Use of existing datasets to inform regulatory decision making

Valentina Mantua, M.D., PhD.
Division of Psychiatry

ISCTM 19th Annual Meeting
February15-17, 2023
Grand Hyatt, Washington DC

Disclaimer for FDA speakers

- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Outline

- ## What we have
  - Customized datasets
    - Example 1: Optimization of schizophrenia trials
    - Example 2: Antipsychotics extrapolation of efficacy from adults to pediatric subjects

- ## What we don't have
  - What we could learn: the FXS example
  - How external stakeholders engage with the FDA

What we have

- Clinical trial data submitted by sponsors
- Most data from phase 3 studies
- One or two exceptions of studies from the NIH
- Includes some data from negative studies

Customized datasets

- Customized databases can be built based on the research question

- Sometimes we can reach out to Sponsors to provide more data relevant to the use of the database

- Examples:
  - Schizophrenia
  - Bipolar Disorder
  - Major Depressive Disorder

Type of data

- Longitudinal rating scales item scores, subscale scores
- AEs
- Dosing
- Limited demographic information (age, sex, gender etc.), not for all studies
- Limited medical history information (e.g., history of schizophrenia), not for all studies

Schizophrenia Database

Size	Products	Previous Use	Future Use?
9,778 Adults 2,122 Pediatrics	12 Atypical antipsychotics	• Extrapolation of efficacy from adults to adolescents to support expedite drug development pathways • Development of disease-drug-trial models to establish extrapolation that could be utilized for future trial simulation • Publications: 4	• Guidance on extrapolation • Utilizing psychometrics to improve PANSS measure

Bipolar Disorder Database

Size	Products	Previous Use	Future Use?
6,781 Adults 2,087 Pediatrics	9 Atypical antipsychotics 1 mood stabilizer	• Extrapolation of efficacy from adults to adolescents to support expedite drug development pathways • Development of disease-drug-trial models to establish extrapolation that could be utilized for future trial simulation • Publications: 2	• Guidance on extrapolation

Major Depressive Disorder Database

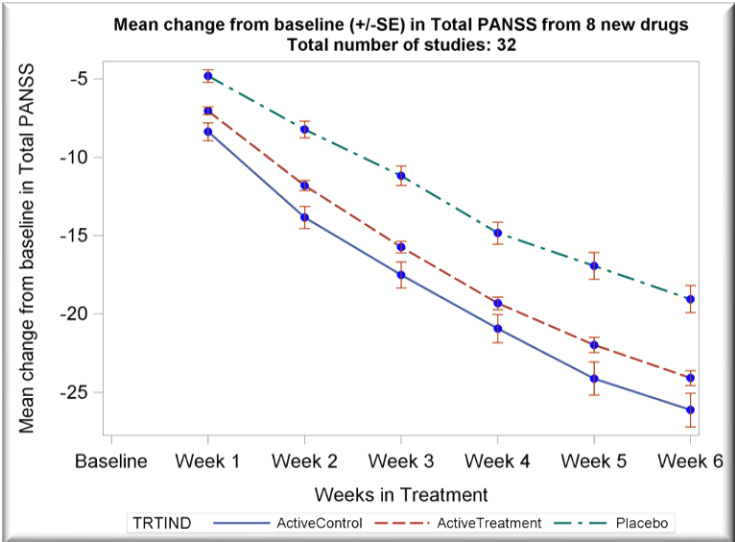| Size	Products	Previous Use	Future Use?
24,860 Adults 6,319 Pediatrics	11 Antidepressants including SSRIs, SNRIs, and other MoAs	• Evaluated the use of suicidality assessment in adult and pediatric trials to inform pending Suicidal Ideation and Behavior Guidance	• Investigate placebo response in trials in pediatrics to inform future development programs

Databases in Development

- ADHD

Schizophrenia database: Example 1

- When it was first created, the schizophrenia database consisted of clinical trial data from 32 PC and RCTs of 8 atypical antipsychotic drugs approved by the FDA between January 2001 and December 2015.

- The database included total and individual PANSS item ratings, demographic characteristics, disposition, and AEs.

- We leveraged knowledge from the schizophrenia database to assess the feasibility of modifying elements of trial design to optimize schizophrenia studies.

