The AB/BA Crossover in the Presence of Dropout

Weang Kee Ho & John Matthews

Joint work with Robin Henderson and Daniel Farewell[1]

University of Newcastle upon Tyne and [1]Cardiff University, UK

Outline

Outline

Outline

Outline

Outline

Example: analgesia trial

- Trial to compare a cannabinoid (Nabilone, A) and dihydrocodeine (B) for the treatment of chronic neuropathic pain (Frank *et al.*, **BMJ**, 2008, 336, 199-201)

Example: analgesia trial

- Trial to compare a cannabinoid (Nabilone, A) and dihydrocodeine (B) for the treatment of chronic neuropathic pain (Frank *et al.*, **BMJ**, 2008, 336, 199-201)
- Trial used the standard two-period AB/BA crossover design, with washout between periods

Example: analgesia trial

- Trial to compare a cannabinoid (Nabilone, A) and dihydrocodeine (B) for the treatment of chronic neuropathic pain (Frank *et al.*, **BMJ**, 2008, 336, 199-201)
- Trial used the standard two-period AB/BA crossover design, with washout between periods
- Large for a crossover trial - 82 patients in our analysis: 45 in AB and 37 in BA

Example: analgesia trial

- Trial to compare a cannabinoid (Nabilone, A) and dihydrocodeine (B) for the treatment of chronic neuropathic pain (Frank *et al.*, **BMJ**, 2008, 336, 199-201)
- Trial used the standard two-period AB/BA crossover design, with washout between periods
- Large for a crossover trial - 82 patients in our analysis: 45 in AB and 37 in BA
- Outcome is VAS pain score (0-100mm)

Example: analgesia trial

- Trial to compare a cannabinoid (Nabilone, A) and dihydrocodeine (B) for the treatment of chronic neuropathic pain (Frank *et al.*, **BMJ**, 2008, 336, 199-201)
- Trial used the standard two-period AB/BA crossover design, with washout between periods
- Large for a crossover trial - 82 patients in our analysis: 45 in AB and 37 in BA
- Outcome is VAS pain score (0-100mm)
- All patients give value in period 1 but 15 drop out in period 2 (10 in AB, 5 in BA)

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j +$$

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj}$$

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj} + \xi_i + \epsilon_{ij}$$

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj} + \xi_i + \epsilon_{ij}$$

$\tau_A = -\tau_B = \tau$, $\pi_1 = -\pi_2 = \pi$, etc

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj} + \xi_i + \epsilon_{ij}$$

$\tau_A = -\tau_B = \tau$, $\pi_1 = -\pi_2 = \pi$, etc

- ξ_i is a patient effect

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj} + \xi_i + \epsilon_{ij}$$

$\tau_A = -\tau_B = \tau$, $\pi_1 = -\pi_2 = \pi$, etc

- ξ_i is a patient effect
  - Could be a fixed parameter - effectively eliminates patients with observations on only one period

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj} + \xi_i + \epsilon_{ij}$$

$\tau_A = -\tau_B = \tau$, $\pi_1 = -\pi_2 = \pi$, etc

- ξ_i is a patient effect
  - Could be a fixed parameter - effectively eliminates patients with observations on only one period
  - Could be random - i.e. a mixed model

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj} + \xi_i + \epsilon_{ij}$$

$\tau_A = -\tau_B = \tau$, $\pi_1 = -\pi_2 = \pi$, etc

- ξ_i is a patient effect
  - Could be a fixed parameter - effectively eliminates patients with observations on only one period
  - Could be random - i.e. a mixed model - includes patients with incomplete data

Usual models for the AB/BA design

- Suppose outcome on patient i in period j is Y_{ij}
- Usual linear model is:

$$Y_{ij} = \mu + \tau_x + \pi_j + (\tau\pi)_{xj} + \xi_i + \epsilon_{ij}$$

$\tau_A = -\tau_B = \tau$, $\pi_1 = -\pi_2 = \pi$, etc

- ξ_i is a patient effect
  - Could be a fixed parameter - effectively eliminates patients with observations on only one period
  - Could be random - i.e. a mixed model - includes patients with incomplete data
- $(\tau\pi)_{xj}$ - interaction term, usually a carryover effect, not now widely used but has a role in our development.

