

# **Major Depressive Disorder – Overview of Diagnosis and Treatment**

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## **Major Depressive Disorder**

- **The World Health Organization ranks Major Depressive Disorder (MDD) as one of the most prevalent and disabling diseases in the world**
- **MDD is estimated to be the leading cause of disability in the United States, accounting for 8% of the total disability-adjusted life-years**
- **The 12-month prevalence for MDD is 5.28% and the lifetime prevalence is 13.23%**

## **Major Depressive Disorder**

- **Patients with MDD frequently have other co-morbid mental health issues including**
  - **anxiety disorders (36.1% 12-month and 41.4% lifetime prevalence),**
  - **personality disorders (37.9% 12-month and 30.8% lifetime prevalence) and**
  - **substance use disorders (4.6% 12-month and 17.2% lifetime prevalence)**
- **MDD associated with an increased all cause mortality risk of 1.81(1.58–2.07)**

## **Screening**

- **The Patient Health Questionnaire PHQ-9 is recommended to screen for Major Depressive Disorder**
- **Can be found at:**  
<http://steppingup.washington.edu/keys/documents/phq-9.pdf>

## **Risk Factors**

- **Higher rates of depression associated with:**
  - Family history of mood disorders
  - Female gender (3:1)
  - Divorced or separated marital status
  - Unemployment
  - Less than 12 years of formal education
  - Tobacco use
  - Heart Disease
  - Obesity
  - Low socioeconomic status

## **DSM-IV TR Criteria**

- ***Major Depressive Disorder* is characterized by one or more *Major Depressive Episodes*, as defined by DSM-IV-TR criteria and a lifelong absence of manic episodes.**
- ***A Major Depressive Episode* is characterized by the presence at least 5 of 9 criteria, broadly grouped into four major categories: mood, psychomotor activity, vegetative function and cognition.**

## **DSM-IV TR Criteria**

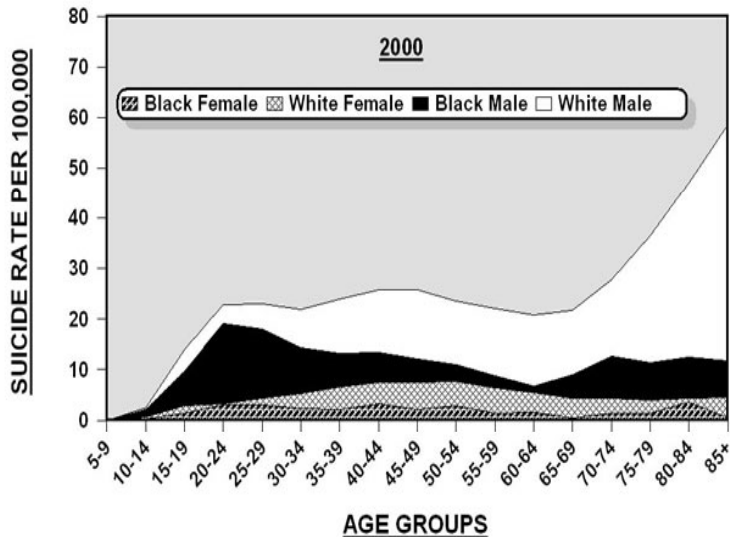
- **The patient must have at least five symptoms for a minimum of 2 weeks: at least one of the symptoms must be depressed mood or anhedonia: a loss of interest or pleasure.**
  - **Depressed mood**
  - **Anhedonia**
  - **Alteration in sleeping patterns**
  - **Alterations in appetite**
  - **Decreased levels of energy**
  - **Decreased levels of concentration**
  - **Increased feelings of guilt**
  - **Psychomotor retardation**
  - **Suicidal ideation**

## **Assessment**

- **Should be in the context of a full history and physical**
- **Screen for a history of mania, hypomania and mixed episodes**
- **Assess for substance abuse issues**
- **Assess for a history of trauma**
- **Obtain thorough family and social history**
- **Screen for suicidal ideation**

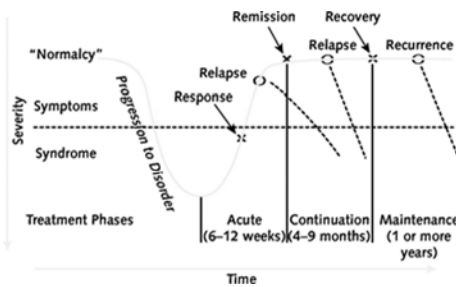
## Assessment for suicide risk “SAD PERSONS”

- S- Male Sex
- A- Age (young/elderly)
- D- Depression
- P- Previous attempts
- E- ETOH
- R- Reality testing (Impaired)
- S- Social support (lack of)
- O- Organized plan
- N- No spouse
- S- Sickness



Source: National Institute of Mental Health  
Data: Centers for Disease Control And Prevention, National Center For Health Statistics

## Phases of Treatment



**Acute Phase (6-12 weeks):** Initial phase of treatment with active signs and symptoms. Treatment targets response and remission

**Continuation (4-9 months):** Following remission, treatment continues with a focus on achieving functional improvement

**Maintenance (years):** Treatment continues until signs and symptoms have fully remitted and functional recovery has been achieved.

