Ethical issues in the planning and conduct of addictions research

RAMS Research Content Webinar

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Disclosures

I have received consulting fees from Analgesic Solutions, Indivior, and Otsuka Pharmaceutical in the past year, and support from VitalHub, Caron treatment program, and Pinney Associates for serving on Advisory Boards.

Outline for This Talk

I. Planning addictions research

II. Conducting the work

III. Summary, some final thoughts and conclusions

Planning addictions research

Why do this research?

Planning addictions research

Why do this research?

Sometimes we hear that we already know answers, that the answers are self-evident

That can certainly be the case in medicine – we don't always need to do a study to know that something works

Planning addictions research

Hazardous journeys

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

(from the BMJ, 2003)

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score >15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

(from the BMJ, 2003)

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But, sometimes we think we know an answer, but we're wrong…

Do patients on methadone experience opioid withdrawal if they miss a dose?

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Example #1:

Study conducted 20 years ago at our program (Walsh et al., 1995), residential participants maintained on 60 mg/day of oral methadone, had a double-blind methadone dose omission to produce mild spontaneous withdrawal

No significant withdrawal was produced

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- No withdrawal – why?
  - Comfortable residential unit, plenty of distractions
  - Supportive staff
  - No expectation on part of participants (was double-blind)

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But, outpatient that wouldn't work, right? If got placebo as an outpatient, they would just drop out of treatment…?

We can all agree on that, right?

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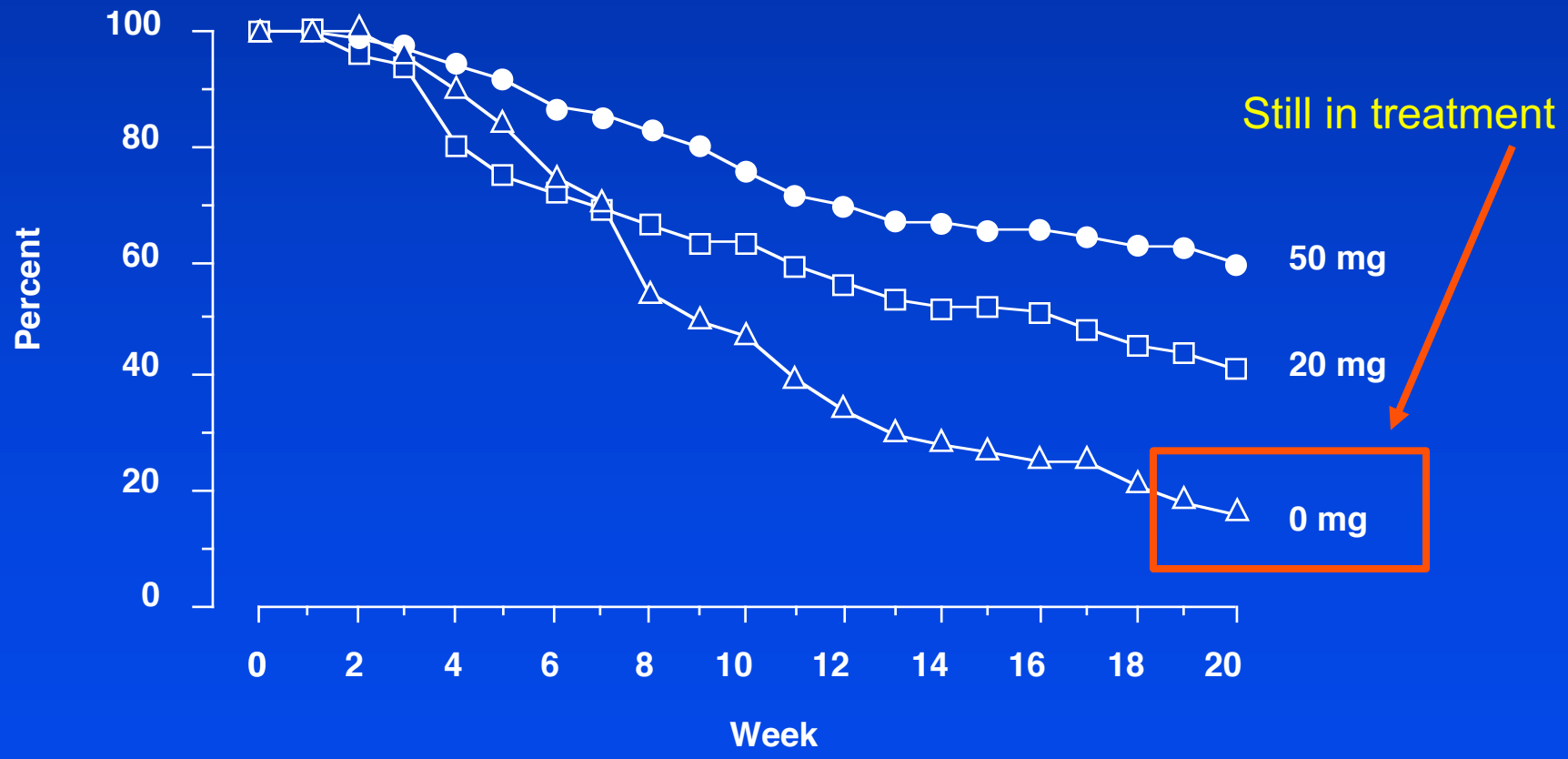
Example #2