Usual analyses

- Fixed subject effects, ξ_i

Usual analyses

- Fixed subject effects, ξ_i
  - use t-tests or

Usual analyses

- Fixed subject effects, ξ_i
  - use t-tests or
  - linear model with REML

Usual analyses

- Fixed subject effects, ξ_i
  - use t-tests or
  - linear model with REML
- Random subject effects, ξ_i

Usual analyses

- Fixed subject effects, ξ_i
  - use t-tests or
  - linear model with REML
- Random subject effects, ξ_i
  - linear mixed model, `PROC MIXED` or `lme` etc.

Usual analyses

- Fixed subject effects, ξ_i
  - use t-tests or
  - linear model with REML
- Random subject effects, ξ_i
  - linear mixed model, `PROC MIXED` or `lme` etc.
  - likelihood analysis - valid if the missing data are Missing At Random (MAR)

Alternative analyses - GEEs

- Generalized Estimating Equations (GEEs) provide an alternative method of analysis

Alternative analyses - GEEs

- Generalized Estimating Equations (GEEs) provide an alternative method of analysis
- If all n patients provide full data then this can be written:

Alternative analyses - GEEs

- Generalized Estimating Equations (GEEs) provide an alternative method of analysis
- If all n patients provide full data then this can be written:

$$\sum_{i=1}^{n} \left\{ x_{1i}^{T}(Y_{1i} - x_{1i}\beta) + x_{2i}^{T}(Y_{2i} - x_{2i}\beta) \right\} = 0$$

Alternative analyses - GEEs

- Generalized Estimating Equations (GEEs) provide an alternative method of analysis
- If all n patients provide full data then this can be written:

$$\sum_{i=1}^{n} \left\{ x_{1i}^T (Y_{1i} - x_{1i}\beta) + x_{2i}^T (Y_{2i} - x_{2i}\beta) \right\} = 0$$

- x_{1i} is the row of the design matrix for period 1 (sim. period 2) and β is vector of parameters $(\mu, \pi, \tau, (\tau\pi))^T$

GEEs with Missing Data I

- Let R_i be indicator of missingness - $R_i = 0$ if period 2 observation missing for patient i.
- GEE becomes

$$\sum_{i=1}^{n} \left\{ x_{1i}^T (Y_{1i} - x_{1i}\beta) + I(R_i = 1) x_{2i}^T (Y_{2i} - x_{2i}\beta) \right\} = 0$$

strictly only valid if data are Missing Completely At Random (MCAR)

GEEs with Missing Data II

- Robins, Rotnitzky and Zhao, *JASA*, (1995) suggest amending to:

$$\sum_{i=1}^{n} \left\{ x_{1i}^T (Y_{1i} - x_{1i}\beta) + \frac{I(R_i = 1)}{p_i} x_{2i}^T (Y_{2i} - x_{2i}\beta) \right\} = 0$$

where $p_i = \Pr(R_i = 1 \mid Y_{1i}, Y_{2i})$ to achieve unbiassed estimates under MAR ($p_i = \Pr(R_i = 1 \mid Y_{1i})$) and, further, to

GEEs with Missing Data II

- Robins, Rotnitzky and Zhao, *JASA*, (1995) suggest amending to:

$$\sum_{i=1}^{n} \left\{ x_{1i}^T (Y_{1i} - x_{1i}\beta) + \frac{I(R_i = 1)}{p_i} x_{2i}^T (Y_{2i} - x_{2i}\beta) \right\} = 0$$

where $p_i = \Pr(R_i = 1 \mid Y_{1i}, Y_{2i})$ to achieve unbiassed estimates under MAR ($p_i = \Pr(R_i = 1 \mid Y_{1i})$) and, further, to

