CAN INDIVIDUALIZED TREATMENT IMPROVE ANTIDEPRESSANT EFFECTIVENESS?

RICHARD J. METZNER, M.D.
LEARNING OBJECTIVES

After completion participants should be able to:

1. Select screening methods that optimize management of depression

2. Discuss the scientific basis for individualizing the treatment of depression

3. Match treatments to patients’ particular needs

4. Understand why remission – not just improvement – should be the standard of care
WHICH OF THE FOLLOWING IS FALSE?

1. Up to half of all patients with major depressive disorder are not recognized and treated.
2. This percentage is even higher for culturally diverse patients.
3. Complicated presentation particularly focused on somatic complaints is one of the barriers to early recognition and treatment.
4. Most patients with major depressive disorder are treated by mental health professionals.
5. All of the above.
CHALLENGES WITH DEPRESSION

- Depression has surpassed all other medical disorders as the number one cause of disability in the world.
- Nine out of ten depressed patients will respond to treatment with antidepressant medication.
- Only one out of five depressed patients receives appropriate treatment.
FROM RECURRENCE TO REMISSION
Ron is a 44-year-old unmarried man whose recurrent depressions began in his 20s. He experiences anxiety, fatigue and body pains when he is depressed.

He is better now after years of going to different doctors and trying many antidepressants, anti-anxiety agents, and sedatives.
1. Psychotic?
   No – He has no delusions of guilt or other indications of being out of touch with reality.

2. Bipolar?
   No – He has never had manic or hypomanic episodes and no family history of bipolarity.

3. Atypical?
   No – His depressions “have a life of their own” once they get started (not reactive to events)

4. Major depression?
CASE 2: NEW SYMPTOMS DEVELOP

- Ron’s sister underwent emergency surgery for a perforated ulcer
- It happened one year after their mother died from cancer
- Ron became terrified that he might lose his sister too
- While she was recuperating without incident he developed anxiety, fatigue and body aches.
THE WORKUP SHOULD INCLUDE?

1. a toxicology screen
2. a PET scan
3. a lumbar puncture
4. a bone marrow biopsy
5. a history of recent stresses
6. None of the above
STRESS AND MOOD

Mood

Stress

Normal

Adjustment Disorder with Depression

Minor Depression

Dysthymia

Major Depression/Bipolar

SEVERITY OF RESPONSE
CASE 2: FAMILY BACKGROUND

- Ron’s mother suffered recurrent depression starting in her 20s
- Ron’s father was depressed from childhood
- Ron’s older brother is currently depressed and taking antidepressants
GENETICS FACTORS PROBABLY:

1. account for 90% of all susceptibility to depression
2. involve only one or two loci
3. do not involve polymorphisms
4. do not interact with environmental factors
5. all of the above
6. none of the above
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
Well-studied biochemical bridge between the mind and the brain.
SEROTONIN SYNTHESIS & METABOLISM

**SYNTHESIS**

DIETARY PROTEIN → TRYPtophan → 5- OH-TRYPTOPHAN (5-HTP) → SEROTONIN (5- OH-TRYPtAMINE or 5-HT)

**METABOLISM**

MAO → 5-HIAA
NEUROTRANSMITTERS AND NORMAL BEHAVIOR

Adapted from Healy and McMonagle (1997)
DEPRESSION

IMPAIRED NEUROTRANSMISSION AND REDUCED NEURAL ADAPTABILITY

SEROTONIN

IMPAIRED MODULATION
Anxiety
Irritability
Hostility
Impulsivity
Agitation
Hypochondriasis
Suicidality

DEPRESSION

Fatigue
Apathy
Anhedonia
Hypersomnia
Lack of initiative
Inability to concentrate
Decreased productivity

NOREPINEPHRINE

IMPAIRED ACTIVATION

DOPAMINE
THE CYCLE OF STRESS AND DEPRESSION

STRESS → INCREASED CORTICO-STEROIDS → DEPRESSION

HPA FEEDBACK ↓ BDNF

NEUROTRANSMITTER DYSFUNCTION

ANTIDEPRESSANTS reverse this process

BDNF = Brain-derived neurotrophic factor
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 DEPRESSION TESTS

Metzner R, APA Annual Meeting, 2005
RATIO OF DEMODULATION TO DEACTIVATION IN 13 DEPRESSION TESTS

Red bars are approximately 1:1

Metzner R, APA Annual Meeting, 2005
The Targeted Treatment Depression Inventory (TTDI) is a free self-administered, computer-scored 17-item questionnaire that has been tested for over 7 years in primary care and psychiatric offices throughout the U.S. Studies on more than a 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
REMISSION RATES AND SCORE CHANGES USING TTDI

Primary care and psychiatric settings

Metzner and Ho, unpublished data, August 2008
SSRI MORE EFFECTIVE IN ANXIOUS DEPRESSION; NRI BETTER IN RETARDED DEPRESSION

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

NRI = norepinephrine reuptake inhibitor

DEPRESSIVE SYMPTOMS CORRELATE WITH DIFFERENT ANATOMIC STRUCTURES

HAM-D vs. PET scan
n=298

DEMODULATED items, e.g.,
insomnia, suicidality

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

## 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>
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</table>

Metzner R, APA Annual Meeting, 2000
### THREE FUNCTIONAL SUBTYPES (CONTINUED)

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>ENERGY</th>
<th>REACTIVITY</th>
<th>SLEEP</th>
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<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>
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Metzner R, APA Annual Meeting, 2000
WHICH OF THE FOLLOWING IS FALSE?

