# REPORTING ADVERSE EVENT DATA FROM CLINICAL TRIALS OF AN ANTIPSYCHOTIC AGENT

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## INTRODUCTION

- Safety data collection in many clinical trials of antipsychotic agents is commonly standardized, and includes spontaneous patient-reported adverse events (AEs), clinical laboratory tests, electrocardiograms, vital signs, suicide-related evaluations, and extrapyramidal symptoms (EPS)
- Clinical trial safety data are generally not as rigorously analyzed as efficacy data because of the frequent lack of well-defined prespecified hypotheses, multiplicity issues, lack of power, and high dropout rates
- AE reports are a common focus. A large number of randomized controlled trials are efficacy trials by design and are not powered to look at AEs, especially rare AEs
  - However, regulators and clinicians have focused on AEs of particular concern, such as EPS, prolactin, and metabolic-related AEs
- The usual method for statistical evaluation and interpretation of AE reports is a tabular format highlighting counts and percentages of patients experiencing events
  - This approach leaves many safety questions unanswered, such as onset after initiation of treatment, duration of occurrence, frequency, severity, and predictors of risk
- Alternatively, common analytic methods and graphic displays can help communicate more concisely and effectively than incidence tables
  - These methods are proposed for exploratory data analysis or signal detection, focusing on AEs that may result from the mechanism of action or AEs of particular concern
- Methods presented here are suggested to confirm and further evaluate known safety signals and to help identify new safety signals

## METHODS

### *Description of the Methodology*[1,2]

#### *Dot Plots of Rates and Relative Risk*

- A 2-panel display is presented for the AEs most frequently occurring (eg, ≥5%) in the active study group
  - First panel displays incidence by treatment group
  - Second panel displays the relative risk (RR) and its 95% confidence interval (CI) of an event in the active group relative to the placebo group, similar to a 2 x 2 table
  - CIs showing ±1 standard error (SE) for RR may be preferred, as this provides information about the AE distribution in the population, if the display is not for regulatory purposes
  - Many clinical trials are powered only for efficacy outcomes. This, in turn, necessitates a discussion of sample size inadequacy (a type 2 error) to identify harm. The statistical power for nonsignificant tests should be considered when interpreting results

### *Hazard Function*

- Of particular interest is the onset of each AE relative to treatment start, specifically when identifying whether the risk for an AE changes over time
- Time-to-event plots for AEs allow for risk evaluation as a function of time
  - Kaplan-Meier plots of the cumulative incidence of AEs of interest could be provided by treatment group (not shown here)
  - Cumulative risk may be similar between treatments at the end of study period, but the instantaneous risk between the treatments may be different
  - Life-table estimates of the hazard function for each treatment group were generated and then displayed graphically with SEs for the EPS-related AEs. Based on weekly intervals, the hazard displayed is for the midpoint of each interval
  - Provides a more direct assessment of evolving risk of the first AE occurring at any given time, while making appropriate adjustments as patients withdraw from the trial
  - Assists the physician in anticipating specific safety events after the initiation of therapy
  - Life-table approach assumes that all censoring occurs at the midpoint of an interval; therefore, the assumed number of censored patients to be at risk for half of the interval is multiplied by 0.5

### *Adverse Event Analysis of Antipsychotic Studies*

#### *Studies*

- Two databases from randomized, double-blind, placebo-controlled studies of oral antipsychotic agents were identified
  - Three 6-week studies in schizophrenia[3-5]
  - Two 6-week studies in schizoaffective disorder[6,7]

#### *Adverse Event Profiling*

- Most common AE incidence rates (≥5%, either group) were evaluated using dot plot of incidence and RR with corresponding 95% CIs of RR
- When numerous CIs are computed, multiplicity issues should be addressed, particularly if there is interest in assessing the statistical significance of RR differences
  - However, because the primary goal of this display is to highlight potential signals by providing an estimate of treatment effect and the precision of that estimate, no adjustments were made for multiplicity
- Life-table estimates of the hazard function for each treatment group were computed for time to first EPS-related AE

