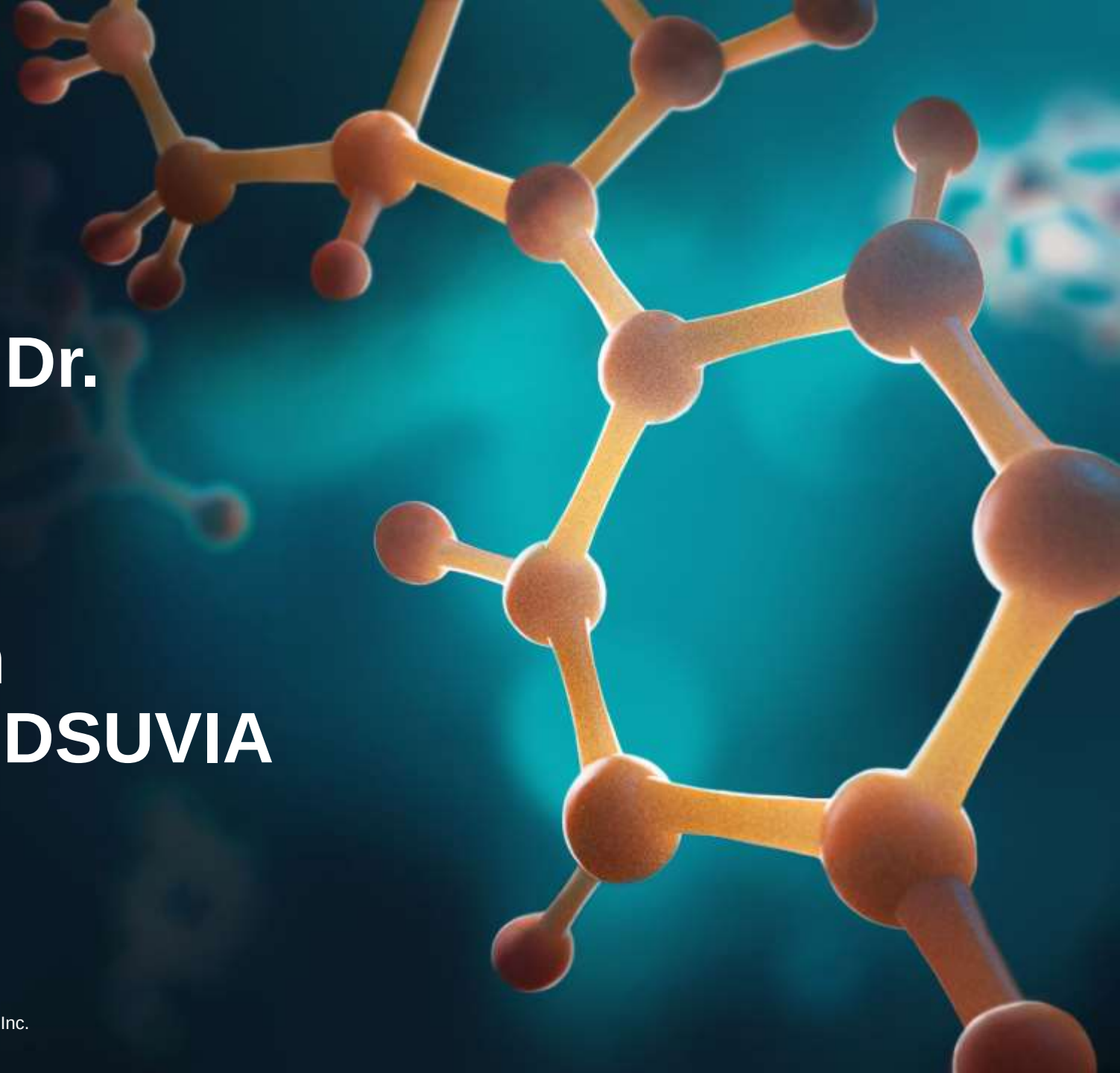
AcelRx Pharmaceuticals, Inc.

Virtual KOL call with Dr. Tvetenstrand and Dr. Cassavaugh:

Real-World Data with Perioperative Use of DSUVIA



A Sublingual Opioid Analgesic for Use in Medically Supervised Settings

DSUVIA® sufentanil sublingual tablet (SST) 30 mcg

DSUVIA is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[1]

- ✓ Transmucosal absorption avoids first-pass effect[1,2]
- ✓ Disposable, prefilled, single-dose applicator[1]
- ✓ Approved by the FDA in November 2018 via the 505(b)(2) pathway[3]

1. DSUVIA [package insert]. Redwood City, CA: AcelRx Pharmaceuticals, Inc; 2019.
2. Fisher DM, et al. *Anesthesiology*. 2018;128(5):943-952.
3. FDA. U.S. Food and Drug Administration. Letter to: AcelRx Pharmaceuticals, Inc. November 02, 2018. website. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/209128Orig1s000Ltr.pdf. Accessed October 22, 2019.

Important Safety Information and Boxed Warning

Important Safety Information

WARNING: ACCIDENTAL EXPOSURE AND DSUVIA REMS PROGRAM; LIFE-THREATENING RESPIRATORY DEPRESSION; ADDICTION, ABUSE, AND MISUSE; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Accidental Exposure and DSUVIA Risk Evaluation and Mitigation Strategy (REMS) Program

Accidental exposure to or ingestion of DSUVIA, especially in children, can result in respiratory depression and death. Because of the potential for life-threatening respiratory depression due to accidental exposure, DSUVIA is only available through a restricted program called the DSUVIA REMS Program.

- **DSUVIA must only be dispensed to patients in a certified medically supervised healthcare setting.**
- **Discontinue use of DSUVIA prior to discharge or transfer from the certified medically supervised healthcare setting.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of DSUVIA. Monitor for respiratory depression, especially during initiation of DSUVIA.

CNS=central nervous system.

Important Safety Information and Boxed Warning (cont.)

Important Safety Information

Addiction, Abuse, and Misuse
DSUVIA exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing DSUVIA, and monitor all patients regularly for the development of these behaviors or conditions.

Cytochrome P450 3A4 Interaction
The concomitant use of DSUVIA with all cytochrome P450 3A4 inhibitors may result in an increase in sufentanil plasma concentrations, which could increase or prolong adverse drug reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in sufentanil plasma concentration. Monitor patients receiving DSUVIA and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CYP=cytochrome P.

Important Safety Information

DSUVIA is contraindicated in patients with significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; known or suspected gastrointestinal obstruction, including paralytic ileus; and known hypersensitivity to sufentanil or components of DSUVIA.

