
Can epidemiologic studies be used to measure abuse-resistance?

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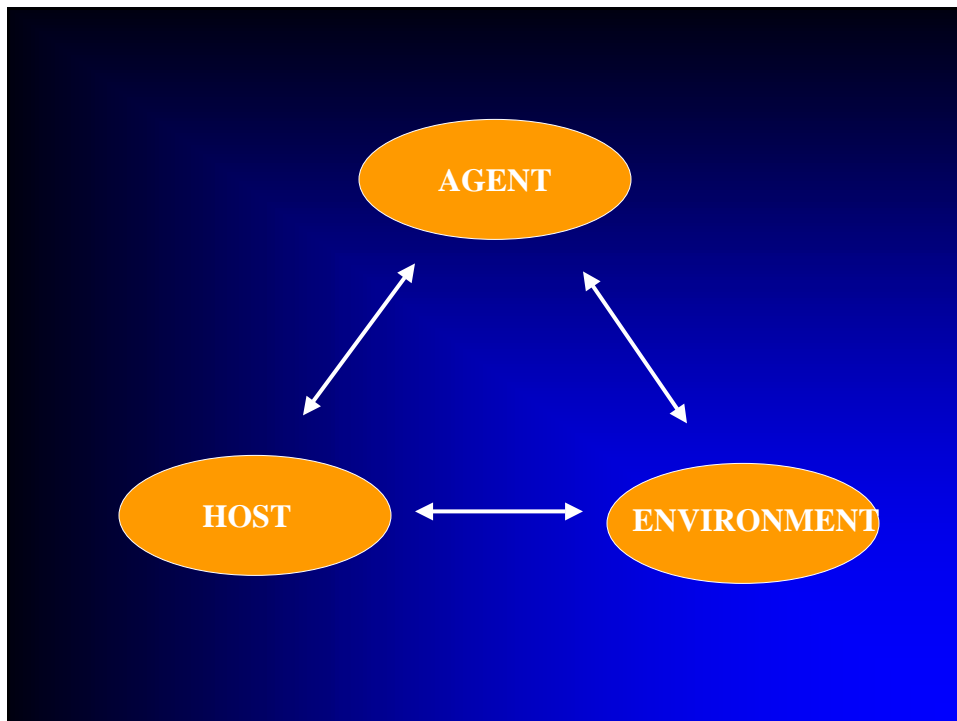
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Unique Contribution of Epidemiologic Research

- Population-based focus
 - Define population (e.g., patients in chronic pain Tx or U.S. general population)
 - Draw sample from population – goal of minimizing selection bias
- Longitudinal Research
 - Temporal sequencing
 - Observation of natural history of abuse
- Incidence and prevalence of abuse/dependence

Infectious Disease Analogy

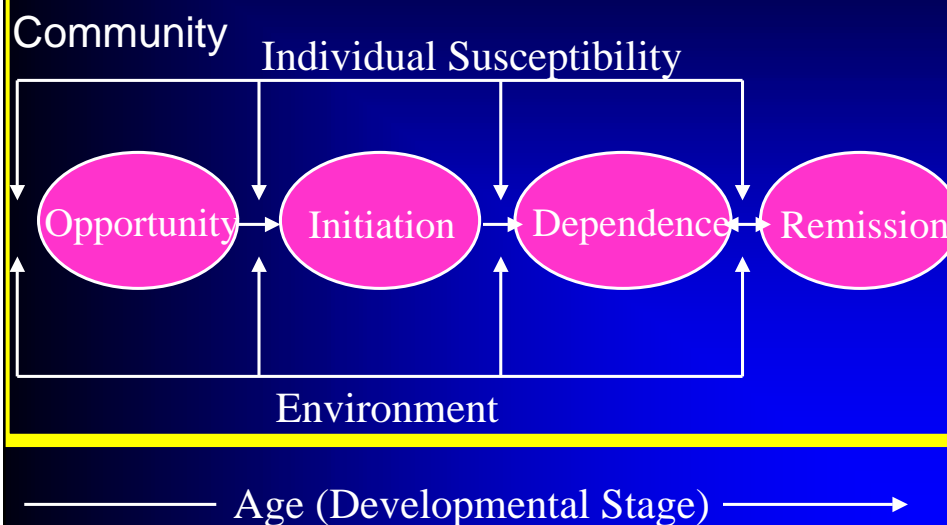
- Variation in prevalence and incidence occur across time and space
- Transmission is person to person (Robins)
- Changes in incidence and prevalence of disease due to changes in exposure to infectious agent (governed by environmental conditions) or changes in susceptibility of the population (Frost)



