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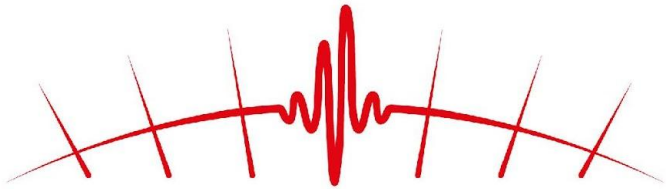
SIMEU

Nuove opzioni: il Sufentanil

Spampinato Michele Domenico



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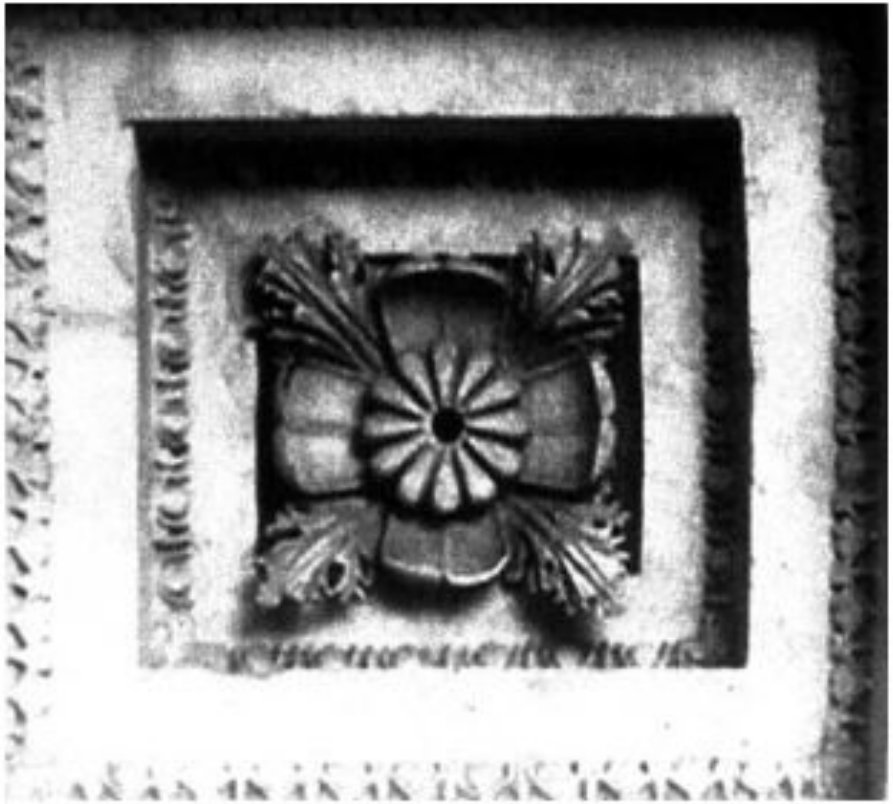
Io sottoscritto
Spampinato Michele Domenico

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009

dichiara

di non aver avuto rapporti di finanziamento
con soggetti portatori di interessi commerciali in campo sanitario

IV secolo a.C. Esculapio guarisce toccando la spalla del paziente durante un atto di “enkoimesis”, mentre una sacerdotessa, che funge da infermiera, guarda. Dal Museo Archeologico del Pireo



380 a.c: Cofanetto di papavero che presenta un fiore aperto di Papaver somniferum che ornava l'edificio di Tholos nell'Asclepieion di Epidauros. Dal Museo Archeologico di Epidauros

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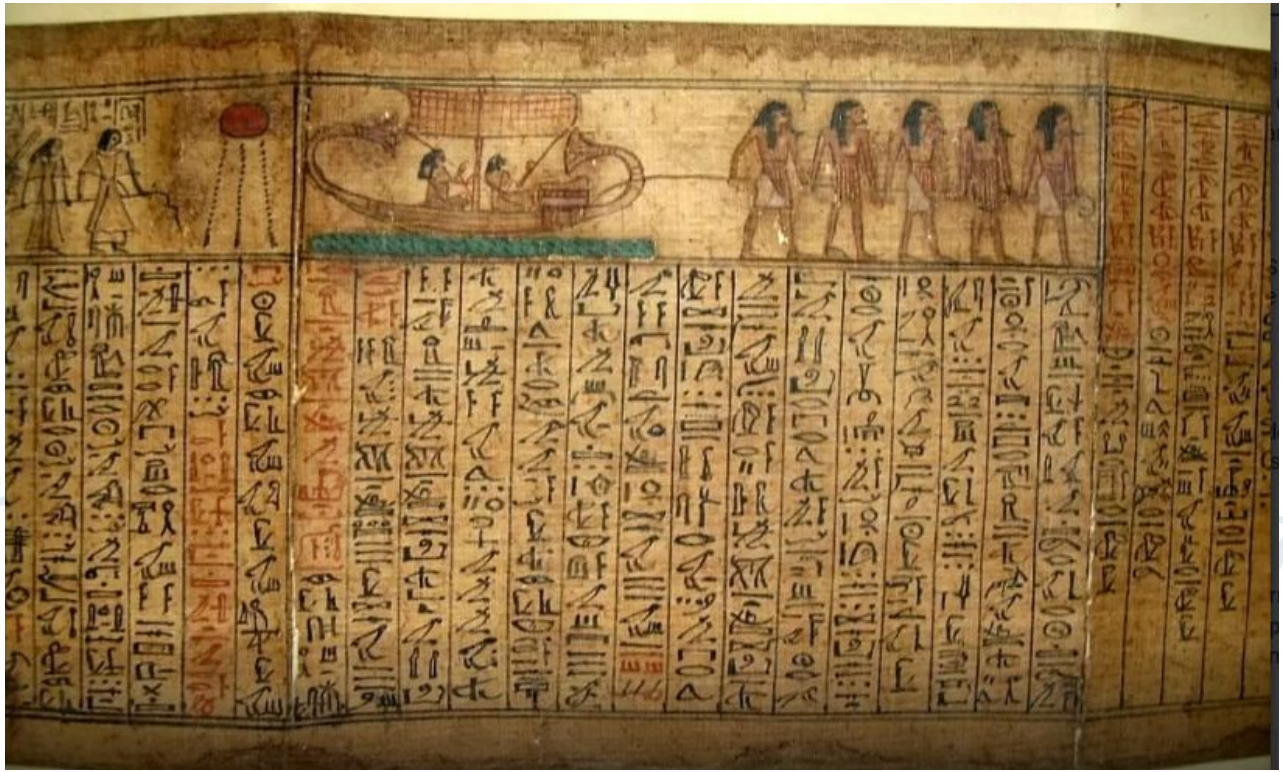
I primo riferimento alla crescita e all'uso dell'oppio risale al 3.400 a.C., quando il papavero da oppio veniva coltivato nella bassa Mesopotamia (Asia sud-occidentale). I Sumeri lo chiamavano Hul Gil, la "pianta della gioia".



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Papiro di Ebers
Trattato di farmacologia e terapia del dolore

Festa dell'anno nuovo, 3º mese di shmu, 9º giorno, levata di Sodpu, 9º anno di regno di Amenhotep I., 1550 a.C. - 1530 a.C..

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Il dolore è malattia
"Sine opio medicina claudicat", Galeno, 129-200 a. C.
Primo Maestro di Anagni, Ippocrate e Galeno, 1231-1255

.

“Infirmorum cura ante omnia et super omnia…”

“Aiuto ipnotico, cioè soporifero, è utile a coloro i quali si curano per mezzo della chirurgia, in maniera che, addormentati, non sentano il dolore del taglio. Si prendano queste cose: *mezza oncia di oppio tebaico, 8 di succo di mandragora, mezza oncia di succo della verde erba di Matala, e di succo di verde giusquiamo*, raccogli così, per mezzo di una spugna essiccata, un’unica pasta e diligentemente lascia asciugare; e quando vorrai farne uso a mezzo della stessa spugna per un’ora immergila in acqua calda e avvicinala alle narici ed avvertirai il paziente che da sé stesso assorba quella essenza per dormire a lungo e, quando lo vorrai risvegliare, applicherai alle sue narici un’altra spugna imbevuta di aceto caldo e potrai, così, scacciare il sonno”

San Benedetto da Norcia, 480-547 d.C..

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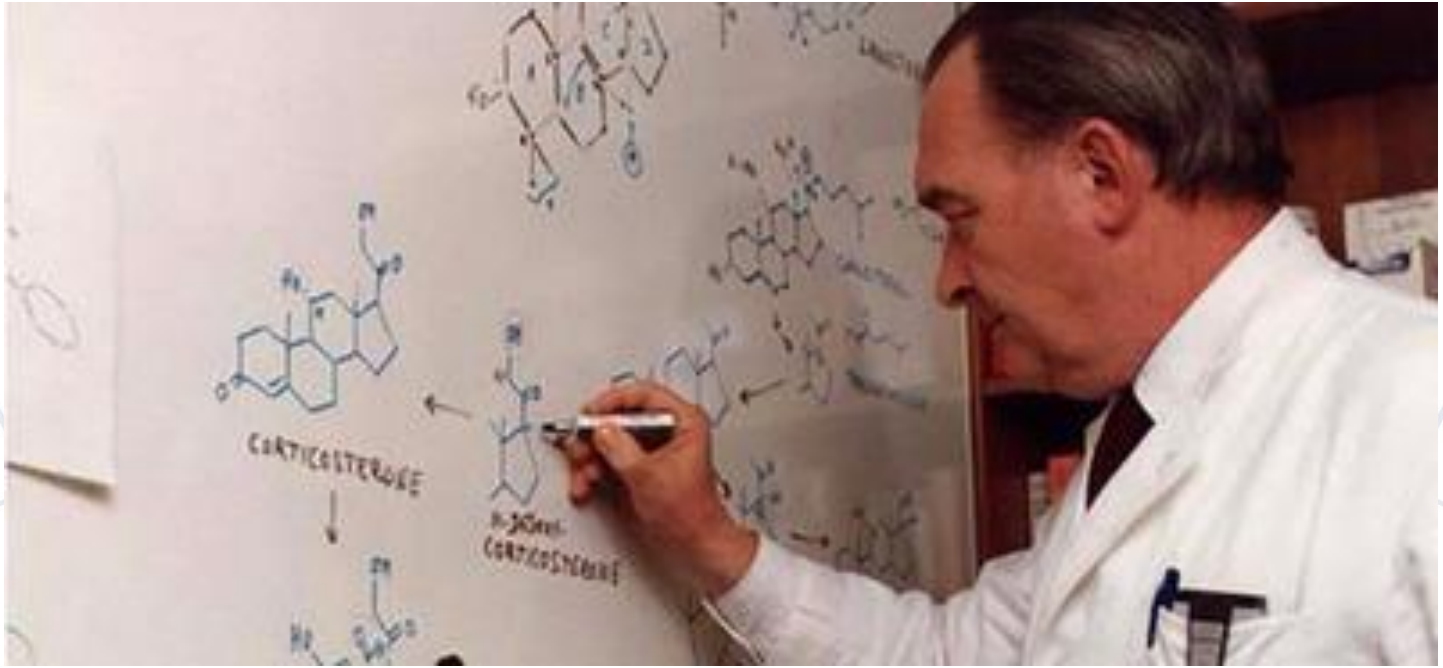
“E’ da rilevare che l’oppio, il giusquiamo e la mandragora producono una profonda sonnolenza, a causa della loro grande umidità, se fate con esse un cataplasma e lo ponete sul luogo dell’incisione esso abolirà completamente la sensibilità per cui il dolore di qualunque specie non viene avvertito”

Scuola Salernitana e Salerno come “Civitas Hippocratica”, prima Università medica, Federico II, 1231.

1803: il farmacista tedesco Friedrich Sertürner isola la morfina dall'oppio.

