FDA Review of Maintenance Trials for Major Depressive Disorder: A 25 Year Perspective

ISCTM

Should the Randomized Withdrawal Design for Relapse Prevention Studies in Mood Disorders be Updated?

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Active Consulting Relationships with Pharmaceutical Companies and NIMH, and Employment Relationship with MGH CTNI

- Part time employee of MGH CTNI
- Consultant to NIMH
- Consultant to Acadia, AgeneBio, Alcobra, Alzheon, Astellas, Avekshan, Axovant, Axsome, Biohaven, Boehringer Ingelheim, Braeburn, Cerecor, CoMentis, DAvia NS, Durect, Edgemont, Fabre Kramer, Forum, Janssen, Lumos, MAPS, Medgenics, Neurocrine, Neurolifesciences, Noven, Pfizer, Praxis, Promentis, Purdue Pharma, Reviva, Rhodes, Sunovion, Teva, Tonix, Transition

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FDA approves antidepressants based on short-term trials

- Patients with MDD based on DSM criteria
- Randomized, double-blind, placebo-controlled design
- 4-8 weeks
- Endpoint: change from baseline on validated rating scale for depression
- About 50% success rate

Maintenance of effect is also clinically important

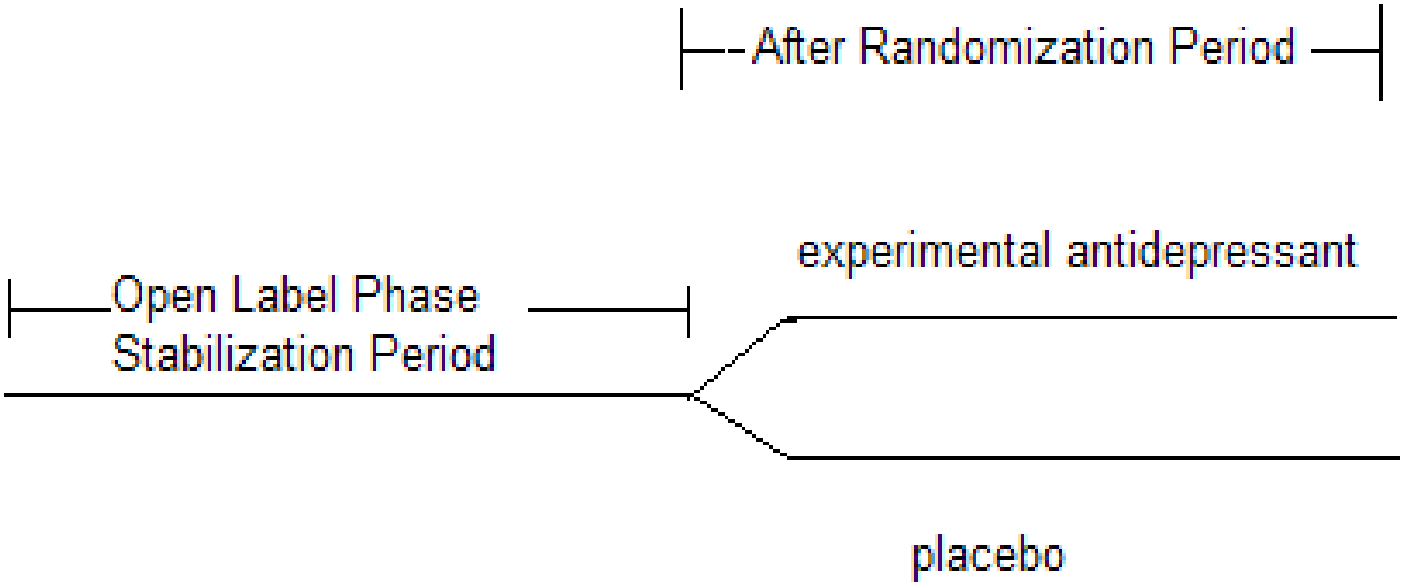
- Depression is a recurrent disorder
- Risk of recurrence increases with the number of depressive episodes
- Prevention of relapse and recurrence are important aspects of antidepressant treatment
  - FDA does not distinguish between relapse and recurrence

