

DEPRESSION IN HIV INFECTION

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Antiretrovirals and Psychotropics: General Points

- ◆ Psychotropic medications maintain efficacy in the HIV+ population.
- ◆ Overlapping metabolic pathways in cytochrome P-450 system (3A4 and 2D6) → drug interactions (often theoretical).
- ◆ May facilitate or inhibit one another's metabolism.
- ◆ Overlapping toxicities, especially liver toxicity among patients co-infected with hepatitis viruses.
- ◆ But most psychotropics can be used safely if **START SLOW, GO SLOW.**

Why is the assessment, diagnosis and treatment of psychiatric symptoms important in HIV illness ?

- ◆ Mental illness (depression, substance use) is a risk factor for acquiring and transmitting HIV
- ◆ HIV invades the brain and may cause psychiatric and neuropsychiatric complications
- ◆ Symptoms resembling mental illness may be signs of HIV infection and its progression
- ◆ Recognizing neuropsychiatric problems is vital for optimum adherence to treatment
- ◆ Untreated mental illness decreases adherence and increases morbidity and mortality among people with HIV infection

PSYCHIATRIC ILLNESS IN HIV

- **Mental disorders are highly prevalent in HIV infection and AIDS**
- **Patients with Chronic Medical Conditions have frequent and severe psychiatric symptoms**
- **Psychiatric symptoms are associated with negative outcomes in treatment**
 - Poor adherence
 - Frequent hospitalizations and clinic visits
 - Increased high risk behaviors

Depression

The most common and of most negative impact if UNTREATED

HIV treatment failure and suicide risk

Major depression in persons with comorbid medical illness, including HIV infection, has been associated with:

- Decreased survival
- Impaired quality of life
- Decreased adherence to antiretroviral therapy (ART)
- Increased risk behaviors
- Suicide
- Longer hospital stays and more frequent medical visits (e.g., emergency room and/or medical clinics)
- Higher treatment costs

IMPACT OF DEPRESSION IN HIV INFECTION

Depression in HIV patients is underdiagnosed

High prevalence

Depression in HIV is undertreated

↑ health costs

Poorer outcome of
HIV disease

↓ quality of life

Prevalence

Psychiatric disorder	Prevalence %	
	VIH+ (N = 2864)	VIH- (N = 9282)
Major depression	36.0	16.6
Disthymia (chronic depression)	26.5	2.5
Generalized Anxiety Disorder	15.8	5.7
Panic disorder	10.5	4.7
Alcohol and drug use	50.1	27.8

Bieng EG, et al. Arch Gen Psychiatry 2001;58:721-728

Burnam MA, et al. Arch Gen Psychiatry 2001;58:729-736

Kessler RC, et al. Arch Gen Psychiatry 2001;58:617-627

Prevalence of psychiatric disorders in an HIV asymptomatic antiretroviral treatment naïve Spanish population

- Previous studies: heterogeneous samples in the stage of HIV illness, used non-diagnostic measures, and/or had potential recruitment biases.
- N= 98 patients
- 62,8% had a psychiatric disorder according to DSM-III-R criteria:
 - > 32.5% - substance abuse disorder as a 1ary diagnosis
 - > 2.8% - major depressive disorder
 - > 12.8 % - generalized anxiety disorder
 - > 2.33% - adjustment disorder
- High prevalence
- Treatment of those with recent HIV infection requires a mental health services infrastructure capable of addressing such prevalence to ensure better health outcomes.

