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A Statistical Look at Treatment of Negative Symptoms: Pseudospecificity or Complex Effects

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Topics Addressed

- **Does treatment of negative symptoms fit the description for pseudospecificity?**
- **How can data from drugs with complex treatment effects be quantified and evaluated, with a focus on the relationships between the complex effects?**

What is Pseudospecificity?

- **A pseudospecific indication or claim is defined as an artificially narrow claim accompanied by a lack of support for that narrow focus.**
- **One potentially pseudospecific claim is for the treatment of a symptom or symptom cluster of a recognized syndrome.**
  - **Example: Claim for "treatment of delusions associated with schizophrenia"**

Treatment for Negative Symptoms May Not Be "Pseudospecific"

- **If it is shown that current drugs do not adequately treat one aspect of an illness, but the new drug does, then a reasonable basis exists for a narrow focus claim and it is not a "pseudospecific" effect.**
  - **If new treatments address these outstanding issues the effect would not be "pseudospecific".**
  - **Example: NSAIDs may treat some or all of the symptoms of fever, inflammation, or pain.**
  - **There is much unmet clinical need in the treatment of negative symptoms.**

Management of Complex Treatment Effects

- If a therapeutic agent treats multiple aspects of an illness, how can we interpret results from clinical trials?
- Specifically, how can data from a drug intended to treat negative symptoms be interpreted, knowing that it might also affect positive symptoms, extrapyramidal symptoms, depression etc?

Quantify Complex Actions

Some questions of interest

- At the group level, how could we contrast the effect on negative symptoms (NegSx) with that on positive symptoms (PosSx)?
- At the individual level, how does change in NegSx correlate with that in PosSx?
- How much of the treatment effect on NegSx could be explained by effects on other symptoms?

Metric Objectives

- **Measuring relationships between treatment effect on negative symptoms and those on other symptoms**
  - **Determine relative effect at the group level.**
  - **Examine correlation between change in negative symptoms score and those in other symptoms scores at the individual level.**
- **Estimating % of treatment effect on negative symptoms that can be explained by the combined effects on other endpoints.**

Relative Effect (RE)

$$RE = \frac{\text{Effect on NegSx / SD of NegSx}}{\text{Effect on PosSx / SD of PosSx}}$$

- **RE = 1 suggests perfect relationship between the effect on NegSx and that on PosSx at the group level.**

At Individual Level

Correlation (NegSx, PosSx | Treatment)

- **Correlation =1 implies a perfect relation between the effect on NegSx and that on PosSx at the individual level.**
- **In the surrogate marker language, RE = 1 and Correlation = 1 fulfill a perfect surrogate.**

Numerical Example

- 50 patients in the drug group, 52 in the placebo group.
- Inclusion criteria
  - In an acute exacerbated state of schizophrenia
  - PANSS score at least 60 at screening and baseline
  - A score ≥ 4 in at ≥ 2 of 5 items on positive subscale
  - A CGI ≥ 4 at baseline
- Endpoints
  - Negative symptoms: PANSS Neg. symptoms scale (NegSx)
  - Positive symptoms: PANSS Pos. symptoms scale (PosSx)
  - EPS: Simpson-Angus Rating scale (SARS)
  - Depression: Calgary depression scale (CDS)

Results on Relative Effect

Endpoint	Trt Effect	Effect / SD	RE
NegSx	1.302	0.214	
PosSx	1.515	0.217	0.986
SARS (EPS)	0.038	0.027	7.926
CDS (Depression)	0.721	0.181	1.182

Results on Correlation

Endpoint	Correlation	
PosSx	0.650	Medium
SARS (EPS)	0.318	Low
CDS (Depression)	0.751	High

% of Effect Explained

$$NegSx = \beta_1 Treatment + error$$

$$NegSx = \beta_2 Treatment + \beta_p PosSx + \beta_e SARS + \beta_d CDS + error$$

- Effect unexplained (β_2 / β_1) =

  0.645 / 1.302 = 0.495 (49.5%)

- Effect explained (1 - β_2 / β_1)

  100% – 49.5% = 0.505 (50.5%)

- Approximately 50% of the treatment effect on NegSx can not be explained by the combined effect on PosSx, SARS, and CDS.

Across Studies

- **Treatment has effect on NegSx that can not be explained by effects on PosSx, SARS, and CDS. Does this mean negative symptoms possess a unique feature not covered by other symptoms scales?**
- **What if the % of effect not explained are similar across studies that have similar designs and inclusion/exclusion criteria?**
- **Does the above provide support to justify a claim for negative symptoms?**

To Limit Confounding

- **Use inclusion/exclusion criteria (baseline)**
  - **Considering lower limits for negative symptoms**
  - **Considering upper limits for positive symptoms**
  - **Considering upper limits for depression**
- **These selection criteria could result in a large effect on NegSx relative to other symptoms, facilitating the interpretation of the NegSx effect.**
- **% of effect explained could still be useful even in this case.**

Cautions

- **Statistical analyses are based on the correlations among endpoints. They cannot be used to draw inference on causal effects.**
- **For example, we cannot say that the change in NegSx is caused by the change in CDS even if the changes are highly correlated.**

Conclusions

- **Statistical methods can be used to contrast and explain treatment effects on various endpoints and their relationships. These methods help explain complex actions.**
- **The quantitative methods could help provide support to justify a claim for negative symptoms.**
- **With sufficient scientific and statistical support, a negative symptoms claim is not pseudospecific.**

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