1. Demodulated patients are often anxious and/or hostile and may respond better to SSRIs.

2. Deactivated patients are frequently fatigued and/or apathetic and may do best with catecholaminergic antidepressants.

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.
SUMMARY OF TTDI METHODS

- 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 antidepressants

- Mixed patients are a combination of the above and may improve most on dual-mechanism regimens

- The TTDI test helps identify these subtypes and determine appropriate treatment
Allen is a 30 year-old-man who became severely anxious and depressed over financial and personal problems.

Treatment with the SSRI citalopram brought Allen to full recovery. He has improved his life in many ways.
Mary is a 75-year-old woman with bipolar disorder whose MD was afraid to treat her depression and possibly induce manic switching.

Bupropion plus a mood stabilizer relieved Mary’s depression.
Eileen: MIXED

Eileen is a 31-year-old married working mother with low energy, crying spells, and high irritability.

Eileen continues to do well on her combined regimen.
## ANTIDEPRESSANTS

<table>
<thead>
<tr>
<th>Demodedulated</th>
<th>SSRI: CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE SERTRALINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deactivated</td>
<td>BUPROPION SR or XL</td>
</tr>
<tr>
<td>Mixed (Primary or Secondary)</td>
<td>SSRI + BUPROPION SR or XL; or DULOXETINE MIRTAZEPINE, or VENLAFAXINE XR</td>
</tr>
</tbody>
</table>

SR = sustained release; XL = extended release.
CASE 2: OVERSEDATION

- Ron’s physician started him on the tricyclic antidepressant amitriptyline
- Then he added the anti-anxiety agent alprazolam
- Then he added the short-acting sleeping pill triazolam
- After that Ron couldn’t concentrate very well
TREATING DEPRESSION WITH BENZODIAZEPINES/SEDATIVES

1. can result in iatrogenic addictive disorders
2. is preferable to using sedating antidepressants
3. is the same as using atypical neuroleptics
4. may be useful on a short-term basis
5. 1 and 4
6. 3 and 4
7. none of the above
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

Answer 5 was correct.
# ATYPICAL NEUROLEPTICS AND MOOD STABILIZERS

<table>
<thead>
<tr>
<th>ATYPICAL NEUROLEPTICS</th>
<th>ARIPIPRAZOLE</th>
<th>OLANZAPINE</th>
<th>PALIPERIDONE</th>
<th>QUETIAPINE</th>
<th>RISPERIDONE</th>
<th>ZIPRASIDONE</th>
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<tbody>
<tr>
<td>MOOD STABILIZERS</td>
<td>CARBAMAZEPINE</td>
<td>LAMOTRIGINE</td>
<td>LITHIUM</td>
<td>VALPROIC ACID</td>
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Note: Not all of these medications are FDA-approved for treatment of depression.
CASE 2: ADJUNCTIVE TREATMENT

- Ron experienced a reduction in body aches with aripiprazole
- Other atypical neuroleptics that he tried:
  - caused weight gain
  - induced tiredness
TREATING DEPRESSION ADJUNCTIVELY WITH ATYPICAL NEUROLEPTICS:

1. can improve results in resistant patients
2. has advantages over benzodiazepines
3. may be associated with weight gain
4. should be carefully monitored in geriatric patients
5. all of the above
6. none of the above
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 (marriage, job, health, etc.)?
  YES -- Consider psychotherapy referral in addition to medication
PSYCHOTHERAPY IN A NUTSHELL

- **COGNITIVE-BEHAVIORAL**
  - Identify depressive thoughts
  - Develop alternatives
  - Practice them outside of therapy

- **PSYCHODYNAMIC**
  - Identify old patterns
  - Link them to present problems
  - Work them out in therapy

- **INTERPERSONAL**
  - Identify social deficits and dysfunctions
  - Correct them
OTHER TARGETS

Medical problems – e.g., endocrine, medication side effects

Nutritional Issues – protein vs. carbohydrates

Addictions – effects of concurrent and past chemical dependencies
WHEN TO REFER A PATIENT TO A MENTAL HEALTH PROFESSIONAL

- Are you outside your comfort level?
- Is the patient taking too much of your time with psychosocial issues?
- Are the psychotropic dosages you are used to using insufficient?
- Is suicidality or other serious deviant behavior a concern?
- Is psychiatric hospitalization a possibility?
INCOMPLETE REMISSION PREDICTS GREATER RELAPSE*

*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

Thase M. J Clin Psychiatr 1999;60(suppl 22)3-6.
Returning to Case 2 -- What happened to Ron?

- After receiving a regimen of bupropion, escitalopram, and aripiprazole, Ron’s depression remitted.

- He attributed his recovery to a combination of:
  - medication
  - psychotherapy
  - the relationship with his health professional.
LEARNING OBJECTIVES ACHIEVED

You should now be ready to:

1. Select screening methods that optimize management of depression

2. Discuss the scientific basis for individualizing the treatment of depression

3. Match treatments to patients’ particular needs

4. Understand why remission – not just improvement – should be the standard of care for depressed patients
Thank you for your participation.

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