Psychopharmacology and the HIV-Positive Patient

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  - Anxiety
  - Sleep disturbance
  - Mood lability and agitation
  - Memory changes
  - Substance abuse

Course Objectives

- Understanding the effects of HIV and HIV-related medications on mental health
- Appreciation for the myriad of drug-drug interactions, and those to avoid
- Familiarity with applying the biopsychosocial model in treating the HIV-positive patient
- Knowledge about drugs of abuse in HIV

Pre-Review Questions

1) What is HIV?
2) What is the medication treatment for people living with HIV?
3) Does HIV enter the brain?
4) Can people with HIV take psychotropic medications?
5) What is lipodystrophy?

HIV

HIV

- Rapidly-mutating retrovirus contracted through exchange of bodily fluids (blood, semen, mother's milk, vaginal secretions)
- Compromises human immune system, notably through destruction of CD4+ t cells, creating vulnerability to viral, fungal, and parasitic infections

HIV and the Brain

HIV enters CNS early, via macrophages; Macrophages and microglial cells responsible for CNS replication.

Subcortical structures are targeted, however the entire brain is vulnerable.

CNS Implications of CD4 Count

- >500 lymphocytes/microliter
  - Acute retroviral syndrome (ARS)
  - Persistent generalized lymphadenopathy (PGL)
  - Aseptic meningitis
  - Minor cognitive motor disorder (MCMD)

CNS Implications of CD4 Count

- 200-500 lymphocytes/microliter
  - Pneumonia - bacterial
  - Kaposi's Sarcoma (KS)
  - B-cell lymphoma
  - Anemia

CNS Implications of CD4 Count

- <200 lymphocytes/microliter
  - *Pneumocystis* Pneumonia (PCP)
  - Disseminated Histoplasmosis and Coccidioidomycosis
  - Extrapulmonary tuberculosis
  - Progressive Multifocal Leukoencephalopathy (PML)
  - Wasting
  - Neuropathy
  - HIV-associated Dementia (HAD)
  - Non-Hodgkin’s Lymphoma (NHL)

CNS Implications of CD4 Count

- <100 lymphocytes/microliter
  - Toxoplasmosis
  - Cryptococcosis

CNS Implications of CD4 Count

- <50 lymphocytes/microliter
  - Disseminated Cytomegalovirus (CMV)
  - Disseminated Mycobacterium avium complex (MAC)
  - CNS Lymphoma

Treatment

- Interrupts the HIV lifecycle by introducing drugs into vulnerable points (mainly enzymes) in the viral replication system
  – reverse transcriptase
  – protease
  – entry
    - binding
    - fusion

Nucleoside-Analogue Reverse Transcriptase Inhibitors

- Includes 3TC(Epivir™), ABC(Ziagen™), AZT(Retrovir™), d4T(Epivir™), ddC(Hivid™), ddI(Videx™), FTC (Emtriva™)
- Primarily eliminated by the kidneys
- CNS Penetration 10-40% (AZT 60%)

Non-Nucleoside Reverse Transcriptase Inhibitors

- Includes NVP(Viramune™), DLV(Rescriptor™), EFV(Sustiva™)
- Many interactions possible due to CYP450 metabolism: substrates, inhibitors, and inducers
- Mental status changes possible

Considerations with Sustiva™

- Most severe side effects occur during first month
- Generally subside by the end of 4 weeks
- Include nervousness, dizziness, depression, mania, psychosis, suicidality, insomnia

Nucleotide Reverse Transcriptase Inhibitors

- Tenofovir (Viread™)
  - Renally eliminated; possibility of competition for active tubular secretion
  - No reported interaction with lithium

Protease Inhibitors

- Includes fAPV(Agenerase™), atazanavir (Reyataz™), IDV(Crixivan™), RTV(Norvir™), SQV(Invirase™,Fortovase™), NFV(Viracept™), LPV/RTV(Kaletra™), tipranavir (Aptivus™)
- Poor-Moderate CNS penetration
- Many serious drug interactions possible, especially involving CYP450

Entry Inhibitors

- Binding
  - CCR5 inhibitors (clinical trials)
- Fusion
  - T-20, enfuvirtide (Fuzeon™)
    - bid subcutaneous injections
    - peptide; metabolism likely not an issue

Other HIV-related medications to consider

- Antifungals (e.g,.itraconazole)
  - very potent 3A4 inhibitors
- IFN-α (Hepatitis treatment)
  - mental status changes possible
- Antiparasitics (e.g., thiabendazole for strongyloidiasis)
  - psychosis, delirium, confusion, depression possible
- Antivirals (e.g., acyclovir for herpes)
  - may cause hallucinations, confusion, insomnia
- Chemotherapy agents (e.g., methotrexate for lymphoma)
  - encephalopathy possible at high doses