FDA Review of Maintenance Trials for MDD

- We compiled efficacy data from all maintenance trials submitted to FDA since approval of first 2nd generation antidepressant in 1987 (Wellbutrin)
- Total of 15 trials
  - Excluded 1 with too few relapse events
  - Able to get patient level data for 14 of 15 trials

Design of Maintenance Trials for MDD

- Randomized withdrawal design: responders to active drug during an open-label phase were randomized to active drug or placebo, and observed for relapse over a period of 6-12 months



Open-Label Phase

- Patients with MDD (DSM) with a current depressive episode
- Total number of patients per study :
  - [Mean(Range)]: 554 (172-866)
- Open-label treatment period with study drug:
  - Ranged across studies from 6-26 weeks
- Stabilization period across studies
  - 7 studies: No stabilization
  - 8 studies: for 7 it was 3 weeks or less; the remaining study was an outlier with a 12 week stabilization period

Open-Label Phase
(continued)

- Response criteria across studies:
  - Threshold for CGI-I, CGI-S, HAMD, or MADRS
  - Single scale or combination
- Mean (range) response rate across studies:
  - 52% (27 % to 78%)

Double-Blind Phase

- Responders randomized to active drug or placebo
- Observation period for relapse: 24-52 weeks
- Total number of patients per study [Mean(Range)]:
  - Placebo: 120 (42-276)
  - Drug: 138 (48-272)

Double-Blind Phase
(continued)

- Relapse criteria:
  - Investigator's judgment
  - Threshold score for CGI-I, CGI-S, HAMD, or MADRS
  - Single scale or combination
- Endpoint
  - Time to relapse (8 studies)
  - Percent relapse (7 studies)

Approaches to Analysis

- Did not do meta-analysis
  - Variability in methodology across studies too great to justify meta-analysis
- Descriptive/exploratory analyses
  - Had patient-level data for 14/15 studies
  - Explore discontinuation symptoms as possible explanation for drug/placebo differences
  - Explore effects of open label phase characteristics on relapse rates and rate differences (duration of stable response, quality of response)
  - Secular trends

Demographic and Baseline Features

- Age: mean age 43
- Gender: about 2/3 female, 1/3 male
- Race: about 88% Caucasian
- Baseline mean HAMD-17
  - Open label phase: 23
  - Double-blind phase: 9

Response and Relapse Rates

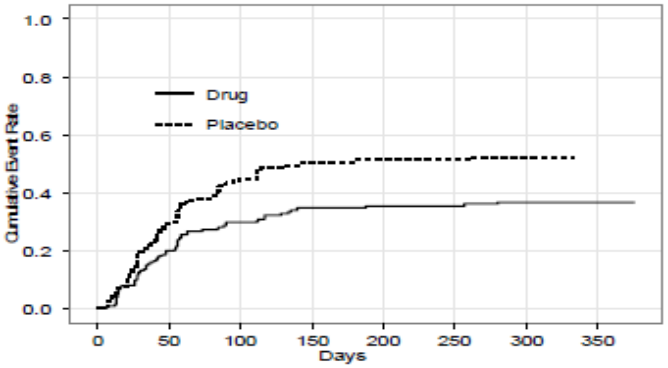
- Response rates (open label)
  - Mean: 52%
  - Range: 27-78%
- Relapse rates (double-blind)
  - Placebo: Mean=37% SD=11
  - Drug: Mean=18% SD=10
  - Difference: Mean=18% SD=6
  - % Reduction: Mean=52% SD=17%

Summary Results

- Drug superior to placebo in all 15 studies
- Average maintenance benefit of 52% reduction in relapse rate compared to placebo
- Discontinuation symptoms did not explain the benefit
  - 94% of relapse events occurred after 2 weeks
  - Overall results similar with censoring of events in first 4 weeks
- Insufficient data to explore duration of stability and relapse rates (all except 1 study had very brief period of stability)
- Secular trend (slightly larger treatment effects in studies before 1995)

