UNIVERSITY OF SOUTH FLORIDA

Management of Depression in Patients Receiving HCV Therapy

Blending Science and Clinical Practice

Francisco Fernandez, M.D.

Professor and Chair

USF Health - Psychiatry

What exactly are we treating?

What is Depression?

Depression – As A Symptom v Disorder

- Everyone occasionally feels blue or sad, but these feelings are usually fleeting and pass within a couple of days.
  - Common non-pathologic processes
    - Grief
    - Sadness
    - Demoralization
    - Disillusionment
    - Despondency
- When a person has a depressive disorder, it interferes with daily life, normal functioning, and causes pain for both the person with the disorder and those who care about him or her.
- Depression is a common but serious illness, and most who experience it need treatment to get better.

Major Depressive Disorder (MDD): *Diagnostic Criteria*

Five or more of the following symptoms are present most of the day, nearly every day, during a period of at least 2 consecutive weeks

At least 1 of these 2 symptoms

1. Depressed mood
2. Loss of interest or pleasure in all, or almost all, usual activities

3. Significant appetite or weight loss or gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate or indecisiveness
9. Recurrent thoughts of death or suicide

Symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

DSM-IV-TR™ 2000.

Is MDD Type Depression Ever "Appropriate"?

- Some patients are under stress
  - Stress is stress → no different
  - Stress can be a precipitant for depression
- Severe life stress increased the odds of developing depression
- Depression as a mood may be transient during stress
- Depressive Disorder (MDD) is never
  - Transient
  - Understandable or appropriate reaction
  - Warrants aggressive effective treatment

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To Prevent Suicide ...

Only medical disorder that extinguishes natural instinct for survival …

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Evaluating Depression

Using The PHQ-9 to Screen for Depression and Other Scales for Diagnosing and Managing

The PHQ-9 As An "MDD" Indicator

- Treatment guideline on depression suggests that screening for depression
  - Include at least 2 questions concerning mood and interest over the past 2-weeks (in UK, past month)

Have you often been bothered by feeling down, depressed, or hopeless?

and

Have you often been bothered by having little interest or pleasure in doing things?

- A "yes" answer to either question is considered a positive test
- A "no" response to both questions makes depression highly unlikely

PHQ – Patient Health Questionnaire
Available at The McArthur Initiative on Depression In Primary Care Site:

http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/.

Depression Rating Scales

- Self-rating scales
  - BDI (Becks Depression Inventory)*
  - Z-SDS (Zung Self-Rating Depression Scale)
- Rating scales
  - HAMD (Hamilton Depression Scale)+
  - MADRS (Montgomery-Åsberg Depression Scale)

*Not in public domain – must be purchased

+Deemed to be best scale

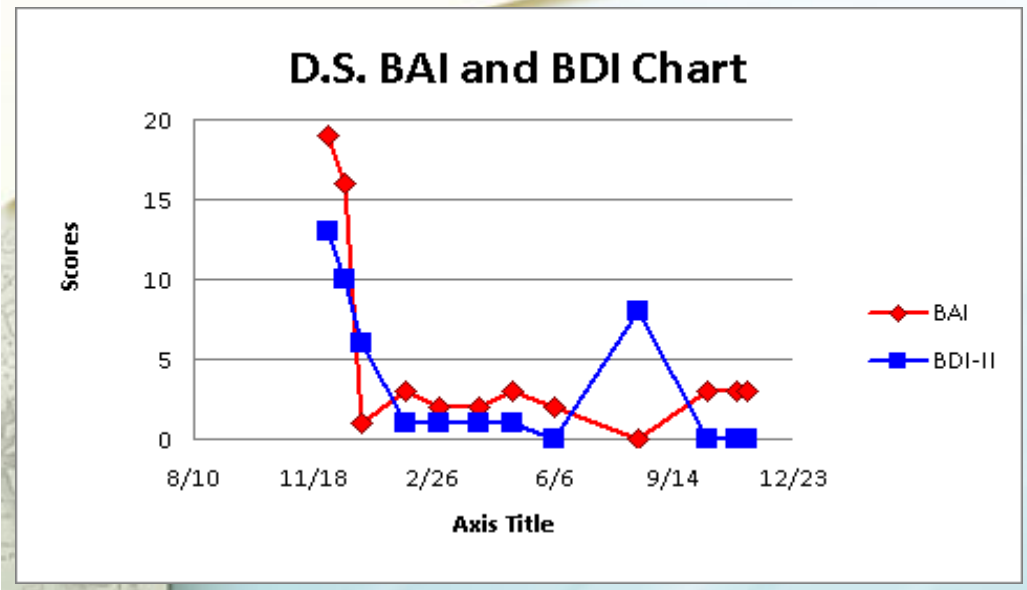
Making The Best Use of Scales

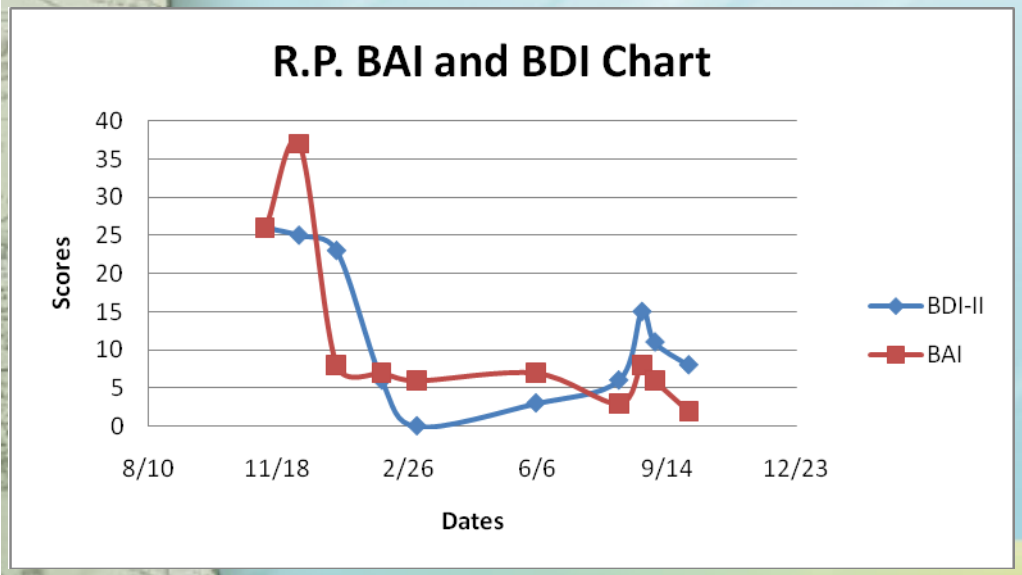
- BDI*, Z-SDS, HAMD, or MADRS
  - Try to quantify the severity of depressive symptoms
  - Show changes in depressive symptoms over time
- Diagnosis of “major depression” (MDD)
  - MDD has to be confirmed clinically by DSM-IV criteria

APA. Diagnostic and Statistical Manual of Mental Disorders Revision IV-TR, 4th ed. 2000. Iannuzzo RW, et al. Psychiatry Res. 2006;145:21-37. Shafer AB. J Clin Psychol. 2006;62:123-146.

