FDA Perspective on Need for Obtaining Long-Term Efficacy Data for Psychiatric Drugs

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Why do we need long-term (LT) efficacy data for schizophrenia, depression, and other psychiatric disorders?

- Most psychiatric disorders are chronic
- LT efficacy data has not been a requirement for initial approval (approvals based on acute data)
- LT/post-approval commitment—do generally get done, but may be several years or longer, and sometimes never
- Rx guidelines for many of indications recommend LT Rx—so not sufficient evidence base to support standard of care at time of most initial approvals of new drugs

What kind of study designs have supported longer-term efficacy in current labeling?

- Can’t do LT pbo-controlled, parallel group trial for most indications
- Alternative: randomized w/d (relapse prevention)
  - Open Rx of symptomatic pts
  - Responders randomized to drg or pbo
  - Look at time to relapse or rate of relapse
- Open run-in phase generally brief (6-12 wks)
- Actual responder status often only a few weeks
- DB observation phase: 6-12 mo

What is the problem with currently used designs?

- Supposed to inform about LT efficacy
- Often characterized in terms of DB phase
- Most of relapses occur early, so few pts left at later times
- Not clear what randomization after only a few weeks in responder status tells you about LT efficacy

Alternative approach to interpreting randomized withdrawal trials

- Focus on open run-in period and the question most clinicians are interested in (how long to Rx a “responding pt”—i.e., what is probability of relapse after X months/years of Rx—is there a continuing benefit?
- For that, we think time in responder status is most critical
- In fact, most clinicians would not stop Rx after a few wks in responder status; so typical trial is not consistent with usual practice—even unethical
- So, in recent years, we have encouraged longer run-in phases

Is the usual distinction made between continuation and maintenance Rx useful?

- Continuation Rx to prevent relapse (i.e., return of Sx in same episode that responded to Rx)
- Maintenance Rx to prevent recurrence (i.e., new episode)
- Distinction based on belief in what is average duration episode of that particular illness—for depression, 6 months
- Of course, can't know what emerging Sx mean in any instant case and can argue that for pt and clinician, it doesn't make any difference
- So we have not made the distinction, and prefer the terms maintenance and relapse, whatever the duration

2005 initiative in what was previously DNDP (now DPP) to change the standard

- Began announcing to sponsors that having LT data is requirement for initial filing for certain chronic psychiatric disorders (depression and schizophrenia), and must be in responder status for at least 6 mo before randomization
- Much resistance
- In effect, served as “straw man”
- Decided to take issue to PDAC

October 25, 2005 PDAC Meeting on LT Efficacy for Psychiatric Drugs

- Focused primarily on MDD for purposes of discussion
- Asked committee if FDA should require demonstration of LT efficacy along with acute efficacy at time of filing NDA
- Asked committee if reasonable standard for randomized withdrawal studies to require 6 months in responder status before randomization
- Several other points about trial design, other chronic psychiatric disorders, and labeling, primarily for purposes of discussion

Outcome of October 25, 2005 PDAC Meeting

- PDAC advised us unanimously not to add requirement for LT efficacy data at time of NDA filing
  - Major concern was that this would delay access to promising new drugs
- PDAC also advised us not to require period of 6 months in responder status before randomization in randomized withdrawal studies

Constant refrain by critics of FDA position: "One Size Does Not Fit All"

- Recommendations for duration of treatment after acute response vary widely by disorder—some don't need LT treatment (e.g., bipolar depression)
- Most patients in reality discontinue or switch medications well before guideline recommended durations
- Different diseases have very different courses
  - Unipolar/bipolar: episodic; 4-6 month duration
  - Schizophrenia: episodic, but duration not defined
  - Anxiety disorders: chronic, fluctuating course

Ethical Dilemma with Placebo-Controlled Randomized Withdrawal Studies in Schizophrenia

- Oct 2005 PDAC Meeting: Schooler argued that use of placebo leads to unacceptable risks
- US and Western European IRBs will not approve such studies—currently done mostly in Eastern Europe

Argument for Non-Inferiority Design in LT Efficacy Trials in Schizophrenia

- Gene Laska made argument at Oct 2005 PDAC meeting
  - Looked at 6-month relapse rates for 11 published placebo-controlled randomized withdrawal studies
    - Mean pbo rate: 56%
    - Mean typical rate: 27%
    - Mean atypical rate: 19%
- Laska argued that available data support use of non-inferiority approach in this setting

Current FDA Position on LT Efficacy Data for Chronic Psychiatric Disorders

- LT efficacy data not required at time of filing an NDA or supplement for any chronic psychiatric disorder
- Claims for longer-term efficacy will have to be supported by data from adequate trials:
  - The placebo-controlled randomized withdrawal design is an appropriate design for generating supportive data
  - 3 months in responder status prior to randomization is the minimum requirement (unless a strong argument can be made for an alternative in a specific instance)
  - A non-inferiority approach is worth considering for generating longer-term efficacy data for schizophrenia, however, more work is needed to flesh out the argument

Example of How Findings from Randomized Withdrawal Study are Characterized in Labeling

Zyprexa/Bipolar/LT (as example)

- Focus is on duration of open run-in period
- Findings included in 3 sections of labeling:
  - Clinical Trials (under Clinical Pharmacology)
  - Indications and Use
  - Dosage and Administration

Clinical Pharmacology/Clinical Trials

Bipolar Disorder

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to $\leq$ 12 and HAM-D 21 to $\leq$ 8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to $\geq$ 15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Indications and Usage

Bipolar Disorder

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (see Clinical Efficacy Data under CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Dosage and Administration

Bipolar Disorder

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (see Clinical Efficacy Data underCLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.