Dose response with MCP-Mod method

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Goal of Clinical Trial

- Explore whether a medical strategy, treatment, or device is safe and effective for humans
- Show which medical approaches work best for certain illnesses or groups of people.
- Clinical trials produce the best data available for health care decision making.
- In pharmceutial company,
  - Clinical trial tests the benefits and risks of a new drug.

Potential Risk

- What if, after running a clinical trial of a new drug, we are more inclined to see the positives than the negatives in the results?
- Perhaps we recommend further trials and further investment, only for the drug to turn out to be useless.
- Money will have been wasted.
- Patients would be exposed to the potential side effects of the failed drug and would not have received the best possible treatment.

Statistician's Responsibility

- Such mistakes could be undetected, either by the drug company itself, or by the regulatory agencies.
- Those who involved in running clinical trails have to be objective to avoid these mistakes.
- Statisticians play a crucial role in ensuring this objectivity by advising on the design of the trail and analyze the trail results in an objective manner

Difficulties Statisticians May Face

- When testing new drugs, researchers are asked to specify their statistical analysis plan before seeing their results.
- However, in the early stage of developing a drug, statisticians may not know what kind of data to expect.
- Difficult to select the most appropriate form of analysis in advance.

MCP-Mod Method

- One way to address this is to use a method, developed by Novartis, "multiple comparisons and modeling", known as MCP-Mod.
- Allows statisticians to specify several candidate models that might describe the observed results.
- Recently recognised by the European Medicines Agency as an efficient statistical method for Phase II dose-finding trials in drug development (bit.ly/28XLtxK).

Our Project

- Learn what is MCP-Mod method and how to use it.
- Use MCP-Mod method to fit a best model for a drug developed by Merck company in 2010, which is designed to treat migraine.
- Related information for this clinal trail study (1.usa.gov/28Xd9Hr)

Brief Introduction of Clinical Trial

- Pre-Clinical Trial
- Phase I Clinical Trial
- Phase II Clinical Trial
- Phase III Clinical Trial
- Phase IV Clinical Trial

Pre-Clinical Trial

Drug Discovery

- Experimentation before a drug is given to human subjects
- In vitro studies

Phase I Clinical Trial

Screening for safety

- Test with a small group of people (20–80).
- Identify possible toxic effects or side effects.
- Determine safe dosage ranges (maximum tolerated dose, MTD).

Phase II Clinical Trial

Screening for efficacy and feasibility

- Test with a larger group of people (100–300).
- Assess side effects and toxicity.
- Establish the efficacy of the drug, usually against a placebo.

Phase III Clinical Trial

Comparative Efficacy Trials

- Test with large groups of people (1,000–3,000)
- Comparison of new intervention (drug or therapy) to the current standard of treatment; both with respect to efficacy and toxicity.
- FDA approval

Phase IV Clinical Trial

Post-marketing surveillance

- Post-marketing studies delineate additional information, including the treatment's risks, benefits, and optimal use, and look for uncommon side effects.
- This type of study design is also used for purposes other than safety and efficacy, such as for marketing.

Demonstation

1. **Basic context**
   - In 2010 Merck developed a new drug to treat acute migraine
   - Phase II trial: targeted to test in migraine patients
   - To find out the optimal dose

2. **Merck's crucial decision**
   - stop evaluating the drug if there was no clear sign that it worked
   - Continue developing the product using specific doses.
   - The latter option implied a major investment in the drug (costing roughly $26,000 dollars per patient)

Demonstation

- The trial contained 517 patients divided into 8 groups: placebo, 2.5, 5, 10, 20, 50, 100 or 200 mg of the new drug.
- In each group they measured how many patients were free of pain 2 hours after taking the drug.
- Each dot represents the percentage of patients with successful outcomes in a specific dose group.