## RESULTS

### *Patients With Schizophrenia*

- Higher incidences of AEs with antipsychotic treatment versus placebo were extrapyramidal disorder, tachycardia, akathisia, sinus tachycardia, and headache (**Figure 1**)
- Higher risk with antipsychotic treatment versus placebo was observed for extrapyramidal disorder (RR = 2.40; 95% CI = 1.14, 5.04) and tachycardia (RR = 2.34; 95% CI = 1.21, 4.53)
- Although the risk of first EPS-related AE decreased over time for both interventions, antipsychotic treatment had a higher risk for EPS-related AEs than placebo during earlier time points (**Figure 2**)

**Figure 1. Most frequent on-therapy adverse events (≥5%, either group) for subjects with schizophrenia sorted by relative risk.**

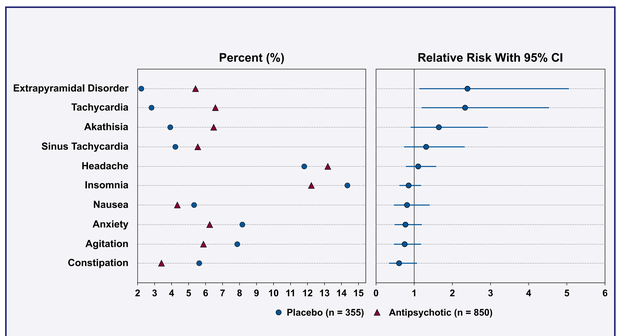
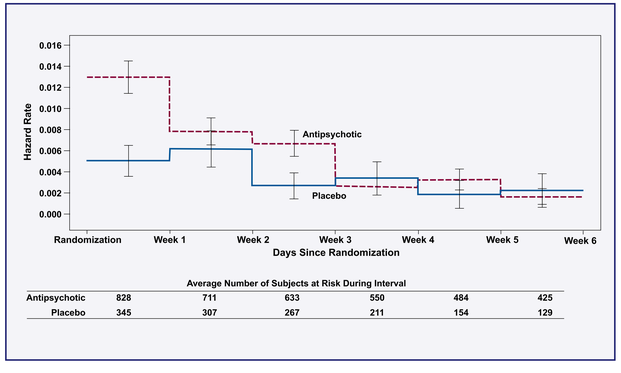


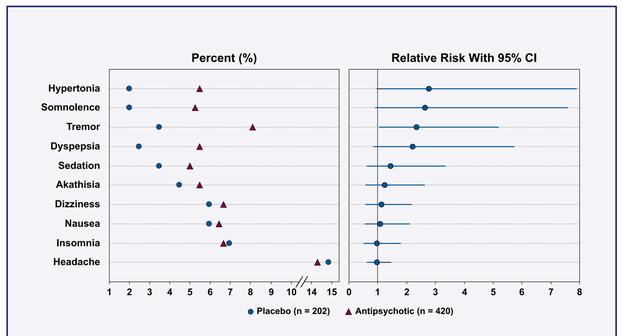

**Figure 2. Hazard function for EPS-related adverse events over time for subjects with schizophrenia.**




### *Patients With Schizoaffective Disorder*

- Higher incidences of AEs with antipsychotic treatment versus placebo were hypertonia, somnolence, tremor, dyspepsia, sedation, akathisia, dizziness, and nausea (**Figure 3**)
- Higher risk with antipsychotic treatment versus placebo was observed for tremor (RR = 2.34; 95% CI = 1.05, 5.18)
- Although the risk of first EPS-related AE decreased over time for both interventions, antipsychotic treatment had a higher risk for EPS-related AEs than placebo during later time points (**Figure 4**)

**Figure 3. Most frequent on-therapy adverse events (≥5%, either group) for subjects with schizoaffective disorder sorted by relative risk.**