-

$$\sum_{i=1}^{n} \frac{I(R_i = 1)}{p_i} \left\{ x_{1i}^T (Y_{1i} - x_{1i}\beta) + x_{2i}^T (Y_{2i} - x_{2i}\beta) \right\} = 0$$

(Rotnitzky, Robins and Scharfstein, *JASA*, 1998) under Missing Not At Random (MNAR)

Probability Model

- Probability of continuation, $p_i = \Pr(R_i = 1 \mid Y_{1i}, Y_{2i})$ depends on (Y_{1i}, Y_{2i}) through

$$\text{logit}\,\Pr(R_i = 1 \mid Y_{1i}, Y_{2i}) = \theta_0 + \theta_1 Y_{1i} + \theta_2 Y_{2i}$$

Probability Model

- Probability of continuation, $p_i = \Pr(R_i = 1 \mid Y_{1i}, Y_{2i})$ depends on (Y_{1i}, Y_{2i}) through

$$\text{logit}\,\Pr(R_i = 1 \mid Y_{1i}, Y_{2i}) = \theta_0 + \theta_1 Y_{1i} + \theta_2 Y_{2i}$$

- Estimate θ_0 and θ_1 by solving

$$\sum_{i=1}^{n} \left(\frac{I(R_i = 1)}{p_i} - 1 \right) \phi(Y_{1i}) = 0$$

for suitable choice of $\phi(.) \in \mathbb{R}^2$

Probability Model

- Probability of continuation, $p_i = \Pr(R_i = 1 \mid Y_{1i}, Y_{2i})$ depends on (Y_{1i}, Y_{2i}) through

$$\text{logit}\,\Pr(R_i = 1 \mid Y_{1i}, Y_{2i}) = \theta_0 + \theta_1 Y_{1i} + \theta_2 Y_{2i}$$

- Estimate θ_0 and θ_1 by solving

$$\sum_{i=1}^{n} \left(\frac{I(R_i = 1)}{p_i} - 1 \right) \phi(Y_{1i}) = 0$$

  for suitable choice of $\phi(.) \in \mathbb{R}^2$
- Need to assume a value for θ_2

Probability Model

- Probability of continuation, $p_i = \Pr(R_i = 1 \mid Y_{1i}, Y_{2i})$ depends on (Y_{1i}, Y_{2i}) through

$$\text{logit}\,\Pr(R_i = 1 \mid Y_{1i}, Y_{2i}) = \theta_0 + \theta_1 Y_{1i} + \theta_2 Y_{2i}$$

- Estimate θ_0 and θ_1 by solving

$$\sum_{i=1}^{n} \left(\frac{I(R_i = 1)}{p_i} - 1 \right) \phi(Y_{1i}) = 0$$

  for suitable choice of $\phi(.) \in \mathbb{R}^2$
- Need to assume a value for θ_2
- What value? $\theta_2 = 0$ corresponds to MAR

Determining θ_2

- For the AB/BA design we usually assume $(\tau\pi) = 0$

Determining θ_2

- For the AB/BA design we usually assume $(\tau\pi) = 0$
- Could choose θ_2 such that $\widehat{(\tau\pi)} = 0$, θ_{20}, say