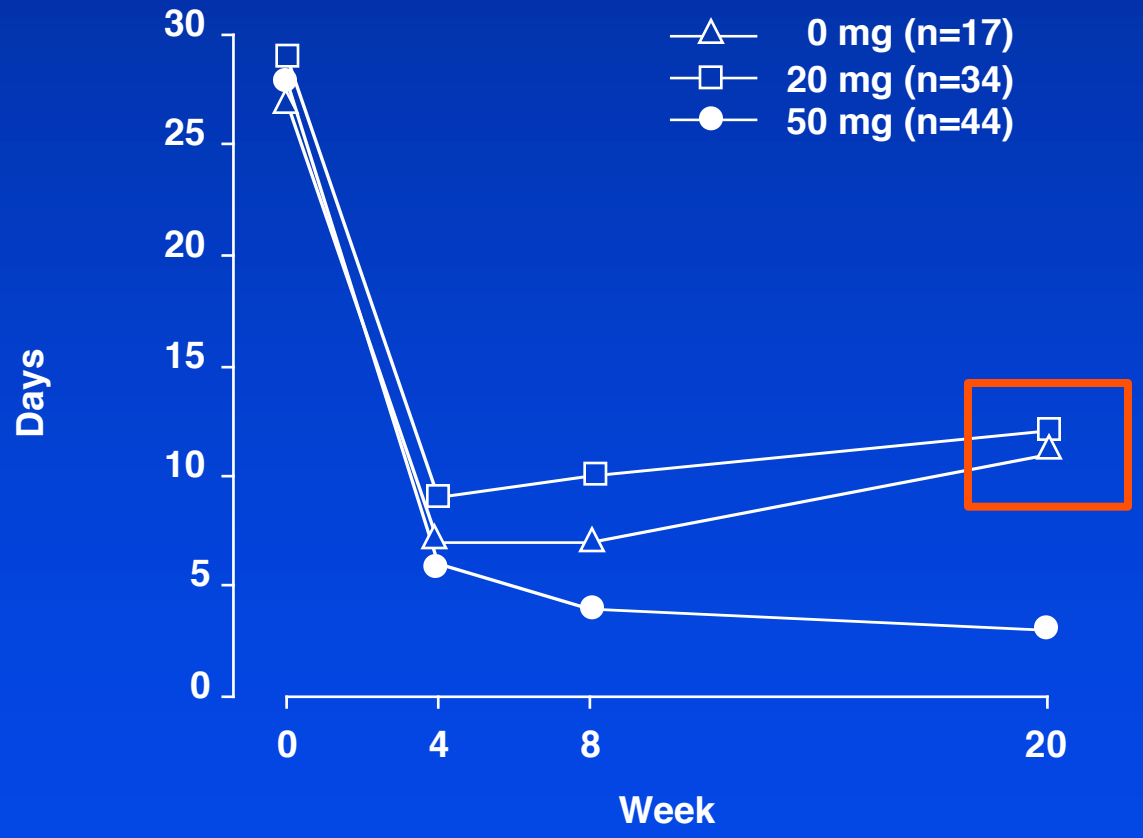
We also know that treating opioid dependent outpatients with placebo won't keep them in treatment and they will do poorly…