Significance of Epidemiologic Studies for Comparing Abuse - resistance

- Only epidemiological studies can measure natural history of “abuse” in populations.
- Onset and course of abuse within individuals who are prescribed a specific drug
- Spread of extramedical use/diversion across time and space

Conceptual Framework



Questions

- What characteristics does an epidemiologic database or epidemiologic study have to have in order to provide robust information about whether one drug is more “abuse-resistant” than another?
- Do any of the existing databases/ongoing studies meet these criteria?
- If not, what types of databases/surveillance systems/epidemiologic studies would need to be developed in order to determine whether product A is “abuse-resistant” compared to product B?

Requirements for Epidemiologic Data

- Different requirements depending on whether the interest is in abuse among those who are prescribed drugs versus extramedical use/diversion
- It is unlikely that a single study or source of data can address in these distinct populations given the unique requirements for each in terms of measures and sampling strategies.
- Regardless of strategy is it important that studies be able to determine additional public health burden due to a specific drug.

Requirements

- Information on exposure to specific analgesics
- Clearly-defined outcomes
- Samples representative of defined populations
- Estimates of risk (numerator and denominator)
- Control of potential confounders
- Control of temporal sequencing between analgesic use and onset of “abuse”
- Measures of vulnerability

Need information on exposure to analgesics

- Medical vs. extramedical use
- Degree of exposure (duration, dose, frequency)
- Specific analgesics used (brand and generic, formulation)

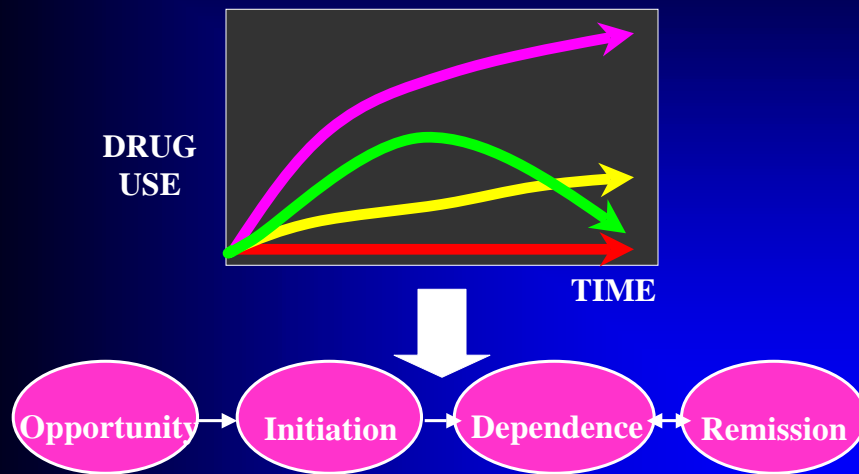
Given drugs that are pharmacologically similar, a variety of drug-related environmental conditions might lead to different abuse potential

- Drug delivery system
- Marketing strategy (increases opportunity to use or interest in using)
- Word-of-mouth, press reports

Outcome

- Opportunities to use
- Use
- Escalation of use
- Dependence/abuse – symptomatology
- Remission
- Consequences

Trajectories of Drug Use



Heterogeneity of Drug Use Outcomes

- Trajectories of use and escalation
- Classes of drug dependence symptoms
- Understanding of heterogeneity in outcomes could be important for demonstrating reduced abuse liability for one agent versus another