## Treatment

- The greater the severity and duration of depressive symptoms, the more clear the benefit of antidepressants.
- **Subthreshold depression:**
  - Treat with support, education and active monitoring.
- **Mild depression:**
  - Low intensity psychosocial interventions are indicated. If these interventions fail, then antidepressants are recommended

## **Treatment**

- **Moderate depression:**
  - antidepressants alone are indicated for moderate depression.
  - Antidepressant and psychotherapy may be used together for patients with significant psychosocial problems or comorbid personality disorder.
- **Severe depression:**
  - A combination of antidepressant medications and evidenced based psychotherapy is indicated
  - Electroconvulsive therapy may also be considered first line in severe depression

## **Antidepressant Medications**

- **First line antidepressant medication treatment is usually with a selective serotonin inhibitor (SSRI)**
  - Side effects are generally more tolerable than other types of antidepressants
  - SSRIs include
    - fluoxetine (Prozac, Sarafem)
    - paroxetine (Paxil)
    - sertraline (Zoloft)
    - citalopram (Celexa)
    - escitalopram (Lexapro)

## Antidepressant Medications

- Before altering any treatment, allow a trial of appropriate duration, usually 2 – 6 weeks (or longer) at adequate doses
  - If there is minimal response, it is preferable to use the *substitution strategy*.
  - If there is a reduction in symptoms, it is preferable to use the *augmentation strategy*

## Substitution Strategy

- When substituting antidepressants, alter the antidepressant class unless the reason for substitution is poor tolerability that has prevented an adequate trial.
- Consider as Second Line:
  - Serotonin and Norepinephrine reuptake inhibitors (SNRIs)
    - Venlafaxine (Effexor)
    - Duloxetine (Cymbalta)
    - Desvenlafaxine (Pristiq)



## **Substitution Strategy**

- **Norepinephrine and Dopamine reuptake inhibitors (NDRIs)**
  - **Bupropion (Wellbutrin)**
- **Norepinephrine and selective serotonergic receptor antidepressants (NaSSAs)**
  - **Mirtazapine (Remeron)**
  - **Nefazodone (Serzone)**
  - **Trazodone (Desyrel)**

## **Substitution Strategy**

- **Tricyclic and Tetracyclic antidepressants (TCAs) - tend to have more numerous and more severe side effects**
  - **Amitriptyline (Elavil)**
  - **Doxepin (Sinequan)**
  - **Nortriptyline (Pamelor)**
  - **Desipramine (Norpramin)**

## Substitution Strategy

- **Monoamine oxidase inhibitors (MAOIs) -** often prescribed as a last resort on other medications haven't worked because of potentially serious harmful side effects. These medications require strict dietary restrictions due to a rare but potentially fatal interaction with foods high in tyramine such as aged cheese and red wine.
  - **Phenelzine (Nardil)**
  - **Tranylcypromine (Parnate)**
  - **Selegiline (Emsam) – a transdermal patch**

## Side Effects of Antidepressants

	SSRI	TCA	SNRI	NDRI	NaSSA	MAOI
GI Distress	+++	0/+	+++	0/+	0/+	+/>+++
Sexual Disturbance	+++	++	+++	0/+	0/+	+/>+++
Weight Gain	0/+	++	0/+	0	+++	++/>+++
Sedation	+/>++	++/>+++	+	+	+++	+/>++
EKG Changes	0/+	++	0/+	0/+	0/+	0/+
Postural Hypotension	0/+	++/>+++	0/+	+	+/>++	++/>+++
Hypertension	0	0/+	+	+	0	+

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## Augmentation Strategies

- Add psychotherapy if patient started on medication alone and add medication if patient started on psychotherapy alone
- If patient is on an anti-depressant, pharmacological augmentation can be considered.
  - Level one augmentation strategies include:
    - Lithium: can be administered in conjunction with all antidepressants and is the most studied approach
    - Atypical antipsychotic medications (aripiprazole, olanzapine, risperidone, quetiapine)
    - Thyroid hormone: Usually T3
    - Also, a short-term benzodiazepine may be helpful for symptom management

## Augmentation Strategies

- Combining antidepressants
  - There is limited controlled evidence to support this approach, but it can be considered to treat resistant depression.
  - Logical combinations include combining serotonergic and noradrenergic acting drugs, or two agents with different pharmacology.
- **Caution:** When employing augmentation strategies or combining antidepressants, monitor carefully for side effects, potential drug-drug interactions and toxicity.

## **Neuromodulation**

- **There are currently three FDA approved neuromodulation therapies for depression**
  - **ECT - Electroconvulsive Therapy**
  - **VNS - Vagal Nerve Stimulation**
  - **TMS - Transcranial Magnetic Stimulation**

## **Electroconvulsive Therapy (ECT)**

- **An often misunderstood treatment that has been in use since the 1930's**
- **Under general anesthesia, electrodes applied to the scalp are used to induce a generalized seizure.**
- **Remission rate after ECT is on the order of 70%–90%, which substantially exceeds that of any other form of antidepressant**
- **Common side effects:**
  - **Headache, nausea, myalgia, post-ictal agitation**
  - **Memory impairment**

## **Vagal Nerve Stimulation (VNS)**

- A surgically implanted pacemaker-like device that delivers regular electrical impulses to the vagus nerve used as an adjunctive treatment for certain types of intractable epilepsy and refractory depression.
- A study in *Biological Psychiatry* in 2005 compared 124 people that received usual treatment to 205 people that received usual treatment plus VNS.
  - After 12 months of treatment, the combination treatment group showed more improvement than the usual treatment group.
  - Significant improvement was seen in 27% of patients that received VNS vs. 13% that did not.
- Possible side effects from VNS
  - Temporary hoarseness, cough, and shortness of breath that occur during active stimulation
  - Risks of surgery, including infection

## **Transcranial Magnetic Stimulation (TMS)**

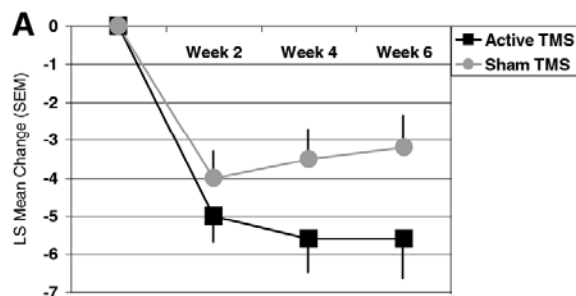
- Uses a focused magnetic field to create an electric current in the brain
- Multiple research applications, such as brain mapping
- One device has FDA approval for treatment of depression
- Treatment consists of stimulating the Left Dorsolateral Prefrontal Cortex (LDPFC)
- A treatment course consists of one hour sessions, 5 days per week for 4 to 6 weeks
- OSU Harding Hospital is in the process of setting up a TMS service that we hope to have up and running by late summer/early fall

## NeuroStar TMS Device



Photograph from <http://www.neuronetics.com/wp-content/uploads/2010/11/PrescribingInformation.pdf>

### Efficacy of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial



( $p=0.057$  for week 4 contrast,  $p=0.058$  for week 6 contrast)

- Average reduction of MADRS score 22.1% with active TMS and 9% for patients receiving inactive (sham) treatment.

- Statistical significance in favor of active TMS was observed at 2, 4 and 6 weeks.

O'Reardon, J. P., H. B. Solvason, et al. (2007). "Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial." *Biol Psychiatry* 62(11): 1208-1216.

## **Open-label outcomes for TMS Therapy**

- **1 in 2 patients suffering with depression improved significantly**
- **1 in 3 patients were completely free of depression symptoms after six weeks of treatment**

Demitrack MA, Thase ME. Clinical significance of transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant depression: synthesis of recent data. *Psychopharm Bull.* 2009, 42(2): 5-38.

## **Key Points in the Approach to Patients with Suboptimal Response**

- **Document improvement or lack thereof**
- **Establish adherence and adequacy of treatment**
- **Assess for comorbid illness, medication side effects, and psychosocial stressors**
- **Optimize treatment – go for remission**
  - **Dose**
  - **Psychotherapy**
  - **Augmentation**

## **Prevention of the Development of Treatment Resistant Depression**

- **Avoid chronicity**
- **Early detection**
- **Treat to complete symptom relief**
- **Prevention of recurrence, 6-12 month treatment**

## **Management Recommendations**

- **Establish and maintain a therapeutic alliance**
  - **Important to collaborate with the patient and family in treatment decisions**
  - **Problems with alliance may adversely effect treatment adherence**
  - **Problems with the alliance may in part be complicated by the depression itself.**
- **Complete the psychiatric assessment**
- **Evaluate the safety of the patient**
- **Establish the appropriate setting for treatment**
- **Evaluate functional impairment and quality of life.**



