

# A systematic analysis and data mining of opioid-related adverse events submitted to the FAERS database

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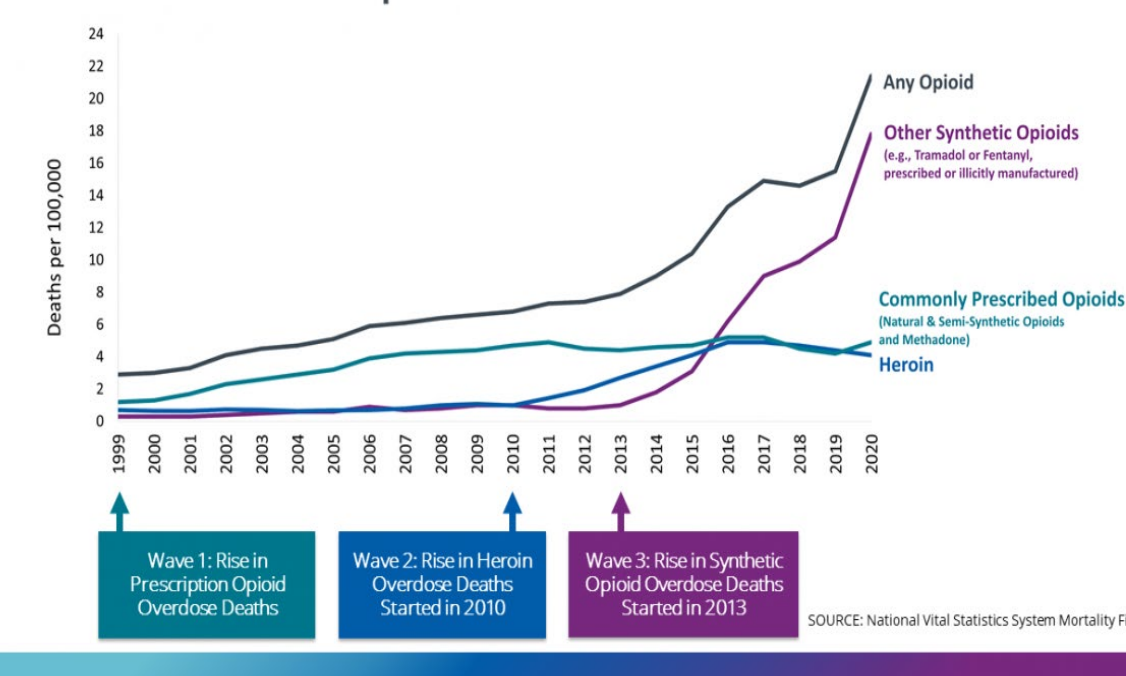
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## Introduction

- Opioids
  - Treat chronic, acute, moderate to severe pain
  - Natural, semi-synthetic, synthetic
  - Prescribed or illicitly manufactured
- Opioid-associated medical disorders
  - Abuse/overdose death
  - Drug dependence/addiction
  - Other adverse effects: cardiovascular, immune, central nervous systems, etc.