Defining populations and drawing samples

- For abuse among those prescribed drugs, population is those given a prescription and taking drug
 - Samples can include chronic pain patients, those picking up prescriptions at a pharmacy – need to consider representativeness
- For extramedical use/diversion population generally is defined by geographic area, although subpopulations might be of interest

Estimates of Risk

- Estimate number of “cases” emerging in specified period of time (numerator)
 - New onset of “abuse” among sample at risk
 - Number of cases captured through surveillance
- Denominator is defined as number at risk of “abuse”
 - Easy to define in cohort studies with longitudinal follow-up
 - More difficult for surveillance

Control for Potential Confounders

- Possible selection bias for those who use one drug versus another (not randomly assigned)
- Variation in availability of different drugs (geographic, physician prescribing practices, marketing factors, number of prescriptions)

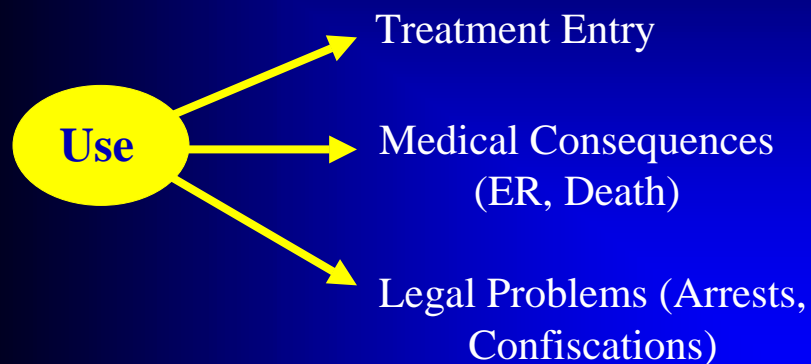
Control of temporal sequencing between analgesic use and onset of “abuse”

- Need to know that “abuse” is due to drug of interest and is not pre-existing
- Can start with “drug-naive” cohort sample, but raises issues of generalizability
- Careful history of other drug use and evidence of prior abuse/dependence is important
- In surveillance studies, useful to know if drug of interest adds to public health burden of drug abuse (i.e., availability of this drug increases incidence of drug use/abuse/dependence that would not have occurred otherwise)

Measures of vulnerability

- Factors that might play a role in the causal pathway to “abuse”
 - Mediators
 - Moderators
- Psychiatric Disorders, Antisocial Behavior
- Screening for vulnerability can aid in the development of more efficient sampling strategies

Indicators of “abuse” useful for surveillance



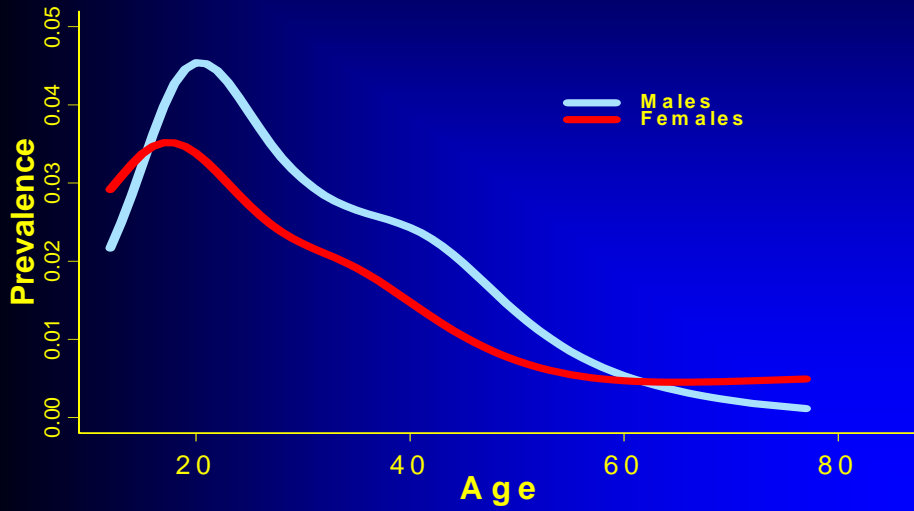
Do any of the existing databases/ongoing studies meet these criteria?