Assess the feasibility of shortening acute schizophrenia trials

Mean change from baseline (+/-SE) in Total PANSS from 8 new drugs
Total number of studies: 32

Comparison of week 4 outcome to week 6 outcome
**Concordance Rate = 93%**

Longitudinal mean change from baseline in total PANSS across all trials
Treatment discrimination from placebo evident in change from baseline-total PANSS from **week 2 onwards**

Week	Concordance Rate	Discordance Rate
Week 1 vs Week 6	68%	32%
Week 2 vs Week 6	74%	26%
Week 3 vs Week 6	83%	17%
Week 4 vs Week 6	93% (80/86)	7% (6/86) [False negatives at week 4]

Adverse event counts captured adequately by week 4 and similar as compared to week 6 counts
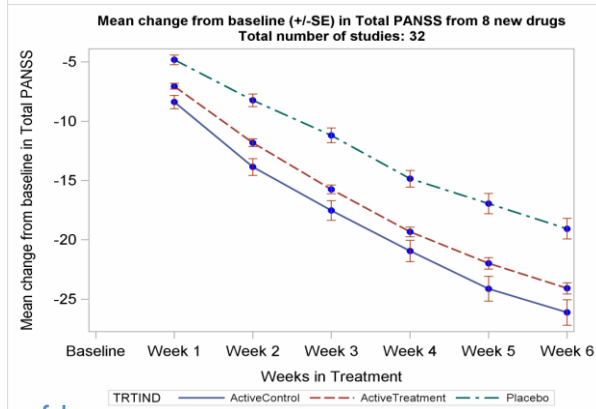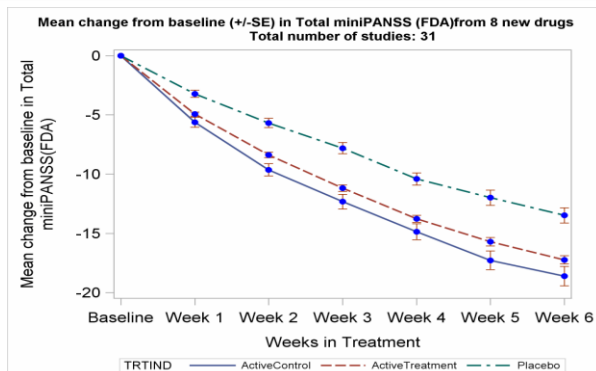
Week 6
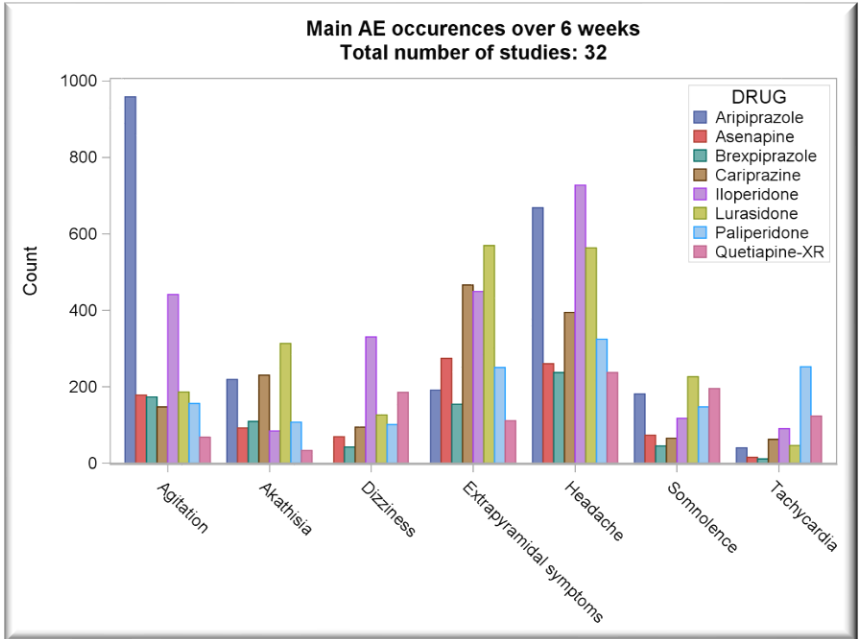
Week 4
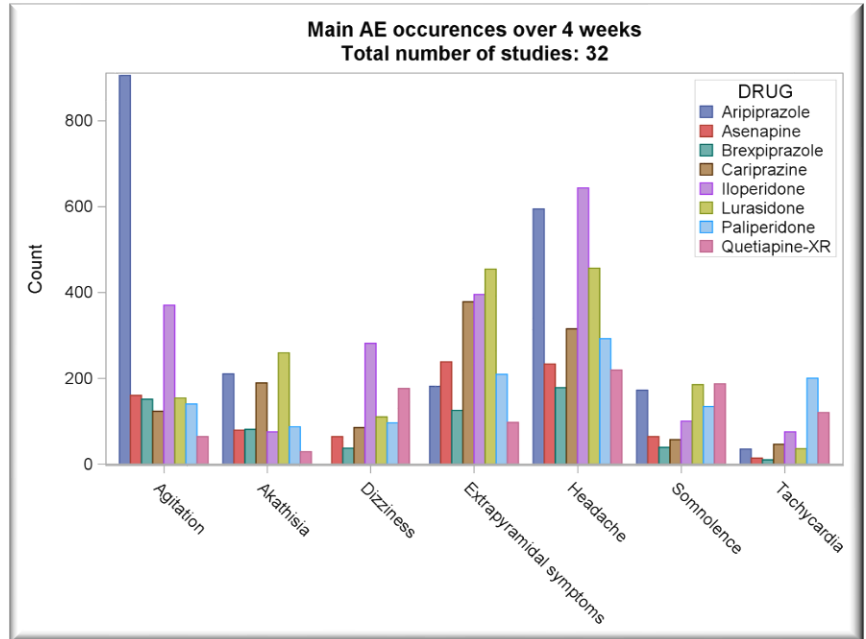
Evaluate modified (shortened) PANSS and shorter duration as an alternate endpoint

