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Overview of Evidence Base for Current & Potential Medical Uses of Marijuana/Components

September 26, 2014 - Scientific Advisory Council Meeting

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Medical Marijuana Research Grant Program Manger

What this overview **"IS NOT"**

- Exhaustive
  - Selective by necessity
  - More detailed for some conditions
- Focused on basic science
- Focused on anecdotal information

What this overview **"IS"**

- Focused on published peer-review studies & reviews
- Focused primarily on RCTs
- Focused on "priority" conditions:
  - On current list of CO debilitating conditions
  - Of potential interest to possibly add to this list
  - Promising - based on evidence to date

Outline

- Pain
- Adverse Effects
- Nausea/vomiting & wasting syndrome
- Epilepsy
- Selected Neurologic Disorders
- PTSD
- Other Psychiatric Disorders
- Inflammatory Bowel Disease
- Glioma
- Opiate dependence & withdrawal

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Pain

Reviews (1)

- Martin-Sanchez E et al. (Spain/Japan) 2009; Pain Med
  - Systematic review & meta-analysis of RCTs through early 2008 of cannabinoids for chronic pain
  - 18 trials included
  - Efficacy analysis displayed statistically significant difference in favor of cannabis arm
  - Quantitative analysis of side effects using odds ratios
  - Conclusion:
    - "… cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms."
    - Not entirely clear how authors concluded "potentially serious harms"

Reviews (2)

- Lynch ME, Campbell F. (Canada) 2011; Br J Clin Pharmacol
  - Systematic review of RCTs of cannabinoids for chronic non-cancer pain
  - 15 of 18 RCTs showed significant analgesic effect compared w/ placebo
  - Adverse effects mostly mild-moderate & generally well tolerated
  - Main limitations: small sample sizes; short duration; modest effect sizes

  - Conclusion:
    - "… it is reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain…"

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Adverse Effects

Review of Adverse Effects

- Wang T, et al. (Canada) 2008; CMAJ
  - Systematic review of adverse effects of cannabinoids for **medical use**
  - 23 RCTs and 8 observational studies through late 2007
    [excluded studies of nabilone and smoked cannabis]
  - Median duration of cannabinoid exposure was 2 weeks
  - 97% of adverse events were non-serious
  - Dizziness was most common
  - Rate was higher with cannabinoid use (RR=1.86, 95% CI: 1.6 – 2.2)
  - Rate of serious adverse events did NOT differ between user and control groups: (RR=1.04, 95% CI: 0.8 – 1.4)

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Nausea, Vomiting & Wasting Syndrome

Chemotherapy-induced Nausea & Vomiting (CINV)

- RCTs show cannabinoids to be better than placebo, but only slightly better than conventional anti-emetics
- Unpublished clinical trials of smoked cannabis indicate similar effectiveness
- Some patients prefer cannabinoids despite side-effects – sedation and euphoria may be considered beneficial vs. "adverse" in this context
- Dronabinol (Marinol) and Nabilone (Cesamet) are [FDA] indicated for management of severe CINV – when conventional drugs have failed

Wasting Syndrome (cachexia)
(anorexia associated with weight loss)

- Clinical trials showed dronabinol and smoked cannabis in HIV+ patients with muscle wasting/weight loss resulted in increased appetite & weight
- Dronabinol (Marinol) is [FDA] indicated for management of: anorexia-associated with weight loss in patients with AIDS

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Epilepsy

Epilepsy

- Pre-clinical Studies
  - In vitro & animal models suggest anti-convulsant role for cannabinoids
  - Also suggest a pro-convulsant role

- Clinical Studies
  - Cochrane Collaboration Review (2014)
    - found 4 small, low quality RCT reports using CBD as Rx
      - Details of randomization not provided
      - No assessment of whether control & treatment groups equivalent
    - "No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy."

Highlights of 4 RCTs of CBD (Adults)

- Mechoulam 1978 [n=9] – very brief report
  - 2 of 4 Rx'd group were sx free x 3 months; 0 of 5 placebo group improved
  - no toxic effects
- Cunha 1980 [n=15] – full report
  - 4 of 8 Rx group showed "considerable improvement"; as did 1 of 7 placebo group
  - well tolerated
- Ames 1985 [n=12] – brief report
  - Institutionalized/mentally handicapped pts.→ no diff in sz freq. between Rx & placebo
  - mild drowsiness reported
- Trembly 1990 [n=12] – conference abstract
  - conf. abstract initially suggested some reduction in sz frequency
  - Later book chapter suggested no changes in sx frequency

Surveys - Self–Reported Data (Peds)