### Three Waves of Opioid Overdose Deaths



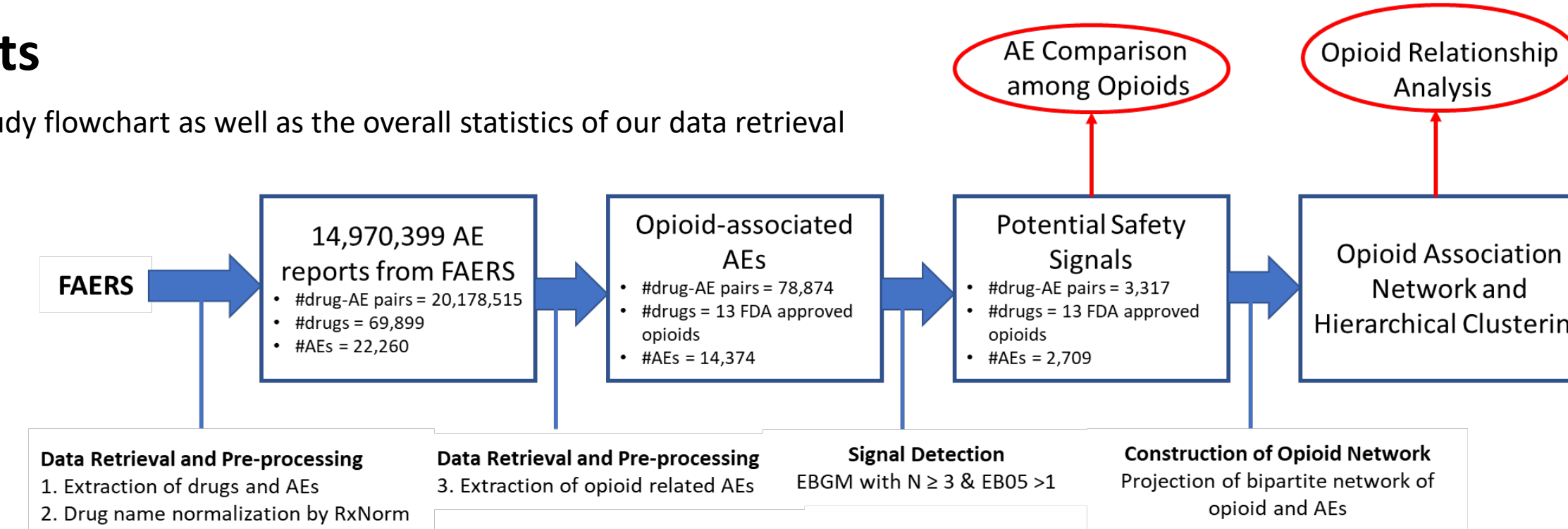
- Problem: there is no comprehensive study which provides a global view of adverse events (AEs) with various opioids from the post-marketing databases

## Materials and Methods

- Data retrieval and pre-processing
  - All AE reports from FAERS from 2004 Quarter I to 2020 Quarter III
    - AEs: coded as Preferred Terms (PTs) in MedDRA
    - Drug names: normalized by RxNorm
  - FDA-approved opioids
    - 92 specific opioids → 13 generic opioids: buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, tapentadol, and tramadol
- Dataset: Pairs of 13 FDA approved opioids and their adverse events
- Potential Safety Signal Detection
  - Empirical Bayes Geometric Mean (EBGM)
  - $N \geq 3$  and  $EB05 > 1$
- Association Network and Hierarchical Clustering
  - Opioid association network
    - weighted, undirected graph
    - Vertices = opioids
    - Weighted edge: connecting 2 opioids if sharing AEs, weight = number of their shared AEs
  - Hierarchical Clustering
    - Opioids' AEs profile = binary matrix
    - Agglomerative clustering algorithm: Jaccard distance + average linkage