Mean change from baseline (+/-SE) in Total miniPANSS (FDA) from 8 new drugs
Total number of studies: 31

Mean change from baseline (+/-SE) in Total PANSS from 8 new drugs
Total number of studies: 32

Derivation of a 19-item PANSS (consisting of sensitive items) using Item Response Theory methodology.

Change from baseline in Modified PANSS at 4 weeks and 6 weeks compared with total PANSS at 6 weeks

Concordance rates for week 4 trial (modified PANSS) outcomes to week 6 outcomes (Total PANSS) was **93%**

Sample size estimates using modified PANSS at 4 weeks **similar** to that of 6 week trial using Total PANSS

Younis et al., JAMA Psychiatry, 2020

Schizophrenia database: Example 2

- Known challenges in conducting clinical trial in the pediatric population include difficulties in recruitment, use of a placebo arm and high placebo response.

- Extrapolation could avoid unnecessary studies in the target population, thereby increasing the efficiency of development.

- We leveraged knowledge from the schizophrenia database to support the use of extrapolation of efficacy between adults and pediatric subjects when developing an antipsychotic with a known mechanism of action

- This approach was based on the original innovative approach successfully conducted and implemented for pediatric partial onset seizures.

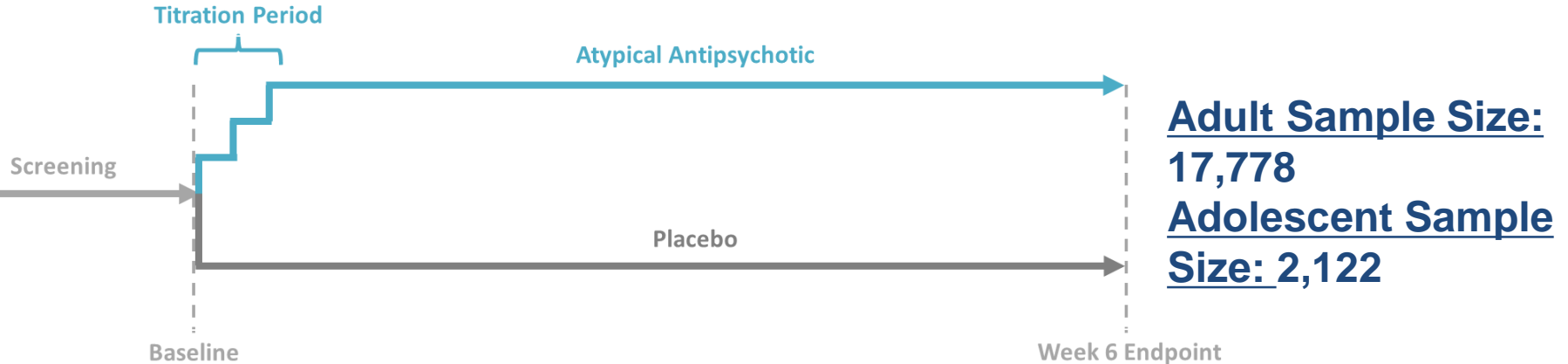# Leveraging Current Knowledge of Antipsychotic Use in Adults and Adolescents
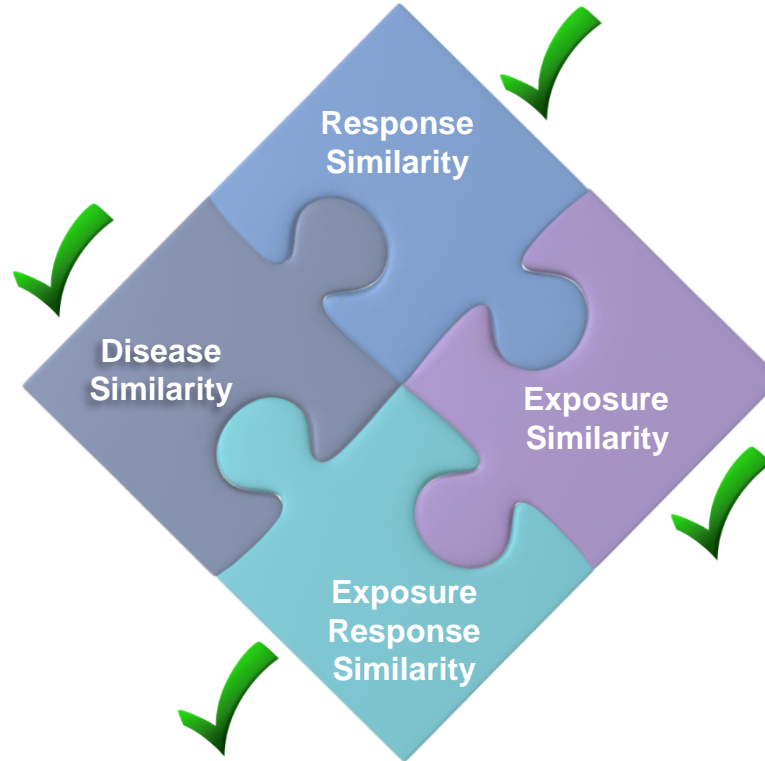
9 Adult Programs