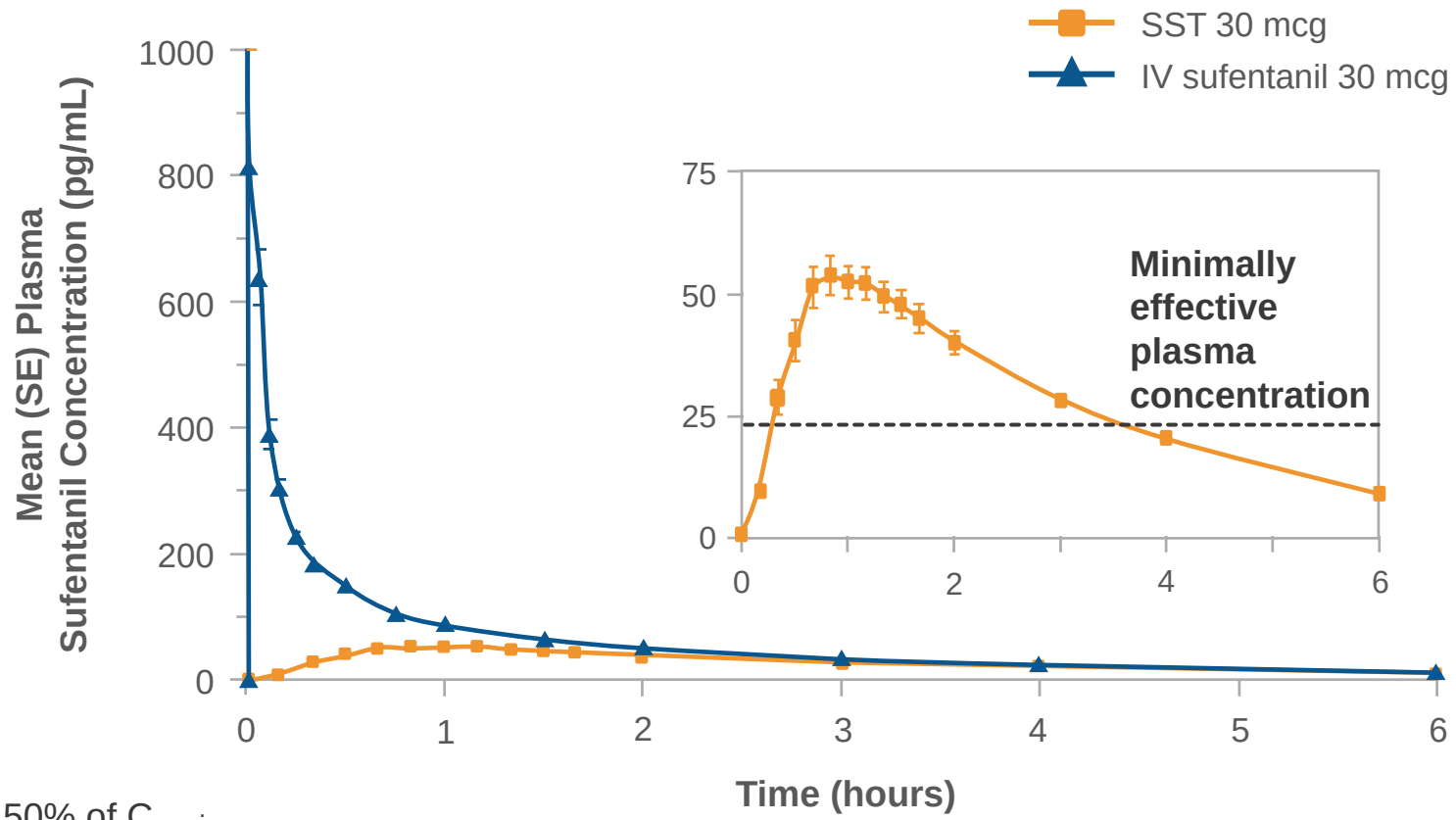
DSUVIA contains sufentanil, a Schedule II controlled substance. As an opioid, DSUVIA exposes users to the risks of addiction, abuse, and misuse. Potential serious adverse events caused by opioids include addiction, abuse, and misuse, life-threatening respiratory depression, neonatal withdrawal syndrome, risks of concomitant use or discontinuation of cytochrome P450 3A4 inhibitors and inducers, risks from concomitant use with benzodiazepines or other CNS depressants, risk of life threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients, adrenal insufficiency, severe hypotension, risks of use in patients with increased intracranial pressure or impaired consciousness, gastrointestinal disorders and seizure disorders. DSUVIA should be used with caution in patients with severe liver or kidney impairment.

This is not a complete list of risks associated with DSUVIA. For additional Important Safety Information please see full Prescribing Information at www.DSUVIA.com.

Sublingual vs IV Sufentanil 30 mcg

Sublingual administration[1,2]:

- ✓ Sufentanil partitions into sublingual mucosa and releases over time
- ✓ Eliminates initial high peak
- ✓ Longer plasma half-time
- ✓ More consistent plasma concentrations over time



Plasma half-time is the time from C_{max} to 50% of C_{max}.

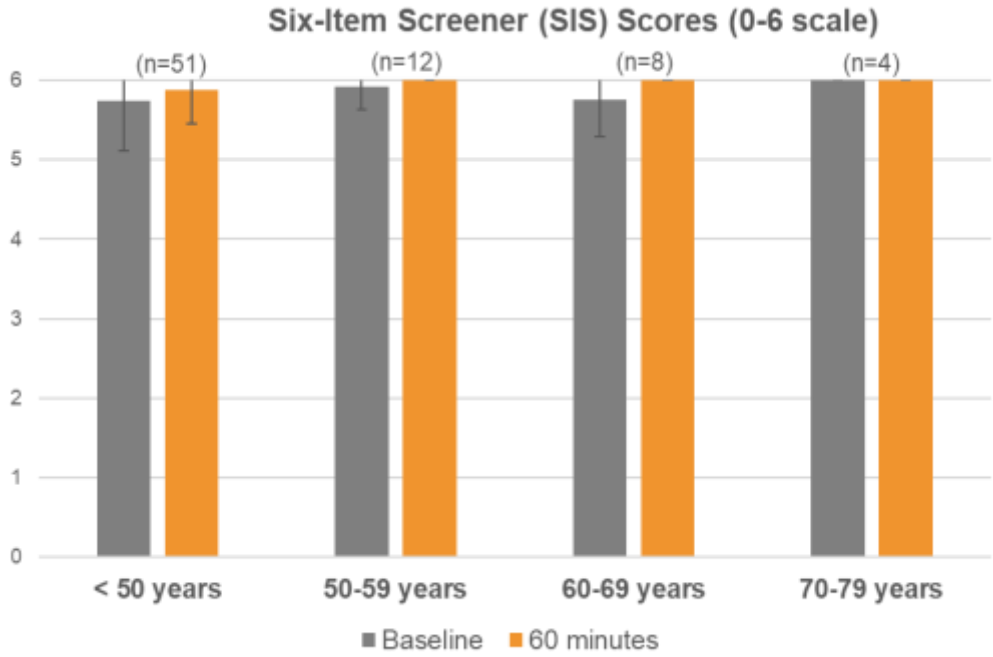
SE=standard error.

