

# Visualizing Patterns of Abuse-Related Adverse Events with Statistical Methods

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# Research Questions

Can statistical techniques applied to adverse event data be useful in detecting and monitoring drug abuse potential?

Can they help to visualize similarities/dissimilarities in the patterns of events between different drugs?

Can they identify meaningful clusters of events?

As a start to answer these questions we evaluated the ability of these methods to appropriately compare/group/classify drugs based on patterns of spontaneously reported abuse-related adverse events

# Dataset Used

- FDA Adverse Event Reporting System (FAERS) database
- Publically available cumulative through 3<sup>rd</sup> quarter 2011
- Events coded using the Medical Dictionary for Regulatory Activities (MedDRA)
- Coded terms at the Preferred term level
- Event-drug pairs for which the drug of interest was considered a suspect drug for the event of interest

# Comprehensive List of Adverse Events to describe Abuse Potential

Abnormal behaviour	Delirium	Euphoric mood	Maternal use of illicit drugs	Sensory disturbance
Abnormal dreams	Delusion	Executive dysfunction	Memory impairment	Sensory level abnormal
Abnormal sleep-related event	Delusion of grandeur	Fear	Mental disability	Sleep sex
Accidental death	Delusion of reference	Feeling abnormal	Mental disorder	Sleep terror
Accidental overdose	Delusion of replacement	Feeling drunk	Mental impairment	Slow speech
Accidental poisoning	Delusional perception	Feeling jittery	Mental status changes	Somatic delusion
Acute psychosis	Delusional disorder, erotomanic type	Feeling of despair	Miosis	Somatic hallucination
Affect lability	Delusional disorder, grandiose type	Feeling of relaxation	Mood altered	Somnolence
Affective disorder	Delusional disorder, jealous type	Flashback	Multiple drug overdose	Staring
Aggression	Delusional disorder, mixed type	Fat affect	Multiple drug overdose accidental	Steroid withdrawal syndrome
Agitation	Delusional disorder, persecutory type	Flight of ideas	Multiple drug overdose intentional	Stupor
Alice in wonderland syndrome	Delusional disorder, somatic type	Formication	Muscle relaxant therapy	Substance abuse
Altered state of consciousness	Delusional disorder, unspecified type	Hallucination	Mydriasis	Substance abuser
Altered visual depth perception	Delusions, mixed	Hallucination, auditory	Nasal necrosis	Substance use
Amnesia	Dependence	Hallucination, gustatory	Nasal septum perforation	Substance-induced mood disorder
Amnestic disorder	Depersonalisation	Hallucination, olfactory	Nasal septum ulceration	Substance-induced psychotic disorder
Amphetamines	Depressed level of consciousness	Hallucination, synaesthetic	Needle track marks	Suicidal behaviour
Amphetamines positive	Depressive delusion	Hallucination, tactile	Neonatal complications of substance abuse	Suicidal ideation
Analgesic therapy	Derailment	Hallucination, visual	Overdose	Suicide attempt
Anger	Derealisation	Hallucinations, mixed	Panic attack	Suspiciousness
Anhedonia	Disinhibition	Hangover	Panic reaction	Tangentiality
Anterograde amnesia	Disorientation	Homicidal ideation	Paramnesia	Thinking abnormal
Antisocial behaviour	Dissociation	Homicide	Paranoia	Thought blocking
Antitussive therapy	Dissociative amnesia	Hostility	Parasomnia	Thought broadcasting
Anxiety	Dissociative identity disorder	Hypervigilance	Paroxysmal perceptual alteration	Thought insertion
Anxiolytic therapy	Disturbance in attention	Hypnagogic hallucination	Persecutory delusion	Thought withdrawal
Apathy	Disturbance in social behaviour	Hypnopompic hallucination	Personality change	Toxicity to various agents
Asocial behaviour	Dopamine dysregulation syndrome	Ideas of reference	Personality disorder	Transient global amnesia
Asthenia	Dopaminergic drug therapy	Illogical thinking	Physical assault	Transient psychosis
Attention-seeking behaviour	Drug abuse	Illusion	Poisoning	Treatment noncompliance
Balance disorder	Drug abuser	Impaired driving ability	Polysubstance dependence	Urine amphetamine
Belligerence	Drug dependence	Impaired reasoning	Prescription form tampering	Urine amphetamine positive
Benzodiazepine drug level	Drug dependence, antepartum	Impulsive behaviour	Product tampering	Violence-related symptom
Blunted affect	Drug dependence, postpartum	Inappropriate affect	Product used for unknown indication	
Bradypnea	Drug detoxification	Incoherent	Psychomotor hyperactivity	
Central nervous system stimulation	Drug diversion	Intentional drug misuse	Psychomotor retardation	
Cognitive disorder	Drug screen positive	Intentional overdose	Psychomotor skills impaired	
Completed suicide	Drug tolerance increased	Intentional self-injury	Psychotic behaviour	
Compulsions	Dyslogia	Irritability	Psychotic disorder	
Confabulation	Dysphoria	Jamais vu	Reactive psychosis	
Confusional arousal	Elevated mood	Jealous delusion	Restlessness	
Confusional state	Emotional disorder	Judgement impaired	Retrograde amnesia	
Consciousness fluctuating	Emotional distress	Loose associations	Sedation	
Coordination abnormal	Energy increased	Magical thinking	Self-injurious behaviour	
Deja vu	Erotomanic delusion	Mania	Self-injurious ideation	