7 Adolescent Programs

2 Adolescent Negative Trials

Titration Period

Atypical Antipsychotic

Screening

Placebo

Baseline

Week 6 Endpoint

Adult Sample Size: 17,778
Adolescent Sample Size: 2,122

Substantial Evidence to Support Full Extrapolation of Efficacy from Adults to Adolescents

Publications

Clinical Pharmacology & Therapeutics

Article | 🔓 Full Access

A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials

Shamir N. Kalaria, Hao Zhu ✉, Tiffany R. Farchione, Mitchell V. Mathis, Mathangi Gopalakrishnan, Ramana Uppoor, Mehul Mehta, Islam Younis

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Pharmacodynamics | 🔓 Full Access

Assessment of Similarity in Antipsychotic Exposure-Response Relationships in Clinical Trials Between Adults and Adolescents With Acute Exacerbation of Schizophrenia

Shamir N. Kalaria PharmD, Tiffany R. Farchione MD, Mitchell V. Mathis MD, Mathangi Gopalakrishnan PhD, Islam Younis PhD, Ramana Uppoor PhD … See all authors ⌄

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Supplement Article | 🔓 Full Access

Extrapolation of Efficacy and Dose Selection in Pediatrics: A Case Example of Atypical Antipsychotics in Adolescents With Schizophrenia and Bipolar I Disorder
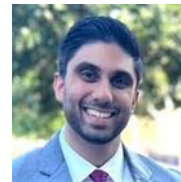
Shamir N. Kalaria PharmD, PhD, Tiffany R. Farchione MD, Ramana Uppoor PhD, Mehul Mehta PhD, Yaning Wang PhD, Hao Zhu PhD ✉

Shamir N Kalaria, PharmD PhD

Similar changes in disease symptomology during an acute exacerbation

FDA

Clinical Pharmacology & Therapeutics

Article | 🔓 Full Access

A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials

Shamir N. Kalaria, Hao Zhu ✉ Tiffany R. Farchione, Mitchell V. Mathis, Mathangi Gopalakrishnan, Ramana Uppoor, Mehul Mehta, Islam Younis

A placebo response-dropout model was developed to describe the time course of total PANSS scores in adults and adolescents.

The model in both populations suggested that patients with higher baseline scores exhibited a greater absolute reduction from baseline.

Higher baseline total PANSS, enrollment in US trials, and increases or small improvements in total PANSS were found to be predictors of dropout in both populations.

Simulated adolescent data using the final adult placebo response model resembled the observed adolescent data.

