What behavioral scientists can learn from the drug development

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Drug Development

- Pre clinical
  - Main goal is to determine a compound that may be safe and effective in treating a condition
- Clinical
  - Phase I Dose finding
  - Phase II prelim. Efficacy and toxicity
  - Phase III Efficacy and AEs
  - Phase IV Post market evaluation

Behavioral Intervention/Modification

- "Pre clinical"
  - develop a new concept or idea
- Clinical
  - Phase I

    determine a treatment level (exercise frequency or intensity, # of self monitoring of blood glucose)
  - Phase II

    Similar aims and study designs as in the drug development
  - Phase III

- Novel ideas presented today
  - Defining new intervention methods
    - Effectiveness
    - Efficiency
  - Preliminary testing
  - Analyzing small data sets
  - New study designs for early phase trials

- “Pre-clinical” : Define an intervention
  - Develop better interventions -Silvia Vergani
  - Identify novel behavior changes -April Carcone
  - MOST -Kari Kugler
- Phase I: refine the intervention to a specific level
  - Modified Toxicity Probability Interval (mTPI) -Yuan Ji
  - Single case experimental designs -Bethany Raiff
    - » Adherence to blood glucose testing

- Early stage (behavioral) studies need a small N (20-40). New statistical techniques are needed as the standard ones may not be appropriate.

- The elaborate mechanism built on the theory of infinitely large samples is not accurate enough for simple laboratory data... Not only does it take a cannon to shoot a sparrow, but it misses the sparrow!“ R.A. Fisher

- Not all behavioral interventions can apply the dose-finding methods (DF)

- If the response is binary and the treatment can be classified into ordered levels, then DF techniques may be used to choose the “best” treatment level to go to the next testing phase.

Dose finding studies

- Broad class of early development trial designs whose purpose is to find a dose (level) of treatment that is optimal with respect to simple criteria

Drug development	Behavioral
– Toxicity	Adherence, Drop-outs, etc
– Efficacy	Efficacy (signal detection)

Phase I study
Basic Assumptions

Isotonic assumption

- Increasing dose levels increases efficacy but also risk (injury, drop-outs, non-compliance)

- Find the maximum tolerated dose (MTD)
- EDp (dose required for desired effect in p% of the patient population)
- Balance the efficacy vs. risk

Behavior modification Examples

- Exercise
  - Dose: intensity or duration, frequency
- Diabetes
  - Dose: # of self monitoring of blood glucose
- Diet
  - Dose: calorie count
- Toxicity
  - SAE, drop-out, adherence

Dose Finding Designs

- Limit number of subjects treated at ineffective dose levels
- Limit number of subjects treated at high doses that may produce SAE, ↑dropouts, or ↑non-adherence
- Find a dose that maximizes therapeutic benefit while maintaining risk below a predetermined threshold

Sequential or adaptive designs

Generally superior in performance to conventional pairwise comparisons (esp when N is small)

In comparison to a standard fixed design, an adaptive dose-response design is more effective in identifying “the right dose”

- Frequentist
- Bayesian

variations for delayed response or accelerated versions of the above have been proposed .

Sequential or adaptive designs

- Frequentist
  - Up and down (U&D) designs
    - Biased Coin Design
    - Group U&D
    - Optimal U&D
  - 3+3 designs (Up no Down)

- Easy to understand and implement (no complicated calculations)

Sequential or adaptive designs

- Bayesian
  - Continual Reassessment Method (CRM) model based (O'Quigley et al. 1990)
    - Modified CRM (Goodman et al. 1995)
    - Extended CRM [2 stage] (Moller, 1995)
    - Restricted CRM (Moller, 1995)
  - Other
    - EWOC (Escalation with Overdose Control (Babb et al. 1998))
    - mTPI (Yuan Ji)

- A potential downside to the Bayesian approach is the computational complexity coupled with the absence of commercial software packages to assist with study design and analysis.
- Less of a problem now