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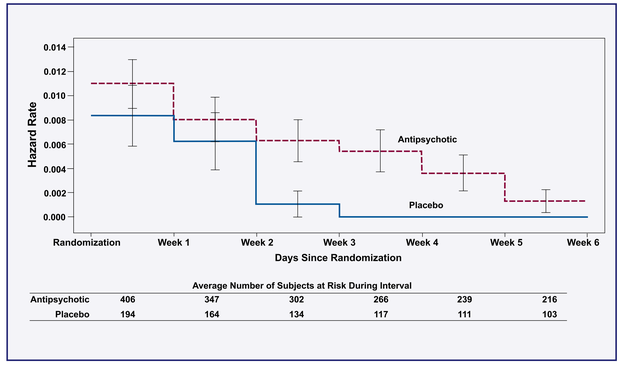


## DISCUSSION AND LIMITATIONS

- Many randomized controlled trials are of short duration, include small numbers of patients, and select patients lacking comorbid conditions
- Although these methods begin to address some limitations in the current analysis of AE data, patient level case-by-case review may be preferable to aggregate summaries of patient data
  - However, this is not easily interpretable in analyses of large clinical trial databases
- In this exploratory analysis, RR with active treatment versus placebo was considered significant when the 95% CI did not cross 1. However, some RRs were greater with active treatment and the 95% CIs just crossed 1; these AEs may also warrant further investigation
- The possible overlap among various AE terms may limit the interpretation of any related analysis
- Time-to-event methodology offers clinically relevant information but can be problematic when data are collected in infrequent intervals, resulting in inadequate precision in the AE onset date
  - These data should be viewed as interval censored and interpreted carefully
- Although the hazard rates were based on the first EPS-related event for a given subject, each subject could have more than 1 event. The frequency of events, their duration, severity, and relationship to trial medication also are relevant to understanding safety data
- Standards for identifying "events of clinical concern/interest/significance" have not been established. Consequently, there is currently no universal way to approach interpretation of this type of analysis

## CONCLUSIONS

- Established methodologies and graphic displays can be used in an exploratory setting to help identify emerging safety signals or, in a more confirmatory setting, to help explain known safety issues
- The use of these analytic approaches may provide the clinician with additional insights into interpreting safety data and may facilitate translation of these data into a clinical setting as more personalized approaches to clinical treatment are developed

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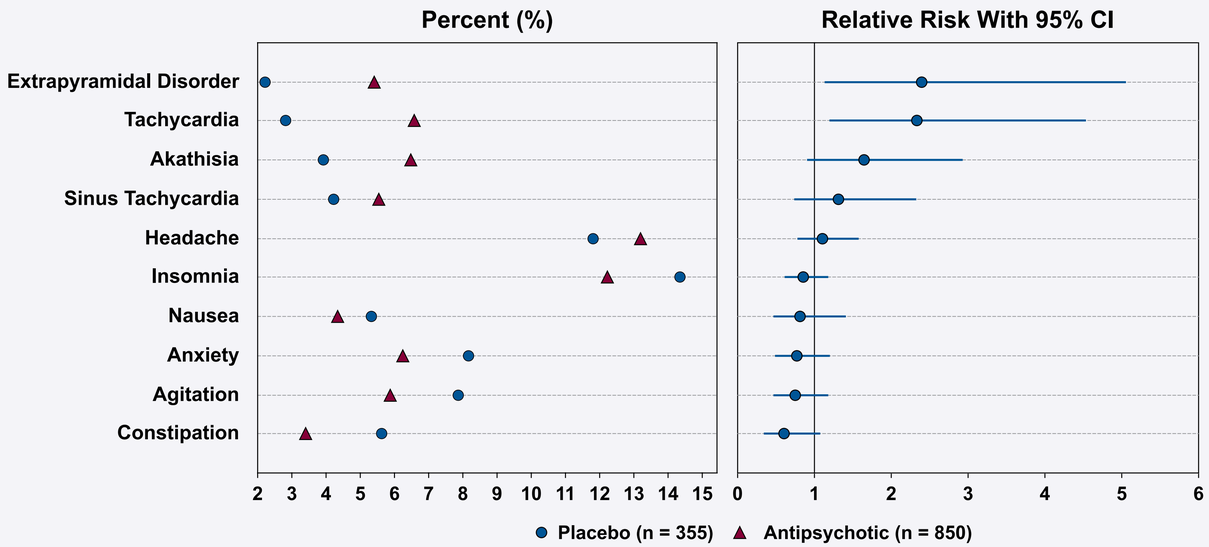