# Adverse Events Groups Determined by MedDRA Hierarchy, Clinical Judgement and/or DSM-V)

Event Groups	Preferred Terms
<b>Abuse</b>	Drug abuse, Drug abuser, Drug administered at inappropriate site, "Drug dependence, antepartum", Drug detoxification, Drug rehabilitation, Drug tolerance, Drug tolerance decreased, Drug toxicity, Intentional drug misuse, Maternal use of illicit drugs, Neonatal complications of substance abuse, Poisoning, Prescription form tampering, Product tampering, Product used for unknown indication, Substance abuse, Substance abuser, Substance use, Therapeutic agent toxicity, Toxicity to various agents, Treatment noncompliance
<b>Activity level</b>	Asthenia, Energy increased
<b>Affect</b>	Affect lability, Affective disorder, Blunted affect, Flat affect, Inappropriate affect, Staring
<b>Anxiety</b>	Anxiety, Fear, Feeling jittery, Panic attack, Panic reaction, Paranoia, Restlessness
<b>Behavior</b>	Abnormal behaviour, Aggression, Antisocial behaviour, Asocial behaviour, Attention-seeking behaviour, Belligerence, Compulsions, Disinhibition, Disturbance in social behaviour, Homicidal ideation, Homicide, Hostility, Impatience, Impulsive behaviour, Indifference, Physical assault, Suspiciousness, Violence-related symptom
<b>Cognitive</b>	Cognitive disorder, Disturbance in attention, Executive dysfunction
<b>Confusion</b>	Confusional arousal, Confusional state, Delirium, Disorientation
<b>Consciousness</b>	Altered state of consciousness, Consciousness fluctuating, Depressed level of consciousness, Hypervigilance, Sedation, Stupor
<b>Coordination</b>	Impaired driving ability, Muscle rigidity
<b>Death</b>	Accidental death
<b>Dependence</b>	Dependence, Drug dependence, Drug dependence, antepartum, Drug tolerance Increased, Polysubstance dependence, Steroid withdrawal syndrome
<b>Dissociative</b>	Depersonalisation, Dissociation, Dissociative amnesia, Dissociative identity disorder
<b>Diversion</b>	Drug diversion
<b>Emotion</b>	Anger, Emotional disorder, Emotional distress
<b>Feelings</b>	Feeling abnormal, Feeling drunk, Feeling of relaxation, Hangover
<b>Hallucination</b>	Hallucination, "Hallucination, auditory", "Hallucination, gustatory", "Hallucination, olfactory", "Hallucination, synaesthetic", "Hallucination, tactile", "Hallucination, visual", "Hallucinations, mixed", Hypnagogic hallucination, Hypnopompic hallucination, Somatic hallucination