## Results

- Our study flowchart as well as the overall statistics of our data retrieval

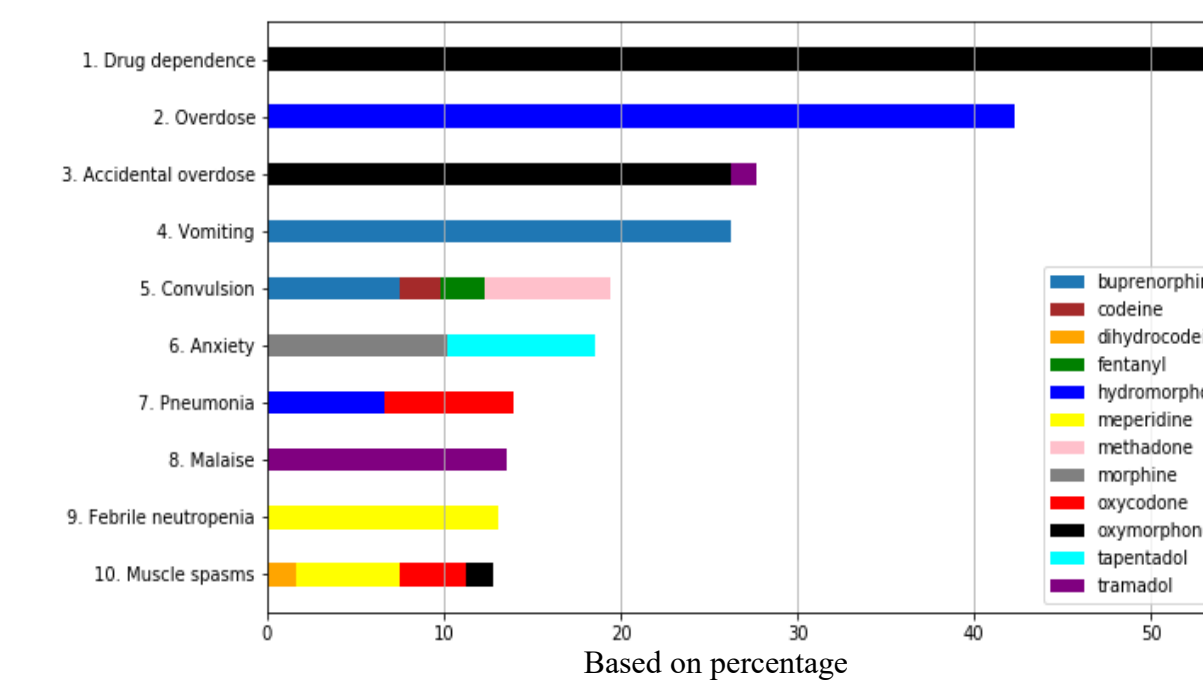
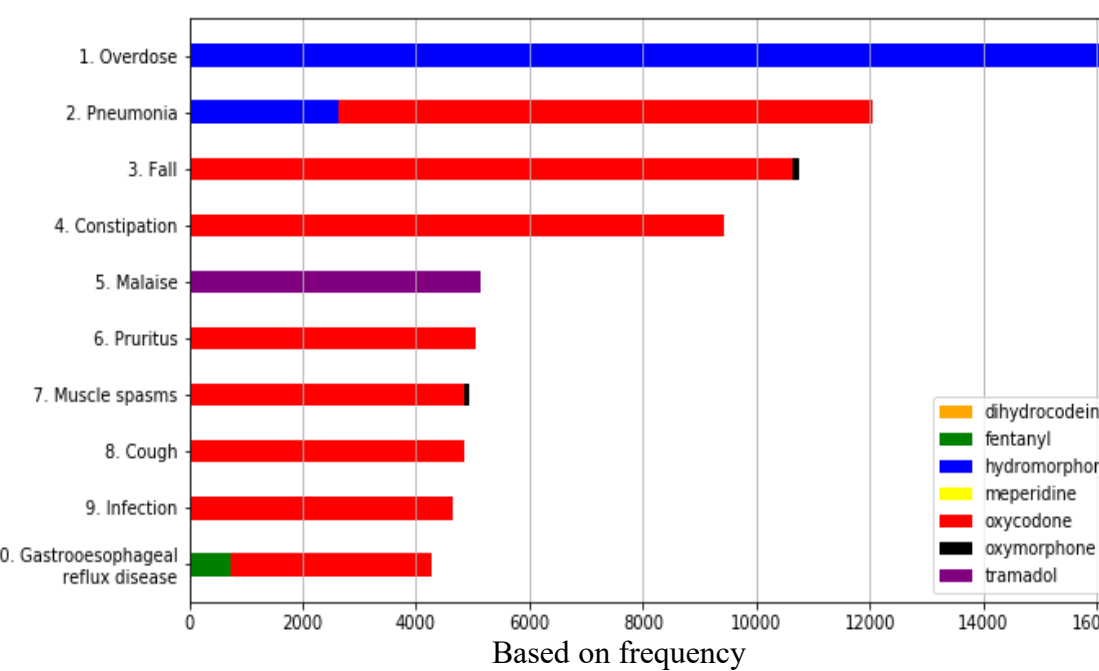