Gustav Ehrhart (1894-1971)
1939, sintesi del Metadone

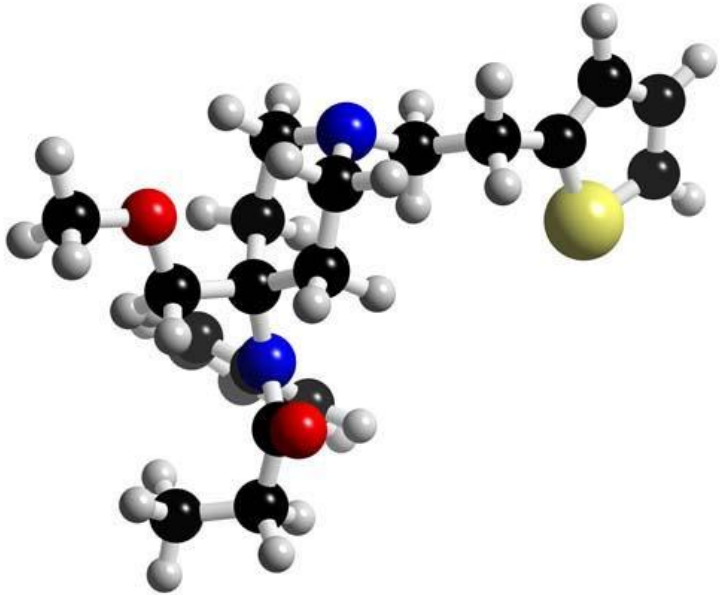


1959 - Sintesi del Fentanyl, Dr. Paul Janssen

"Scegliete la vita, scegliete un lavoro, scegliete una carriera, scegliete la famiglia, scegliete un maxitelevisore del cazzo, scegliete lavatrice, macchina, lettore cd e apriscatole elettrici. Scegliete la buona salute, il colesterolo basso e la polizza vita; scegliete mutuo a interessi fissi, scegliete una prima casa, scegliete gli amici. Scegliete una moda casual e le valigie in tinta, scegliete un salotto di tre pezzi a rate e ricopritelo con una stoffa del cazzo, scegliete il fai-da-te e il chiedetevi chi siete la domenica mattina. Scegliete di sedervi sul divano a spappolarvi il cervello e lo spirito con i quiz, mentre vi ingozzate di schifezze da mangiare. Alla fine scegliete di marcire, di tirare le cuoia in uno squallido ospizio, ridotti a motivo di imbarazzo di stronzetti viziati ed egoisti che avete figliato per rimpiazzarvi. Scegliete il futuro, scegliete la vita. Ma perché dovrei fare una cosa cosí?

World Health Organization
Model List of Essential Medicines

2.2 Opioid analgesics	
codeine	**Tablet:** 30 mg (phosphate).
fentanyl*	**Transdermal patch:** 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr. *For the management of cancer pain
☐ morphine Therapeutic alternatives: - hydromorphone - oxycodone	**Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. **Oral liquid:** 10 mg/5 mL (morphine hydrochloride or morphine sulfate). **Tablet (slow release):** 10 mg to 200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate).
Complementary list	
*methadone**	***Tablet:*** *5 mg; 10 mg (hydrochloride)* ***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL (hydrochloride)* ***Concentrate for oral liquid:*** *5 mg/mL; 10 mg/mL (hydrochloride)* **For the management of cancer pain.*



$C_{22}H_{30}N_2O_2S$

Analgesico oppiaceo; Anilidopiperidina; Anestetico generale

Sufentanil: Drug information

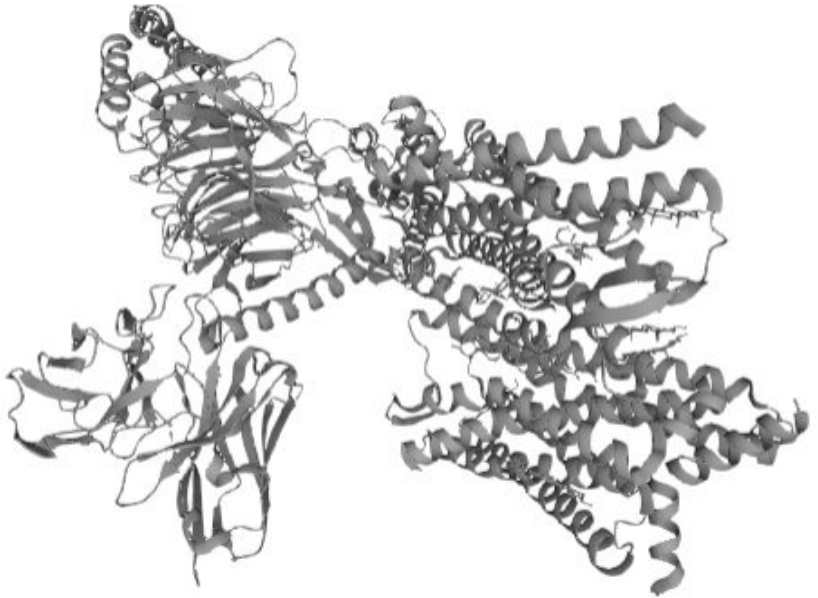
Acute pain management (sublingual tablet): Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate

Limitations of use: Because of the risks of substance use disorder, abuse, and misuse with opioids, which may occur at any dosage or duration, reserve sufentanil for use in patients for whom alternative treatment options (eg, nonopioid analgesics, opioid combination products) have not been tolerated or are not expected to be tolerated, have not provided adequate analgesia, or are not expected to provide adequate analgesia. Administer by health care provider in a health care setting (eg, hospital, surgical center, emergency department) only; not for home use. Do not administer >72 hours (has not been studied).

Epidural analgesia (injection): For epidural administration as an analgesic combined with low-dose bupivacaine during labor and vaginal delivery.

Surgical analgesia (injection): Analgesic adjunct for the maintenance of balanced general anesthesia in patients who are intubated and ventilated.

Surgical anesthesia (injection): As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures; in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position; to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.



Recommended name: Mu-type opioid receptor
Short names: M-OR-1; MOR-1
Organism: Homo sapiens (Human)

Taxonomic lineage
cellular organisms > Eukaryota (eucaryotes) > Opisthokonta > Metazoa (metazoans) > Eumetazoa > Bilateria > Deuterostomia > Chordata (chordates) > Craniata > Vertebrata (vertebrates) > Gnathostomata (jawed vertebrates) > Teleostomi > Euteleostomi (bony vertebrates) > Sarcopterygii > Dipnotetrapodomorpha > Tetrapoda (tetrapods) > Amniota (amniotes) > Mammalia (mammals) > Theria > Eutheria (placentals) > Boreoeutheria > Euarchontoglires > Primates > Haplorrhini > Simiiformes > Catarrhini > Hominoidea (apes) > Hominidae (great apes) > Homininae > Homo

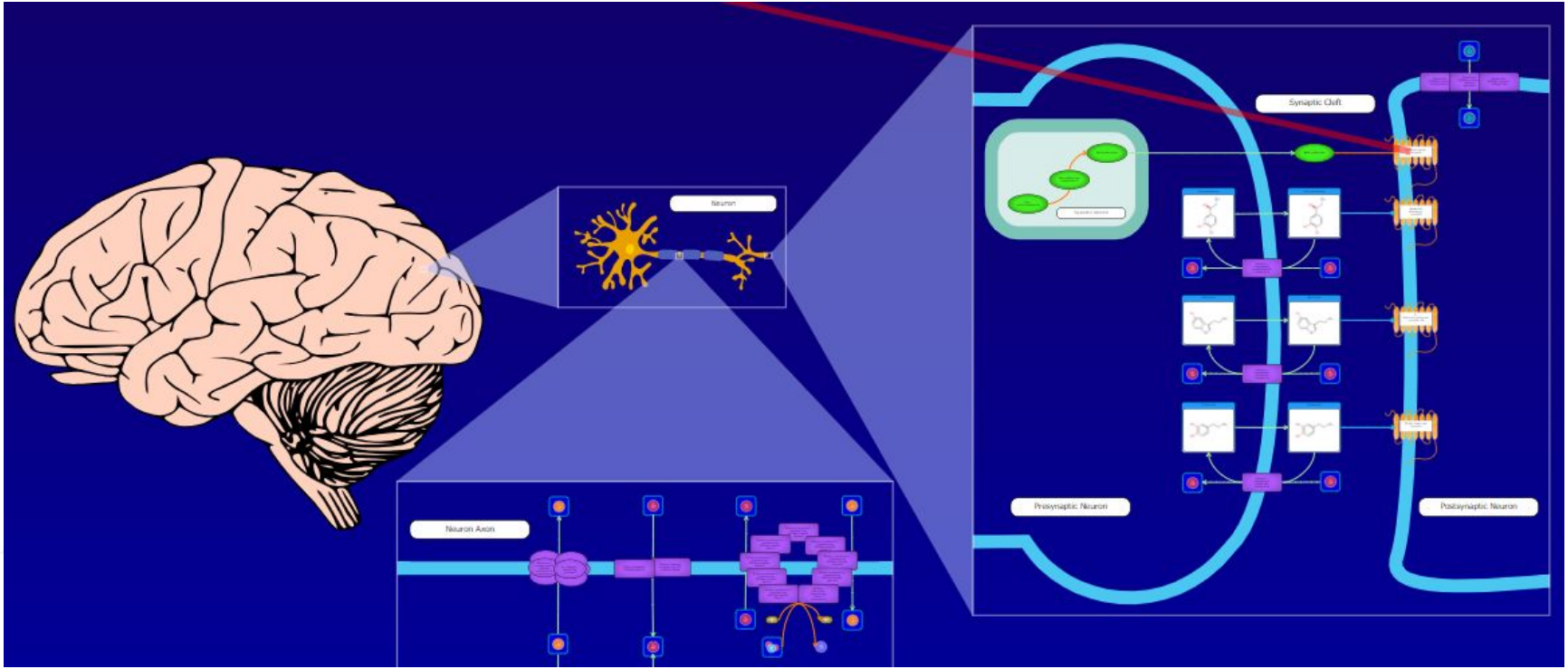


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Table I. Physicochemical properties and pharmacokinetics of alfentanil, fentanyl, and sufentanil compared with morphine after bolus administration as a single representative mean.[11-13] It has to be mentioned that these parameters are characterised by a great variability which is not included in the table

Parameters	Alfentanil	Fentanyl	Sufentanil	Morphine
Lipid solubility (octanol/water distribution coefficient)	129	816	1727	1,4
Non-ionised fraction at pH 7.4 (%)	89	8.5	20	23
Plasma protein binding at pH 7.4 (%)	92.1	84.4	92.5	30
Analgesic onset (min)	0.75	1.5	1	7.5
Time to peak effect (%)	1.5	4.5	2.5	25
Volume of distribution (L/kg)	0.75	4.0	2.9	3.2
Distribution half-life (min)	0.4	1.7	1.4	1.65
Elimination half-life (min)	94	219	164	177
Total body clearance (L/h/kg)	0.48	0.78	0.762	0.9

Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clin Pharmacokinet. 1996;31(4):275-292. doi:10.2165/00003088-199631040-00004

	Sublinguale	Epidurale
Assorbimento	52%, 35% con dosi ripetute < 10% se ingerito	Dopo dosi di 5-40 mcg, le concentrazioni plasmatiche sono sotto il limite di determinazione di 0.05-0.1 ng/mL
Metabolismo	Epatico e piccolo intestino; rapidamente metabolizzato a metaboliti inattivi	
Emivita	dopo dose di 15 mcg, osservate emivite di 6-10 ore, fino a 18 con somministrazioni ripetute	
Tossicità	EV: LD_{50}: 18.7 mg/kg	
	Carcinogenesi: non nota, mutagenesi: non evidenziata in batteri in vitro, Embrione: sui ratti, se trattata con dosi 2.5-20 volte maggiori che umane durante gravidanza. Allattamento; escreto con il latte quando somministrato endovenoso, no dati disponibili. No effetto sul lattante quando somministrato via epidurale	

