

Case Study for Dose Finding Using Adaptive Treatment Assignment
Determination of Target Dose Of
Calcitonin Gene-Related Peptide Receptor Antagonist
For Abortive Treatment of Migraine

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General Notions

- x_i , $i = 1, \dots, k$: dose levels
- θ = targeted proportion of patients with event
- x^* = dose at which targeted proportion is achieved

$$Y_j = \begin{cases} 1 & \text{if event occurs for patient } j \\ 0 & \text{if event does not occur for patient } j \end{cases}$$

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- $\Pr(Y_j = 1) = \theta$ at x^*
- Goal: Find the dose, x^* , at which the targeted proportion, θ , is achieved

Case Study

- Olesen, J, et al. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine.
N Engl J Med 2004;350:1104-10
- Primary outcome: response to abortive treatment of migraine, where response is defined as reduction of migraine pain intensity from moderate or severe at baseline to none or mild at 2 hours after treatment
- Objective: find the dose at which at least 60% of the patients respond, i.e., $\theta = 0.60$.
- Doses: 0.1, 0.25, 0.5, 1, 2.5, 5, or 10 mg of BIBN 4096 BS

Case Study (continued)

The article describes the dose finding sequentially adapted scheme as follows:

- Groups of 6 patients were randomized, 4 to one dose of BIBN 4096 BS and 2 to placebo, starting at 1.0 mg
- The dose for each succeeding group was determined on the basis of the response observed in the preceding group
- The dose in the next group was decreased if at least 3 of the 4 patients on BIBN 4096 BS had a response; otherwise, the dose was increased

Case Study (continued)

- At the highest dose or lowest dose, the rule was modified to avoid treatment outside the target range
- If the results for the preceding 6 patients were not available to guide the dose for the next group, the next lower dose was used
- This up-and-down process was to be terminated when one of the doses satisfied the selection criteria: the dose had been tested in at least 5 groups, and the response was observed in at least 4 groups among at least 3 of the 4 patients in each group who received BIBN 4096 BS
- If the threshold for stopping was reached before 3 groups had been treated with the highest dose, then

Comments

- The description of the methods is inadequate to determine what was actually done
- No rule for determining the target dose was specified
- The up-and-down method used here does not capitalize on the full accumulated data
- It seems likely that the objective of this study could have been met much more efficiently with a continual reassessment method (CRM) which uses all of the accumulated data in making a

Continual Reassessment Method (CRM)

- $\Pr(Y_j = 1) = \psi(x_i, a_0)$: parametric dose response model - probability of response at dose x_i and the true value of a , a_0
- $\psi(x^*, a_0) = \theta$
- Assume a prior distribution for a
- Starting at a dose that is thought to be close to x^* , sample patients and their responses sequentially
- Before treating the next patient and after obtaining the response of the most recent patient at his/her assigned dose, update the distribution of a based on the observed sequence of doses and responses up to that time

CRM (continued)

- Based on this revised distribution of a , the expected probability of response at each possible dose level is calculated; the next dose is chosen as the dose whose expected response is closest to that of the target dose
- Continue sampling and assigning doses in this manner until the last patient is finished
- The dose assigned at this time is the estimated target dose