1. Fisher DM, et al. *Anesthesiology*. 2018;128(5):943-952.
2. Data on file. AcelRx Pharmaceuticals, Inc.

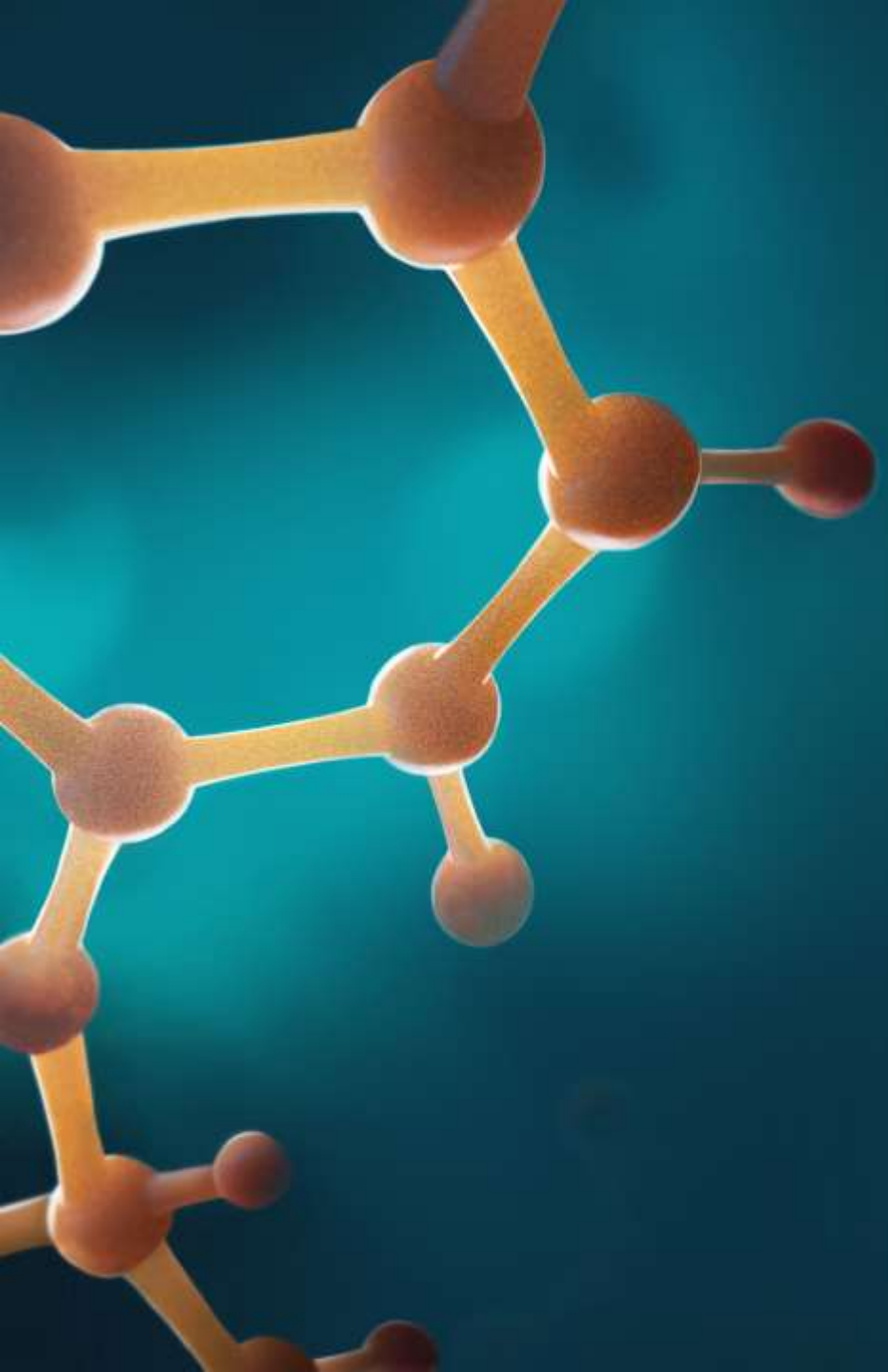
SAP 302 Open-Label ED Study: Six-Item Screener (SIS) Assessment of Cognitive Impairment

Majority of Patients Had No Change in Six-Item Screener Score From Baseline to 1 Hour[1]

SIS Score Change	Baseline to 1 Hour, n (%)
-1	2 (2.7)
0	64 (85.3)
1	7 (9.3)
2	2 (2.7)



mean ± standard deviation; 60-minute SIS scores assessed at Cmax for SST 30 mcg



Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

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*Paid consultant AcelRx Pharmaceuticals

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Medical writing support (funded by AcelRx Pharmaceuticals, Inc.) was provided by Eric R Kinzler, PhD and Gerald E Dodson, PhD of Neura Therapeutik who, on the behalf of the authors, developed the first draft based on an author-approved outline and assisted in implementing author revisions throughout the editorial process

https://scholars.direct/Articles/anesthesia-and-pain-management/jcapm-4-027.php?jid=anesthesia-and-pain-management

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

Study Design

- Prospective medication use evaluation assessing the use of preoperative Sublingual Sufentanil Tablet 30 mcg (SST) in a single site ambulatory surgery setting
  - Prospective group: SST 30 mcg administered approximately 30 minutes prior to incision
  - Control group: Patients in both groups were found to be similar with respect to mean age, body-mass index (BMI), and length of surgery time

- In both groups, more than 75% of surgeries were abdominal in nature (e.g., cholecystectomy, hernia repair)

- Patients were considered eligible if they were undergoing ambulatory surgery defined as an anticipated discharge on same day and were 18 years of age or older

- Patients who had surgical complications, or stayed overnight, were omitted from these analyses

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

Study Design

- Control group (n = 80 patients)
  - Patients in both groups were found to be similar with respect to mean age, body-mass index (BMI), and length of surgery time
  - Typical opioid administration consisted of IV fentanyl bolus just prior to incision
  - Additional intraoperative and postoperative opioids administered as needed
  - IV acetaminophen dosed preoperatively unless contraindicated

