

Trial for a new drug in Alzheimer disease

Methodological considerations

D SOMME

First : the risk profile

- Low risk profile: Perlinpinpin powder
- High risk profile: Dr Jekyll potion
- The risk profile is based on :
 - Studies on animal model
 - Biological mechanism of action
 - Phase I and phase II study results

Low risk profile: Perlinpinin powder

- Randomized controlled trial necessary
- No magic:
 - RCT is not insurance for quality
- Prepare the RCT considering the method of analyzing critically his results

CONSORT statement

JAMA 2001;285:1987-1991

- **Methodological article**
 - the **setting**
 - Even with the same eligibility criteria, patients are very different in memory clinics and in first line medicine particularly on concordance rate
 - the **administration way of the drug**
 - Number of consultations
- Think about the **participant flow** (0 = little external validity)
 - **From a general public health point of view**
- Results had to expressed the denominator not only the rate (**10/20 and not 50%**) and/or the effect size with **95% IC** had to be done for all endpoint

High risk profile: The Dr Jekyll potion

- Same prestudy requirements
- Small RCT needed
- Doubt persist
 - Selection bias problem

Statistical consideration about RCT and observational studies results

- Selection bias is always a problem (for RCT and OS)
 - Patients in RCT are not the same than in real life
 - Patients in real life are not treated in the same way by two different good MD

Statistical consideration about RCT and observational studies results

- When 2 therapeutic strategies have similar clinical indication and risk, RCT and OS show greatest similarities (N Eng J Med 2000; 342:1878-1886 & 1887-1892)
 - OS is a way of having information of the real life
 - Classical methods to control bias are relevant (Multivariate analyses, propensity score, propensity matched analyses)
- When one therapeutic procedure is more risky, selection bias is difficult to address with classical methods
 - Instrumental variables (the physician, the ZIP code zone, etc...) could be more appropriate (JAMA 2007;297:278)

Whatever the risk

The comparison group
The endpoint

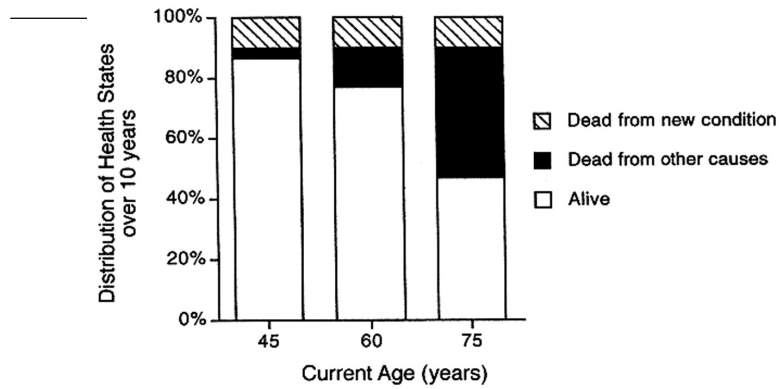
Comparison group

- Currently, In AD,
 - no drug have fulfilled the CONSORT statement criteria (BMJ 2005;331:321)
 - no drug have currently prove utility on clinically relevant endpoint (nice guidance, www.nice.org.uk)
- Thus :
 - It could be easy to argue in favor of placebo controlled RCT or OS
 - A three groups allocation procedure (Cholinesterase inhibitors; Placebo; New drug) could be appropriate

Endpoint : communicate about benefits

- Primary endpoint:
 - Clearly meaningful for the patient and/or his family
 - Loss of one functional ability
 - Institutionalization
 - Repeated unplanned hospitalizations
 - Loss of cognitive function (more than 4 points in ADASCog considering an expert consensus)
 - Sufficient delay 1 or 2 years
- Secondary endpoints:
 - Targeted and non numerous

Effect of age on 10 y vital status after diagnosis of a disease with a 10% mortality probability at 10 y



Welch, H. G. et. al. Ann Intern Med 1996;124:577-584

Annals of Internal Medicine

Qualitative research

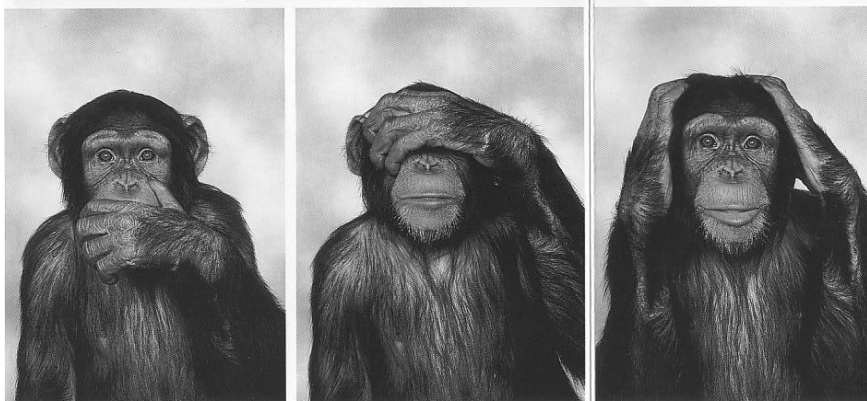
- With patients
- With families
- With professionals