* Not in the public domain – must be purchased

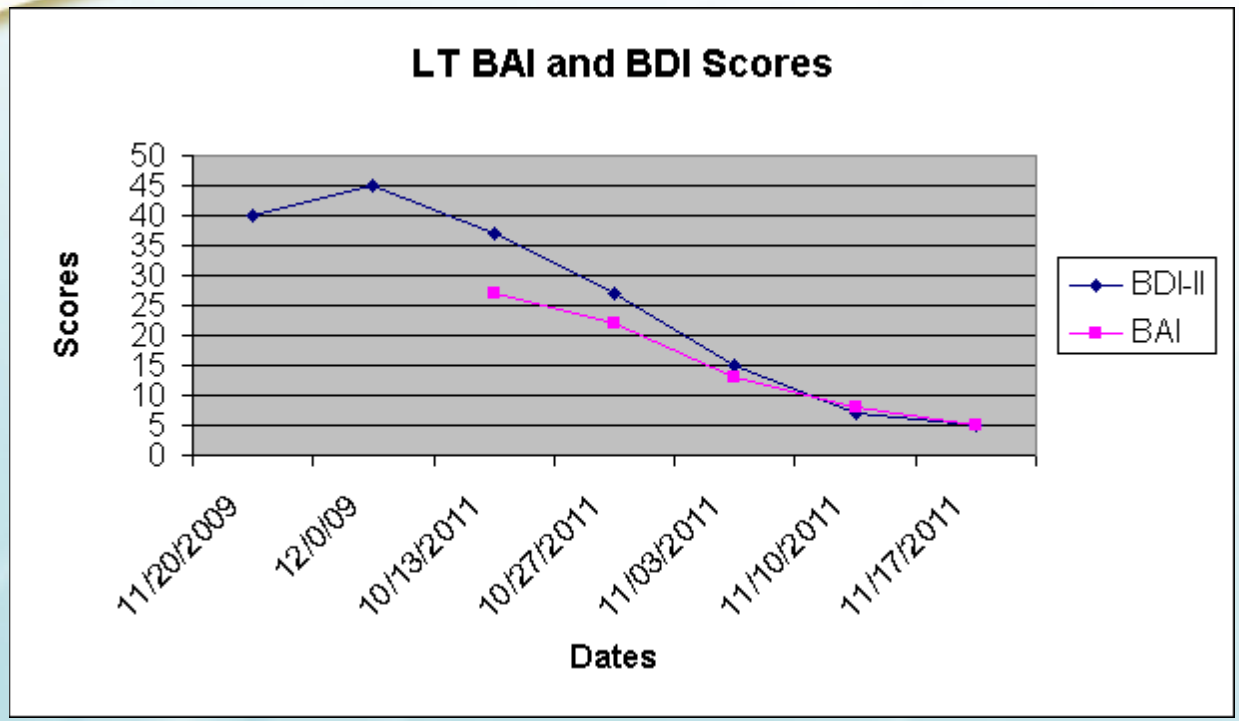
Best Use of Scales - Examples





- Both patients received pre-HCV rx education
- Both patients not tolerating HCV rx
- Both patients severely depressed
  - Both patients w PPHx of MDD
- Both patients responded briskly
  - Both remitted in acute phase
  - Both maintained in remission
    - DS full remission
    - RP partial remission
- Both patients received supportive tx
  - HCRC group based rx
    - Planning ~ 6-10 mos of disability, work loss, financial hardship, emotional & physical distress
    - Unmanaged comorbidities
      - ✓ PTSD, irritability, anger, anxiety, mania, SA
      - ✓ Relapse plan, trigger & craving awareness, sponsor/support, injection issues

Best Use of Scales – Examples



- Patient with pre-existing severe, non-psychotic depression – melancholia
- Unresponsive to optimal medication management
- Serious suicide attempt x 2 → psychiatric hospitalization
- Failed course of ECT x 2
- Hepatology declared him ineligible for HCV-treatment
- Trial of repetitive, transcranial magnetic stimulation (rTMS) → Complete remission

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Treatment Options for Depression In Context of HCV Therapy

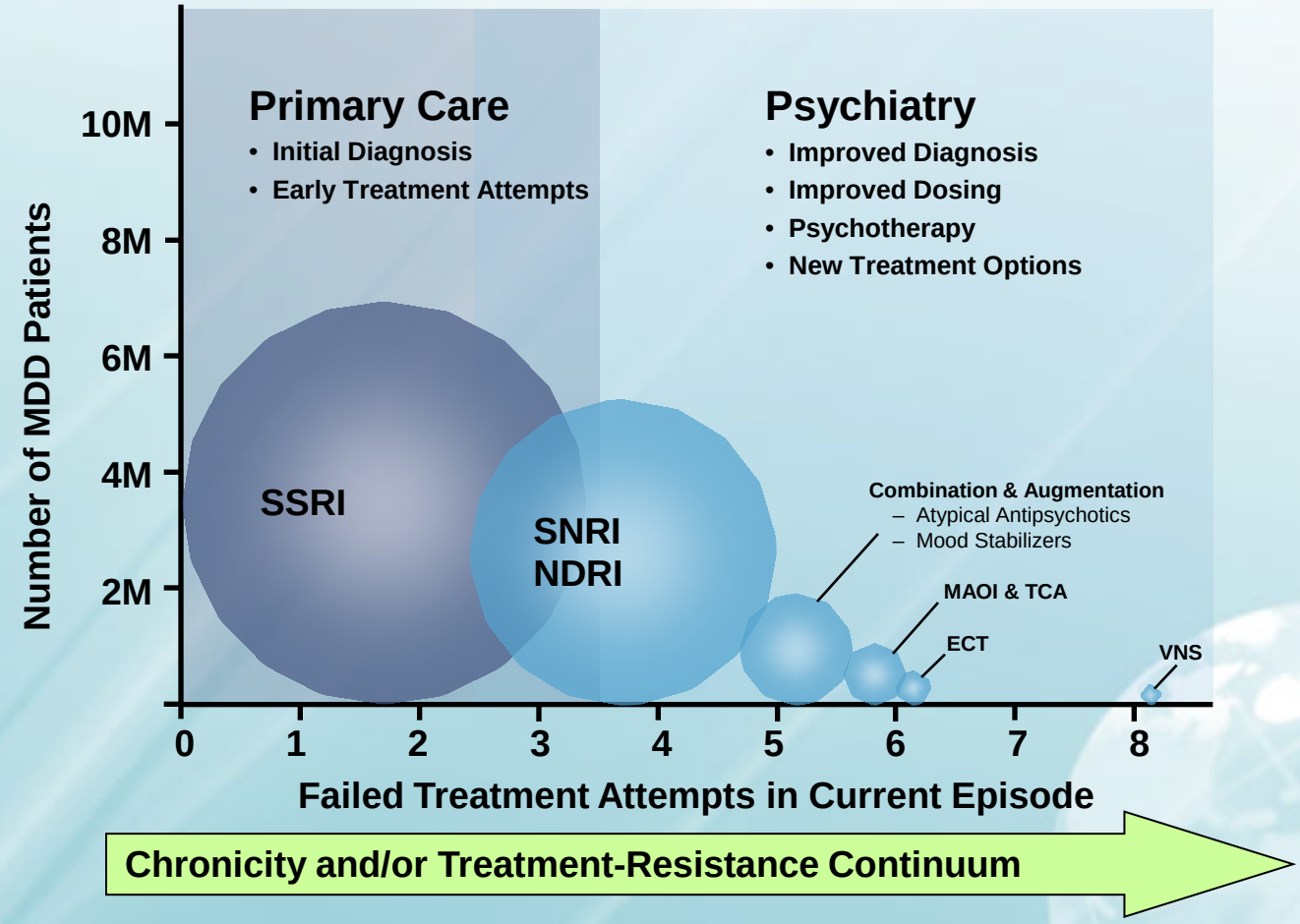
The Good, The Bad and The Ugly

Making Life Better ™

Approach to Managing Psychiatric Issues During HCV Treatment

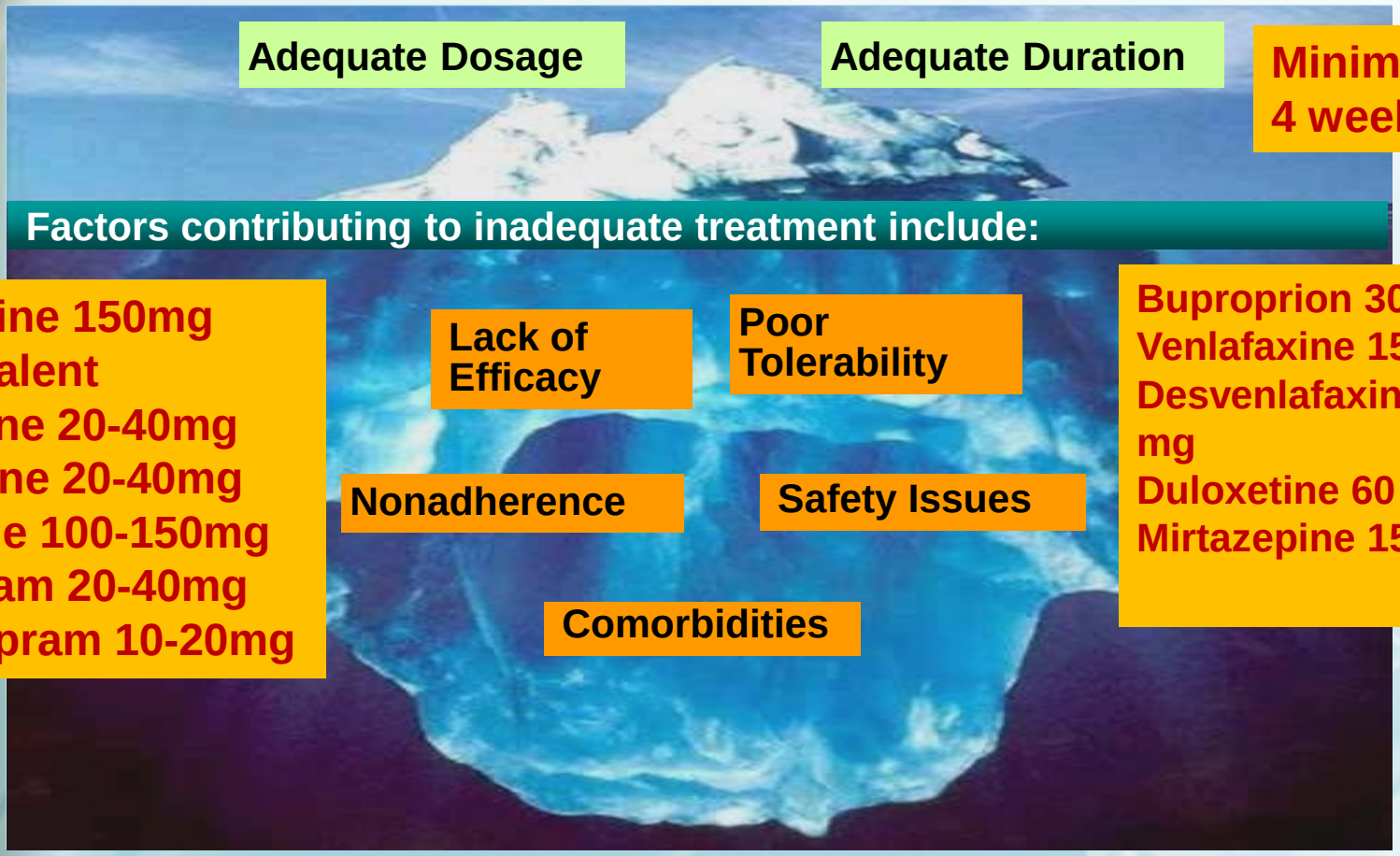
- Education, monitoring, and support
  - Information and psychoeducation before and during treatment
  - Monitoring of patients and psychiatric issues
  - Supportive psychotherapy
  - Regulation of sleep
- Pharmaceutical strategies
  - Antidepressant treatment
  - Other treatments: antipsychotics, benzodiazepines (mood stabilisers, amphetamines, naltrexone, tryptophan, etc)
  - Antiviral therapy dose reduction, discontinuation

