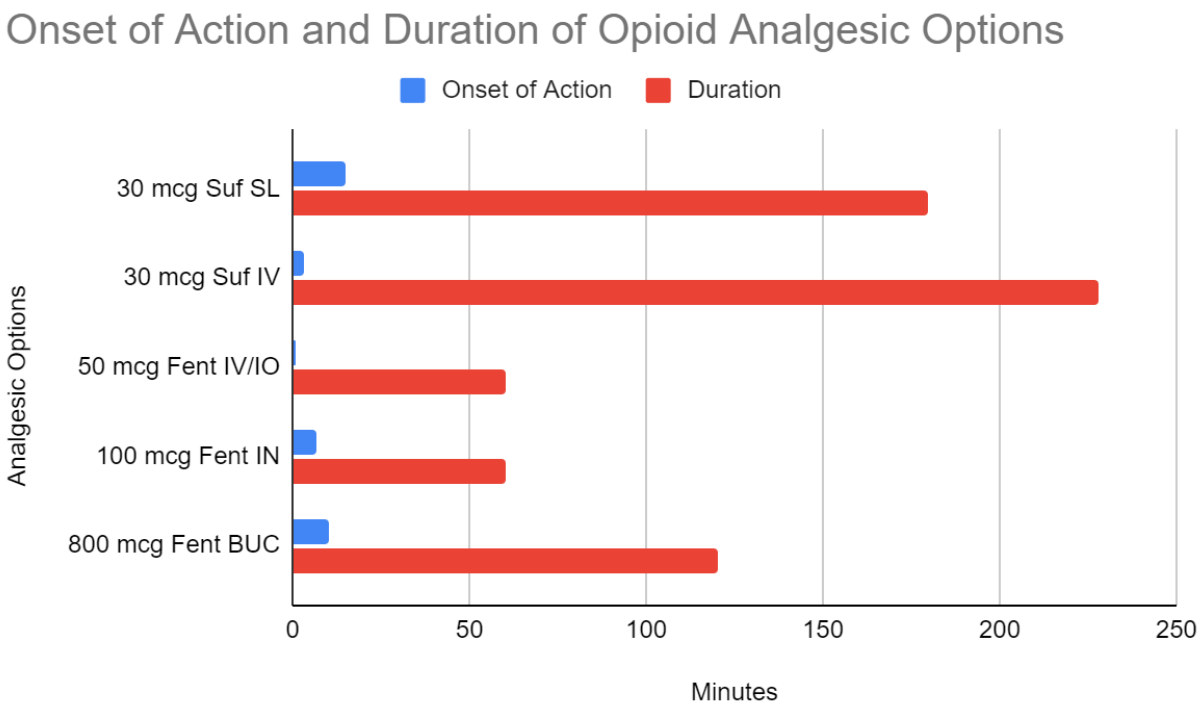
- Long-term analgesic efficacy
- Preoperative pain scores
- Larger sample sizes

A broader research approach could yield more comprehensive and clinically meaningful findings, ultimately guiding the optimal use of SSTS in both civilian and military settings.




*Graph 2 Comparison of the oral Morphine Equivalent Multiplication Factor of sublingual and IV Sufentanil and intranasal, IV, and transmucosal Fentanyl, the current opioid analgesic recommended for battlefield analgesia in the Tactical Combat Casualty Care guidelines. Oral Morphine Equivalent Multiplication Factor serving as imperfect proxy for strength of analgesic effect that each dose and administration method provides.*

*Data obtained from: Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf. 2016 Jun;25(6):733-7. doi: 10.1002/pds.3945. Epub 2015 Dec 22. PMID: 26693665.*
*As well as*
*FDA approval certification of SSTS*




*Graph 3 Comparison of the Onset of Action and Duration in minutes of sublingual and IV Sufentanil and intranasal, IV, and transmucosal Fentanyl, the current opioid analgesic recommended for battlefield analgesia in the Tactical Combat Casualty Care guidelines. (Data obtained from Medscape and the FDA approval)*

**Conclusion:**

The primary advantages of SSTS include its rapid onset of pain relief and its ability to minimize gaps in pain management. While SSTS has limitations, its non-invasive sublingual delivery system and favorable pharmacological profile offer a promising approach to addressing unmet battlefield analgesia needs, potentially reducing the risk of side effects and dependence.

Facilitating pain management at the point of injury is critical, and any intervention that simplifies analgesic administration is beneficial. However, further research is needed to determine whether SSTS offers a significant practical advantage over current battlefield pain management strategies, which are already effective.

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