Spotlight on drugs

Advanced courses 2019

Dr Andrew Wilcock DM FRCP
andrew.wilcock@nottingham.ac.uk

The University of Nottingham

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Developments in opioid analgesics

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Outline of talk

- background
  - cancer pain / strong opioids
- pharmacology
- new approaches (as we go)
- summary
- discussion/questions.

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Background

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Opioids

- central to the management of moderate–severe acute pain and cancer pain.

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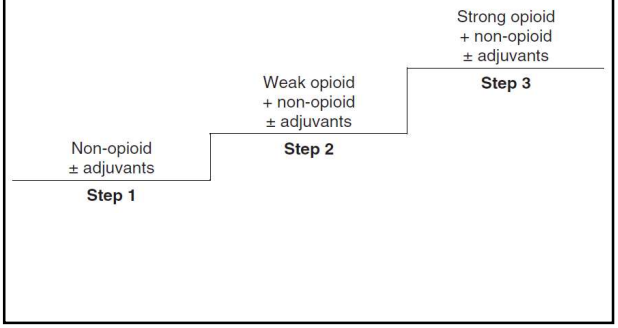
WHO analgesic ladder for cancer pain



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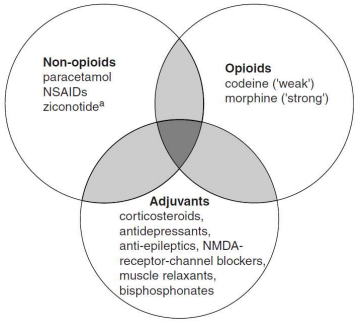
Broad-spectrum analgesia



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Opioids: why improve?

Ultimate aim to:

- improve efficacy
- eliminate / reduce risk of undesirable effects, e.g.:
  - constipation
  - dependence
  - respiratory depression
  - sedation
  - tolerance.

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Pharmacology

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Opioids: chemical classification

Phenanthrenes	*Benzomorphans*	*Phenylpiperidines*	*Diphenylheptanes*
Codeine Dihydrocodeine Hydrocodone Tramadol	Diphenoxylate Loperamide Pentazocine[a]	Fentanils Pethidine[a]	Dextropropoxyphene Methadone
Morphine Diamorphine Buprenorphine Hydromorphone Oxycodone Oxymorphone Tapentadol			

a. not recommended for use in palliative care.

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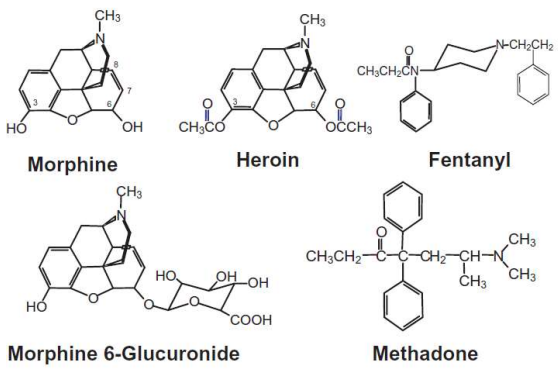

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Opioid: receptors

Four main types:

- μ
- κ
- δ
- opioid-receptor-like 1 (OPRL-1)
  - opioid-related nociceptin receptor 1
  - nociceptin opioid peptide (NOP)
  - nociceptin/orphanin FQ (N/OFQ).

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Opioid: receptors

Receptors	Mu (μ)	Delta (δ)	Kappa (κ)	Opioid receptor-like 1 (ORPL-1)
Endogenous opioid	β-Endorphin Endormorphins	Enkephalins	Dynorphins	Nociceptin
Exogenous agonist	Morphine Buprenorphine[b] Codeine Dextropropoxphene Diamorphine Dihydrocodeine Fentanils Hydromorphone Methadone[c] Oxycodone Pethidine Tapentadol[c] Tramadol[c]	DSTBULET	U50488H Pentazocine	Buprenorphine[b]
Antagonists	Naloxone Naltrexone Pentazocine	Buprenorphine Naloxone	Buprenorphine Naloxone	
Effector mechanism	G protein opens K^+ channel	G protein opens K^+ channel	G protein closes Ca^{++} channel	G protein opens K^+ channel
Effects[d]	*Hyperpolarization of neurons, inhibition of neurotransmitter release*			
	Analgesia Euphoria Nausea Constipation Cough suppression Dependence Respiratory depression Miosis	Similar to μ but less marked	Analgesia Aversion Diuresis Dysphoria	Mixed analgesia (spinal) and anti-analgesia (brain)

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Opioids

Generally:

- μ-opioid receptor clinically most relevant for analgesia and undesirable effects
- Centrally: dorsal horn, higher centres
  - pre-synaptic: inhibit release of neurotransmitters
  - post-synaptic: hyperpolarize neurone
- Peripherally: nerve endings, DRG, (immune cells)
  - inflammation upregulates opioid receptors

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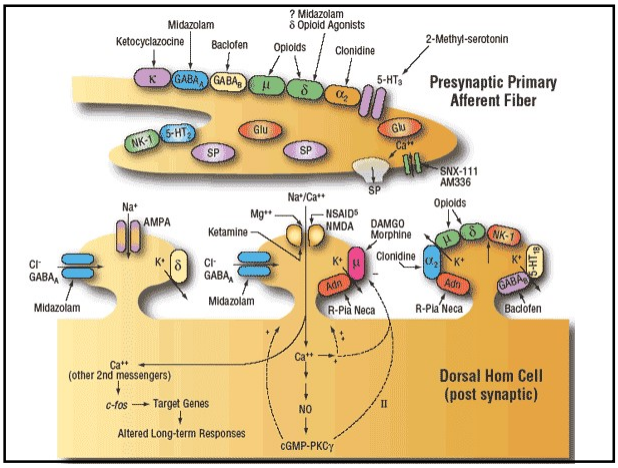

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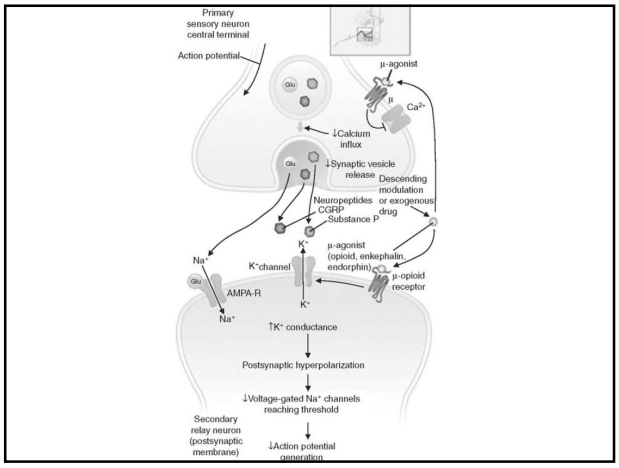

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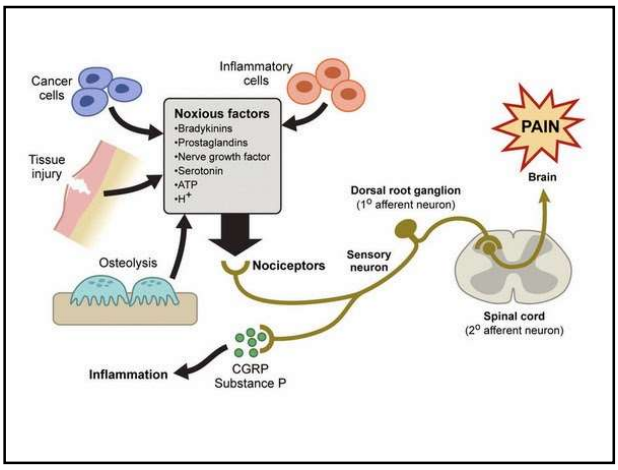

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New approaches for opioid analgesics

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New approaches for opioid analgesics

Include:

1. Broad-spectrum
2. Injury-targeted
3. Biased agonists

Not exhaustive list, but main finds when searching the literature.

Gunther T *et al.* (2018); Chan HCS *et al.* (2017)

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1. 'Broad-spectrum' opioid agonists

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'Broad-spectrum' opioid agonists

- μ most important analgesia / UE
- selective κ and δ agonists
  - limited analgesia / own UE
  - κ (e.g. dysphoria, sedation) [? peripherally limited]
  - δ (e.g. seizures)
- selective NOP agonists
  - mixed effects (analgesia / UE)
  - [? NOP antagonists + MOR agonist in NP]

Gunther T *et al.* (2018)

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Differential analgesic and UE of opioid receptors

Targeting multiple receptors may have synergistic analgesic effects & lower UE

		μ receptor	κ receptor	δ receptor	NOP receptor
Analgesic effects	Acute pain	+++	+	+	–
	Chronic pain	++	+	+++	++
	Neuropathic pain	+	+	+	+
	Inflammatory pain	+	+	+++	++
	Migraine	+	n.a.	+	n.a.
	Visceral pain	n.a.	+	n.a.	+
	Anti-allodynic	+	+	–/+	+
	Anti-depressant	+	+	+	–
Side effects	Rewarding	+	–	+	–
	Respiratory depression, cough reflex	+++	–	+	–
	Constipation, gastric motility	+++	+	+	–
	Euphoria	+	n.a.	n.a.	n.a.
	Dysphoria	n.a.	+	n.a.	n.a.
	Epilepsy	+	–	+	–
	Nausea, vomiting tolerance	+	–	–	–
	Dependence	+++	–	+	–
	Itch	+++	–	n.a.	–
	Renal function	+	+	+	+

The severity of the indicated effect is expressed as high (+++), moderate (++), low (+) or absent (–). No data available (n.a.).

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'Broad-spectrum' opioid agonists

- bind with high affinity to multiple opioid receptors
- aim to improve analgesia with fewer undesirable effects
- bi- or multifunctional ligands, targeting two or more receptors.

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Bi- or multifunctional opioid ligands

Substance	μ receptor	κ receptor	δ receptor	NOP receptor	Profile/activity	Source
Dihydroetorphine	+++	+++	+++	n.a./–	analgesic for severe and cancer pain	Ohmori *et al.* 2000, Ohmori and Morimoto, 2002, Ranganathan *et al.*, 2012
Nalfurafine	+++	+++	+	+	antipruritic and antinociceptive activity; clinical trial for pruritus	Kumagai *et al.*, 2010, Nakao *et al.*, 2016, Endoh *et al.*, 1999
Buprenorphine	++	n.a./–	n.a./–	+	opioid substitution therapy; postoperative pain control; chronic pain; cancer pain; neuropathic pain in combination with full μ receptor agonists	Lutfy and Cowan, 2004, Huang *et al.*, 2001, Khroyan *et al.*, 2009a, 2009b, van Niel *et al.*, 2016, Bomhomme *et al.*, 2012
BU08028	+++	–	+	++	antinociceptive, antihypersensitive and antiallodynic activity; absence of respiratory and cardiovascular activities; absence of physical dependence and pruritus	Ding *et al.*, 2016, Khroyan *et al.*, 2011
SR14150 (AT-200)	++	+	n.a.	+++	antinociceptive	Spagnolo *et al.* 2008, Khroyan *et al.*, 2007, Toll *et al.*, 2009, Sukhtankar *et al.*, 2013
SR16435 (AT-201)	+++	+	–	++	antinociceptive and antiallodynic, induces CPP, slower development of tolerance compared to μ receptor agonists under neuropathic pain	
SR16835 (AT-202)	++	+	n.a.	+++	not antinociceptive, induces no CPP, attenuates morphine-mediated CPP	
Cebranopadol	+++	++	+	+++	clinical trial for severe chronic and neuropathic pain	Linz *et al.* 2014

The grade of intrinsic activity is expressed as high (+++), moderate (++), low (+) or absense (–) of intrinsic activity determined by GTPγS assay. (n.a.) Data are either not available or were not determined.

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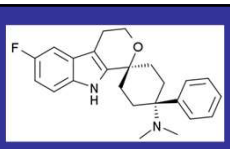
Cebranopadol



- most progressed example
- NOP and μ agonist
- Tmax 4–6h; long halflife (15h) = o.d. dosing
- NOP analgesic effects at spinal/peripheral level; antagonistic effects supraspinal level
  - ? ↓ tolerance/dependence/respiratory depression.

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Cebranopadol

- broad activity across *animal* models of acute nociceptive, inflammatory, neuropathic and cancer pain
- more potent than morphine in chronic pain, particularly neuropathic
- without effect on motor co-ordination (sedation) or respiratory function.

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Cebranopadol

- Phase II RCT study in postoperative pain (bunionectomy); compared single PO doses of:
  - placebo
  - cebranopadol 200, 400, 600microgram
  - morphine m/r 60mg
- 1st/2nd line rescue analgesics = paracetamol / diclofenac
- primary outcome = sum of pain intensity 2–10h after investigational treatment (NRS)

Scholz A *et al*. (2018)

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Cebranopadol: postoperative pain

- 400 and 600microgram doses more effective than placebo
- associated with greater patient satisfaction and ↓ adverse events cf. morphine
- dosing at different time points ±1h local anaesthetic infusion discontinued.

Scholz A *et al*. (2018)

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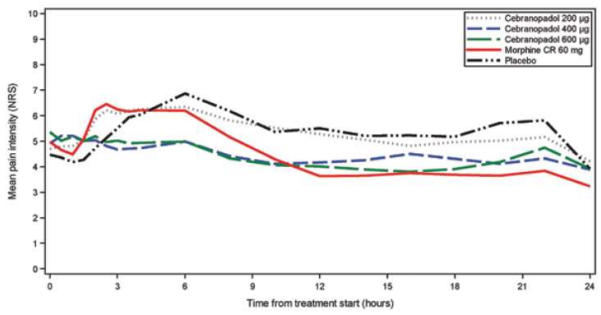
Primary outcome SPI 2–10h



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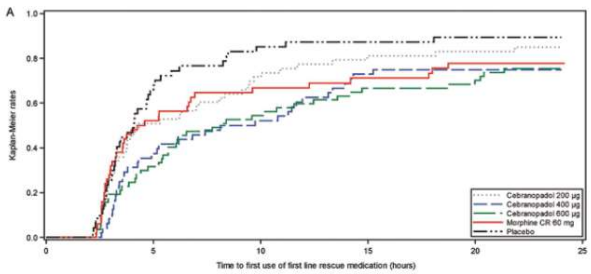
Time to 1st line rescue dose



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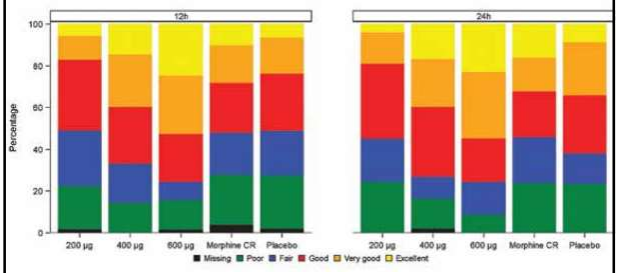
Patient global impression



Cebranopadol 600microgram significantly better than placebo, morphine

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Cebranopadol: postoperative pain

- frequency of any undesirable effect

		% of patients
Placebo		68
Cebranopadol	200	67
	400	78
	600	84
Morphine		92

- 600microgram and morphine same frequency of common UE (e.g. nausea, vomiting, dizziness, drowsiness)

Scholz A *et al.* (2018)

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Cebranopadol

- can provide effective analgesia
- but similar rates of opioid UE in acute pain
- similar findings in chronic pain
  - study in chronic back pain with placebo/tapentadol as comparators

Scholz A *et al.* (2018); Christoph A *et al.* (2017)

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Research Paper

PAIN

OPEN

Cebranopadol, a novel first-in-class analgesic drug candidate: first experience in patients with chronic low back pain in a randomized clinical trial

Annette Christoph[a,*], Marie-Henriette Eerdekens[a], Maurits Kok[a], Gisela Volkers[a], Rainer Freynhagen[b,c]

Abstract

Chronic low back pain (LBP) is a common condition, usually with the involvement of nociceptive and neuropathic pain components, high economic burden and impact on quality of life. Cebranopadol is a potent, first-in-class drug candidate with a novel mechanistic approach, combining nociceptin/orphanin FQ peptide and opioid peptide receptor agonism. We conducted the first phase II, randomized, double-blind, placebo- and active-controlled trial, evaluating the analgesic efficacy, safety, and tolerability of cebranopadol in patients with moderate-to-severe chronic LBP with and without neuropathic pain component. Patients were treated for 14 weeks with cebranopadol 200, 400, or 600 µg once daily, tapentadol 200 mg twice daily, or placebo. The primary efficacy endpoints were the change from baseline pain to the weekly average 24-hour pain during the entire 12 weeks and during week 12 of the maintenance phase. Cebranopadol demonstrated analgesic efficacy, with statistically significant and clinically relevant improvements over placebo for all doses as did tapentadol. The responder analysis (≥30% or ≥50% pain reduction) confirmed these results. Cebranopadol and tapentadol displayed beneficial effects on sleep and functionality. Cebranopadol treatment was safe, with higher doses leading to higher treatment discontinuations because of treatment–emergent adverse events occurring mostly during titration. Those patients reaching the target doses had an acceptable tolerability profile. The incidence rate of most frequently reported treatment–emergent adverse events during maintenance phase was ≤10%. Although further optimizing the titration scheme to the optimal dose for individual patients is essential, cebranopadol is a new drug candidate with a novel mechanistic approach for potential chronic LBP treatment.

Keywords: Chronic low back pain, Cebranopadol, Nociceptin/orphanin FQ, Randomized controlled trial, Placebo control, First-in-class drug, First human phase II RCT

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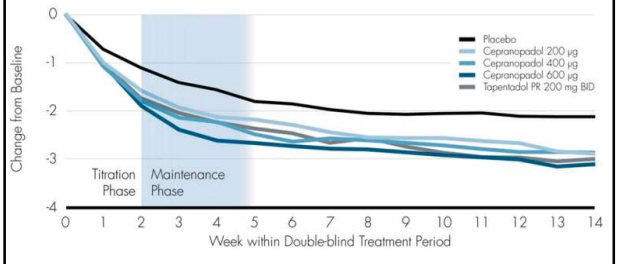
Cebranopadol: efficacy in chronic back pain



Christoph A *et al.* (2017)

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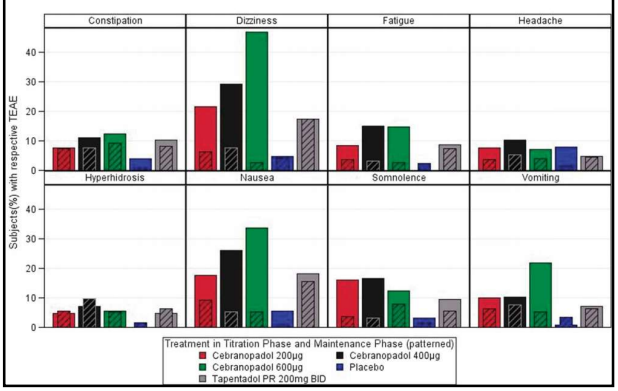
Cebranopadol: tolerability in chronic back pain



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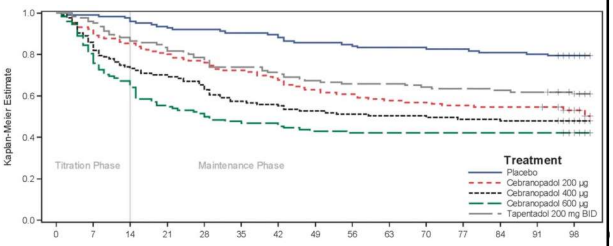
Cebranopadol: withdrawals in chronic back pain



Overall cebranoprolol > tapentadol >> placebo

Christoph A *et al.* (2017)

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Cebranopadol

- has typical opioid UE limiting tolerability
  - more UE than tapentadol for similar analgesia

Still has possible advantages of:

- lack of physical dependence
  - no withdrawal Sx on sudden cessation
- a ceiling effect for respiratory depression (600microgram in young healthy volunteers)
  - but clinically significant respiratory depression could still occur in patients.

Dahan A *et al.* (2017); Christoph A *et al.* (2017)

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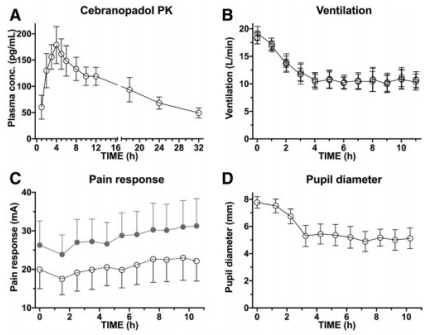
Cebranopadol: effects in healthy volunteers



Dahan A *et al.* (2017)

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Cebranopadol: Cancer pain

- phase III noninferiority study
- cebranopadol
  - 200, 400, 600, 800, 1,000microgram o.d. vs.
- morphine m/r
  - 15, 30, 45, 60, 75mg b.d.
- titrated every 3–4 days → fixed-dose 4 week maintenance
- allowed morphine i/r 10mg p.r.n.
- primary endpoint = mean amount of daily rescue morphine over last 2 weeks

Eerdekens M-H *et al.* (2019)

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Cebranopadol: main endpoints

Primary

- mean amount of daily rescue morphine over last 2 weeks
  - noninferiority margin 8mg (upper limit 95% CI)
  - 170 per group 90% power, sig level 0.025

Eerdekens M-H *et al.* (2019)

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Cebranopadol: main endpoints

Secondary

- response, defined as (any of) average pain:
  - <4/10 over last 2 weeks
  - ↓ ≥30% or ≥2 points from baseline
- undesirable effects.

Eerdekens M-H *et al.* (2019)

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Cebranopadol: Cancer pain

Inclusion criteria included:

- on ≤90mg morphine/day (or equivalent)
  - included weak opioids
- dissatisfied with current pain treatment
  - poor relief/tolerability
- average pain over 24h a mean of ≥5/10.

Eerdekens M-H *et al.* (2019)

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Cebranopadol: Cancer pain

- terminated due to low accrual (2013–15)
- 126 treated (of 524 planned)
- thus, underpowered
- mean age 62 years, most stage IV
- details on the proportion on weak/strong opioids / OME at baseline not given.

Eerdekens M-H *et al.* (2019)

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Primary outcome

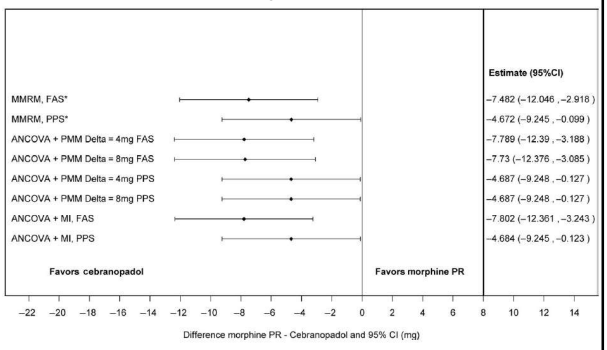

FIGURE 3 Forest plot of the primary efficacy endpoint results from the primary analysis model. ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; MI, multiple imputation; MMRM, mixed-effects model for repeated-measures; PMM, pattern mixture model; PPS, per protocol set; PR, prolonged release

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Cebranopadol: Cancer pain

- noninferior for amount of rescue medication
- mean difference 5–7mg/day
  - favouring cebranopadol (but underpowered)

Eerdekens M-H *et al.* (2019)

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Response: noninferiority not met

Table S3: Proportion of patients with clinically relevant pain reduction in the last 2 weeks of the Maintenance Phase – Observed values – Descriptive analysis – Full Analysis Set and Per Protocol Set.

Clinically relevant pain reduction[a], n (%)	Cebranopadol	Morphine PR, n (%)
Full Analysis Set	**N = 64**	**N = 61**
Yes	48 (75.0)	51 (83.6)
No	16 (25.0)	10 (16.4)
Per Protocol Set	**N = 43**	**N = 45**
Yes	35 (81.4)	40 (88.9)
No	8 (18.6)	5 (11.1)

Missing data were imputed using a multiple imputation on the weekly average pain intensity. Patients that discontinued from the trial due to a lack of efficacy were classified as non-responders.

N = number of patients in the population, n = number of patients with this observation, PR = prolonged release.

[a] Clinically relevant pain reduction (Yes/No) in the last 2 weeks of the Maintenance Phase.

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Table S4: Median of daily rescue medication intake (mg) by week over the Treatment Period – Full Analysis Set and Per Protocol Set.

	Group	
Week in Treatment Period, Median (Q1, Q3)	Cebranopadol	Morphine PR
Full Analysis Set		
Titration Week 1	5.00 (0.0, 11.3)	6.25 (1.3, 20.6)
Titration Week 2	1.18 (0.0, 7.8)	2.50 (0.0, 18.8)
Maintenance Week 1	0.00 (0.0, 2.9)	0.00 (0.0, 13.3)
Maintenance Week 2	0.00 (0.0, 5.7)	2.86 (0.0, 15.7)
Maintenance Week 3	0.00 (0.0, 2.9)	0.00 (0.0, 11.4)
Maintenance Week 4	0.00 (0.0, 4.0)	0.00 (0.0, 20.0)

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Table S5: Maintenance Phase dose levels – Descriptive statistics – Safety Set.

Number of patients per dose level in Maintenance Phase[a], n (%)	Cebranopadol N = 65	Morphine PR N = 61
Level 1 - 200 µg/30 mg	12 (18.5)	11 (18.0)
Level 2 - 400 µg/60 mg	13 (20.0)	18 (29.5)
Level 3 - 600 µg/90 mg	11 (16.9)	8 (13.1)
Level 4 - 800 µg/120 mg	13 (20.0)	10 (16.4)
Level 5 - 1000 µg/150 mg	4 (6.2)	8 (13.1)
Missing plus discontinuation during Titration Phase[b]	12 (18.5)	6 (9.8)

[a] Final dose level (cebranopadol in µg, or morphine PR in mg) at the end of the Titration Phase going into the Maintenance Phase.
[b] The number of patients with missing data is mostly due to discontinuation during the Titration Phase.
N = number of patients in the population, n = number of patients with this observation, PR = prolonged release.

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Cebranopadol: Cancer pain

UEs similar in cebranopadol vs. morphine:

- 83% vs. 82% of patients
- 254 events in 65 patients / 245 events in 61
- generally similar pattern, though in cebrano:
  - more peripheral oedema (11% vs. 0%)
  - less constipation (12% vs. 25%).

Eerdekens M-H *et al.* (2019)

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Cebranopadol: abuse potential

In healthy recreational opioid misusers:

- 200 & 400microgram same as placebo
  - "anticipated dose range 200–600microgram"
- 800microgram similar liking to 8mg hydromorphone (and less than 16mg HM)
  - "800microgram…assumed supratherapeutic"
- longer time to maximum effect (3h vs. 1.5h)
- vomiting ≥3x higher cebran 800 vs. HM.

Gohler K *et al.* (2019)

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Cebranopadol: Cancer pain

In summary:

- more data would be nice to 'place patients'
  - many on weak opioids at baseline?
  - tested over relatively low OME (≤60mg b.d.)
  - [about = tapentadol 200mg b.d. in back pain study]
- overall advantage (efficacy/tolerability/abuse) appears low??
- unlikely to be cost effective??

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BU08028

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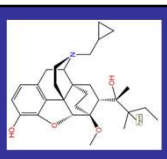
BU08028



Buprenorphine analogue:

- agonist at μ and NOP (6 x higher than buprenorphine); binds to κ and δ but no effect
- in *primates*:
  - analgesic (both μ and NOP contribute)
  - lower reinforcing (addictive) effects cf. cocaine/other opioids
  - lacks physical dependence, respiratory depression.

Ding H *et al.* (2016)

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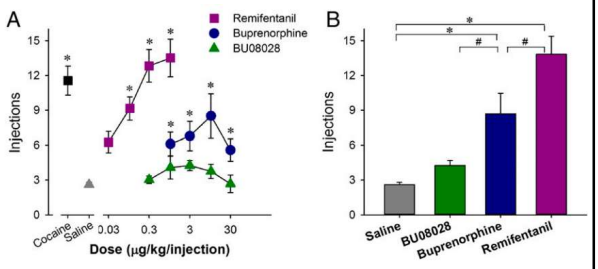
BU08028 lacks reinforcing effects



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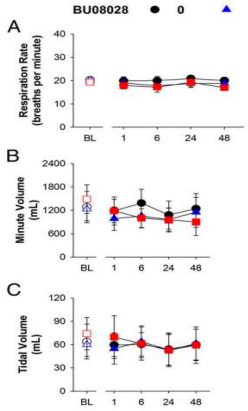
BU08028 does not cause respiratory depression



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'broad-spectrum' opioids

In summary:

- interesting concept and initial data
- will it deliver?
  - difference in acute opioid UE – possibly not
  - less respiratory depression/dependence – remains to be seen
- still a way to go.

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2. Opioid agonist 'targeted' to inflamed tissues

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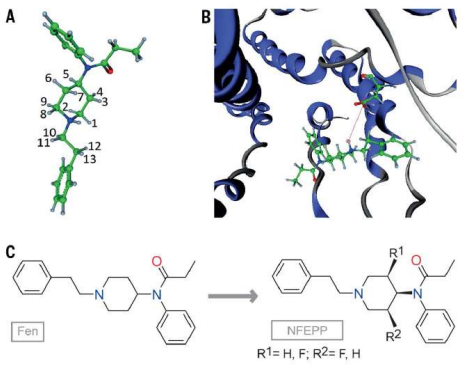
'Injury-targeted' opioid

- opioids mediate +ve and -ve effects via opioid receptors in inflamed and healthy tissue (brain, GIT)
- NFEPP (N-(3-fluoro-1-phenethylpiperidine-4-yl)-N-phenyl propionamide) is a compound that is activated by protonation in inflamed tissue where pH is acidic
- selective binding to opioid receptors at the site of injury could improve pain whilst avoiding undesirable effects.

Rodriguez-Gaztelumendi A *et al.* (2018); Spahn V *et al.* (2017)

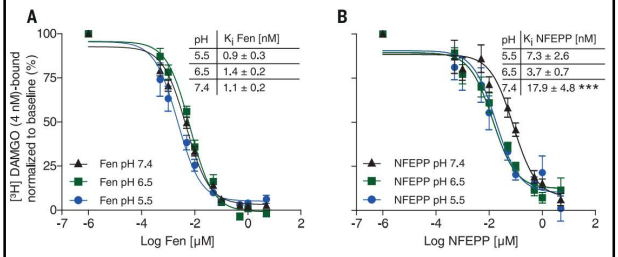
59

NFEPP 'fluorinated fentanyl'



60

Binding affinities of fentanyl (A) and NFEPP (B) at different pH



61

‘Injury-targeted’ opioid

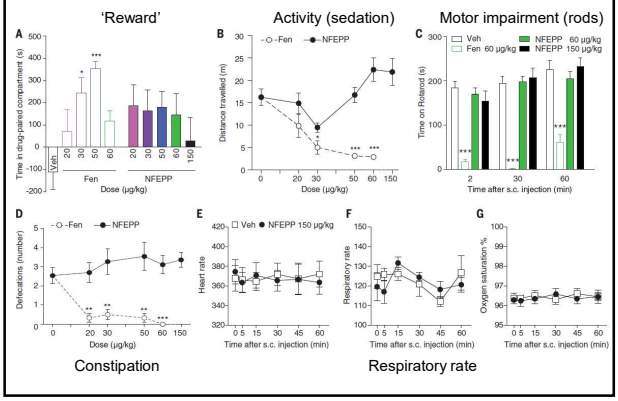
To date, NFEPP tested only in animal models:

- significantly lower binding affinity of NFEPP compared with fentanyl at pH 7.4
- produces analgesia in models of inflammatory, postoperative and neuropathic pain, without exhibiting typical opioid UE
- NFEPP-induced analgesia fully reversed by a peripherally restricted opioid receptor antagonist.

Rodriguez-Gaztelumendi A *et al.* (2018); Spahn V *et al.* (2017)

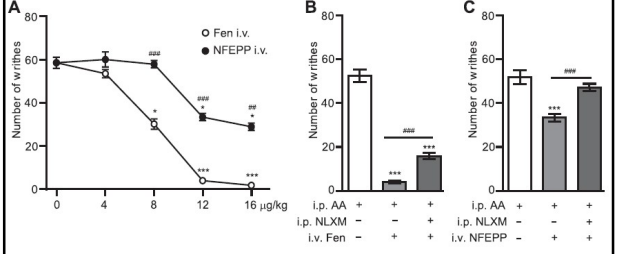
62

Comparison of systemic effects (rats)



63

NFEPP-induced analgesia fully reversed by a peripheral opioid antagonist (rats)



Rodriguez-Gaztelumendi A *et al.* (2018)

64

‘Injury-targeted’ opioid

In summary:

- interesting concept and initial data
- still a long way to go.

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3. Biased μ-receptor agonists

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Biased μ-receptor agonists

Induce receptor conformations that:

- preferentially trigger Gi-dependent signalling
- minimise/avoid activating β-arrestin pathways
- = functional selectivity
  - i.e. although activating the same receptor, different agonists evoke different signalling cascades.

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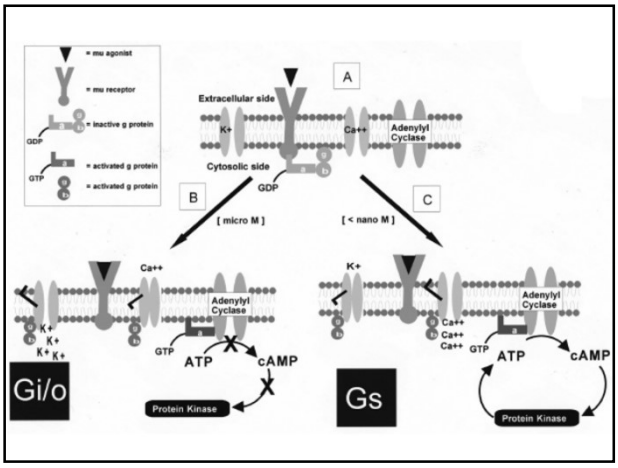
Opioid receptors

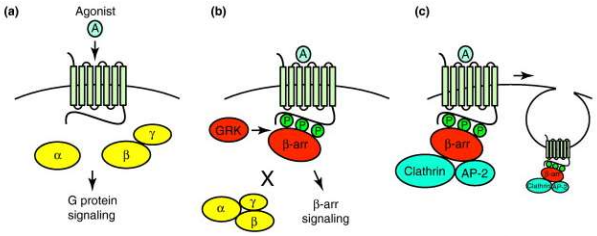
- G-protein coupled receptors
- oscillates between active and inactive states until opioid agonist binds
- conformational change occurs to allow interaction with a G-protein
- G-protein dissociates into subunits which have various 'downstream' effects

68



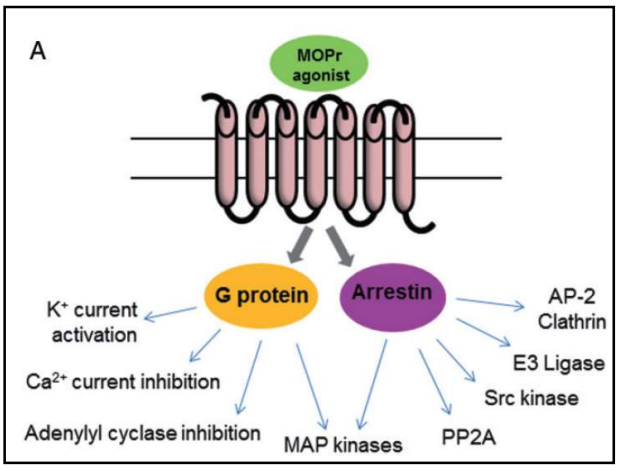
69

Opioid receptor internalization



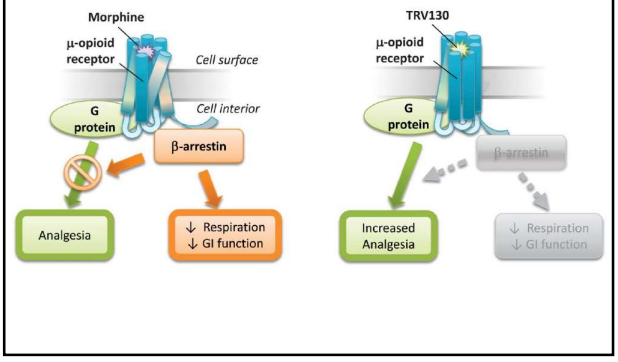
- receptor recycled or destroyed
- contributes towards receptor desensitization and development of tolerance.

70



71

Biased agonists



72

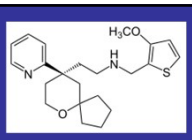
μ-opioid biased-agonist

Two have been examined:

- oliceridine and PZM21
- stimulates μ-opioid receptor coupling with G-proteins as usual
- but subsequently less phosphorylation and recruitment of β-arrestin2.

73

Oliceridine

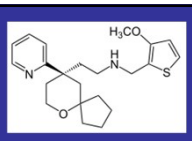


- novel structure
- highly selective for MOR
- more potent than morphine
- fast onset of effect
- metabolized CYP 3A4 and 2D6
- no active metabolites
- 3x preference for G-protein pathway over β-arrestin2 relative to morphine/fantanyl.

Urtis I *et al.* (2019)

74

Oliceridine



- authorization pending USA?

Singla N *et al*. (2017); Viscusi ER *et al*. (2019)

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Trevena Sees Path Forward for Rejected Opioid Pain Medicine

Published: Jan 29, 2019 | By Alex Keown

Shares of **Trevena** soared nearly 120 percent in Monday trading after the company announced it has **found a path forward** for its intravenous opioid-pain reliever oliceridine.

The U.S. **Food and Drug Administration (FDA) issued a Complete Response Letter** to the company in November, one month after an advisory committee rejected the drug. When the FDA issued the CRL, the regulatory agency requested additional clinical data on QT prolongation and indicated that the submitted safety database is not of adequate size for the proposed dosing. The FDA also requested certain additional nonclinical data and validation reports, Trevena said in November.

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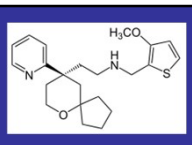
Oliceridine



- authorization pending USA?
- focus is moderate-severe postoperative pain
- IV route of administration
- two phase II studies (PCA, injection)
- one phase III study (PCA)
- ? another study including medical patients requiring IV PCA.

Singla N *et al*. (2017); Viscusi ER *et al*. (2019)

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Oliceridine in abdominoplasty

- double-blind RCT 24h postoperatively
- two different PCA loading/on demand doses IV
- compared with morphine and placebo
- Oliceridine associated with:
  - similar pain relief to morphine
  - lower prevalence of N&V, respiratory effects

Singla N *et al*. (2017)

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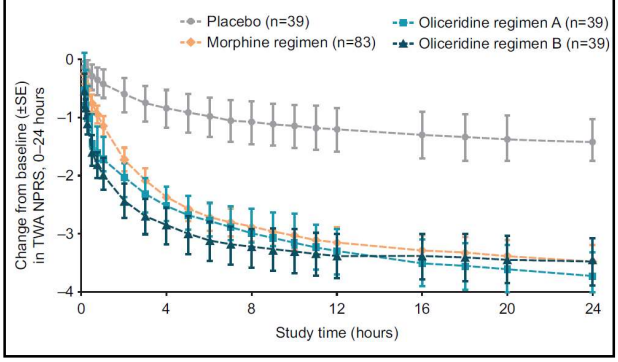
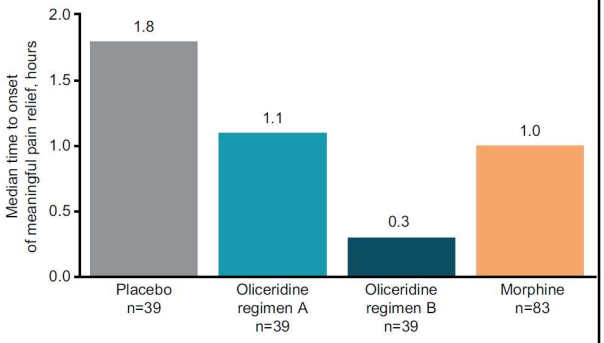
Oliceridine IV PCA postoperative pain



79

Oliceridine IV PCA postoperative pain



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Oliceridine IV PCA postoperative pain

Table 2 TEAEs in ≥10% of patients

	Placebo (n=39)	Oliceridine		Morphine regimen (n=83)
		Regimen A (n=39)	Regimen B (n=39)	
TEAEs in ≥10% of patients				
Patients with ≥1 TEAE	24 (62%) [48]	26 (67%) [54]	32 (82%) [67]	78 (94%) [238]
Gastrointestinal disorders				
Nausea	7 (18%) [7]	16 (41%) [17]	18 (46%) [18]	60 (72%) [63]
Vomiting	3 (8%) [3]	6 (15%) [6]	6 (15%) [6]	35 (42%) [35]
Nervous system disorders				
Headache	5 (13%) [5]	6 (15%) [6]	6 (15%) [6]	14 (17%) [14]
Dizziness	1 (3%) [1]	1 (3%) [1]	4 (10%) [4]	7 (8%) [7]
Somnolence	0	0	2 (5%) [2]	10 (12%) [10]
Vascular disorders				
Hypotension	1 (3%) [1]	6 (15%) [6]	3 (8%) [3]	7 (8%) [7]
Phlebitis	4 (10%) [4]	0	2 (5%) [2]	1 (1%) [2]
Respiratory, thoracic, and mediastinal disorders				
Hypoventilation	4 (10%) [5]	4 (10%) [4]	12 (31%) [12]	34 (41%) [34]
Respiratory depression	0 (0) [0]	3 (8%) [3]	0 (0) [0]	9 (11%) [10]

Notes: Data are number of patients (%) [number of events]. Loading/demand doses (mg/mg): oliceridine regimen A, 1.5/0.10; oliceridine regimen B, 1.5/0.35; morphine, 4.0/1.0.

Reduced N&V, respiratory effects

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Oliceridine IV PCA postoperative pain

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Notes: Data are number of patients (% 4.0/1.0. 0.35; morphine,

Reduced N&V, respiratory effects

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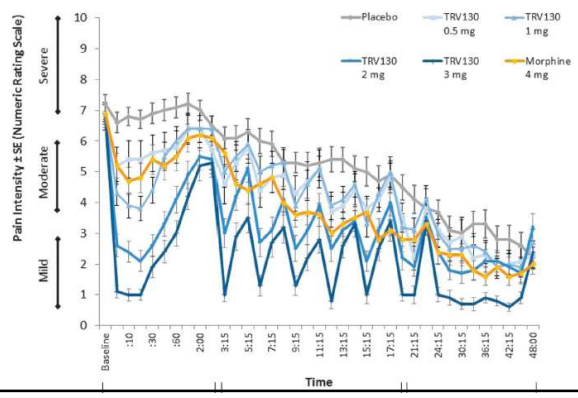
Oliceridine in bunionectomy

- double-blind RCT 48h postoperatively
- 4 groups increasing doses of oliceridine IV q3h
- compared with IV morphine and placebo q4h
- higher doses oliceridine associated with:
  - similar pain relief to morphine overall
  - more rapid analgesia after first dose
  - similar UE as morphine

Viscusi ER *et al*. (2016)

83

Oliceridine in bunionectomy



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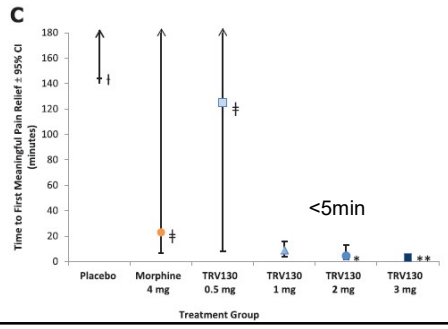
Oliceridine in bunionectomy

Time to meaningful pain relief

After first injection (min)



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Oliceridine in bunionectomy

	Placebo (N = 28)	TRV130 3 mg q3h (N = 31)	Morphine 4 mg q4h (N = 39)
Most frequent adverse events in ≥ 10% of patients in any treatment group			
Nausea	7 (25.0) [8]	23 (74.2) [35]	22 (56.4) [26]
Dizziness	4 (14.3) [5]	18 (58.1) [25]	17 (43.6) [22]
Headache	5 (17.9) [5]	7 (22.6) [7]	9 (23.1) [11]
Vomiting	0	17 (54.8) [19]	12 (30.8) [14]‖
Somnolence	3 (10.7) [3]	4 (12.9) [4]	7 (17.9) [7]
Constipation	1 (3.6) [1]	5 (16.1) [5]	2 (5.1) [2]
Flushing	0	3 (9.7) [3]	4 (10.3) [4]
Hot flush	0	4 (12.9) [4]	4 (10.3) [4]
Pruritus	2 (7.1) [3]	3 (9.7) [3]	2 (5.1) [2]
Dry mouth	2 (7.1) [2]	1 (3.2) [1]	1 (2.6) [1]
Hyperhidrosis	0	5 (16.1) [5]	1 (2.6) [1]
Feeling hot	0	4 (12.9) [4]	1 (2.6) [1]
Pruritus generalized	0	2 (6.5) [2]	4 (10.3) [4]
Patients with adverse events by severity			
Mild	11 (39.3) [17]	6 (19.4) [16]	10 (25.6) [25]
Moderate	7 (25.0) [10]	14 (45.2) [33]	16 (41.0) [31]
Severe	2 (7.1) [3]	8 (25.8) [12]	5 (12.8) [7]

Similar N&V, dizziness, sweating, constipation with oliceridine

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Oliceridine

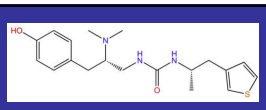
In animal and human studies:

- abuse potential remains
- comparable to morphine, oxycodone.

Urtis I *et al.* (2019) Negus SS *et al.* (2018)

87

PZM21



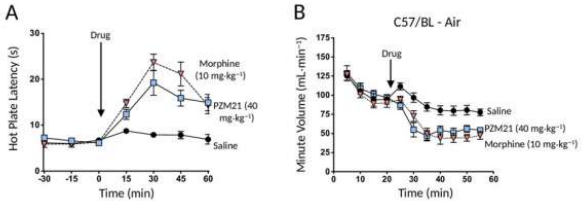
Despite initial positive findings (in rodents), testing by an independent group found:

- low efficacy agonist for both Gi activation and arrestin recruitment
- significant respiratory depression similar to an equi-analgesic dose of morphine.

Hill R *et al.* (2018)

88

Antinociception and respiratory depression induced by PZM21 and morphine in mice



Hill R *et al.* (2018)

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μ-opioid biased-agonists

In summary:

- oliceridine most developed to date
- promising [but inconsistent] preclinical data
- clinical data (oliceridine) suggests short-term in postoperative pain:
  - as effective as morphine overall
  - more rapid onset after a single dose
  - UEs similar to morphine; incidence lower by PCA but same IV
- several others in development.

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Summary

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Summary of main points

- a lot of activity around trying to improve analgesic effect of opioids whilst reducing UE
- many different approaches are being pursued
- none likely to fully overcome acute UE of μ-opioid agonists
- it remains to be seen if they significantly reduce tolerance, dependence and respiratory depression in clinical practice
- still a case of ‘watch this space’.

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