National Center for Health Statistics

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Drug Overdose Death Data: Shaping the Vision for Using Death Certificate Literal Text

Categorization and classification of drugs

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NIH U.S. National Library of Medicine

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Outline

- Drug classification systems in action
  - RxClass demo
- Desiderata for drug classification systems
- Opioid drugs in drug classification systems
  - ATC
  - ICD-10
- Classifying illicit drugs

Drug classification systems in action

- RxClass

https://mor.nlm.nih.gov/RxClass/

  - Developed by the National Library of Medicine
  - Linked to RxNorm drugs
  - Integrates multiple drug classification systems
    - Anatomical Therapeutic Chemical (ATC) drug classification – WHO
    - Established Pharmacological Classes (EPC) – VA/FDA (MED-RT)
    - Pharmacological Actions – NLM (MeSH)
    - Chemical structure – FDA (MED-RT)
    - Mechanism of action – FDA (MED-RT)
    - Physiologic effect – FDA (MED-RT)
    - Therapeutic use & contraindications – VA (MED-RT)
    - VA Formulary classes – VA (VANDF)

https://mor.nlm.nih.gov/RxClass/

Class Browser

- Anatomical Therapeutic Chemical (ATC1-4)
- Established Pharmacologic Classes (EPC) [from DailyMed]
- MeSH Pharmacologic Actions (MESHPA)
- Diseases, Life Phases and Physiologic States
- Substances and Cells (CHEM) [from DailyMed]
- Mechanism of Action (MoA) [from DailyMed]
- Physiologic Effect (PE) [from DailyMed]
- Pharmacokinetics (PK)
- VA Classes (VA)
- Therapeutic Categories (TC)

RxCLASS
Exploring Classes for RxNorm Drugs

Search...

by class name/id | by RxNorm drug name/id | show source data | Edit Drug Sources

Class Name

https://mor.nlm.nih.gov/RxClass/

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About FAQ Tutorial

Class Browser

- Anatomical Therapeutic Chemical (ATC1-4)
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RxCLASS
Exploring Classes for RxNorm Drugs

fentanyl

by class name/id | by RxNorm drug name/id | show source data | Edit Drug Sources

Fentanyl

Print

19 classes found for drug **'fentanyl'**
[Ingredient(s):Fentanyl]

Member of [through ingredient]

- Opioid anesthetics in ATC1-4
- Phenylpiperidine derivatives in ATC1-4
- Drug Hypersensitivity in DISEASE (**ci_with**)
- High Pressure Neurological Syndrome in DIS
- Liver Failure in DISEASE (**ci_with**)
- Pregnancy in DISEASE (**ci_with**)
- Renal Insufficiency in DISEASE (**ci_with**)

19 classes found for drug **'fentanyl'**
[Ingredient(s):Fentanyl]

- Renal Insufficiency in DISEASE (**ci_with**)
- Respiratory Tract Diseases in DISEASE
- Pain in DISEASE (**may_treat**)
- Opioid Agonist in EPC (**has_EPC**)
- Adjuvants, Anesthesia in MESHPA
- Analgesics, Opioid in MESHPA
- Anesthetics, Intravenous in MESHPA
- Narcotics in MESHPA

19 classes found for drug **'fentanyl'**
[Ingredient(s):Fentanyl]

- Narcotics in MESHPA
- Full Opioid Agonists in MOA (**has_MoA**)

Member of [through multiple ingredients]

- Analgesics in MESHPA
- Anesthetics, Combined in MESHPA

Member of [through products]

- OPIOID ANALGESICS in VA (**has_VAClass_extended**)
- OPIOID ANALGESICS in VA (**has_VAClass**)

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SEX HORMONES (157)
- MUSCULO-SKELETAL SYSTEM (125)
- NERVOUS SYSTEM (417)
  - ANALGESICS (68)
  - ANESTHETICS (41)
    - ANESTHETICS, GENERAL (23)
      - Barbiturates in combination with other drugs (0)
      - Barbiturates, plain (3)
      - Ethers (0)
      - Halogenated hydrocarbons (6)
      - Opioid anesthetics (6)
      - Other general anesthetics (8)
    - ANESTHETICS, LOCAL (18)
  - ANTI-PARKINSON DRUGS (27)
  - ANTIEPILEPTICS (40)
  - OTHER NERVOUS SYSTEM DRUGS (32)
  - PSYCHOANALEPTICS (85)
  - PSYCHOLEPTICS (130)
- RESPIRATORY SYSTEM (209)
- SENSORY ORGANS (168)
- SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS (60)
- VARIOUS (136)
- Established Pharmacologic Classes (EPC) [from DailyMed]
- MeSH Pharmacologic Actions (MESHPA)
- Diseases, Life Phases and Physiologic States
- Substances and Cells (CHEM) [from DailyMed]
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- Pharmacokinetics (PK)
- VA Classes (VA)
- Therapeutic Categories (TC)