- Not really
- Major surveys of drug abuse lack information on specific opioid analgesics
- These surveys also fail to distinguish using more than prescribed from use of drug obtained illegally
- Surveillance systems have potential to detect major signals, but lack resolution to detect a range of “abuse” except for that which might lead users to enter treatment or have problem with law

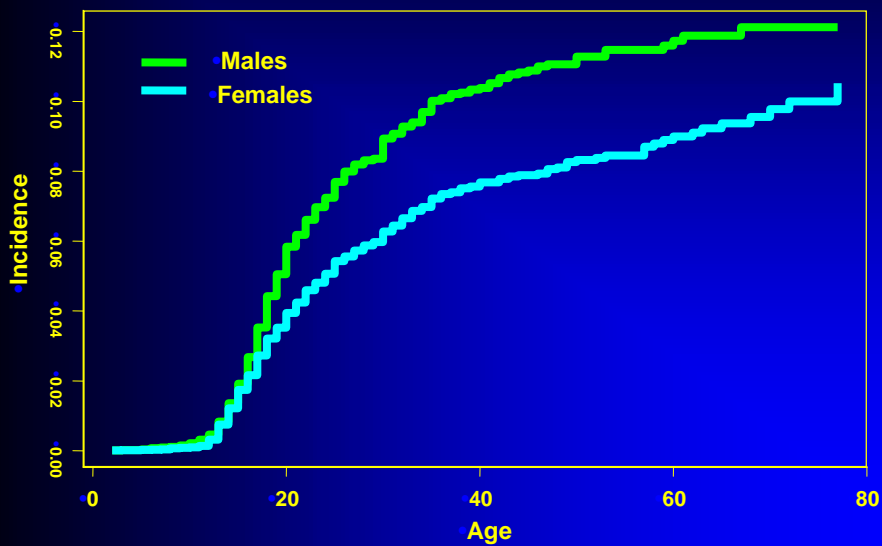
Do any of the existing databases/ongoing studies meet these criteria?

- Drug Abuse Warning Network (DAWN) only detects severe outcomes and brand names not always available
- Health Information Systems such as Kaiser, Group Health have the ability to link pharmacy records with health outcomes but only include limited outcomes (seeking treatment)
- Drug Abuse Treatment Systems such as Drug Evaluation Network System (DENS) or Treatment Episode Data System (TEDS) are limited to those seeking treatment and specific drug info can be limited

Prevalence of Extramedical Analgesic Use in the Past Year (1998)

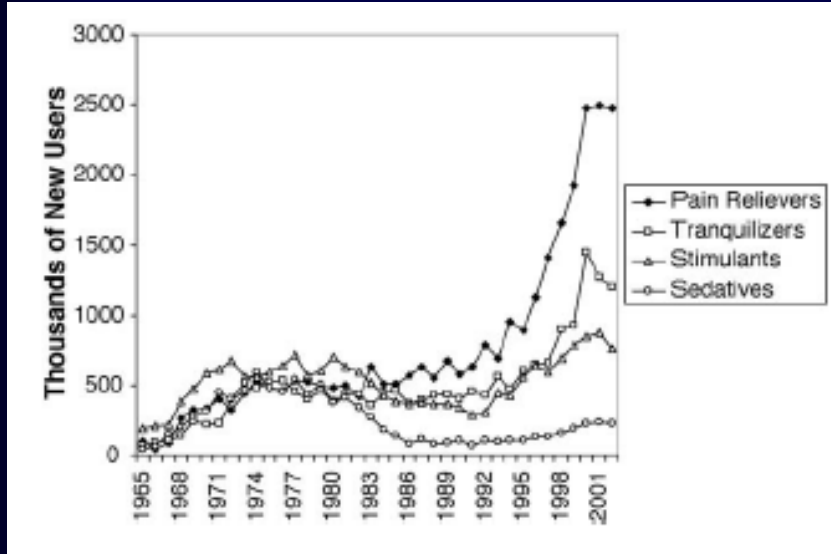


Cumulative Incidence of Analgesic Use



Incidence of Extramedical Prescription Drug Use

(from SAMSHA, 2003)