- Statistics of our dataset after signal detection

	Prescription Opioids	AE Reports			
natural	codeine	19200	5.3	264	
	morphine	25047	6.9	318	
	dihydrocodeine	1106	0.3	73	
semi-synthetic	hydrocodone	56126	15.6	494	
	hydromorphone	39229	10.9	350	
	oxycodone	129800	36.0	510	
	oxymorphone	4553	1.3	52	
	buprenorphine	11125	3.1	188	
synthetic	fentanyl	28109	7.8	416	
	meperidine	458	0.1	57	
	methadone	5442	1.5	191	
	tapentadol	2215	0.6	91	
	tramadol	38035	10.6	313	
	<b>Total</b>	<b>360445</b>	<b>100</b>	<b>2709</b>	

Statistics of AEs for 13 FDA-approved opioids

- Top 10 Adverse Events with breakdown by opioids



- Top 10 Adverse Events for each opioid

oxycodone	N	%
1 fall	10647	8.20
2 pneumonia	9427	7.26
3 constipation	9425	7.26
4 pruritus	5060	3.90
5 cough	4861	3.74
6 muscle spasms	4809	3.70
7 infection	4635	3.57
8 chronic kidney disease	4112	3.17
9 gastroesophageal reflux disease	3540	2.73
10 pleural effusion	3197	2.46

hydrocodone	N	%
1 diabetes mellitus	2432	4.33
2 amnesia	2305	4.11
3 haemoglobin decreased	2257	4.02
4 sleep apnoea syndrome	1713	3.05
5 tachycardia	1658	2.95
6 haemorrhage	1629	2.90
7 cardiomegaly	1570	2.80
8 surgery	1551	2.76
9 dental caries	1454	2.59
10 drug effect decreased	1406	2.51

hydromorphone	N	%
1 overdose	16574	42.25
2 pneumonia	2620	6.68
3 emotional distress	1068	2.72
4 feeling abnormal	1003	2.56
5 synovitis	802	2.04
6 hypersensitivity	779	1.99
7 coma	688	1.75
8 product use issue	616	1.57
9 atrial fibrillation	614	1.57
10 intervertebral disc protrusion	595	1.52

fentanyl	N	%
1 emotional distress	1370	4.87
2 serotonin syndrome	1055	3.75
3 pulmonary oedema	1026	3.65
4 haemoglobin decreased	925	3.29
5 platelet count decreased	882	3.14
6 hallucination	849	3.02
7 atrial fibrillation	825	2.94
8 hypokalaemia	766	2.73
9 gastroesophageal reflux disease	742	2.64
10 convulsion	702	2.50

tramadol	N	%
1 malaise	5147	13.53
2 toxicity to various agents	4016	10.56
3 rash	3340	8.78
4 loss of consciousness	2378	6.25
5 contusion	1717	4.51
6 hypokalaemia	1058	2.78
7 coronary artery disease	953	2.51
8 burning sensation	892	2.35
9 cognitive disorder	714	1.88
10 tinnitus	688	1.81