RxClass
Exploring Classes for RxNorm Drugs

fentanyl

by class name/id | by RxNorm drug name/id | show source data | Edit Drug Sources

Opioid anesthetics

class: **Opioid anesthetics** / id: **N01AH** / class type: **ATC1-4** / show context

Print

6 RxNorm generic drugs in ATC / similar classes

Type	RXCUI	RxNorm Name	Source Id	Source Name	Relation	All classes
IN	480	Alfentanil	N01AH02	alfentanil	DIRECT	Show
IN	17933	anileridine	N01AH05	anileridine	DIRECT	Show
IN	4337	Fentanyl	N01AH01	fentanyl	DIRECT	Show
IN	8143	Phenoperidine	N01AH04	phenoperidine	DIRECT	Show
IN	73032	remifentanil	N01AH06	remifentanil	DIRECT	Show
IN	56795	Sufentanil	N01AH03	sufentanil	[	

N NERVOUS SYSTEM
N01 ANESTHETICS
N01A ANESTHETICS, GENERAL
N01AH Opioid anesthetics

ATC code	Name
N01AH01	fentanyl
N01AH02	alfentanil
N01AH03	sufentanil
N01AH04	phenoperidine
N01AH05	anileridine
N01AH06	remifentanil
N01AH51	fentanyl, combinations

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Desiderata for drug classification systems

- From the perspective of drug analytics in large clinical datasets
  - May not be directly applicable to opioids in death certificates
- Kury FSP, Bodenreider O. Desiderata for drug classification systems for their use in analyzing large drug prescription datasets. *Proceedings of the 3rd Workshop on Data Mining for Medical Informatics (DMMI 2016)* **2016**. https://mor.nlm.nih.gov/pubs/pdf/2016-dmmi-fk.pdf

Desiderata for drug classification systems

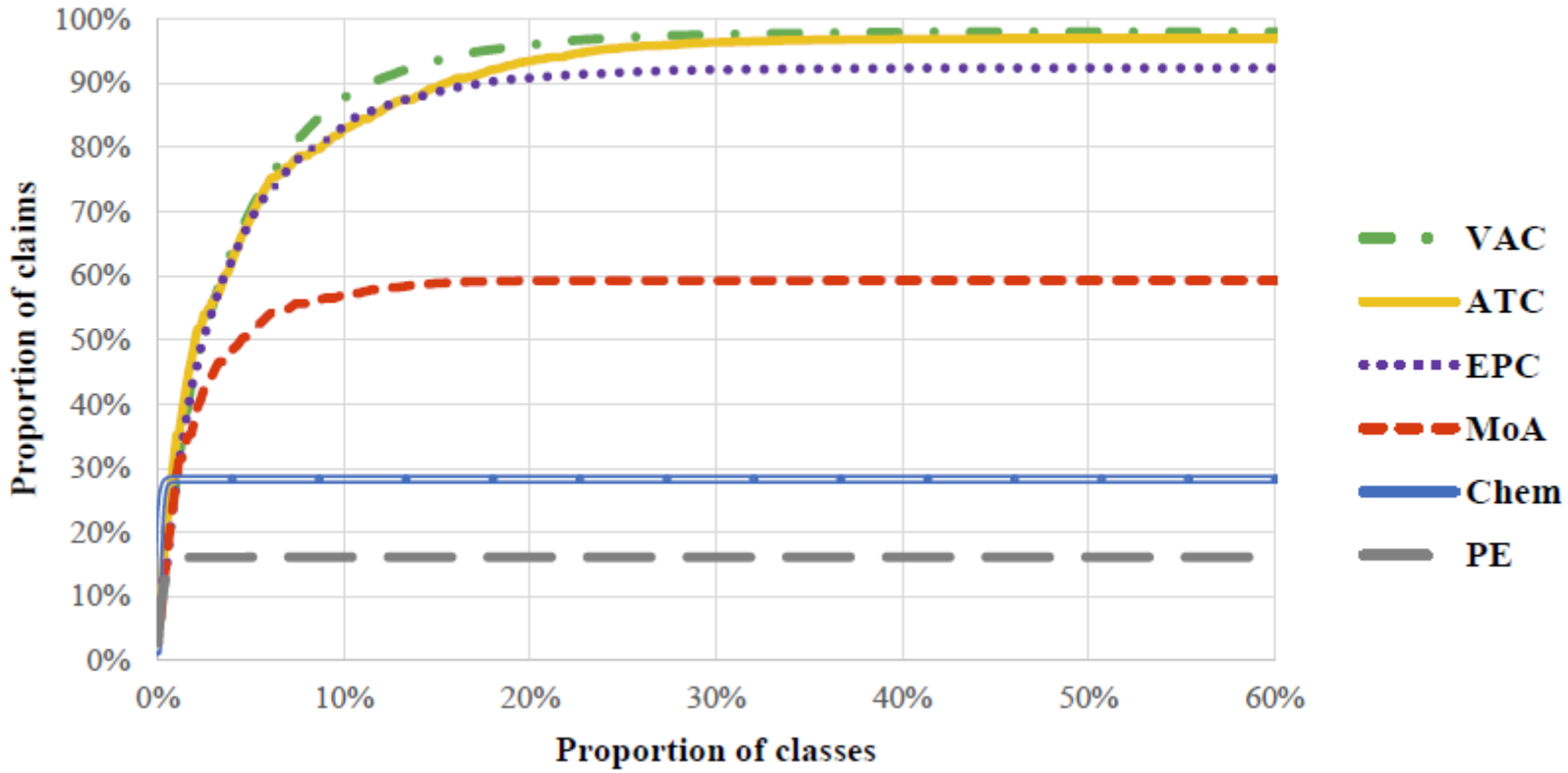
- Administrative desiderata
  - Authoritative source
  - Regular updates
  - License?
- Hierarchical structure
  - Support for aggregation (vs. flat list)
  - Avoid double counting (single vs. multiple parents)
  - Number of levels (fixed vs. variable)
  - Drugs at the lowest level?