- DSUVIA group (n = 47 patients)
  - Dosed with a single preoperative dose of sufentanil 30 mcg sublingual tablet
  - Dosing on average occurred 34.6 (range 3 – 92) minutes prior to incision
  - Additional intraoperative and postoperative opioids administered as needed
  - Preoperative IV acetaminophen was not standardized

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

Patient Demographics

Demographic Comparison	Control	SST
Mean Age, years (Range)	52.1 (22 – 90, n=80)	54.2 (18 – 86, n=47)
Mean BMI, kg/m^2 (Range)	32.7 (16.3 – 59.8, n=80)	32.2 (15.3 – 61.4, n=47)
Mean Length of Surgery, mins (Range)	40.7 (11 – 131, n=78)	37.3 (12 – 100, n=47)

The n's represent actual number of patients included in each analysis. In cases where data were missing or incomplete, patients' data were not included; BMI=body-mass index

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

Pre- and Intraoperative Opioid Use was Reduced by 46%

	Control (n = 80)	SST (n = 47)
Patients Receiving Intraoperative IV opioids	97.5%	61.7%†
Pre- and Intraoperative Total Opioid Dose (MME; Mean ± SEM)[a]	20.0 ± 1.3 mg	10.9 ± 1.0 mg‡

[a]Includes MME of 5 mg IV morphine in the SST group to account for preoperative SST dosing (Miner et al., 2019);
†$p < 0.001$ via Chi Square Test;
‡$p < 0.001$ via Student's T Test;
MME = morphine milligram equivalents;
SEM=standard error of the mean

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

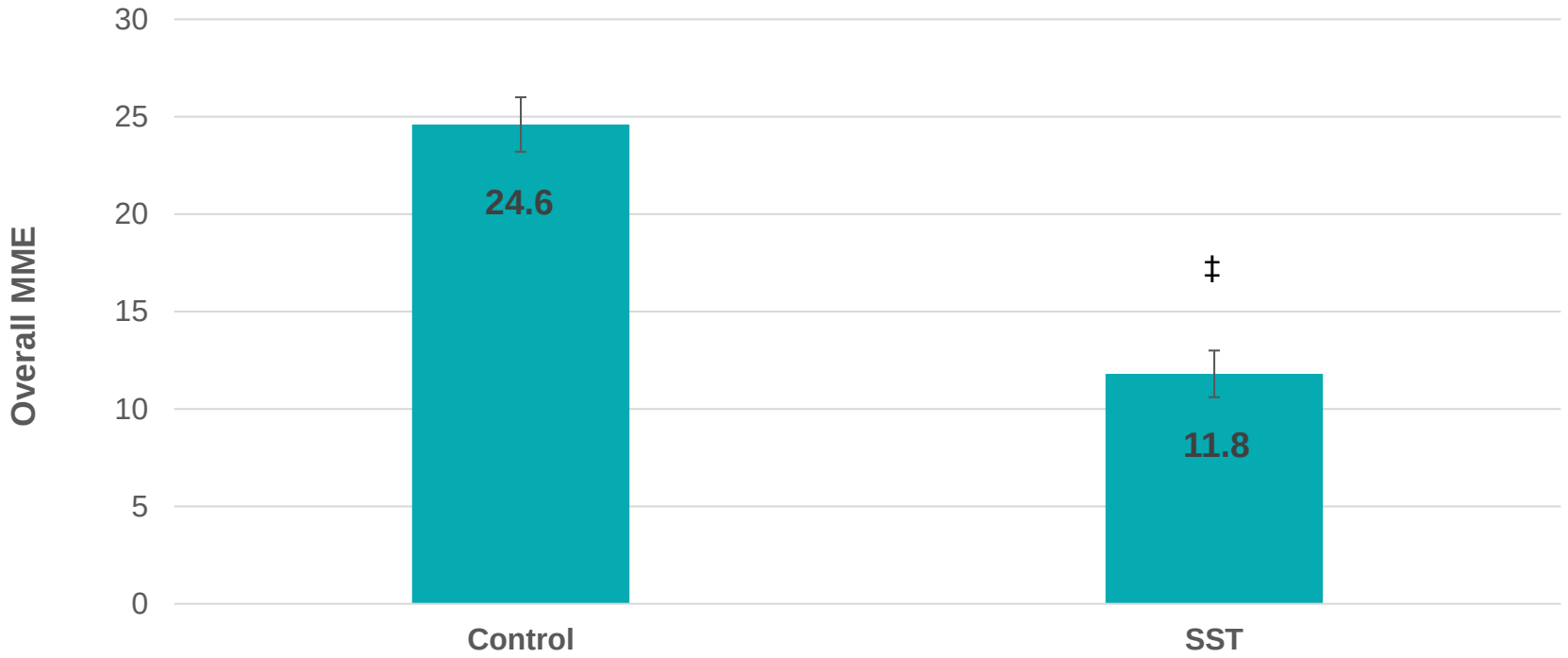
Postoperative Opioid Use was Reduced by 80%

	Control (n = 80)	SST (n = 47)
Patients Requiring Postoperative Opioids	63.0%	10.6%†
Postoperative Total Opioid Dose (MME; Mean ± SEM)[a]	4.4 ± 0.5 mg	0.9 ± 0.4 mg‡

[a]Includes IV and oral opioids administered in the post-anesthesia care unit
†$p < 0.001$ via Chi Square Test
‡$p < 0.001$ via Student's T Test
MME=morphine milligram equivalents; SEM=standard error of the mean