- Gedde & Maa (2013 Annual Meeting: American Epilepsy Society)
  - Only 13 Charlotte's Web patients identified that "met criteria"
  - 11 of 11 (completed interviews) reported decreased motor type sz frequency
  - 8 of these reported 98-100% reduction; 5 were seizure-free
- Porter & Jacobsen (2013 – Epilepsy & Behavior)
  - Survey presented to parents belonging to Facebook group
  - 19 responses met inclusion criteria (Rx-resistant sz's & use of CBD-enriched cannabis)
  - 16 of 19 reported reduction in sz frequency
  - 8 reported >80% reduction; 2 reported being seizure-free

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Selected Neurologic Disorders

Review

- Koppel BS, et al. (USA) 2014; Neurology
  - American Academy of Neurology (AAN) convened expert panel
  - Systematic review of medical marijuana studies through 2013 for:
    - **MS** (spasticity, pain, bladder dysfunction, involuntary movements)
    - **movement disorders** (Huntington, Parkinson, Tourette, cervical dystonia)
    - **epilepsy**
  - 34 RCTs included

AAN Review - MS

- Spasticity
  - Oral cannabis extract (OCE) is effective
  - Oral mucosal spray (OMS) & THC are probably effective
  - More improvements seen in subjective than objective measures
- Central Pain or Painful Spasms
  - OCE is effective
  - THC and OMS are probably effective
- Urinary Dysfunction
  - OMS, THC, OCE are probably effective
- Tremor
  - THC & OCE probably not effective; OMS possibly not effective

AAN Review – Movement Disorders

- Parkinson Disease
  - OCE is probably not effective for L-dopa-induced dyskinesias
- Huntington Disease
  - Oral cannabinoids of unknown efficacy in non-chorea-related symptoms
- Tourette syndrome
  - Oral cannabinoids of unknown efficacy
- Cervical Dystonia
  - Oral cannabinoids of unknown efficacy

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Post Traumatic Stress Disorder (PTSD)

PTSD

- Pre-clinical Studies
  - Suggest role for endocannabinoid system in extinction of aversive memories
  - Suggest endocannabinoid system may be valid therapeutic target

- U. of Arizona College of Public Health: 2013 evidence review
  - Observational studies of varying quality demonstrate assn. between PTSD and use of various substances – to cope w/ symptoms of PTSD
  - Not possible to determine causative relationships
  - The evidence regarding effects of using MJ/cannabinoids to treat PTSD … "should be considered very low quality with a high degree of uncertainty."

PTSD – Clinical Trials

- Fraser GA (Canada) 2009; CNS Neurosci Ther
  - Retrospective chart review
  - Open label, non-controlled trial of nabilone (synthetic THC analogue)
  - 47 pts. w/ Dx of PTSD and RX-resistant nightmares
  - 72% self-reported significant reduction or cessation of nightmares
  - 28% experienced mild-moderate side effects & discontinued Rx

- Roitman & Mechoulam et al.(Israel); 2014 Clin Drug Investig (online)
  - Open label, non-controlled, prospective pilot study x 3 weeks
  - To evaluate tolerability & safety of orally absorbable THC for PTSD
  - 10 pts. w/ Dx of PTSD received THC as add-on Rx
  - 40% experienced mild side effects; no discontinuations
  - Significant decrease in self-reported symptom severity by standardized surveys

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Other Psychiatric Disorders

Other Psychiatric Disorders

- Anxiety & Depression
  - Limited clinical evidence indicates cannabinoids may be adjuncts in context of certain chronic diseases (e.g., HIV)
  - Of note: CB-1 receptor antagonist, rimonabant, associated with anxiety, depression and suicide
  - RCT (small) of CBD: associated with significant reduction in social anxiety in simulated public speaking test
- Schizophrenia
  - Cochrane Review (2008): insufficient evidence to support or refute; more RCTs needed
- Bipolar Affective Disorder
  - 2005 review: no systematic studies found through literature search
- Dementia
  - Cochrane Review (2009): found no evidence in support; more RCTs needed

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Inflammatory Bowel Disease (IBD)

IBD (Crohns's Disease & Ulcerative Colitis)

- Pre-clinical Studies
  - Suggest cannabinoids may limit intestinal inflammation & disease severity
- Observational Studies
  - retrospective and prospective designs
  - primarily Crohn's pts.
  - Improvements in self-reported:
    - disease activity
    - quality of life
    - pain
    - need for other medication
    - need for surgery
    - Weight* (measured)

