

Do morphine delays mean fentanyl's the way?

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Trauma

- Most common reasons to visit an emergency department in Ontario, Alberta and the United States
 - From 1998 to 2000
- Prevalence of under treatment of acute pain in trauma patients ~43%
- Adequate pain control is an essential goal
 - Leads to decreased human suffering and emotional distress

Opioids

- Standard of care for the treatment of acute severe pain
- Requirements between individuals may differ by 8 to 10 fold
- Differing pharmacokinetic profiles = variability in analgesic effects
 - Onset
 - Extent
 - Duration
- Optimization of pain relief
 - Titration to effect with intravenous administration
 - Knowledge of pharmacokinetic-pharmacodynamic parameters

Pharmacokinetic-Pharmacodynamics

- Concentration profile is not useful for all opioids
 - The analgesic effect lags behind the peak concentration
- Explained by physicochemical properties
 - % unionized
 - lipid solubility

Equilibrium delays

- Discordance between plasma concentrations and effect explained by an effect compartment
- k_{eo} = a rate constant between plasma and effect site
 - used to describe the equilibration half life $T_{1/2\ keo}$, or equilibrium delays
 - $T_{1/2\ keo} = 0.693/k_{eo}$
 - smaller (slower) rate constant = longer $T_{1/2\ keo}$ = delay in equilibrium between plasma and effect site

Review articles: PK-PD implications

- “Opioids with a delay in time courses from the plasma to effect site are not ideal for titration of effects required immediately”
- “Hydromorphone has a shorter plasma:central nervous effect-site equilibration half-life than morphine and because of this, hydromorphone may be better suited for titration of acute analgesia”
- “Characteristics of morphine make it relatively slow and difficult to control”
 - Clin Pharmacokinet 2006; 45 (11): 1051-60
 - Br J Anaesth. 2011;107(3):319-28
 - Expert Rev. Clin. Pharmacol. 2011;4(6): 719–28

Equilibrium delays

	t ½ keo	Comments
Morphine	1.6 to 4.8 hrs	Transcutaneous electrical stimulation, respiration, VAS, pupil diameter
M6G	2.72 to 6.4 hrs	Respiration, transcutaneous electrical stimulation
Fentanyl	16.4 minutes	Respiration

Dosing recommendations in acute pain

Protocol Type	Intravenous Dose ^a	Frequency
Morphine		
Standard		
weight-based	0.1 mg/kg	10-15 min
fixed dose	6-10 mg	
Nurse-initiated ^b	2.5 mg	5 min
Hydromorphone		
Standard		
weight-based	0.015 mg/kg	10-15 min
fixed dose	1-1.5 mg	
Nurse-initiated ^b	0.4 mg	5 min
Fentanyl		
Standard		
weight-based	1 µg/kg	5 min
fixed dose	60-100 µg	
Nurse-initiated ^b	25 µg	5 min

Time profiles

Drug	Onset (min)	Tmax (min)	Relative duration (min)
Morphine	6	19	96
Fentanyl	2	4	7

Clinical question

P	Trauma patients Acute severe pain Emergency department or on route	
I	Morphine IV	
C	Fentanyl IV	
O	Pain control Patient satisfaction	Adverse events <ul style="list-style-type: none">➤ Respiratory depression➤ Hypotension➤ Decrease in LOC➤ Nausea➤ Pruritus

Search Strategy

Databases	PubMed, Cochrane, Clinical trials.gov, Google Scholar, IPA, Web of Science, EMBASE
Search Terms	Fentanyl, morphine, intravenous, acute trauma, trauma, acute pain
Limits	Human, English, Clinical trial
Results	1 RCT 1 Prospective non-randomized 1 Retrospective chart review, pre hospital setting 1 Retrospective chart review, Emergency Department (ED)

A randomized, double-blind study comparing morphine with fentanyl in prehospital analgesia[☆]

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Loïc Tual MD, MS^d, Vincent Van Laer MD^e, Jean-Yves Lardeur MD^f,
Frédéric Lapostolle MD^a, Frédéric Adnet MD, PhD^a**

American Journal of Emergency Medicine (2005) 23, 114–119

Galinski M et al. 2005

Design	Prospective, MC, DB, RCT, prehospital setting
Patients	Severe acute pain n=54, age 18 to 70 61% trauma VASS>60/100
Intervention	Morphine 0.1 mg/kg IV then 3 mg every 5 minutes prn
Comparator	Fentanyl 1 mcg/kg IV then 30 mcg every 5 minutes prn
Objective	To determine whether fentanyl is more or less effective than morphine
Endpoint	Difference in visual analog scale score at 30 minutes

Galinski M et al. 2005

Table 1 Baseline characteristics of patients from groups

	M group (n = 26)	F group (n = 28)
Mean age [y (SD)]	40 (13)	45 (13)
Sex ratio (F/M)	3:23	6:22
Mean BMI [kg/m ² (SD)]	24 (3)	24 (4)
Cumulative volume administered at		
T0 [mL (SD)]	7 (1)	7 (2)
T30 [mL (SD)]	16 (5)	15 (6)
Etiology of pain		
Trauma [n (%)]	19 (73)	14 (50)
Nontrauma [n (%)]	7 (27)	14 (50)
Comorbidity [n (%)]		
Coronary artery disease	1 (4)	1 (4)
Hypertension	1 (4)	3 (11)
Diabetes/dyslipidemia	2 (8)	3 (11)

