The Use of Psychotropic Drugs in the Clinical Care of HIV+ Patients

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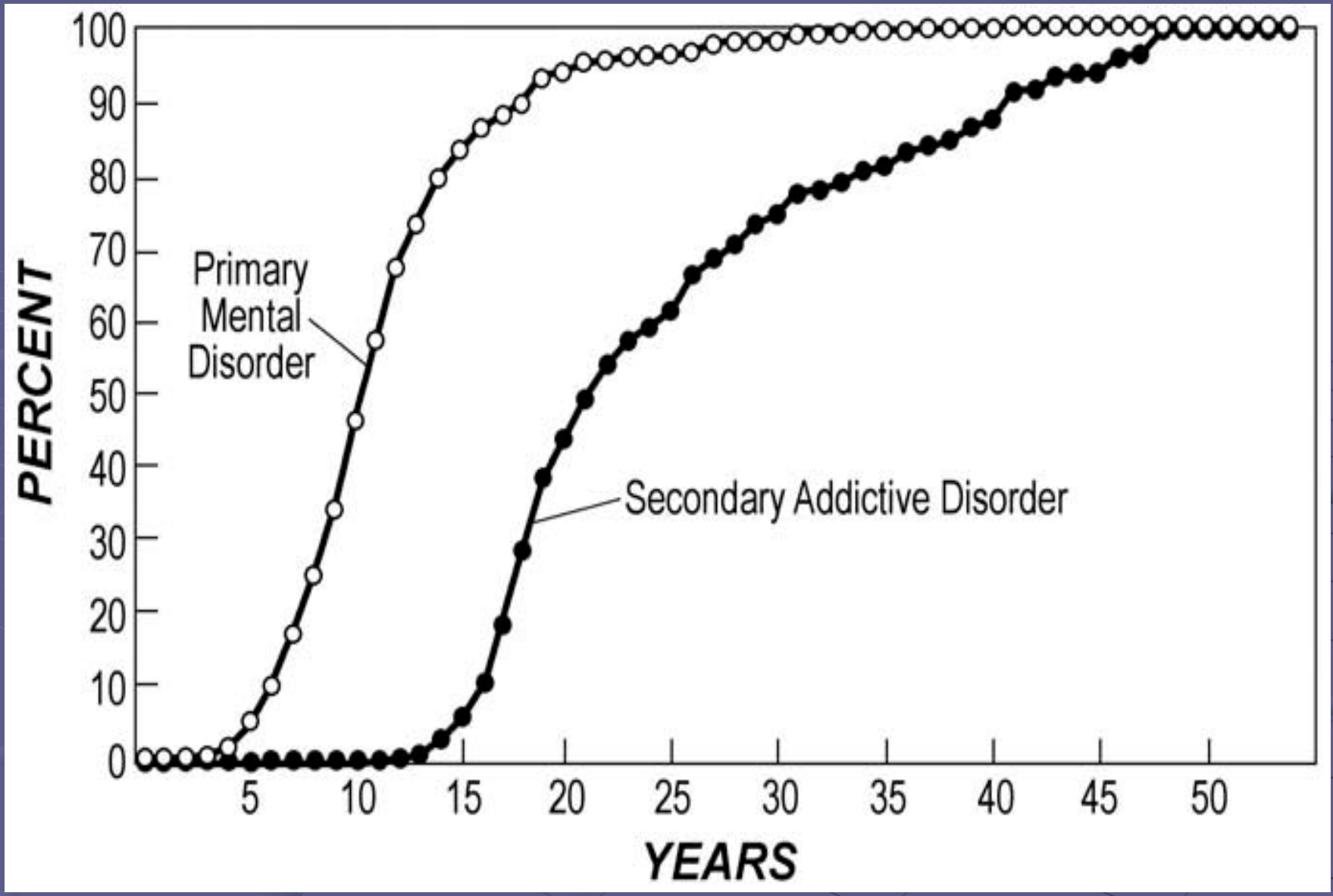

Age of onset: Primary mental disorders co-occurring with secondary addictive disorders. (R. Kessler, Biological Psychiatry, 2004)

Assessing Mental Status Changes in Symptomatic HIV Infection

Look for underlying biological cause

1. **Medications: HIV, psychiatric, other**
2. **Substances: Alcohol, drugs, herbal, other**
3. **Non-HIV medical problems**
4. **HIV-related illnesses:**
   - **CNS lesions, infections**
   - **Non-CNS medical problems**

and/or

Psychiatric Syndromes

HIV Neurocognitive Disorders (HAND):
- Mild
- Severe – HIV Associated Dementia (HAD)

Use of Psychiatric Medications in Patients with HIV Infection

- Psychiatric medications maintain efficacy in the presence of HIV neuropsychiatric manifestations
- Problems that may arise
  - Increased sensitivity to side effects
  - Overlapping toxicities
  - Drug interactions (often theoretical)
  - Liver toxicity among patients co-infected with hepatitis viruses
- In advanced HIV disease, follow rule as with elderly: start low, go slow

Antiretrovirals and Psychotropics: General Points

- Overlapping metabolic pathways in cytochrome P-450 system (3A4 and 2D6) → drug interactions.
- May facilitate or inhibit one another's metabolism. Websites, online resources are available for information.
- Overlapping toxicities, especially liver toxicity among patients co-infected with hepatitis viruses.
- But most psychotropics can be used safely if start low, go slow.

