Updated Therapeutic Strategies for Partial or Nonresponse to Treatment in Major Depressive Disorder (MDD)

Presented by Mark Rosenberg
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Presentation Objectives

• Upon completion of this activity participants should be able to:
  
  - Discuss emerging therapeutic strategies in patients with MD whose current treatment options still produce symptoms
  - Analyze the impact of inadequate or nonresponse to pharmacologic treatment in MDD
  - Implement updated MDD guidelines into individualized strategies for pharmacologic augmentation of antidepressants to achieve optimal efficacy with the least side effect burden
  - Assess management strategies to improve patient adherence to emerging treatment plans
  - Incorporate effective approaches to achieving remission in patients with unsuccessful treatment of MDD

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Presentation Overview

Disease Overview
Costs of MDD
Diagnosis Strategies for MDD
Treating The Whole Patient
Strategies for Treatment Resistant Depression
Improving the Outcome

DISEASE OVERVIEW
Prevalence of the MDD

- In any given year 19 million American adults, or 9.5% of the US population, suffer from depressive disorders.
- Depression is the leading cause of disability in the US.
- By 2020 it is projected that depression will be the leading cause of disability worldwide.
- Average age of onset 50 years ago = 29
- Average age of onset today = 14.5

Prevalence of MDD

Age-standardized* percentage of adults meeting criteria for current depression,* by state/territory — Behavioral Risk Factor Surveillance System, United States, 2006 and 2008

* Age standardized to the 2000 U.S. standard population.
* Based on responses to Patient Health Questionnaire-8.
Data presented were collected by 16 states in 2006 and by 29 different states, the District of Columbia, and two territories in 2008. Five states (Kentucky, New Jersey, North Carolina, Pennsylvania, and South Dakota) did not participate in either year. Nine states (Florida, Kansas, Louisiana, Maine, Mississippi, Nebraska, North Dakota, Vermont and Washington) participated in both years, but only 2008 data were included.

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Prevalence of MDD

- High rate of occurrence – 17% lifetime prevalence, this prevalence corresponds to a national population projection of 32.69 to 35.1 million US adults with lifetime MDD and 13.1 to 14.2 million US adults with a 12 month prevalence of MDD
- Episodes of long duration - 33% of patients have episodes > 2 years’ duration
- >50% rate of recurrence within 2-3 years of recovery (8 weeks of minimal depressive symptoms)
- Morbidity comparable to angina and advanced coronary artery disease
- High mortality (15%) from suicide in depressed patients hospitalized once for depression


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Major Depression Disorder (MDD): Urgency to Treat

- MDD has become a major public health concern and is responsible for significant social impairment, including deterioration of family and interpersonal relationships, lost work productivity, and general suffering
- MDD is the most common psychiatric disorder in the United States
- Few patients receive adequate treatment
- Depression is frequently associated with, and may negatively impact other medical disorders
- Inadequately treated depression may have progressive course and may be associated with functional and structural changes in the brain


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MDD: Progression to Disorder and Recovery

- Treatment Phases: Acute, Continuation/Maintenance
- Treatment Goals: Remission, Delay Time to Major Depressive Episode
- Nonadherence:
  - Up to 50% up to 70%
- Response:
  - Efficacy: up to 50%
  - Safety & Tolerability: up to 70%
- Time:
  - Acute: 10-12 wks
  - Continuation/Maintenance: > 12 wks

VHA/DoD Major Depressive Disorder Working Group 2000 (Module A). 1-35

Progression of Depression: Adverse Effects of each Successive Episode

Risk of depression onset per month
Female subjects only n = 2395

There are at Least Two Sides to the Neurotransmitter Story

Functional domains of Serotonin and Norepinephrine

- **Serotonin (5-HT)**
  - Sex
  - Appetite
  - Aggression

- **Norepinephrine (NE)**
  - Depressed Mood
  - Anxiety
  - Vague Aches and pain
  - Thought process
  - Irritability
  - Concentration
  - Interest
  - Motivation

Both serotonin and norepinephrine mediate a broad spectrum of depressive symptoms

References:

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MDD is Disabling and an Economic Burden

Disability Rank

<table>
<thead>
<tr>
<th>Rank</th>
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<th>2020 (est.)</th>
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<tbody>
<tr>
<td>1.</td>
<td>Lower respiratory infections</td>
<td>Ischemic heart disease</td>
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<tr>
<td>2.</td>
<td>Peri-natal conditions</td>
<td>Major Depressive Disorder</td>
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<td>3.</td>
<td>HIV/AIDS</td>
<td>Road Traffic Accidents</td>
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<tr>
<td>4.</td>
<td>Major Depressive Disorder</td>
<td>Cerebro-vascular disease</td>
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<tr>
<td>5.</td>
<td>Diarrheal diseases</td>
<td>Chronic obstructive pulmonary disease</td>
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The High Cost of MDD

