

FDA Perspective on Negative Symptoms in Schizophrenia as a Target for a Drug Treatment Claim

Thomas Laughren, M.D.

Director, Division of Psychiatry Products

Food and Drug Administration

Current Approaches to Drug Treatment Claims in Psychopharmacology

- **Specific diseases/syndromes**
 - e.g., schizophrenia
- **Specific symptoms or symptom clusters**
 - e.g., agitation in schizophrenia
 - e.g., suicidality in schizophrenia
 - **Note: FDA has accepted cognitive impairment in schizophrenia as legitimate target**
- **Nonspecific symptoms**
 - e.g., pain or fever (no current examples in psychopharmacology)

Current Regulatory Approach to Schizophrenia

- **Schizophrenia generally viewed as single clinical target**
 - **New antipsychotics approved for the “treatment of schizophrenia”**
 - **Exceptions (agitation; suicidality; cognitive impairment)**
- **Negative symptoms acknowledged as one aspect of the schizophrenic syndrome (DSM-IV)**
 - **FDA has permitted specific negative symptom findings to be mentioned in clinical trials section**
 - **Premature judgement (see later)**
- **Trial Designs**
 - **4-6 week acute studies**
 - **Randomized withdrawal studies for longer-term efficacy**

Regulatory Challenge for Claim Focused on Negative Symptoms in Schizophrenia as a Distinct Target

- **Question: Is this a pseudospecific claim (artificially narrow)?**
 - E.g., hallucinations in schizophrenia
- **Alternative View: a legitimate claim because negative symptoms:**
 - Represent a distinct aspect of schizophrenic syndrome
 - Respond differently to treatment than other symptoms (i.e., patients may have residual negative symptoms)

Questions to Ask in Attempting to Establish Negative Symptoms in Schizophrenia as a Unique Aspect of this Illness for Drug Development

- Phenomenology and Course
 - Negative symptoms distinguishable from other aspects of illness?
 - Distinguishable course for negative symptoms in schizophrenia?
 - Must show distinctness from cognitive impairment if want both claims
- Expert Opinion
 - Distinctness of negative symptoms in diagnostic nomenclature
 - Experts view on distinctness of negative symptoms
- Differential Response
 - Distinctness of treatment response
- Mechanism
 - Understanding at mechanistic level (unique pathophysiology)?

Issues to Consider in Drug Development Programs Targeting Negative Symptoms in Schizophrenia

- **Population to target**
- **Phase of illness to target**
- **Negative Symptoms: single target vs separate domains**
- **Functional improvement?**
- **Key design questions**

Population to Target for Negative Symptoms in Schizophrenia

- **What patients need treatment for negative symptoms?**
- **How are negative symptoms distributed in schizophrenic population?**
 - **All patients (continuum)**
 - **Subgroup with prominent negative symptoms**
- **How to select patients for negative symptom studies?**

What Phase of Illness to Target

- **Acute (prominent positive symptoms)**
- **Residual (minimal/stable positive symptoms)**
- **Prodromal**

Negative Symptoms: What to Target?

- **Single target vs separate domains**
- **Yet another pseudospecificity question**
 - **Can patients be sorted into subgroups based on domain-specific impairments?**
 - **Can drugs be sorted into subgroups based on domain-specific effects?**
 - **Are these useful subgroups?**

Functional Improvement with Improvement in Negative Symptoms

- **How would function be expected to improve with improvement in negative symptoms?**
- **What would expected time course be for functional improvement?**
- **Are there tools available for measuring functional improvement in this population?**

Key Design Questions

- **Duration of trials**
 - **FDA view:**
 - **A treatment for residual phase symptoms would be expected to be durable**
 - **6 month trial would be proposed standard**
- **Adjunctive vs broad spectrum claim**