The eight groups figure

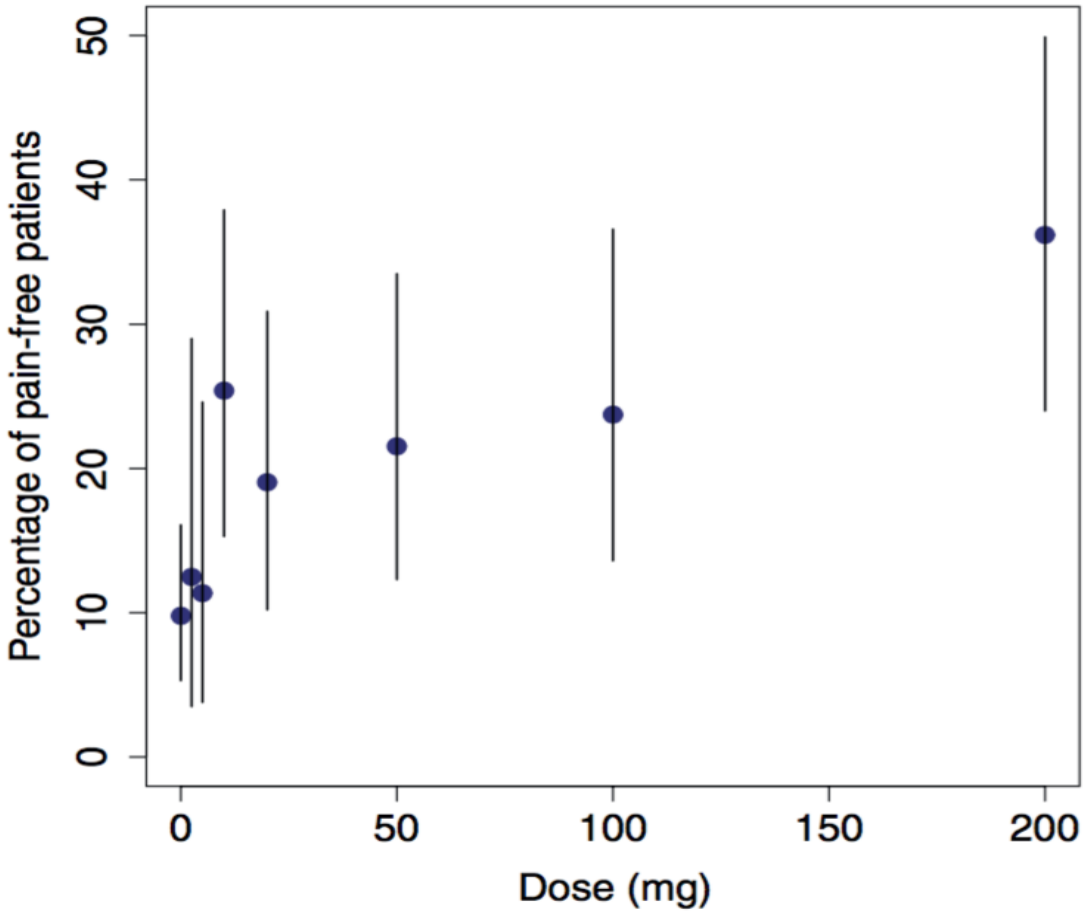


FIGURE 1 The results from Merck's trial on a drug to treat migraine. Dose groups included 133, 32, 44, 63, 63, 65, 59 and 58 patients, respectively. Vertical bars present 95% confidence intervals

Demonstation

- The results look promising, but can we draw conclusions by just looking at such a plot?
- To get an understanding of the uncertainty of response in in each dose group, we can look at intervals(the vertical bars in Figure 1).
- Therefore, we would like to analyze our results using a formal statistical approach that takes and also the three-stage nature of the experimental design, into account.