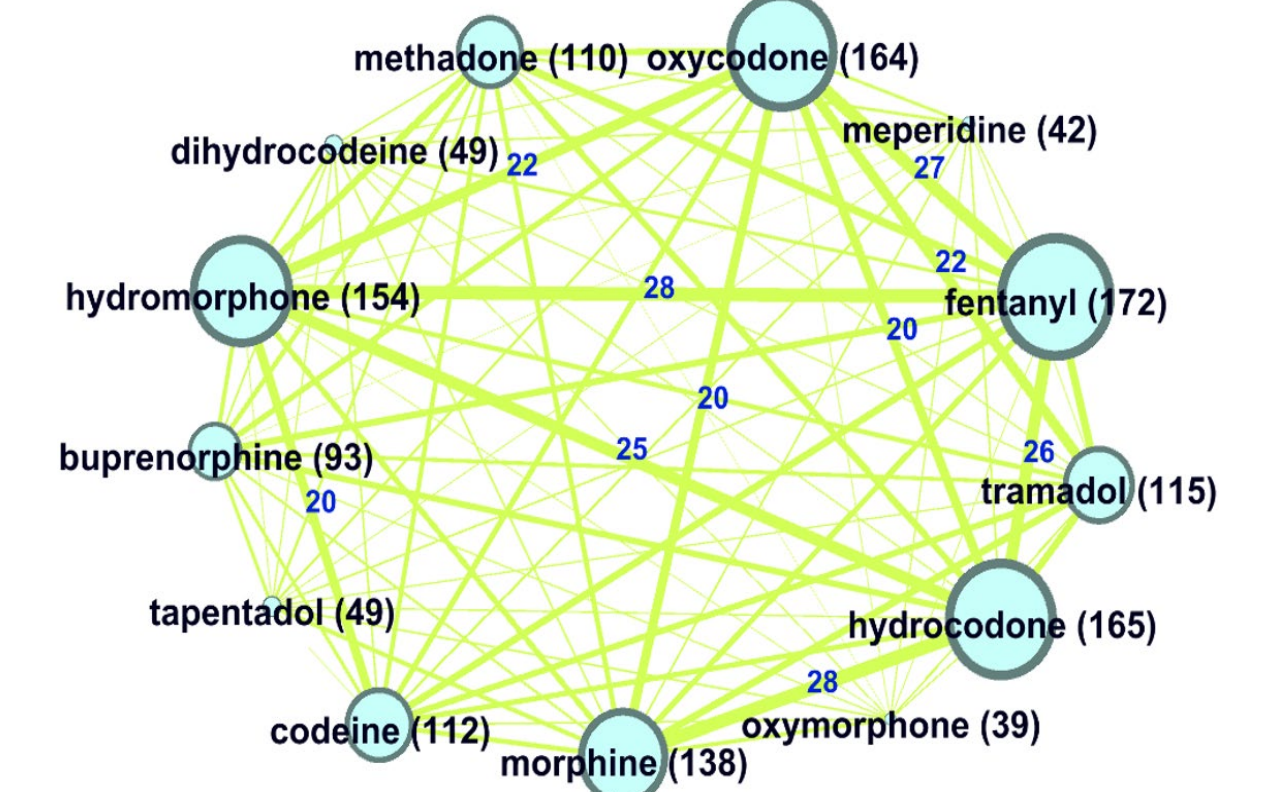
morphine	N	%
1 anxiety	2563	10.23
2 abdominal pain	1857	7.41
3 confusional state	1851	7.39
4 gait disturbance	1169	4.67
5 condition aggravated	1126	4.50
6 bone disorder	1066	4.26
7 neuropathy peripheral	848	3.39
8 mental status changes	686	2.74
9 memory impairment	621	2.48
10 hypersensitivity	600	2.40

