STATISTICAL CONSIDERATION

Utility of Multivariate Failure Time Analysis Method - An approach for Alcohol Treatment Clinical Trials

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OUTLINE

- Statistical experience from Naltrexone NDA
- Alcohol Treatment Trials
  - Types of study population of interest
  - Outcome measure(s)
  - Applicable statistical analysis method
    - Frequency
    - Handling of dropout patients
    - Time-to-event

STATISTICAL EXPERIENCE - 1
(Naltrexone)

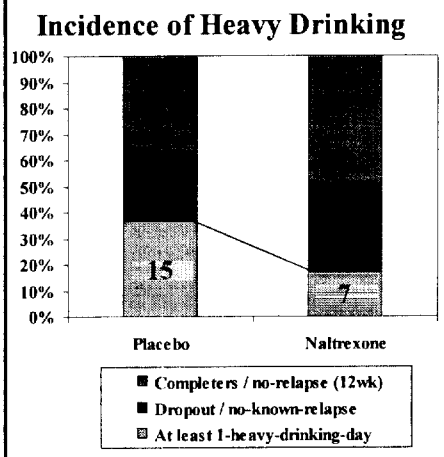
- Design
  - Randomized and double-blind 12-week study of Naltrexone vs. placebo in conjunction with psychotherapy
  - Volpicelli: one psychotherapy was used
  - O'Malley: two kinds of psychotherapy were used

STATISTICAL EXPERIENCE - 2
(Naltrexone)

- Outcome Measures reported by patients
  - time-to-1st-drink
  - time-to-1st-heavy-drinking-day(e.g., ≥ 5 drinks/day)
  - relapse to heavy drinking
  - complete abstinence from drinking
  - number of days on which patients drank or were drunk
  - craving for alcohol
- Lab measurements
  - blood alcohol
  - liver enzyme levels

CLINICAL RESPONSE (Yes/No)

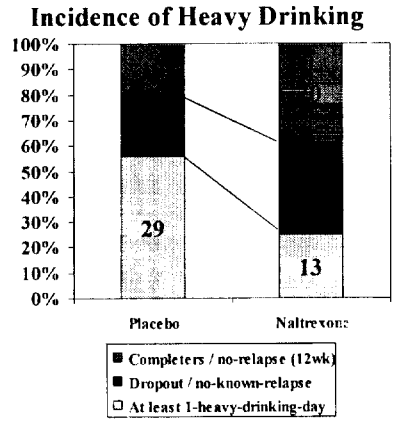
(Volpicelli et al., n=41 per group)



- **% patients w/ ≥ 1-heavy-drinking-day**
  17% (N) vs. 37% (P), p=0.05 (X^2)
- **% dropout, no-known-relapse**
  34% (N) vs. 27% (P)
- **% patients completed, no-relapse**
  49% (N) vs. 37% (P), p=0.37
- From Dr. Permutt's review(11/23/94)

CLINICAL RESPONSE (Yes/No)

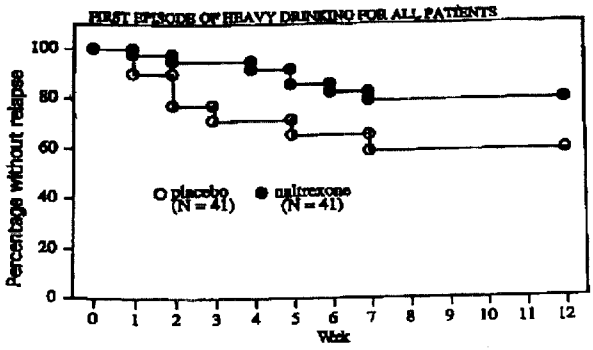
(O'Malley et al., n=52 /per group)



- **% patients w/ ≥ 1-heavy-drinking-day**
  25% (N) vs. 56% (P), p=0.0025
- **% dropout, no-known-relapse**
  37% (N) vs. 25% (P)
- **% patients completed, no-relapse**
  38% (N) vs. 19% (P), p=0.05
- From Dr. Permutt's review(11/23/94)

TIME TO FIRST-EVENT

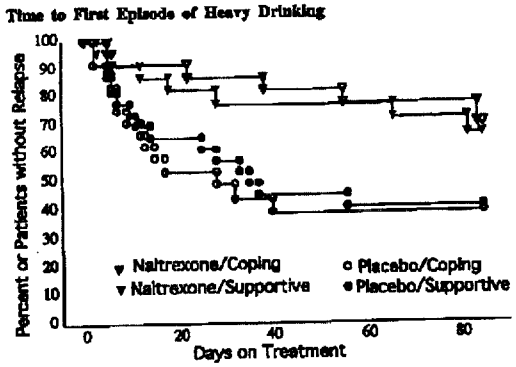
(Volpicelli et al., n=41/per group)



Time-to-first-episode-of-heavy-drinking
*Log-Rank Test, p-value = 0.04
*proportional-hazard model, p-val slightly above 0.05

TIME TO FIRST-EVENT

(O'Malley et al., n=52/per group)



*Log-Rank Test, p=0.001
*proportional-hazard model, p=0.001

STATISTICAL METHODS USED

(Naltrexone)

- Log-rank test and Cox-regression analysis for time-to-first-event outcomes
  - time-to-first-drink
  - time-to-first-heavy-drinking-day
- Chi-square test or Fisher's Exact test for Clinical Response (Yes/No) data
  - % of patients w/ at least one heavy-drinking-day
  - % of patients completed the trial w/o relapse
  - % of patients completed the trial and abstinence