# Adverse Event Groups (cont'd)

<b>Memory</b>	Amnesia, Amnesic disorder, Anterograde amnesia, Memory impairment, Paramnesia, Retrograde amnesia, Transient global amnesia
<b>Mental</b>	Mental disability, Mental disorder, Mental Impairment, Mental status changes
<b>MOA</b>	Central nervous system stimulation, Dopamine dysregulation syndrome
<b>Mood</b>	Agitation, Anhedonia, Apathy, Dysphoria, Elevated mood, Euphoric mood, Feeling of despair, Irritability, Mood altered, Mood swings, Substance-induced mood disorder
<b>Movement</b>	Balance disorder, Coordination abnormal, Psychomotor hyperactivity, Psychomotor retardation, Psychomotor skills impaired
<b>Overdose</b>	Accidental overdose, Accidental poisoning, Intentional overdose, Multiple drug overdose, Multiple drug overdose accidental, Multiple drug overdose Intentional, Overdose
<b>Perception</b>	Deja vu, Derealisation, Flashback, Formication, Illusion, Jamais vu, Paroxysmal perceptual alteration, Sensory disturbance, Sensory level abnormal
<b>Personality</b>	Personality change, Personality disorder
<b>Physical signs</b>	Miosis, Mydriasis, Nasal necrosis, Nasal septum perforation, Nasal septum ulceration, Needle track marks
<b>Psychosis-delusion</b>	Acute psychosis, Alice in wonderland syndrome, Delusion, Delusion of grandeur, Delusion of reference, Delusion of replacement, "Delusional disorder, erotomanic type", "Delusional disorder, grandiose type", "Delusional disorder, jealous type", "Delusional disorder, mixed type", "Delusional disorder, persecutory type", "Delusional disorder, somatic type", "Delusional disorder, unspecified type", Delusional perception, "Delusions, mixed", Depressive delusion, Erotomanic delusion, Jealous delusion, Mania, Persecutory delusion, Psychotic behaviour, Psychotic disorder, Reactive psychosis, Somatic delusion, Substance-induced psychotic disorder, Thought broadcasting, Thought insertion, Thought withdrawal, Transient psychosis
<b>Sensory</b>	Altered visual depth perception
<b>Sleep</b>	Abnormal dreams, Abnormal sleep-related event, Parasomnia, Sleep sex, Sleep terror, Somnolence
<b>Suicide</b>	Completed suicide, Intentional self-injury, Self injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, Suicide attempt
<b>Test</b>	Amphetamines, Amphetamines positive, Benzodiazepine drug level, Drug level above therapeutic, Drug level increased, Drug screen, Drug screen positive, Urine amphetamine, Urine amphetamine positive
<b>Therapy</b>	Analgesic therapy, Antitussive therapy, Muscle relaxant therapy
<b>Thinking</b>	Bradyphrenia, Confabulation, Derailment, Flight of ideas, Ideas of reference, Illogical thinking, Impaired reasoning, Incoherent, Judgement impaired, Loose associations, Magical thinking, Tangentiality, Thinking abnormal, Thought blocking
<b>Vocal</b>	Dysarthria, Dyslogia, Slow speech