Depression

The most common and of most negative impact if UNTREATED

Depression and Mortality

- HERS cohort (Ickovics et al JAMA 2001): 765 HIV+ women at 4 sites followed for up to 7 years
  - Mortality predictors: chronic depression, CD4 count, HAART duration, age
  - After adjusting for all other variables, women with chronic depressive symptoms were twice as likely to die as women with limited or no depressive symptoms
- Depression significantly worsens HAART adherence and HIV viral control. Compliant SSRI use is associated with improved HIV adherence and laboratory parameters. (Horberg 2007)

Depression and Mortality

WIHS cohort: 2,059 HIV + women

- Replicated HERS results: Chronic depressive symptoms associated with AIDS mortality (N = 1,761; Cook, 2004)
- Use of antidepressants + MH therapy, or MH therapy alone, associated with increased HAART utilization (N = 1,371; Cook, 2006)
- Depression + illicit drug use, or recent drug use alone, associated with decreased HAART utilization (N = 1.710; Cook, 2007)

Treatment of Depression in People with HIV

- Modify contributing factors
  - Treat underlying medical illness
  - Modify medication side effects and use of substances
  - Address psychosocial problems
- Psychotherapies – some manualized
  - Cognitive behavioral therapy (CBT)
  - Interpersonal psychotherapy (IPT)
  - Others (some include psychodynamic strategies)
- Psychopharmacology
- Inpatient care (suicide risk, medical work-up, grave disability)
- ECT
- Experimental brain stimulation treatments

Agents Used for Depression in Patients with HIV

- Antidepressants
  - SSRIs
  - TCA (tricyclic antidepressants)
  - Novel antidepressants
- Psychostimulants
- Hormonal treatment—check for / treat ↓ testosterone levels in men and women
  - Follow up irritability
  - PSA in men
  - *"aging men with clinically significant hypogonadal symptoms and testosterone values repeatedly in the range of 200-300 ng/dl (range=241-827 ng/dl) or less may benefit from testosterone treatment after adequate risk and benefits counseling."*

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 fluoxetine and paroxetine
- Side effects: nausea, jitteriness, weight loss, insomnia, sexual dysfunction

Antidepressants: SSRIs

- Sertraline (Zoloft) 25 - 200 mg/day
  - low affinity for CYP450 enzymes
- Escitalopram (Lexapro) 10 – 20 mg/day
  - low affinity for CYP450 enzymes
- Citalopram (Celexa) 20 - 40 mg/day)
  - low affinity for CYP P450 enzymes
- *Fluoxetine* (Prozac)* 10 - 60 mg/day
  - potent inhibitor of CYP450 2D6 enzymes
- *Paroxetine* (Paxil)* 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:
  - 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 (Effexor) XR 75-300 mg qd
  - useful in SSRI nonresponders
  - extended release form preferable
  - may decrease indinavir levels - significance unknown
- Mirtazapine (Remeron) 15-45 mg qHS
  - very useful in patients with insomnia and wasting
- Duloxetine (Cymbalta) 20-60 mg qd
  - effective for symptoms of physical pain associated with depression
  - indicated for diabetic neuropathy

Other Antidepressants

- Trazadone (Desyrel)
  - good in low doses for sleep
  - infrequently, arrhythmias and priaprism occur
  - levels may be elevated by PIs
- Bupropion (Wellbutrin, Zyban)
  - often chosen for low sexual side effects
  - may cause anxiety or insomnia
  - levels may be increased by efavirenz and protease inhibitors

Anxiety

Anxiety and Milestones of HIV Disease / Progression

- HIV Testing
- News of HIV positive status
- Appearance of first illness symptoms
- Changes in CD4 count & viral load
- Onset of AIDS-defining illness

Anxiety May be Caused by Substance Use / Withdrawal

USE:

- Amphetamines
- Ecstasy
- Caffeine
- Cocaine
- Nicotine

WITHDRAWAL:

- Alcohol
- Benzodiazepines
- Opiates

Management of Anxiety

- Try non-pharmacological strategies first—stress reduction techniques, psychosocial support, breathing techniques, etc.
- Reduce / discontinue anxiety-provoking substances
- Consider CBT, IPT and other ECT interventions if available

Pharmacotherapy of Anxiety Disorders in HIV+ Patients

- SSRI's
  - Helpful for many anxiety disorders:
    - Social phobia, panic disorder, OCD, PTSD, GAD
- Venlafaxine (Effexor)
  - Approved for treatment Generalized Anxiety DO
  - Few drug-drug interactions
  - No abuse potential
  - May decrease indinavir levels-significance unknown
- Buspirone (Buspar)
  - Levels may be increased by protease inhibitors