Desiderata for drug classification systems

- Coverage
  - All/most drugs of interest need to be covered
- Granularity
  - Necessary to support fined-grained analyses
- Non-ambiguity
  - Does the classification provide enough information for automatic classification?
- Dispersion
  - Cases analyzed should be distributed among as many classes as meaningfully possible

Application to Medicare data

Figure 2. Desideratum F: *Dispersion.* Proportion of Medicare Part D claims from 2006 to 2014 covered by a given proportion of classes.*



https://www.whocc.no/atc_ddd_index/

Opioids in ATC

- 3 main ATC classes for opioids
  - N01AH Opioid anesthetics
  - N02A OPIOIDS
  - N07BC Drugs used in opioid dependence

N NERVOUS SYSTEM
N01 ANESTHETICS
N01A ANESTHETICS, GENERAL
N01AH Opioid anesthetics

ATC code	Name
N01AH01	fentanyl
N01AH02	alfentanil
N01AH03	sufentanil
N01AH04	phenoperidine
N01AH05	anileridine
N01AH06	remifentanil
N01AH51	fentanyl, combinations

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AA Natural opium alkaloids
N02AB Phenylpiperidine derivatives
N02AC Diphenylpropylamine derivatives
N02AD Benzomorphan derivatives
N02AE Oripavine derivatives
N02AF Morphinan derivatives
N02AG Opioids in combination with antispasmodics
N02AJ Opioids in combination with non-opioid analgesics
N02AX Other opioids

N NERVOUS SYSTEM
N07 OTHER NERVOUS SYSTEM DRUGS
N07B DRUGS USED IN ADDICTIVE DISORDERS
N07BC Drugs used in opioid dependence

ATC code	Name	DDD
N07BC01	buprenorphine	8
N07BC02	methadone	25
		25
N07BC03	levacetylmethadol	
N07BC04	lofexidine	1.4
N07BC05	levomethadone	
N07BC06	diamorphine	
N07BC51	buprenorphine, combinations	8

N02A subclasses

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AA Natural opium alkaloids
N02AB Phenylpiperidine derivatives
N02AC Diphenylpropylamine derivatives
N02AD Benzomorphan derivatives
N02AE Oripavine derivatives
N02AF Morphinan derivatives
N02AG Opioids in combination with antispasmodics
N02AJ Opioids in combination with non-opioid analgesics
N02AX Other opioids