Take home messages

- Currently available anti-Alzheimer drugs show a very low level of evidence
- Randomized controlled trials are not the unique way to make an appropriate assessment of efficacy of a drug
- Randomized controlled trials have to fulfill the CONSORT statement criteria to be valid
- Instrumental variable is a good way to cope with selection bias
- Qualitative research is needed to explore anti-Alzheimer drug efficacy
- Appropriate role for the industry

Trials in AD and older people

they don't speak about them, they don't look them, they don't listen them



Trials pitfalls in Geriatrics

- Frequency of co-morbidity implying the multiplication of exclusion criteria
- Cognitive troubles pose an inform consent problem
- No expected benefit for the patient himself of the endpoints meaningful for younger patient (mortality)
- Ethical challenge if complementary studies are judged necessary
- Bed willing of MD
- Ageism
- The limitation of time to see an eventual effect considering the limited life expectancy

CONSORT statement (1)

JAMA 2001;285:1987-1991

- Randomization (1), scientific background (2)
- Participants (3): the **setting**
 - In anti-Alzheimer: memory clinic patients are very different of community dwelling patient particularly on concordance rate
- Interventions (4): the **administration of the drug**
 - Number of consultations

CONSORT statement (2)

JAMA 2001;285:1987-1991

- Number of words in article is limited
- **Methodological article** had to be published before the end of the study (very frequent in cardiovascular research)
 - objectives and hypotheses (5)
 - detailed program of statistical analyses (13)
 - all pre-specified primary and secondary endpoint (6) and method used to enhance quality of measurements
 - sample size calculation and interim procedures (7)
 - randomization (8,9) and blinding (12) procedures

CONSORT statement (3)

JAMA 2001;285:1987-1991

- Think about the **participant flow** (13) (0 = little external validity)
 - **From a general public health point of view**
 - With dates defining the recruitments periods (14)
 - With baseline characteristics (15)
- Results had to expressed the denominator not only the rate (**10/20 and not 50%**)
 - and precise if the analyze was in « intention to treat » (16)
- The effect size with **95% IC** had to be done for all endpoint (17)
- All ancillary analyses defined as pre-specified or exploratory (18)
- All adverse event had to be monitored (19)

CONSORT statement (4)

JAMA 2001;285:1987-1991

- The discussion (20, 22) had to address the generalizability (**external validity** of the study) (21)

Propensity score and instrumental variables

- A population with known characteristics
- Calculation of the probability of having one therapeutic procedure : the PS
- Thus we can make a deciles scale of PS
 - Cox models can be used to compare mortality (or another endpoint) between the two therapeutic procedure adjusted for the PS (that means the probability of having one or the other)
 - Or control patients are selected to patients receiving the new strategy with respect to PS (discarding unmatched individuals): matching on many confounders simultaneously

Propensity score and instrumental variables

- Instrumental variable
 - Remove hidden bias
- Characteristics
 - Highly related to the probability of treatment
 - Not related to outcome
- For example
 - Cardiac catheterization rate
 - Highly different between ZIP code regions
 - All known prognosis factor of AMI does not differ

Comparison of methods

JAMA 2007;297:278

- 122 124 patients (73 238 received cardiac catheterization)
- 65 covariates
- 1y-Mortality rate 14.2% if CC 38.6% if not
- Survival model with PS: relative mortality rate 0.5 (same with PS matched)
- Instrumental variable adjusted model : relative mortality rate 0.85 (very close to the 0,8 reported in RCT)
- Difference are related to hidden factors related to the selection of lower-risk of mortality patients for CC
- IV: Region catheterization rate quintile (from 29.2 to 82.3%) with no differences according to 65 covariates including prognostic index

Observational studies challenges

- Size of the population have to be sufficient
- Motivation of all partners
- Quality of procedures of screening
- Standardization of data collection
- Quality of data management

Start low

- and

■ **DON'T
FORGET TO
GO** slow