## **Management Recommendations**

- **Coordinate care with other clinicians**
- **Regularly monitor the patients psychiatric status**
- **Integrate measurements, such as PHQ-9, into the psychiatric management.**
- **Provide education to the patient and the family**
  - **Optimize treatment adherence**
  - **Frame depression as illness – no one to blame**
  - **Benefits and risks of medication**
  - **Identify and problem solve barriers to treatment**

## **Special Populations**

## **Special Populations (Child/Adolescent)**

- **Pre-pubertal children**
  - **More likely to have:**
    - **somatic complaints**
    - **psychomotor agitation**
    - **mood congruent hallucinations**
  - **Less likely to have:**
    - **disturbances in sleep and appetite**

## **Special Populations (Child/Adolescent)**

- **Adolescents**
  - **increased oppositional behavior**
  - **substance abuse**
  - **irritability**
  - **social withdrawal**
  - **increased rejection sensitivity and a**
  - **decline in school performance**

## **Pediatric Depressive Disorders**

- **Psychiatric comorbidity**
  - 1/3 to 2/3 of depressed patients
- **Risk of future bipolar disorder**
  - Bipolar disorder develops in 10 to 30%
- **Predictors of future bipolar disorder**
  - Psychosis
  - FH of bipolar disorder
  - Pharmacologically induced mania/hypomania
  - Rapid onset/offset of depressed mood

## **Psychosocial Stressors that Affect Treatment Outcome**

<u>Stressor</u>	<u>Intervention</u>
Parental depression	Treatment of parent improves child
History of abuse	CBT, IPT, respond worse; need to address trauma
Bullying	School mandated to intervene
Family discord	Predicts non-response, relapse; improvement related to response
Sexual orientation	Increased bullying, family discord
Loss	Traumatic grief treatment

## **Special Populations (Child/Adolescent)**

- The serotonin re-uptake inhibitors (SSRI's) effective in treating depression in this population.
- There is some evidence that treatment of adolescents and young adults may lead to increased suicidal ideation and this has resulted in an FDA “black box” warning.
  - It is important that these patients be treated for depression
  - Monitor closely for suicidal thoughts, especially shortly after treatment with an SSRI has started

## **Special Populations (Geriatric)**

- Depression is not a normal part of aging
- Older depressed patients can also present
  - Increased somatic complaints
  - memory loss
  - inattention
  - withdrawal from daily activities
  - confusion
  - lapses in personal hygiene and social skills
- Distinguishing depression in the elderly from dementia is essential for correct diagnostic and therapeutic follow-up

## **Special Populations (Geriatric)**

- **More vulnerable to develop melancholic depression, which is characterized by**
  - **early morning awakening,**
  - **diurnal variation in mood,**
  - **low self-esteem, and**
  - **low mood reactivity**
- **Depression in the elderly associated with**
  - **loss of autonomy**
  - **loss of loved ones and friends**
  - **co-morbid health issues**

## **Special Populations (Geriatric)**

- **ECT is more effective in the elderly compared to the younger population**
- **Suicide rates increase with age, especially in Caucasian males**
- **Careful consideration needs to be given medication dosing and potential adverse drug interactions**

## **Special Populations (Pregnancy)**

- Discontinuing medications during pregnancy can lead to relapse of symptoms for up to 68% of women
- Depression associated with low birth weight and pre-term labor
- All anti-depressant medications are category C
- Most safety data available for SSRI's, particularly for fluoxetine (Prozac)
  - Some risk for preterm labor
  - Some risk for serotonin withdrawal in the neonate
  - Small risk for persistent pulmonary hypertension (has only been reported with paroxetine (Paxil))
- ECT is a consideration, late term introduces some risks with anesthesia

## **Special Populations (Post-Partum)**

- **Post-Partum Blues**
  - Symptoms of depression are common in the postnatal period.
  - Up to 65% of mothers report some depressed mood after childbirth, often called "postpartum blues."
  - Symptoms are generally mild and transient, although in 10% of mothers, it may lead to a full-fledged Post-Partum Depression

## **Special Populations (Post-Partum)**

- **Post-Partum Depression**
  - The signs and symptoms of postpartum depression are similar to those of a major depressive disorder, but the onset is within four weeks of delivery
- **Risk Factors**
  - History of a mood disorder
  - Marital conflict
  - Limited assistance with infant care
  - Multiparous birth

## **Special Populations (Post-Partum)**

- **Breast feeding while on antidepressants**
  - Studies of sertraline (Zoloft) and paroxetine (Paxil) use while breastfeeding suggest that transfer of these agents into milk is quite minimal, and virtually no side effects have been reported in numerous breastfed infants
  - In a number of studies sertraline (Zoloft) and paroxetine (Paxil) usually produce undetectable levels in the infants