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

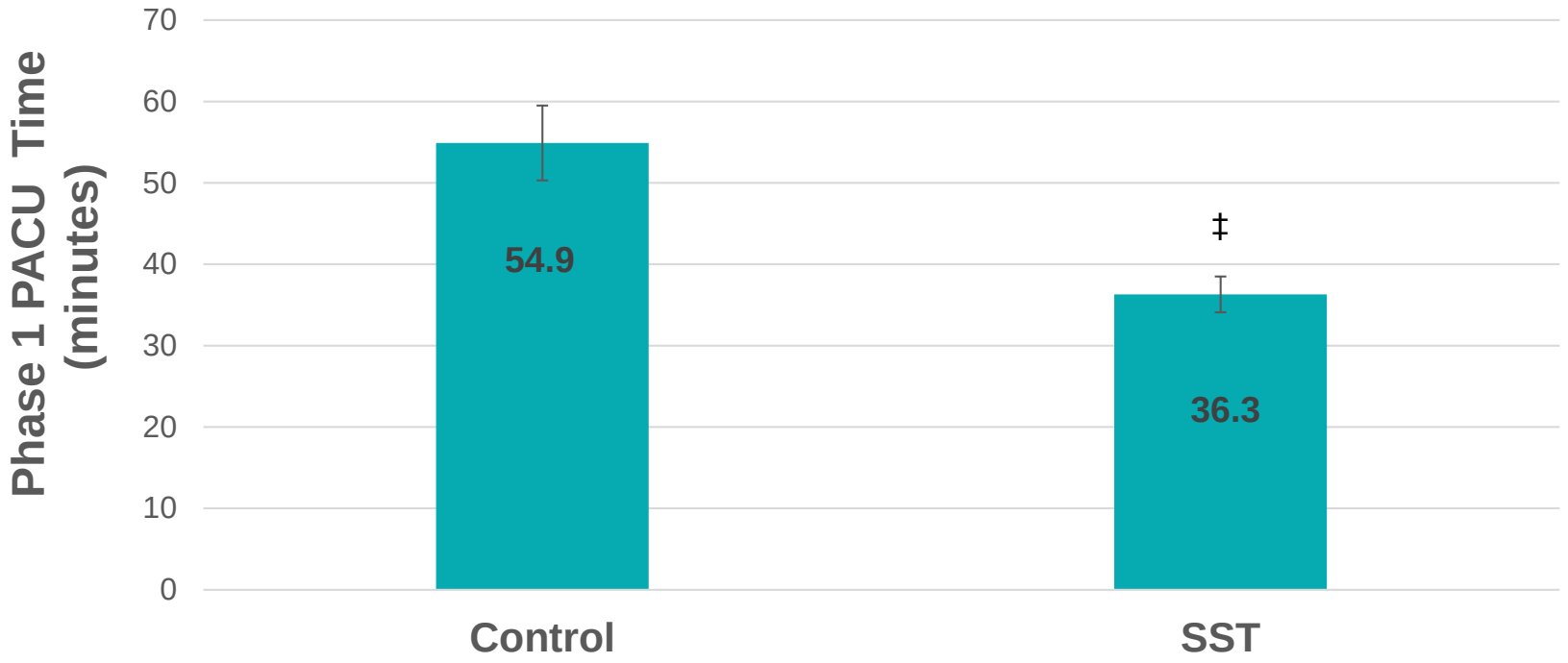
Overall Morphine Milligram Equivalents Utilized from Preoperative to PACU Discharge



Data presented as mean ± standard error of the mean
‡p < 0.001 via Student's T Test; MME=morphine milligram equivalents

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

Phase 1 Postanesthesia Care Unit Time



Data presented as mean ± standard error of the mean
‡ p < 0.001 via Student's T Test; PACU=postanesthesia care unit

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

Patients Receiving Supplemental IV Medication

	Controls (n = 80)	SST (n = 47)
Adrenergic Agonist Use[a]	40%	19%†
IV Acetaminophen	90%	38%‡
Naloxone	0%	0%

[a]ephedrine, norepinephrine, or phenylephrine
†p = 0.015 via Chi Square Test
‡p < 0.001 via Chi Square Test

Reduced Opioid Use and Reduced Time in the Post Anesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

Adverse Event Profile

- Due to a lack of consistent adverse event reporting for historical controls, no comparisons can be made
  - No patient required naloxone or any other treatment for respiratory depression
  - Overall, DSUVIA was well tolerated as evidenced by shorter PACU times

Pharmacoeconomic Analysis of Tvetenstrand et al., 2020

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Reduced Opioid Use and Reduced Time in the Postanesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

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[1]Southern Tier Surgical Clinic, Johnson City, NY, USA

[2]United Health Services, Johnson City, NY, USA

[1]Paid consultant of AcelRx Pharmaceuticals

Pharmacoeconomic Analysis

- DSUVIA is more expensive than generic injectable opioids, such as IV fentanyl or IV morphine
- While showing reduced overall opioid exposure is advantageous from an opioid stewardship perspective, better patient care does not have to come at a higher price tag
- Wholesale Acquisition Cost of DSUVIA = $58.31[1]
- Cost is offset by reduced expenditures in other areas:
  - Decreased supplemental IV medications
  - Decreased PACU discharge time
- The intent of presenting this economic information is to portray the experience one site had when they added DSUVIA to their treatment armamentarium - results may vary

[1]Symphony Health Wholesale Acquisition Cost database, 2020 for DSUVIA 30 mcg (AcelRx)

IV Opioids

Intraoperatively

- 9.1 mg of additional morphine milligram equivalents (MME) was required in the control group
- Typically IV fentanyl is utilized as the intraoperative opioid
- The smallest vial is a 2 mL vial of 50 mcg/cc = 100 mcg which is equivalent to 10 MME[2]

ADDITIONAL COST = $2

Intraoperatively	Control (n = 80)	SST (n = 47)
Patients Receiving Intraoperative IV opioids	97.5%	61.7%
Pre- and Intraoperative Total Opioid Dose (MME; Mean ± SEM)	20.0 ± 1.3 mg	10.9 ± 1.0 mg

2. Symphony Health Wholesale Acquisition Cost database, 2020 for fentanyl 100 mcg/2mL (Acorn)

IV Opioids

Postoperatively

- 52% more patients in the PACU used opioids in the control group than DSUVIA-treated patients (63% vs 11%)
- Both groups used less than 10 MME on average
- Typically IV fentanyl is used in Phase 1 of PACU with smallest fentanyl vial $2[2] x 52% greater use in control group

ADDITIONAL COST = $1

Postoperatively	Control (n = 80)	SST (n = 47)
Patients Requiring Postoperative Opioids	63.0%	10.6%
Postoperative Total Opioid Dose (MME; Mean ± SEM)	4.4 ± 0.5 mg	0.9 ± 0.4 mg

2. Symphony Health Wholesale Acquisition Cost database, 2020 for fentanyl 100 mcg/2mL (Acorn)

Additional Drugs Required in Control Group Patients

- IV Acetaminophen:
  - $47/1 g dose[3] x 52% greater use in control group

  ADDITIONAL COST = $24

- IV Adrenergic Stimulants:
  - ephedrine $29/50 mg[4] x 21% greater use in control group

  ADDITIONAL COST = $6

	Controls (n = 80)	SST (n = 47)
Adrenergic Agonist Use[a]	40%	19%
IV Acetaminophen	90%	38%
Naloxone	0%	0%

3. Symphony Health Wholesale Acquisition Cost database, 2020 for Ofirmev 1000 mg/100 mL (Mallinckrodt)
4. Symphony Health Wholesale Acquisition Cost database, 2020 for ephedrine 50 mg/mL (Par Pharma)