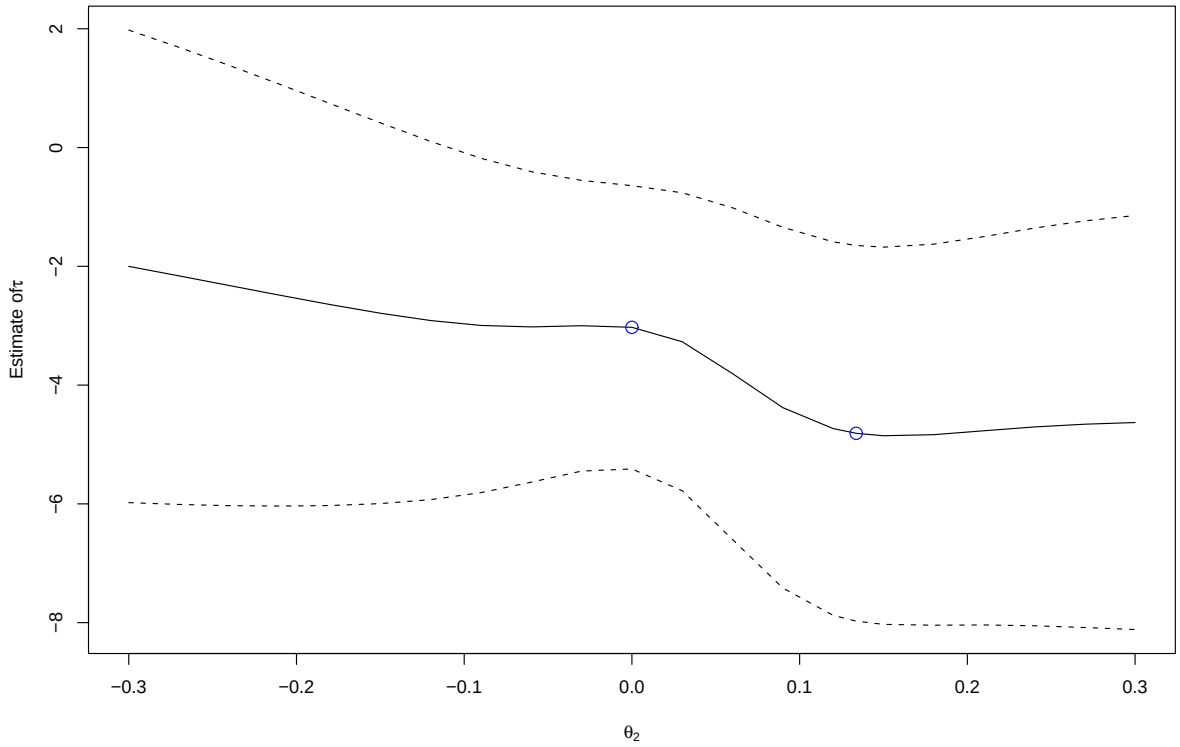
Determining θ_2

- For the AB/BA design we usually assume $(\tau\pi) = 0$
- Could choose θ_2 such that $\widehat{(\tau\pi)} = 0$, θ_{20}, say
- Re-fit model omitting $(\tau\pi)$ but using $\theta_2 = \theta_{20}$

Sensitivity of $\hat{\tau}$ to θ_2

- $\theta_2 = \theta_{20} = 0.134 (\Rightarrow \widehat{(\tau\pi)} = 0)$ is as plausible as $\theta_2 = 0$