Methadone Study: Treatment retention



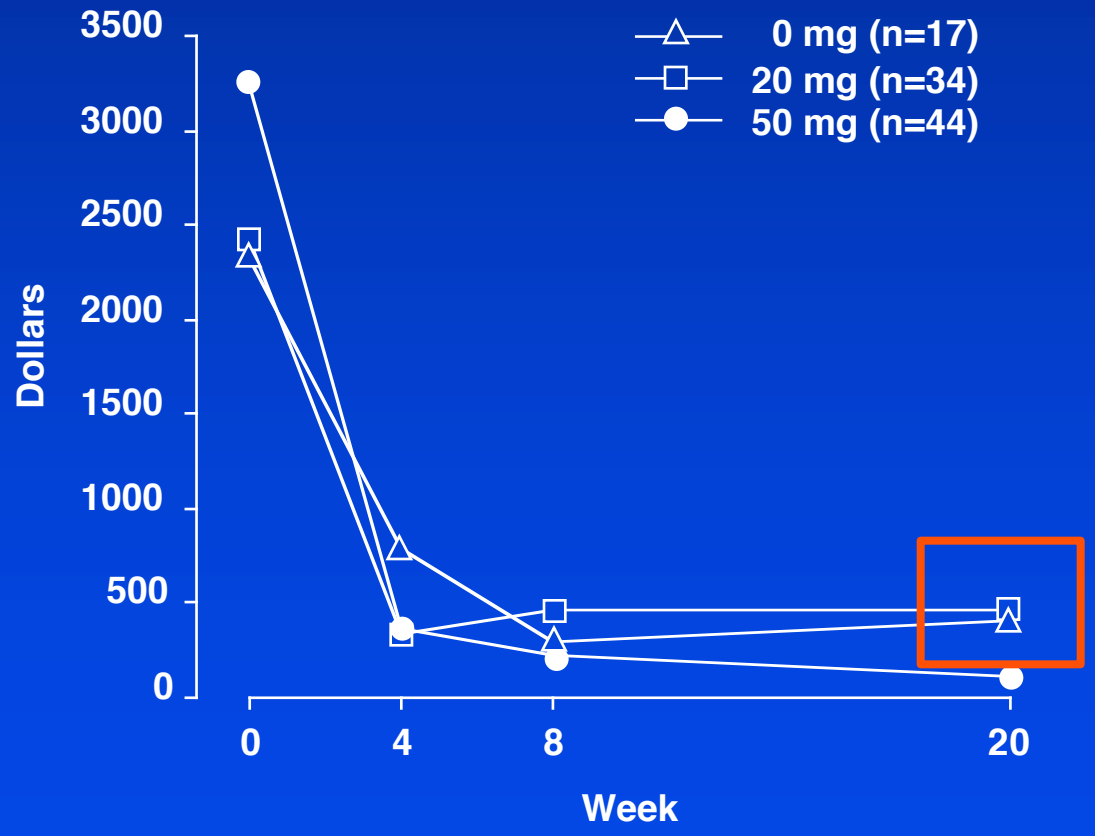
From Strain et al., 1993

Methadone Study 1: Heroin use



From Strain et al., 1994

Methadone Study 1: Money spent on drugs



From Strain et al., 1994

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Example #2

Some patients getting daily placebo methadone seemed to do okay

Good counseling provided in the study

(Most did not do well, and trend for retention was not good… I am not advocating placebo methadone!)

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Example #3 (last one)

Medical withdrawal doesn't work, and we should stop doing it and just use maintenance treatments (methadone, buprenorphine), right?

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Am J Drug Alcohol Abuse. 2001 Feb;27(1):19-44.

One-, three-, and six-month outcomes after brief inpatient opioid detoxification.

Chutuape MA[1], Jasinski DR, Fingerhood MI, Stitzer ML.