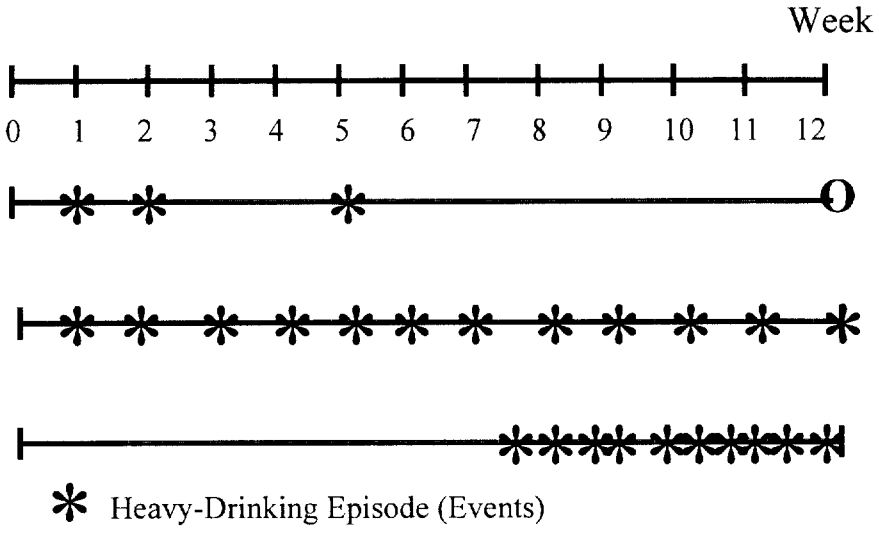
ALCOHOL TREATMENT TRIALS

- **Study population of interest ???**
  - alcoholics
  - nearly alcoholics
  - excessive alcohol users
- **Minimize Dropout Rate**
  - scheduled visits (schema)
  - retrieved-dropout

ALCOHOL TREATMENT TRIALS

- **Treatment effect of primary interest**
  - **Time-to-first-event and gap-times between events**
    - **Time-to-all-heavy-drinking-days**
  - **Quantitative outcome**
    - **Number of heavy drinking days**
    - **Number of low-risk drinking days (<=2 drinks/day for male and <=1 drink/day for female)**
  - **Binary outcome**
    - **% of patients having >=1 heavy drinking days**
    - **% of patients with low-risk drinking**

DEFINITION OF IMPROVEMENT



CONVENTIONAL ANALYSIS METHOD

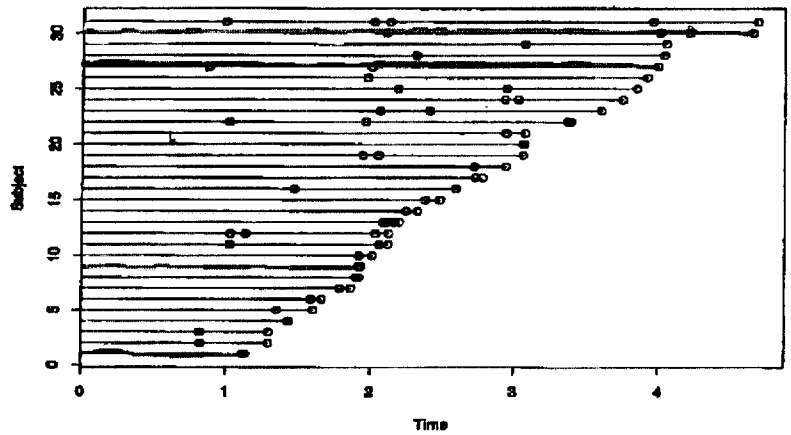
- Time-to-first event
  - main objective
  - application area
    - treatment may be very effective
    - mortality (time-to-death)
- When treatment effect cannot be distinguished based on time-to-**first** event

ALTERNATIVE STATISTICAL APPROACH

- **Time-to-recurrent-event analysis method can incorporate gap times between heavy-drinking-days and takes into account**
  - **time-to-each-heavy-drinking-day**
  - **time-to-overall-heavy-drinking-day**
  - **increased gap-time between events and/or decreased frequency of events**

MULTIPLE FAILURE TIMES

(Therneau, 1996)



RECURRENT EVENTS

- Cardiovascular trial
  - # of infarctions occurring over time in same patient
- chemotherapeutic trial
  - repeated infections reported by cancer patients
- asthma clinical trial
  - multiple asthma attacks in a patient
- seizure study
  - recurrent seizures in a patient during trial period

EXAMPLE - 1

- Time-to-first-event show treatment difference
- Time-to-recurrent-event strengthen the evaluation of treatment effect

EXAMPLE - 2

- Time-to-first-event fail to show treatment difference
- Time-to-recurrent-events show treatment difference
  - (Barai and Teoh, 1997) - repeated infections in the growth factor studies (patients with high grade malignant non-Hodgkin's lymphoma)

ANALYSIS METHODS FOR TIME-TO-RECURRENT-EVENT

- References
  - AG model (1982, Annals of Stat)
    - recurrent infection in bladder cancer patients, etc.
  - PWP total/gap time model (1981, Biometrika)
    - Infection incidence in bone marrow transplant recipients, etc.
  - Marginal Model of WLW (1989, JASA)
    - AIDS clinical trial, etc.
- Software available
  - MULCOX (Fortran); Splus; SAS

ALCOHOL TREATMENT TRIALS

- A More Defined Study Population ?
- Outcome Measure(s) of Primary Interest ?
  - Time to first heavy drinking
  - **Time to all heavy drinking days**
  - % patients abstinence during the 12-week
  - Number of heavy drinking days
  - Number of low-risk drinking days
- Time-to-recurrent-event-analysis-method ?