Improving Outcomes with Depressed Patients

An Individualized Case-Based Approach

Richard J. Metzner, M.D.

Learning Objectives

After completion participants should be able to:

1. Communicate with patients in a way that improves communication and speeds recovery

2. Select screening methods that optimize outcomes in the treatment of depression

3. Match appropriate treatments to the individual needs of depressed patient

4. Understand why remission rather than response should be the standard of care in treating depression
Which of the Following is False?

1. Depression has surpassed all other medical disorders as the number one cause of disability in the world
2. In the U.S. 21% of women and 13% of men will have at least one depressive episode
3. Depression increases morbidity and mortality associated with other illnesses
4. Most depression is recognized by primary care physicians.

Answer 4 was False

1. Depression has surpassed all other medical disorders as the number one cause of disability in the world
2. In the U.S. 21% of women and 13% of men will have at least one depressive episode
3. Depression increases morbidity and mortality associated with other illnesses
4. **Up to 50% of depressed patients are NOT recognized by primary care physicians.**
The Cost of Depression

- Depression has surpassed all other medical disorders as the number one cause of disability in the world.
- In the U.S. 21% of women and 13% of men will have at least one depressive episode.
- Depression increases morbidity and mortality associated with other illnesses.
- Only one out of five depressed patients receive proper treatment.

Challenges with Depression

- Up to half of all patients with major depressive disorder are not recognized and treated.
- This percentage is even higher for culturally diverse patients.
- Complicated presentation particularly focused on somatic complaints is one of the barriers to early recognition and treatment.
- Most patients with major depressive disorder are not treated by mental health professionals.
How to Treat Individuals with Depression

- Remember that every depressed patient is different:
  - NEUROPHYSIOLOGICALLY
  - PSYCHOSOCIALLY
### Three Functional Subtypes

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>TRADITIONAL TERMS</th>
<th>OPTIMAL TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEMODULATED</td>
<td>anxious, agitated, hostile, hypochondriacal</td>
<td>serotonergic</td>
</tr>
<tr>
<td>DEACTIVATED</td>
<td>psychomotor-retarded, blunted, apathetic</td>
<td>catecholaminergic</td>
</tr>
<tr>
<td>MIXED</td>
<td>melancholic, atypical, resistant</td>
<td>dual-mechanism</td>
</tr>
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</table>

Metzner R, APA Annual Meeting, 2000

### Three Functional Subtypes (cont.)

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>ENERGY</th>
<th>REACTIVITY</th>
<th>SLEEP</th>
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</thead>
<tbody>
<tr>
<td>DEMODULATED</td>
<td>same or increased</td>
<td>increased</td>
<td>decreased</td>
</tr>
<tr>
<td>DEACTIVATED</td>
<td>decreased</td>
<td>decreased</td>
<td>increased</td>
</tr>
<tr>
<td>MIXED</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
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</tbody>
</table>

Metzner R, APA Annual Meeting, 2000
Summary of the Targeted Treatment of Depression

- Demodulated patients are often anxious and/or hostile and may respond better to SSRIs
- Deactivated patients are frequently fatigued and/or apathetic and may do best with catecholaminergic ADs
- Mixed patients are a combination of the above and may improve most on dual-mechanism regimens

Case 1 – Dan

- Dan is a 21 year old unmarried man who works with his parents in a family business.
- He started taking paroxetine 20 mgm for moderate anxiety and depression a year ago.
- He comes in today saying he was ok for a while but feels much more anxious and depressed now.

Based on an actual case – Name changed and picture simulated
Initial Findings

- The history is unremarkable except for increased beer drinking in the past 6 months – “at least a six-pack a day.”
- The PE is normal except for mild tremulousness.
- He denies any suicidal ideation.
- He says with intensity “Please give me something for the anxiety.”

What Should You Do Now?