Exclusion

- Renal or hepatic insufficiency
- Treatment of chronic pain
- Acute hemodynamic, respiratory, or neurological compromise

Results: change in VASS

	Baseline	30 min	Change
Morphine	83 (78-88)	40 (28-52)	45 (34-56)
Fentanyl	77 (72-82)	35 (27-43)	42 (32-52)

*Mean (95% CI)

Galinski M et al. 2005

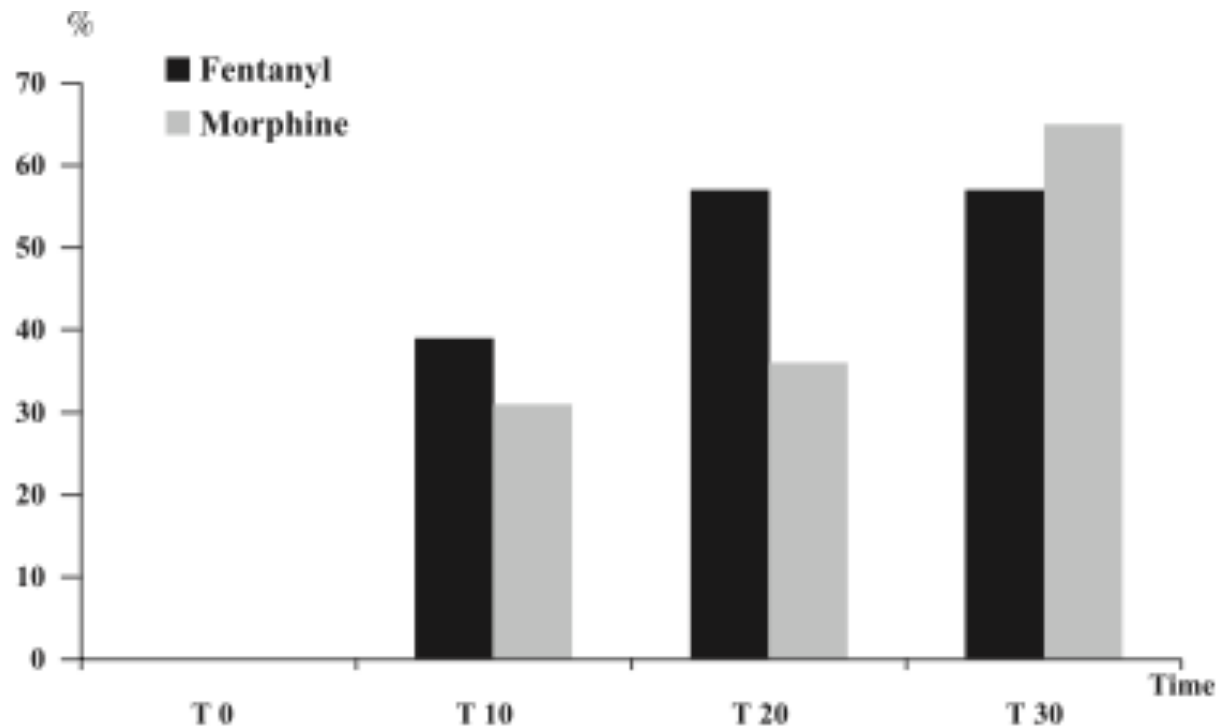


Fig. 4 Percentage of patients with a VASS of 30/100 or lower at 10 (T10), 20 (T20), and 30 (T30) minutes in the F and M groups. There was no statistical difference ($P > .05$).

Table 2 Comparison of different analgesia parameters between the M group and F group

	M group (n = 26)	F group (n = 28)	<i>P</i>
Side effects [n (%)]	10 (38)	10 (36)	NS
Nausea	3	6	
Emesis	3	3	
Dysphoria	1	1	
Pruritus	2	0	
Dizziness	1	0	
Sedation score = 2 [n (%)]	3 (11)	0 (0)	NS
Patient satisfaction: excellent/good (%)	62	76	NS
Duration from T0 to hospital [min (mean SD)]	39 (15)	34 (10)	NS
Systolic blood pressure [mm Hg (mean SD)] at			
T0	133 (24)	132 (18)	NS
T30	129 (13)	131 (22)	
Heart rate [beats/min (mean SD)] at			NS
T0	81 (16)	84 (20)	
T30	82 (16)	81 (17)	
Respiratory rate [beats/min (mean SD)] at			NS
T0	19 (4)	20 (6)	
T30	16 (3)	17 (5)	
SpO ₂ [% (mean SD)] at			NS
T0	98 (2)	98 (2)	
T30	98 (3)	98 (3)	

Summary

- “This study demonstrates that morphine and fentanyl were comparable in treating severe, acute pain in a prehospital setting during the first 30 minutes in spontaneous breathing patients.”
- Higher initial pain scores in the morphine group
- Conservative dosing of fentanyl, kinetics suggest titrate every 2 to 3 min
- Rationale for study was fentanyl works faster and has a shorter duration, yet primary outcome and patient satisfaction assessed at 30 min
- No difference in adverse events
 - Recorded at 30 min
 - Patients were not followed after arrival to hospital
 - Numerically more sedation in the morphine group (11% vs 0%)
- Randomized, double blind, equipotent doses