# Drugs Grouped by DEA Schedule Level

	Generic Name
CS1	Dextromoramide, Diamorphine, Dimethyltryptamine, Gamma-Hydroxybutyrate, Ibogaine, Ketobemidone, Lysergide, Marijuana, Mescaline, Methaqualone, Methoxyamphetamine, Methylenedioxyamphetamine, Methylenedioxymethamphetamine, Phenoperidine, Pholcodine, Piriramide, Tetrahydrocannabinol, Thebacon, Tilidine
CS2	Alfentanil, Alphaprodine, Amphetamine, Amobarbital, Anileridine, Cocaine, Codeine, Diphenoxylate, Ethylmorphine, Fentanyl, Fentanyl Sustained-Release, Glutethimide, Hydrocodone, Hydromorphone, Levacetylmethadol, Levorphanol, Lisdexamphetamine, Metamphetamine, Methadone, Methylphenidate, Methylphenidate Extended Release, Methylphenidate Sustained Release, Morphine, Morphine Extended Release, Morphine Tartrate, Nabilone, Opium, Opium Alkaloid, Opium Tincture, Oxycodone, Oxymorphone, Oxymorphone Extended Release, Pethidine, Phencyclidine, Phenmetrazine, Remifentanyl, Sufentanil, Tapentadol, Tapentadol Extended Release, Acetaminophen And Hydromorphone, Acetaminophen And Oxycodone, Acetylsalicylic Acid And Oxycodone, Amphetamine And Dexamphetamine, Amphetamine And Dexamphetamine Extended Release, Amitriptyline And Methadone, Aspirin And Oxycodone, Atropine And Hydromorphone, Atropine And Pethidine, Bupivacaine And Fentanyl, Bupivacaine And Hydromorphone, Bupivacaine And Sufentanyl, Cocaine And Epinephrine And Tetracaine, Cocaine And Ethanol, Cocaine And Metoprolol, Diphenhydramine And Fentanyl, Droperidol And Fentanyl, Ethanol And Oxycodone, Etomidate And Fentanyl And Mivacurium, Fentanyl And Ropivacaine, Ibuprofen And Oxycodone, Naloxone And Oxycodone, Pethidine And Promethazine
CS3	Anabolic Steroid, Aprobarbital, Barbiturate, Benzphetamine, Buprenorphine, Butabarbital, Butalbital, Butobarbital, Calusterone, Chlorphentermine, Dronabinol, Ethylestrenol, Fluoxymesterone, Ketamine, Mesterolone, Methyltestosterone, Methypylon, Nandrolone, Norethandrolone, Oxandrolone, Oxymetholone, Perampanel, Phendimetrazine, Stanozolol, Talbutal, Testolactone, Testosterone, Thiamylal, Thiopental, Acetaminophen And Aspirin And Butalbital, Acetaminophen And Butabarbital, Acetaminophen And Butalbital, Acetaminophen And Butalbital And Caffeine, Acetaminophen And Butalbital And Caffeine And Ethanol, Acetaminophen And Caffeine And Chlorphenamine And Hydrocodone And Phenylephrine, Acetaminophen And Ethanol And Hydrocodone, Acetaminophen And Hydrocodone, Acetaminophen And Morphine, Aminophylline And Amobarbital And Ephedrine, Ammonium Chloride And Chlorphenamine And Hydrocodone And Phenindamine And Phenylephrine And Pylamine, Aspirin And Butalbital, Aspirin And Butalbital And Caffeine, Aspirin And Hydrocodone, Atropine And Chlorphenamine And Hydrocodone And Hyoscyamine And Phenylephrine And Phenylpropanolamine And Scopolamine, Bupivacaine And Morphine, Buprenorphine And Naloxone, Butalbital And Caffeine, Carbromal And Pentobarbital, Chlorphenamine And Ephedrine And Hydrocodone, Chlorphenamine And Hydrocodone, Chlorphenamine And Hydrocodone And Phenylephrine, Chlorphenamine And Hydrocodone And Pseudoephedrine, Cyclizine And Morphine, Estradiol And Testosterone, Estrogens And Progesterone And Testosterone, Estrogens Conjugated And Methyltestosterone, Estrogens Esterified And Methyltestosterone, Glucose And Morphine, Guaifenesin And Hydrocodone, Guaifenesin And Hydrocodone And Phenylephrine, Homatropine And Hydrocodone, Hydrocodone And Ibuprofen, Hydrocodone And Ketoprofen And Lidocaine, Hydrocodone And Pheniramine And Phenylpropanolamine And Pylamine, Hydrocodone And Phenylpropanolamine, Hydrocodone And Phenyltoloxamine, Hydrocodone And Pseudoephedrine, Morphine And Naltrexone, Morphine And Scopolamine, Thiopental And Vecuronium