1. Tell him that his increased drinking is a major part of the problem
2. Strongly encourage him to taper all alcohol consumption
3. Prescribe alprazolam 1.0 mgm q 6h prn for anxiety
4. Increase the paroxetine to 30 mgm qd
5. 1, 2 and 4
6. All of the above
You Should

1. Tell him that his increased drinking is a major part of the problem
2. Strongly encourage him to taper all alcohol consumption
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4. Increase the paroxetine to 30 mgm qd
5. 1, 2 and 4
6. All of the above

Dan Returns 2 Weeks Later

- He says he’s down to just “1 or 2” beers and feels less anxious
- He says he’s not as depressed either
- But he complains that he lacks interest in “getting off the couch” and has missed work for several days
Your Next Step Should Be To

1. Increase the paroxetine to 40 mgm daily
2. Augment the paroxetine with bupropion XL 150 mgm each morning
3. Stop the paroxetine and refer Dan to cognitive behavioral therapy
4. Accuse him of lying about his alcohol consumption and refer him to a rehab center
5. 1 and 2
6. 3 and 4

Your Next Step Should Be To

1. Increase the paroxetine to 40 mgm daily
2. **Augment the paroxetine with bupropion XL 150 mgm each morning**
3. Stop the paroxetine and refer Dan to cognitive behavioral therapy
4. Accuse him of lying about his alcohol consumption and refer him to a rehab center
5. 1 and 2
6. 3 and 4
Dan’s Status 2 Years Later

- He is being careful about alcohol use
- He continues to use paroxetine 30 mgm daily and bupropion XL 150 mgm each morning
- He is enjoying taking more responsibility at work
- He no longer feels anxious or depressed

Dan’s Treatment Reviewed

- Thorough history and PE
- Addictive alcohol use confronted
- Increased anxiety addressed by increasing SSRI, not adding another addictive agent
- SSRI-induced deactivation treated by augmenting SSRI with an NDRI
A New Test to Individualize Antidepressant Treatment: The Targeted Treatment Depression Inventory (TTDI)®

Deactivation (A) 25 20 15
Demodulation (M)

SCORE
A=11 M=7
Add Bupropion XL 150 mg
Remission
A=-3 M=1

Initial TTDI Scores 2 Weeks Later 3 ½ Weeks Later

Stress and Mood
Mood Normal
Stress
Adjustment Disorder with Depression Minor Depression Dysthymia Major Depression/Bipolar

SEVERITY OF RESPONSE
The Cycle of Stress and Depression

- STRESS → CORTICO-STEROIDS → HPA FEEDBACK → DEPRESSION
- Antidepressants reverse this process
- NEUROTRANSMITTER DYSFUNCTION

Genetics and Depression

- Genetic factors may account for as much as 30% of the variance in susceptibility to depression
- Functional polymorphisms in promoter regions for the serotonin transporter may be among these factors
- It is likely that there are numerous separate loci combining to form each depressive genotype
- Environmental and internal triggers such as emotional stress and physical illness act upon these diatheses to bring about clinical depression
Risk Factors for Depression

**GENETIC** Family History
- e.g., Systemic Illness, Chronic Pain, Endocrine Disorder

**SOMATIC**
- e.g., Low Self-Esteem, Poor Coping Skills

**PSYCHOLOGICAL**
- e.g., Unemployment, Divorce, Abuse, Bereavement

**ENVIRONMENTAL**

Neurotransmitters Offer a Well-Studied Biochemical Bridge Between the Mind and the Brain.
Serotonin Synthesis and Metabolism

**SYNTHESIS**

DIETARY PROTEIN

↓

TRYPTOPHAN

↓

5-OH-TRYPTOPHAN

(5-HTP)

↓

SEROTONIN

(5-OH-TRYPTAMINE or 5-HT)

**METABOLISM**

MAO

5-HIAA

Catecholamine Synthesis and Metabolism

**SYNTHESIS**

DIETARY PROTEIN

↓

TYROSINE

↓

L-DOPA

↓

DOPAMINE

MAO

HVA

**METABOLISM**

MAO

MHPG

NE

DA

NOREPINEPHRINE

HVA

DOPAMINE

L-DOPA

TYROSINE

TRYPTOPHAN

5-OH-TRYPTOPHAN

(5-HTP)

SEROTONIN

(5-OH-TRYPTAMINE or 5-HT)

MAO

5-HIAA

MHPG

DA

NE

Catecholamine Synthesis and Metabolism
APA Guideline-based Antidepressant Selection Algorithms