THE EFFECTIVENESS AND ADVERSE EVENTS OF MORPHINE VERSUS FENTANYL ON A PHYSICIAN-STAFFED HELICOPTER

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Smith MD et al. 2012

Design	Prospective, non randomized double-blinded comparison trial Prehospital setting Physician staffed helicopter
Patients	Severe acute pain n=204, age 18 to 64 Trauma NRS≥8/10
Intervention	Morphine 4 mg IV repeated q 5 min prn
Comparator	Fentanyl 50 mcg IV repeated q 5 min prn
Objective	To evaluate the effectiveness and safety of fentanyl vs morphine for traumatic injury
Endpoint	Difference between the change in pain score provided by fentanyl and morphine

Enrolment:

✧ Odd calendar dates = morphine

✧ Even calendar dates = fentanyl

Table 1. Demographic Characteristics of Patients in Morphine and Fentanyl Arms

	Morphine (n = 104)	Fentanyl (n = 100)
Mean age, years	38	39
Gender		
Males	75%	76%
Females	25%	24%
Race		
Caucasian	80.8%	81.0%
African-American	16.4%	14.0%
Other	2.9%	5.0%
Trauma mechanism		
Blunt	90.0%	85.0%
Penetrating	10.0%	15.0%

➤ 57.5% received analgesics prior to enrolment

Results

Table 2. Administration Characteristics

	Morphine	Fentanyl
Mean initial pain score	8.0	8.0
Median initial pain score	8.0	8.0
Mean final pain score	5.8	5.5
Median final pain score	5	5
Mean no. doses given	3.0	3.3
Mean transport time	37 min	43 min

✧ Each patient was allowed a maximum of five doses of the study drug (25 min)

▪ Final pain score was pain score after the last dose

✧ Significant change in pain score was a change of ≥ 2

▪ Seen in 61.5% in morphine group and 69% in fentanyl

Adverse events

- Absence of
 - pruritus
 - nausea/vomiting
 - hypotension
 - hypoxia

Summary

- No difference in change in final pain score
 - Equianalgesic doses
 - Titration of fentanyl not optimized
 - Final pain score was not assessed at a standardized time
- No adverse events
 - No follow up after arrival to hospital
- Blinded but not randomized
- 57.5% of subjects received analgesics before study enrollment

Effectiveness and Safety of Fentanyl Compared with Morphine for Out-of-Hospital Analgesia

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Prehosp Emerg Care. 2010 April 6; 14(2): 167–175.

Fleischman RJ et al. 2010

Design	Retrospective chart review, prehospital setting Before and after a change in protocol
Patients	N=718 , Age 13 to 99 years 8.2/10
Intervention	Morphine 2 to 5 mg IV q 5 minutes (maximum 20 mg)
Comparator	Fentanyl 50 mcg IV then 25 to 50 mcg q 3 to 5 minutes (maximum of 200 mcg)
Objective	To determine if a protocol change to fentanyl resulted in improved efficacy and reduced adverse effects vs morphine
Endpoint	Change in pain score on a 0 to 10 scale

Baseline characteristics

	Morphine (<i>n</i> = 355)		Fentanyl (<i>n</i> = 363)		<i>P</i> value
Mechanism of Injury					0.34
Fall from ground level or stairs	147	(41.4%)	176	(48.5%)	
Lifting/straining/reaching/repetitive	23	(6.5%)	16	(4.4%)	
Bicycle and non-motorized vehicle	11	(3.1%)	11	(3.0%)	
Motor vehicle crash	11	(3.1%)	7	(1.9%)	
Motorcycle/All terrain vehicle	6	(1.7%)	6	(1.7%)	
Chronic pain	3	(0.8%)	7	(1.9%)	
Fall from height	4	(1.1%)	4	(1.1%)	
Other, unknown or no trauma	141	(39.7%)	132	(36.4%)	