Current Treatment Practices in MDD



Kessler RC et al. *Arch Gen Psychiatry*. 2005;62(6):617-627; Kessler RC et al. *JAMA*. 2003;289(23):3095-3105; Herrmann RC et al. *Am J Psychiatry*. 1995;152(6):869-875.

In HCV-Related Depression, "Adequate" Treatment Is Difficult to Achieve



Imipramine 150mg or equivalent
Fluoxetine 20-40mg
Paroxetine 20-40mg
Sertraline 100-150mg
Citalopram 20-40mg
Escitalopram 10-20mg

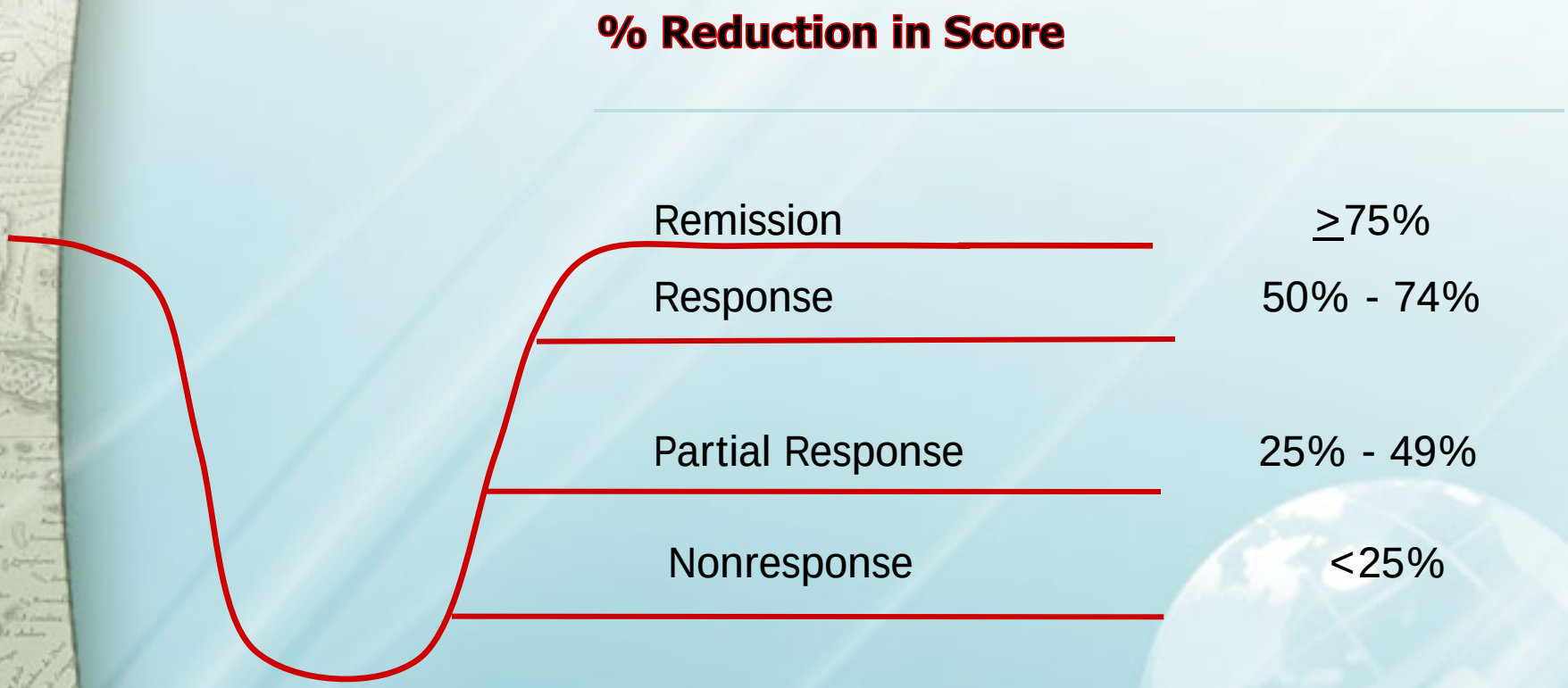
Buproprion 300mg
Venlafaxine 150-225mg
Desvenlafaxine 50-100 mg
Duloxetine 60 – 90 mg
Mirtazepine 15mg

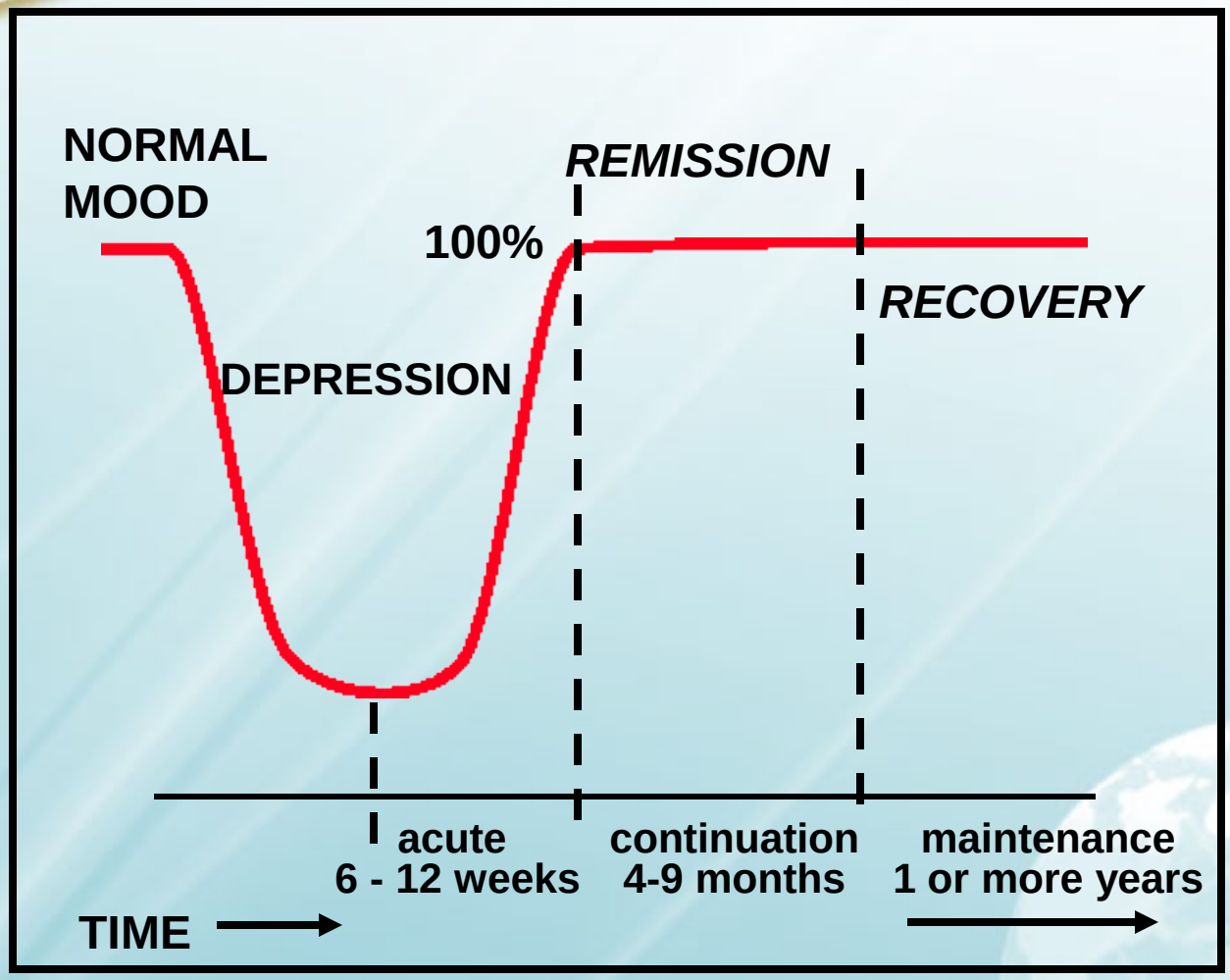
1. Nemeroff CB. *Depress Anxiety*. 1996/1997;4(4):169-181; 2. Oquendo MA et al. *J Clin Psychiatry*. 2003;64(7):825-833; 3. Oquendo MA et al. *Am J Psychiatry*. 1999;156(2):190-194.