IBD – Clinical Studies

Naftali et al.(Israel) 2013; Clin Gastro Hepatol

- RCT: N=21; all Crohn's & not responsove to conventional Rx
- Randomized to smoked cannabis (hi THC/low CBD) or placebo
- 5 of 11 study grp vs 1 of placebo grp achieved full remission (NS)
- 90% of study grp vs 40% of placebo grp showed clinical response
- Mean reduction in disease activity score (study vs placebo) was significant

Limitations

- small size
- no objective evidence of reduced inflammation (measured by CRP)
- blinding assessment: only 2 placebo grp couldn't tell what they were taking

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Gliomas

Gliomas

- Background
  - Glioblastoma multiforme (GBM) or grade IV astrocytoma
  - most frequent class of malignant primary brain tumor
  - one of most aggressive cancers; survival after Dx typically 6-12 mos.
  - high resistance to standard chemo and radiation

- Pre-clinical Studies
  - induce glioma cell death in vitro
  - inhibit tumor angiogenesis (new blood vessel formation)
  - inhibit glioma tumor growth in animal models (rats & mice)
  - selective for tumor cells while not affecting normal brain cells

Gliomas – Phase I Clinical Trial

Guzman et al. (Spain) 2006; Br J Cancer

- Pilot phase I clinical trial of THC for GBM
- 9 pts w/ recurrent GBM despite standard Rx
- THC injected intra-tumorally
- Primary endpoint to determine safety of intra-tumoral THC admin.
- Median duration of Rx was 15 days
- No significant psychoactive effects
- No significant alterations in physical or lab parameters
- 2 Pts' biopsies post-Rx showed decreased tumor cell proliferation & increased cell death

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Opiate Dependence & Withdrawal

Opiate Dependence & Withdrawal

- Scavone JL et al. (US) 2013; Neuroscience
  - Challenge: high rates of relapse and limited treatment success rates; many addicts also have poly-drug use & co-morbid psychiatric disorders
  - Cannabinoids may modulate opioid function at receptor/cellular level
  - Cannabinoids thought to have potential therapeutic benefit for opioid withdrawal; supportive evidence from animal models
  - Observational studies: to date findings equivocal re: impact of cannabis use on medication-assisted treatment (for opioid dependence)
  - Some data suggests detrimental effects of cannabis on Rx for opioid dependence

Conclusions

- Cannabis has some fairly well documented medical benefits
- Clear need for RCTs for most of the conditions for which cannabis already officially “accepted”as effective, as well as for many other conditions of interest and possible use

Challenges

- Federal restrictions & requirements re: RCTs
- Multiple natural & synthetic drugs/drug products
- Multiple formulations & doses
- Multiple diseases & conditions of interest
- Ability to achieve effective blinding in RCTs
- Many outcomes depend on self-reported data
- Most studies of small size & short duration
- Adequate funding

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BUSINESS

September 26, 2014 - Scientific Advisory Council Meeting

Board of Health – 9/16 meeting

<u>Approved modification to 5 CCR 1006-2: Regulation 6(D)(3)(b)</u>

Debilitating Medical Conditions and The Process for Adding New Debilitating Medical Conditions

- "The medical marijuana scientific advisory council will review petitions to add debilitating medical conditions if the conditions for denial set forth in paragraphs (2)(A), (B) and (C) of this section D are not met. When reviewing petitions to add debilitating medical conditions to the registry, the ad hoc member of the council may be replaced by an ad hoc physician in the field relevant to the petition. Such individual may be recommended by the petitioner."

Grant Review Planning - Update

- 87 Letters of Intent (required) received last week

- 6 "additional" (non-SAC) reviewers recruited
  - Therefore, 18 reviewers for primary review
  - Functionally - 6 "teams" of 3 reviewers
  - Estimated 12-14 reviews per person
  - Question: electronic vs. hard copies ?

- Timeline:
  - Grants due October 14
  - Latest grants will be distributed: OCTOBER 23 (possibly earlier)
  - Review scores due: NOVEMBER 5
  - Patient advocate & statistical review of top scores: NOVEMBER 10-19

Grant Scoring Overview

- November 21: SAC-Grant Review meeting
  - Top scoring grants from primary review discussed & scored by full SAC
  - Overall Impact Scores provided by SAC members
  - 10 point scale [10 = exceptional; 1 = poor]
  - Averaged and multiplied by 10
  - “Perfect score” = 100
  - Preference points added

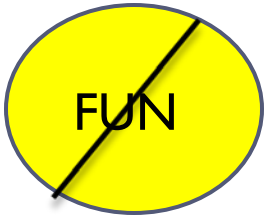
Preference Points - Proposal

- **From RFA:**
  - *[p. 4] "Preference will be given to applications with Colorado investigators or co-investigators, and to studies involving Colorado patients."*
  - *[p. 5] "Priority will be given to clinical trials and observational studies in humans …"*
  - *[p. 14] **"Finally, any preference points for Colorado investigators, Colorado based studies, and priority study designs (clinical trials and observational studies) will be added …"***