Standard of Care - Lab Data

- Routine
  - Viral load
  - CD4+ T cells count (absolute and percent)
  - Liver function tests
  - Renal function, electrolytes
  - Complete blood cell count
  - Thyroid function and testosterone level (free and total)
- Specialized
  - Resistance testing
  - Therapeutic Drug Monitoring - Investigative
  - Toxicology and sexually transmitted disease screening

HIV and Mental Illness

HIV and Mental Health

- Elevated incidence of mental illness -- may occur before and/or after infection
- Elevated incidence of substance abuse
- Mental health considerations in the selection of HIV antiretrovirals
  - some antiretrovirals have potentially severe CNS side effects, including suicidality
- Non-Adherence
  - risk factors predominately psychosocial, however may also represent cognitive disease

Neurocognitive Disorders in HIV

- Minor Cognitive Motor Disorder (MCMD)
- HIV-associated Dementia (HAD)
- Delirium

Minor Cognitive-Motor Disorder

- At least two of the following
  - Impaired attention, concentration or memory
  - Mental and psychomotor slowing
  - Personality change
- Rule out other causes (e.g., medication induced, opportunistic infection)

HIV-Associated Dementia

- Acquired cognitive abnormality in two or more domains, causing functional impairment
- Acquired abnormality in motor performance or behavior
- No clouding of consciousness or other confounding etiology

HIV-Associated Dementia Staging

• Stage 0	Normal
• Stage 0.5	Equivocal symptoms of cognitive or motor dysfunction, but no impairment
• Stage 1	Mild; evidence of intellectual or motor impairment
• Stage 2	Unable to work but can manage self-care
• Stage 3	Major intellectual incapacity or motor disability
• Stage 4	Nearly vegetative

Treatment for MCMD and HAD

- Immune reconstitution with antiretrovirals
- Neurotransmitter manipulation
    - stimulating antidepressants
    - stimulants
- Symptomatic treatments for comorbid depression, agitation, anxiety, insomnia

Delirium

- A medical condition developing rapidly over a short period
- Symptoms include
  - Fluctuating level of consciousness
  - Hallucinations (primarily visual), delusions
  - Cognitive deficits
  - Disturbance in psychomotor activity
  - Emotional lability
  - Sleep disturbance (daytime lethargy, nighttime agitation)
  - Neurological abnormalities
    - Tremors, myoclonus, asterixis, nystagmus, ataxia, cranial nerve palsies, cerebellar signs
- Treatment requires medical assessment and intervention

Special Topics in HIV Relevant to Mental Health and Psychopharmacology

- Lipodystrophy ("fat redistribution")
  - Disturbing body changes may occur, including deformation of face, limbs, trunk
- Metabolic abnormalities
  - May include insulin resistance, lipid elevations
- Disconnect Syndrome
  - Viral load and CD4 no longer maintain an inverse relationship -> implications for elevated CNS burden of virus and cognitive dysfunction

Drug-Drug Interactions

Systems to consider:

- CYP450
- Glucuronidation
- Alcohol Dehydrogenase
- Renal elimination
- P-glycoprotein

Drug Metabolism in HIV

- Cytochrome P450 System
  - Most major isoenzymes potentially involved in metabolism of HIV antiretrovirals
    - 3A4 involved in most serious drug-drug interactions
    - Some antiretrovirals less predictable (e.g., efavirenz both inhibits and induces 3A4)

Drug Metabolism in HIV

- UGT (uridine diphosphate-glucuronosyltranserase) system
  - Consider when prescribing protease inhibitors with some opiate analgesics, tricyclics, lamotrigene, olanzapine, and 3-hydroxysubstituted benzodiazepines

CYP450 Example 1

- CYP P450 interaction example
  - Ritonavir is a very strong inhibitor of 3A4
  - Triazolam is a substrate of 3A4
    - the combination would lead to an increase in the half-life of triazolam from 3.7 hours to 50 hours

CYP450 Example 2

- St. John's Wort is an inducer of 3A4
- Ritonavir is a substrate of 3A4
  - The combination leads to a decrease in the concentration of ritonavir in the bloodstream, which can lead to increase in virus and resistance

CYP450 Example 3

- Freda comes in with chief complaint "My boyfriend is cheating on me!"
- Labs: no abnormalities; denies drug use; meds: ritonavir, lopinavir, olanzapine
- Drug-drug interaction: ritonavir induces 1A2; olanzapine is a 1A2 substrate
- Result: decreased serum concentration of olanzapine
- plan: increase olanzapine dose

Glucuronidation Example 1

- Anxious patient who has been stable on lorazapam 0.5 mg twice daily now finds herself acutely nervous 1 week after starting antiretroviral regimen.
- Ritonavir induces glucuronidation, leading to decreased serum concentration of lorazepam
- Would be reasonable to increase her lorazepam dose (e.g., 1 mg twice daily).