Analysing the data

A popular method : **"Pairwise Comparisons"**

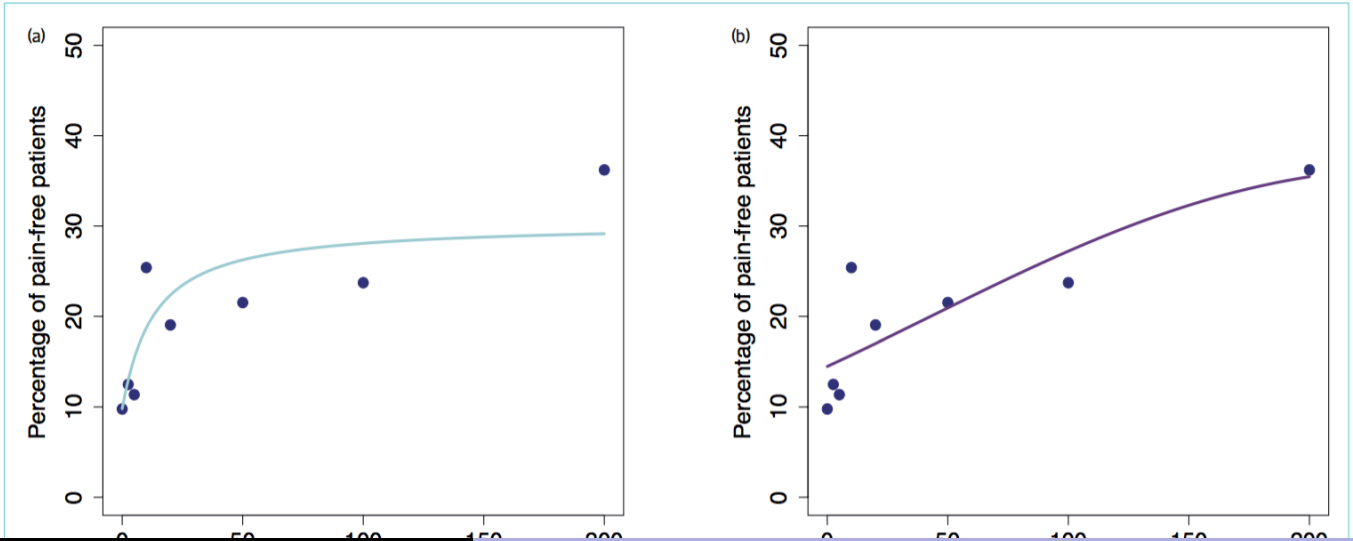
- Tells us whether the difference between the mean responses in the dose groups.
- Usually comparing each dose group with the placebo group to see whether any dose works better than placebo.
- Limitation
  - It only works with pairs of tested doeses.
  - It fails to tell the mean response of a dose which was not included in the study. (e.g. 150mg)

Analysing the data

Alternative method : Fitting statistical models - We can come up with several scenarios..

(a) **Emax model** : Assuming the effect of the drug increases almost linearly at first and then flattens off.

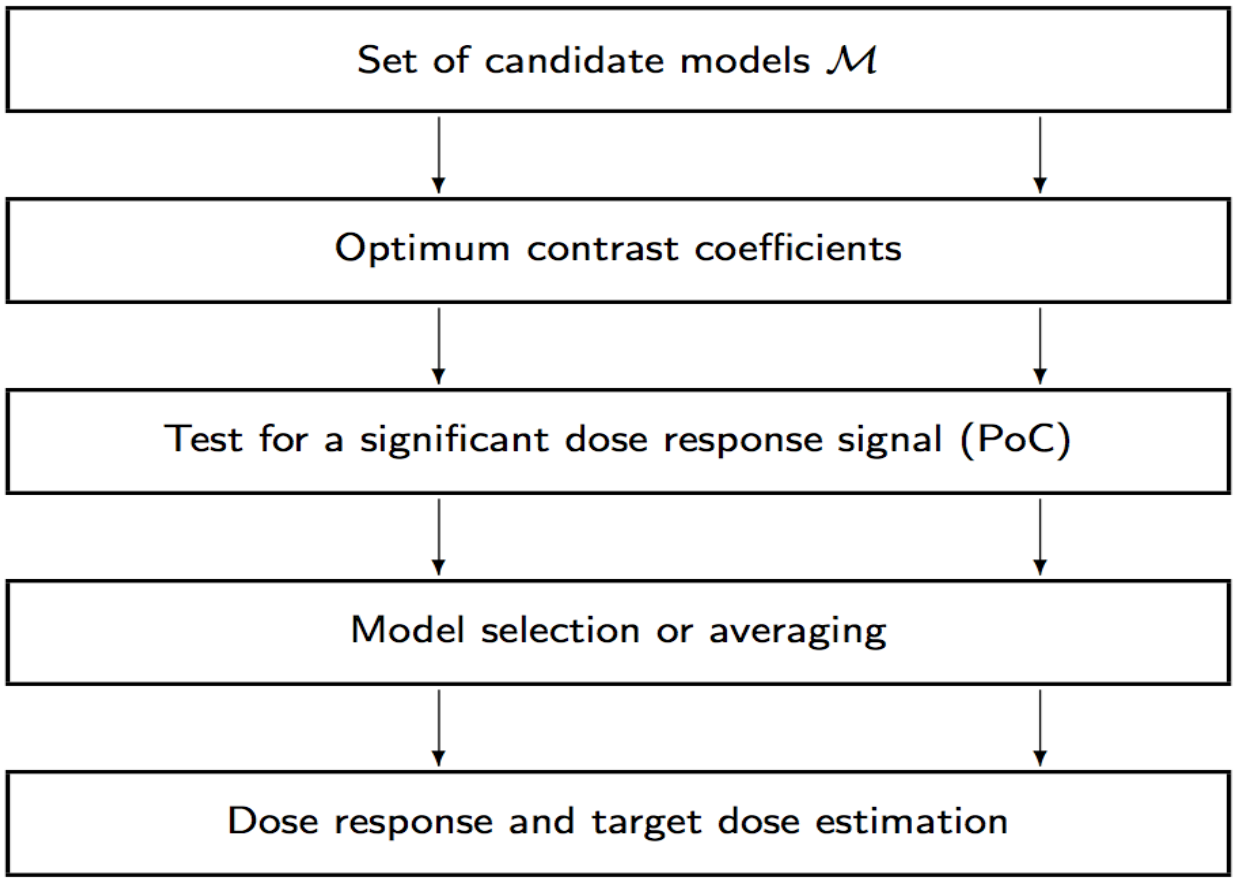
(b) **Quadratic model** : There may be a lower threshold before the drug starts working, then there is an almost linear increase, and then an upper threshold is reached and the effect flattens out.



Analysing the data

- Both models tell us what percentage of pain- free patients we could expect for every possible dose.
- Next question will be.. Can we make an objective choice between these two models?
- Choosing the most appropriate model is challenging issue to pharmaceutical companies.
- **Novatis** proposed a method called, "MCP-MOD" (Biometrics, 2005, F.Bretz) : Allow us to analyze dose responses under model uncertainty.

Multiple comparisons and Modeling Techniques : MCP-Mod



Set of candidate models M

(i) A set M of candidate models covering a suitable range of dose response shapes. Also, unrealistic pattern that describes the data needs to be excluded.

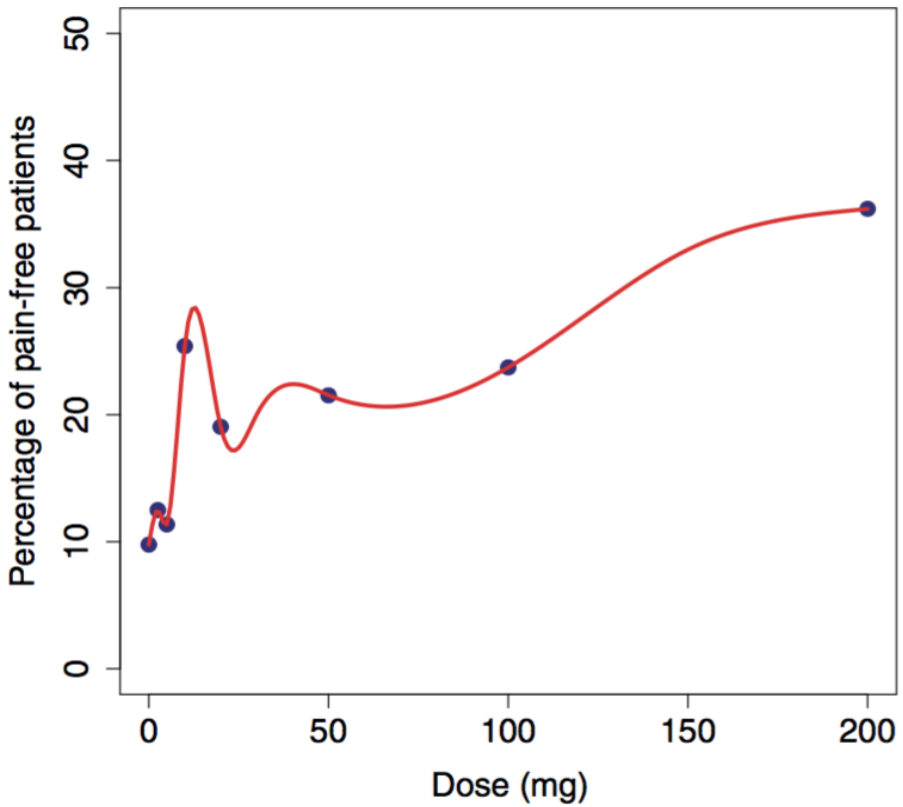


FIGURE 4 An unrealistic pattern that describes the results perfectly

Optimum contrast coefficients

(ii) Choose best the contrast coefficients to maximize the power of detecting the m-th model.

$$H_0^m : C_m'\mu = 0 \quad V.S. \quad H_1^m : C_m'\mu > 0$$

$$T_m = \frac{\sum_{i=1}^{k} C_{m_i}\bar{y}_i}{\sqrt{S^2 \sum^k C_{m_i}^2/n_i}}$$

C_{m_i} : Every single contrast test is to determine whether the given dose response shape is statistically significant.

Model selection

(iii) Combining the test statistics T_m into a single decision rule is to take the maximum

$$T_m = max_m T_m \quad (min_m P_m < \alpha)$$

- None of models could be significant
  - When the set M is poorly chosen.
  - Small sample size n, High variance.
- At least one model needs to be significant.

Dose response and target dose estimation

Fitting the selected model to the data and estimating adequacy

$$MED = argmin_{\{d \in (d_1, d_k]\}} \{f(d, \theta) > f(d_1, \theta) + \Delta\}$$

- Δ denote the clinically relevant difference (A dose better than placebo)
- The smallest dose which shows a clinically relevant and a statistically significant effect.

Data analysis

1. Fitting models to Merck's data and applying MCP-Mod
2. Simulated data
   (i) The power to detect a dose-response relationship. (Comparing with the LRT)
   (ii) Estimation of a dose close to the desired level taking into account both statistical significance and clinical relevance.(dose-selection performance)

- Fitting different types of model $\mu(d)$(Next page)

$$Y \sim N(\mu(d), \sigma^2)$$

- n=10, 25, 50, 75, 100, and 150
- d=0, 0.05, 0.2, 0.6, 1

Name	$f(d,\boldsymbol{\theta})$	$f^0(d,\boldsymbol{\theta}^*)$
`linear`	$E_0+\delta d$	d
`linlog`	$E_0+\delta\log(d+c)$	$\log(d+c)$
`quadratic`	$E_0+\beta_1 d+\beta_2 d^2$	$d+\delta d^2$ if $\beta_2<0$
`emax`	$E_0+E_{\max}d/(\mathrm{ED}_{50}+d)$	$d/(\mathrm{ED}_{50}+d)$
`logistic`	$E_0+E_{\max}/\{1+\exp[(\mathrm{ED}_{50}-d)/\delta]\}$	$1/\{1+\exp[(\mathrm{ED}_{50}-d)/\delta]\}$
`exponential`	$E_0+E_1(\exp(d/\delta)-1)$	$\exp(d/\delta)-1$
`sigEmax`	$E_0+E_{\max}d^h/(\mathrm{ED}_{50}^h+d^h)$	$d^h/(\mathrm{ED}_{50}^h+d^h)$
`betaMod`	$E_0+E_{\max}B(\delta_1,\delta_2)(d/D)^{\delta_1}(1-d/D)^{\delta_2}$	$B(\delta_1,\delta_2)(d/D)^{\delta_1}(1-d/D)^{\delta_2}$

Conclusion

- The flexibility to consider more than one possible model to describe how a drug works.
- Avoid the possibility of subjective decision-making.
- Merck discontinued development after discovering its negative effect on the liver although the trial showed likely to reduce pain for migraine patients, safety problem was greater than the benefit
- The MCP-Mod is being used successfully in many clinical trials.