- Workplace
- Suicide Related
- Direct Medical

Total Costs of $83.1 Billion (2000)

Disability Rank

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Depression Quick Facts

Major Depressive Disorder is significant due to its early onset, severity, likelihood of comorbidity, and overall economic and societal costs

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MDD: A Global Crisis

MDD and Healthcare Costs

- Depression is one of the top ten conditions driving medical costs, ranking 7th in a national survey of employers
  - The greatest cause of productivity loss among workers
- Depression is an important factor in health disease
- The presence of type 2 diabetes nearly doubles an individual’s risk of depression and an estimated 28.5% of diabetic patients meet criteria for clinical depression
- Back/neck and other chronic pain also have a significant depression/SA component
Impact on Healthcare Costs

- High costs of unmet Behavioral Health needs and other unsuccessful chronic disease management due to the BH needs
- High costs of fragmented and uncoordinated care from PC to BH and inpatient settings
  - BH disorders account for half as many disability days as “all” physical conditions
  - Annual medical expenses—chronic medical & behavioral health conditions combined cost 46% more than those with only a chronic medical condition
  - Top five conditions driving overall health cost
    - (work related productivity + medical + pharmacy cost)

Impact on Healthcare Cost Cont.

- Healthcare use/costs twice as high in diabetes and heart disease patients with depression
- Untreated mental disorders in chronic illness is projected to cost commercial and Medicare purchasers between $130 and $350 billion annually
- Approximately 217 million days of work are lost annually to related mental illness and substance use disorders (costing employers $17 billion/year)

<table>
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<th>Condition</th>
<th>Annual Cost – those without MH Condition</th>
<th>Annual Cost – those with MH condition</th>
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<tr>
<td>Heart Condition</td>
<td>$4697</td>
<td>$6919</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>$3481</td>
<td>$5492</td>
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<tr>
<td>Asthma</td>
<td>$2908</td>
<td>$4028</td>
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<tr>
<td>Diabetes</td>
<td>$4172</td>
<td>$5559</td>
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DIAGNOSIS STRATEGIES FOR MAJOR DEPRESSIVE DISORDER

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DSM 5 Updates

• Neither the core criterion symptoms applied to the diagnosis of MDD, nor the duration requirement of 2 weeks have changed
• Criterion A for MDD is identical in both DSM 5 and DSM IV
• Premenstrual Dysphoric Disorder has been moved from DSM IV Appendix B to the main body of DSM 5
• Dysthymia now falls under the category of persistent depressive disorder, which includes both chronic MDD and the previous Dysthymic Disorder (combined with specifies)
• Bereavement exclusion has been eliminated
• Specifier has been added to indicate the presence of mixed symptoms across bipolar and the depressive disorders

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DSM-V Depression Criteria

* Five or more of these symptoms must be present in order for a diagnosis of depression to be made. One of these symptoms must be either #1 or #2

- DSM Depression Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Depressed mood*</td>
</tr>
<tr>
<td>2. Loss of Interest or pleasure</td>
</tr>
<tr>
<td>3. Weight loss or weight gain</td>
</tr>
<tr>
<td>4. Sleep disturbance</td>
</tr>
<tr>
<td>5. Fatigue</td>
</tr>
<tr>
<td>6. Mood swings</td>
</tr>
<tr>
<td>7. Loss of concentration</td>
</tr>
<tr>
<td>8. Low self esteem or guilt</td>
</tr>
<tr>
<td>9. Suicidal ideation or thoughts of death</td>
</tr>
</tbody>
</table>

When MDD Cannot be Diagnosed

- If the patient has a history of manic, hypo manic, or mixed episodes
- If the depressed mood is better accounted for by schizoaffective disorder and is not superimposed on schizophrenia
- If the symptoms cannot be accounted for due to bereavement and persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation
In primary care, physical symptoms are often the chief complaint in depressed patients. In a New England Journal of Medicine study, 69% of diagnosed depressed patients reported unexplained physical symptoms as their chief complaint.1

Reference:

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Depression Treatment Stepped Care Model

The stepped care model

The recommendations in this guideline are presented within a stepped care framework that aims to match the needs of people with depression to the most appropriate services, depending on the characteristics of their illness and their personal and social circumstances. Each step represents increased complexity of intervention, with higher steps assuming interventions in previous steps.