Depression is common and undertreated

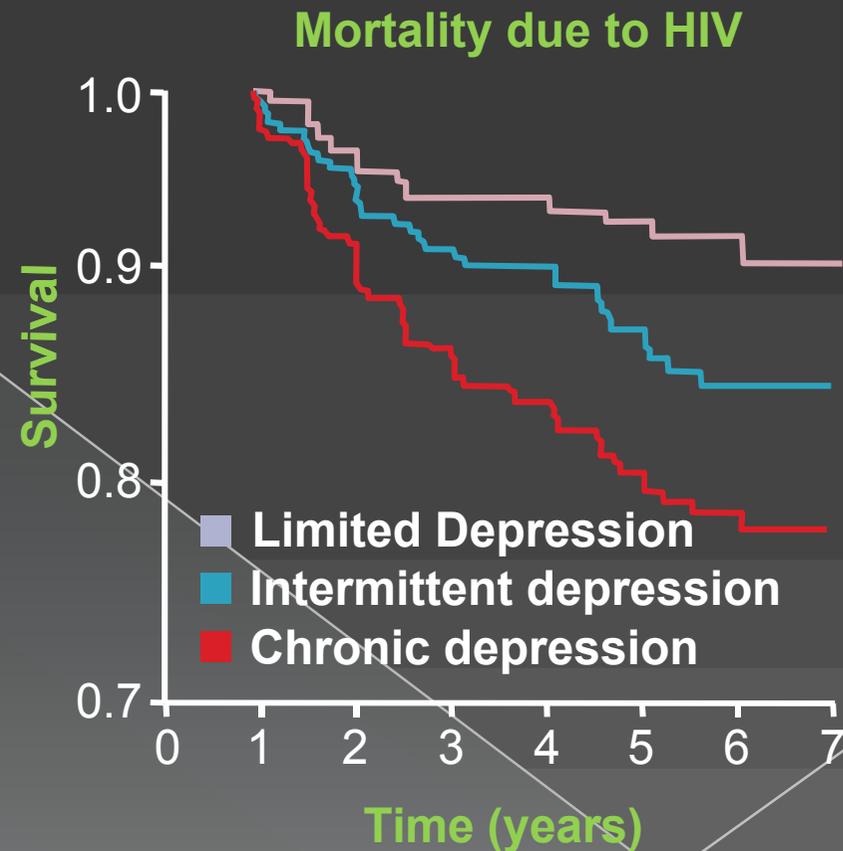
- RAND HCSUS Study: 2,864 HIV+ Medical Patients
- Any Psychiatric Disorder: 48%
- Major depression 36%
- Dysthymia 27%
- Generalized anxiety disorder 16%
- Panic attack 11%
- Drug dependence 13%
- Problematic alcohol use 19%

- 21% took antidepressants
 - > ~ 50% major depression did not receive antidepressants

(Bing et al Arch. Gen. Psych. 2001)

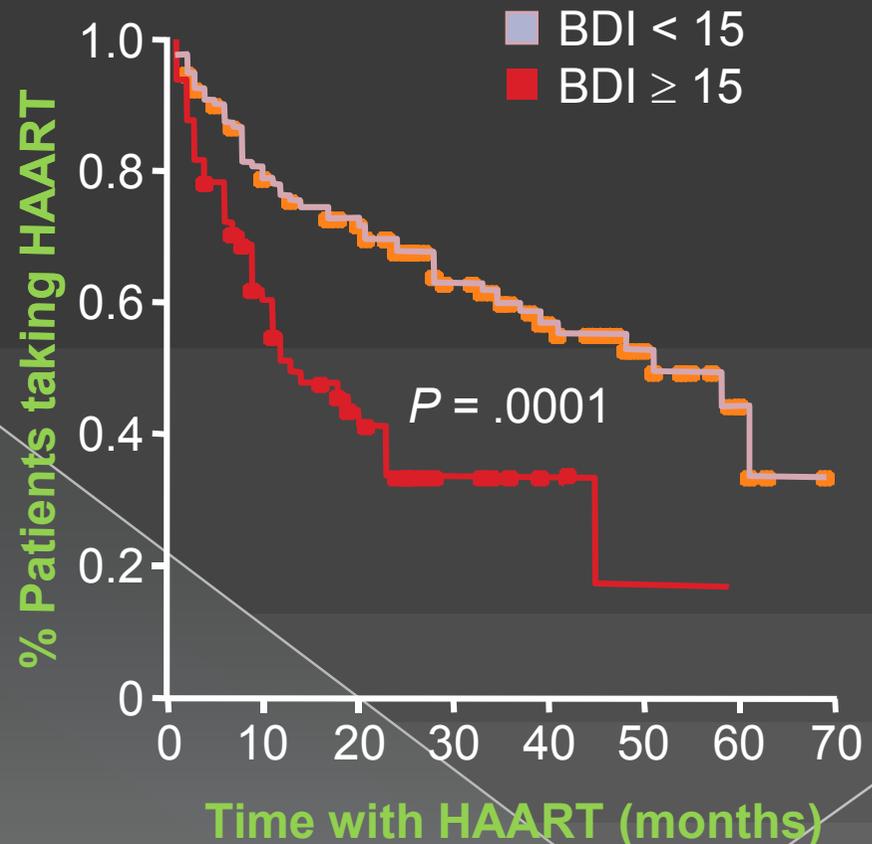
DEPRESSION INCREASES MORTALITY

- HERS cohort: 765 HIV+ women
- Depression measured by CES-D scale and classified in 3 types: limited, intermittent and chronic
- 2.0 greater risk of mortality in patients with chronic depression against patients with limited or without depressive symptoms