Similarity in exposure-response for efficacy

The Journal of
Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Pharmacodynamics | 🔓 Full Access

Assessment of Similarity in Antipsychotic Exposure-Response Relationships in Clinical Trials Between Adults and Adolescents With Acute Exacerbation of Schizophrenia

Shamir N. Kalaria PharmD, Tiffany R. Farchione MD, Mitchell V. Mathis MD,
Mathangi Gopalakrishnan PhD, Islam Younis PhD, Ramana Uppoor PhD ... See all authors ⌄

- The developed disease–drug trial models adequately predicted the longitudinal trend in total PANSS scores in both adults and adolescents
- Maximum drug effect was similar between the two populations and was estimated to be between a range of 5% to 11% in adults and 5% to 7% in adolescents.
- Half maximal effective concentration parameter estimates also indicated similar exposure-response relationships in adults and adolescents across 4 antipsychotics.
- Simulated adolescent data using final model parameter estimates from the adult model were in agreement with adolescent observations.
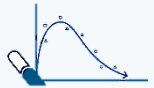
Extrapolation of Efficacy from Adults to Pediatrics
January 2020 General Advice Letter

FDA
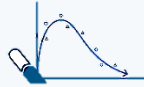

Drugs with Similar MoA
Extrapolation of Efficacy

- Pharmacokinetic Study
- Open Label Safety Study

Drugs with New MoA
Inclusion of Pediatrics in Adult Registration Trials

- Pharmacokinetic Study
- Placebo-Control, Parallel Fixed Dose Design
- Open Label Safety Study

*Juvenile animal studies needed for bipolar I indications less than 12 years of age

**Open label safety studies could concurrently enroll patients with bipolar I and schizophrenia adult and pediatric patients

Approvals based on current policy:
Brexpiprazole

What we typically *don't* have

- Data from research INDs because they are not intended for filing

- Data from negative programs, which don't make it to filing

"The greatest teacher, failure is."

Yoda

What we could learn
A challenging area of development: FXS

- There is no approved treatment for Fragile X syndrome (FXS)
- Despite the rarity of the disease, many late-stage clinical trials were conducted exploring drugs with different targets
- Despite FXS being a genetic disorder, the phenotype is very heterogeneous, and population stratification in clinical trials is challenging
- Because FXS is a neurodevelopmental disorder, it is unclear what is the optimal intervention window and what could be an adequate length of clinical studies to observe meaningful change.
- Other challenges include the need for fit-for-purpose outcome measures validated across age groups and a range of abilities

What we could learn

Fragile X Syndrome late-stage clinical studies

FDA

Study	Drug	Design	Population	Duration	Outcome
Berry-Kravis et al., 2020	Trofinetide, analogue of the amino-terminal tripeptide of insulin-like growth factor 1 (IGF-1[1-3])	Phase 2, PC, DB	Males FSX, age: 12 to 41 years	14 days placebo lead-in, 28 days DB	Fragile X syndrome rating scale (FXSRS), fragile X syndrome domain-specific concerns (FXSDSC) visual analog scale (VAS).
Youssef et al., 2018	Basimglurant, mGluR5 antagonist	Phase 2, R, PC, DB	N=185 Stratified by sex and age group (adolescents 14 to 17 years old **vs** adults 18 to 50 years old)	12-week DB	Anxiety Depression and Mood Scale (ADAMS)
Berry-Kravis et al., 2021	BPN14770, PDE4D allosteric inhibitor	Phase 2 R, DB, cross-over	N=30 Adult males (18 to 41 years).	12 weeks two-period crossover no washout	NIH-Toolbox Cognition Battery, KiTAP, ABC. ADAMS, Vineland-3
Berry-Kravis et al., 2022	YN002, transdermal cannabidiol gel	Phase 3 R, PC, DB	pediatric and adolescent patients with FXS aged 3 to < 18 years	2-week, single-blind placebo run-in, 12-week DB	ABC-C (FXS)

How do we collaborate with external stakeholders?

Extramural Research

- FDA's Broad Agency Announcement (BAA) program
- FDA's Centers for Excellence in Regulatory Science and Innovation (CERSI) program. https://www.fda.gov/science-research/advancing-regulatory-science/centers-excellence-regulatory-science-and-innovation-cersis
- Public-private partnerships (PPPs) and consortia to provide FDA's perspective on multi-stakeholder driven scientific research.

Intramural Research

- The Oak Ridge Institute for Science and Education (ORISE) fellowship
- Translational Science Interagency Fellowship (TSIF).

Useful links

FDA

OND Research

https://www.fda.gov/science-research/advancing-regulatory-science/centers-excellence-regulatory-science-and-innovation-cersis