⊕ **Author information**

Abstract

The purpose of this study was to investigate short-term outcomes of a 3-day inpatient medical detoxification. Heroin abusers (n = 116; 66% male, 77% African-American, X = 38 years old), completed the Addiction Severity Index during detoxification, and at 1, 3, and 6 months after detoxification; 94.5% of the postdetoxification interviews were completed. During the 30 days before detoxification, mean days of self-reported use for heroin was 28, for cocaine 19, and for alcohol 14; a mean of $1,975 was spent on drugs. Across the postdetoxification interviews, mean days of reported heroin use ranged from 11 to 14; 21-30% of patients reported no heroin use, whereas 25-36% reported almost daily use. Reported use of cocaine and alcohol showed similar reductions from pre- to postdetoxification. Reports of heroin and cocaine abstinence were generally verified through urine tests. Other psychosocial factors improved as well from pre- to postdetoxification (e.g., employment increased and needle use decreased). During the 6-month evaluation, at least 41% reported engaging in formal inpatient or outpatient treatment; another 25-33% reported attending self-help groups. Engaging in formal treatment (at least 7 days duration) was associated with significantly better outcome. Nevertheless, pre- to postdetoxification changes were significant and robust for the entire study sample. These findings demonstrate that brief inpatient detoxification is followed by reduced drug use over several months and is accompanied by substantial treatment-seeking behavior. Thus brief detoxification may serve as an effective harm-reduction intervention.