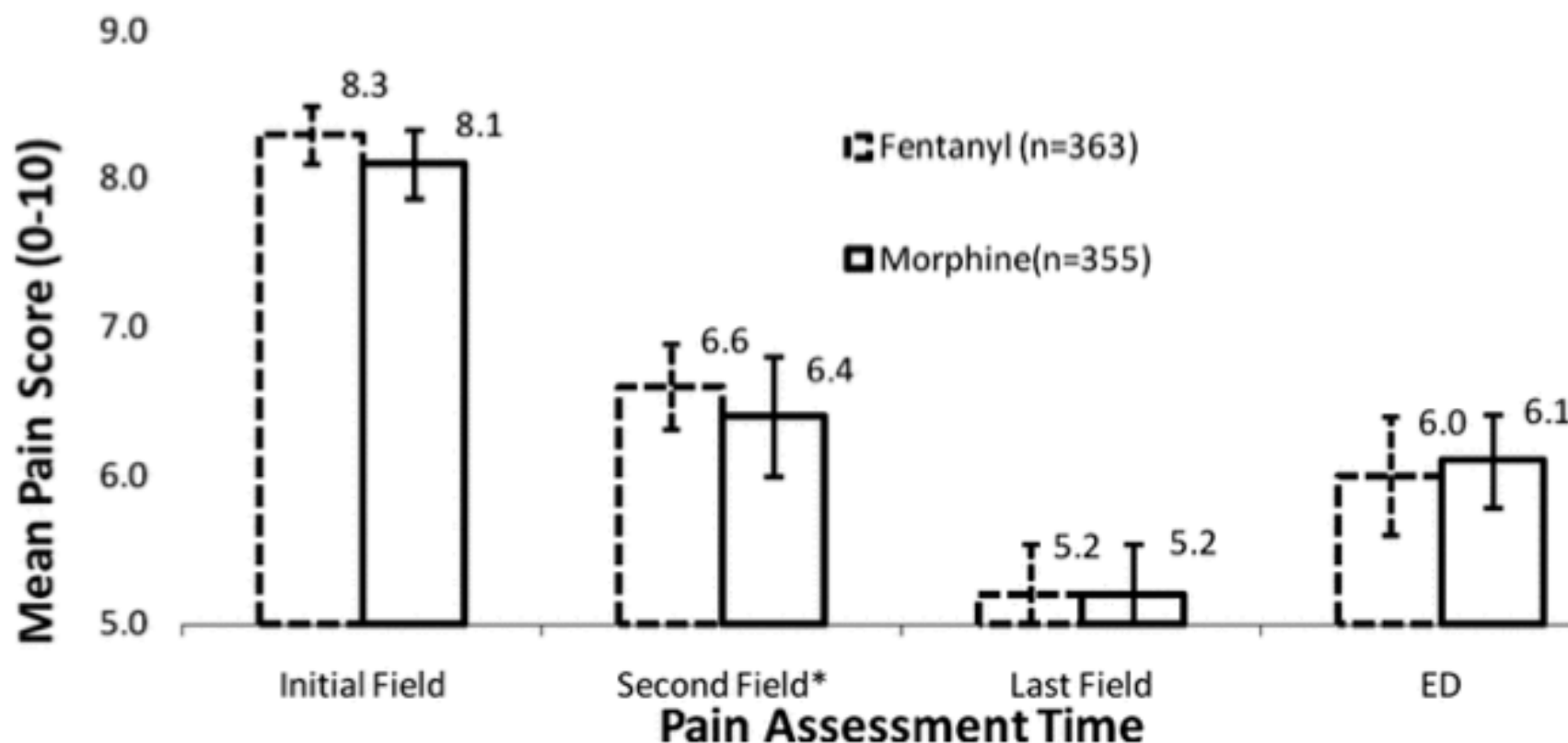
Baseline characteristics

	Morphine (<i>n</i> = 355)		Fentanyl (<i>n</i> = 363)		<i>P</i> value
Male sex	150	(42.2%)	133	(36.6%)	0.13
Age. Median (95% CI)	59	(56--61)	61	(59--63)	0.14
Weight, kg. Mean (95% CI)	79.5	(77--82)	78.3	(75--81)	0.49
Charlson co-morbidity score. Mean (95% CI)	0.71	(0.6--0.8)	0.84	(0.7--9)	0.15
Chief Complaint					< 0. 01
Extremity and hip pain and burns	240	(68%)	244	(67%)	
Atraumatic abdominal and pelvic pain	31	(8.7%)	50	(13.8%)	
Suspected ischemic chest pain	50	(14%)	23	(6.3%)	
Back pain	23	(6.4%)	33	(9.1%)	
Other chest pain	9	(2.5%)	10	(2.8%)	