- **Proposed:**
  - **10 points** for clinical trial or observational study in humans
  - **5 points** for Colorado investigator/co-investigator
  - **5 points** for Colorado study (i.e., study subjects**)**

  - Maximum preference points = 20
  - Maximum ("perfect") score = 120

Conflict of Interest (COI) Matrix

- Necessary for assigning primary reviews while “managing” COI
- See handout – template
- To be sent to you electronically early next week
- PLEASE complete & return within 1 week
- 87 applications x 18 reviewers = 

DISCLOSURE OF CONFLICT OF INTEREST FOR PRIMARY GRANT REVIEW
Medical Marijuana - Scientific Advisory Council

I have a potential conflict of interest with the application below because "I am.." or "I have .."	Principal investigator		Co-investigator or key partner		Same organization (Div./Dept/Program/Unit)		Substantial professional or personal association		Direct competitor in same topical area		Financial interest		Other: [specify]	
Letter of Intent: Agency PI Disease/condition Co-investigators	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1) Agency PI Disease/condition Co-investigators														
2) Agency PI Disease/condition Co-investigators														
3) Agency PI Disease/condition Co-investigators														
4) Agency PI Disease/condition Co-investigators														

Inferring causation from observational studies:

Considerations for medical marijuana research

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26 September, 2014
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Epidemiology

- The study of disease occurrence in human populations.

Epidemiology

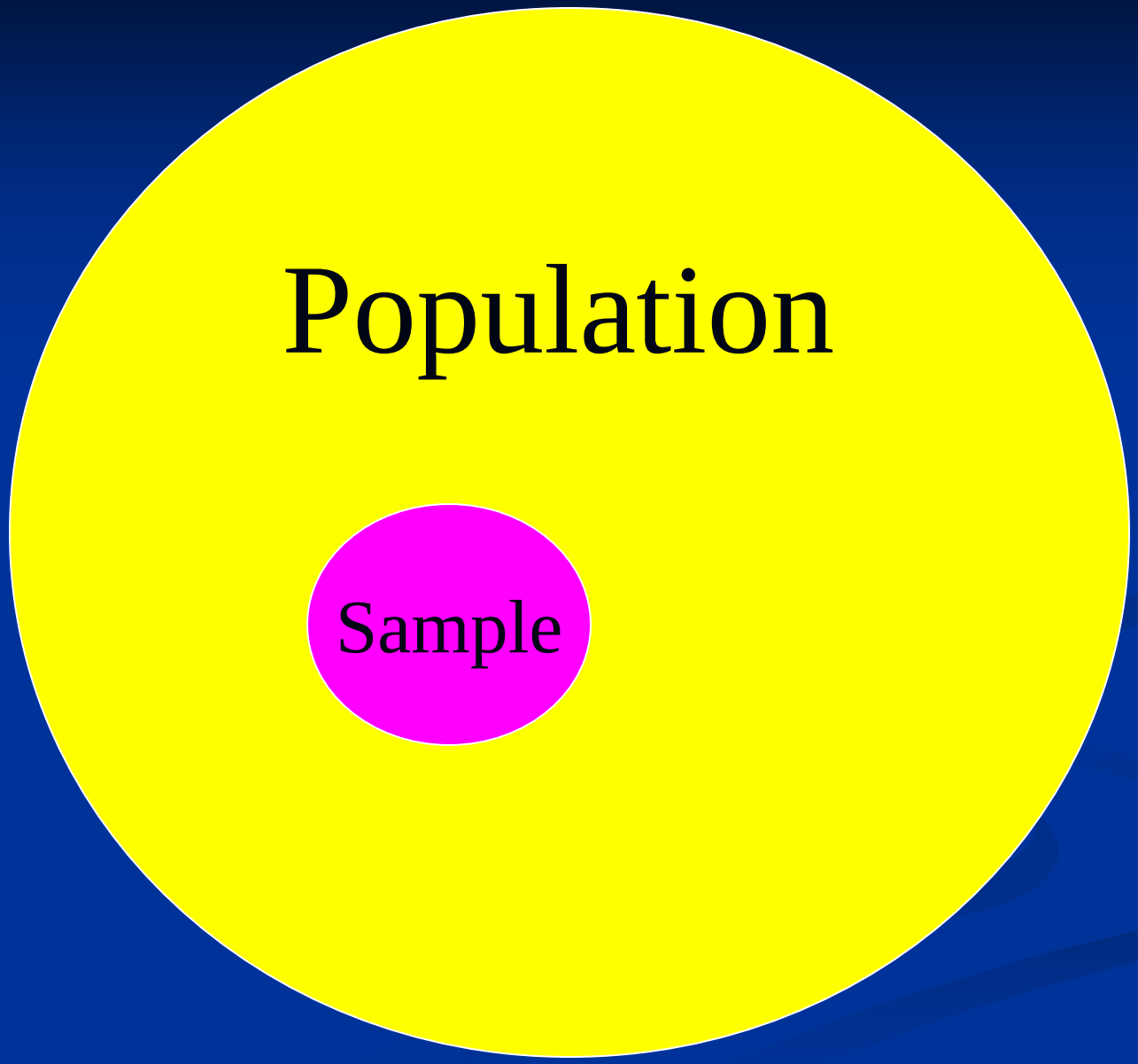
- The study of disease occurrence in human populations.
- The study of people broken down by age and sex.