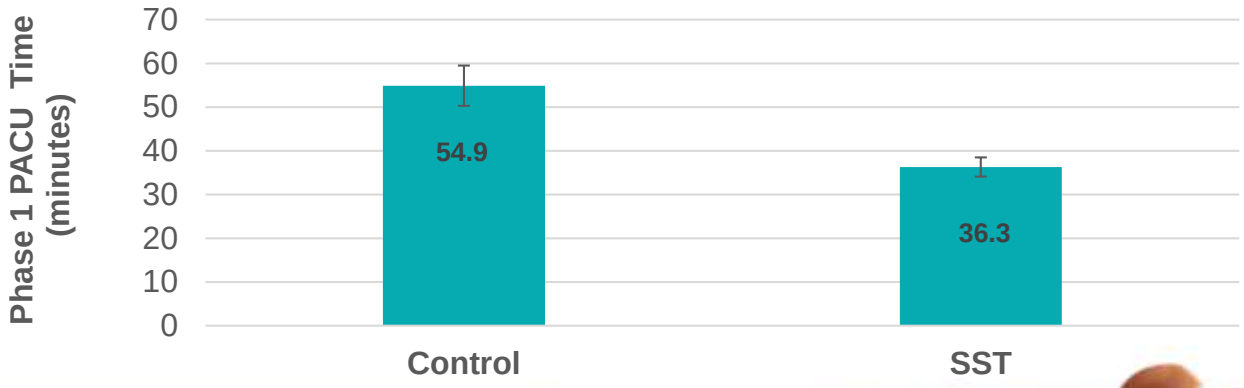
Cost of additional PACU time required in control group patients:

- Control group
  - Additional Phase 1 PACU recovery time: 18.6 minutes
  - Cost of ASC PACU time = $7 per minute[5] if PACU bed availability is not limiting OR surgical cases

ADDITIONAL COST = $130

- Add an additional $15 per minute[6] if lack of PACU bed availability leads to decreased operating room efficiency due to loss of indirect overhead revenues.

ADDITIONAL COST = $279 if PACU bed availability limits OR cases



5. https://www.beckershospitalreview.com/november-ceo-roundtable-conference/docs/Wednesday,%20November%2018/Track%20D/2_Wed_945am_OR_Efficiency_&_Cost_Effectiveness.pdf
6. Childers CP, Maggard-Gibbons M. Understanding costs of care in the operating room. JAMA Surg 2018;153(4):e176233.

Summary

- While the cost of IV fentanyl per 100 mcg dose is low, the rapid peak following IV bolus administration results in increased use of ephedrine and other vasopressors to maintain blood pressure and heart rate during surgery
- The short duration of action results in frequent redosing, which overall increases the exposure to opioids throughout the study
- The short duration of action also leads to frequent breakthrough pain, which resulted in more use of IV acetaminophen
- The DSUVIA-treated patients required little to no PACU opioid dosing and had shorter PACU stays

The reduction in supplemental IV medications (opioids, acetaminophen and ephedrine) and the decreased PACU time create

Cost savings observed with DSUVIA of $163 - $58 = $105

If delayed discharge from the PACU becomes the limiting factor for surgical productivity

Cost savings is increased to $442 - $58 = $384

DSUVIA® Use Across Surgical Subspecialties

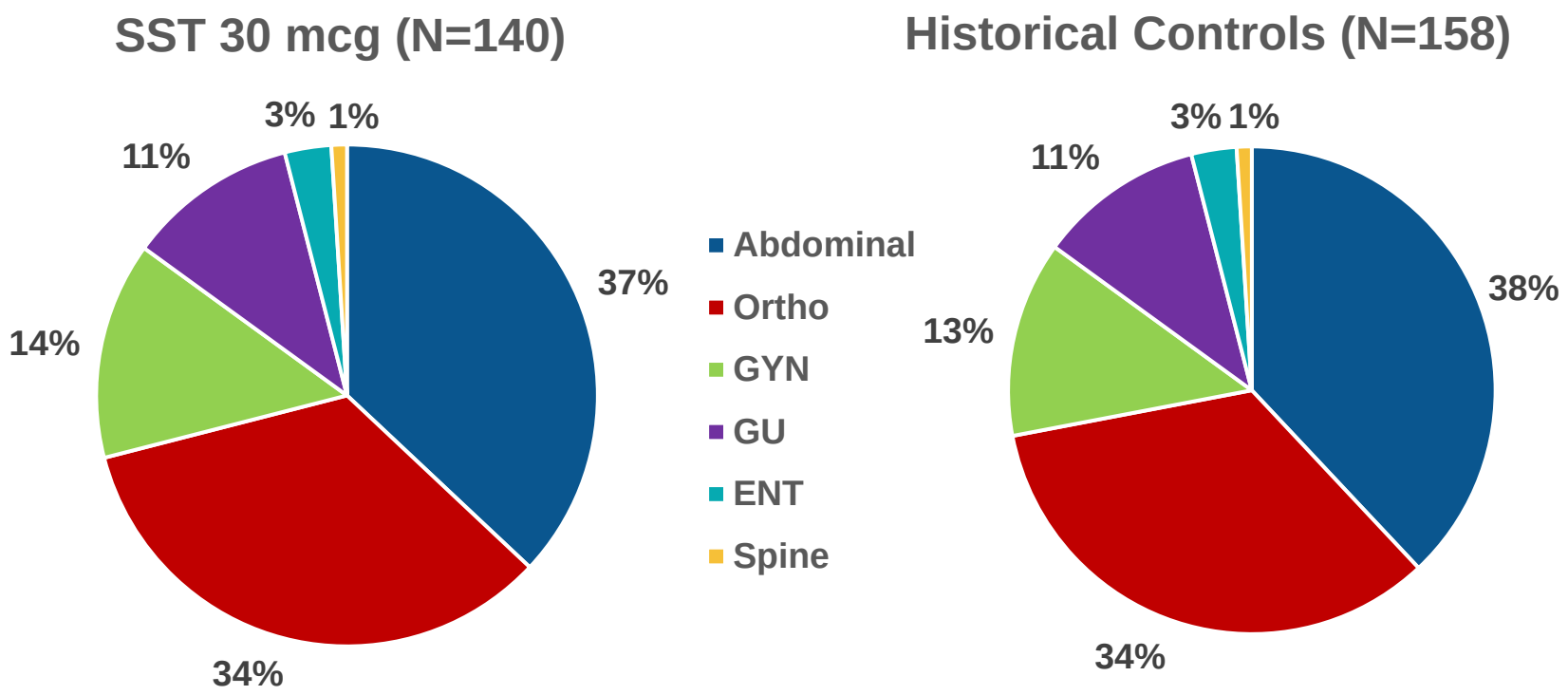
Koth Cassavaugh, PharmD
Director of Pharmacy
Auburn Community Hospital,
Auburn NY

Patient Characteristics

Patient Demographics	SST 30 mcg (N=140)	Historical Controls (N=158)
Sex (female)	68%	70%
Age, years (mean [SD])	49.6 [6.5]	52.0 [18.4]
Weight, kg (mean[SD])	93.3 [27.7]	93.4 [24.1]

Sufentanil Sublingual Tablet 30 mcg (SST 30 mcg)

Surgical Procedures Studied



Dosing of SST 30 mcg During the Study Period: 90% of Patients Received 1 Dose of SST 30 mcg

The vast majority (137/140) received SST 30 mcg preoperatively, approximately 15 min prior to intubation, or intraoperatively 30 min prior to extubation for longer duration surgeries.