PICK A CARD, ANY CARD

STAR*D Remission Rates

Getting It Right the First Time

Individualized Algorithms

- Derived from studies that distinguish patients by empirically-derived symptom profiles
- Use measurement-based case management to select initial treatment and maintain remission
- May anticipate endogenotypic differences between depressed patients
**Impaired Neurotransmission and Reduced Neural Adaptability**

**SEROTONIN**
- IMPAIRED MODULATION
- Depression
  - Anxiety
  - Irritability
  - Hostility
  - Impulsivity
  - Agitation
  - Hypochondriasis
  - Suicidality

**NOREPINEPHRINE**
- IMPAIRED ACTIVATION
- Fatigue
- Apathy
- Anhedonia
- Hypersomnia
- Lack of initiative
- Inability to concentrate
- Decreased productivity

**DOPAMINE**

**DSM-IV Criteria for Major Depression**

- Persistent depressed mood (+)(-)
- Anhedonia (+)
- Weight loss (+) or gain (-)
- Insomnia (+) or hypersomnia (-)
- Agitation (+) or retardation (-)
- Excessive worthlessness or guilt (+)
- Diminished cognitive function (-)
- Suicidal ideation (+)

(+)=DEMODULATED   (-)=DEACTIVATED
Depression Assessment Tools

- Professionally-Rated
  - Hamilton Depression Rating Scale (HDRS) – 17 item, 21 item & other versions
  - Montgomery Asberg Depression Rating Scale (MADRS)

- Self-Rating Scales
  - Beck Depression Inventory (BDI)
  - Zung Self Rated Depression Scale (ZUNG SRS)
  - Hospital Anxiety and Depression Scale (HADS)
  - Major Depression Inventory (MDI)
  - Harvard National Depression Screening Scale
  - Goldberg Depression & Mania Scales
  - Depression Anxiety Stress Scales (DASS)
  - Clinically Useful Depression Outcome Scale (CUDOS)
  - Targeted Treatment Depression Inventory

Source: http://www.neurotransmitter.net/depressionscales.html

Deactivation, Demodulation & Distress Items in 13 Mood Measuring Scales

(larger areas = more items)

Ratio = 4:6:3
TTDI: The First Depression Test Designed to Guide Antidepressant Treatment

- The Targeted Treatment Depression Inventory (TTDI) is a free self-administered, computer-scored 17-item questionnaire that has been tested for over 6 years in primary care and psychiatric offices throughout the U.S.

- Preliminary studies on nearly two thousand patients indicate that it rapidly provides a quantified measure of demodulation and deactivation that can help guide antidepressant selection.
TTDI: Distinguishing Features

- High reliability bivalent scales (minus and plus values) designed to measure severity of depression, mania and emotional blunting

- Two independent subscales - modulation (M) and activation (A) for diagnosing subtypes and guiding choice of antidepressants

- Single depression score (D=M+A) to measure overall severity

www.ttdi.info

U.S. Patent 7553834 issued June 30, 2009

TTDI Algorithm

DEMODULATED → DEACTIVATED

DEMODULATED → MIXED

DEMODULATED → USE SSRI

DEMODULATED → USE NDRI

DEACTIVATED → MIXED

DEACTIVATED → USE SSRI

DEACTIVATED → USE NDRI

NO

YES

NO

YES
Results with TTDI in Primary Care & Psychiatric Settings

Patients tested >1 week to 141 weeks apart (n = 206)

<table>
<thead>
<tr>
<th>Remission Rate</th>
<th>∆ SCORE</th>
<th>Level</th>
<th>n</th>
<th>Time (weeks)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>-12.5*</td>
<td>1</td>
<td>96</td>
<td>T = 15.3</td>
</tr>
<tr>
<td></td>
<td>-9.7*</td>
<td>2</td>
<td>64</td>
<td>T = 19.5</td>
</tr>
<tr>
<td></td>
<td>-2.1†</td>
<td>Non-AD</td>
<td>46</td>
<td>T = 21.1</td>
</tr>
</tbody>
</table>

* p < .001
† n.s.