DEPRESSION REDUCES ADHERENCE

- Depressive symptoms measured by BDI* in 83 HIV infected patients
- Less depressive: BDI <15 (n=50); more depressive: BDI ≥15 (n=33)
- Patients with BDI <15 were on HAART longer time (35 ms) than patients with BDI ≥ 15 ($P=.01$)
- Viral load <400: 40% in pt with BDI <15 vs. 15% of pts with BDI ≥ 15
- Adherence measured by MEMS and pill counts
- Better adherence in patients with BDI < 15 measured by MEMS (79% vs. 53%; $P = .02$) or pill count (66% vs. 44%; $P = .02$)



Bangsberg DR, et al. ICAAC 2001. Abstract 1721.

*BDI – Beck Depression Inventory

ANTIDEPRESSANTS AND ADHERENCE

- **Retrospective study**
- **1713 HIV+ patients from an urban center in USA:**
 - > **57% had depression**
 - 46% on antidepressants
 - 52% on ART
- **Non treated depressive patients were less adherent to ART ($P < .005$)**
 - > **Another way of looking at this, once treated for depression, adherence improved.**

Yun LW, et al. J Acquir Immune Defic Syndr 2005;38:432-438.

Depression, Adherence and Mortality

WIHS cohort: 2,059 HIV + women

- Replicated HERS results: Chronic depressive symptoms associated with AIDS **mortality** (N = 1,761; Cook, 2004)
- Depression + illicit drug use, or recent drug use alone, associated with **decreased HAART utilization** (N = 1,710; Cook, 2007)
- Use of antidepressants + MH therapy, or MH therapy alone, associated with **increased HAART utilization** (N = 1,371; Cook, 2006)

- 30 yo gay man, living alone, high level job, HIV+ since 1981 – asymptomatic, hemophilia, HCV, hypogonadism (on testosterone replacement), recurrent depression (on SSRIs), alcohol & recreational drug abuse (on remission).
 - > Pre-HAART: CD4 = 212; viral load=182,000
 - > Post-HAART: CD4 ~ 600's; undetectable VL.
- 9 months of low energy and feeling slowed down, depressed, hopeless, anhedonic, isolated, poor appetite, interrupted sleep, mild suicidal thoughts. MSE: Distracted, wrinkle shirt.
- Labs: Thyroid, Liver enz, testosterone: wnl; VL/CD4: no changes
- What's going on
 - a) Recurrent Depression
 - b) Recurrence of alcohol and/or ecstasy abuse
 - c) All of the above
 - d) None of the above

Depression and HIV Neurocognitive Disorders?

- Psychomotor retardation or apathy of **HIV dementia** may be confused with depression
- Common physical symptoms of depression can overlap with **HIV dementia** (e.g., fatigue, eating disturbance)
- Depressive symptoms can often be the first sign of **cognitive motor disorder**

Differential Diagnosis for Depression and HAD

MDD

- No behavioral manifestations of cog impairment (despite detailed complaints of cog dysfunction)
- Diminished self-esteem
- Fully aware of deficits
- Disorientation/ confusion is rare
- Inconsistent memory impairment of formal assessment

HAD

- Behavioral manifestations that are consistent with cog impairment (e.g. agitation, verbal outbursts, repetitive behavior, wandering, and aggression)
- Self-esteem is variable
- Minimally aware of deficits
- Confusion is common
- Consistent memory impairment of formal assessment
- Cog impairment is not due to something else (like MDD) and causes ADL problems.

Psychiatric Symptoms

Look for underlying biological cause

1. Medications: HIV (Efavirenz), psychiatric, other
2. Substances: Alcohol, drugs, herbal, over-the-counter, other
3. Non-HIV medical problems
4. HIV-related illnesses:
 - CNS lesions, infections
 - Non-CNS medical problems

IF YES--- address the problem
IF NOT--- consider...