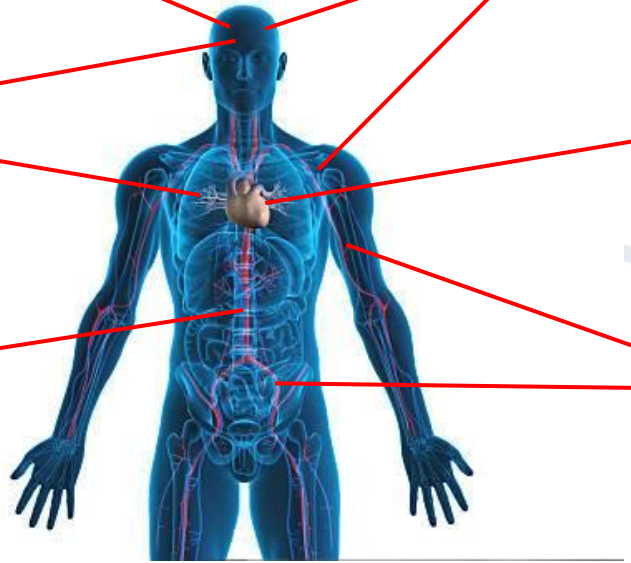
EFFETTI AVVERSI

IPNOTICO

RIGIDITÀ MUSCOLARE

DEPRESSIONE RESPIRATORIA

VASODILATAZIONE possibile BRADICARDIA



RIDUZIONE MOTILITÀ GI

PRURITO, SUDORAZIONE, VASODILATAZIONE, IPOTENSIONE

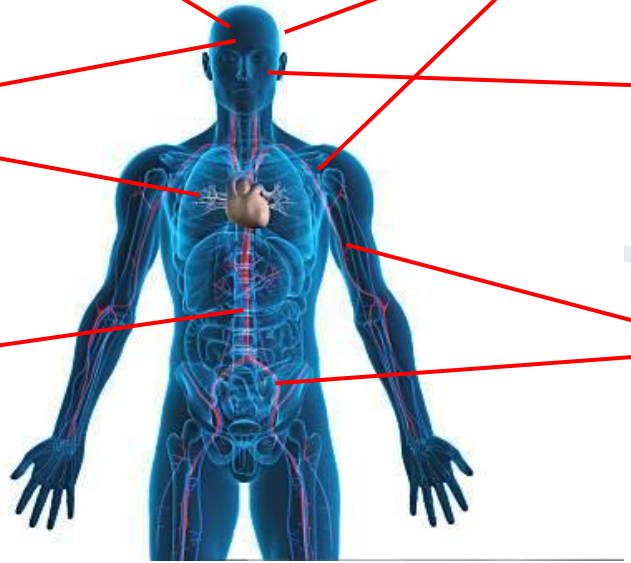
OVERDOSE

SONNOLENZA, STUPOR, COMA

FLACCIDITÀ MUSCOLARE

DEPRESSIONE RESPIRATORIA, OSTRUZIONE PARZIALE o TOTALE ALTE VIE

MIOSI → MIDRIASI MARCATA da ipossia



RIDUZIONE MOTILITÀ GI

PRURITO, SUDORAZIONE, VASODILATAZIONE, IPOTENSIONE

Marco, 47 anni

Beve e fuma, fuma e beve.
Ha bussato a mille porte, spesso alla tua, e nell'eroina l'unica casa.

Ha deciso di lasciare quella casa, ha deciso di lasciare questo mondo.

Marco, 47 anni

All’arrivo dei soccorsi :
O2, V2, M4
FR 38, SpO2 86%
FC 125, PA 80/50
Non muove le gambe
Frattura arti inferiori

---> IOT, drenato PNX, Cintura pelvica, condotto in Shock Room.

Marco, 47 anni

In Shock Room :
GCS 3 in midazolam in IC
FR 16, SpO2 98% in IOT, FiO2 40%
FC 115, PA 110/60

E-FAST: negativa
EGA: Hb 13, pH 7.25, Lac 4 mmol/L
RX: frattura bacino, frattura costale bilaterale

Marco, 47 anni

Sufentanil, EV: fiale da 50 mcg/ml

- boli da 10 - 25 mcg o 0.1-0.25 mcg/kg, con max 1 mcg/kg/ora
- IC: 0.5-1 mcg/kg/ora

Maria, 73 anni

Vive in casa da sola, non ha figli, ed una pensione che spesso non le basta all'affitto ed al cibo.
Tutte le mattine il vicino le porta la spesa, ma questa mattina bussa e non risponde.
Apre la porta, è al buio, a terra, sofferente.

Maria, 73 anni

All’arrivo dei soccorsi:
Vigile, sofferente.
FR 32, SpO2 97% in aa
FC 105, PA 150/90
Non deficit neurologici
Arto inferiore accorciato, extraruotato

Maria, 73 anni

Sufentanil, compresse sublinguali da 30 mcg:

- ***Ripetibile*** al bisogno, con intervallo minimo di 1 ora;
- Dose massima: 360 mcg/24 ore (12 compresse)
- Non utilizzare per > 72 ore


118


Accettazione Triage
Check in Triage
Accettazione Triage
Check in Triage
CODICI BIANCHI
CODES
Accoglienz
Punto Informaz
Reception
Information Point
Pronto
Soccorso
Emergency

3. FORMA FARMACEUTICA

Compressa sublinguale.

Compressa di colore blu, con superficie piatta e bordi arrotondati e un diametro di 3 mm.

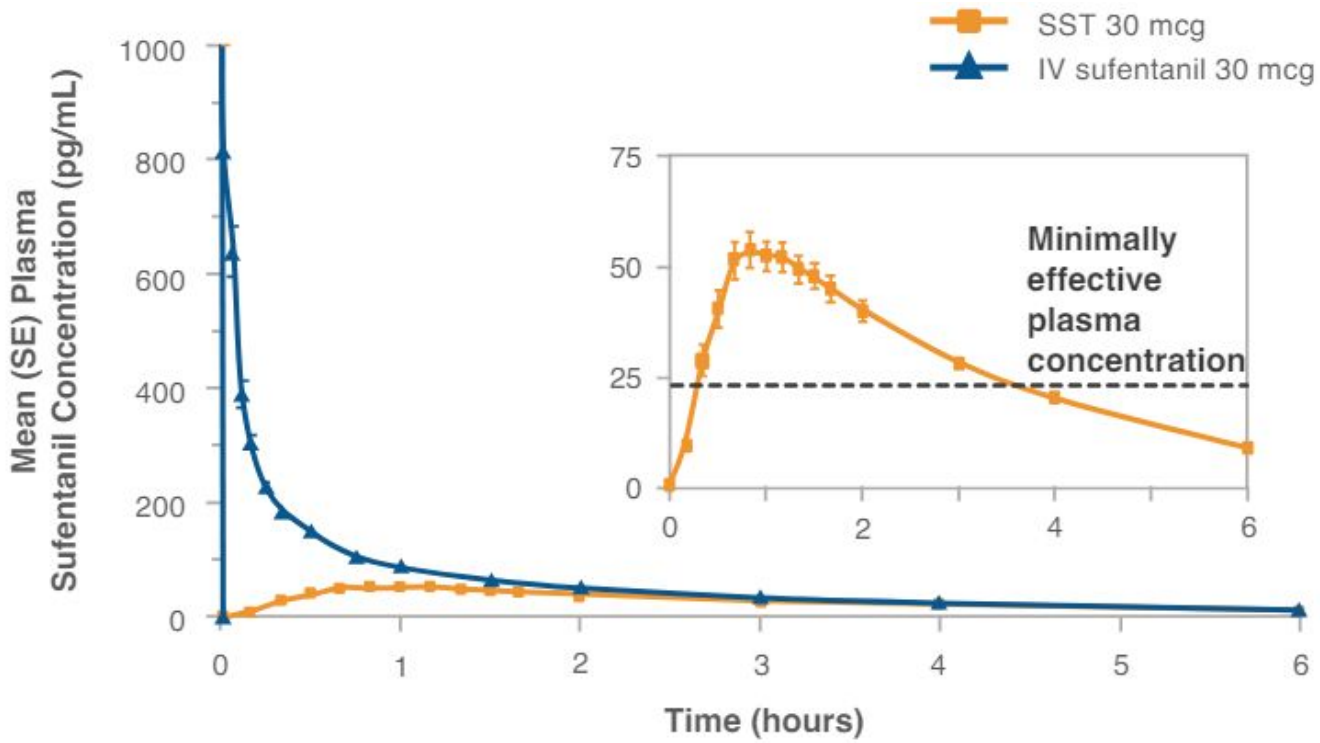
4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

[redacted] è indicato nei pazienti adulti per la gestione del dolore acuto da moderato a grave.

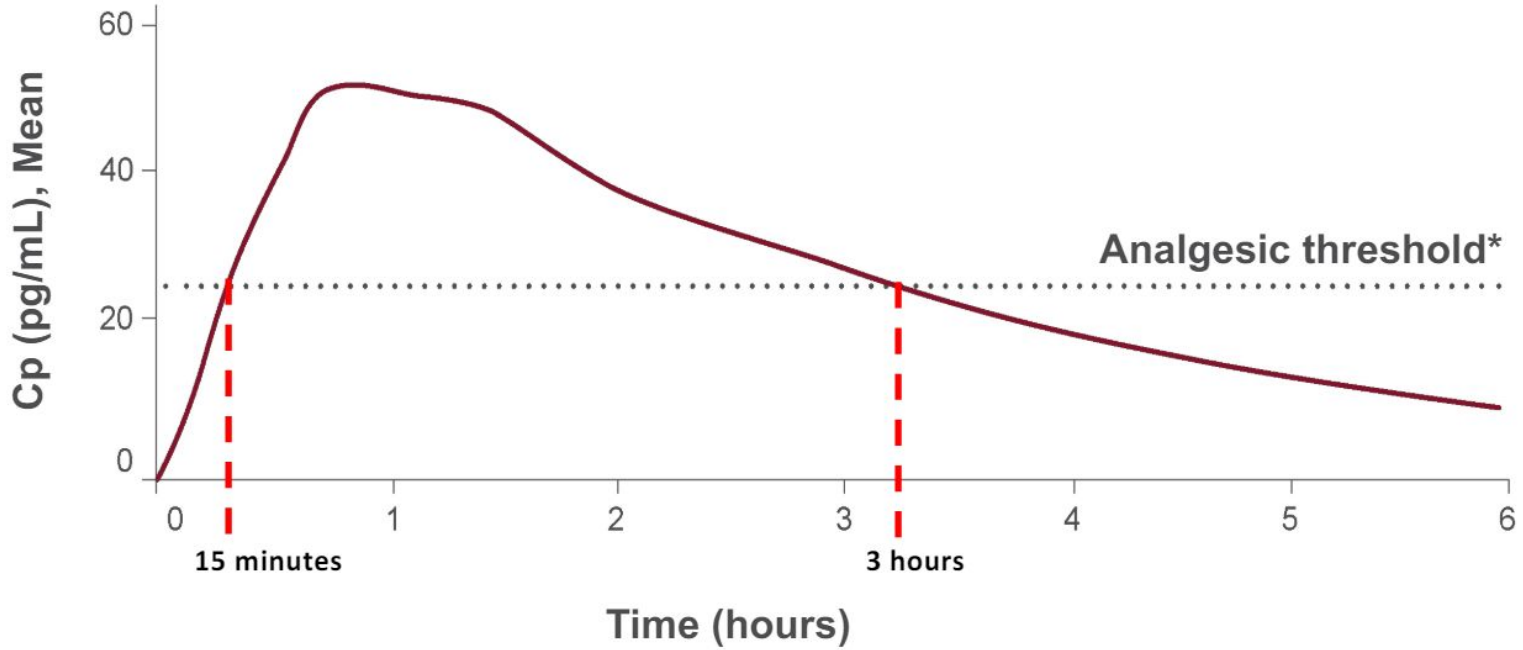
4.2 Posologia e modo di somministrazione

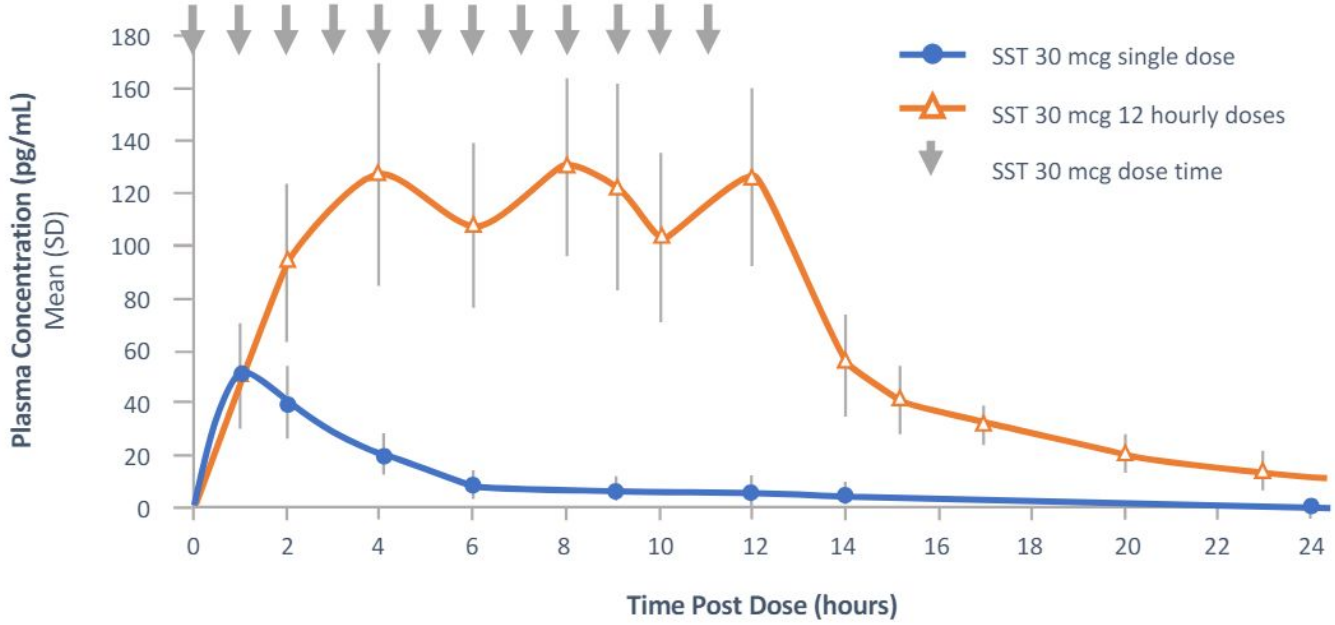
[redacted] deve essere somministrato esclusivamente da un operatore sanitario in ambiente sotto stretto controllo medico. Un ambiente simile deve essere dotato di attrezzature e di personale adeguatamente formato a individuare e a gestire l'ipoventilazione, oltre ad avere a disposizione ossigeno supplementare e antagonisti degli oppioidi, quali il naloxone. [redacted] deve essere prescritto e somministrato esclusivamente da operatori sanitari esperti nella gestione della terapia con oppioidi, in particolare delle reazioni avverse agli oppioidi, quali la depressione respiratoria (vedere paragrafo 4.4).



