Past Data Mining Efforts and Challenges

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Use of Existing Data to Inform and Speed Development of Personalized Medicine for CNS Disorders
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Disclaimer

This presentation reflects the views of the speaker and may not be understood or quoted as being made on behalf or reflecting the position of the agencies or organizations with which the speaker was/is affiliated.

Of note, this speaker contributed to part of the work which would be covered in this presentation, while she was employed with the US Food and Drug Administration. Currently, the speaker is an employee of Neurocrine Biosciences, Inc., San Diego, CA.

Overview

- FDA regulation defines substantial evidence as evidence consisting of “adequate and well controlled investigations”
  - Interpreted ordinarily to require two positive randomized controlled clinical trials

- Holistic approach in review of clinical efficacy and safety data from CNS trials
  - Data from both positive studies and negative/failed studies in NDA packages submitted
  - Maintenance efficacy: Mostly post approval in the US

Past Data Mining Efforts

- Concerns:

  Increase in placebo response and decline in treatment effect over time in psychiatry trials

  The implications of increasing conduct of trials outside the US and the applicability of data from non-US sites in the US population

Past Efforts: Exploratory Analyses on Data from Major Depressive Disorder (MDD) and Schizophrenia Trials Submitted to US FDA

Data Level

- Trial-level data
- Subject-level data

Endpoint Measures

- MDD: Hamilton Depression Rating Scale (HAMD-17) Total Score
- Schizophrenia: Positive and Negative Syndrome Scale (PANSS)

Summary of findings along with the processes and challenges experienced in these past data mining effort would be shared.

MDD and Schizophrenia Past Data Mining Efforts

Original Data Mining Effort by Clinical and Statistical Team

- MDD began in 2008
- Schizophrenia in 2009

MDD Trial Level Data

- 81 randomized double-blind placebo-controlled, short-term trials (1983-2008)
- N=21,611
- 81% enrolled in US sites
- 87% Whites, 61% Females, Mean age 42.8 yrs
- Mean baseline HAMD score ~24; Dropout rate ~33%
- Explored treatment effect and trial success rates
  - based on question raised about the applicability of data from non-US sites to the US population

Ref: Khin NA et al. J Clin Psychiatry. 2011 Apr;72(4):464-72.

MDD Trial Level Data: US vs. Non-US

- Both placebo and drug groups from non-US (-9.5, -12.5) tended to be larger change from baseline in HAMD-17 than those observed in the US (-8, -10.4)

	Placebo	Drug
Non-US	-9.5 (-4.8, -13.8)	-12.5 (-6.3, -15.4)
US	-8 (-3.7,-12.4)	-10.4 (-5.3, -16.1)

- Treatment effect (drug-placebo difference) on average about the same for US and non-US (~-2.5)
- Over the 25-year period
  - increasing placebo response and declining treatment effect (moving from ~-3 to -2 point difference in HAMD)
  - trial success rates 55% (1983-1995; 27/49) vs 50% (1995-2008; 16/32)

Ref: Khin NA et al. J Clin Psychiatry. 2011 Apr;72(4):464-72.

MDD Trial Level Data: Fixed vs. Flexible Dose

- 65% of the MDD trials utilized a flexible dosing regimen
- Placebo responses (-8 HAMD units) were similar; Treatment effect was larger for flexible dose studies (-2.9) as compared to fixed dose (-2)
    - Used data from Arms vs. Trials in these calculation
- Slightly higher trial success rate for fixed dose (57%) vs flex (50%)
    - Used numbers of trials instead of numbers of treatment arms as denominator in success rate calculation

Ref: Khin NA et al. J Clin Psychiatry. 2011 Apr;72(4):464-7; Khan et al., Fava et al.

MDD Subject Level Data: Responder Definition

- Initial subject level dataset built in 2012
- 24 randomized double-blind placebo-controlled trials
- N~7400

Responder Definition:

1) 50% change from baseline – Use of % change alone is sufficient
2) HAMD total cut off score also needed? – Not necessarily
3) Any excursions allowed? – Yes but pre-define

Optimal Trial Duration?

Time to Discontinuation as potential alternate primary end point

Ref: Khin NA, NCDEU Annual Meeting Regulatory Session, May 2013

MDD Subject Level Data: Mitigation of High Dropouts

- Continued to built database from initial 24 RCT to 45 MDD trials (1997-2014) both subject and item level data
- N=16,073 (n=5666 placebo)
- 83% Whites, 63% Females, Mean age 43 yrs
- Mean baseline HAMD score ~23; dropout rate ~20%
- Trial duration 6-10 weeks (majority n=35 were 8-week trials)

Question on design approaches raised:

- Shortening Trial Duration?