# Drug Groups (cont'd)

<b>CS4</b>	<p>Alprazolam, Barbitol, Bromazepam, Butorphanol, Carisoprodol, Cathine, Chloral Betaine, Chloral Hydrate, Chlordiazepoxide, Clobazam, Clonazepam, Clorazepate, Clotiazepam, Cloxazolam, Delorazepam, Dexfenfluramine, Diazepam, Dichloralphenazone, Diethylpropion, Estazolam, Ethchlorvynol, Ethinamate, Ethyl Loflazepate, Fenfluramine, Fenproporex, Fludiazepam, Flunitrazepam, Flurazepam, Fospropofol, Halazepam, Haloxazolam, Ketazolam, Loprazolam, Lorazepam, Lormetazepam, Mazindol, Medazepam, Meprobamate, Methohexital, Methylphenobarbital, Midazolam, Modafinil, Nimetazepam, Nitrazepam, Nordazepam, Oxazepam, Paraldehyde, Pemoline, Pentazocine, Phenobarbital, Phentermine, Prazepam, Quazepam, Sibutramine, Temazepam, Tetrazepam, Triazolam, Zaleplon, Zolpidem, Zopiclone, Dextropropoxyphene, Acepromazine And Aceprometazine And Clorazepate, Acepromazine And Clorazepate, Aceprometazine And Meprobamate, Acetaminophen And Caffeine And Carbasalate And Chlorphenamine And Dextropropoxyphene, Acetaminophen And Caffeine And Carisoprodol And Diclofenac, Acetaminophen And Caffeine And Dextropropoxyphene, Acetaminophen And Caffeine And Dextropropoxyphene And Diphenhydramine, Acetaminophen And Carisoprodol And Metamizole, Acetaminophen And Dextropropoxyphene, Acetaminophen And Dextropropoxyphene And Metformin, Acetaminophen And Meprobamate, Acetaminophen And Pentazocine, Alprazolam And Bisoprolol, Amino Acid Mixture And Nitrazepam, Amitriptyline And Chlordiazepoxide, Aspirin And Caffeine And Dextropropoxyphene, Aspirin And Caffeine And Dextropropoxyphene And Phenacetin, Aspirin And Carisoprodol, Aspirin And Dextropropoxyphene, Aspirin And Meprobamate, Aspirin And Pentazocine, Aspirin And Phenobarbital, Atropa Belladonna And Caffeine And Phenobarbital, Atropa Belladonna And Ergotamine And Phenobarbital, Atropa Belladonna And Phenobarbital, Atropine And Hyoscyamine And Phenobarbital And Scopolamine, Biotin And Phenobarbital, Bromazepam And Sulpiride, Caffeine And Carisoprodol And Phenacetin, Caffeine And Chlorcyclizine And Ergotamine And Meprobamate, Caffeine And Chlordiazepoxide And Metamizole And Vitamin B1 And Vitamin B12 And Vitamin B6, Caffeine And Dyphylline And Ephedrine And Phenobarbital, Caffeine And Phenobarbital, Caffeine And Phenobarbital And Phenytoin And Sodium Benzoate, Carisoprodol And Mirtazapine, Chlordiazepoxide And Clidinium, Chlordiazepoxide And Lithium, Chlorpromazine And Phenobarbital, Chlorpromazine And Phenobarbital And Promethazine, Clonazepam And Escitalopram, Clotrimazole And Zolpidem, Diazepam And Isopropamide, Dichloralphenazone And Isometheptene, Dicycloverine And Phenobarbital, Diphenhydramine And Lorazepam, Ephedrine And Phenobarbital And Potassium Iodide And Theophylline Calcium Salicylate, Ephedrine And Phenobarbital And Theophylline, Estrogens Conjugated And Meprobamate, Flunitrazepam And Sodium Chloride, Hyoscyamine And Phenobarbital, Hyoscyamus Niger And Phenobarbital And Quinine And Valerian, Isosorbide And Phenobarbital, Mepenzolate And Phenobarbital, Mephenytoin And Phenobarbital, Naloxone And Pentazocine, Phenobarbital And Phenytoin, Phenobarbital And Propantheline, Phenobarbital And Scopolamine, Phentermine And Resin, Phentermine And Topiramate, Quetiapine And Zolpidem</p>
<b>CS5</b>	Lacosamide, Pregabalin, Retigabine, Atropine And Diphenoxylate
<b>NCS</b>	<p>Atomoxetine, Baclofen, Bupropion, Bupropion Extended Release, Bupropion Slow Release, Buspirone, Cabergoline, Citalopram, Diclofenac, Diphenhydramine, Duloxetine, Escitalopram, Fluoxetine, Gabapentin, Naproxen, Olanzapine, Paroxetine, Pergolide, Piroxicam, Sertraline, Topiramate, Valproic Acid, Valproic Acid Delayed Release, Valproic Acid Extended Release, Venlafaxine, Venlafaxine</p>



# Statistical Methods Evaluated

- Data mining to identify signals of disproportionate reporting (SDRs)
  - Used to identify potential drug-event associations by calculating ratios of observed-to-expected reporting frequencies, proportions or odds
- Hierarchical cluster analysis
  - Used to visualize the distances/similarities/dissimilarities between drugs/drug groups or events
- Correspondence analysis
  - Used to visualize the similarities/dissimilarities in a low-dimensional space based on a distance metric (chi squared distance metric)