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

Fisher DM, et al. Anesthesiology. 2018;128(5):943-952.


Cp (pg/mL), Mean
60
40
20
0
Analgesic threshold*
0
1
2
3
4
5
6
15 minutes
3 hours
Time (hours)



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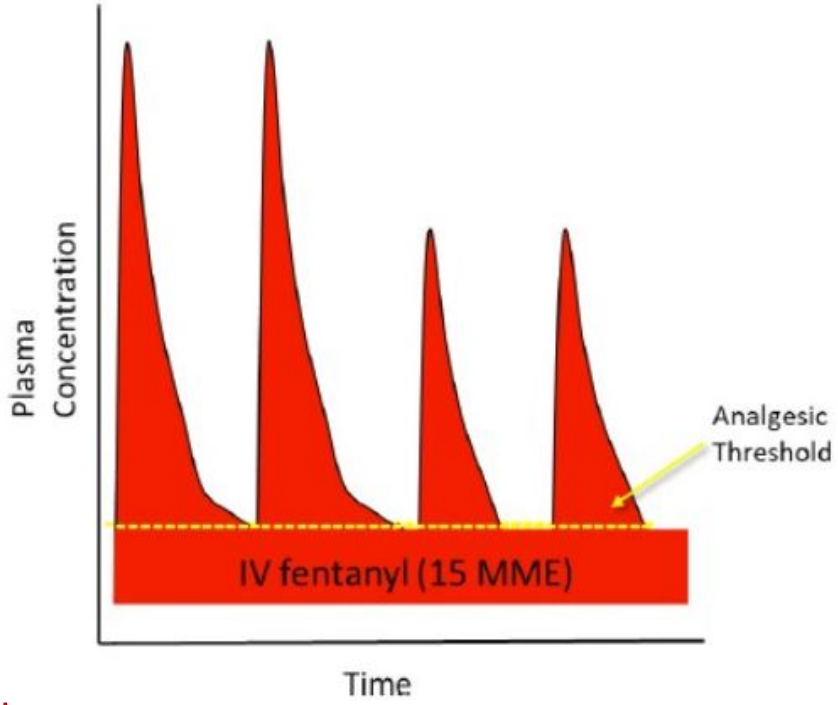
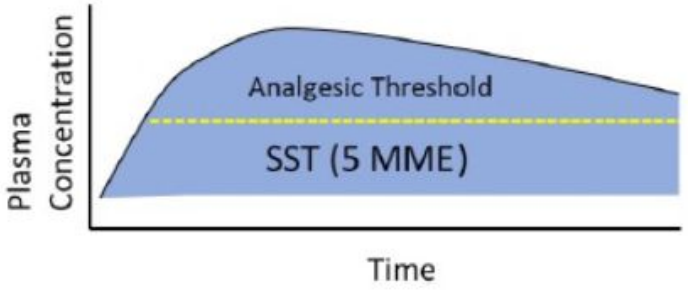

Plasma Concentration
Analgesic Threshold
IV fentanyl (15 MME)
Time


Plasma Concentration
Analgesic Threshold
SST (5 MME)
Time

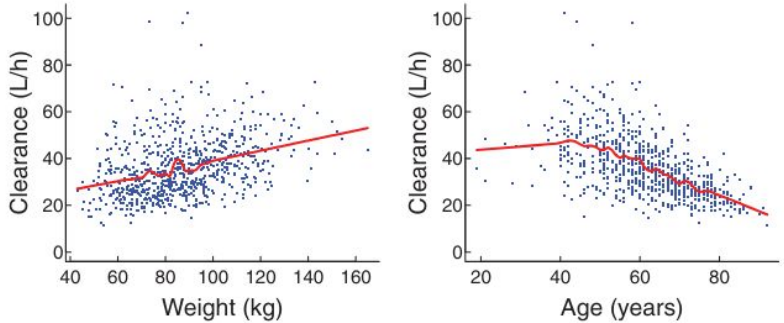


Fig. 5. Individual (*post hoc*) estimates for clearance from the optimal population pharmacokinetic model are displayed against weight (*left*) and age (*right*). The *red line* is a smoother (Supersmoother).

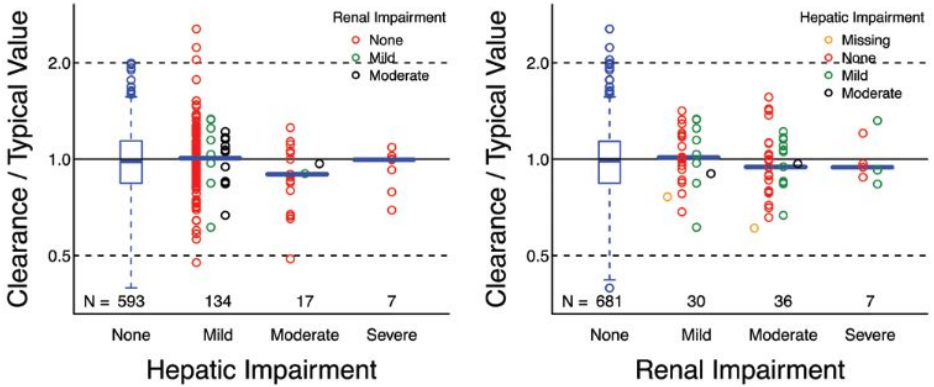


Fig. 6. The ratio of values for clearance to the typical value (log scale) are displayed as a function of hepatic (*left*) and renal impairment (*right*) in surgical patients (excluding subjects from two studies). For subjects with normal hepatic or renal function, values are displayed as a box plot. For the other groups, individual values are displayed as *circles*, color-coded to indicate

Fisher DM, et al. Anesthesiology. 2018;128(5):943-952.

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Original Contribution

Sufentanil sublingual tablet 30 mcg for moderate-to-severe acute pain in the ED

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Analgesics, opioid
Administration, oral
Clinical trial

ABSTRACT

Background: Pharmacological properties of the sufentanil sublingual tablet 30 mcg (SST 30 mcg) could offer potential analgesic advantages in settings requiring noninvasive, acute pain management. The feasibility of using SST 30 mcg for moderate-to-severe pain management in the emergency department (ED) was evaluated.
Methods: This open-label, multicenter feasibility study included patients aged ≥18 years who presented to the ED with moderate-to-severe pain (≥4 on the numeric rating scale of pain intensity (NRS); opioid-tolerant patients were excluded. Patients received a single SST 30-mcg dose (single-dose cohort) or, upon request, ≤3 additional doses ≥60 min apart (multiple-dose cohort) and were evaluated over 1 or 2 h. Effectiveness was assessed by patient-reported pain scores (11-point NRS; 5-point pain relief scale). Safety and tolerability were also assessed.
Results: Overall, 76 patients enrolled into the single-dose ($n = 40$) and multiple-dose ($n = 36$) cohorts. In the first hour (combined cohorts), mean pain intensity was significantly lower 15-min post-dosing ($P < 0.001$; clinically meaningful within 30-minutes post-dosing) and continued to decrease during the first hour ($P < 0.001$ for each 15-minute interval). Mean pain intensity (multiple-dose cohort) decreased from 7.6 at baseline to 4.5 at 1 h and to 4.6 at 2 h ($P < 0.001$ for both); mean pain relief increased from baseline to 1.9 at 1 h ($P < 0.001$) and to 2.0 at 2 h ($P < 0.001$). Most (79%) patients had no adverse events (AEs), and there were no severe AEs.
Conclusions: SST 30 mcg was feasible for managing moderate-to-severe acute pain in an ED setting.

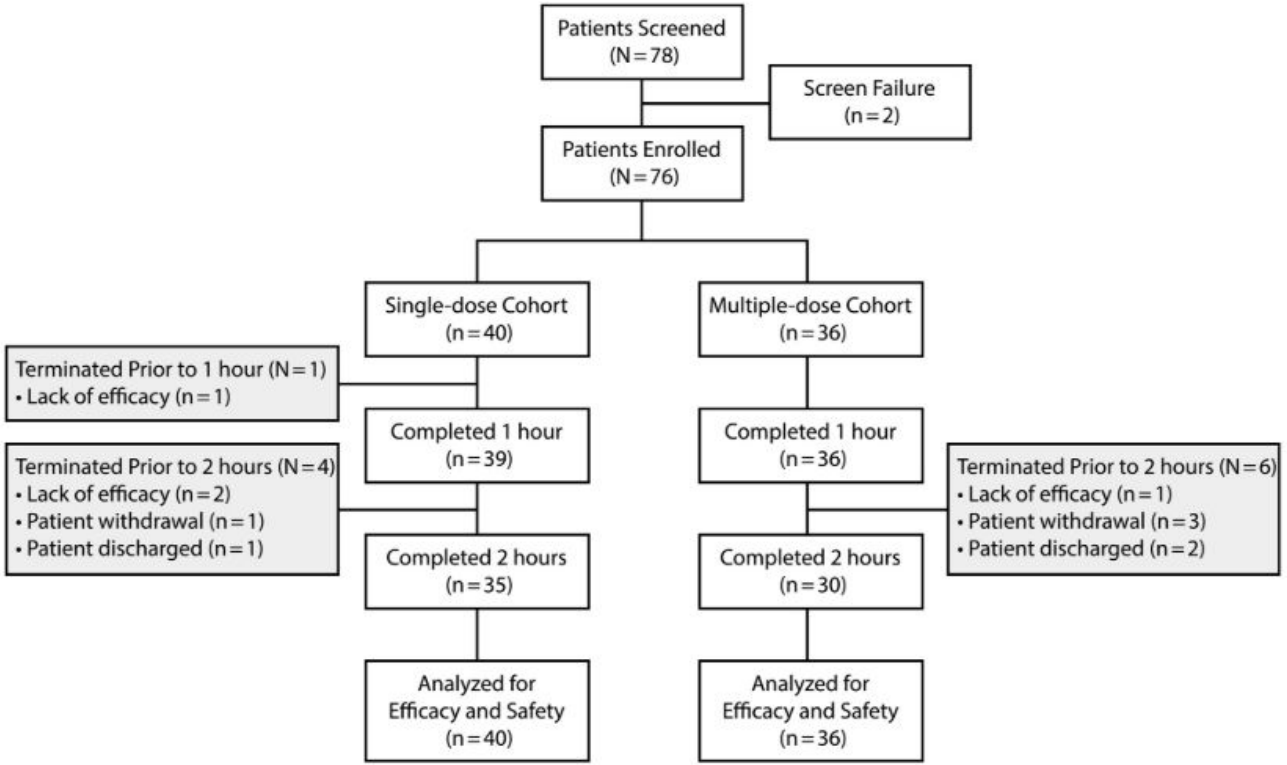
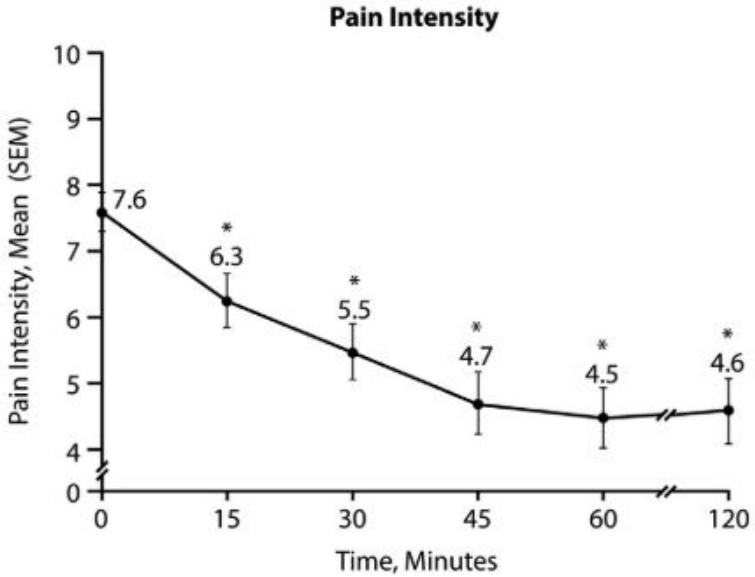


Fig. 1. Patient disposition.