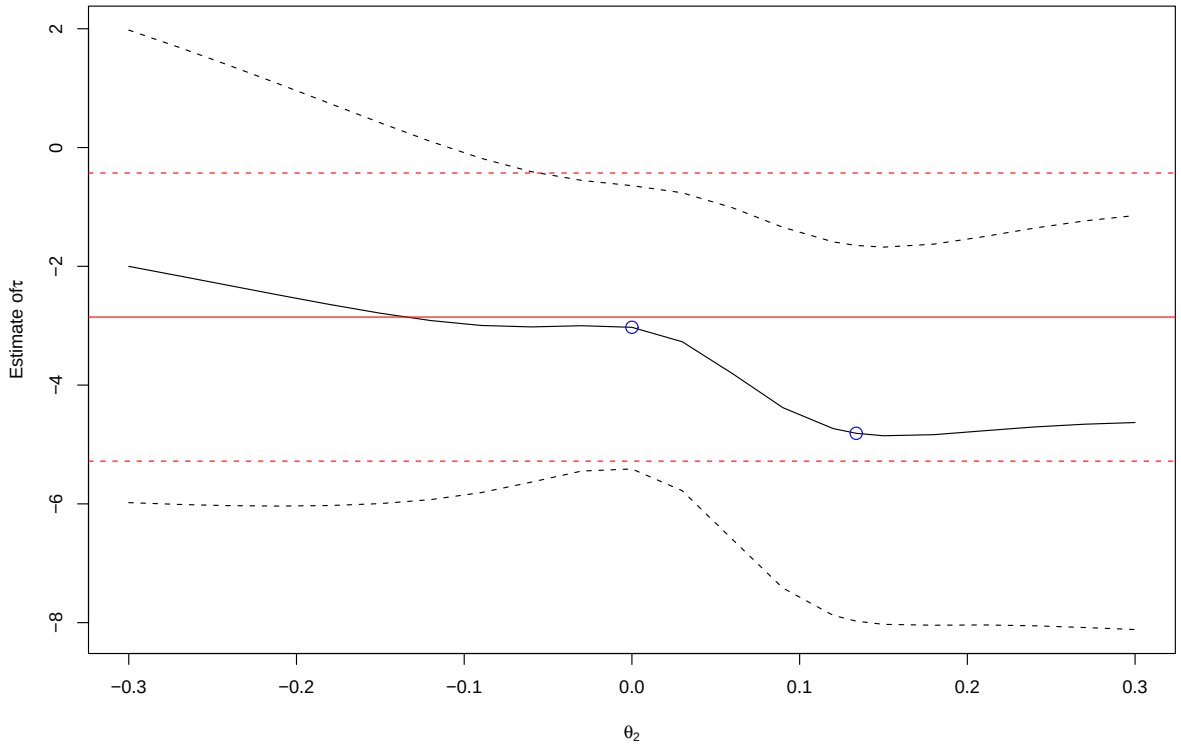
Plot of $\hat{\tau}$ (mm) versus θ_2



Sensitivity of $\hat{\tau}$ to θ_2

- $\theta_2 = \theta_{20} = 0.134 (\Rightarrow \widehat{(\tau\pi)} = 0)$ is as plausible as $\theta_2 = 0$

Plot of $\hat{\tau}$ (mm) versus θ_2:complete case analysis in red



Some point estimates

Analysis	$\hat{\tau}$	SE
MAR `lme`	-3.11	1.19
MAR GEE	-3.30	1.19
$\theta_2 = 0.134$ GEE	-4.81	1.58
Complete Case	-2.85	1.21

Concluding comments

- Analysis based on mixed model is valid only if data MAR and this may be questionable in many instances.

Concluding comments

- Analysis based on mixed model is valid only if data MAR and this may be questionable in many instances.
- Alternative, plausible dropout models can give markedly different $\hat{\tau}$s

Concluding comments

- Analysis based on mixed model is valid only if data MAR and this may be questionable in many instances.
- Alternative, plausible dropout models can give markedly different $\hat{\tau}$s
- Is all this statistical wizardry necessary?

Concluding comments

- Analysis based on mixed model is valid only if data MAR and this may be questionable in many instances.
- Alternative, plausible dropout models can give markedly different $\hat{\tau}$s
- Is all this statistical wizardry necessary?
- Aim is to compare two analgesics

Concluding comments

- Analysis based on mixed model is valid only if data MAR and this may be questionable in many instances.
- Alternative, plausible dropout models can give markedly different $\hat{\tau}$s
- Is all this statistical wizardry necessary?
- Aim is to compare two analgesics
- Only if patient can tolerate both agents is the comparison relevant

Concluding comments

- Analysis based on mixed model is valid only if data MAR and this may be questionable in many instances.
- Alternative, plausible dropout models can give markedly different $\hat{\tau}$s
- Is all this statistical wizardry necessary?
- Aim is to compare two analgesics
- Only if patient can tolerate both agents is the comparison relevant
- So relevant comparison arises only from patients who provide data in both periods

Concluding comments

- Analysis based on mixed model is valid only if data MAR and this may be questionable in many instances.
- Alternative, plausible dropout models can give markedly different $\hat{\tau}$s
- Is all this statistical wizardry necessary?
- Aim is to compare two analgesics
- Only if patient can tolerate both agents is the comparison relevant
- So relevant comparison arises only from patients who provide data in both periods
- That is, use a complete case analysis (fixed patient effects)