https://biostatistics.mdanderson.org/SoftwareDownload/

http://compgenome.org/NGDF/

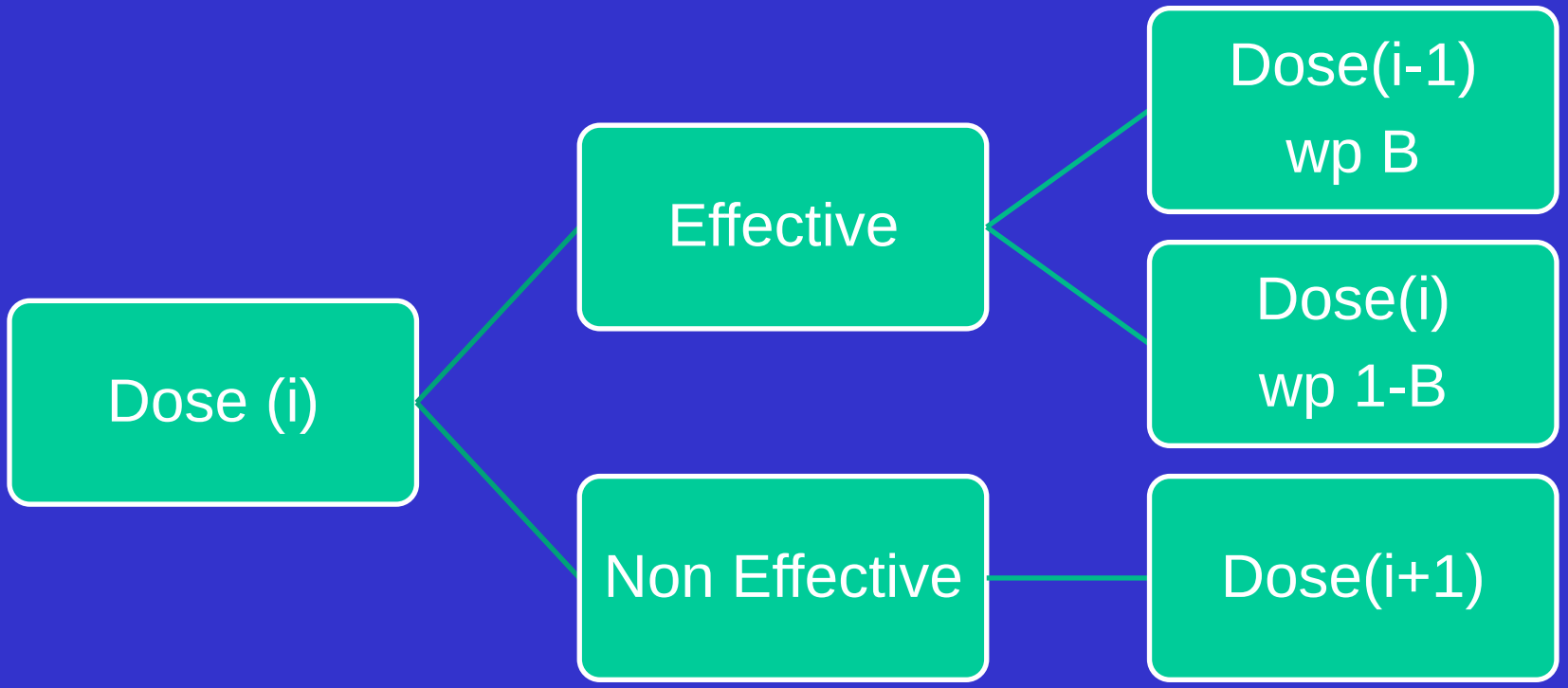
Biased Coin Design

- Find
  - MTD
    - dose with target toxicity < T, T<.50
      - Exercise intensity level (dose) vs drop-out (risk)
  - Effective dose
    - dose that is effective to at least 100T% in the subject population, T>.5
      - # of self monitoring of BG (dose) vs non-adherence (risk)

Find MTD with BCD

T=target Pr(tox) <.50
B=T/(1-T)

Find min ED with BCD



T=target Pr(effect) >.50
B=(1-T)/T

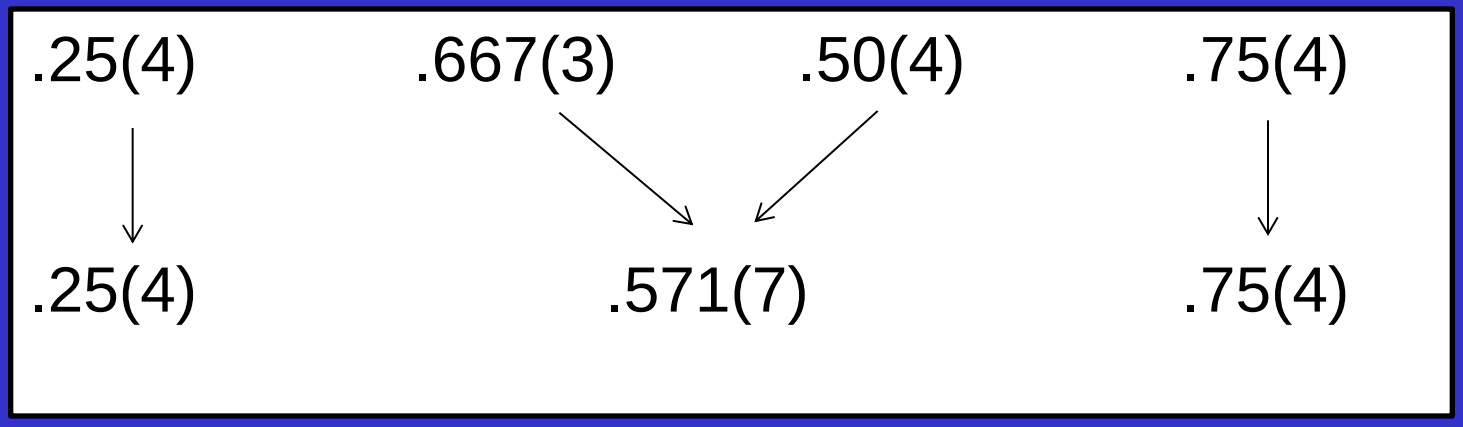
BCD Properties

- Easy to implement
- Works with any target level
- No parametric dose response model needed
- BCD is optimal in the large class of generalized up-and-down biased coin designs (dose distn is peaked around target dose (Giovagnoli and Pintacuda 1998)
- Performs as well or better than Continual Reassessment Method (CRM)

Isotonic Regression
Pool Adjacent Violators Algorithm (PAVA)

Dose (x)	A	B	C	D	E
	0	0	0	1	
	0	1	1	1	
	0	1	1	1	
	1		0	0	
N(x)	4	3	4	4	0
N(tox)	1	2	2	3	
p_i	.25	.667	.50	.75	
p_i^*	.25	.571	.571	.75	

Pool Adjacent Violators Algorithm (PAVA)



Conclusions

- Not all behavioral interventions can apply dose-response methods but if they can then:
  - Implementation of sequential UD designs is simple; Bayesian adaptive designs can by simplified with available software
  - No major assumptions are needed
  - Isotonic estimator of dose-response curve is recommended and easy to derive
  - Solutions to the long response times or long waiting times have been proposed
  - Performance of sequential designs are generally better than non-sequential designs