# Statistical Methods Evaluated (cont'd)

- Metric-multidimensional scaling
  - Used to visualize the similarities/dissimilarities in a low-dimensional space based on a distance metric (euclidian distance metric)
- Exploratory factor analysis
  - used to search for groups of variables with substantial shared variance that collectively might represent a single underlying concept
- K-means cluster analysis
  - Used to partition data into a predetermined number of clusters with observations going to the cluster with the nearest mean
- Discriminant analysis
  - Used to predict group membership based on a set of weighted predictor variables, ie a discriminant function

# Data Mining: Signals of Disproportionate Reporting Show Differing Patterns Based on Drug Scheduling Level

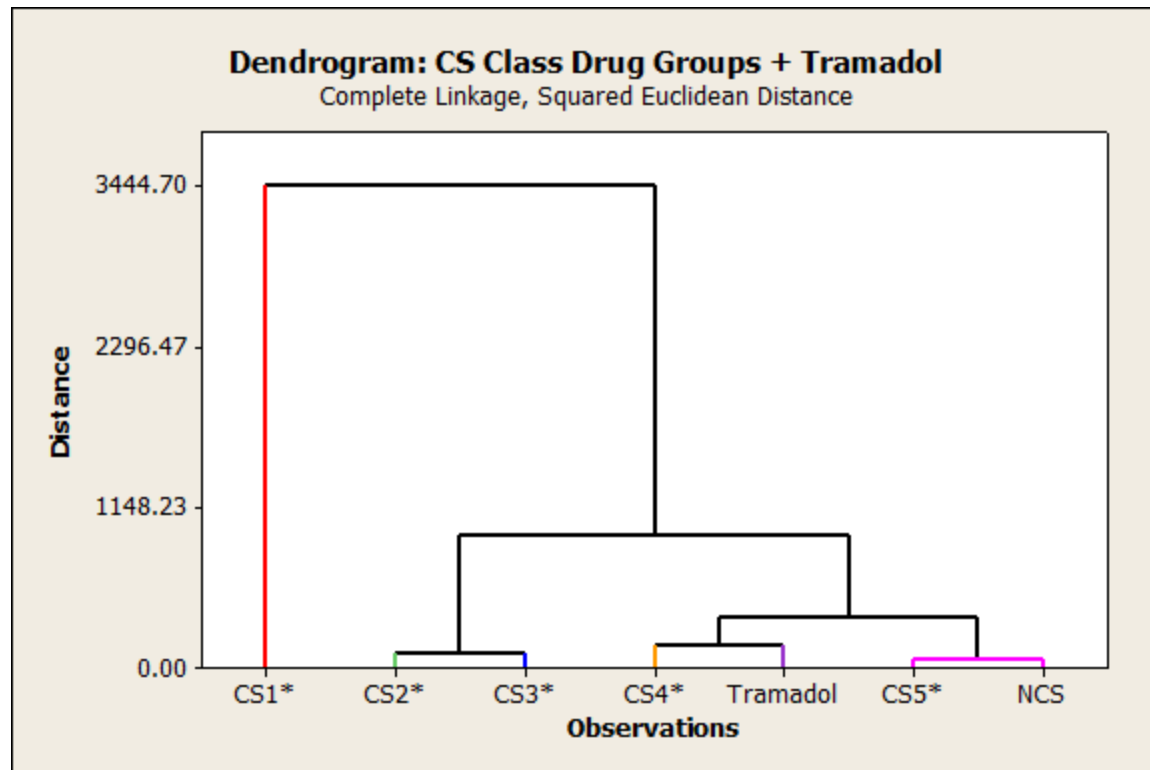
## Drug Groups

Adverse Event Groups

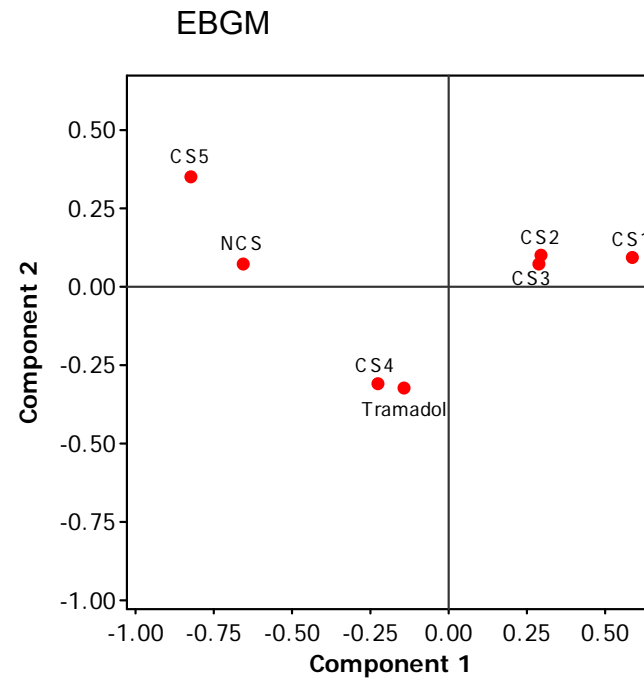
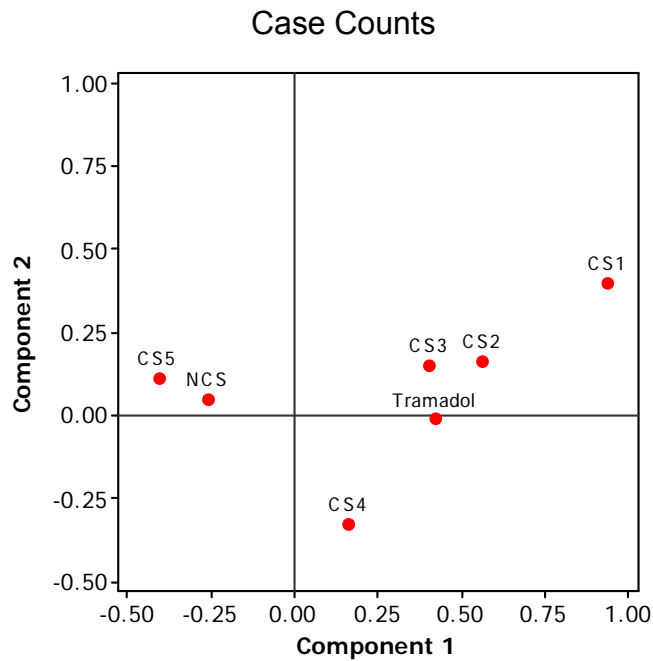
