Psychopharmacology and the HIV-Positive Patient

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Outline

- Major Teaching Points
- HIV Review
- HIV and Mental Illness
- Drug-Drug Interactions
- Psychiatric assessment and management of common symptoms in the HIV-positive patient
  - Depression
  - Anxiety
  - Sleep disturbance
  - Mood lability and agitation
  - Memory changes
  - Substance abuse

Major Teaching Points

- Understand the effects of HIV and HIV-related medications on mental health
- Appreciate the myriad of drug-drug interactions, and those to avoid
- Apply the biopsychosocial model in treating the HIV-positive patient
- Recognize drugs of abuse in HIV

Pre-Review Questions

1) What is lipodystrophy?

- **A. Uncontrollable smacking of the mouth due to HIV medications**
- **B. Generalized fungal infection in people living with HIV**
- **C. Body fat changes in some people living with HIV**
- **D. Neuronal loss in the basal ganglia**
- **E. A and D**

2) What is the significance of the CD4 count?

- **A. Lower count indicates an increased vulnerability to fungal infections**
- **B. Lower count indicates an increased risk of viral infections**
- **C. Higher count predisposes patient to CNS parasitic infections**
- **D. A and B**
- **E. A and C**

3) Which benzodiazepine(s) would be safest for someone taking a potent 3A4 inhibitor?

- **A. lorazepam**
- **B. oxazepam**
- **C. alprazolam**
- **D. All of the above**
- **E. A and B**

4) A patient with HIV is injecting methamphetamine. What is your advice?

- **A. Methamphetamine has proven long-term benefits for cognitive function in HIV+ patients**
- **B. Methamphetamine is safe to smoke but not inject**
- **C. Methamphetamine interacts with some HIV medications**
- **D. Methamphetamine is a depressant and can cause drowsiness when mixed with alcohol**
- **E. None of the above**

5) Primary care MD approaches you, "I want to start Charlie on efavirenz." What would you advise this doctor?

- **A. Efavirenz has no proven benefit in an HIV regimen**
- **B. Efavirenz may lower the concentration of medications metabolized by CYP3A4**
- **C. Efavirenz may cause temporary neuropsychological changes**
- **D. All of the above**
- **E. B and C**

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 lymphocytes, creating vulnerability to viral, fungal, and parasitic infections

HIV and the Brain

HIV enters CNS early, via monocytes; 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
  - integrase

Nucleoside-Analogue Reverse Transcriptase Inhibitors

- Includes
  - 3TC (Lamivudine, Epivir™)
  - Abacavir (Ziagen™)
  - AZT (Zidovudine, Retrovir™)
  - ddC (Hivid™)
  - ddi (Didanosine, Videx™)
  - Emtricitabine (Emtriva™)
  - d4T (Stavudine, