Naltrexone and buprenorphine for the reversal of overdose from long-acting opioids: Iranian experience

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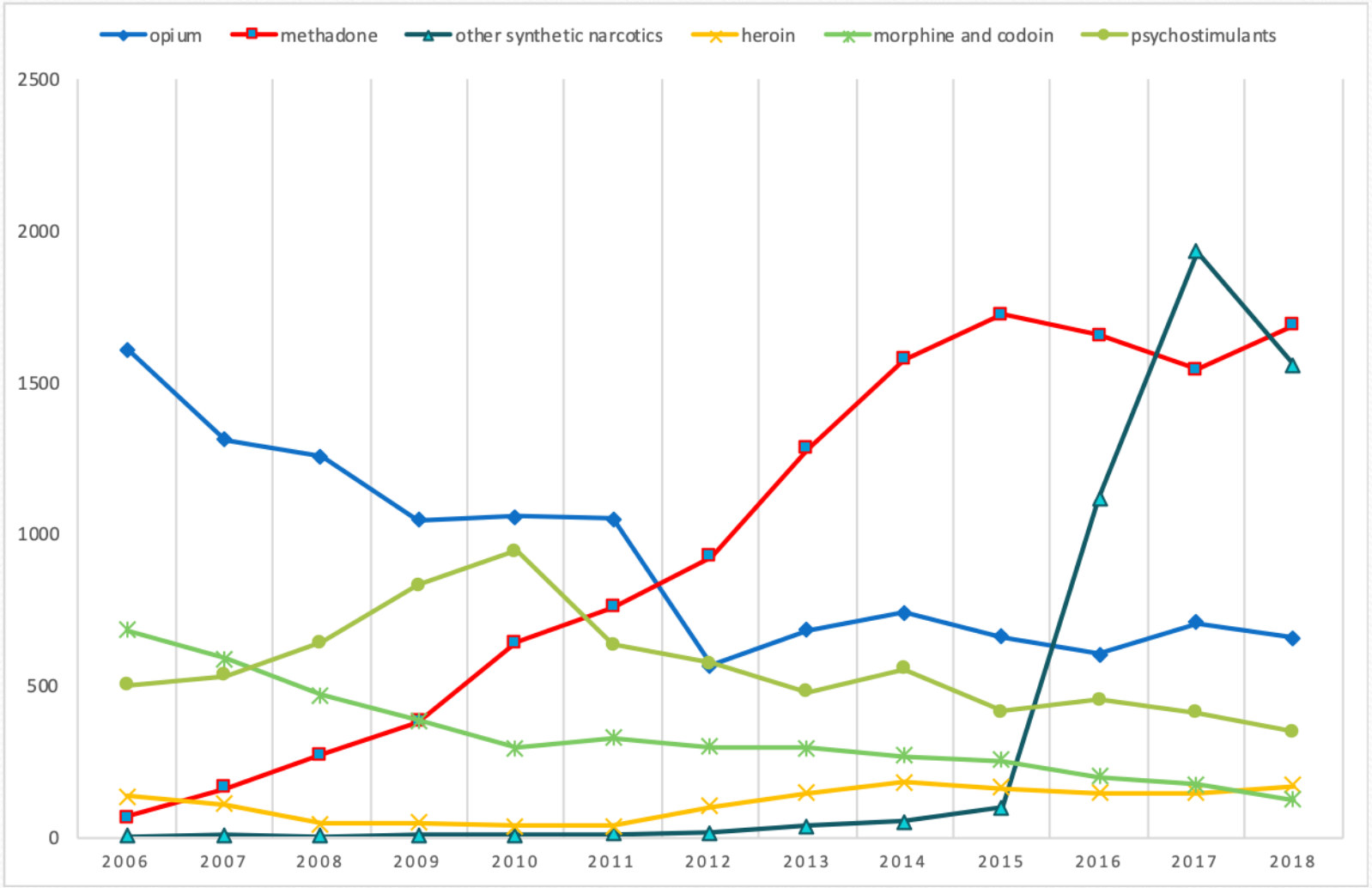
Welcome to Loghman Hakim Hospital (LHH)

… aka: the busiest Clinical Toxicology Centre in the world.