Step 1: Recognition in primary care and general hospital settings
Step 2: Treatment of mild depression in primary care
Step 3: Treatment of mild-moderate to severe depression in primary care
Step 4: Treatment of depression by mental health specialists
Step 5: Inpatient treatment for depression

What is responsible for care? What is the focus? What do they do?

Step 5: Inpatient care, crisis teams
Risk to life, severe self-harm
Medication, combined treatments, ICT

Step 4: Mental health specialists, secondary care
Recommended treatments, complex modalities and primary depression
Medication, complex psychological interventions, combined treatments

Step 3: Primary care team, primary care mental health worker
Mood disorders, severe depression
Medication, psychological interventions, social support

Step 2: Primary care team, primary care mental health worker
Mild depression
Walk-in clinics, guided self-help, componential CBT, exercise, brief psychological interventions

Step 1: Primary care team, primary care mental health worker
Recognition
Assessment

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Depression Chronic Care Model

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TREATING THE WHOLE PATIENT

### Treatment Options

#### Pharmacologic Options
- serotonin selective reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- monoamine oxidase inhibitors
- adjunct therapies
  - atypical antipsychotics
  - mood stabilizers
  - anxiolytics

#### Psychotherapy
- cognitive behavioral therapy
- interpersonal therapy
- problem-solving therapy
- supportive therapy
- group therapy

### Medical Devices

### Alternative Treatments
Depression: Current treatment outcomes

- Up to 70% of depressed patients respond (≥ 50% decrease in HAM-D score) to treatment but fail to achieve remission from their emotional and physical symptoms
- Approximately 30% of depressed patients achieve remission (≤ 7 score on the HAM-D) with treatment

References:

* Antidepressant clinical drug trials.

Patient Treatment Preference Predicts Outcome

In 429 patients with MDD who participated in a large multisite study of nefazodone vs Cognitive Behavioral Analysis System of Psychotherapy vs a combination of both modalities, patient preference strongly predicted outcomes over 12 weeks of treatment. Patients did better when they were randomly assigned to the treatment they would have preferred if given a choice.

**Beauty in Nature and the Impact on Depression**

![Graph showing Montgomery-Asberg Rating Scale scores over weeks for Forest, Hospital, and Control groups.](Image)

**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Salivary Cortisol (µg/dL) Before 4-week program</th>
<th>Salivary Cortisol (µg/dL) After 4-week program</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forest</td>
<td>0.113(0.053)</td>
<td>0.082(0.044)</td>
<td>2.97</td>
<td>0.008</td>
</tr>
<tr>
<td>Hospital</td>
<td>0.125(0.052)</td>
<td>0.132(0.057)</td>
<td>-1.62</td>
<td>0.121</td>
</tr>
<tr>
<td>Controls</td>
<td>0.137(0.100)</td>
<td>0.148(0.106)</td>
<td>-1.31</td>
<td>0.206</td>
</tr>
</tbody>
</table>

Montgomery-Asberg Rating Scale Score Mean (SD), paired t-test

**References:**


**Cardiovascular Fitness and Depression Correlation**

![Graph showing cumulative incidence rate of cardiorespiratory fitness level for men and women.](Image)

Objectively assessed cardiorespiratory fitness independently predicted development of clinical depression over a 12-year follow-up period in 11,258 men and 3,085 women.


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While the presence of depressive symptoms did not predict subsequent dietary patterns, consumption of a diet rich in processed foods independently increased the risk of developing depressive symptoms over the ensuing 5 years, whereas a diet rich in whole foods was found to protect against the development of depression.

Acute Phase

- Choose an initial treatment modality
  - Should be aimed at inducing remission of major depressive episodes and achieving a full return to baseline functions
  - May include pharmacotherapy, depression-focused psychotherapy, combination medicines and psychotherapy, or other somatic therapies
  - Initial treatment modality should be influenced by clinical features and treatment preferences as well as take into account treatments being provided for other diagnosis

Acute Phase

- Antidepressant medication is recommended as an initial treatment for patient with mild to moderate depression, and should definitely be provided to those with severe depression
  - Medications are generally comparable between classes, so selection will largely depend on factors such as side effects, costs, and patient preference
  - Once medication has been initiated, the rate of titration will depend on age, treatment setting, and co-occurring illness
  - Frequency of monitoring will be dependent upon symptom severity
  - If side effects occur initial steps should be taken to decrease dosage or change to a medication not linked to that side effect
Acute Phase