SSRI more Effective in Anxious Depression; Catecholaminergic Better in Retarded Depression

A 16 week double-blind study of post-stroke depressed patients; improvement was measured using a 26-symptom subtyping scale

Depressive Symptoms Correlate with Different Neuroanatomic Structures

HAM-D vs. PET scan  
n=298

DEMODULATED items, e.g., insomnia, suicidality

DEACTIVATED items, e.g., apathy, low libido

Case 2 – Allen

- Allen is a 30 year old male software expert who became severely anxious and depressed over financial and personal problems.

- When asked how he feels, he says: “Down, depressed, anxious – like I just wish I wasn’t in my body – like I want to jump out of my skin.”
Case 2 – Allen

Using the Targeted Treatment of Depression model, Allen’s type of depression might be called:

1. Demodulated
2. Deactivated
3. Mixed
4. Bipolar
5. Desquamating

Allen - DEMODULATED

Deactivation (A)  Demodulation (M)

Treatment with the SSRI citalopram brought Allen to full recovery.
Case 3 – Mary

- Mary is a 75 year old former nurse with bipolar disorder whose MD was afraid to treat her depression and possibly induce manic switching.
- She feels very non-productive and fatigued.
- She says: “It’s hard to move and do the things I’m used to doing.”

Case 3 – Mary

Using both the TTD model and traditional terminology, Mary’s depression might be called:
1. Demodulated
2. Deactivated
3. Mixed
4. Bipolar
5. Psychomotor-retarded
6. Demodulated & Bipolar
7. Deactivated, Bipolar & Psychomotor-retarded
Bupropion plus a mood stabilizer relieved Mary’s depression.

**Case 4 – Eileen**

- Eileen is a 31 year old married working mother with low energy, crying spells, and high irritability.
- She says she wants to have more energy and to feel ok.
- The smallest things make her feel like she’s “going to snap.”
- She has never experienced mania or hypomania.
Case 4 – Eileen

Using the TTD model, Eileen’s depression might be called:

1. Demodulated
2. Deactivated
3. Mixed
4. Bipolar
5. Anaclitic
6. Deactivated and Bipolar
7. Demodulated and Anaclitic

Eileen – MIXED

Eileen continues to do well on her combined regimen.
Which of the Following is False?

1. Demodulated patients are often anxious and/or hostile and may respond better to SSRI’s
2. Deactivated patients are frequently fatigued and/or apathetic and may do best with catecholaminergic AD’s
3. Mixed patients are a combination of the above and may improve most on dual-mechanism regimens
4. There is no test for identifying these subtypes and determining appropriate treatment

Answer 4 was False

1. Demodulated patients are often anxious and/or hostile and may respond better to SSRI’s
2. Deactivated patients are frequently fatigued and/or apathetic and may do best with catecholaminergic AD’s
3. Mixed patients are a combination of the above and may improve most on dual-mechanism regimens
4. **There is a test for identifying these subtypes and determining appropriate treatment – the TTDI.**
### Antidepressants

<table>
<thead>
<tr>
<th>Demodulated</th>
<th>SSRI:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CITALOPRAM (CELEXA)</td>
</tr>
<tr>
<td></td>
<td>ESCITALOPRAM (LEXAPRO)</td>
</tr>
<tr>
<td></td>
<td>FLUOXETINE (PROZAC)</td>
</tr>
<tr>
<td></td>
<td>PAROXETINE (PAXIL)</td>
</tr>
<tr>
<td></td>
<td>SERTRALINE (ZOLOFT)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deactivated</th>
<th>BUPROPION (WELLBUTRIN) SR or XL</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Mixed (Primary or Secondary)</th>
<th>SSRI + BUPROPION SR or XL; or</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DULOXETINE (CYMBALTA)</td>
</tr>
<tr>
<td></td>
<td>MIRTAZEPINE (REMERON)</td>
</tr>
<tr>
<td></td>
<td>VENLAFAXINE (EFFEXOR) XR</td>
</tr>
</tbody>
</table>

### Treating Depression with Benzodiazepines/Sedatives

- Can result in iatrogenic addictive disorders
- Is not preferable to using sedating antidepressants
- Is not the same as using atypical neuroleptics
- May be useful on a short-term basis
## Atypical Neuroleptics and Mood Stabilizers