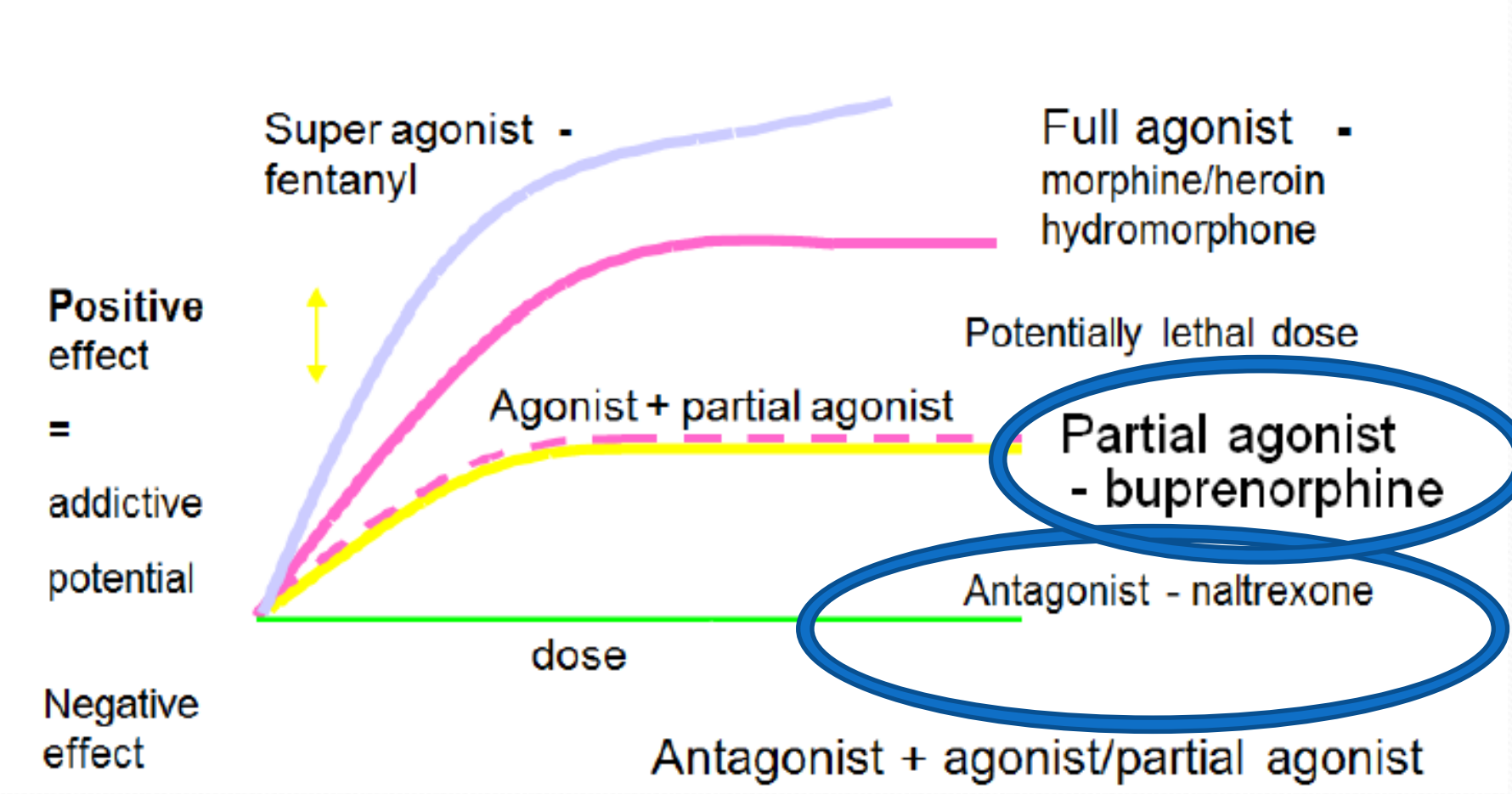
Medical Toxicology Service at LHH: Our facilities

- Dedicated Emergency Room (ER) for intoxicated cases: 10 beds + separate CPR room
- Medical Toxicology Intensive Care Unit (MTICU): 18 beds
- Poisoning Wards: 31 beds (men) + 24 beds (women)
- Toxicological Research Center (TRC)
- Methadone Maintenance Treatment (MMT) Clinic
- Drug and Poison Information Center (DPIC)
- Outpatient Clinic
- Psychology & Psychiatry Unit

Trend in admissions for opioid and stimulant-induced poisoning at Loghman Hakim Hospital (2006-18)



Rationale for using naltrexone and buprenorphine



New opioid antidotes: Possible advantages and disadvantages

- Naltrexone
  - Population: Naïve adults / children
  - Harms: Precipitated withdrawal syndrome
  - Benefits: Long half-life, no need for ICU & monitoring, low-cost
- Buprenorphine
  - Population: Opioid-dependent adults
  - Harms: ?
  - Benefits: Long half-life, no need for ICU & monitoring, less withdrawal; possible induction onto long-term buprenorphine “maintenance treatment”

NALTREXONE

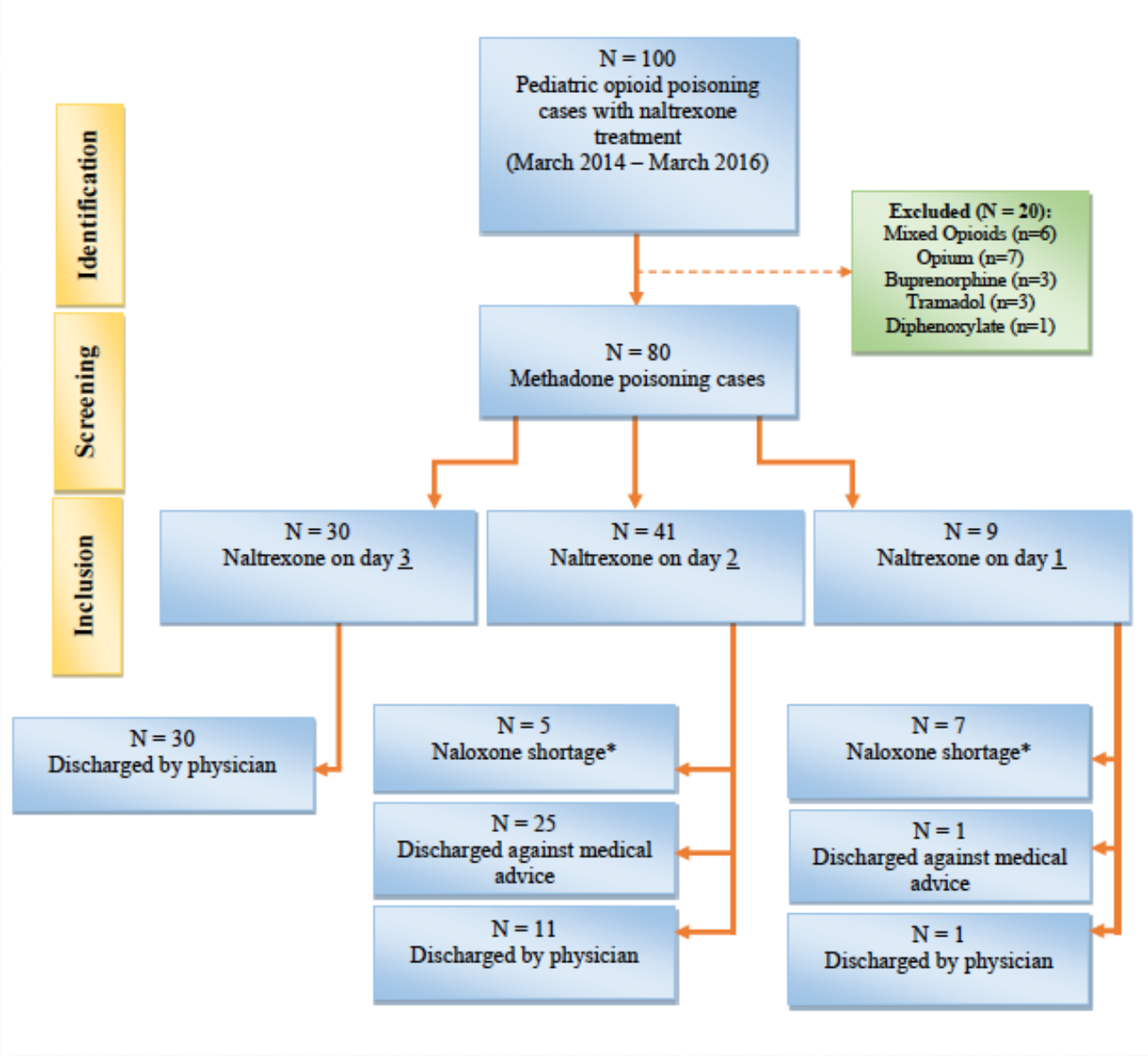
Comparison of adult patients' clinical status using naltrexone (50mg) during hospitalization

Outcome	Total	NLTX $n = 27$	Placebo $n = 27$	P value
Abnormality				
Loss of consciousness	10 (18.5%)	0 (0.0%)	10 (37.0%)	<0.01*
Bradypnea	11 (20.4%)	0 (0.0%)	11 (40.7%)	<0.01*
Apnea	5 (9.3%)	0 (0.0%)	5 (18.5%)	0.02*
ABG				
Respiratory acidosis & hypercapnia	8 (14.8%)	1 (3.7%)	7 (25.9%)	0.05**
Hypoxia	9 (16.7%)	1 (3.7%)	8 (29.6%)	0.02**
Taking naloxone bolus	13 (24.1%)	1 (3.7%)	12 (44.4%)	<0.01*
Other clinical status				
Naloxone iv Infusion	10 (18.5%)	0 (0.0%)	10 (37.0%)	<0.01*
Need for ICU care	14 (25.9%)	0 (0.0%)	14 (51.9%)	<0.01*
Hospital staying (hrs)				
Mean ± SD	32 ± 20	26 ± 17	38 ± 21	0.009‡
Median (range)	24 (12 to 96)	20 (14 to 96)	32 (12 to 96)	

*Based on Chi-Square test. **Based on Fisher's exact test. ‡Based on Mann-Whitney U test.

Aghabiklooei A, Hassanian-Moghaddam H, Zamani N, Shadnia S, Mashayekhian M, Rahimi M, Nasouhi S, Ghoochani A. Effectiveness of naltrexone in the prevention of delayed respiratory arrest in opioid-naive methadone-intoxicated patients. Biomed Res Int. 2013;2013:903172. doi: 10.1155/2013/903172. Epub 2013 Sep 9. PMID: 24089691; PMCID: PMC3781921.

Effectiveness of naltrexone (1 mg/kg) in preventing recurrence of methadone poisoning in opioid-naive children



In print (D&AD)

Demographics and presentation at ED admission

Characteristics	Total (n=80)
Age (years): Median [IQR] (min, max)	3.0 [2.0, 4.4] (0.2, 12.0)
Sex	
Male n (%)	44 (55)
Female n (%)	36 (45)
Methadone: Ingested dose^	
(mg): Median [IQR] (min, max)	10 [5, 15] (3, 40)
(mg/kg): Median [IQR] (min, max)	0.6 [0.4, 1.1] (0.2, 3.3)
Level of Consciousness	
Awake n (%)	5 (6)
Verbal stimulation n (%)	35 (44)
Painful stimulation n (%)	22 (27)
Unresponsive n (%)	18 (23)
Respiratory rate (breaths/minute): Median [IQR] (min, max)	20 [18, 24] (0, 40)
Miotic pupils	
Yes n (%)	70 (87)
No n (%)	10 (13)
pH: Median [IQR] (min, max)	7.35 [7.32, 7.40] (7.17, 7.55)
PCO2 (mmHg): Median [IQR] (min, max)	39.6 [35.1, 45.0] (23.0, 63.0)
HCO3 (mmHg): Median [IQR] (min, max)	22.4 [20.6, 25.0] (13.6, 45.8)
Pruritus	
Yes n (%)	15 (19)
No n (%)	65 (81)
Primary respiratory acidosis in ED n (%)	6 (8)

† VBG was taken after initial resuscitation and naloxone administration

^ Missing data in 31 cases

In print (D&AD)