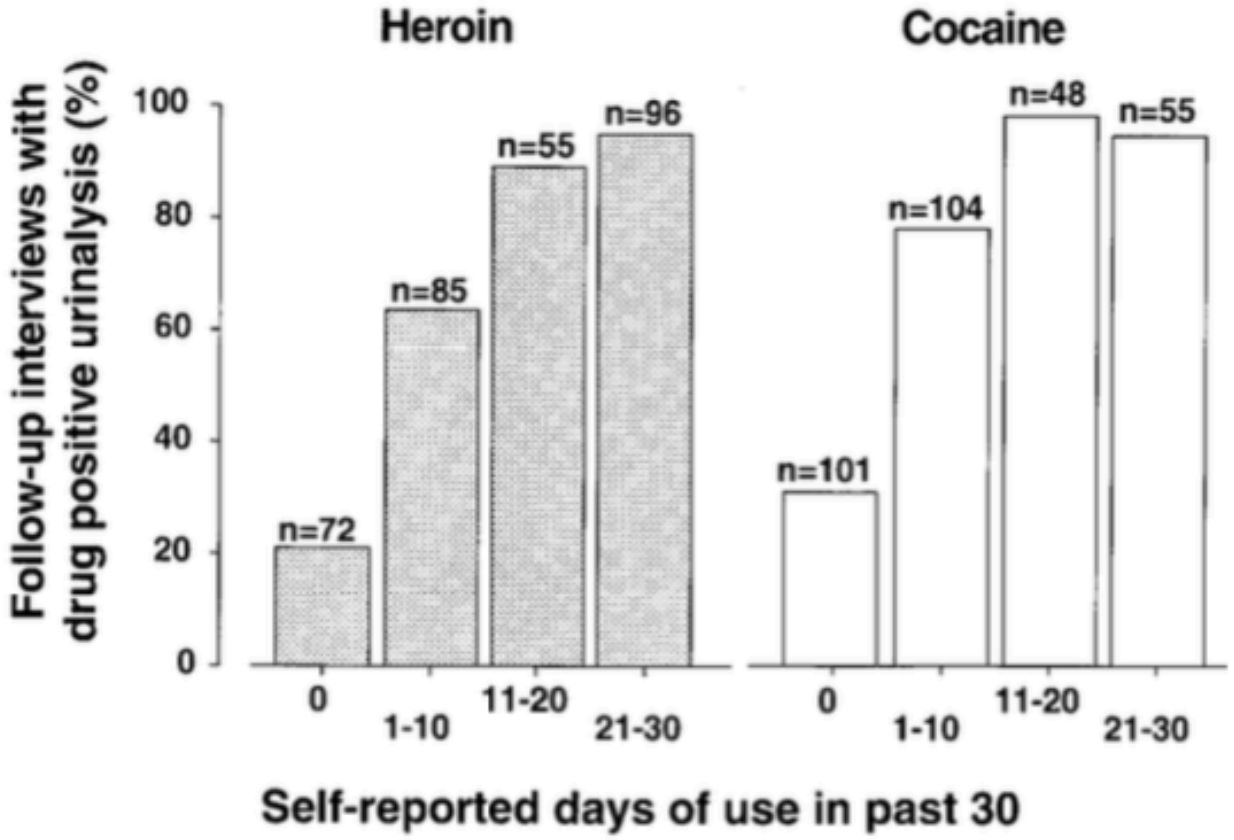

Figure 3. Percent of interviews that had a corresponding positive urine sample for heroin (*left*) and cocaine (*right*). Interviews were distributed into categories based on reported days of drug use in previous month (0, 1–10, 11–20, 21–30 days of use). Data were collected from patients 1, 3, and 6 months after brief inpatient opioid detoxification (N = 116). Out of a possible 348 interviews, 314 were completed and a urine sample collected. Percentages are based on the number of interviews in each category.

Urine samples generally supported the self-reports of drug use

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Example #3 (last one)

Tread carefully when we assume we know the answer already, and that we don't need to study it

But, we need to do studies in a way that

minimizes risk while getting benefit

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A. Protocol designs

B. Study populations

C. Checks and balances

Planning addictions research

Protocol designs

If you are going to do something, do it right

Why?

Because studies almost always involve some form of risk, and if we put people at risk, then we should get results that are of value and move the field forward

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Protocol designs

- Randomized controlled trials
- Blinding
- Placebo conditions
- Number of participants

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Protocol designs: Randomized controlled trials (RCTs)

- Gold standard for addressing a research question
- Consider your control condition
- Be prepared to explain to volunteers the study, that a study is not the same as community based (routine) treatment – the person is in a study

Planning addictions research

Protocol designs

- Randomized controlled trials
- Blinding
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Planning addictions research

Protocol designs: Blinding

Blinding of conditions not always possible – for example, can blind a medication, but not as easy to blind a psychotherapy

Masking of blind should be tested (did it work?)

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Protocol designs: Blinding

- Blinding in drug abuse research can be a challenge
- Medications with acute effects that can be detected; for example:
  - Acute dose of methadone often detected as an opioid agonist
  - Acute dose of naltrexone can precipitate withdrawal in an opioid dependent person

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Protocol designs: Blinding

If a study can't be blinded, is it appropriate to do it? Are participants being subjected to risks without the overall trial benefits of getting useful data?

(Can you think of ways to have a blind?)

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Protocol designs: Blinding

- Use of peppermint drops in the mouth to mask flavor of a medication
- Use of an active but lower dose of the medication (vs. placebo)
- Use of flexible vs. fixed doses of a medication

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Protocol designs

- Randomized controlled trials
- Blinding
- Placebo conditions
- Number of participants

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Protocol designs: Placebo conditions

Having a placebo condition can be a standard set by a regulatory agency (for example, the Food and Drug Administration)

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Protocol designs: Placebo conditions

What if there is a known treatment that has efficacy? Is it appropriate to then have a person receive placebo?

Does placebo work for some people? (Earlier example of methadone dose study)

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Protocol designs: Placebo conditions

Does the risk of getting treated with placebo outweigh the potential study benefits?

This can depend upon the study and the target condition. For example, a study of headache doesn't carry the same risk ratio as a study of cancer treatment. Both have known treatments, we don't judge the "cost" of on-going headache to be the same as untreated cancer.

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Protocol designs: Placebo conditions

- Can be clever in methodological design
  - Fast track admissions for treatment that usually has a wait list
  - Give a choice to opt out of a condition
  - Conduct blinded rescue if person doesn’t do well

Planning addictions research

Drug and Alcohol Dependence 40 (1995) 17–25

A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence

Rolley E. Johnson*, Thomas Eissenberg, Maxine L. Stitzer, Eric C. Strain, Ira A. Liebson, George E. Bigelow

Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Behavioral Pharmacology Research Unit, 5510 Nathan Shock Drive, Baltimore, MD 21224-6823, USA

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Protocol designs: Placebo conditions

- Rapid intake to 14 day protocol (then on-going treatment)
- Randomized to 0, 2 or 8 mg per day of sublingual buprenorphine
- Participants knew possible doses, and could make a choice to have a double-blind switch to one of two other doses
- Idea was that 0 mg group would switch more