How to best treat …

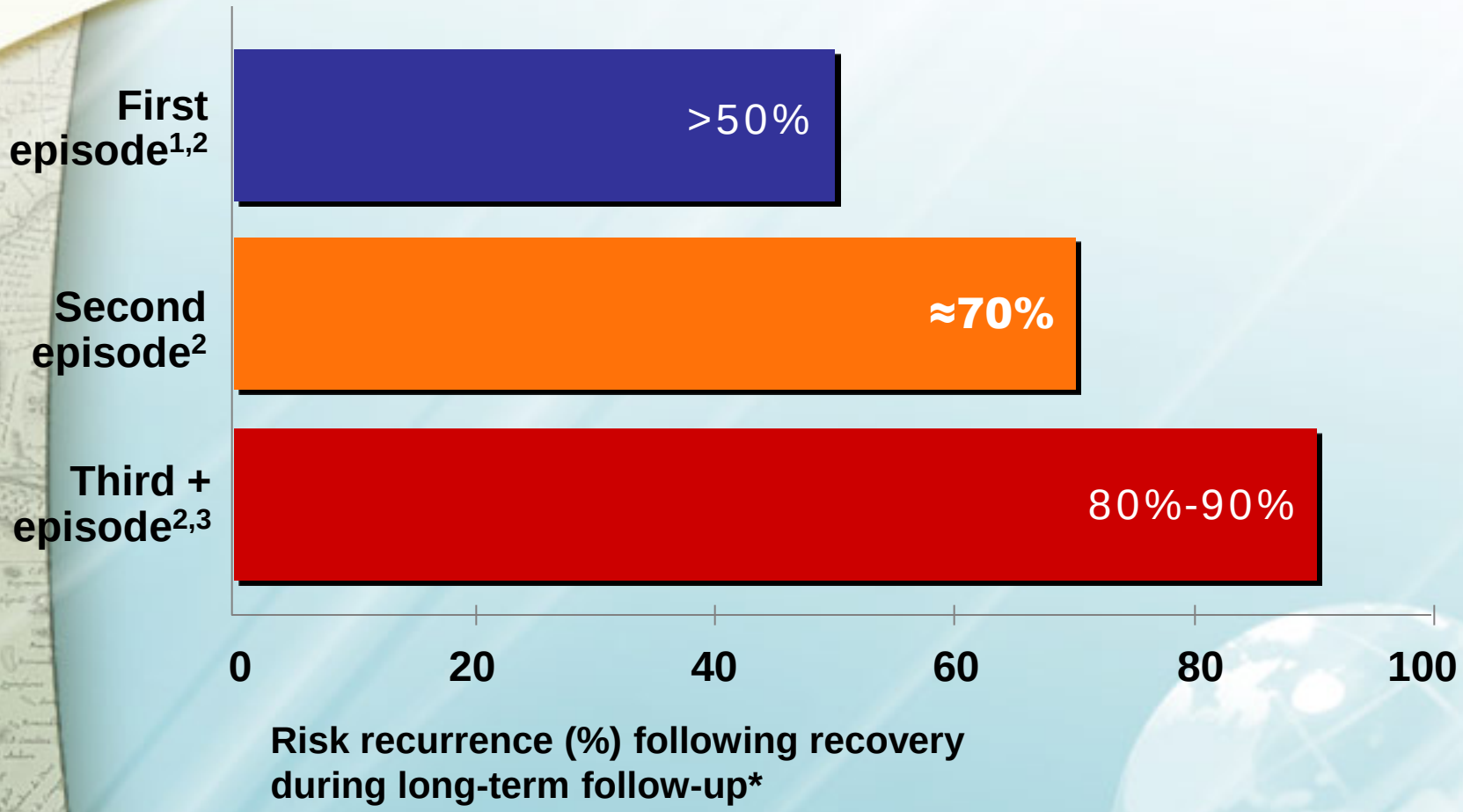
Achieving Remission Is the Name of the Game …

Definitions of Response and Remission



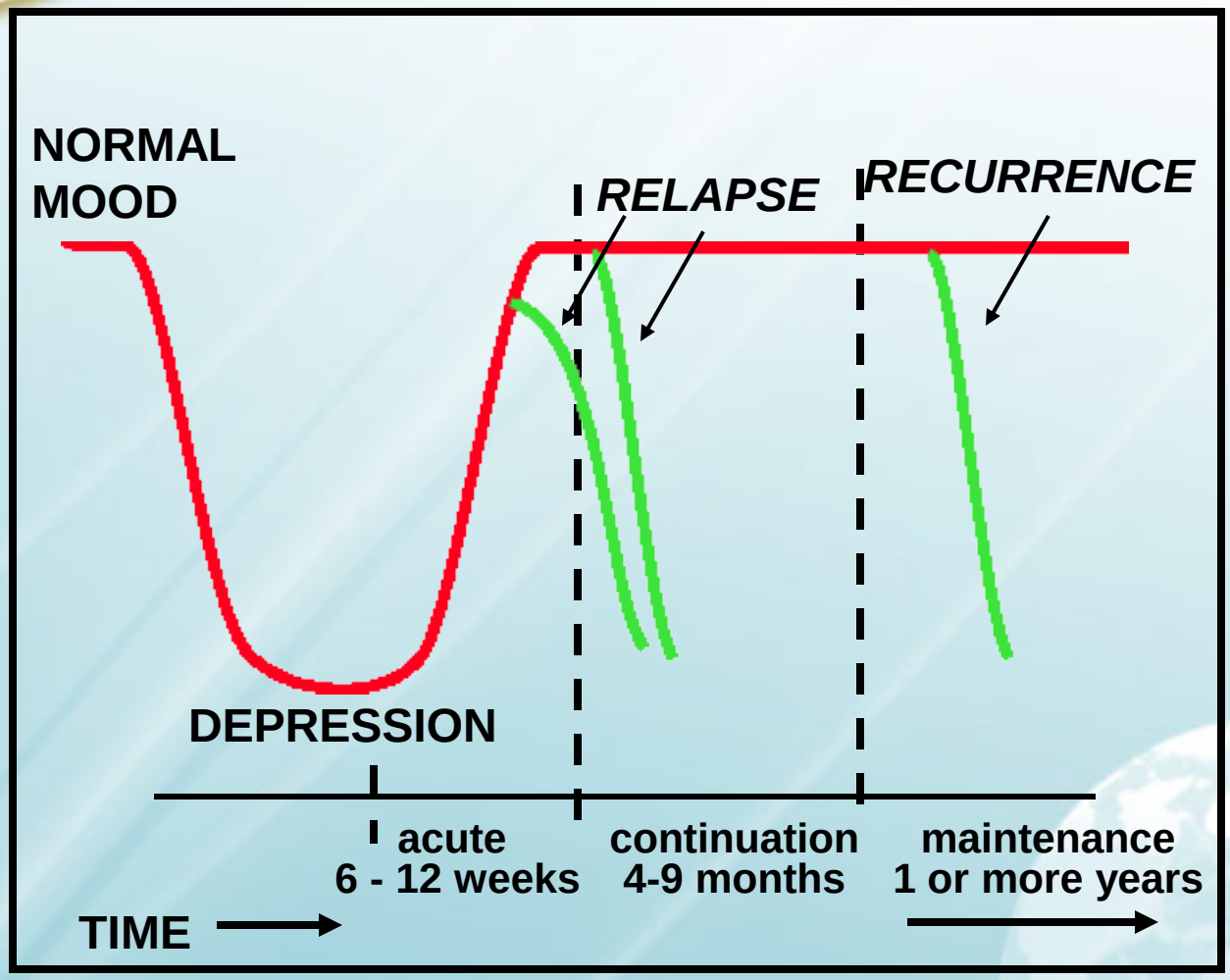

NORMAL MOOD
REMISSION
100%
RECOVERY
DEPRESSION
acute
6 - 12 weeks
continuation
4-9 months
maintenance
1 or more years
TIME

Recurrence Becomes More Likely With Each Episode of Depression



*Patients were followed for 3 to 15 years following recovery of previous episode.