  May be shortened to 6 weeks (provided drug-placebo difference on total HAMD-17 reaches 2 units at week 6)
- Time to treatment discontinuation as an alternative primary endpoint?

  Not supportive

Ref: Zhong J et al, Contemp Clin Trials. 2018 Feb; 65:69-75.

MDD Maintenance Trial Data: Randomized Withdrawal

- Design: Open-label response stabilization period followed by double-blind randomized withdrawal
- Endpoint: Time to relapse or Relapse rate
- Trial level data from 15 trials (1987-2012)
  - Subject Disposition: 89% Whites, 68% Females, mean age 43 yrs
  - Average number of subjects per study (N=554)
  - Mean HAMD score at baseline prior to open label treatment 23.3; at randomization 9.4
  - Response and relapse criteria: Varied among studies
  - Stabilization period: Varied
  - Number of relapse events

Ref: Borges S, et.al., J Clin Psychiatry. 2014 Mar;75(3):205-14.

MDD Maintenance Trial Data: Randomized Withdrawal

- Trial level data from 15 trials
  - Open label phase - mean response rate 52% (range 27-78%)
  - Double-blind randomized withdrawal phase – average 52% reduction in relapse rate (range 29-86%) in drug treatment group compared to placebo

- Subject level data from 14 trials:
  - Produced Kaplan-Meier Curves
  - Randomized treatment
  - Time to Relapse calculation
  - Censoring Time: 2 wk or 4 wk (mean relapse rate minimal change)

Ref: Borges S, et.al., J Clin Psychiatry. 2014 Mar;75(3):205-14.

MDD Sexual Dysfunction Project

- Literature Search
- Database Search
- Regulatory Science Symposium with Stakeholders (including Academia and Industry)
    - Regulatory & Scientific Considerations
- Note: Funding received from FDA Office of Women's Health, Medical Student Summer Internship, ORISE Fellowship

Ref: Kronstein PD et al., J Clin Psychiatry. 2015 Aug;76(8):1050-9. Khin NA et al., J Clin Psychiatry. 2015 Aug;76(8):1060-3.

Schizophrenia Trial Level Data

- 32 randomized double-blind placebo-controlled clinical trials (1991-2009): 11 were MRCT (after 1999)
- N=11,567
- Mean age 39 yrs; Sex 26% Females (40% in MRCT); Mean body weight/BMI: 85 kg/29 kg/m2 (NA) vs 72 kg/25 kg/m2 (MRCT)
- Mean baseline PANSS total score range: 87-100
- Observed increasing placebo responses (-2.3 to -7), stable drug response (-13) and decreasing treatment effect (-10.8 to -6) over time in NA
- Treatment effect decreased as body weight increased in NA
- Overall trial success rate was 78% (~85% to 74%)

Ref: Khin NA et. al., J Clin Psychiatry. 2012 Jun;73(6):856-64; Abbreviation: NA=North America (mostly US & Canada)

Schizophrenia Subject Level Data: MRCT

- 33 Schizophrenia RCT
- N=12,585
- 63.8% from North America
- Empirical Modeling – Potential impact of baseline covariates on treatment effect in MRCT
  - Baseline PANSS total score as one of the most important covariates explaining a treatment effect.
  - Region also played a role in explaining potential treatment effect heterogeneity.
  - When baseline body weight/BMI was considered as a covariate in an empiric model, it alone did not seem to be an important factor in explaining regional difference.

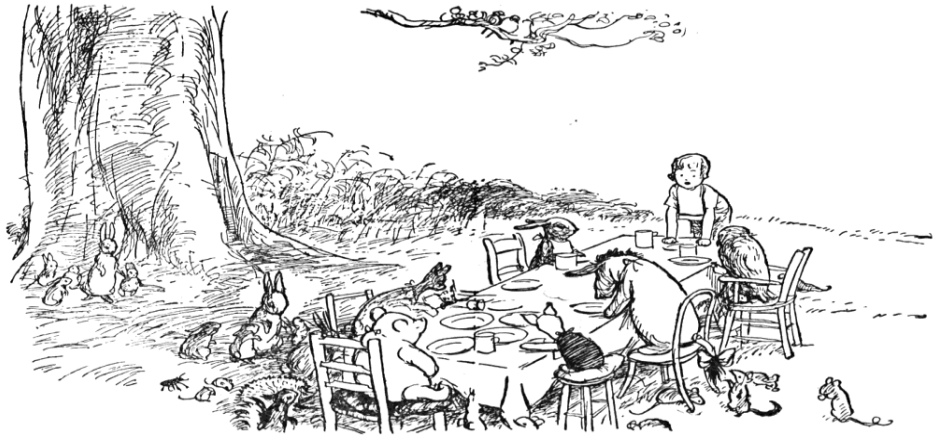
Chen YF et. al., Pharm Stat. 2010 Jul-Sep;9(3):217-29.