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AA Natural opium alkaloids

ATC code	Name
N02AA01	morphine
N02AA02	opium
N02AA03	hydromorphone
N02AA04	nicomorphine
N02AA05	oxycodone
N02AA08	dihydrocodeine
N02AA10	papaveretum
N02AA51	morphine, combinations
N02AA55	oxycodone and naloxone
N02AA58	dihydrocodeine, combinations
N02AA59	codeine, combinations excl. psycholeptics
N02AA79	codeine, combinations with psycholeptics

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AB Phenylpiperidine derivatives

ATC code	Name
N02AB01	ketobemidone
N02AB02	pethidine
N02AB03	fentanyl
N02AB52	pethidine, combinations excl. psycholeptics
N02AB72	pethidine, combinations with psycholeptics

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AC Diphenylpropylamine derivatives

ATC code	Name
N02AC01	dextromoramide
N02AC03	piritramide
N02AC04	dextropropoxyphene
N02AC05	bezitramide
N02AC52	methadone, combinations excl. psycholeptics
N02AC54	dextropropoxyphene, combinations excl. psycholeptics
N02AC74	dextropropoxyphene, combinations with psycholeptics

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AD Benzomorphan derivatives

ATC code	Name	DDD
N02AD01	pentazocine	0.2 0.2
N02AD02	phenazocine	3

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AE Oripavine derivatives

ATC code	Name	DDD
N02AE01	buprenorphine	1.2

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AF Morphinan derivatives

ATC code	Name	DDD
N02AF01	butorphanol	12
N02AF02	nalbuphine	80

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AX Other opioids

ATC code	Name	DDD
N02AX01	tilidine	0.2 0.2
N02AX02	tramadol	0.3 0.3 0.3
N02AX03	dezocine	
N02AX05	meptazinol	1.2 1.2
N02AX06	tapentadol	0.4

Where is codeine?

- Codeine is not listed (as a single-ingredient drug) under the main class N02A OPIOIDS

R RESPIRATORY SYSTEM
R05 COUGH AND COLD PREPARATIONS
R05D COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS
R05DA Opium alkaloids and derivatives

ATC code	Name	DDD	U	Adm.R	Note
R05DA04	codeine	0.1	g	O	

N NERVOUS SYSTEM
N02 ANALGESICS
N02A OPIOIDS
N02AJ Opioids in combination with non-opioid analgesics

ATC code	Name
N02AJ01	dihydrocodeine and paracetamol
N02AJ02	dihydrocodeine and acetylsalicylic acid
N02AJ03	dihydrocodeine and other non-opioid analgesics
N02AJ06	codeine and paracetamol
N02AJ07	codeine and acetylsalicylic acid
N02AJ08	codeine and ibuprofen
N02AJ09	codeine and other non-opioid analgesics
N02AJ13	tramadol and paracetamol
N02AJ14	tramadol and dexketoprofen
N02AJ15	tramadol and other non-opioid analgesics
N02AJ17	oxycodone and paracetamol
N02AJ18	oxycodone and acetylsalicylic acid
N02AJ19	oxycodone and ibuprofen

Opioids in ICD-10

T40	**Poisoning by narcotics and psychodysleptics [hallucinogens]**
	Excl.: intoxication meaning inebriation (F10-F19)
T40.0	**Opium**
T40.1	**Heroin**
T40.2	**Other opioids** Codeine Morphine
T40.3	**Methadone**
T40.4	**Other synthetic narcotics** Pethidine
T40.5	**Cocaine**
T40.6	**Other and unspecified narcotics**
T40.7	**Cannabis (derivatives)**
T40.8	**Lysergide [LSD]**
T40.9	**Other and unspecified psychodysleptics [hallucinogens]** Mescaline Psilocin Psilocybine

- Insufficient granularity for analyzing individual drugs (e.g., Fentanyl)

Illicit drugs

- Not covered by the clinical drug classification systems
- Alternative sources
  - National Forensic Laboratory Information System (NFLIS)