Event Groups	CS1	CS2	CS3	CS4	CS5	NCS
Overdose	5.95	3.80	2.29	3.77	0.89	2.15
Physical signs	5.71	3.98	2.92	2.99	1.23	2.06
Test	7.30	2.62	2.86	1.78	1.40	1.65
Death	26.07	16.21	6.80	10.19	0.32	2.10
Abuse	12.90	6.15	4.35	3.96	0.96	1.29
Diversion	28.44	20.81	16.03	4.72	0.15	0.52
Memory	1.31	1.20	1.10	5.02	2.70	2.03
MOA	0.707	0.947	0.135	6.458		2.394
Personality	0.74	1.56	1.07	4.13	2.23	3.04
Suicide	2.11	2.02	3.21	4.03	1.36	3.88
Anxiety	1.19	1.30	1.46	2.83	1.13	2.40
Feelings	0.56	1.22	1.00	1.50	3.45	2.43
Movement	0.80	0.90	0.65	2.13	4.04	1.80
Sleep	1.99	2.26	1.60	3.20	4.54	3.00
Thinking	1.04	1.75	1.17	2.98	3.99	3.05
Vocal	1.50	1.57	1.52	2.19	3.59	1.66
Cognitive	0.54	1.36	0.74	2.10	4.57	2.88
Confusion	1.71	2.15	1.31	2.74	3.07	1.96
Affect	0.84	1.76	1.12	1.49	1.29	2.78
Perception	0.58	1.32	0.73	1.40	1.74	2.39

$0 \leq EB05 \leq 1$  <  $1 < EB05 \leq 2$  <  $2 < EB05 \leq 4$  <  $4 < EB05 \leq 8$  <  $8 < EB05 < \infty$