Head and neck pain	2	(0.6%)	3	(0.8%)	

Baseline characteristics

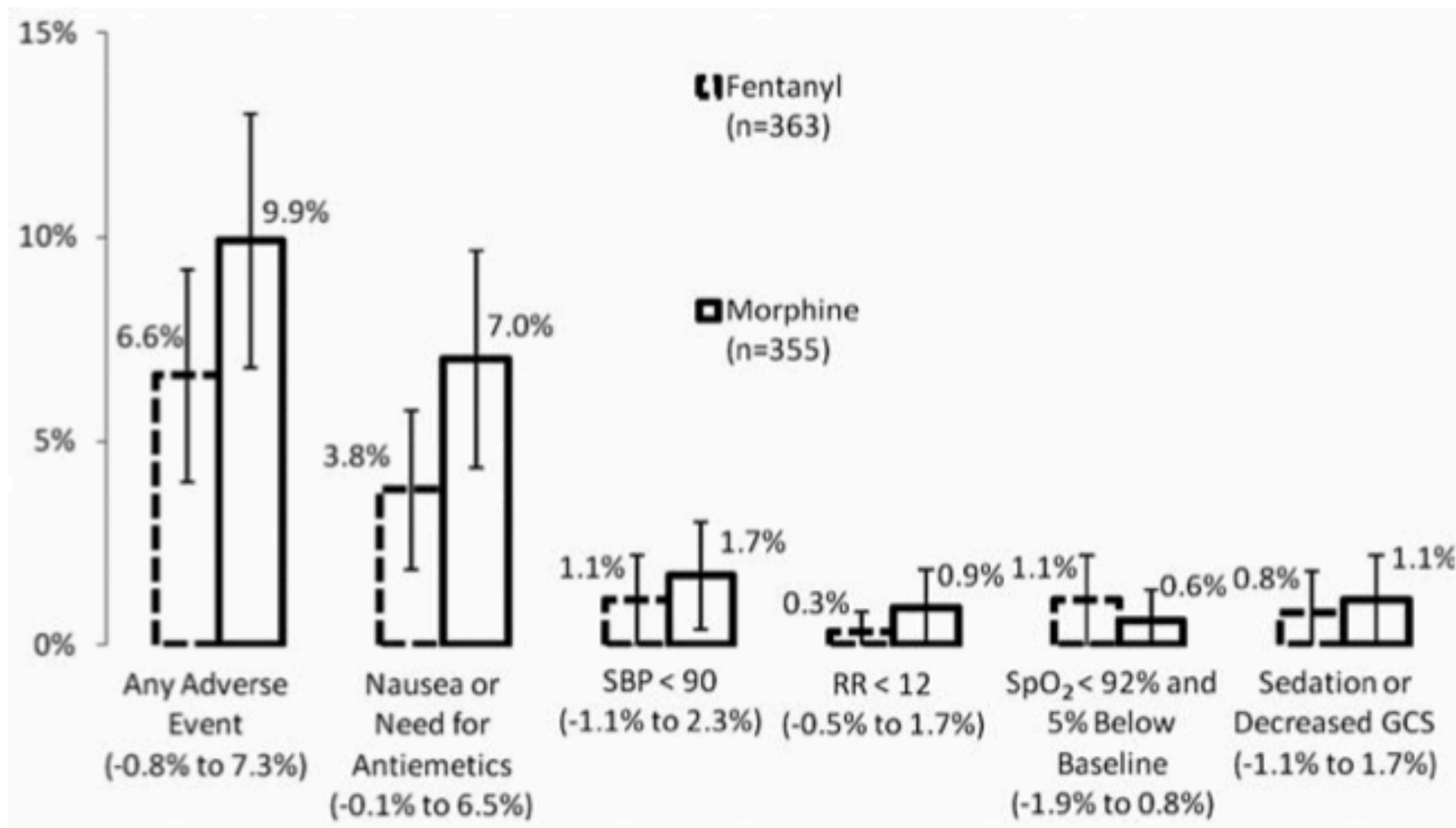
	Morphine (<i>n</i> = 355)		Fentanyl (<i>n</i> = 363)		<i>P</i> value
On-protocol indication for opioid	289	(81%)	260	(72%)	0.002
Opioid doses. Mean (95% CI)	2.2	(2.1--2.3)	2.2	(2.1--2.3)	0.93
Morphine equivalents. mg (95% CI)	7.7	(7.2--8.1)	9.2	(8.7--9.8)	0.001
Morphine equivalents by kg. mg/kg (95% CI)	0.10	(0.10-.11)	0.12	(0.12-.13)	0.001
Home opioids	105	(30%)	121	(33%)	
Cancer	21	(5.9%)	34	(9.4%)	0.08
Liver disease	2	(0.6%)	4	(1.1%)	0.43
Renal dysfunction	8	(2.3%)	4	(1.1%)	0.23