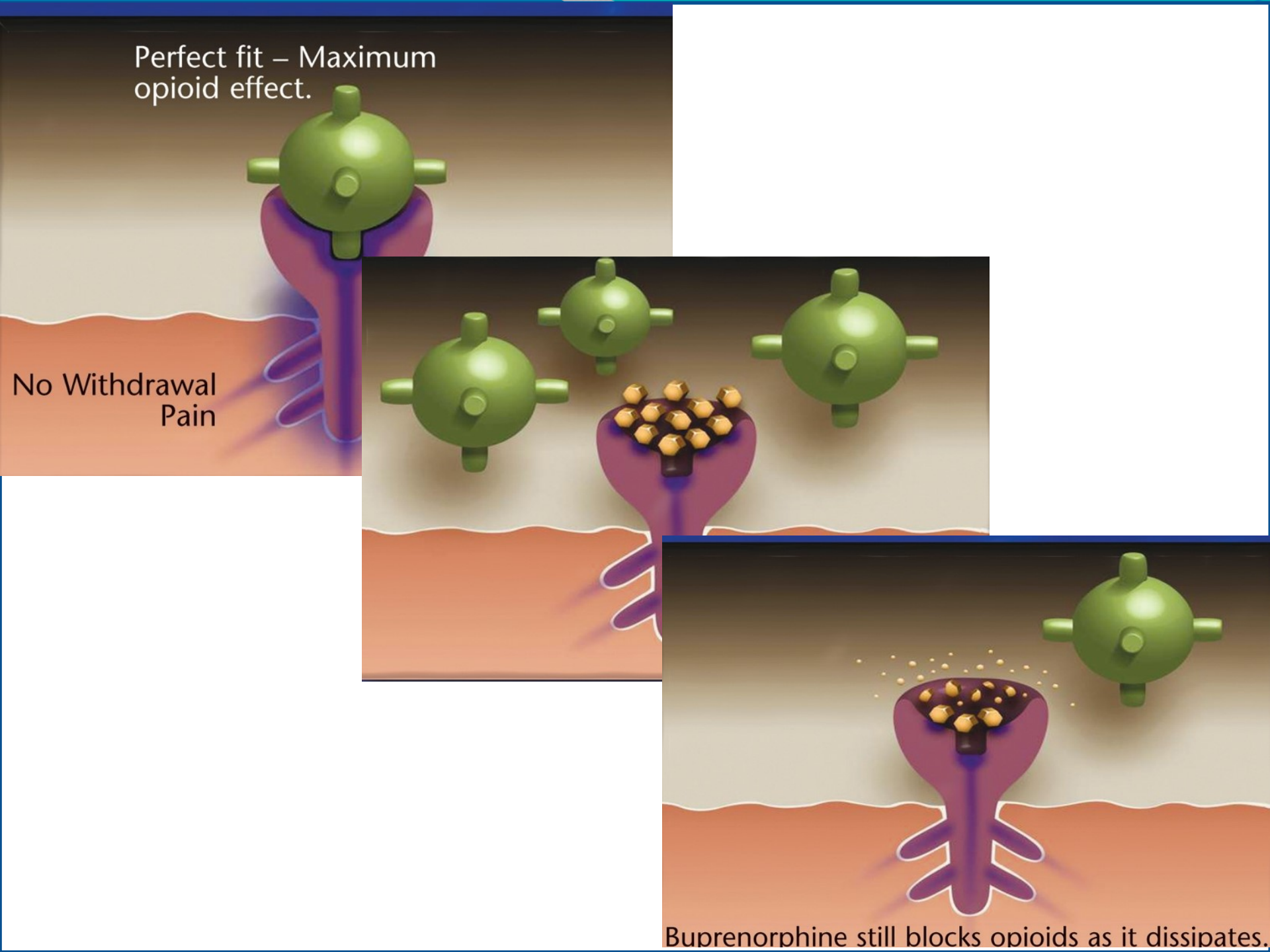
Naltrexone: Clinical characteristics by day

	Day 1 (n=9)	Day 2 (n=41)	Day 3 (n=30)	Total (n=80)
Methadone: Ingested dose (mg/kg):	0.40	0.50	0.90	0.6 [0.4, 1.1]
Median [IQR] (min, max)	[0.28, 0.90] (0.25, 1.0)	[0.38, 1.0] (0.20, 1.6)	[0.48, 1.42] (0.25, 3.3)	(0.2, 3.3)
Naloxone: ED dose (mg):	0	0.4	0	0.2
Median [IQR] (min, max)	[0, 1.4] (0, 2.0)	[0, 0.8] (0, 8.0)	[0, 0.6] (0, 4.0)	[0, 0.8] (0, 8)
Naloxone: Total cumulative dose† (mg):	4.8	18.0	31.2	21.4
Median [IQR] (min, max)	[0.8, 18] (0, 36)	[10.2, 32.6] (2.4, 74.0)	[18.6, 47.7] (6.0, 86.4)	[11.3, 36.6] (0, 86.4)
Naloxone: Duration of administration	12	34	55	37
(h): Median [IQR] (min, max)	[4, 20] (0, 20)	[28, 37] (25, 46)	[50, 69] (50, 72)	[30, 52] (0, 72)
Naltrexone: Reason for administration				
Shortage of naloxone*	7 (78%)	5 (12%)	0	12 (15%)
Discharge against medical advice	1 (11%)	25 (61%)	0	26 (33%)
Discharge by physician	1 (11%)	11 (27%)	30 (100%)	42 (52%)
Duration of hospitalization:	72	48	55	53
Median [IQR] (min, max)	[48, 72] (36, 72)	[38, 72] (26, 72)	[50, 69] (50, 72)	[48, 72] (26, 72)