24 overlapped AEs out of 130 → most AEs are different for each opioid

## Results (continued)

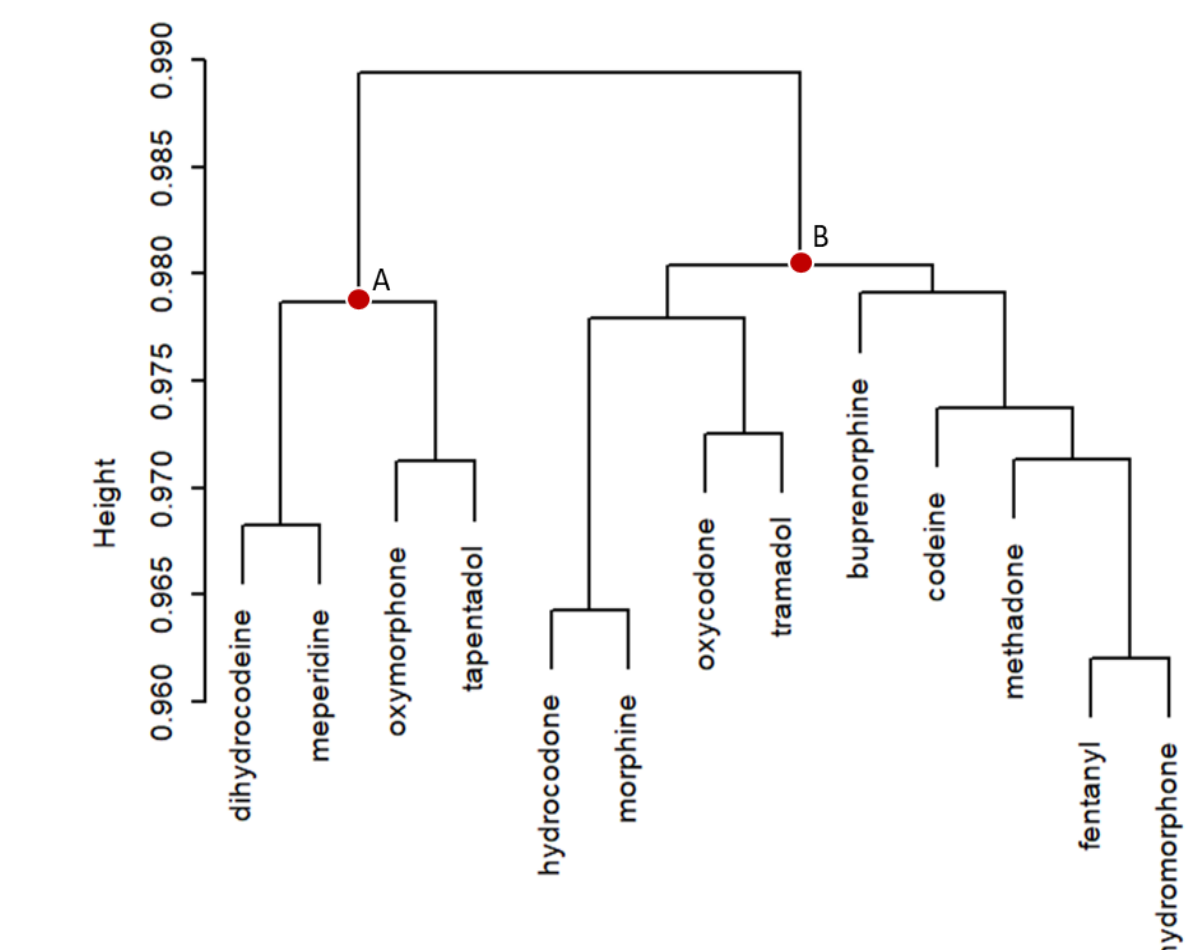
- Opioid Relationship Analysis

- Opioid association network based on common AEs



- a close association among fentanyl, oxycodone, hydrocodone, and hydromorphone by sharing more than 22 AEs, and the much less common AEs shared among dihydrocodeine, meperidine, oxymorphone, and tapentadol

- Hierarchical clustering based on all opioids' AEs



- 13 opioids were classified into two classes by comparing their full profiles of presence/absence of AEs. The results of association network analysis and hierarchical clustering analysis were not only consistent and validated with each other, but also provided a better and deeper understanding on the relationships of the 13 opioids from various aspects

## Conclusion

- The results on FAERS reports analysis revealed the potential AEs with significance which were associated with different prescription opioids. The comparative studies provided a global overview of the current status of opioid-associated AEs and could be as a reference to select potential alternatives to avoid severe AEs in opioid therapies
- Our results also improve the knowledge and insights for patients, physicians, and healthcare providers in terms of safe opioid usage