Change in NRS

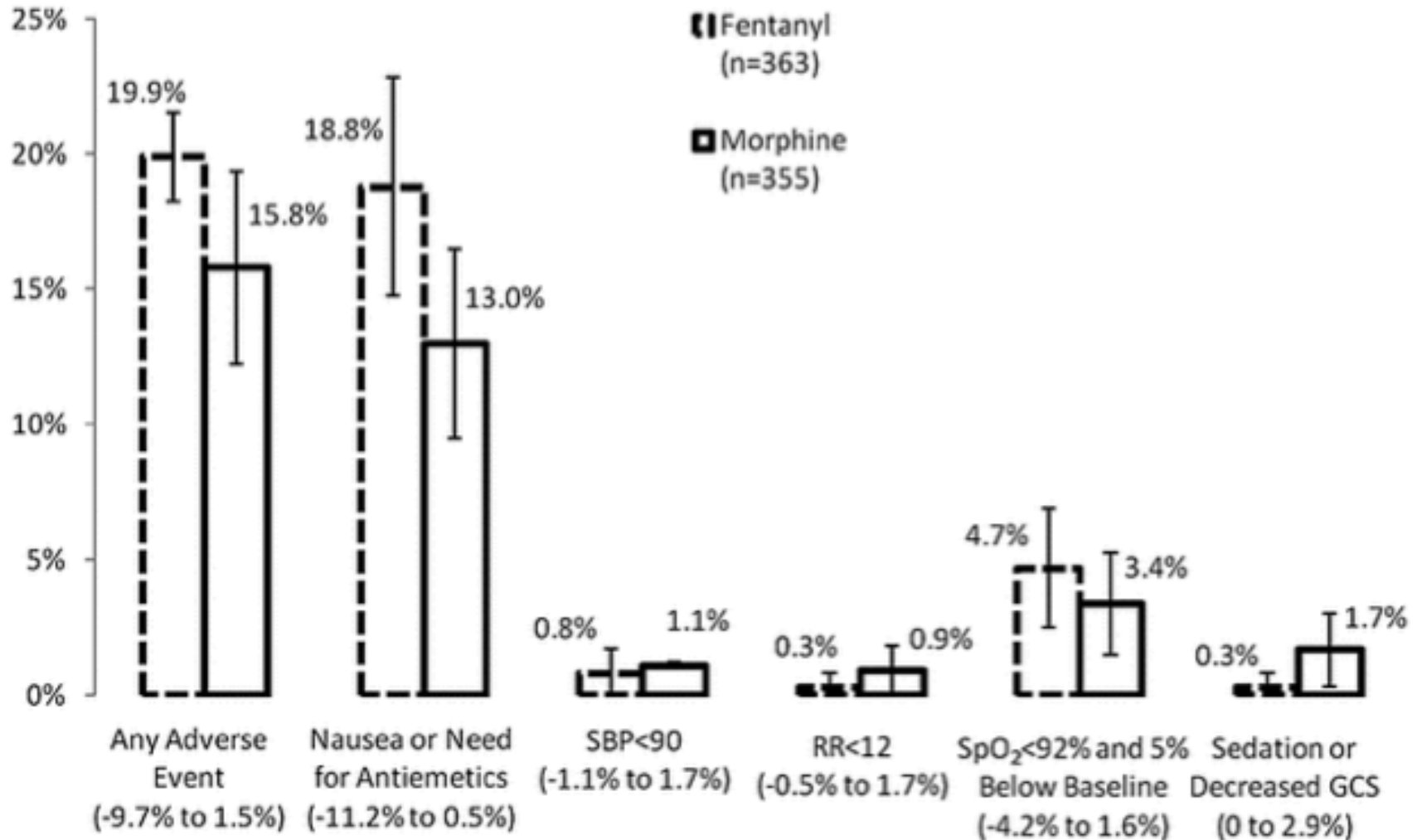


	Baseline	Change
Morphine	8.1 (CI 7.9 to 8.4)	2.9 (CI 2.5 to 3.2)
Fentanyl	8.3 (CI 8.1 to 8.5)	3.1 (CI 2.8 to 3.4)

Adverse events – prehospital



Adverse events in ED



Summary

- “Morphine and fentanyl provide similar degrees of out-of-hospital analgesia. Both medications had low rates of adverse events”
- Fentanyl patients received a higher morphine equivalent dose
- Time frame of analgesia not described
- Retrospective
 - Before and after a protocol change
 - Multivariable linear regression
- Large sample size
 - May improve the characterization of ADE

Morphine Versus Fentanyl for Pain Due to Traumatic Injury in the Emergency Department

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Richard Amini, MD ■ Asad E. Patanwala, PharmD

J Trauma Nurs 2013;20(1) 10-15

Wenderoth BR et al. 2013

Design	Retrospective cohort study, single center, emergency department
Patients	Severe acute pain n=168, Age 18 to 70 100% trauma NRS $\geq 4/10$
Intervention	morphine 4 mg IV
Comparator	fentanyl 50 mcg IV
Objective	To compare morphine and fentanyl with regard to the analgesic response in trauma patients in the ED
Endpoint	Difference between change in pain score (NRS) within 2 hours post dose

TABLE 1 Patient Demographics and Clinical Data (n = 84)

	Morphine Median (IQR)	Fentanyl Median (IQR)	<i>P</i>
Demographics			
Age, y	37 (24-51)	38 (24-53)	.88
Sex, men	67%	68%	.87
Weight, kg	80 (68-95)	81 (66-98)	.68
Race, %			.38 ^a
White	61	50	
Hispanic	30	38	
Other	9	12	
Vital signs and scores			
Systolic blood pressure, mm Hg	139 (125-149)	133 (122-148)	.15
Heart rate, beats per min	91 (81-101)	92 (85-100)	.46
Respiratory rate, breaths per min	18 (16-20)	20 (18-22)	.02
Oxygen saturation, %	98 (96-100)	99 (97-100)	.52
Glasgow coma score	15 (15-15)	15 (15-15)	.84
Injury severity score	5 (1-9)	9 (3-12)	.03
Opioid and pain data			
Prehospital opioid dose, ^b mg	8 (4-10)	10 (5-15)	.08

Results

	Pre dose pain score	Change in pain score	% additional opioids at 30 min	Lowest post dose pain score (min)
Morphine	8	2	20.9	47
Fentanyl	10	2	43.8	22
	NS	NS	$P = 0.004$	$P < .001$

- Change in pain score = baseline – final post dose
- Final post dose = lowest achieved in 2 hours, prior to additional doses
- The time to lowest pain score was that recorded before any subsequent dose was given

Adverse events

Fentanyl (n=84)

Systolic BP <90 n=5

RR<12 n=2

O2 Sat <90% n=1

Treatment of nausea 15.5%

Morphine (n=84)

Itching n=1

Treatment of nausea 7.1% *

*21.4% received prophylactic antiemetics

Summary

- “Fentanyl produced a similar analgesic response to morphine for traumatic injuries in the ED. However, the response and redosing was more rapid with fentanyl.”
 - Pain not assessed in a standardized fashion
- Retrospective
 - Linear multivariate regression
- Outcome is pain control following one dose
 - Titration not assessed
 - No standard pain management protocol
- Standardized forms used for data collection
- 2nd investigator confirmed all data collection
- Comparable morphine and fentanyl doses
- Sample size calculation

Summary

Study	Intervention	Comparator	Change in pain score
Galinski M RCT Prehospital	Morphine 0.1 mg/kg then 3 mg q 5 min	Fentanyl 1 mcg/kg then 30 mcg q5min	No difference at 30 min
Smith MD Prospective Prehospital	Morphine 4 mg IV repeated q 5 min prn	Fentanyl 50 mcg IV repeated q 5 min prn	No difference
Fleischman RJ Retrospective Prehospital	Morphine 2 to 5 mg IV q 5 min	Fentanyl 50 mcg IV then 25 to 50 mcg q 3 to 5 min	No difference
Wenderoth BR Retrospective ED	Morphine 4 mg IV	Fentanyl 50 mcg IV	No difference

Clinical question

- Fentanyl vs morphine for:
 - Pain control ☒
 - Patient satisfaction ☒
 - Adverse events ? ☒
 - Respiratory depression
 - Hypotension
 - Decrease in LOC
 - Nausea
 - Pruritus

Bottom line

- There is no evidence that fentanyl is better than morphine for acute severe pain
- PK-PD delays do not appear to translate into ↓ overall pain control
- Because of the potential for delayed effects, avoid repeated **high** doses
- Possible explanations
 - PK-PD studies in healthy subjects use endpoints such as miosis and trancutaneous stimulation
 - Pain is a complex emotional and physical experience and surrogates may not correlate with clinical scenarios
 - Morphine is thought to have a relatively flat effect site concentration profile. Rising to 80% of its peak quickly and exhibiting a delay until peak

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Extras....