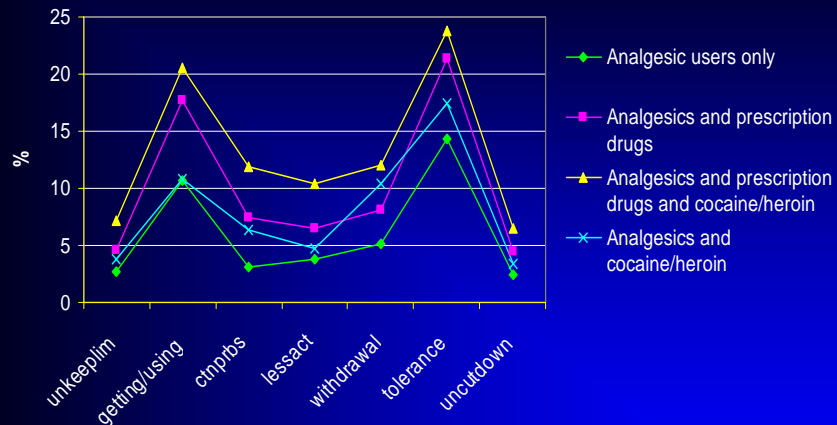
Use of Specific Opioid Analgesics (N=7766)

Drug	Any Use		Only Use	
	Total N	Prevalence (%)	N	% of drug users
Darvocet, darvon, or Tylenol with codeine	4916	8.15	1876	38.16
Vicodin lartab or lorcet	4072	5.63	1025	25.17
Percodan, percocet, or Tylex	2548	4.16	333	13.07
Codeine	1976	3.00	169	8.55
Hydrocodone	1433	1.94	91	6.35
Oxycontin	792	0.84	34	4.29
Demerol	721	1.27	33	4.58
Morphine	715	0.91	33	4.62
Methadone	338	0.40	15	4.44
Phenaphen with codeine	240	0.38	6	2.50

Users of a Single Opioid Analgesic (N=3860)

Drug	N	Percent
Darvocet, darvon, or Tylenol with codeine	1876	50.98
Vicodin lartab or lorcet	1025	27.85
Percodan, percocet, or Tylex	333	9.05
Codeine	169	4.59
Hydrocodone	91	2.47
Oxycontin	34	0.92
Demerol	33	0.90
Morphine	33	0.90
Methadone	15	0.41
Phenaphen with codeine	6	0.16

Past year analgesic dependence in subgroups of past year analgesic users - NSDUH 2002-2003



* symptoms: 1- Use is in larger amounts or for longer periods than intended; 2- Great deal of time spent getting or using substance/recovering from its effects; 3- Use is continued despite problems; 4: Important activities are given up or reduced due to substance use; 5: Withdrawal; 6: Tolerance; 7: Persistent desire/unsuccesful efforts to cut down/control use.

Latent Class Analysis of analgesic dependence symptoms in past year analgesic users, NSDUH, 2002-2003

	Total	Class 1	Class 2	Class 3	Class 4
	%	Symptom%	Symptom%	Symptom%	Symptom%
Great deal of time spent getting or using substance/recovering from its effects	14.35	3.8	69.8	45.6	99.2
Use is in larger amounts or for longer periods than intended	3.21	0.3	13.7	4.7	57.5
Tolerance	17.59	6.0	82.2	51.0	97.0
Persistent desire/unsuccessful efforts to cut down/control use	3.29	0.9	11.1	10.0	43.6
Use is continued despite problems	5.04	0.3	9.8	45.8	87.7
Important activities are given up or reduced due to substance use	5.40	0.9	10.0	49.2	76.7
Withdrawal	6.94	1.6	21.4	49.5	68.12
Class Size	---	84%	10%	4%	2%