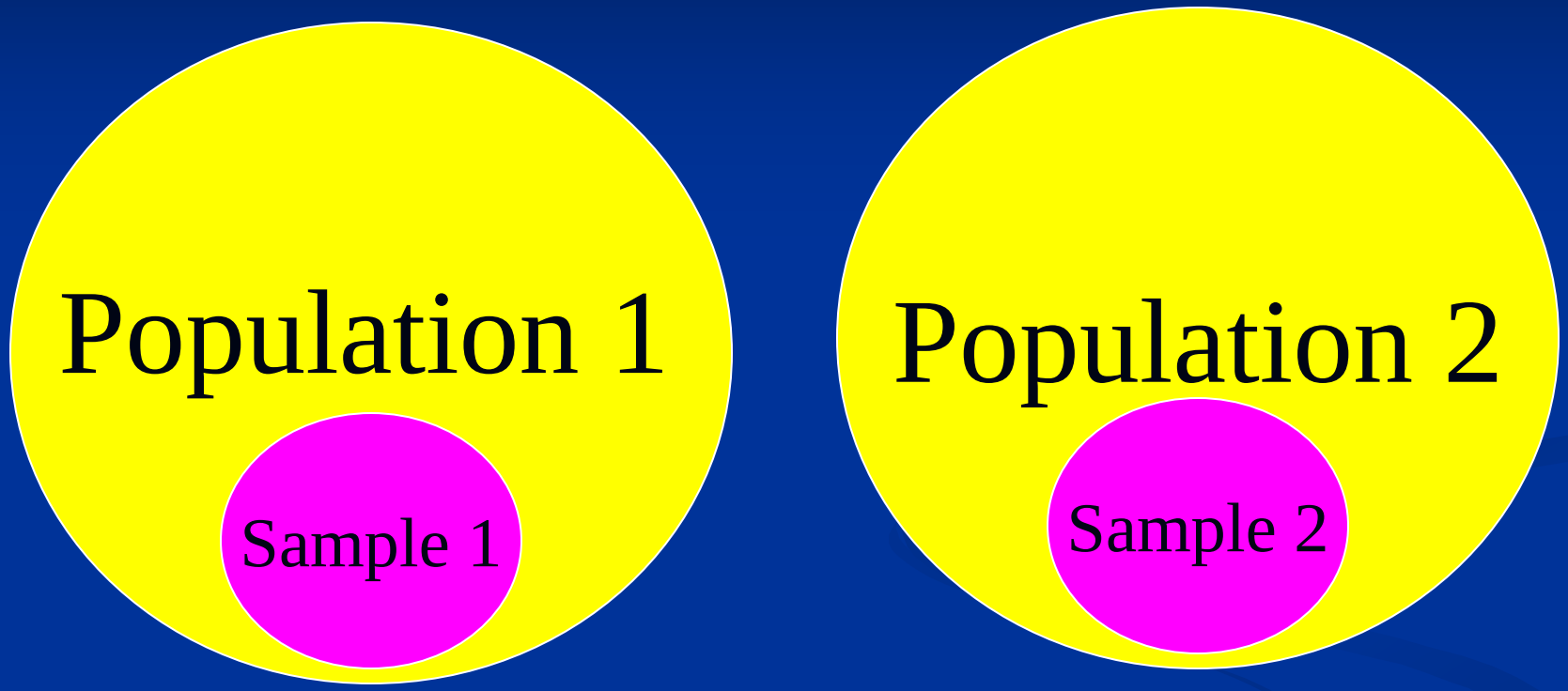
Epidemiology

- The study of disease occurrence in human populations.
- The study of people broken down by age and sex.
- The study of suffering with the tears wiped away.