Table II. Time to 25% and 50% reduction in initial pain intensity for 25% and 50% of patients

	<i>Time to 25% reduction in initial pain intensity (min)</i>		<i>Time to 50% reduction in initial pain intensity (min)</i>	
	<i>25% of patients</i>	<i>50% of patients</i>	<i>25% of patients</i>	<i>50% of patients</i>
Morphine, 10 mg	1.8*	4.0*	6.0†	13.9†
Morphine, 5 mg	4.0‡	9.1‡	15.0	>60.0
Placebo	6.0	>60.0	40.0	>60.0

*Morphine, 10 mg, versus placebo, $p < 0.01$; Morphine, 10 mg, versus morphine, 5 mg, $p = 0.02$.

†Morphine, 10 mg, versus placebo, $p < 0.01$.

‡Morphine, 5 mg, versus placebo, $p = 0.048$.

Cost

- Fentanyl 0.05mg/mL
 - Unit Price: 1.76
- Morphine 2mg/mL
 - Unit Price: 0.25

Galinski M et al. 2005: Blinding protocol

- 20 mL syringes
- 1 mg/mL morphine
- 10 mcg/mL fentanyl
- First dose
 - 1 mL per 10 kg
 - 0.1 mg/kg of morphine
 - 1 mcg/kg of fentanyl
- Followed by additional volumes of 3 mL until pain relief

Galinski M et al. 2005: Sample size

- Calculated to detect a VASS difference higher than 14/100 in favor of fentanyl
- Using an α error of .05 and a β error of .10
- Resulted in a minimum of 26 patients needed for each group

Galinski M et al. 2005

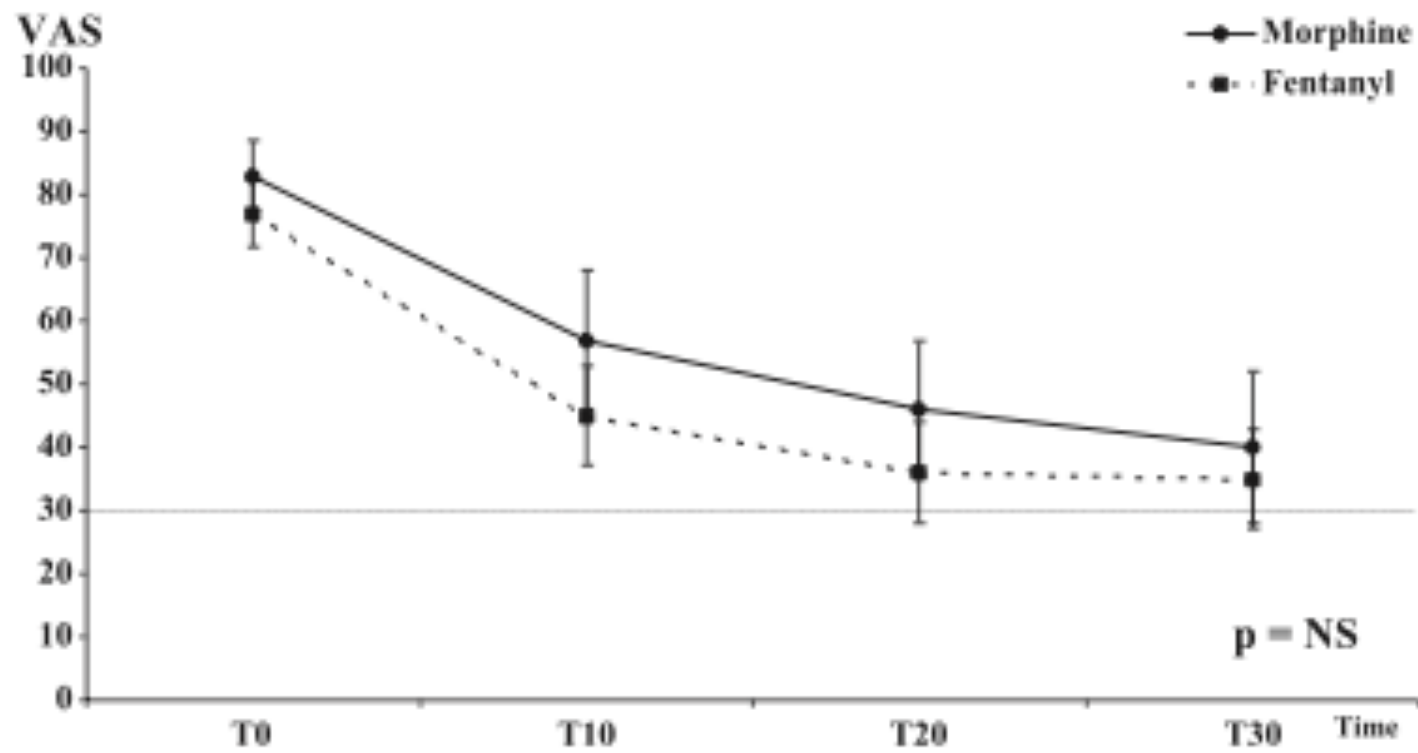
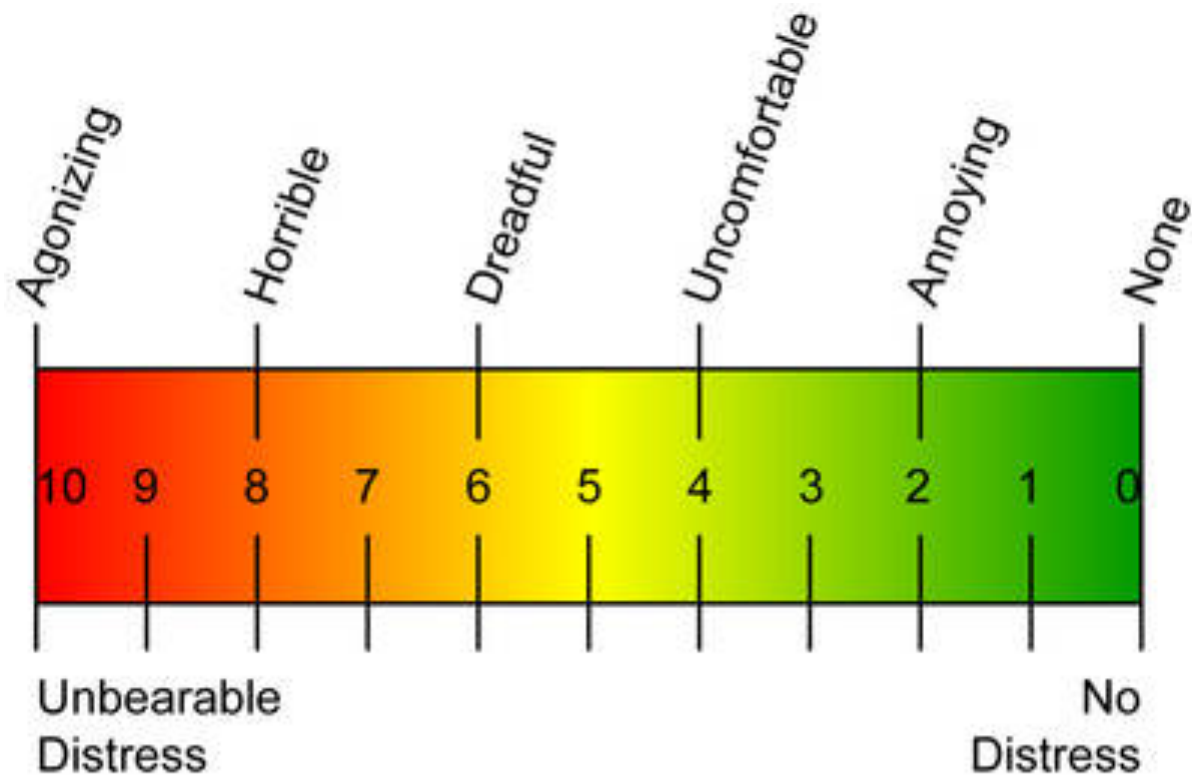