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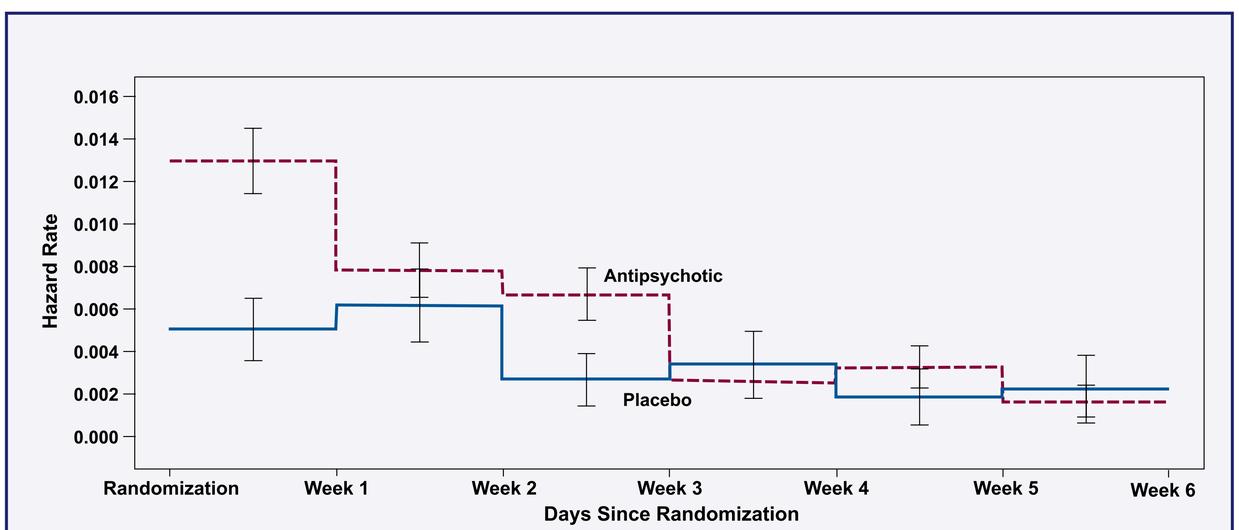
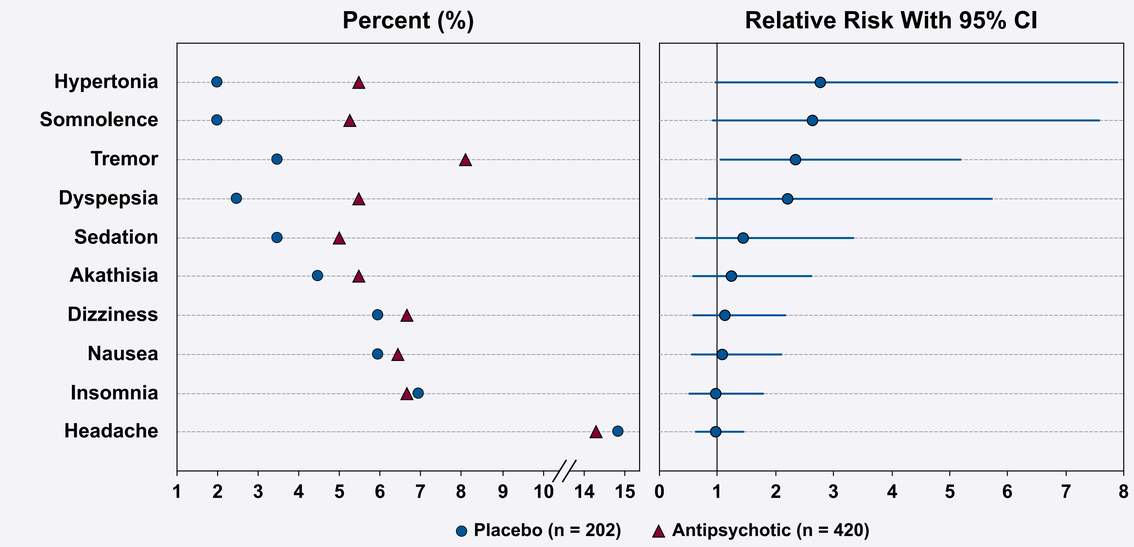