Prevalence of DSM-IV Analgesic Dependence by Latent Class

Class	Prevalence of Analgesic Dependence (%)
1	0.3
2	38.1
3	65.5
4	97.6

Estimated Odds Ratios and 95% confidence intervals: a Latent Class Regression analysis of all past year analgesic users, National Survey on Drug Use and Health, 2002-2003

	Class 2 vs 1		Class 3 vs 1		Class 4 vs 1	
	OR	95% CI	OR	95% CI	OR	95% CI
Gender						
Female	1.00	---	1.00	---	1.0	---
Male	1.26	1.1-1.5	1.43	1.0-1.9	1.78	1.3-2.4
Age						
12-17 year olds	1.00	---	1.00	---	1.0	---
18-25 year olds	0.73	0.61-0.87	0.44	0.3-0.6	0.83	0.6-1.2
26-35 year olds	0.88	0.6-1.2	0.37	0.2-0.8	1.39	0.8-2.3
35 years and older	0.78	0.6-1.1	.65	0.4-1.1	1.87	1.2-2.9
Race/Ethnicity						
Whites	1.00	---	1.00	---	1.0	---
African Americans	1.45	1.1-1.9	1.3	0.8-2.2	1.03	0.6-1.9
Hispanics	1.03	0.8-1.3	1.26	0.8-2.0	0.68	0.4-1.2
Analgesic groups						
Analgesic users only	1.00	---	1.00	---	1.0	---
Analgesics & prescription drugs	2.34	1.90-2.9	2.12	1.5-3.0	3.89	2.6-5.8
Analgesics/ prescription/ heroin/cocaine	2.94	2.4-3.6	1.55	0.9-2.5	10.43	7.1-15.3
Analgesics & heroin/cocaine	1.16	0.8-1.6	1.28	0.7-2.4	3.97	2.3-6.9

Extramedical Analgesic Dependence : Lifetime Comorbidity with Psychiatric Disorders

	Analgesic Dependence Present (%) n = 68	Analgesic Dependence Absent (%) n = 8030	Adjusted OR (95% CI)
Depression	43.8	16.9	2.63 (1.36 - 5.08)
Agoraphobia	17.9	6.4	2.25 (0.82 - 6.13)
Simple Phobia	30.0	11.7	2.13 (1.07 - 4.22)
Social Phobia	28.3	12.3	1.82 (0.71 - 4.67)
Panic Attack	29.5	7.1	3.88 (1.88 - 8.01)
Antisoc. Personality Disorder	36.8	2.9	15.14 (6.99 - 32.79)
Lifetime Cocaine Dependence	39.7	3.0	16.53 (8.82 - 30.97)

Odds Ratios & 95% CI for Analgesic Dependence, Given Use

	Separate model for each psychiatric disorder		Model containing Conduct Disorder and Depression	
	OR*	95% CI	OR*	95% CI
Female	1.20	.66 – 2.16	1.49	.80 – 2.79
Conduct Disorder	3.11	1.68 – 5.75	3.02	1.63 – 5.62
Antisocial Personality	5.10	2.64 – 9.83		
Depression	1.56	.87 – 2.82	1.45	.80 – 2.64