1. Judd LL, et al. *Am J Psychiatry.* 2000; 157:1501-1504. 2. Mueller TI, et al. *Am J Psychiatry.* 1999;156:1000-1006. 3. Frank E, et al. *Arch Gen Psychiatry.* 1990;47:1093-1099.


NORMAL MOOD
RELAPSE
RECURRENCE
DEPRESSION
acute
6 - 12 weeks
continuation
4-9 months
maintenance
1 or more years
TIME

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Since all ADs are created equal …

How do you pick one?

Considerations When Choosing AD

- Family history
- Past Psychiatric history
- Comorbidities
  - Active
  - Remission
- Ensuring compliance

Considerations: Potential Side-Effects → Avoid v Advantage

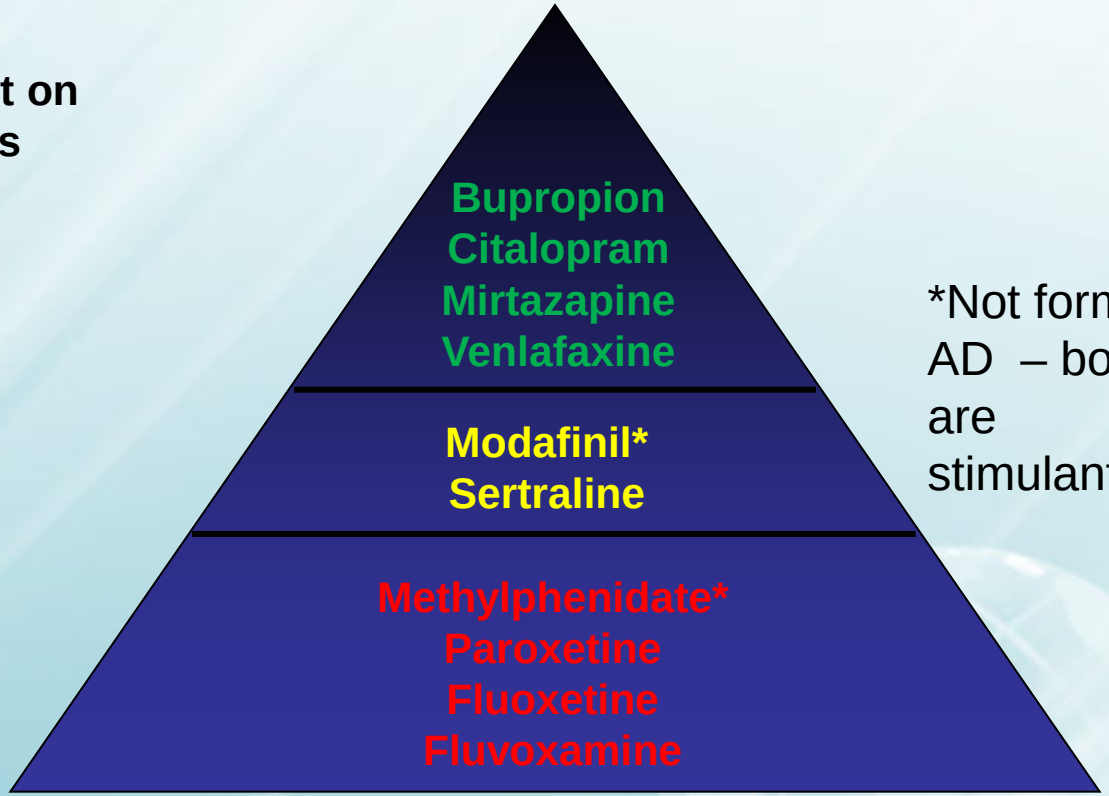
Type	Features
SSRIs	Sexual dysfunction, GI adverse effects, tremors
TCAs	Potential for lethal overdose Alpha-adrenergic effects Delirium risk from anticholinergic/antihistamine adverse effects Cardiac conduction prolongation
Venlafaxine	Minimal protein binding Blood pressure risk
Mirtazapine	Risk of decreased WBC count Risk of weight gain Sedation
Bupropion	May increase risk of IFN-associated seizures

Modified from CCO module 2007

Raison C, et al. CNS Drugs. 2005;19:105-123.

Considerations: Potential for Drug-Drug Interactions

Low P450 blockers:
Likely to have little impact on metabolism of other drugs

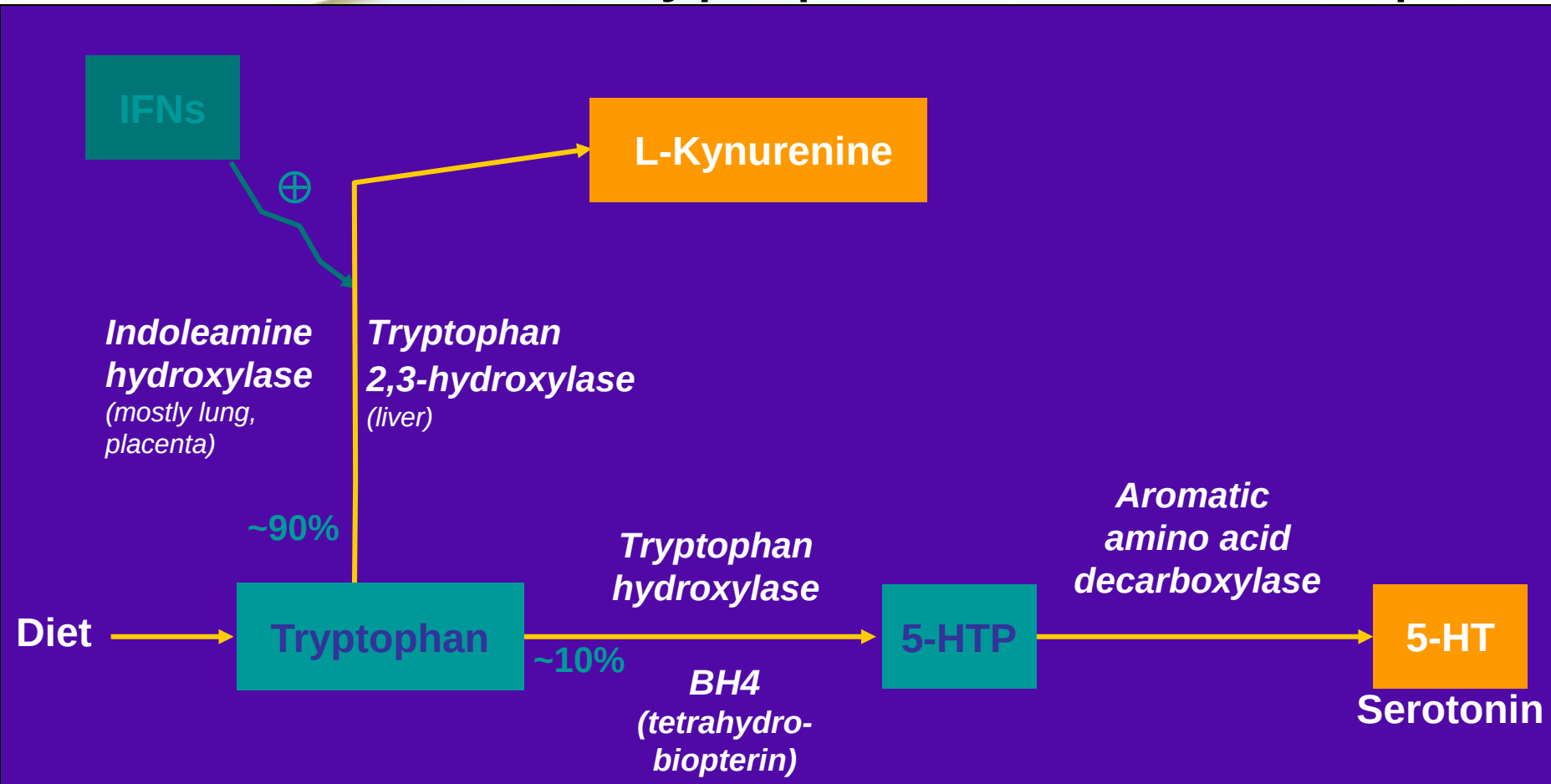


*Not formal AD – both are stimulants

Potent P450 blockers:
Potential for strong impact on metabolism of other drugs

Crewe HK, et al. Br J Clin Pharmacol. 1992;34:262-265. Nemeroff CB, et al. Am J Psychiatry. 1996;153:311-320. von Moltke LL, et al. J Clin Psychopharmacol. 1994;14:1-4. von Motkle LL, et al. Clin Pharmacokinet. 1995;20(suppl 1):33.