Issues Pertinent to Two General Approaches to Establishing Claims

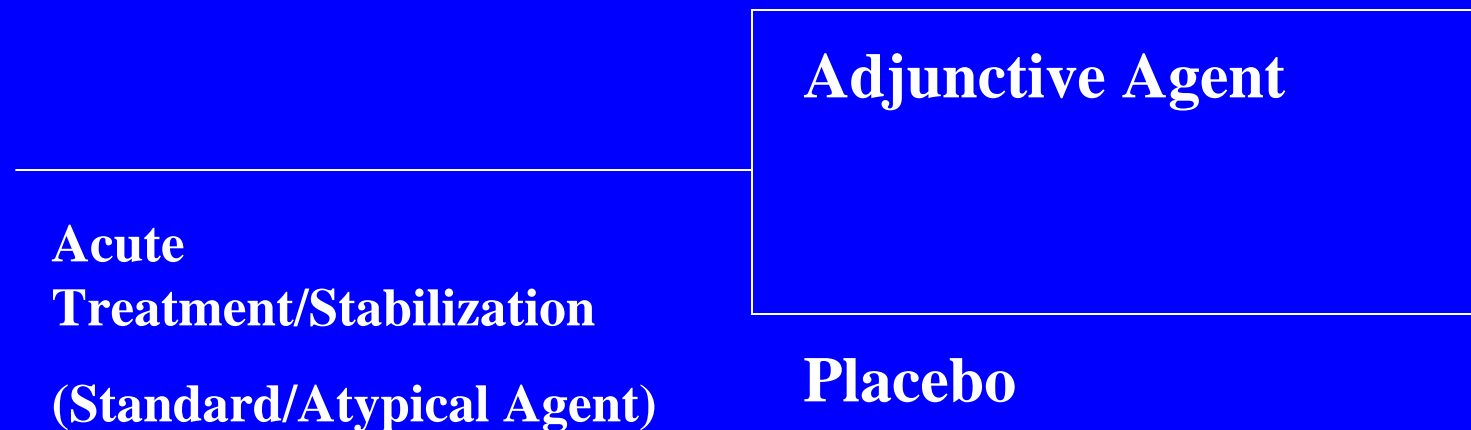
- **Adjunctive**
- **Broad spectrum**

Key Adjunctive Question

- **What therapy can the new treatment be added to?**
- **Design of studies depends on this decision**
 - **Single drug**
 - **In this case, need to address combination policy (factorial design)**
 - **“All-comers” (or several drugs)**
 - **Add-on design would suffice**

Proposed Design for Study of “Adjunctive” Agent During Residual Phase of Schizophrenia

- **Achieve optimal control/stability for positive symptoms with standard (or atypical) antipsychotic agent in acutely psychotic patients (open)**
- **Continue on that treatment during RCT phase (and maintain stability regarding positive symptoms)**
- **Randomize (during residual phase) to addition of adjunctive agent or placebo**