Fig. 2 Evolution of VASS in the F and M groups.

Numeric rating scale (NRS)

- Verbally administered
- Severity of pain before and after drug administration
- 11-points (0 to 10)
- 0 = no pain, 10 = worst pain possible
- Validated in the ED against a 10-cm visual analog scale
- Minimum clinically significant difference = 1.3 points

Visual analog scale (VAS)



Fentanyl in acute pain: Curtis KM et al.

Group A	Group B	Group C
No analgesics	Stable physiology	Normal Physiology
	Fentanyl q 15 min prn	Fentanyl q 5 min prn

- Stable physiology based on hemodynamics and GCS score
- >40 kg = Fentanyl 25-50 mcg IV
- <40 kg = Fentanyl 10-25 mcg IV
- 52% (n=21) achieved a > 2 point ↓ in 30 to 90 min
- 11-point scale

Morphine in acute pain: Bijur PE et al

- Prospective convenient cohort (n=119)
- Morphine 0.1 mg/kg in patients with acute, severe pain (baseline NRS=10)
- Primary outcome 50% decrease in pain from baseline on an 11 point NRS at 30 min
 - 80 patients did not active this
 - (67%; 95% CI 58% to 76%)
- Conclusion: this dose of morphine may not be adequate

Morphine in acute pain: Bounes V et al.

	Group A (n=53)	Group B (n=53)
	0.05 mg/kg morphine then 0.025 mg/kg every 5 minutes	0.1 mg/kg morphine then 0.05 mg/kg every 5 minutes
% NRS at ≤ 30 10 min	17%	40%
% NRS ≤ 30 at 30 min	66%	76%

- Odds of achieving NRS ≤ 30 within 10 min was 3.4 times higher in group B ($P<.01$; 95% CI, 1.3-8.8)
- Prehospital setting

Morphine acute pain: Birnbaum A. et al.

Morphine 0.10mg/kg IV

Morphine 0.15 mg/kg IV

- R, DB, PC n=280
- Baseline pain score=10
- Proportion experiencing $\geq 50\%$ reduction in pain from baseline to 60 minutes
 - 67% vs 53%
- Greater decrease in mean NRS at 60 min
 - 0.8 [95% CI 0.1 to 1.5]

Smith MD et al. 2012

	Baseline	End transport time	Change
Morphine	8 ± 2	5.8 ± 2.7	2.2
Fentanyl	8 ± 1.8	5.5 ± 2.4	2.5

Significant change in pain score was a change of ≥ 2

Significant change morphine (61.5%) and fentanyl (69%)