Etiology of IFN-Induced Depression: Possible Tryptophan-Serotonin Depletion



Tryptophan Metabolic Pathway

Bonaccorso et al. *J Clin Psychopharmacol*. 2002;22:86-90.

Capuron et al. *Mol Psychiatry*. 2002;7:468-73.

HCRC VA Hepatitis C Resource Centers

HCV Infection: Reduced Dopamine, Serotonin Transporter Binding

Impact of HCV Infection on Transporter Binding			
Outcome	**Controls**	**HCV-Infected Patients**	***P* Value**
DAT	9.39	6.91	< .0006
SERT	3.02	2.58	< .0001

DAT, dopamine transporter binding; SERT, serotonin transporter binding.

Weissenborn K, et al. Gut. 2006;55:1624-1630.

Modified from CCO 2007

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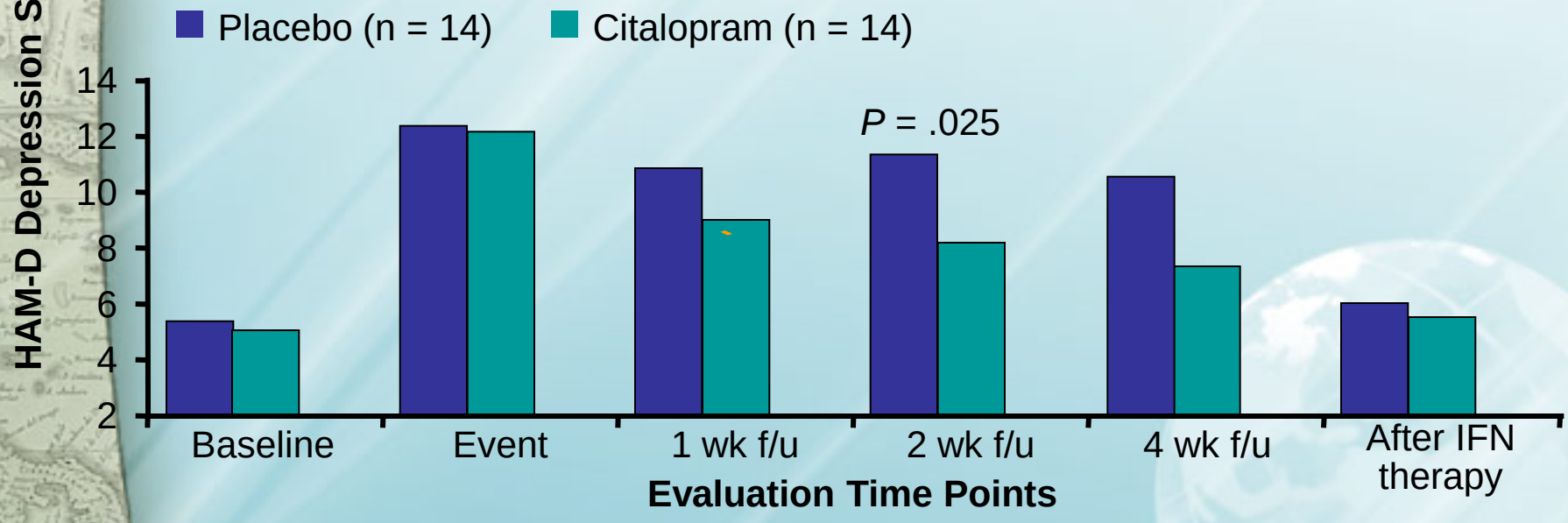
The Good News …

ADs Work In All Cases of MDD

Depression …

Efficacy of Citalopram for Treatment Related Depression Associated With PegIFN and Ribavirin – *A Fighting Chance!*

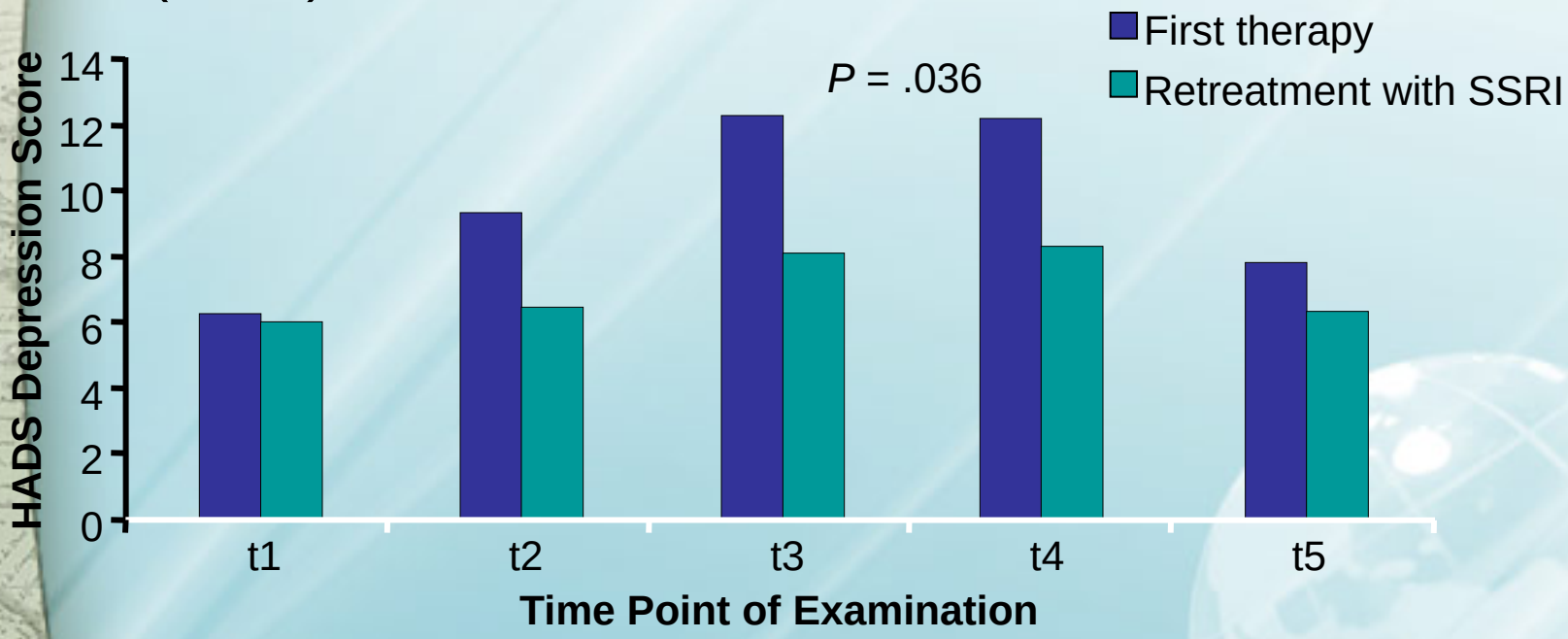
Adapted from Kraus MR, et al, 2008.
Gut 2008;57:531-536 doi:10.1136/gut.2007.131607



(Modified from CCO in HCV 2007)

Use of SSRI Pretreatment in Patients Receiving HCV Retreatment

- Patients experiencing major depression during first course of HCV treatment received SSRI pretreatment when retreated for HCV (N = 8)