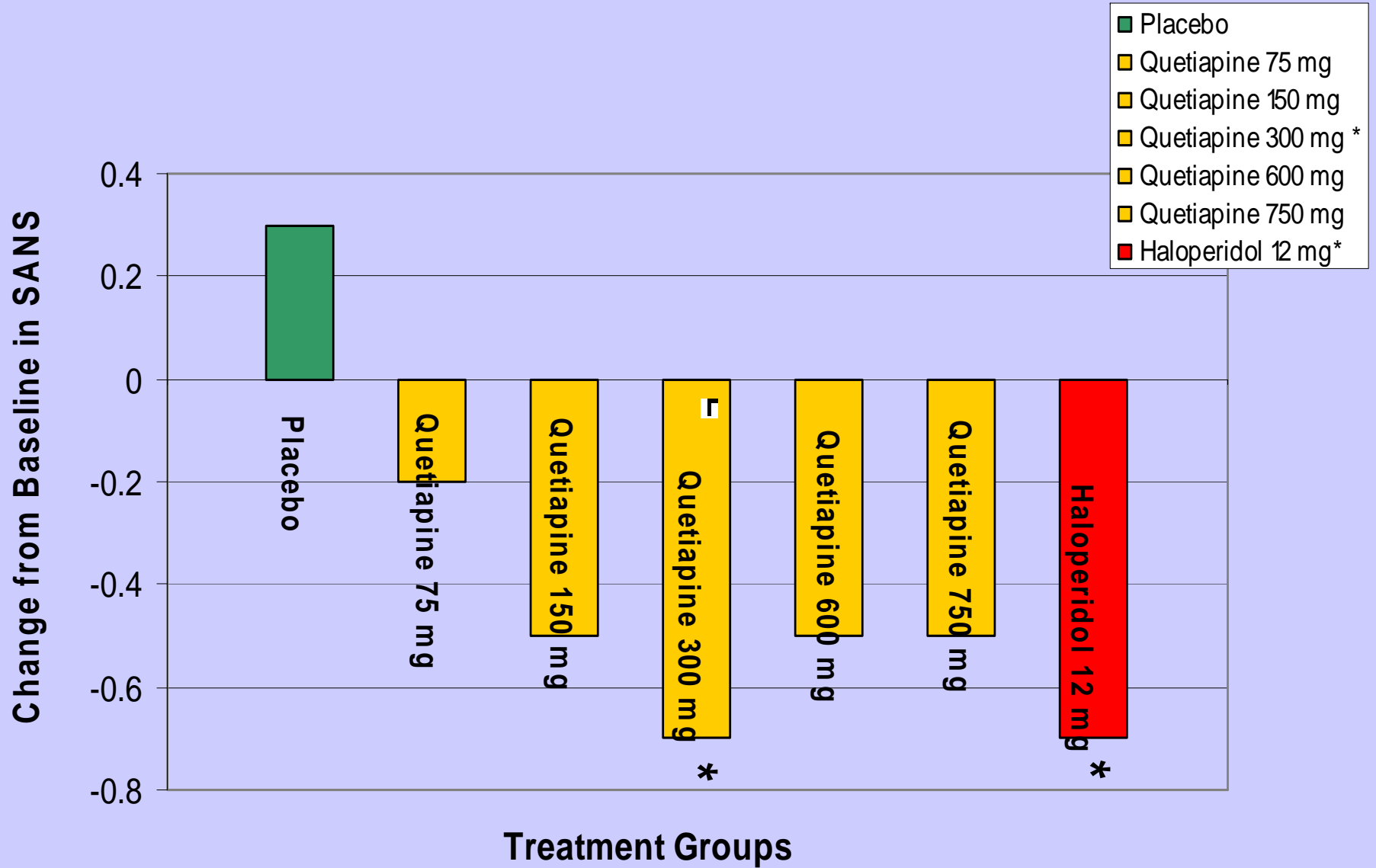


Key Broad Spectrum Question

- **Is the apparent effect on negative symptoms independent of effect on positive symptoms?**
- **How to establish such independence may not be clear (possible confounding by effect on positive symptoms)**

Effectiveness of Quetiapine and Haloperidol on Negative Symptoms (SANS)

Trial: Acutely exacerbated schizophrenic patients; 6 weeks; fixed dose



Need Separate Studies for Positive Symptoms and Negative Symptoms for Broad Spectrum Agents

- **Need typical acute studies for positive symptoms**
- **Need residual phase studies for negative symptoms**

Proposed Design for Study of “Broad Spectrum” Agent During Residual Phase of Schizophrenia

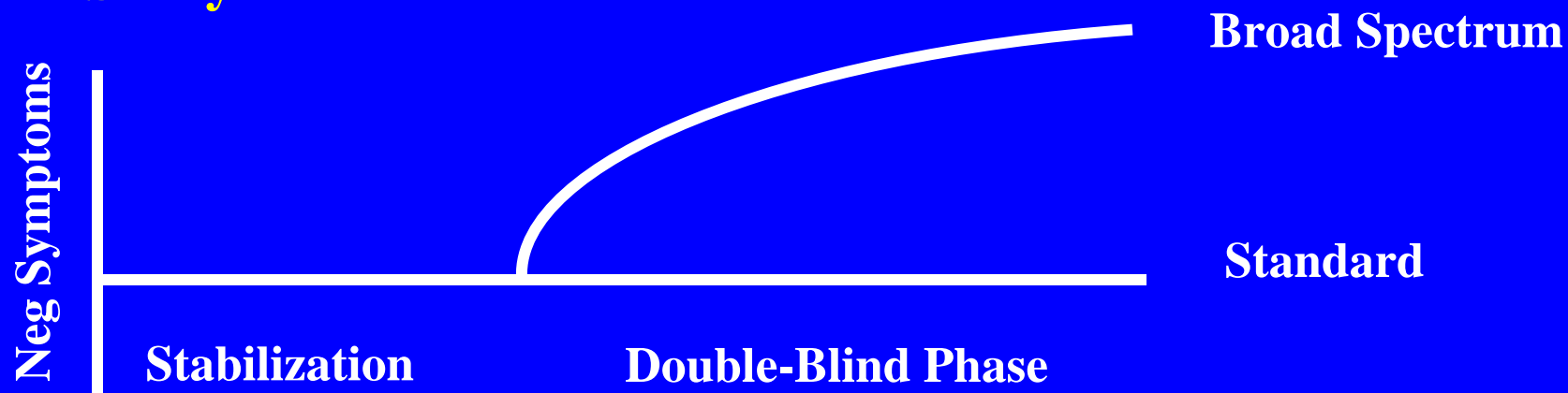
- Achieve optimal control/stability for positive symptoms with standard antipsychotic agent in acutely psychotic patients (open)
- Randomize (during residual phase) to:
 - Continuation of standard agent
 - Switch to broad spectrum agent

Acute
Treatment/Stabilization
(Standard Agent)

Broad Spectrum Agent

Standard Agent

Anticipated Outcome of “Broad Spectrum” Residual Phase Study



Difficulties in Interpreting Anticipated Outcome of Superiority of Broad Spectrum Agent (BSA) over Standard Agent (SA) in Residual Phase Study

- Assume level of positive symptom control equivalent for BSA & SA
- Assume “fair” comparison
- Several Possible Interpretations
 - BSA improves negative symptoms
 - BSA has no effect on neg symptoms, but SA causes neg symptoms
 - Both BSA and SA cause neg symptoms, but $BSA < SA$