Challenges

- Datasets
  - Availability: no subject level data for trials conducted before 1997 & some after 1997 as part of the electronic archives
  - Data elements: **“Data Standard”** issue

- Confidentiality/Privacy

- Resources
  - Human Resource
  - Funding



- Collaboration, Collaboration, Collaboration

Ref: FDA study data for submission to CDER and CBER: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber; CDISC Therapeutic areas user guides https://www.cdisc.org/standards/therapeutic-areas

Additional Data Mining Efforts

Other FDA Groups –

Clinical Pharmacology Team: Schizophrenia

Clinical Psychiatry Safety Team: MDD

Schizophrenia Trial Level Data

- Pre & Post 2009 period (1991-2009; 2009-2015)
- Pre-2009: 32 trials, N = 11,567; Post-2009: 14 trials, N=6434
- Post-2009: predominantly MRCT
- Dropout rates higher (55% in NA; 33% in MRCT)
- Continuing trend of increasing placebo responses (-10.5) and decreasing treatment effect (-5.8) over the 24-year period
- Note: ORISE Fellowship Support

Ref: Gopalakrishnan M et al. J Clin Psychiatry. 2020 Mar 3;81(2):19r12960.

Schizophrenia Subject Level Data: PANSS Items

- 32 Schizophrenia RCT (2001-2015)
- N = 14,219
- Mean age 39 yrs, 51.5% Whites, 69% Males
- Mean baseline total PANSS 94.4
- Dropout 50%, Trial success rate 62%
- Modified PANSS (19 out of 30 PANSS: 5-P, 6-N, 8-G items) as an alternate primary endpoint
- Overall concordance rate between total and modified PANSS at wk 4 – 93%; wk 6 - 97.4%
- Shortening trial duration to 4 weeks – using total PANSS, increase sample size to 502
- Reduction in sample size – 32% (380 => 296) (90% power, model estimated mean CFB ~5 units) if mPANSS is used

Ref: Younis IR, NCDEU Annual Meeting Regulatory Session, May 2013; Younis IR et al., JAMA Psychiatry. 2020 Oct 1;77(10):1064-1071.

Schizophrenia Subject Level Data: PANSS Items

- Same 32 Schizophrenia RCT database
- Feasibility of Modified PANSS (19 out of 30 PANSS: 5-P, 6-N, 8-G items) as an alternate primary endpoint
- Item Response Theory Analysis in identifying the best performance items for modified PANSS
- Individual PANSS item response analysis – Item Characteristic Curves
- Effect size: mPANSS total (0.38); PANSS total (0.33) at wk 6
- Modified PANSS needs psychometric validation
- Note: ORISE Fellowship support

Ref: Gopalakrishnan M et al, Psychiatr Res Clin Pract. 2020 Nov 6;3(1):38-45.

MDD Participant Data Analysis

- Characterization of individual participant level response distribution
- 232 randomized double-blind placebo-controlled trials (1979-2016); included post approval trials
- N=73,388 adults and peds; available subject level data, with observations only for baseline and end of treatment
- 104/232 studies used HAMD; Responses converted to HAMD17 equivalent scores*
- Mean drug and placebo differences 1.75 points (1.63-1.86), ±0.232
- Age, Sex, Baseline Severity and their interactions were included in the model.
- 3 response distributions: 16±4.2 (large), 8.9±7 (non-specific), 1.7±3 (minimal) points
- Treated with a drug more likely to have a large response (24.5% drug vs 9.6%)
- About 15% of participants have a substantial antidepressant effect beyond placebo effect
- Highlighted the need for predictors of meaningful response to drug treatment

Ref: Stone MB, et.al., BMJ. 2022 Aug 2;378:e067606. doi: 10.1136/bmj-2021-067606. PMID: 35918097; PMCID: PMC9344377. *The supplementary materials details score coversion.

Additional Considerations using Existing Data and Beyond

MDD Subject and Item Level Data

- Early Responders
- Onset of Efficacy
- Remission Definition
- HAMD-6 and other sub-scale items (e.g., sleep, anxiety)
- Dose Response

Data Governance

- Therapeutic area specific data standards

Partnership among all stakeholders

- ISCTM working group as a forum for further discussions?
- Others…