- Assessing adequacy of treatment
  - Ensure treatment has been administered for an appropriate amount of time prior to determining responsiveness (generally 4-8 weeks, and no longer than a month)

Strategies to Address Nonresponse

- Acute phase should not conclude prematurely
- Assess the quality of the therapeutic alliance and treatment adherence
- For patients in psychotherapy assess frequency of sessions and if this approach is appropriately meeting patient needs
- Make appropriate medication adjustments and allow additional 4-8 weeks to assess responsiveness
- If minimal or no improvement is apparent psychiatrist should conduct additional thorough review of contributory factors and make changes in the treatment plan
Strategies for Changed Treatment Plans

- For antidepressant treatment optimize the dose if the side effect burden is tolerable and the upper limit of dosage has not been reached
- Consider augmenting medication with depression focused psychotherapy
- Consider medication changes
  - Change to another non MAOI antidepressant
  - Change to antidepressant in same class (SSRI to SSRI)
  - Change to antidepressant in another class (SSRI to TCA)
  - For patients who do not respond to SSRIs, a trial of an SNRI may be helpful
  - Augmentation of depressants can now include another non MAOI depressant from another class, or a non depressant medication such as lithium, thyroid hormone, or second gen. anti-psychotic

- Consider Medication Changes (cont.)
  - Additional strategies may include the addition of an atypical antipsychotic anticonvulsant, omega-3 fatty acids, folate, or psychostimulant medication including modafinil
  - For anxiety or insomnia consider giving anxiolytic and sedative hypnotic medications including buspirone, benzodiazepines, and select gamma aminobutyric acid (GABA) agonist hypnotics
  - For patients who are resistant to medication, ECT remains an effective therapy for consideration
  - In patients capable of adhering to dietary and medication restrictions, an additional options is changing to a nonselective MAOI after allowing sufficient time between medications to avoid interactions, or consider transcranial magnetic stimulation
  - For patients who have not responded to 4 antidepressant trials, or ECT Vagus nerve stimulation may be another treatment option
Strategies for Changed Treatment Plans

- For patients with psychotherapy as primary treatment plan intensity, frequency, and duration as well as changing treatment type should be considered
- For patients utilizing psychotherapy alone, medications should be considered
- Patient who have a history of poor adherence or incomplete response to single modalities may benefit from combined treatment (medication and psychotherapy)

Continuation Phase

- During continuation phase patient should be monitored for relapse
- Assessment of symptoms should continue
- Patients treated successfully in acute phase should continue treatment (medication/therapy)
- To prevent a relapse of depression in continuation phase psychotherapy (cognitive behavioral therapy) is recommended
- Patients who respond to ECT should receive pharmacotherapy (lithium and nortriptyline); if response to acute course of ECT, may be given continuation of ECT if other interventions have proven unsuccessful
Maintenance Phase

- In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior episodes, or who have chronic major depressive disorder should proceed to the maintenance phase of treatment post continuation.
  - During maintenance, antidepressant medication that produced symptom remission during acute phase and maintained remission during continuation should be continued at full dose.
  - If therapy was the method of treatment, maintenance treatment should be considered with reduced frequency of sessions.
  - For patients whose depressive episodes have not responded to acute or continuation treatment, but have responded to ECT, ECT maintenance should be considered.
  - Maintenance treatment with vagus nerve stimulation is also appropriate for individuals whose symptoms have responded to treatment modality.

Discontinuation of Treatment

- Taper medication over several weeks for pharmacotherapy discontinuation.
- Stow taper or temp. change to a longer half life antidepressant may reduce risk of discontinuation syndrome.
- Patient should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in this event.
- After discontinuation of medication, patients should be monitored for a duration of several months, and receive another course of acute treatment if symptoms occur.
Treatment Resistant Depression

- Between 10% and 30% of depressed patients taking an antidepressant are partially or totally resistant to treatment.
- Reasons for treatment may include:
  - Undiagnosed or misdiagnosed medical conditions (such as anemia).
  - Nonpsychiatric drugs such as Aldomet or Serpasil can negatively impact depression.
  - Comorbid disorders such as eating disorders, or substance abuse.
  - Adverse effects and poor compliance of current treatment regime.
5 Strategies to Overcome Treatment Resistance

Optimization
Drug Substitution
Combination Therapy
Augmentation Therapy

Optimization

- If the dosage prescribed is too low, or the length of treatment time is inadequate
- When a patient's history suggests inadequate therapy, the clinician should maximize the dosage or duration of the therapy

An adequate duration for a trial of antidepressant therapy has been defined by some clinicians as four to six weeks. Others assert that a minimum of six weeks is necessary.
Drug Substitution

- People who have not responded to traditional antidepressant therapy may benefit from drug substitution.
- Changing from one antidepressant to another in the same class has not produced impressive response rates; however.
- Some studies suggest that switching to an antidepressant with a different mechanism of action is often associated with a better response rate.