NFLIS classification

Categories/Subcategories	Count
Analgesics	**89**
Narcotic Analgesics	89
Antidepressants	**12**
Antidepressants	12
Benzodiazepines	**15**
Benzodiazepines	15
Cannabinoids	**16**
Cannabinoids	16
Cocaine Alkaloids	**9**
Cocaine Alkaloids	9
Depressants and Tranquilizers	**192**
Benzodiazepines	15
Depressants and Tranquilizers	177
Hallucinogens	**309**
Hallucinogens	63
Phenethylamines (2C Series) (H)	20
Phenethylamines (Aminoindanes) (H)	4
Phenethylamines (Amphetamines) (H)	27
Phenethylamines (D Series) (H)	7
Phenethylamines (Other) (H)	10
Piperazines (Hallucinogen)	7
Psychedelic	9
Synthetic Cannabinoids	127
Synthetic Cathinones (Hallucinogen)	3
Tryptamines	32
Heroin	**1**
Heroin	1
Narcotic Analgesics	**89**
Narcotic Analgesics	89
Narcotics	**233**
Narcotic Analgesics	89
Narcotics	144
New Drug	**143**
New Drug	143
No substance identified	**16**
No substance identified	16
Other	**219**
Other	219

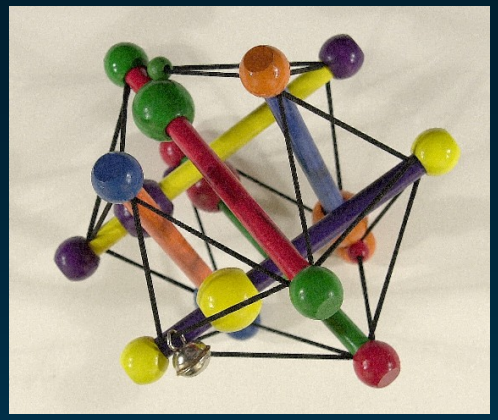
Categories/Subcategories	Count
Other substances	**1626**
Narcotic Analgesics	89
Other	219
Other substances	1318
Phenethylamines	**157**
Phenethylamines (2C Series) (H)	20
Phenethylamines (Aminoindanes) (H)	4
Phenethylamines (Amphetamines) (H)	27
Phenethylamines (Amphetamines) (S)	21
Phenethylamines (D Series) (H)	7
Phenethylamines (Other) (H)	10
Phenethylamines (Other) (S)	11
Synthetic Cathinones	54
Synthetic Cathinones (Hallucinogen)	3
Phenethylamines (2C Series) (H)	**20**
Phenethylamines (2C Series) (H)	20
Phenethylamines (Aminoindanes) (H)	**4**
Phenethylamines (Aminoindanes) (H)	4
Phenethylamines (Amphetamines) (H)	**27**
Phenethylamines (Amphetamines) (H)	27
Phenethylamines (Amphetamines) (S)	**21**
Phenethylamines (Amphetamines) (S)	21
Phenethylamines (D Series) (H)	**7**
Phenethylamines (D Series) (H)	7
Phenethylamines (Hallucinogen)	**71**
Phenethylamines (2C Series) (H)	20
Phenethylamines (Aminoindanes) (H)	4
Phenethylamines (Amphetamines) (H)	27
Phenethylamines (D Series) (H)	7
Phenethylamines (Other) (H)	10
Synthetic Cathinones (Hallucinogen)	3
Phenethylamines (Other) (H)	**10**
Phenethylamines (Other) (H)	10
Phenethylamines (Other) (S)	**11**
Phenethylamines (Other) (S)	11
Phenethylamines (Stimulant)	**86**
Phenethylamines (Amphetamines) (S)	21
Phenethylamines (Other) (S)	11
Synthetic Cathinones	54

Categories/Subcategories	Count
Piperazines (Hallucinogen)	**7**
Piperazines (Hallucinogen)	7
Piperazines (Stimulant)	**5**
Piperazines (Stimulant)	5
Piperidines/PEA	**5**
Piperidines/PEA	5
Psychedelic	**9**
Psychedelic	9
Steroids	**86**
Steroids	86
Stimulants	**153**
Antidepressants	12
Phenethylamines (Amphetamines) (S)	21
Phenethylamines (Other) (S)	11
Piperazines (Stimulant)	5
Piperidines/PEA	5
Stimulants	45
Synthetic Cathinones	54
Synthetic Cannabinoids	**127**
Synthetic Cannabinoids	127
Synthetic Cathinones	**57**
Synthetic Cathinones	54
Synthetic Cathinones (Hallucinogen)	3
Synthetic Cathinones (Hallucinogen)	**3**
Synthetic Cathinones (Hallucinogen)	3
Tryptamines	**32**
Tryptamines	32
Grand Total	**3867**

Requirements and use cases

- If drug classification systems are the solution, what is the problem?

- Use cases
  - Drug-related mortality statistics
  - Others?
- Requirements
  - Drugs vs. substances
  - Granularity (coarse vs. fine-grained classes)
  - National vs. international
  - …



Medical Ontology Research

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