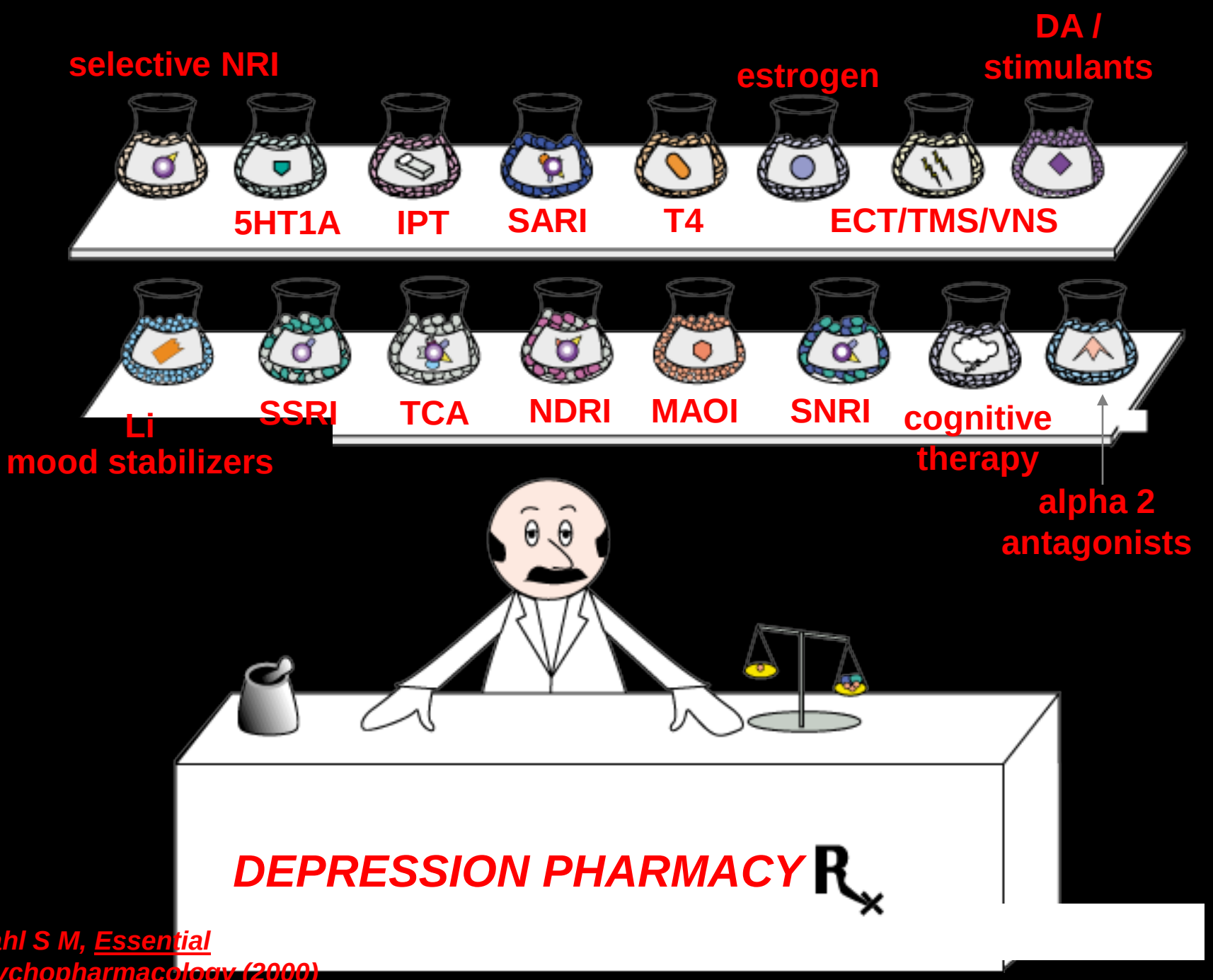
Kraus MR, et al. J Viral Hepatitis. 2005;12:96-100.

(Modified from CCO in HCV 2007)


CURRENTLY ON
Zoloft
Prozac
Paxil
Buspar
Celexa

What to do when …

First Trial of AD Fails?



Stahl S M, Essential Psychopharmacology (2000)

Pharmacological Options After Failure of First Antidepressant

- Optimize dose and address adherence
- Change to another antidepressant
  - Same class
  - Different class
- Add a second antidepressant
- Add a non-antidepressant
  - Lithium or other mood stabilizer
  - Thyroid hormone
  - Psychostimulant
  - Atypical antipsychotic

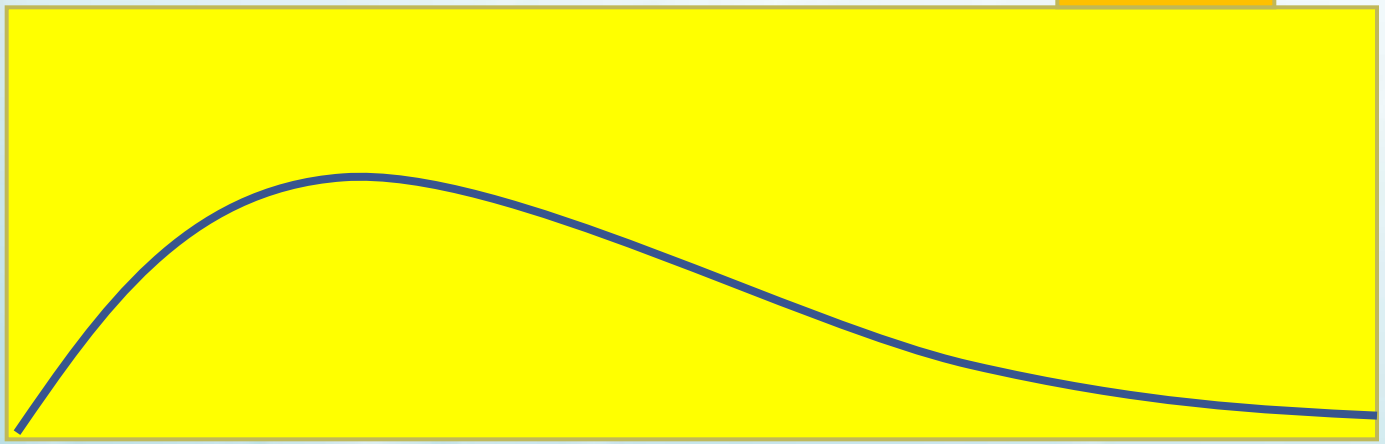
Cognitive Behavioral Therapy or Interpersonal Therapy

Monotherapy **TMS** Adjunctive Rx

Monotherapy **DRUGS** Polypharmacy

ECT

VNS



 # Patients with MDD

Chronicity and/or Treatment Resistance Continuum →

Treatment of Major Depression: A Continuum of Care

USF rTMS – 12/10

Male:	16
Female:	8

# of TMS	Initial Beck	Last Beck	Initial IDS-SR	Last IDS-SR	Initial QIDS	Last QIDS-SR
27	34	23	45	25	30	22

Off label	4

Remission	10
Response	6
Partial Response	4
Failure	4

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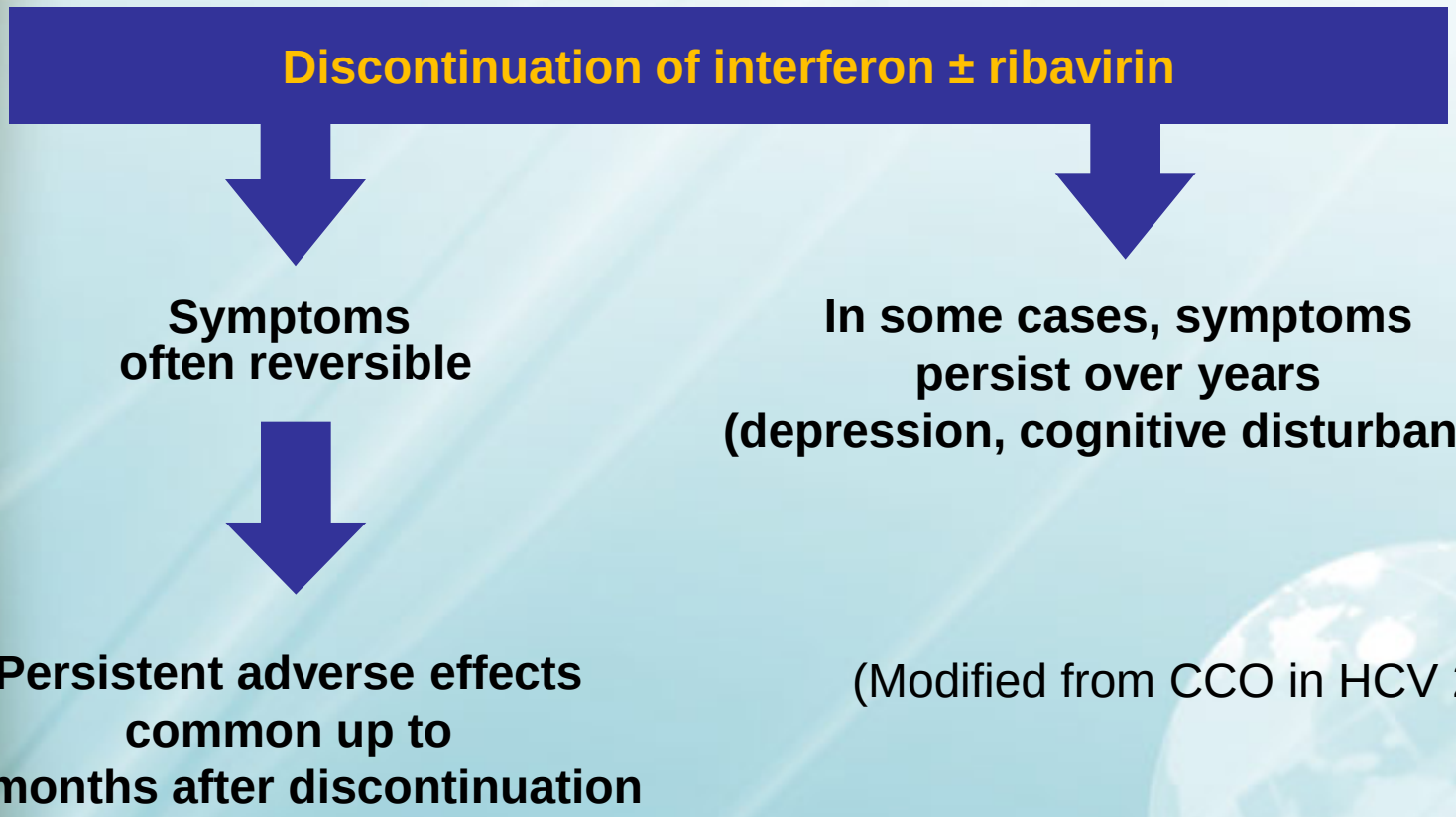
What if …