Studies have shown that non-responders who are switched from a tricyclic antidepressant to an alternative antidepressant class may result in a 50% to 60% positive response rate.

Combination Therapy

- Combination therapy involves the addition of a second antidepressant agent to the therapeutic regimen.
- Combination therapy may also include concurrent administration of two or more anti-depressant agents.
  - Example: adding trazodone, desipramine, or bupropion to fluoxetine.
- Therapeutic responses of combination therapy may be different than a response achieved by either drug alone, and may be potentially beneficial during the early stages of MDD.
Augmentation Therapy

- Augmentation therapy consists of adding a second agent, not routinely prescribed for depression, to the therapeutic regimen when there is a limited response to the antidepressant.
- Common augmentation therapy agents include:
  - Lithium
  - Atypical Antipsychotics
  - Thyroid hormone
  - Beta blocker pindolol (Visken)
  - Buspirone (Buspar)

Recommendations for nonresponse or incomplete response

<table>
<thead>
<tr>
<th>First Line: (level 1 or level 2 evidence, plus clinical support) Add on another agent</th>
<th>Second Line: (level 3 evidence or higher, plus clinical support) Add on another agent</th>
<th>Third Line: (level 4 evidence or higher, plus clinical support) Add on another agent</th>
</tr>
</thead>
</table>
| • Aripiprazole (level 1)  
• Lithium (level 1)  
• Olanzapine (level 1)  
• Risperidone (level 2) | • Bupropion (level 2)  
• Mirtazapine/mianserin (level 2)  
• Quetiapine (level 2)  
• Triiodothyronine (level 2)  
• Other antidepressants (level 3) | • Buspirone (level 3)  
• Modafinil (level 2)  
• Ziprasidone (level 3)  
• Stimulants (level 3) |

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### Combination/Augmentation Strategies: General Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>• Strategy builds on therapeutic gains</td>
<td>• Increased potential of drug interaction</td>
</tr>
<tr>
<td>• Addition of second compound is generally well tolerated</td>
<td>• Reduced compliance</td>
</tr>
<tr>
<td>• More rapid onset of antidepressant effects during crucial early phase</td>
<td>• Increased adverse effects</td>
</tr>
<tr>
<td>• Response rate comparable or superior to drug substitution</td>
<td>• Efficacy and long term effects may not yet be known in some cases</td>
</tr>
</tbody>
</table>

Common Issues Regarding Antidepressant Therapy

- Non compliance is an important reason for suboptimal treatment outcomes.
- Patients frequently report the following:
  - Read up on it on the internet and didn’t like side effects.
  - Took it for a week then stopped.
  - Only take it when I feel bad.
  - Once I felt better I stopped the medication.
- 75% of antidepressants are discontinued by month 4

Interventions to Reduce Non-Compliance

- Educate patients regarding the disease and treatment options.
- Discuss common side effects of the antidepressant medication openly with patients.
- Reassure patients that other medication options will be explored in case of side effects.
- Emphasis that these medications need to be taken on a daily basis to be effective.
- Reassure patients that Antidepressant medications are not addictive.
- Explain to patients that continued treatment with antidepressant medication has a neuro protective effect.
Behavioral Modifications

- Understanding the Mind Body Connection in Depression can inform a variety of treatment methods to provide optimal patient care. For instance:
  - Encourage physical activity which increases BDNF (Brain-derived neurotrophic factor)
  - Encourage a healthy diet and limitation of processed foods
  - Let the patient preference inform treatment
  - Engage patients in support groups, and if possible conduct support groups outdoors or in aesthetically pleasing environments
  - Educate patients on importance of structure in daily life, need to continue with ADLs and avoid spending increase time in bed.
  - Patients need to adhere to regular sleep and wake times.
  - Involve family members early in treatment. Educate them regarding the disease process. They can provide extra support and help implement recommendations, monitor medication compliance, and provide better feedback on patients functioning.

Management of Patients who are not Responding to Treatment

- Allowing patient preference to shape treatment, and consider lifestyle in mind-body treatments
- Reconsider diagnosis
- Refer to Psychiatrist
- Implement case management
- Monitor med compliance through pharmacy services
- Consider more aggressive Pharmacotherapy
Question and Answer Session

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