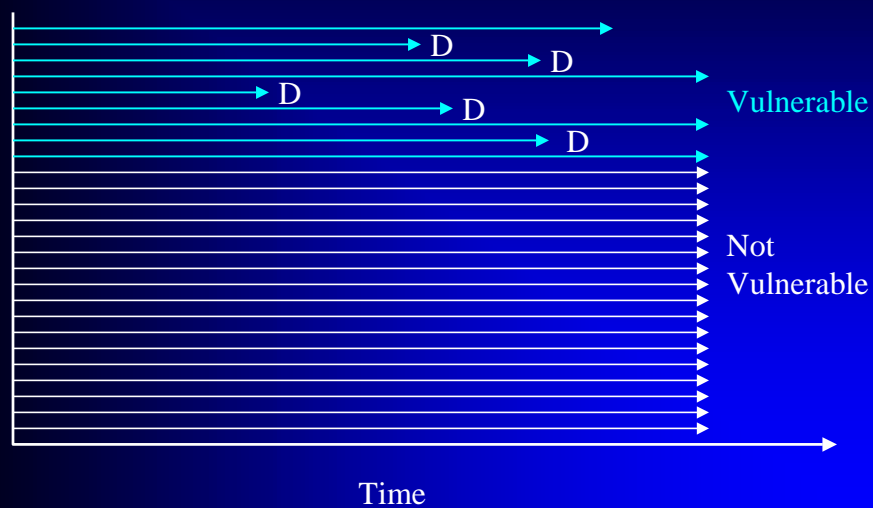
* Adjusted for age, race, education

If not, what types of databases/ surveillance systems/epidemiologic studies would need to be developed in order to determine whether product A is “abuse-resistant” compared to product B?

Designing Studies to Compare Abuse Resistance

- Incidence of DSM-defined dependence is likely to be low
 - Requires efficient sampling strategies
 - More sensitive outcome
- Types of studies
 - Prospective
 - Development of screening instruments for vulnerability
 - Oversampling of high vulnerability
 - Heterogeneity
 - Surveillance

Relevance of Vulnerability to Abuse



Approaches

- Rare exposure
 - Regardless of extramedical use or use as prescribed
- Requires cohort study design to define exposure to specific drugs
- Compare incidence of “abuse”

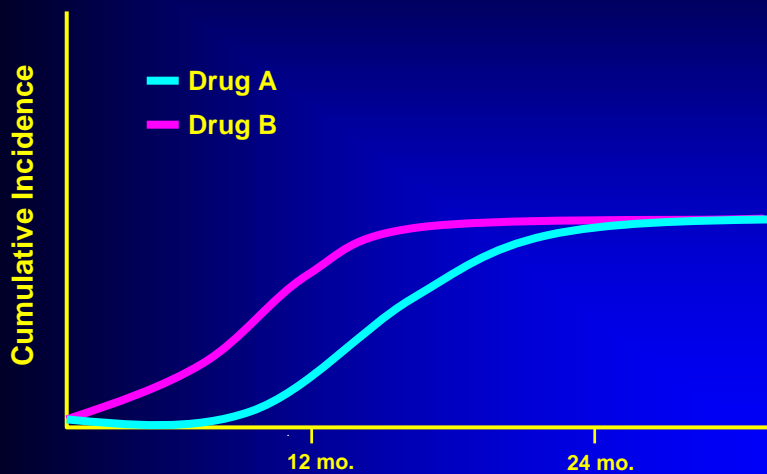
Prospective Studies

- Select a sample of those prescribed opioid medications of interest
 - Pain clinics
 - Pharmacies
- Need large samples because outcome is likely to be rare
- Need baseline/screening data on history of drug use, psychiatric and personality disorders, demographic characteristics, family history

Use of existing epidemiologic data to inform study design

- Informative selection of study participants
- Study design (e.g., necessary length of follow-up)
- Understanding of confounders and effect modifiers
- Selection of outcome and risk factor measures

Cumulative Incidence of "Abuse" Over Time



Considerations for follow-up

- Ideally, study participants should be followed up regularly (e.g, every three months) to detect emergence of symptoms of abuse and dependence
- Use of automated data collection systems such as by phone with voice recognition
- Pharmacy-based data collection
- Incentives to maximize response rates

Sampling considerations

- Newly prescribed or longer term users
- Exclusion criteria
 - Can exclude those with history of drug and psychiatric disorders, but ...
 - Trade-off of isolating drug effects versus generalizability to population of those exposed
- Oversampling by potential vulnerability can result in smaller sample size requirements and weighting can allow generalizability to population

Analytic Issues

- Need to adjust for potential confounder
- Test for differences in abuse-resistance by sample subgroups (e.g., in those with hx of psychiatric disorders).
- Consider time to event
- Consider latent variable or other analytic approaches that take into account empirical distribution of potential outcomes (while avoiding fishing expeditions!)

Potential Confounders/ Mediators/Effect Modifiers

- Other drug use
- Psychiatric disorders
- Antisocial behaviors