Pharmacotherapy of Anxiety

Benzodiazepines

- Often used for time-limited treatment
- Dependence/withdrawal possible
- Low doses are often adequate
- Drug-drug interactions possible, especially Cytochrome P450 inhibition by protease inhibitors
- Fewer P450 interactions with lorazepam (Ativan), oxazepam (Serax), temazepam (Restoril)- metabolized by glucuronidation

Mania

- Psychopharmacology
  - Antipsychotics at lower doses
  - Mood stabilizers:
    - Lithium
    - Anticonvulsants, however,
      - Carbamazepine: potent CYP3A4 enzyme inducer, may decrease levels of PIs and NNRTIs
      - Valproic acid: inhibitor of glucuronidation; increases zidovidune, but dosage adjustment not recommended
      - Consider side effects & toxicities; labs
  - Benzodiazepines as adjunct
- Electroconvulsive therapy (ECT)

Antipsychotics

- Older neuroleptics – high rates of extrapyramidal side effects
- Newer "atypical" antipsychotics – easier to use, but have metabolic complications
  - Zyprexa / olanzapine: ↑risk diabetes
  - Clozaril / clozapine: ↑risk diabetes; bone marrow suppression; ↑risk seizures on ritonavir / other PIs
  - Geodon / ziprasidone: ↑QT interval—caution with drugs that also have this effect (e.g., protease inhibitors, ketoconazole)

HIV Associated Neurocognitive Disorder HAND

To date, no therapies, diagnostics, or predictive markers have entered clinical practice

New definitions of HIV – HAND

NIMH working group, Neurology 2007

- **Asymptomatic neurocognitive impairment (ANI),**
- **HIV-associated mild neurocognitive disorder (MND)**
- **HIV-associated dementia (HAD)**
- **A recognition of the importance of comorbid, potentially confounding conditions and that HAND is dynamic.**

HAND

- Antiretroviral medications
- Neurotransmitter manipulation
- Nutritional interventions
- Non-pharmacological treatments
- Environmental engineering
- Education
- Supportive Therapy

Does CNS penetration profile matter?

- Sacktor N, 2001: no effect on cognitive function
- Cysique L, 2004: effect only in cognitively impaired
- Letendre S., Arch Neurol., 20072007 ~ new index of penetration

	Good **1**	Fair 0.5	Poor 0
NRTIs	**Abacavir** **Zidovudine**	Emtricitabine Lamiduvine Stavudine	Didanosine Tenofovir Zalcitabine
NNRTIs	**Delavirdine** **Nevirapine**	Efavirenz	
PIs	**Indinavir** **Indinavir-r** **Lopinavir-r**	Amprenavir-r Atazanavir Atazanavir-r Darunavir-r	Amprenavir Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Fusion Inhibitors			Enfuvirtide

Alcohol & Other Drug Use (AOD)

- AOD Users less likely to be tested and diagnosed
- More likely to develop Opportunistic Infections and complications
- Less likely to have access to medical care
- Less likely to be offered optimal treatments
- Less likely to adhere if offered ART

Substance Use Treatment

- Traditional treatments – abstinence based + AA
- Harm Reduction: Motivational Interviewing, Cognitive Behavioral Therapies
- Relapse prevention for alcohol
  - Naltrexone (ReVia)
  - Disulfiram (Antabuse)
  - Acamprosate (Campral)
- Relapse prevention for opiates
  - Methadone
  - Buprenorphine

Interactions Between Antiretrovirals and Alternative / Recreational Drugs

- Interactions can occur -- much is unknown
- Methadone dose may need to increase (or, less often, decrease) depending on the antiretroviral regimen
- Concerns about the interaction between ritonavir and ecstasy
- St. John's Wort may lower levels of NNRTIs and protease inhibitors

Other Neuropsychiatric Disorders: Some Key Points

- Sleep and pain problems are very common and undertreated; newer sleep medications (zolpidem/Ambien, zaleplon/Sonata, eszopindone/Lunesta) and most benzodiazepines must be used cautiously with patients taking protease inhibitors
- Do not use benzodiazepines to treat delirium in medically ill HIV+ patients
- Mild/moderate neurocognitive disorders are under-diagnosed and may be present even when patients are otherwise well-controlled (e.g., stable ARV regimen, undetectable viral load)

Neuropsychiatric Complications of Hepatitis C (HCV) Co-Infection

- HCV Co-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
- Treatment: peginterferon alpha 2a+ribivarin
  - High rates of psychiatric disorder (esp. depression) – requires monitoring and access to mental health care during HCV treatment

Psychiatric Illness and Adherence

- 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

Before we get to the conclusions…

- The Miriam Acevedo Syndrome

Common Treatment Dilemmas in Patients with HIV, Mental Illness, and AOD

- Adequate access to and integration of mental health and substance use services.
- Maintaining adherence in patients with three chronic relapsing disorders.
- Provider countertransference reactions to “self-destructive” and “manipulative” patient behaviors.
- Balancing harm reduction approaches with sensible limit-setting.

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 worst than the disease!

Educational Resources on HIV and Mental Health

- NYS AIDS Institute: www.hivguidelines.org
- American Psychiatric Association Office of HIV Psychiatry: www.psych.org/AIDS
- National Resource Center www.aidsetc.org
- HIV InSite http://hivinsite.ucsf.edu