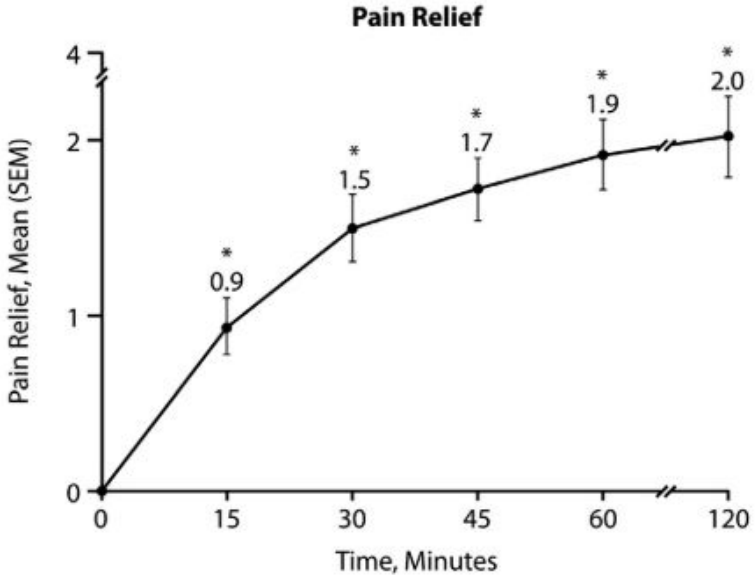


Fig. 3. Mean pain intensity and pain relief from baseline, over the first 2 h of treatment (multiple-dose cohort; N = 36). SEM = standard error of the mean. *Difference from baseline ($P < 0.001$).

Table 4
Summary of AEs and related AEs (combined cohorts)

	N = 76
Summary of AEs, patients, %	
No AEs	79
≥1AE	21
≥1 related AE	15
SAEs	1
Severe AEs	0
AEs leading to SST 30 mcg discontinuation	0

Patients with AEs, %	All AEs[a]	Related AEs[a]
Nausea	9	7
Somnolence	5	3
Vomiting	4	4
Oxygen desaturation	3[b]	3[b]
Angina pectoris	1	1
Conversion disorder	1	0
Feeling hot	1	0
Dizziness	1	1
Facial hypoesthesia	1	0
Pruritus	1	1

AE = adverse event; SAE = serious AE; SST = sufentanil sublingual tablet.

[a] All events were considered to be mild in severity with the exception of angina pectoris ($n = 1$; related) and nausea (n = 1, unrelated) that were considered moderate in severity.

[b] Two patients experienced transient room air oxygen desaturations below 95% (88% and 94%) which immediately improved with nasal cannula oxygen.

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Research

Pooled Dosing and Efficacy Analysis of the Sufentanil Sublingual Tablet 30 mcg Across Demographic Subgroups for the Management of Moderate-to-Severe Acute Pain

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Keywords:
analgesia
opioid
acute pain
sublingual

A B S T R A C T

Purpose: To aid nurses in dosing sufentanil sublingual tablet (SST) 30 mcg administered via a single-dose applicator, dosing requirements and efficacy of SST 30 mcg were analyzed across age, sex, race, and body mass index subgroups.

Design: Patient characteristics were pooled from three postoperative studies (two placebo-controlled and one open-label) and one open-label emergency department study. Drug dosing and efficacy data were pooled from the postoperative studies.

Methods: Efficacy was assessed through summed pain intensity difference to baseline during 12 hours across subgroups.

Findings: Mean (standard deviation) drug doses administered from 0 to 12 hours was 3.9 (2.0) for SST 30 mcg and was less frequent for older (≥65 years) versus younger patients. The summed pain intensity difference to baseline during 12 hours was superior with SST 30 mcg versus placebo across all subgroups.

Conclusions: SST 30 mcg is a sublingual opioid analgesic with efficacy across demographic subgroups.

Subgroup	SST 30 mcg n	SST 30 mcg SPID12	Placebo n	Placebo SPID12	LS mean difference[a]	P-value[b]	Difference in SPID12 (95% CI)
Age < 65 years	144	13.5	72	1.2	12.3	< .001	(7.8–16.9)
Male	54	8.2	28	-2.0	10.3	.005	(3.2–17.3)
Female	93	19.6	46	5.1	14.5	< .001	(8.4–20.6)
Caucasian	62	14.2	34	1.3	12.9	< .001	(6.1–19.7)
Non-Caucasian	85	14.9	40	2.3	12.5	< .001	(6.2–18.9)
BMI < 30 kg/m²	105	16.3	48	1.3	15.0	< .001	(9.2–20.9)
BMI ≥ 30 kg/m²	42	10.9	26	2.8	8.0	.030	(0.8–15.3)

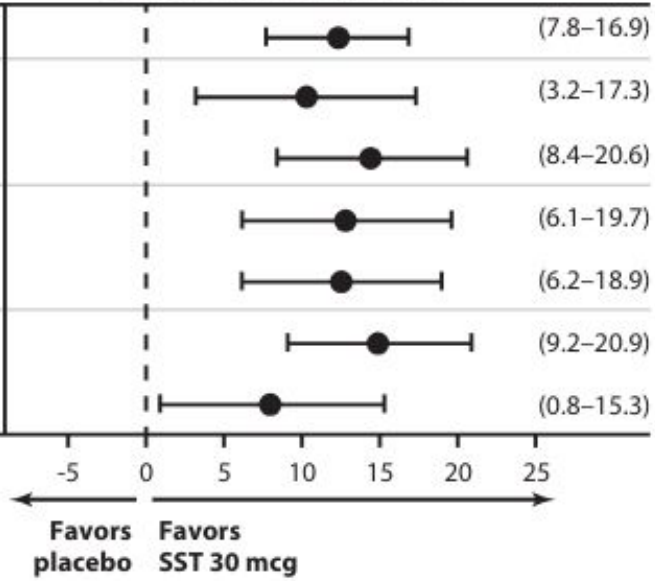

Figure 2. Primary efficacy for subgroups pooled across the placebo-controlled studies[22,25]; [a]LS mean difference between SST 30 mcg and placebo; [b]*P* value for the overall comparison among treatment groups is based on the F test of type III treatment factor from the analysis of covariance model including treatment and study factors and baseline pain intensity as a covariate. SST, sufentanil sublingual tablet; LS, least squares; SPID12, summed pain intensity difference from baseline during 12 hours; 95% CI, 95% confidence interval; BMI, body mass index.

ORIGINAL ARTICLE

Sufentanil Sublingual Tablet System vs. Intravenous Patient-Controlled Analgesia with Morphine for Postoperative Pain Control: A Randomized, Active-Comparator Trial

Timothy I. Melson, MD*; David L. Boyer, MD†; Harold S. Minkowitz, MD‡; Alparslan Turan, MD§; Yu-Kun Chiang, PhD¶; Mark A. Evashenk, BS**; Pamela P. Palmer, MD, PhD**

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Table 1. Demographics and Baseline Characteristics: ITT Population

Characteristic	SSTS *n* (%) (*n* = 177)	IV PCA MS *n* (%) (*n* = 180)	Total *n* (%) (*n* = 357)
Age (years)			
< 65	85 (48.0)	85 (47.2)	170 (47.6)
≥ 65	92 (52.0)	95 (52.8)	187 (52.4)
Mean (SD)	63.8 (12.1)	64.0 (12.6)	63.9 (12.4)
Sex			
Male	54 (30.5)	72 (40.0)	126 (35.3)
Female	123 (69.5)	108 (60.0)	231 (64.7)
Race			
White	160 (90.4)	162 (90.0)	322 (90.2)
Black or African American	17 (9.6)	17 (9.4)	34 (9.5)
Other	0	1 (0.6)	1 (0.3)
Ethnicity			
Hispanic or Latino	1 (0.6)	1 (0.6)	2 (0.6)
Not Hispanic or Latino	176 (99.4)	178 (99.4)	354 (99.4)
Weight (kg)			
Mean (SD)	84.3 (22.0)	87.1 (22.3)	85.7 (22.2)
Body mass index (kg/m^2)			
< 30	105 (59.3)	99 (55.0)	204 (57.1)
≥ 30	72 (40.7)	81 (45.0)	153 (42.9)
Mean (SD)	29.5 (6.3)	30.3 (6.6)	29.9 (6.4)
Type of surgery			
Knee arthroplasty	56 (31.6)	60 (33.3)	116 (32.5)
Hip arthroplasty	84 (47.5)	78 (43.3)	162 (45.4)
Open abdominal	37 (20.9)	42 (23.3)	79 (22.1)

ITT, intent-to-treat; IV PCA MS, Intravenous patient-controlled analgesia morphine sulfate; SSTS, sufentanil sublingual tablet system.

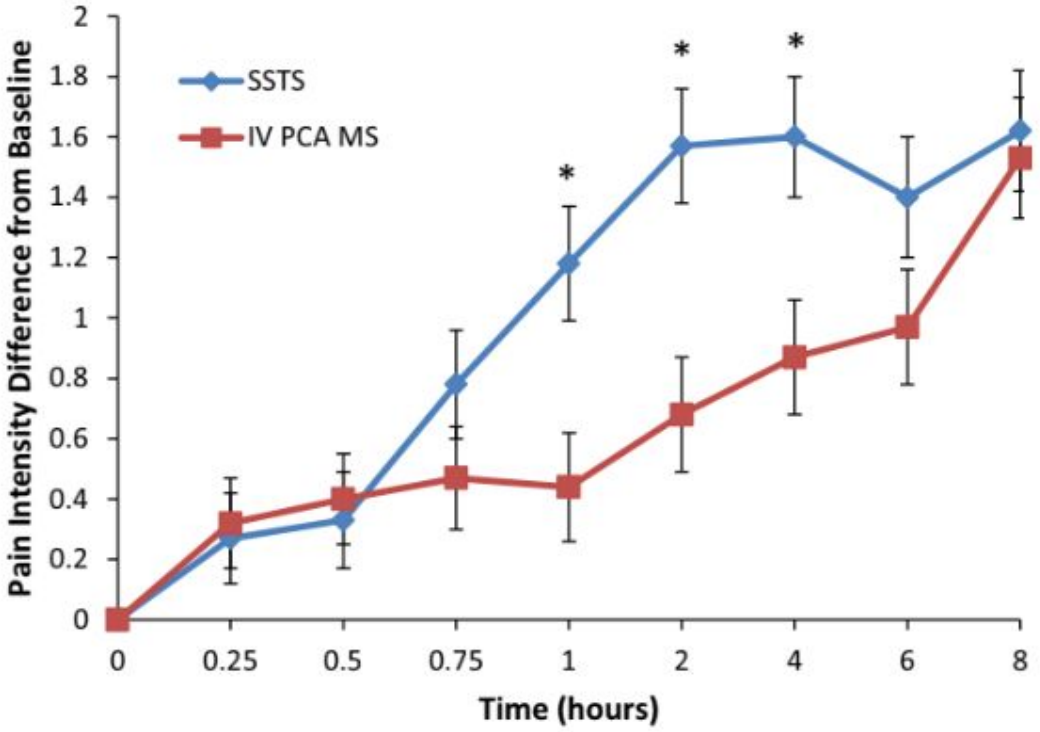


Figure 3. The pain intensity difference to baseline (PID) over the first 8 hours; * $P < 0.01$.