HIV-Neurocognitive Disorders:

- Mild (Minor Cognitive Motor disorder-MCMD)
- Moderate to Severe (HIV Associated dementia-HAD)

+/-

Psychiatric Syndromes

Psychosocial Issues

- Acute vs Chronic
- Reversible or not
- More than one can be present...

DIAGNOSIS OF MAJOR DEPRESSION

- ❖ Depressed mood
- ❖ Loss of interest or pleasure
- ❖ Decrease in appetite
- ❖ Insomnia
- ❖ Psychomotor agitation or retardation
- ❖ Fatigue or loss of energy
- ❖ Feelings of excessive guilt
- ❖ Diminished ability to think or concentrate
- ❖ Recurrent thoughts of death, recurrent suicidal ideation

Screening for Depression

PHQ-2

Over the past two weeks, how often have you been bothered by any of the following problems?

Little interest or pleasure in doing things.

0 = Not at all

1 = Several days

2 = More than half the days

3 = Nearly every day

Feeling down, depressed, or hopeless.

0 = Not at all

1 = Several days

2 = More than half the days

3 = Nearly every day

Total point score: _____

Score interpretation:

<i>PHQ-2 score</i>	<i>Probability of major depressive disorder (%)</i>	<i>Probability of any depressive disorder (%)</i>
1	15.4	36.9
2	21.1	48.3
3	38.4	75.0
4	45.5	81.2
5	56.4	84.6
6	78.6	92.9

- When? Yearly or when symptoms present
 - Should trigger further assessment

Evaluation

- The diagnosis is based on clinical criteria after ruling out medical and other causes.
- An initial screening includes:
 - > Labs: cbc, electrolytes, creatinine, BUN, glucose
 - Thyroid function tests (TSH, T4)
 - Vitamin B12 and folate levels
 - Testosterone (both in men and women)
 - Other tests as suggested by history and physical examination
 - > Neurocognitive assessment

MEDICAL DIFFERENTIAL DIAGNOSIS OF HIV RELATED DEPRESSIVE ILLNESS

- **Substance abuse**
- **Endocrine abnormalities (thyroid disease, hypogonadism, adrenal insufficiency)**
- **Medication effects: EFV**
- **CNS opportunistic illnesses and cancers**
- **CNS HIV and HCV cognitive disorders**
 - **Neurocognitive syndrome may mimic depression: apathy, memory changes, sleep/energy/appetite changes, functional impairment, low mood, social withdrawal**

HIV-RELATED MEDICATIONS THAT MAY INDUCE MOOD DISORDER SYMPTOMS

- **Steroids: depression or euphoria**
- **Interferon: neurasthenia, fatigue syndrome, depression**
- **Zidovudine: depression or euphoria**
- **Efavirenz: decreased concentration, depression, nervousness, nightmares**

Treatment

- ◆ General Practitioner: Psychopharmacology
- ◆ MH Providers:
 - ◆ **Psychotherapies**
 - ◆ Cognitive behavioral therapy (CBT) (negative automatic thoughts)
 - ◆ Interpersonal psychotherapy (IPT) (interpersonal difficulties)
 - ◆ Others (some include psychodynamic strategies)
 - ◆ **Refer to psychiatrist or consider inpatient care if:**
 - ◆ **suicide risk, medical work-up, grave disability, bipolar/psychotic, or not responding to treatment**
 - ◆ **ECT**

PHARMACOTHERAPY

- Previous personal or family history of response
- Target symptoms
- Side-effects (exacerbate the medical illness)
- Elimination via liver or kidney or both
- Time to expected *onset* of action
- Expected *duration* of action
- “*Less is better*”
- Drug-drug Interactions with ARV

Antidepressants: SSRIs

- In general, SSRIs are well tolerated, safe, and have lower rates of drug discontinuation in studies with HIV-infected patients – all have equal efficacy
- SSRIs have proven efficacy in clinical trials with HIV+ depressed patients
- Drug interactions need to be considered with fluvoxamine, fluoxetine and paroxetine
- Side effects: nausea, jitteriness, weight loss, insomnia, sexual dysfunction