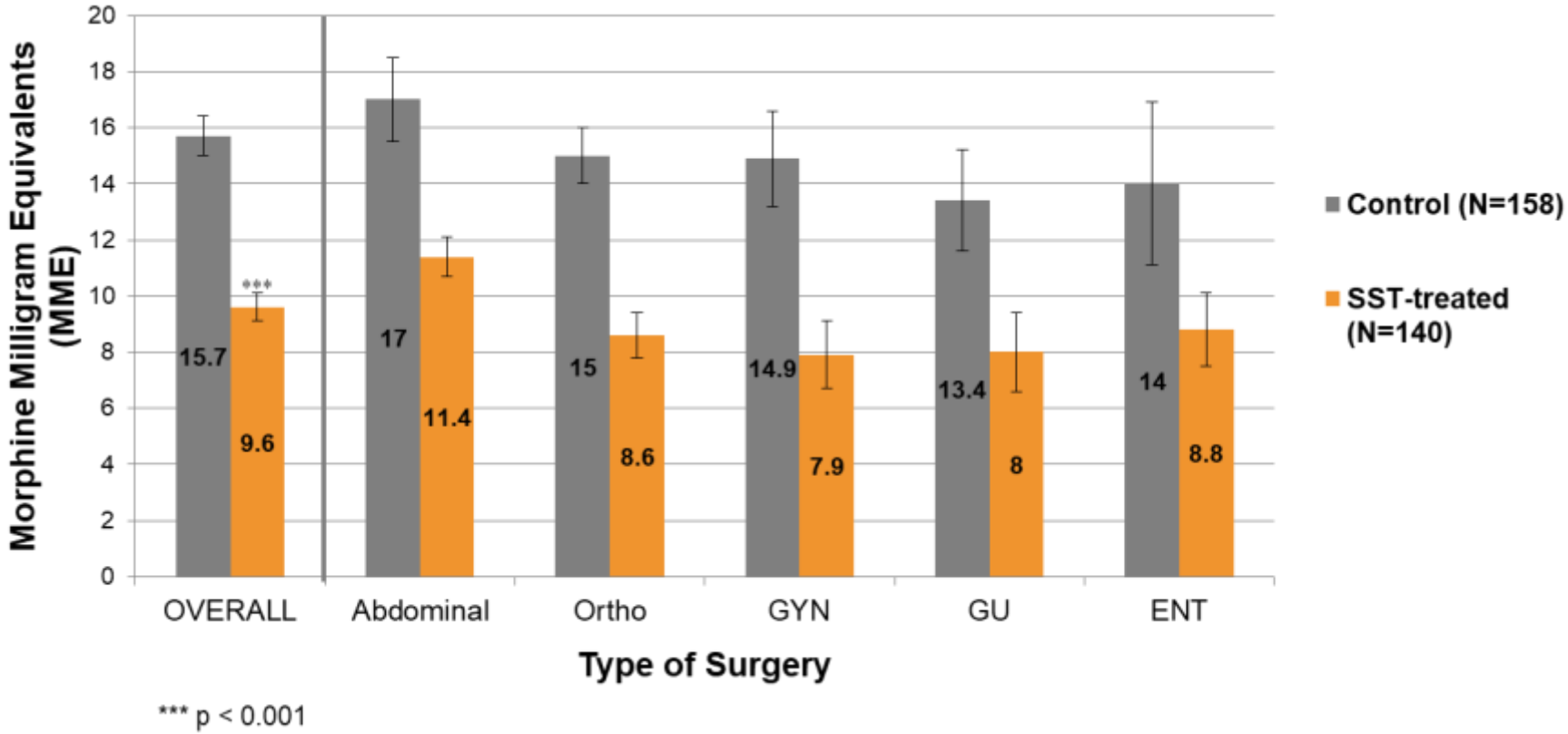
The 140 SST 30 mcg treated patients received a total of 154 doses during the study period.

- Fourteen patients required a second dose of SST in the PACU* (these doses were included in the total MME for each patient).
- Three patients received a single dose of SST 30 mcg only in the PACU.