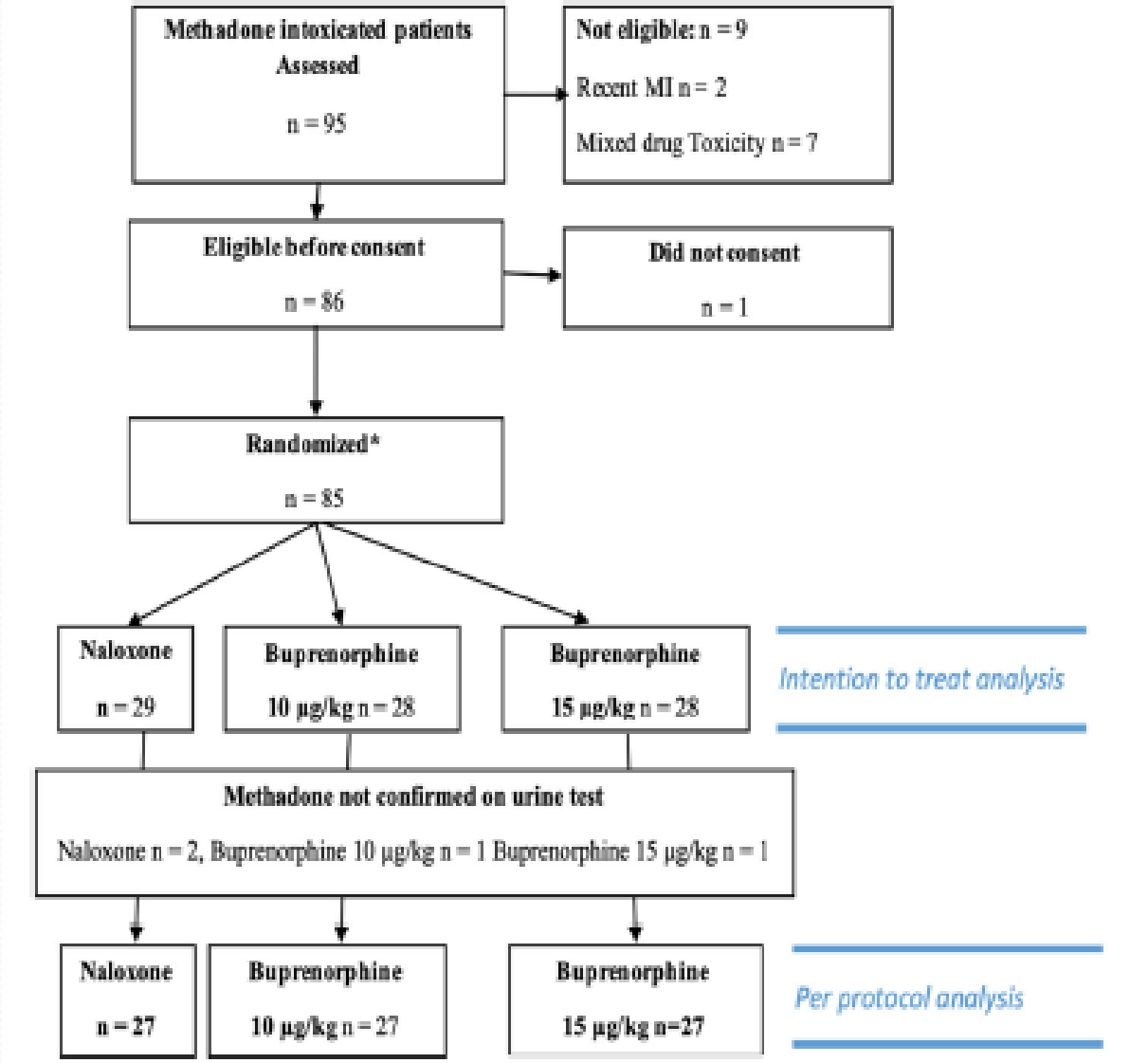
† Only during hospitalization period, not included the dose of naloxone given by the ambulance crew. *Comprise two children who did not receive naloxone infusion in day one

In print (D&AD)

BUPRENORPHINE

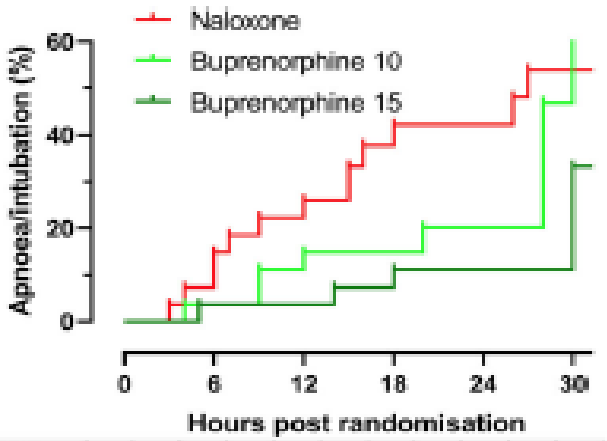

Perfect fit – Maximum opioid effect.
No Withdrawal Pain
Buprenorphine still blocks opioids as it dissipates.