<table>
<thead>
<tr>
<th>ATYPICAL NEUROLEPTICS</th>
<th>ARIPIPRAZOLE (ABILIFY)</th>
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<tbody>
<tr>
<td></td>
<td>OLANZAPINE (ZYPREXA)</td>
</tr>
<tr>
<td></td>
<td>PALIPERIDONE (INVEGA)</td>
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<td>LAMOTRIGINE (LAMICTAL)</td>
</tr>
<tr>
<td></td>
<td>LITHIUM (LITHOBID)</td>
</tr>
<tr>
<td></td>
<td>VALPROIC ACID (DEPAKOTE)</td>
</tr>
</tbody>
</table>

## Treating Depression Adjunctively with Atypical Neuroleptics:

- Can improve results in resistant patients
- Unlike benzodiazepines atypical neuroleptics are non-addictive
- May be associated with weight gain
- Should be carefully monitored in geriatric patients
Key Questions in Evaluating Depression

- Is the patient suicidal? YES? Start SSRI
- Is the patient bipolar? YES? Start atypical neuroleptic or mood stabilizer before antidepressant
- Can the patient identify the source of sadness or worry, (e.g., my marriage, job, health, etc.)? YES? Consider psychotherapy referral in addition to medication

Treating Patients as Individuals

PSYCHOSOCIALLY

Talk Therapies
Advantages of Familiarity with Basic Elements of Psychotherapy

- Although the primary care practitioner will not be doing formal psychotherapy in most cases, legal responsibility for necessary care may be attributed to the physician who did or did not make a referral.

- Familiarity with the basic features of various psychotherapies helps both patients and practitioners select wisely.

Types of Psychotherapy

- Behavioral
- Supportive
- Psychodynamic

Psychotherapy slides co-authored with Allen Pack, M.D.
Behavioral Therapy

- Pavlov
- Reward and punishment
- Desensitization through exposure
  - Relaxation
  - Immersion

Supportive Therapy

- Accentuate the positive
- Relieve stress
- “Scaffolding,” not structural change
Psychodynamic Therapy

- Freud
- Self-defeating unconscious defenses
- Identify, interpret, uncover, clarify

Manualized Therapies

- Originally designed as research protocols
- CBT: “Cognitive Behavioral Therapy”
- Combines supportive, behavioral and psychodynamic
Which of the Following is False?

1. Behavioral therapies such as systematic desensitization can be helpful in treating phobic disorders
2. Supportive therapies can be helpful in the short-term treatment of stress reactions
3. Psychodynamic therapies have shown superiority in treating personality disorders
4. CBT has proven effective in treating depression
5. None of the above.

None are False – 5 is Correct

1. Behavioral therapies such as systematic desensitization can be helpful in treating phobic disorders
2. Supportive therapies can be helpful in the short-term treatment of stress reactions
3. Psychodynamic therapies have shown superiority in treating personality disorders
4. CBT has proven effective in treating depression
5. None of the above.
Choosing Therapies

- Pragmatism
  - Cost
  - Availability
- Types
  - Psychodynamic, CBT, combined with medication
- Practitioner
  - The person vs the credentials

Other Targets
When to Refer a Patient to a Mental Health Professional

- Are you within your comfort level?
- Is the patient taking too much of your time with psychosocial issues?
- Are the psychotropic dosages you used to using insufficient?
- Is suicidality or some other serious deviant behavior a concern?
- Is psychiatric hospitalization a possibility?

Incomplete Remission Predicts Greater Relapse*

![Graph showing probability of remaining symptom-free over months of follow-up.](image)

*After termination of cognitive behavior therapy for depressed patients.

Consequences of Failing to Achieve Remission

- Greater risk of relapse
- Continued psychosocial limitations
- Continued impairments at work
- Worsened prognosis of Axis III disorders
- Increased utilization of medical services
- Sustained elevation of suicide and substance abuse risks


Learning Objectives Achieved

- Communicate about depression with patients and families in a way that will increase treatment compliance and promote recovery
- Select screening methods that optimize management of depressed patients
- Target different types of depressed patients with treatments that match their particular needs
- Understand why remission – not just improvement – is the standard of care for depressed patients
Thank You for Your Participation

Information on the TTDI® test is available at www.ttdi.info