Table 4. Possibly or Probably Related Adverse Events (> 2% in either treatment group)

Adverse Event	SSTS *n* (%) (*n* = 177)	IV PCA MS *n* (%) (*n* = 180)	Total *n* (%) (*n* = 357)
Nausea	76 (42.9)	72 (40.0)	148 (41.5)
Vomiting	23 (13.0)	20 (11.1)	43 (12.0)
Constipation	20 (11.3)	15 (8.3)	35 (9.8)
Oxygen saturation decreased	17 (9.6)	17 (9.4)	34 (9.5)
Headache	14 (7.9)	12 (6.7)	26 (7.3)
Hypotension	11 (6.2)	20 (11.1)	31 (8.7)
Dizziness	10 (5.6)	6 (3.3)	16 (4.5)
Pruritus	7 (4.0)	14 (7.8)	21 (5.9)
Dyspepsia	6 (3.4)	2 (1.1)	8 (2.2)
Confusional state	4 (2.3)	3 (1.7)	7 (2.0)
Othostatic hypotension	4 (2.3)	2 (1.1)	6 (1.7)
Urinary retention	2 (1.1)	5 (2.8)	7 (2.0)

IV PCA MS, Intravenous patient-controlled analgesia morphine sulfate; SSTS, sufentanil sublingual tablet system.

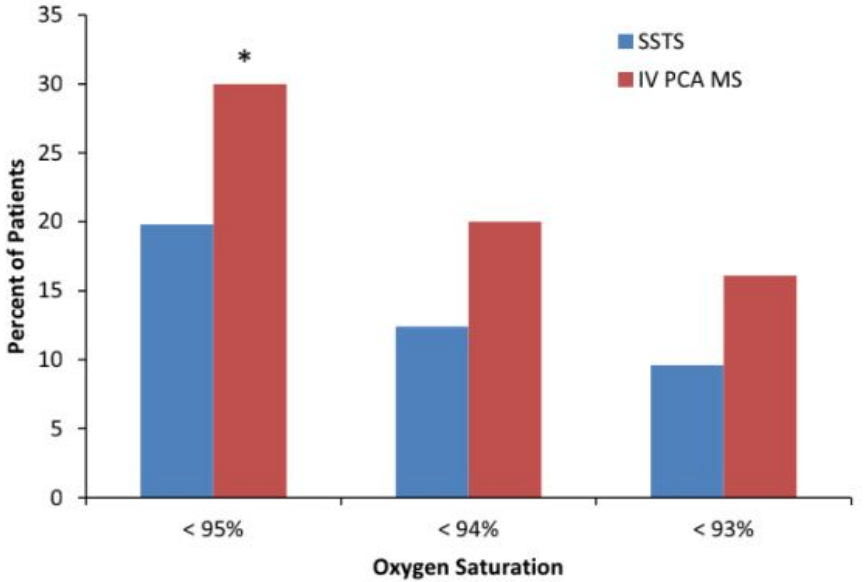
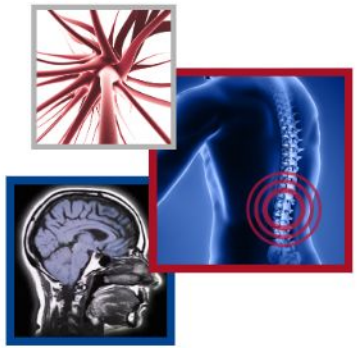


Figure 5. Percent of patients with oxygen desaturation events; *$P = 0.028$.

Research Article

Pain Management



Pooled Phase III safety analysis of sufentanil sublingual tablets for short-term treatment of moderate-to-severe acute pain

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Table 1. Patient study pools for safety analysis.

Procedure (Clinicaltrials.gov identifier)	Study design†	Comparator	Number of patients in pooled safety analysis/full study	Study duration	Rescue medication	Ref.
SST 30 mcg						
Phase III						
Ambulatory abdominal surgery (NCT02356588)	Multicenter, randomized double-blind placebo controlled	Placebo	161/161	48 h	IV morphine	[19]
Emergency department trauma or injury (NCT02662556)	Multicenter, open-label	None	76/76	2 h (single-dose cohort; n = 40) 5 h (multiple-dose cohort; n = 36)	IV morphine or oral oxycodone elixir	[21]
Inpatient and outpatient surgery (NCT02447848)	Multicenter, open-label	None	140/140	12 h	IV morphine	[20]
SST 15 mcg‡						
Phase II						
Knee replacement (NCT00859313)	Multicenter, open-label	None	18/30	12 h	None	
Total knee replacement (NCT00612534)	Multicenter, randomized double-blind placebo controlled	SST 5 mcg; SST 10 mcg; placebo	27/94	12 h	None	[23]
Open abdominal surgery (NCT00718081)	Multicenter, randomized double-blind placebo controlled	SST 10 mcg; Placebo	14/88	12 h	None	[23]
Phase III						
Open abdominal surgery or knee/hip replacement (NCT01539538)	Multicenter, randomized double-blind active control	IV morphine	94/357	72 h	IV morphine	[18]
Open abdominal surgery (NCT01539642)	Multicenter, randomized double-blind placebo controlled	Placebo	78/172	72 h	IV morphine	[17]
Total knee or hip replacement (NCT01660763)	Multicenter, randomized double-blind placebo controlled	Placebo	196/419	72 h	IV morphine	[16]

†For eligibility, all patients must have had a pain intensity rating of ≥4, on a numeric rating scale from 0 to 10 [24,25].
‡Analysis included a subset of patients from the SST 15 mcg studies who received two doses of SST 15 mcg within 20–25 min (30-mcg dose-equivalent).
IV: Intravenous; SST: Sufentanil sublingual tablet.

Table 3. Adverse events in the sufentanil sublingual tablet clinical studies (pooled): all adverse events and adverse events related[†] to study treatment.

Patients, n (%)	SST 15 mcg[‡] (n = 323)	SST 30 mcg (n = 323)	Total SST[§] (n = 646)	Total placebo (n = 158)	SST[§] vs placebo, difference, % (95% CI)
All AEs					
Number of AEs					
None	62 (19.2)	193 (59.8)	255 (39.5)	61 (38.6)	
≥1	261 (80.8)	130 (40.2)	391 (60.5)	97 (61.4)	-0.9 (-9.4 to 7.6)
All AEs[¶] (≥2% of patients in any study group)					
Nausea	155 (48.0)	80 (24.8)	235 (36.4)	49 (31.0)	5.4 (-2.7 to 13.5)
Headache	34 (10.5)	29 (9.0)	63 (9.8)	15 (9.5)	0.3 (-4.8 to 5.4)
Pyrexia	56 (17.3)	0	56 (8.7)	13 (8.2)	0.5 (-4.3 to 5.3)
Vomiting	41 (12.7)	12 (3.7)	53 (8.2)	6 (3.8)	4.4 (0.7, 8.1)
Anemia	33 (10.2)	0	33 (5.1)	3 (1.9)	3.2 (0.5, 5.9)
Dizziness	18 (5.6)	13 (4.0)	31 (4.8)	4 (2.5)	2.3 (-0.6 to 5.2)
Pruritus	24 (7.4)	7 (2.2)	31 (4.8)	4 (2.5)	2.3 (-0.6 to 5.2)
Hypotension	14 (4.3)	8 (2.5)	22 (3.4)	6 (3.8)	-0.4 (-3.7 to 2.9)
Oxygen saturation decreased	20 (6.2)	6 (1.9)	26 (4.0)	1 (0.6)	3.4 (1.5 to 5.3)

Constipation	20 (6.2)	1 (0.3)	21 (3.3)	1 (0.6)	2.7 (0.9 to 4.5)
Hypertension	11 (3.4)	3 (0.9)	14 (2.2)	5 (3.2)	-1.0 (-4.0 to 2.0)
Insomnia	12 (3.7)	0	12 (1.9)	3 (1.9)	0.0 (-2.4 to 2.4)
Tachycardia	9 (2.8)	4 (1.2)	13 (2.0)	2 (1.3)	0.7 (-1.4 to 2.8)
Hypocalcemia	12 (3.7)	0	12 (1.9)	2 (1.3)	0.6 (-1.5 to 2.7)
Leukocytosis	11 (3.4)	0	11 (1.7)	3 (1.9)	-0.2 (-2.6 to 2.2)
Sinus tachycardia	11 (3.4)	0	11 (1.7)	2 (1.3)	0.4 (-1.6 to 2.4)
Somnolence	3 (0.9)	7 (2.2)	10 (1.5)	3 (1.9)	-0.4 (-2.7 to 1.9)
Anemia postoperative	10 (3.1)	0	10 (1.5)	1 (0.6)	0.9 (-0.6 to 2.4)
Body temperature increased	10 (3.1)	0	10 (1.5)	1 (0.6)	0.9 (-0.6 to 2.4)
Confusional state	8 (2.5)	1 (0.3)	9 (1.4)	2 (1.3)	0.1 (-1.9 to 2.1)
Dyspepsia	9 (2.8)	1 (0.3)	10 (1.5)	1 (0.6)	0.9 (-0.6 to 2.4)
Hypoalbuminemia	10 (3.1)	0	10 (1.5)	1 (0.6)	0.9 (-0.6 to 2.4)
Hypokalemia	10 (3.1)	0	10 (1.5)	1 (0.6)	0.9 (-0.6 to 2.4)
Muscle spasms	7 (2.2)	1 (0.3)	8 (1.2)	3 (1.9)	-0.7 (-3.0 to 1.6)
Anxiety	8 (2.5)	0	8 (1.2)	2 (1.3)	-0.1 (-2.1 to 1.9)
Flatulence	1 (0.3)	4 (1.2)	5 (0.8)	5 (3.2)	-2.4 (-5.2 to 0.4)
Hyponatremia	8 (2.5)	0	8 (1.2)	1 (0.6)	0.6 (-0.9 to 2.1)
Hypoxia	6 (1.9)	1 (0.3)	7 (1.1)	2 (1.3)	-0.2 (-2.1 to 1.7)
Urinary retention	8 (2.5)	0	8 (1.2)	0	1.2 (0.4 to 2.0)
Pharyngolaryngeal pain	5 (1.5)	2 (0.6)	7 (1.1)	0	1.1 (0.3 to 1.9)
Procedural nausea	0	3 (0.9)	3 (0.5)	3 (1.9)	-1.4 (-3.6 to 0.8)
Sedation	5 (1.5)	0	5 (0.8)	0	0.8 (0.1 to 1.5)

Table 4. Serious adverse events.

Serious AE† (n = 1 each)	Study type	Treatment	Severity	Relationship to treatment	Outcome	Ref.
Angina pectoris	Phase III; open-label; emergency department	SST 30 mcg	Moderate	Possibly related	Dose not changed and patient recovered	[21]
Atrial fibrillation	Phase III; placebo-controlled; orthopedic surgery	SST 15 mg	Moderate	Not related	Dose not changed and patient recovered	[16]
Confusional state‡	Phase III; placebo-controlled; orthopedic surgery	SST 15 mcg	Moderate	Possibly related	Dose not changed and patient recovered	[16]
Hemiparesis	Phase III; placebo-controlled; abdominal surgery	Placebo	Severe	Possibly related	Drug withdrawn and patient recovered	[19]
Hypoxia‡	Phase III; placebo-controlled; orthopedic surgery	SST 15 mcg	Moderate	Not related	Dose not changed and patient recovered	[16]
Oxygen saturation decreased§	Phase III; placebo-controlled; orthopedic surgery	SST 15 mcg	Severe	Probably related	Drug withdrawn and patient recovered	[16]
Postoperative ileus	Phase III; active comparator; mixed surgery	SST 15 mcg	Severe	Not related	Dose not changed and patient recovered	[18]
Pulmonary embolism‡	Phase III; placebo-controlled; orthopedic surgery	SST 15 mcg	Mild	Not related	Dose not changed and patient recovered	[16]
Syncope	Phase III; placebo-controlled; abdominal surgery	Placebo	Moderate	Possibly related	Drug withdrawn and patient recovered	[19]

DECLARATION OF MONTREAL

Declaration that Access to Pain Management Is a Fundamental Human Right

We, as delegates to the International Pain Summit (IPS) of the International Association for the Study of Pain (IASP) (comprising IASP representatives from Chapters in 64 countries plus members in 129 countries, as well as members of the community), have given in-depth attention to the unrelieved pain in the world,

And, recognizing the intrinsic dignity of all persons and that withholding of pain treatment is profoundly wrong, leading to unnecessary suffering which is harmful; we declare that the following human rights must be recognized throughout the world:

Article 1. The right of all people to have access to pain management without discrimination (Footnotes 1-4).

Article 2. The right of people in pain to acknowledgment of their pain and to be informed about how it can be assessed and managed (Footnote 5).

Article 3. The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals (Footnotes 6-8).