BUP vs naloxone: Efficacy/safety in reversing respiratory depression

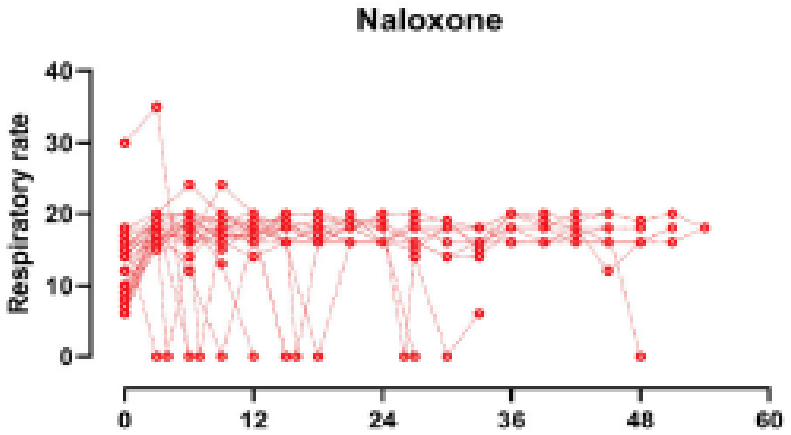


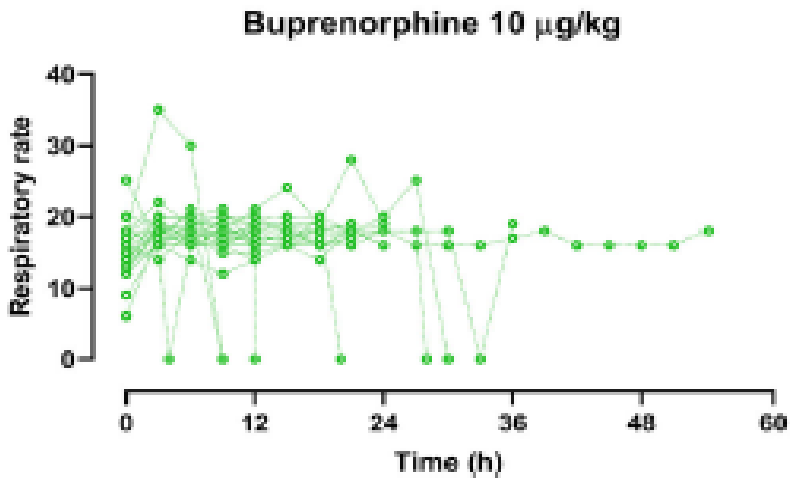
Zamani N, Buckley NA, Hassanian-Moghaddam H. Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial. Crit Care. 2020 Feb 7;24(1):44. doi: 10.1186/s13054-020-2740-y. PMID: 32033582; PMCID: PMC7006192.

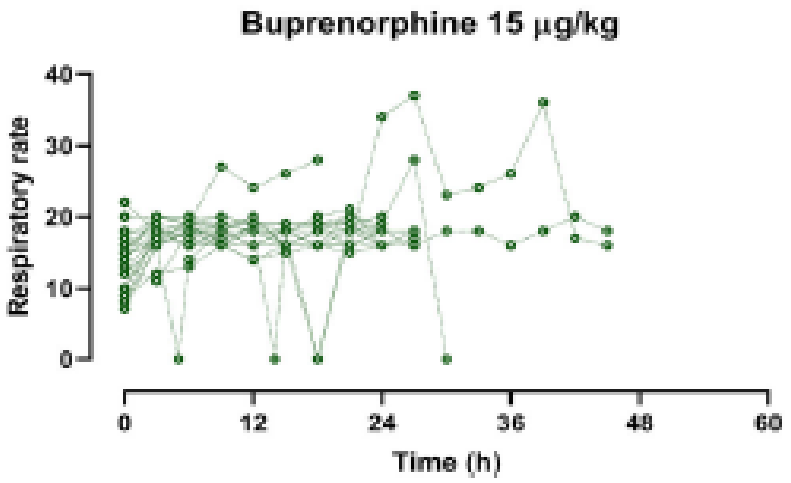
BUP vs naloxone:
Respiratory rate over time and episodes of opioid induced apnea