Depression Persists …

Persistence of Psychiatric Symptoms After Discontinuation of HCV Therapy



(Modified from CCO in HCV 2007)

Meyers, CA. Neurology. 1991;41:672-676. Dieperink E, et al. Am J Psychiatry. 2000;157:867-876.

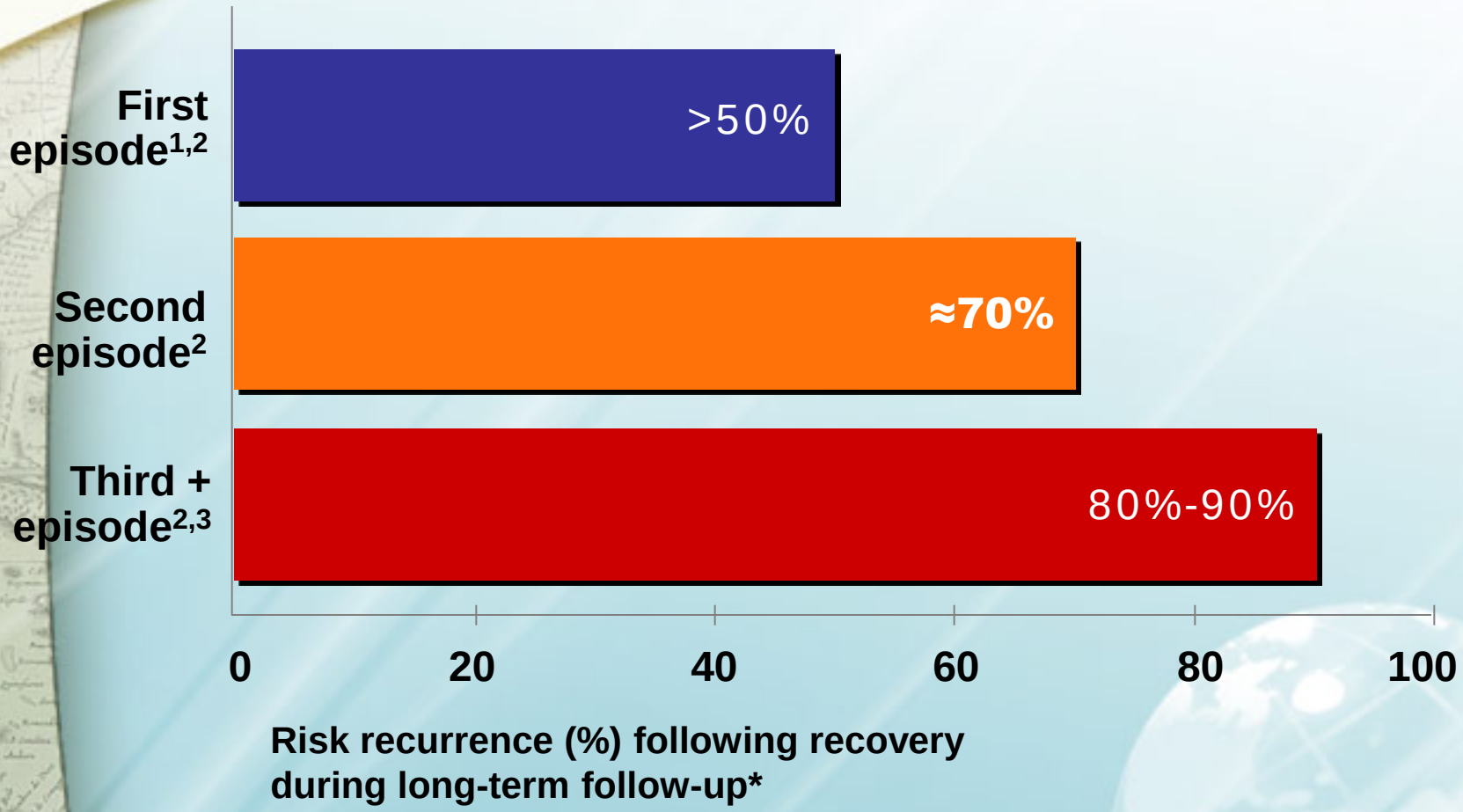
Refer the Patient to a Psychiatrist

- Consider treatment discontinuation
- Diagnosis in question or complicated by other psychiatric factors
  - Comorbidities
    - Alcohol or substance abuse
    - Personality disorders
- Management is complex, response to medication is not optimal, or considering prescribing multiple agents in combination
- Hospitalization is indicated
  - Psychosis
  - Suspected risk of suicide
  - Homocidal ideation
- Complex psychosocial situation
- Psychotherapeutic treatment is required
- Neurostimulation is necessary

Is it true …

That ADs Are Forever …

Recurrence Becomes More Likely With Each Episode of Depression



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How Long Should Patients Remain on Antidepressant Treatment?

- Case reports
  - 25-40% experience a recurrence
  - Recurrence of depression and suicidal thoughts can continue up to 6 months after end of antiviral treatment
  - 20-30% who experience depression go on to chronic state
- All possible efforts should be undertaken to prevent relapse and achieve remission
  - Select optimal treatments
  - Achieve remission in acute phase of depression (the first 10-12 weeks)
  - Continue treatment for 6-10 months beyond
  - Consider maintenance for at risk patients

Nickel T, et al. Pharmacopsychiatry. 2005;38:102-104. Gohier B, et al. World J Biol Psychiatry. 2003;4:115-118.

Summary & Conclusions

- Depression is a painful and debilitating condition and deserves aggressive treatment
- Antidepressant treatment in patients with depressive symptoms during HCV treatment is highly effective
- Prophylactic use of antidepressants should be offered to:
  - Patients with pre-existing history of depression
  - Patients with a history of treatment-associated depression during previous HCV therapy
- Antidepressant treatment should be continued for at least
  - 10 months after achieving remission
  - 3 months after the end of antiviral treatment
- Most side-effects can be managed without dose reduction or discontinuation of antiviral therapy

Muchas Gracias For Your Attention!

HCV On the Web

- USF Hep-C ETAC
  - ✓ http://health.usf.edu/medicine/internalmedicine/infectious/etac/index.htm
- VA National Hepatitis C Program - Info for patients & providers
  - ✓ www.hepatitis.va.gov
    - Documents, video & tools for mood, SA, MI, and interventions
- Centers for Disease Control & Prevention
  - ✓ www.cdc.gov/ncidod/diseases/hepatitis/c/
- Hepatitis C Advocate
  - ✓ www.hcvadvocate.org

Contact Information

- Francisco Fernandez, M.D.
- Best way to reach me:
  - Alissa Phelps, MPH
  - ETAC Research Support Specialist (813) 844-7479
  - alissa.w.phelps@gmail.com
- 2nd best way to reach me:
  - Office: (813) 974-1437 - Assistant: Shawn Hood
  - My EMA: ffernand@health.usf.edu