| Average Number of Subjects at Risk During Interval | | | | | | |
|---|---|---|---|---|---|---|
| Antipsychotic | 828 | 711 | 633 | 550 | 484 | 425 |
| Placebo | 345 | 307 | 267 | 211 | 154 | 129 |

## Figure 3. Most frequent on-therapy adverse events (≥5%, either group) for subjects with schizoaffective disorder sorted by relative risk.

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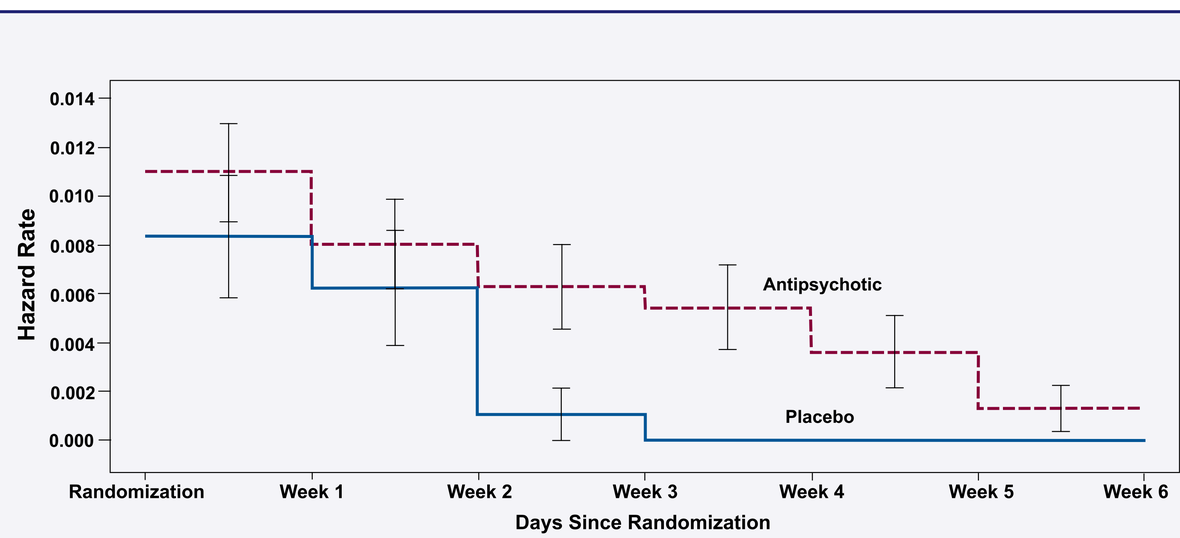


| Average Number of Subjects at Risk During Interval | | | | | | |
|---|---|---|---|---|---|---|
| Antipsychotic | 406 | 347 | 302 | 266 | 239 | 216 |
| Placebo | 194 | 164 | 134 | 117 | 111 | 103 |

# DISCUSSION AND LIMITATIONS

- Many randomized controlled trials are of short duration, include small numbers of patients, and select patients lacking comorbid conditions
- Although these methods begin to address some limitations in the current analysis of AE data, patient level case-by-case review may be preferable to aggregate summaries of patient data
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