EMERGENCY


HOLLY
STAR

A WORLD OF PAIN

60%

DOI: 10.1053/ajem.2002.32643

90

DOI: 10.1016/j.jpain.2006.12.005

14-32%

DOI: 10.3390/jcm12093289

74%

DOI: 10.1016/j.jpain.2006.12.005

Scacco matto al dolore in 8 mosse

1 - ***Rivela*** i bisogni essenziali
2 - ***Valuta*** il dolore nella maniera corretta
3 - Inizia la ***"conversazione difficile"***
4 - ***Tratta*** il dolore per via non farmacologica, farmacologica, ed interventive
5 - Segui la regola del ***MME*** nei pazienti in terapia con oppiacei
6 - Valuta la necessità di ***sedazione palliativa***
7 - ***Coinvolgi*** gli altri specialisti ed il care-giver
8 - ***Anticipa*** il trattamento del dolore

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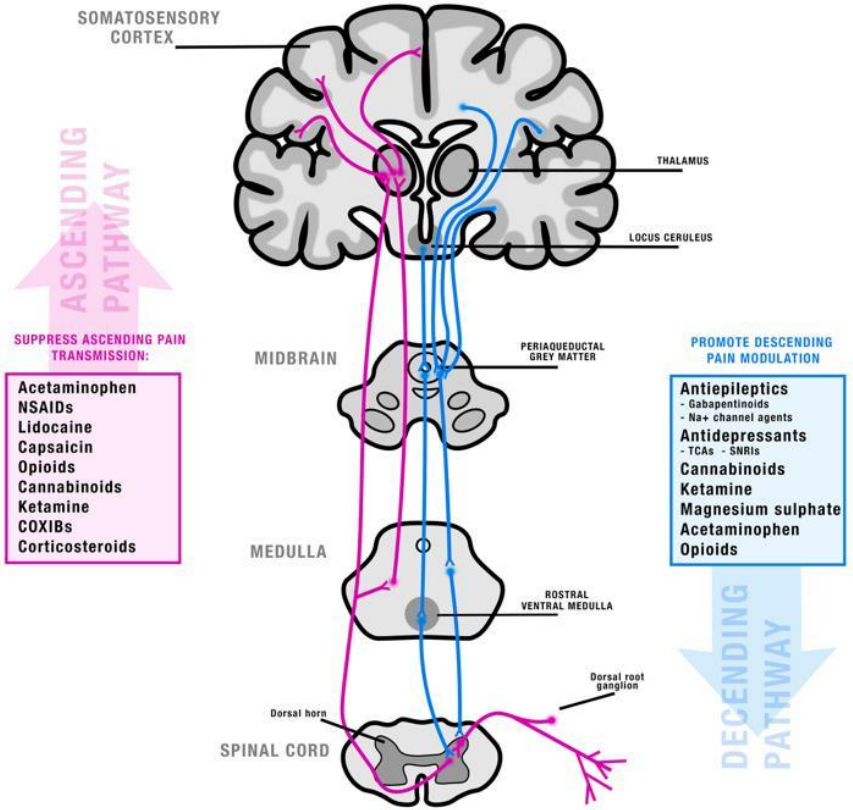
Serra et al. Pain Management at the End of Life in the Emergency Department: A Narrative Review of the Literature and a Practical Clinical Approach. *J. Clin. Med.* **2023**, *12*, 4357



Serra et al. Pain Management at the End of Life in the Emergency Department: A Narrative Review of the Literature and a Practical Clinical Approach. *J. Clin. Med.* **2023**, *12*, 4357

Game changer, Bansky

Oligoanalgesia in the Emergency Department

JAMES E. WILSON, MD,*† JILL M. PENDLETON, BS†

A review of the charts of 198 patients who were admitted through the emergency department with a variety of acutely painful medical and surgical conditions revealed that 56% received no analgesic medication while in the emergency department. In the 44% of patients who received pain medication, 69% waited more than 1 hour while 42% waited more than 2 hours before narcotic analgesia was administered. In addition, 32% initially received less than an optimal equianalgesic dose of narcotic when compared with morphine. This study demonstrates that narcotic misuse, in the form of oligoanalgesia, is prevalent and is the shared responsibility of both emergency physicians and housestaff consultants. (Am J Emerg Med 1989;7:620-623. © 1989 by W.B. Saunders Company.)

eastern Ohio Universities College of Medicine. The ED has a yearly volume of 60,000 patients, of whom 40% are privately insured, 40% are covered by Medicare/Medicaid, and 20% are indigent. The ED is staffed 24 hours a day by board-certified emergency medicine faculty and residents of its residency program in emergency medicine. Seven other residencies exist within the hospital with a total of 132 residents in various medical and surgical teaching programs. Junior- and senior-level residents from these programs serve as consultants for patients in the ED when requested by the emergency medicine faculty. All pa-

analgesia in the Emergency Department


I.MEU
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“start low and go slow”

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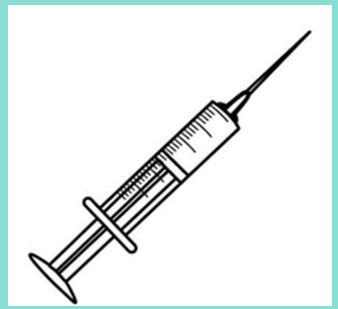

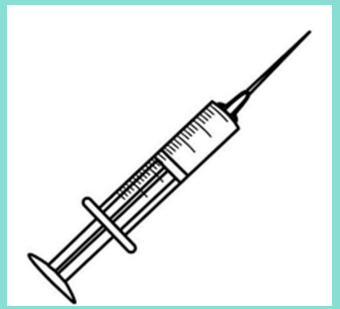

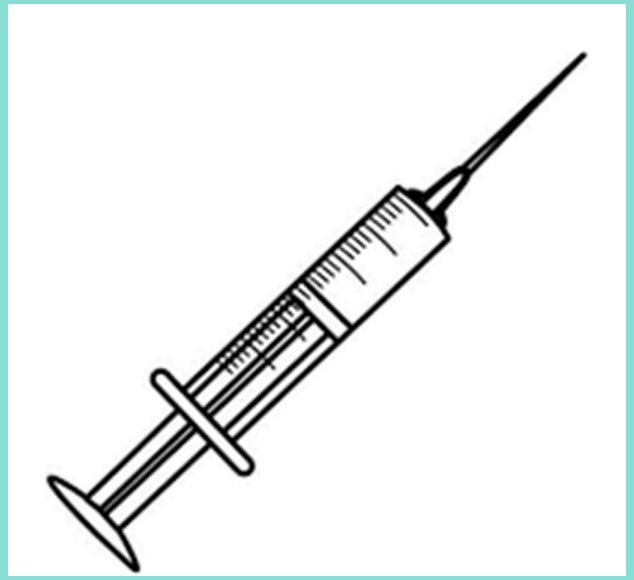

MULTIMODAL

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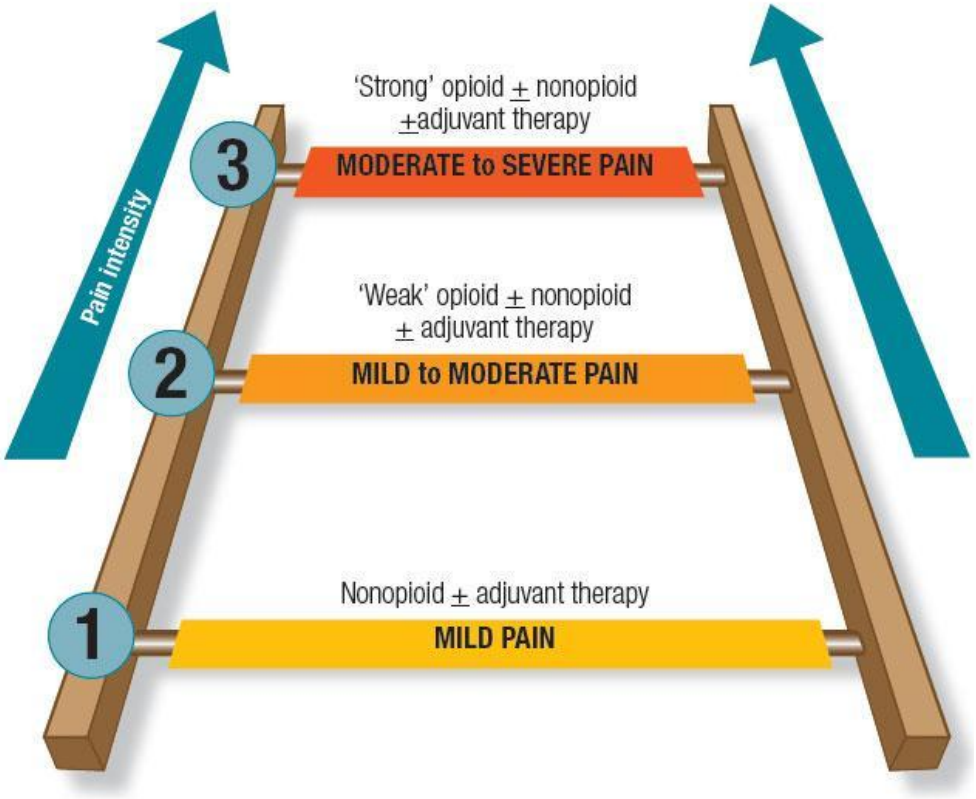
4 - Tratta il dolore: la via farmacologica



WHO, 1962, The Pain Ladder

5 - Segui la regola del MME nei pazienti in terapia con oppiacei

Calcolo dose in equivalenti di Morfina per bocca, somma:

Table I. Equianalgesia table.

Opiate	Morphine[17]	Morphine[13,17]	Morphine[17]	Morphine[17]	Morphine[17]	Codeine[17]	Tramadol[17,33]	Tramadol[33]	Tapentadol[16,34]	Oxycodone[2,13,16-18,25-26,35]	Oxycodone[2,13,16-18,25-26,35]	Hydromorphone[2,13, 16, 17,32]	Fentanyl[13,36]	Buprenorphine[27,37]	Fentanyl[1,2,17,28-31]	Buprenorphine[17,27,37]	Sufentanil[39]
Form	OS ATC	SC	IV	PD	SA	OS	OS	IM/IV	OS	OS	SC/IV	OS	IV	IM/IV	TTS	TTS	SL
Unit	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	µg/h	µg/h	µg
	7.5	3.75*	2.5*	0.38*	0.04*	30*	37.5*	25*	25*	3.75*	1.88*	1.5*	0.1*		3*	5	7.5*
	15	7,5*	5*	0.75*	0.08*	60*	75*	50*	50	7.5*	3.75*	3*	0.2*		6*	10	15*
	22.5	11.3*	7.5*	1.13*	0.11*	90*	113*	75*	75	11.3*	5.63*	4.5*	0.3*		9*	15	22.5*
	30	**15**	**10**	**1.5**	**0.15**	**120**	**150**	**100**	**100**	**15**	**7.5**	**6**	**0.4**	**0.3**	**12**	**20**	**30**
	60	30	20	3	0.3	240	300	200	200	30	15	12	0.8	0,6	25	35	60
	90									45	22.5	18	#	0.9	37.5*	52.5	90
	120	60	40	6	0.6	#	#	400**	400	60	30	24	#	1.2	50	70	120
	180														75	#	180
	240	120	80	12	1.2	#	#	#	#	120	60	48	#	2.4	100	#	240
	300	150	100	15	1.5	#	#	#	#	150**	75	60**	#	#	#	#	300

330 mg morfina po

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Pharmacology in Emergency Medicine

INTRANASAL SUFENTANIL VERSUS INTRAVENOUS MORPHINE FOR ACUTE PAIN IN THE EMERGENCY DEPARTMENT: A RANDOMIZED PILOT TRIAL

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PLOS | MEDICINE

RESEARCH ARTICLE

Intranasal sufentanil versus intravenous morphine for acute severe trauma pain: A double-blind randomized non-inferiority study

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Abstract

Table 1. Baseline characteristics of participants (per protocol).