How do we study disease in populations?

Population


Population
Sample


Population 1
Sample 1
Population 2
Sample 2

Association:
The basis of epidemiology

ASSOCIATION

EXPOSED	DISEASED: yes	DISEASED: no
yes	A	B
no	C	D

Reasons for an association between a factor and a disease

- Bias in the sampling of subjects
- Bias in the measurement of the factor
- Confounding by another factor
- Chance
- Transposition of cause and effect
- Causal

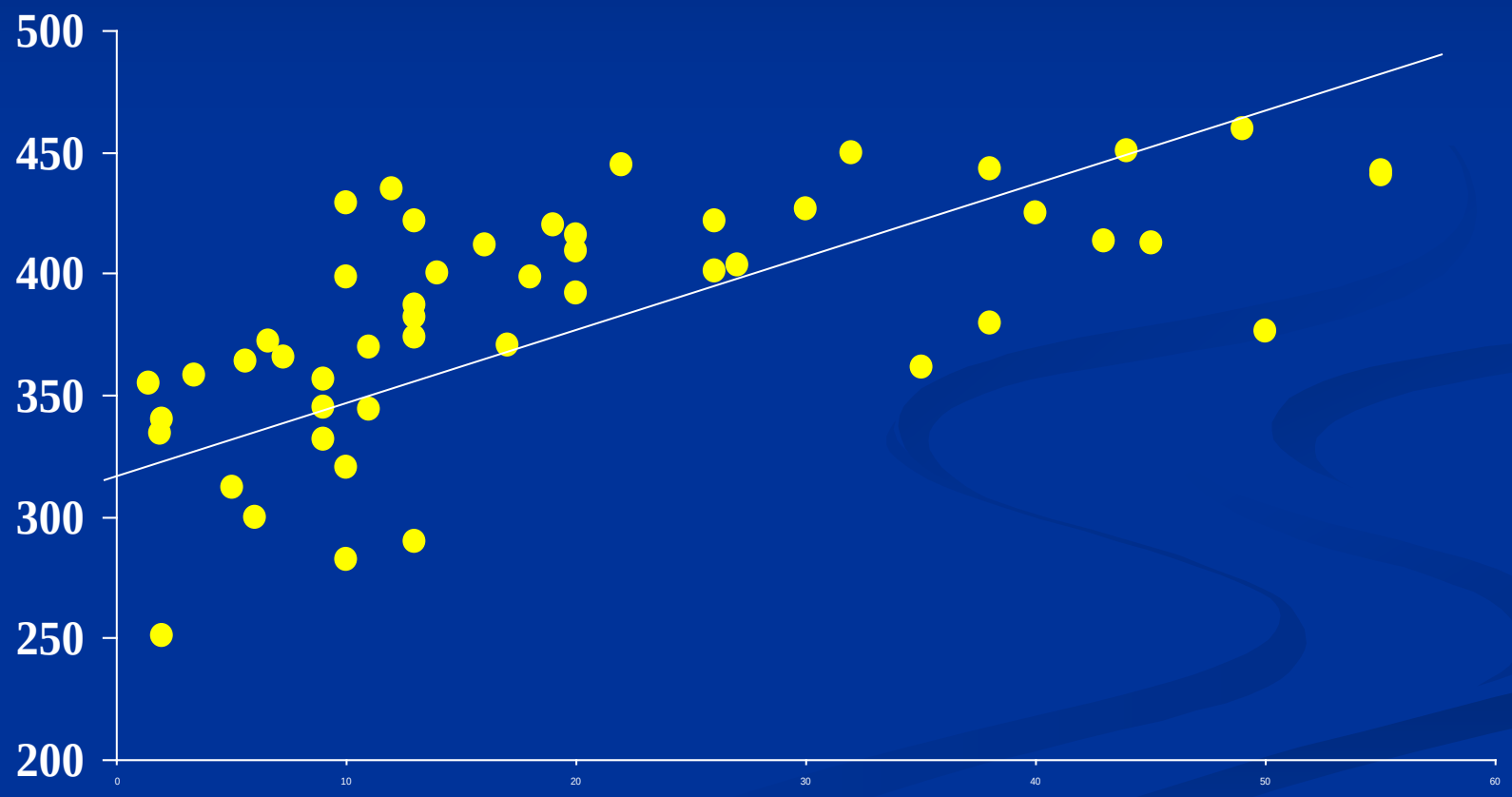
Study designs

- Ecologic (correlational)
- Cross-sectional (eg, survey)
- Case-control (retrospective)
- Cohort (prospective)
- Experimental (intervention)