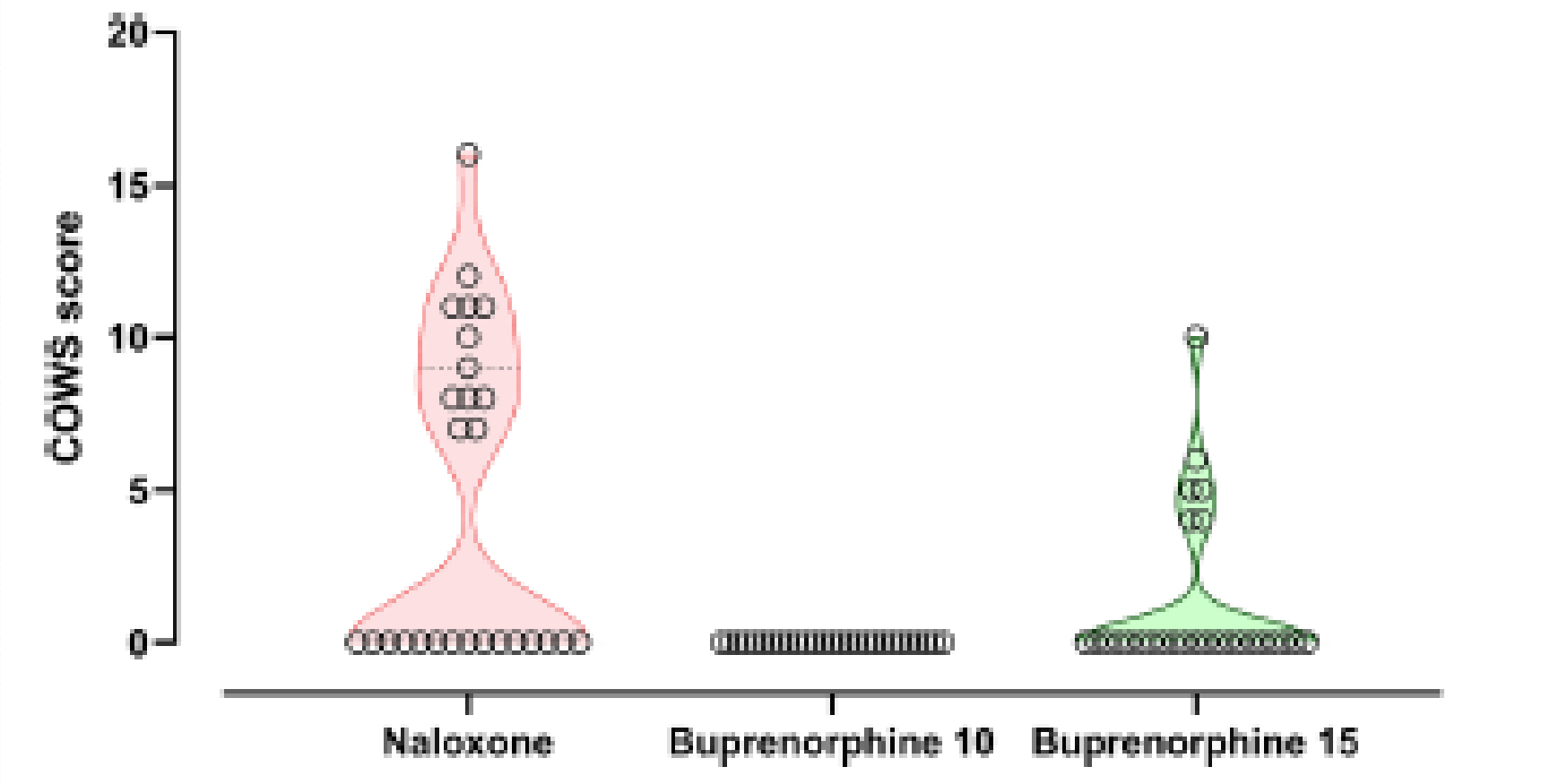
Number at risk											
Naloxone	27	27	25	22	23	21	20	14	11	9	9
Buprenorphine 10	27	27	27	26	25	24	22	19	15	9	2
Buprenorphine 15	27	27	27	27	27	27	26	25	21	9	4







BUP vs naloxone: COWS score



NEXT STEPS

International collaboration

- Multisite RCT: BUP vs naloxone for ED-based treatment of methadone OD
  - Application to UKRI Joint Global Health Trials scheme submitted October 2020
  - PI: Prof Michael Eddleston (Edinburgh)
  - Co-Investigators:
    - Iran: Drs Maryam Soleimaini Movahed, Nasim Zamani
    - Sydney (AUS): Prof Nick Buckley
    - Edinburgh: Profs James Dear, John Norrie, Roy Robertson; Dr Suvodip Shaw
    - King's College London: Dr Rebecca McDonald

QUESTIONS?

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