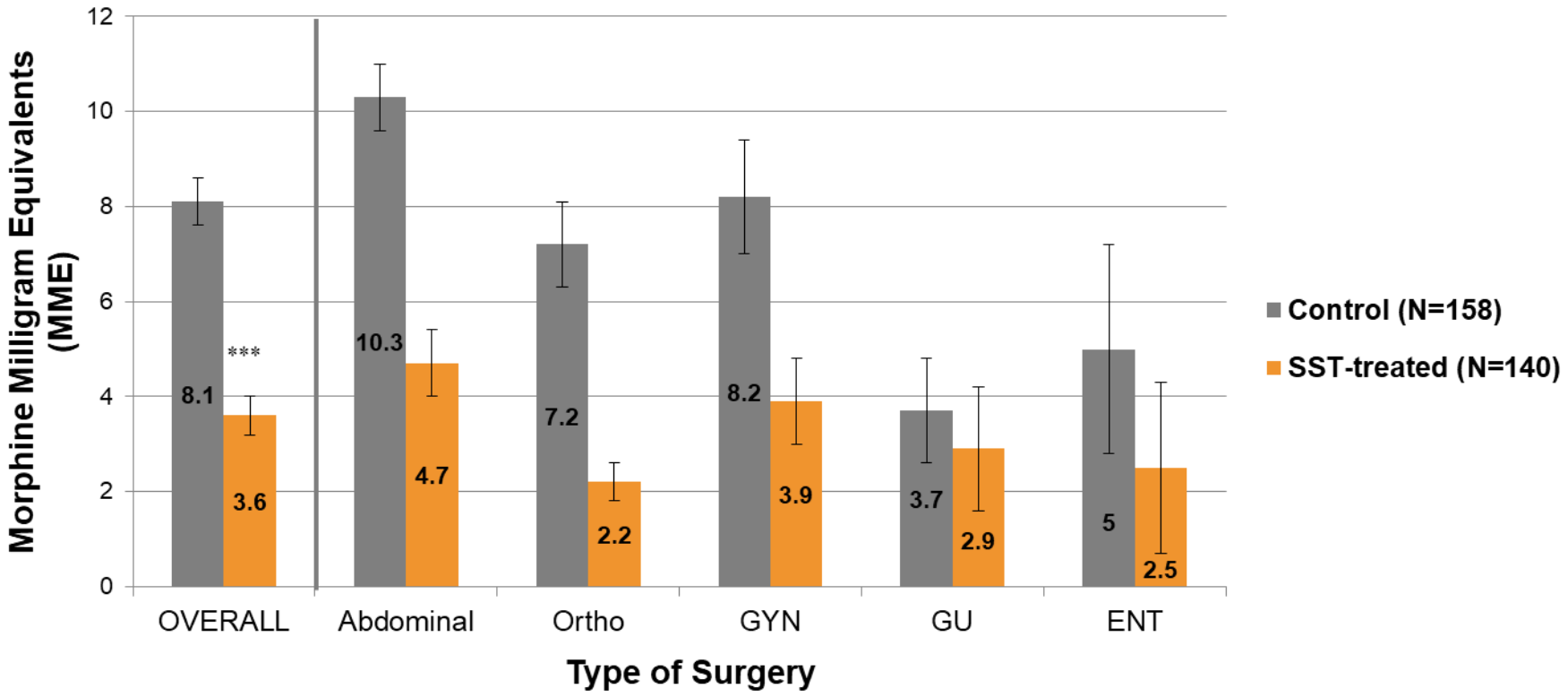
*9 of the 14 doses were within the first 3 weeks of use

https://opioidcalculator.practicalpainmanagement.com/

Reduced Intraoperative Use of IV Opioids Associated with SST 30 mcg

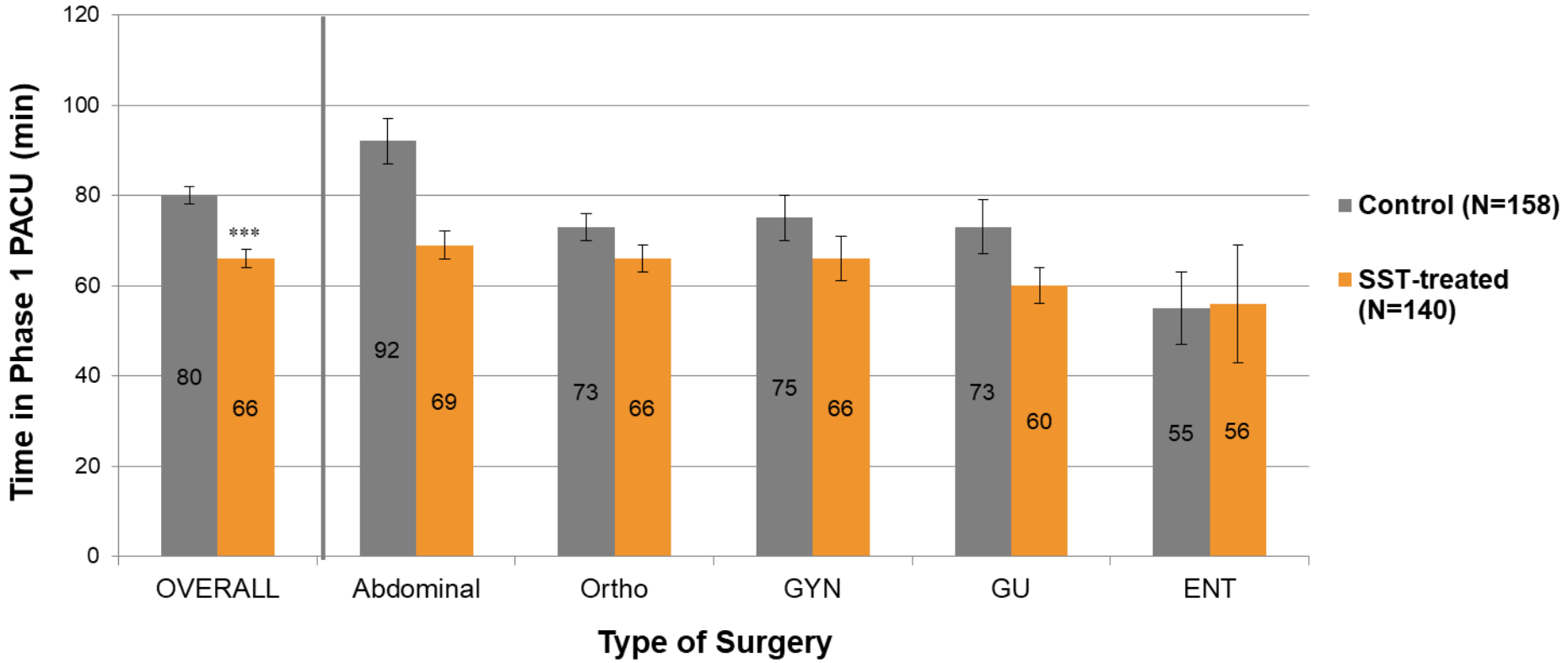


Greater than 50% Reduction in Postoperative MMEs Associated with SST 30 mcg



*** p < 0.001

Reduction of PACU Time Associated With Use of SST 30 mcg



*** p < 0.001

Related Adverse Events

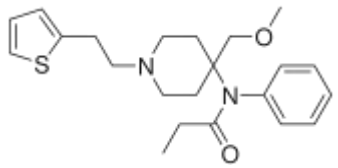
Adverse Event Intervention	SST 30 mcg (N=140)	Historical Controls (N=158)
Antiemetic Use‡ (n)*	10% (14) **	16.5% (26) **
Naloxone [for O_2 sat < 94%] (n)	0% (0)	2% (3)

‡ promethazine; ondansetron
* p=0.10
** 2 patients in the SST 30 mcg group and 6 patients in the historical control group received both antiemetics

Questions?

Sufentanil molecule and sublingual administration combine to create DSUVIA's unique pharmacokinetics and pharmacodynamics

Sufentanil



Lipophilic (fat-loving)

High therapeutic index
(Lethal Dose/Effective Dose)

Sublingual Administration

Low peak plasma concentration

Onset

Duration

AE profile

Cognition

Lower MME
(morphine milligram equivalents)

Enhanced recovery for patient

Reduced patient discharge time