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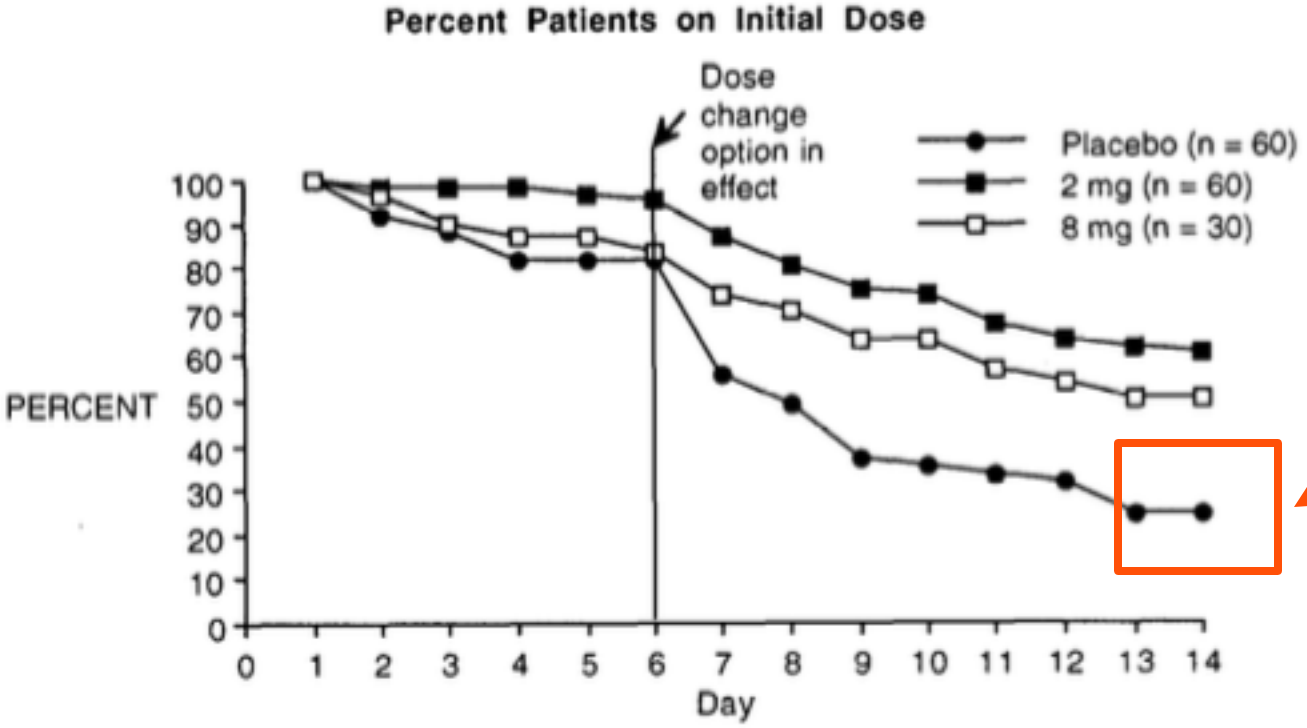

Fig. 1. Percent of patients on initial dose, by group (0 mg, 2 mg or 8 mg buprenorphine) and day for all patients (n = 150).