Glucuronidation Example 2

- Patient doing well on HIV med's, including zidovudine (ZDV). Due to recent diagnosis of bipolar affective disorder, he was started on valproic acid. A couple of weeks later he began developing fatigue and shortness of breath. Hematocrit checked = 29%.
- Valproate inhibition of glucuronidation -> increase in serum concentration of ZDV, and increased likelihood of ZDV-induced anemia
- Consider alternate mood stabilizer (e.g., lithium)

Other Systems

- Alcohol Dehydrogenase
  - e.g., facilitates interaction between abacavir and chloral hydrate
- Renal Elimination
  - consider with tenofovir, nucleoside analog reverse transcriptase inhibitors
- P-Glycoprotein
  - extent of involvement not entirely clear, however this system can also be induced and inhibited, thus affecting serum drug levels

Psychotropic Cautions

Antidepressants

Review P450 of psychotropic(s) and HIV-related medications when selecting antidepressant

Anticonvulsants

Caution with those that induce P450; immune function considerations

Anxiolytics; sedative-hypnotics

P450 and UGT interactions

Antipsychotics

Caution with cardiac conduction, immune function, and metabolic abnormalities

Herbal Medication Cautions

St John’s Wort

Garlic Capsules

Milk Thistle

Cat’s Claw (Uña de Gato)

Psychiatric Assessment and Management

General Assessment for all HIV Psychiatric Patients

- Review current medications: side effects and interactions. Adherence?
- Review physical health. Check labs for abnormalities.
- Explore substance abuse and STD exposure
- Taking herbals?
- Consider CNS workup if symptoms are new and CD4<200 (I.e., imaging, EEG, LP, additional labs)

Assessment - Psychosocial

- Psychological
  - Defenses employed
  - Flexibility; resiliency
- Socioeconomic
  - Finances
  - Current relationships
  - Losses
  - Supports
  - Housing

Treatment Approach - Depression

- Biological
  - Screen for bipolar disorder
  - Select antidepressants based on maximum efficacy and minimal drug interactions and side effects
  - Other pharmacotherapy (mood stabilizers, stimulants)
  - Substance abuse treatment
  - Changing HIV antiretroviral medications
- Psychological Issues
  - Individual, group psychotherapy
  - Supportive versus insight-oriented
- Socioeconomic Issues
  - address losses, finances, employment, housing

Treatment Approach - Anxiety

- Biological
  - SSRIs
  - Anxiolytics: Benzodiazepines and others
  - Substance abuse treatment
  - Changing HIV antiretrovirals
- Psychological
  - Individual, Group
  - CBT, supportive, insight-oriented
- Socioeconomic
  - address losses, finances, employment, housing

Treatment Approach - Insomnia, Vivid Dreams

- Assure patients that vivid dreams are very common; avoid attempts to interpret dreams
- Review sleep hygiene. Substance abuse?
- Selection of sleep medications depends on etiology of insomnia and concurrent HIV-related medications
  - sedating antidepressants
  - anxiolytics, sedative-hypnotics, antihistamines
  - neuroleptics
  - Other, including changing HIV antiretrovirals

Treatment Approach- Memory Changes

- Biological
  - Consider MCMD, HAD, and delirium in the differential
  - Maximizing HIV antiretrovirals for CNS penetration
    - zidovudine, nevirapine, and indinavir have highest CNS penetration
  - Assure adherence to HAART
  - Stimulants (e.g., methylphenidate 5 milligrams twice daily)

Treatment Approach- Memory Changes

- Psychological
  - Individual therapy aimed at helping patient cope with losses
- Socioeconomic
  - Assistance at home; making lists
  - Consider safety at work and driving
  - Family involvement
  - Conservatorship if indicated

Treatment Approach - Agitation, Mood Lability

- Neuroleptics
  - newer atypical preferable due to HIV effects on basal ganglia, however caution with metabolic abnormalities (lipids, glucose)
- Benzodiazepines
  - caution with interactions, substance abuse, severely medically ill
- Anticonvulsants
  - caution with interactions
- Lithium
  - toxicity may occur rapidly
- Working with primary care provider to change HIV antiretrovirals if all else fails

Substance Abuse in HIV

- Alcohol
  - liver disease
- Club Drugs - Ketamine, GHB, Ecstasy
  - potentially deadly interactions with HIV antiretrovirals
- Cocaine
  - leads to dramatically increased viral load
- Opiates, Opioids
  - significant interactions with HIV antiretrovirals

Substance Abuse in HIV

- Methamphetamine
  - leads to neurocognitive dysfunction and brain structural changes
  - more severe functional changes when HIV and hepatitis C present
  - may includes risky sexual practices, so consider screening for other sexually transmitted diseases (e.g., syphilis)

Review Questions

1) What are the five major classes of antiretroviral medications?

2) What is the significance of the CD4 count? Of the viral load?

3) Which benzodiazepines would be safest for someone taking a potent 3A4 inhibitor?

4) A patient on HAART is recreationally taking crystal methamphetamine. What is your advice?

5) Primary care MD approaches you, "I want to start Charlie on Sustiva™." What would you want to know about Charlie, and how would you advise this doctor?