Examples of Kaplan-Meier Curves

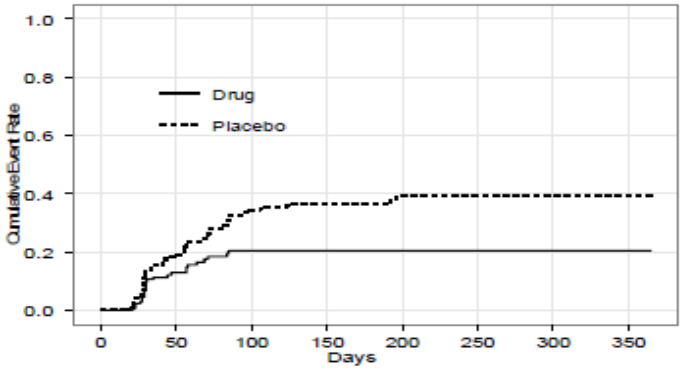
Study K



Drug	207	160	125	104	94	87	81	1
Placebo	210	135	98	76	65	62	59	0

Number of Patients at Risk for Relapse

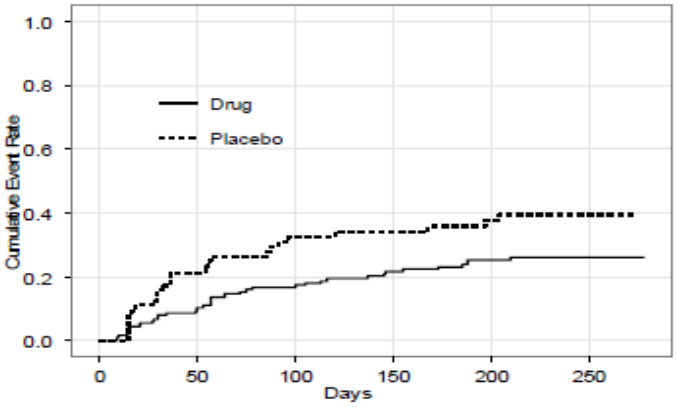
Study L



Drug	149	100	75	64	51	44	38	32
Placebo	163	111	67	57	43	37	31	29

Number of Patients at Risk for Relapse

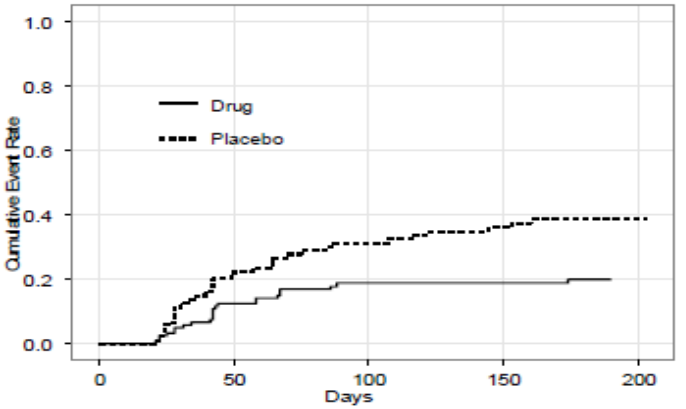
Study M



Drug	181	148	122	107	96	80
Placebo	92	60	44	38	34	26

Number of Patients at Risk for Relapse

Study N



Drug	132	102	83	77	0
Placebo	137	76	59	50	1

Number of Patients at Risk for Relapse

Study with 12 Weeks of Stability

- 2 maintenance studies for this drug
  - Initial one with no stable period, at higher dose
  - Later one with 12 weeks stability, at lower dose
- Initial study:
  - Higher relapse rates early, plateau by 4 months
- Later study:
  - Lower relapse rates, but continued to separate from placebo out to 6 months

Remaining Questions

- How long beyond 6 months should antidepressants be continued?
- How long a period of stability should there be prior to randomization?
- How should relapse be defined?