Did show the effect as planned

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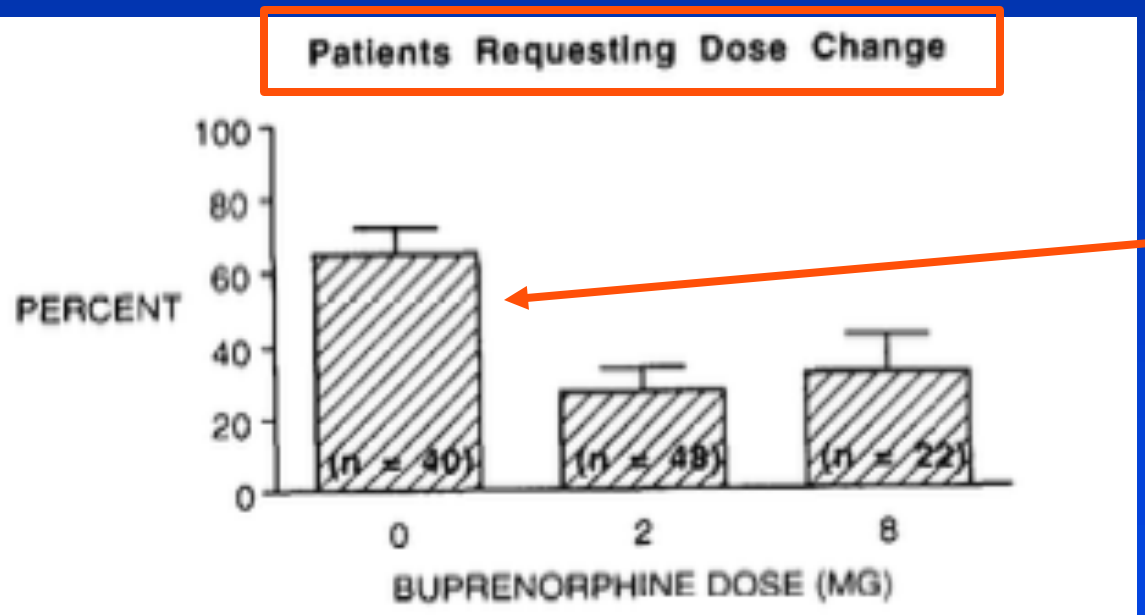

Fig. 2. Percent of patients who requested a dose change by group (0 mg, 2 mg or 8 mg buprenorphine) for patients who completed the study through day 14 ($n = 110$). Brackets indicate S.E.M.

Significantly more dose change requests for 0 mg group

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Protocol designs: Placebo conditions

Such a design assumes that some treatment is better than no treatment

It is also predicated upon the situation where no immediate treatment is available

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Protocol designs: Placebo conditions

Can also design a rescue procedure

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The New England Journal of Medicine

A COMPARISON OF LEVOMETHADYL ACETATE, BUPRENORPHINE, AND METHADONE FOR OPIOID DEPENDENCE

ROLLEY E. JOHNSON, PHARM.D., MARY ANN CHUTUAPE, PH.D., ERIC C. STRAIN, M.D., SHARON L. WALSH, PH.D., MAXINE L. STITZER, PH.D., AND GEORGE E. BIGELOW, PH.D.

Abstract

Background Opioid dependence is a chronic, relapsing disorder with important public health implications.

Methods In a 17-week randomized study of 220 patients, we compared levomethadyl acetate (75 to 115 mg), buprenorphine (16 to 32 mg), and high-dose (60 to 100 mg) and low-dose (20 mg) methadone as treatments for opioid dependence. Levomethadyl acetate and buprenorphine were administered three times a week. Methadone was administered daily. Doses were individualized except in the group assigned to low-dose methadone. Patients with poor responses to treatment were switched to methadone.

Results There were 55 patients in each group; 51 percent completed the trial. The mean (±SE) number of days that a patient remained in the study was significantly higher for those receiving levomethadyl acetate (89±6), buprenorphine (96±4), and high-dose methadone (105±4) than for those receiving low-dose methadone (70±4, $P<0.001$). Continued participation in the study was also significantly more frequent among patients receiving high-dose methadone than among those receiving levomethadyl acetate ($P=0.02$). The percentage of patients with 12 or more consecutive opioid-negative urine specimens was 36 percent in the levomethadyl acetate group, 26 percent in the buprenorphine group, 28 percent in the high-dose methadone group, and 8 percent in the low-dose methadone group ($P=0.005$). At the time of their last report, patients reported on a scale of 0 to 100 that their drug problem had a mean severity of 35 with levomethadyl acetate, 34 with buprenorphine, 38 with high-dose methadone, and 53 with low-dose methadone ($P=0.002$).

Conclusions As compared with low-dose methadone, levomethadyl acetate, buprenorphine, and high-dose methadone substantially reduce the use of illicit opioids. (N Engl J Med 2000;343:1290-7.)

While 20 mg dose of methadone is low (placebo-like, although not completely ineffective), study permitted all patients to switch to higher dose methadone if didn't do well in the study.