Characteristic	IVM (*n* = 69)	INS (*n* = 67)
Patient characteristic		
Median [IQR] age (years)	41 [28 to 54]	38 [30 to 55]
Men	40 (58)	31 (46)
Median [IQR] weight (kg)	74 [61 to 83]	70 [60 to 80]
Trauma area*		
Head	2 (2.9)	1 (1.5)
Shoulder	7 (10.1)	12 (17.9)
Arm/elbow	12 (17.4)	9 (13.4)
Wrist or hand	17 (24.6)	8 (11.9)
Thorax wall	3 (4.4)	5 (7.5)
Rachis	12 (17.4)	8 (11.9)
Pelvis/hip	10 (14.5)	5 (7.5)
Leg/knee	8 (11.6)	13 (19.4)
Ankle or foot	11 (15.9)	13 (19.4)
Vital parameters at inclusion		
Median [IQR] HR (per minute)	76 [68 to 91]	74 [67 to 84]
Median [IQR] RR (per minute)	16 [15 to 19]	18 [15 to 20]
Median [IQR] SpO_2 (%)	99 [97 to 100]	99 [97 to 100]
Median [IQR] MAP (mm Hg)	98 [91 to 104]	94 [85 to 103]
Median [IQR] NRS (/10)	8 [7 to 8]	8 [7 to 9]
Co-analgesia*	**23 (33)**	**15 (22)**
Paracetamol	22 (32)	15 (22)
Codeine	2 (3)	2 (3)
Ketoprofen	4 (6)	1 (1)
Inclusion site		
Grenoble (north site)	41 (59.4)	42 (62.7)
Grenoble (south site)	2 (2.9)	2 (3.0)
Saint-Jean-de-Maurienne	10 (14.5)	8 (11.9)
Annecy	9 (13.0)	8 (11.9)
Chambery	4 (5.8)	3 (4.5)
Albertville	3 (4.3)	3 (4.5)
Voiron	0 (0)	1 (1.5)

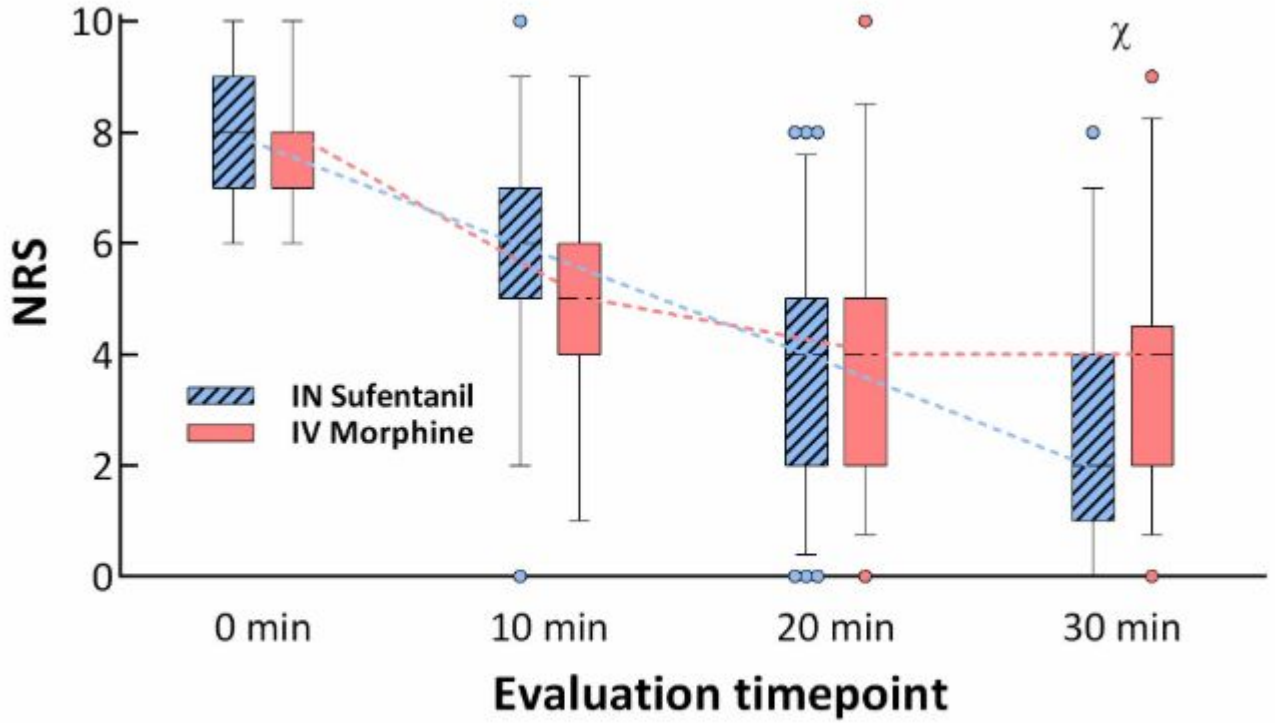

Fig 2. NRS at the different time points by group. The box extends from the 25th to the 75th percentile, and the whiskers are drawn down to the 5th percentile and up to the 95th. Points below and above the whiskers are drawn as individual points. No significant differences were observed in NRS values between groups at the 10-minute and 20-minute time points. IN sufentanil was non-inferior and superior to IV morphine in NRS reduction from drug administration to 30 minutes ($NRS_{T30} - NRS_{T0}$). IN, intranasal; IV, intravenous; NRS, numerical pain rating scale.

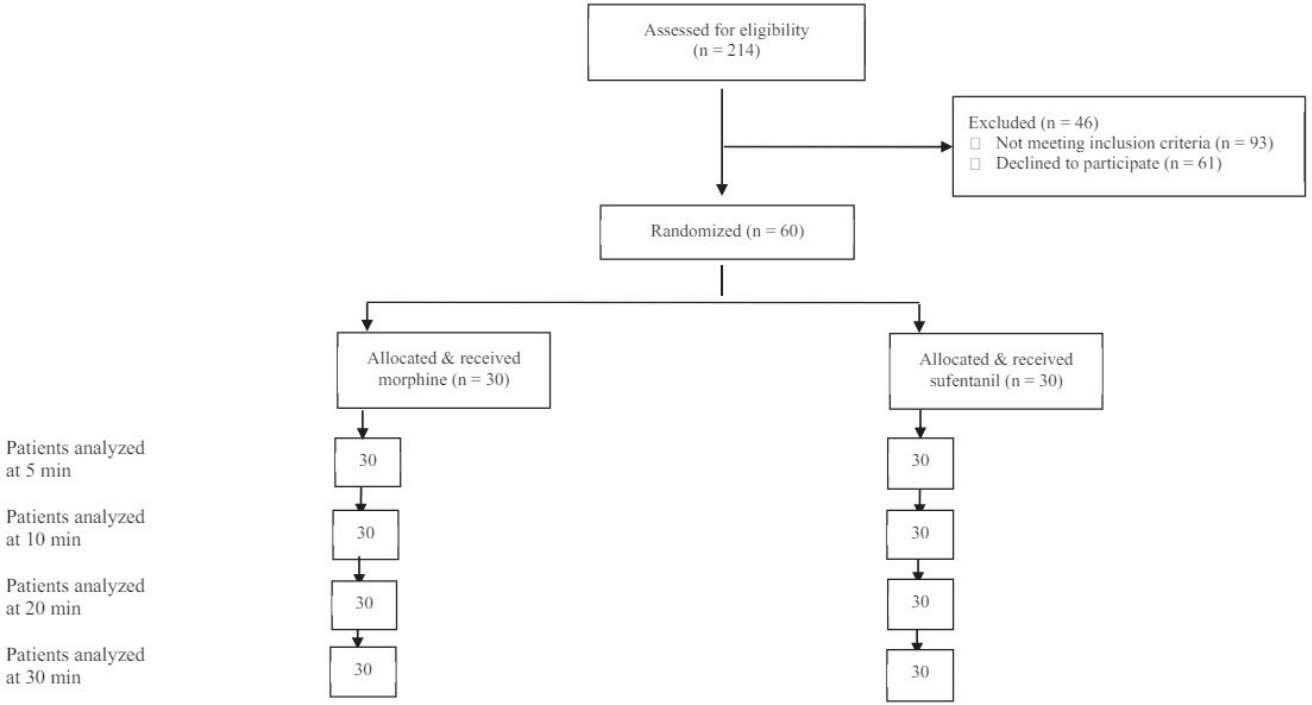

Figure 1. Participant flow diagram.

Table 2. Pain Scores Recorded During Designated Intervals

	Pain NRS, Median (IQR)		
Time Interval	Morphine (n = 30)	Sufentanil (n = 30)	*p*-Value
*t*0	9.0 (6.0–0.0)	10.0 (8.0–10.0)	0.224
*t*5	2.0 (0–5.3)	2.0 (1.0–3.0)	0.340
*t*10	3.0 (2.0–5.3)	2.0 (2.0–3.3)	0.198
*t*20	4.0 (2.4–6.0)	3.0 (2.0–6.3)	0.766
*t*30	5.0 (3.0–6.0)	5.0 (2.8–8.3)	0.255

NRS = numeric rating scale; IQR = interquartile range.

ALERT

ESPOSIZIONE ACCIDENTALE ED AZIONI DI MITIGAZIONE DEL RISCHIO:
REMS program (per somministrazione sublinguale)

DEPRESSIONE RESPIRATORIA FATALE

DIPENDENZA, ABUSO

INTERAZIONE CITOCROMO P450 3A4

CONCOMITANTE USO DEPRESSORI SNC

F.D.A. REMS program

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Per ottenere la certificazione per la dispensazione	***Essere in grado di gestire l'overdose acuta di oppioidi, compresa la depressione respiratoria.*** Designare un rappresentante autorizzato a svolgere il processo di certificazione e a supervisionare l'implementazione e la conformità al Programma REMS per conto del centro di cura. Chiedere al rappresentante autorizzato di iscriversi al Programma REMS completando il Modulo di iscrizione all'assistenza sanitaria e inviandolo al Programma REMS. Istruire tutto il personale interessato che DSUVIA *non deve essere dispensato per l'uso al di fuori dell'ambiente sanitario certificato.* Istruire tutto il personale coinvolto nella somministrazione di DSUVIA affinché faccia riferimento alle Istruzioni per l'uso prima della somministrazione. Stabilire processi e procedure per verificare che DSUVIA *non venga dispensato per l'uso al di fuori del contesto sanitario certificato.*
Per mantenere la certificazione di dispensazione	Chiedere a un nuovo rappresentante autorizzato di iscriversi al programma REMS compilando il modulo di iscrizione all'assistenza sanitaria se il rappresentante autorizzato cambia.
In ogni momento	*Non dispensare DSUVIA per l'uso al di fuori dell'ambiente sanitario certificato.* *Non distribuire, trasferire, prestare o vendere DSUVIA.* Conservare le registrazioni della formazione del personale. Conservare le registrazioni di tutti i processi e le procedure, compresa la conformità a tali processi e procedure. Rispettare gli audit di Vertical Pharmaceuticals, LLC o di una terza parte che agisce per conto di Vertical Pharmaceuticals, LLC per garantire che tutti i processi e le procedure siano in atto e vengano rispettati.

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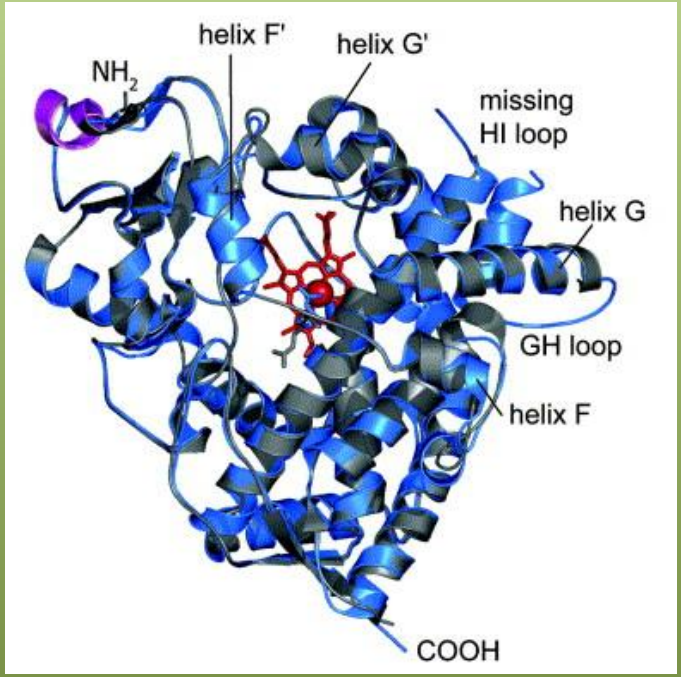

INIBITORI	INDUTTORI
Antiaritmici: Amiodarone	**Antibiotici:** Isoniazide, Rifampicina
Antibiotici: Ciprofloxacina, Claritromicina, Eritromicina, Metronidazolo	**Antiepilettici:** Carbamazepina
Antifungini: azolici	**Cortisonici:** Desametasone, Prednisone
Calcio antagonisti: Diltiazem, Verapamil	
IPP: Omeprazolo	
Altri: Paroxetina, Sertralina, Saquinavir, Ritonavir…	

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