Ecologic studies

- AKA "correlational studies"
- Compare
  - same population over time
  - different populations at same time
- The key feature of this study design is that comparisons are made at the group level (not individuals)
- Susceptible to the "ecological fallacy"

Death rates from cancer, among various countries, 1995



Dietary fat intake

Possible medical marijuana ecologic studies

- Not likely
- Correlation between medical marijuana use across various subgroups of the population and indicators of group-level disease outcomes

Cross-sectional studies

- Typically surveys
- Can include exams or questionnaires
- Sample should be representative
- Can produce estimates of prevalence
- Uncertainty of separating cause vs effect is a serious limitation

Possible medical marijuana cross-sectional studies

- Surveys of medical marijuana users
- Surveys of general population
- Descriptive purposes: To describe characteristics of users and non-users according to disease condition, age, race, gender, etc.
- Analytic purposes: To assess the association between current condition and use history according to dose, duration, mode of use, etc.

Case-control studies

Case-control studies

Exposure (a)

No exposure(c)

Disease

Exposure (b)

No exposure (d)

No disease

THE PAST ← TODAY

Possible medical marijuana case-control studies

- Not likely as case-control studies are best for assessing causal factors for disease incidence.

- "Case" status could be defined as having a disease under control, and "control" status defined as a disease not under control, and a case-control design could then assess the impact of prior history of usage, dose, variety, delivery mechanism, etc, on disease control.

Cohort studies

- AKA "prospective studies"
- Requires assembly of cohort and follow-up over time
- Limited utility for very rare outcomes or very long latencies

Strengths of cohort studies

- Risk factors measured before disease
- Direct measures can be made of disease risk
- Multiple outcomes can be assessed

Limitations of cohort studies

- Rare outcomes can usually not be assessed
- Patience is needed for long-term follow-up
- Unless re-measures are made, exposures may be distant from outcomes

Methods to control for confounding

- Matching
- Stratification in analysis
- Adjustment in analysis
  - Direct adjustment (eg, age-adjusted rates)
  - Multivariate analysis

Validity

- **Internal validity**

  The ability of a study to correctly measure the association that exists within the study group

- **External validity**

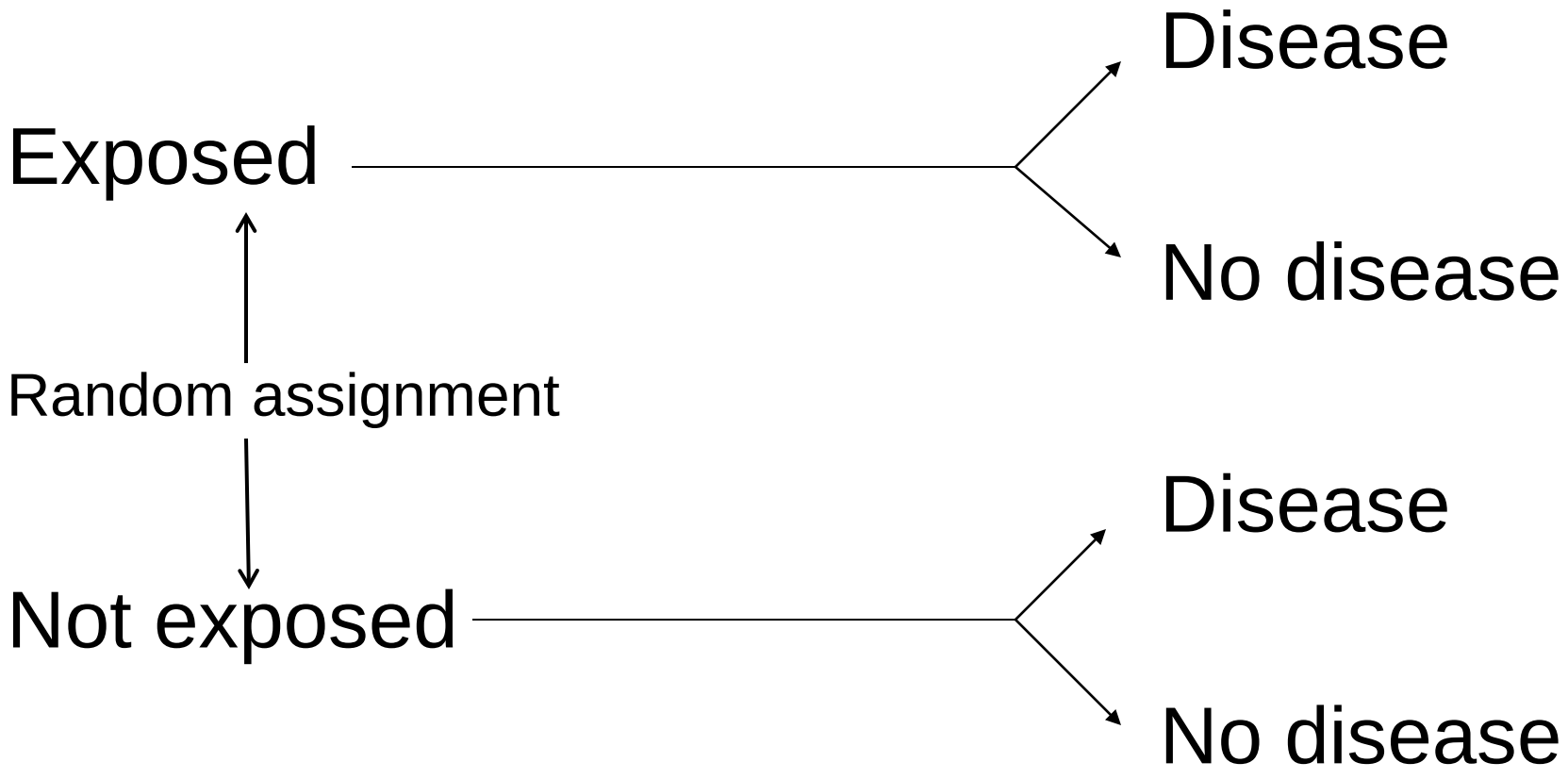
  The ability of a study to correctly reflect the association in the population that the study group is intended to represent