Antidepressants: SSRIs

- Sertraline 25 - 200 mg/day
 - > low affinity for CYP450 enzymes
- Escitalopram 10 - 20 mg/day
 - > low affinity for CYP450 enzymes
- Citalopram 20 - 40 mg/day
 - > low affinity for CYP P450 enzymes
- *Fluoxetine* * 10 - 60 mg/day
 - > potent inhibitor of CYP450 2D6 enzymes
- *Paroxetine* * 10 - 60 mg/day
 - > induces its own metabolism
 - > potent inhibitor of CYP450 2D6 enzymes

***More likely to cause drug interactions**

Tricyclic Antidepressants: Potential Useful Properties

- Anti-diarrhea
- Sedation
- Anti-neuropathic pain
- Can monitor correct dose by blood levels (overdose risk):
 - > imipramine, desipramine, nortriptyline
 - > Monitor liver function tests

Tricyclic Antidepressant / Antiretroviral Drug Interactions

- Tricyclics (TCAs) are metabolized principally by CYP 2D6
- Ritonavir is a moderate inhibitor of CYP 2D6 & and may cause higher blood levels of TCAs
- TCAs can delay cardiac conduction and cause arrhythmias, especially at high levels
- EKG and plasma TCA monitoring is recommended when these drugs are co-administered with ritonavir or other inhibitors of 2D6
- TCAs are dangerous in overdose--avoid giving large quantities to suicidal patients

Antidepressants: SNRIs

- Venlafaxine XR 75-300 mg qd
 - > useful in SSRI nonresponders
 - > extended release form preferable
 - > may decrease indinavir levels - significance unknown

- Duloxetine 20-60 mg qd
 - > effective for symptoms of physical pain associated with depression
 - > indicated for diabetic neuropathy