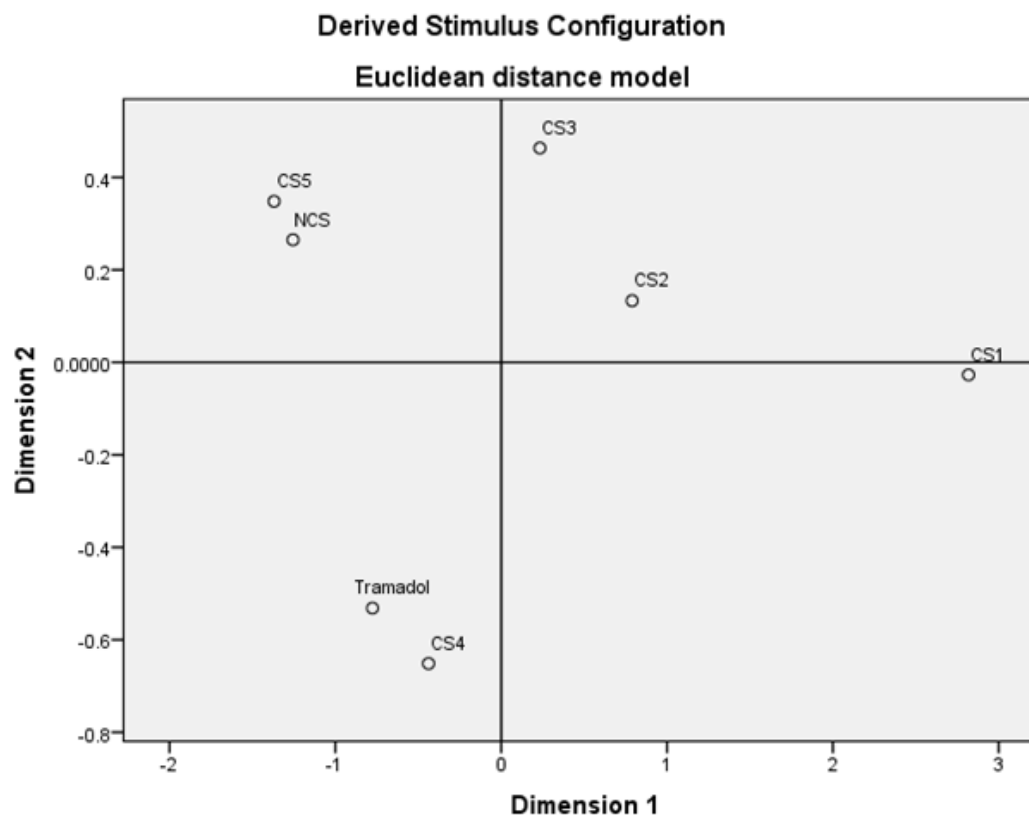
# Hierarchical Cluster Analysis: Drug Groups Based on Schedule Level Show Logical Clustering, Tramadol Clusters with Schedule IV Drugs



# Simple Correspondence Analysis: Clear Distinction Between Drug Groups, Tramadol Most Closely Positioned with Schedule IV Drugs Based on EBGm Values



# Metric Multidimensional Scaling: Confirms Simple Correspondence Analysis Results – Distinction Between Drug Groups, Tramadol Positioned Closest to Schedule IV Drugs



# Conclusions

- Statistical approaches have the potential to be useful for visualizing complex patterns of abuse potential AEs
- Results across the different methods show that there is separation of drugs by scheduling class in “AE space”.
- Data mining results showed differing patterns in the types of AEs showing SDRs and in the strength of SDRs by drug schedule class:
  - overt abuse related terms associated with higher scheduling levels (ie, Schedule I & II)
  - mood/mental state terms associated with lower scheduling levels (ie, Schedule IV & V)
- Multivariate analyses confirmed the similarity of tramadol to other Schedule IV drugs, suggesting these methods may be useful in scheduling decisions.



# Some Limitations of the Data/Methods

- AE data represents spontaneously /voluntarily reported events
  - Subject to external influences, ie media attention
  - May or may not be confirmed
  - May be biased towards people who had a prescription
  - Drug-event associations do not confirm causality
  - Duplicative reporting
- Violations of statistical assumptions (eg, multivariate normality, linearity, equality of variance/covariance matrices, independence of predictors, lack of high multi-collinearity)
- Marked class imbalance with some drug scheduling classes being sparsely populated.
- Graphical representations in dendrograms and biplots are exact mappings, ie entails some degree of distortion.

# Applications to Clinical Trial Data

- Multivariate statistical approaches may be directly applied to large clinical trial datasets in which event frequencies are relatively high
- Assessing postmarketing data from the same or a similar class of drugs may help inform which events might be expected in clinical trials and warrant closer scrutiny
- Postmarketing data can help to identify events which cluster together to determine a composite endpoint/clinical phenotype
- Based on the results seen with tramadol, these types of data may also be useful in decisions of schedule level.

# ResearchTeam

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