Advancing our Thinking About Partially Responsive MDD and TRD

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Current & Past Consulting Relationships

- Part time employee of MGH CTNI
- Consultant to NIMH
- Consultant to AbbVie, Acadia, Alcobra, Astra Zeneca, Camurus, Cerecor, Corcept, Curemark, Dart NeuroScience, Delpor, Edgemont, EnVivo, Fabre Kramer, Gedeon Richter, Janssen, JDS Therapeutics, Lilly, MAPS, Medgenics, Naurex, Neuren, Neurocrine Biosciences, Noven, Omeros, Pfizer, Retrophin, Reviva, Roche, Shire, Spinifex, Sunovion, Taisho, Targacept, Teva, Theravance, Tonics, Transition, Zogenix
- Consultant to ERT, MedAvante, Salamandra
- Consultant to Quinn Emanuel, Ulmer & Berne, King & Spalding

Current Regulatory Policy (FDA and EMA)

- Augmentation approach for partial responders
  - Add-on design
  - Show that adding on new drug is superior to adding on placebo
- Switching approach for TRD
  - Randomize to failed drug vs new drug
  - Show that new drug is superior to failed drug

What Options Do Clinicians Have?
(for a patient who does not fully respond to the initial treatment)

- Increase dose (above recommended target)
- Add a second drug (augmentation)
- Switch to another drug
  - Note: Clinicians may not distinguish between partial response and treatment resistance

What is augmentation? (adding a second agent)

- Timing of augmentation?
  - Use combo from day 1
    - For enhancing the MDD response overall
    - For targeted aspect of MDD
  - Adding second drug later
    - **For enhancing the MDD response overall**
    - For targeted aspect of MDD

Why is it important to include augmentation and switching strategies in development programs?

- Reducing the burden of depression
  - Substantial unmet need with monotherapy
- Common clinical practice
  - Important to know what works and what doesn't
- Pharma perspective
  - Important to be able to distinguish a company's product from others in a crowded marketplace

Programs Targeting Augmentation for Partial Responders (when goal is to improve effect for syndrome overall)

- For patient who has had a sufficient response to justify continuing treatment, but only partial, and therefore is a candidate for adjunctive therapy
- Assume adjunctive agent has different pharmacology than primary agent
- Need to define "partial/minimal/suboptimal response"
  - No standard definition as yet (would be useful to get consensus on a definition)
  - Prospective or by history?

Programs Targeting Augmentation for Partial Responders (when goal is to improve effect for syndrome overall)

- Preferred study design
  - 6-8 week add-on (new drug or pbo)
  - "all comers" approach: generally means several representatives from each major class of antidepressants (SSRIs and SNRIs)
  - Broad assessment (MADRS or HAMD)
  - Ideally would assess dose/response
  - **Important Flaw: does not answer question of new drug alone**

Drugs Approved in US for Adjunctive Treatment of MDD (when goal is to improve effect for syndrome overall)

- Seroquel XR (quetiapine)
  - Criteria for partial responders:
    - Inadequate response to at least one antidepressant
- Abilify (aripiprazole)
  - Criteria for partial responders:
    - Inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response to 8 weeks of prospective antidepressant therapy
- Wording of labeling claim for augmentation:
  - "SEROQUEL XR is indicated for use as adjunctive therapy to antidepressants for the treatment of MDD."

Targeting Treatment Resistant Depression (TRD)

- TRD: Patient with so little benefit from at least 2 standard therapies of different classes that clinician decides to switch to therapy with a different agent (i.e., different than adding a second agent)
  - Question: does it have to be 2 different classes?
- Establishing TRD: FDA prefers at least one prospective determination of treatment resistance (but not a requirement)
- Products approved for treatment resistant psychiatric illness in US:
  - Symbyax (olanzapine + fluoxetine) for MDD
    - Somewhat unusual since a combo
  - Clozapine for schizophrenia

Targeting Treatment Resistant Depression (TRD)

- Design considerations: For FDA, need to show that new agent is better than a standard agent
- FDA's optimal design: randomize patients who fail on agent A to either agent A or agent B
  - Must show that agent B is superior to agent A in these patients
  - **Important Flaw: Doesn't look at A + B vs each alone**
- Not a bright line between partial response and treatment resistance
  - In fact, now data showing that patients benefit from adjunctive aripiprazole even if minimal or no response to original antidepressant
  - May be time to re-think regulatory policy

Are Maintenance Data Needed for Augmentation Programs?

- FDA has not required maintenance data for initial approvals, and does not require them in this setting
- Still, how long adjunctive Rx is needed is an important question
- If maintenance studies are done and positive, this information would likely be added to labeling
- May use maintenance model for looking at monotherapy

Concepts Needing Consensus Definition

- Response
- Partial/Minimal/Suboptimal response
- Treatment resistant depression (TRD)

Overview of Options					
		New Drug (ND) +	New Drug (ND) -	Current Approaches	Other Questions
Initial Antidepressant	+	a = AD + ND	b = AD + Pbo	Adjunctive (a vs. b) TRD (b vs. c) Combo (a vs. b & a vs. c)	a vs. c ? b vs. c? a vs. b & a vs. c ? b vs c?
	–	c = ND + Pbo	d = Pbo + Pbo		