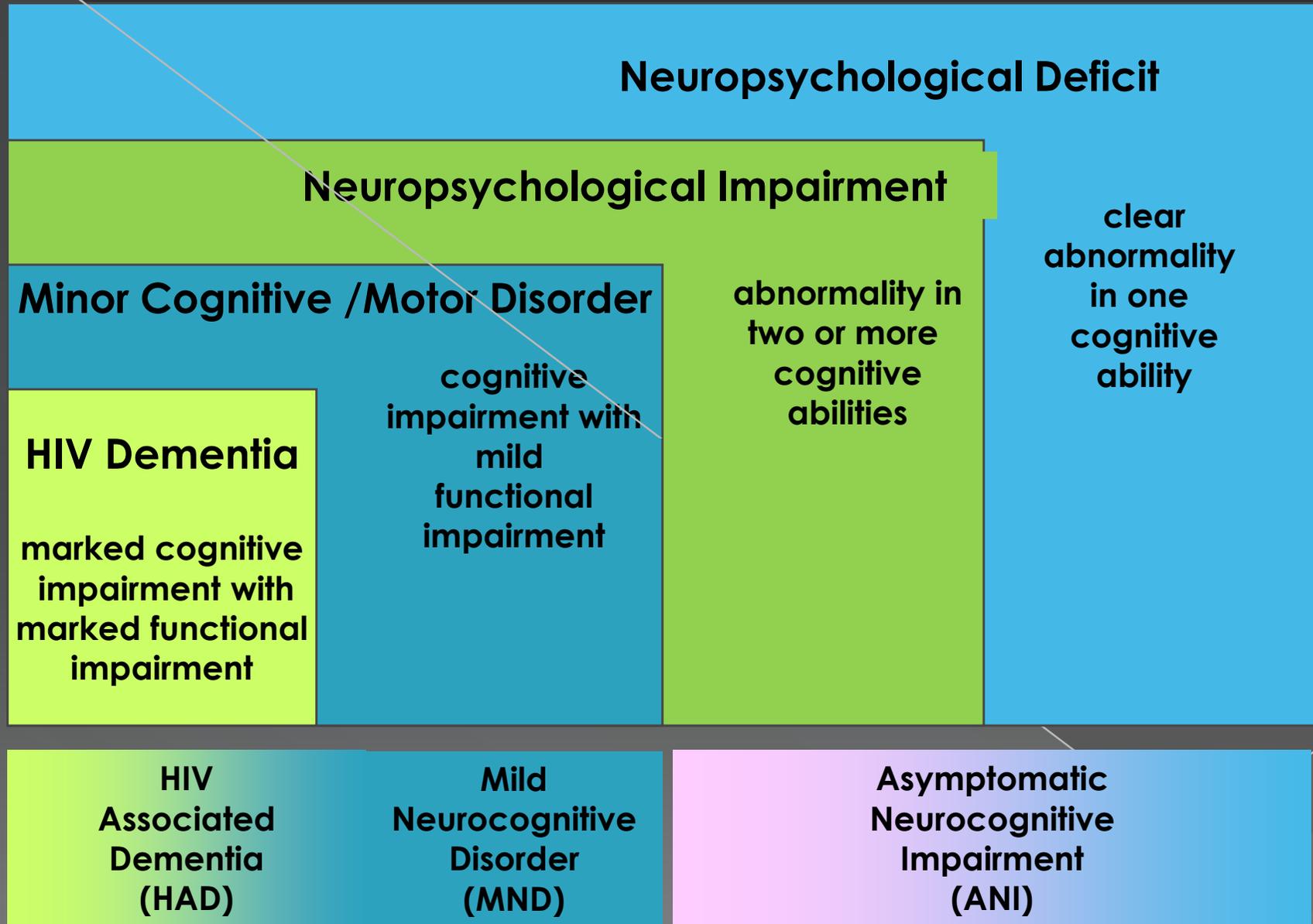
Other Antidepressants

- Trazadone
 - > good in low doses for sleep
 - > infrequently, arrhythmias and priapism occur
 - > levels may be elevated by PIs
- Bupropion
 - > often chosen for low sexual side effects
 - > may cause anxiety or insomnia
 - > levels may be increased by efavirenz and protease inhibitors
- Mirtazapine 15-45 mg qHS
 - > very useful in patients with insomnia and wasting

Other Agents

- Psychostimulants
- Hormonal treatment—
 - > Testosterone:
 - check for / treat ↓ testosterone levels in men and women
 - Follow up irritability; PSA in men
 - > Dehydroepiandrosterone

HAND – HIV Associated Neurocognitive Disorders



Neuropsychiatric Complications of Hepatitis C (HCV) Infection

- HCV infection is a leading cause of death among HIV-infected people
- HCV is neurotropic and replicates in the CNS
- HCV is associated with cognitive impairment even in the absence of liver failure
- High rates of psychiatric disorder (esp. depression): requires careful monitoring and access to mental health care during HCV treatment (peginterferon alpha 2a + ribivarin)

Adherence to Antiretroviral Treatment Among People with Mental Illness/Substance Use Disorders

Psychiatric Illness and Adherence: Overview

- ◆ Substance use, depression, and other mental illnesses can undermine adherence: Treat these disorders
- ◆ Creating stable life conditions enhances adherence
- ◆ Patient's readiness to adhere must be individually assessed
- ◆ Consider adherence support – Strategies:
 - > Therapeutic alliance
 - > Patient education
 - > Memory aids
 - > Observed medication administration
 - > Integrated care
 - > Outreach (“Inreach”)
 - > Incentives—offer what is desired
- ◆ Motivational Interviewing

American Psychiatric Association Practice Guidelines and other reference documents www.psych.org/aids

Adherence to ARVs

- ◆ 542 HIV+ individuals with mental illness/substance abuse disorders who were on ARVs
 - ◆ Of those on ART, 55% were completely adherent in the past 3 days
 - ◆ Of those on psych meds and ART, 62% were completely adherent in the past 3 days
- ◆ Non-adherence associated with
 - > current alcohol, cannabis, crack cocaine use
 - > Psychological distress
 - > Low self-reported spirituality
 - > Non-attendance of medical appointments
- ◆ Adherence to psychiatric meds associated with adherence to ART

Conclusion

- Depression is very prevalent in HIV disease
 - > Neurocognitive disorders can resemble depression and are seldom diagnosed
- Depression has a very negative impact on HIV illness
- Depression is seldom screened and diagnosed – even though it is easy to diagnosed
 - > Screen yearly or when symptoms appear – follow up!
- Once diagnosed, it is seldom treated – even though many efficacious treatments (therapies and medications) are available
 - > Treat it!
- Some interactions are easy to address
- Once treated, adherence improves, preventing illness progression = good prognosis

A Couple of Words About Our Work...

- Get to know your patients, understand them – feel free to ask!
- Know your role – know what is “None of your business!” (religion, sexuality, politics, etc.)
- Adjust to them, not the other way around – if uncomfortable, get supervision
- We all have experience prejudices – connect with that
- However, not over identify – at times the medicine can be worse than the disease!

Miriam Acevedo



Gràcies!