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Protocol designs: Placebo conditions

Bottom line on placebo conditions:

- Can be indicated when there is no effective treatment
- Can be used when an effective treatment, but should think carefully about how used/study design

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Protocol designs

- Randomized controlled trials
- Blinding
- Placebo conditions
- Number of participants

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Protocol designs: Sample sizes

Can be value in pilot studies to test a hypothesis

However, if seeking to answer a question, then have a sample size that will answer that question (make sure you are powered)

The risks need to be justified by the benefits

Conclusions that someone else will need to replicate and do it right are maddening!

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A. Protocol designs

B. Study populations

C. Checks and balances

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Study populations

People with the disorder (a substance use disorder), vs healthy controls

Exposure to drugs in persons with no prior experience carries risk

Exposure to drugs in persons with prior experience carries risk, too!

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Study populations: No prior experience

Should the person be exposed to an addictive drug?

Can vulnerable persons be screened out in some way?

How addictive is the drug?

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Study populations: Prior experience

Is the person actively using? If not, should they be exposed to a drug for which they are not currently using?

If they are using a drug, do study procedures help them or run a risk of harming them?

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Study populations: Other considerations

Studies with vulnerable populations need to be given special consideration – groups such as prisoners, pregnant women, children, diminished capacity to make independent decisions

Study populations

A. Protocol designs

B. Study populations

C. Checks and balances

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Checks and balances

Does the study have systems designed in to it, that allow for ensuring the welfare of the participant is being considered?

For example, are there medical staff who are not study investigators, who can assess and make decisions on whether to continue the study for a participant?

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Checks and balances

In the U.S., requirement to have Data and Safety Monitoring Plans (DSMPs) for NIH studies

These may include a Data and Safety Monitoring Board (DSMB), that is independent and can make decisions about individual cases as well as the overall study

Outline for This Talk

I. Planning addictions research

II. Conducting the work

III. Summary, some final thoughts and conclusions

Conducting the work

- Staff training
- Confidentiality
- Data collection
- Stopping early

Conducting the work

- Staff training
- Confidentiality
- Data collection
- Stopping early

Conducting the work

Staff training

- May be institutional requirements for training (compliance, ethics, human subjects)
- Consider own training specific to the study, local environment

Conducting the work

Staff training

Message to staff about how to conduct research, act toward participants

Balance between acting on behalf of participant, not "going rogue" if an ethical concern arises

Can think of an example of a staff member going rogue?

Conducting the work

Staff training

Staff also need to be aware of professionalism, treating participants with respect but not becoming overly friendly/crossing boundaries

Can you think of an example of this?

Conducting the work

Staff training

Lead by example!

Conducting the work

- Staff training
- Confidentiality
- Data collection
- Stopping early

Conducting the work

Confidentiality

- Training with staff
- Recognizing that stigma of substance abuse can be a concern to participants

Conducting the work

Confidentiality

- When should confidentiality be broken?
- Reported abuse (child, adult) – physical, mental, sexual
- What if someone breaks the law?
- What if they threaten staff?
- What if they show up at study site intoxicated, and drove a car there?

Conducting the work

Confidentiality

Lead by example!

Conducting the work

- Staff training
- Confidentiality
- Data collection
- Stopping early

Conducting the work

Data collection

- Keeping data secure
- Risk when staff have ability to access data remotely (e.g., loss of confidentiality)
- Who should have access to data?
- Are you collecting more than is needed?

Conducting the work

- Staff training
- Confidentiality
- Data collection
- Stopping early

Conducting the work

Stopping early

- Can consider interim analysis, but take a statistical hit when do so
- But, what if there is reason to think something is really working – or it is failing miserably? (No one is getting better…)
- Don’t underestimate the power of placebo responses

Conducting the work

Stopping early: Breaking the blind

What if a participant really wants to know what they received or are receiving? How balance the integrity of the trial with the need that the participant has?

Examples?

Outline for this talk

I. Planning addictions research

II. Conducting the work

III. Summary, some final thoughts and conclusions

Summary and conclusions (I of II)

Ethical issues in addictions research can be a challenge, and some aspects of this work are particularly novel in clinical research (unique in medicine)

Design and methodology can address some of these challenges, and provide opportunities for creativity

Summary and conclusions (II of II)

- Important to consider these ethical issues at all stages of the work
- While not addressed today, aspects of publication process that are also relevant to this conversation (e.g., authorship, plagiarism)

Thank you.