Possible medical marijuana cohort studies

- **Historical cohorts**
  exposure assessment using past records, and association determined by current follow-up

- **Prospective cohorts**
  exposure assessed now and follow-up for outcomes into the future

Randomized Controlled Trials



RCTs

- Essentially the same as a cohort study, except the investigator decides who gets the exposure, using random assignment
- Strongest study design of all, maximizing internal validity (usually at the expense of external validity)
- Maximizes internal validity by the equal distribution of potential confounders into exposed and unexposed groups

Blinding

- Subjects should be blinded (e.g. with placebo treatment) to which study group (experimental vs. control) if possible
  - » Addresses placebo effect and cross-overs
- Researchers should be blinded to study group when ascertaining outcomes
  - » Addresses investigator bias
- Both = double-blind trial

Issues in RCTs

- Lengthy and expensive
- Ethical and legal issues
- Blinding can be difficult, cross-overs may be common, and drop-outs and lost to follow-up are major problems
- Strong internal validity is strong is achieved at the expense of external validity
- Power issues become important when effect sizes are inadequate to reach statistical significance

Possible medical marijuana RCTs

- Many possibilities
- This is by far the best study design for medical marijuana health outcomes
- Limitations by regulatory barriers, informed consent, and blinding

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

BMJ 2003;327:1459–61

Other types of intervention studies

- Natural experiments
- Group randomized designs
- Quasi-experiments
  - Before-after
  - Non-equivalent control group
  - Time-series

Natural experiments

- Researcher does not determine the group receiving the intervention, which occurs "naturally" or under control of some other process

- Examples:
  - » What happened to obesity in Colorado after the light rail was completed?
  - » What happened to birth outcomes after Medicaid expansion?

Group randomized trials

- Instead of individuals being randomized, groups of individuals are randomly assigned to study groups

- Example:
  - 16 Kaiser Permanente offices are randomly assigned so that patients receiving care at eight offices get sun exposure counseling to prevent skin cancer

Quasi-experimental designs

<u>Non-equivalent control group design</u>

Study groups are assembled in a non-randomized fashion intended to minimize unequal distribution of important confounders, and researcher decides which group(s) gets the intervention

Group A	O_1	X	O_2
Group B	O_1		O_2

Possible medical marijuana non-randomized experimental studies

- Many possibilities
- Since barriers of regulation still need to be overcome, this type of study is less likely to be informative than an RCT.

Meta-analysis

- A very well specified method
- Not to "analysis" as physics is to meta-physics
- Serves as basis for many publications, guidelines
- May eventually be informative for medical marijuana if sufficient literature

Reasons for an association between a factor and a disease

- Bias in the sampling of subjects
- Bias in the measurement of the factor
- Confounding by another factor
- Chance
- Transposition of cause and effect
- Causal

Study designs relevant to medical marijuana

- Surveys
  - Descriptive studies of practices and histories of current users (likely)
- Case-control studies
  - Case status defined by degree of disease control (unlikely)
- Cohorts
  - Based on either current exposure with future follow-up or records of past exposure with current follow-up (likely)
- Randomized controlled trials
  - Best design, but operational challenges may limit these

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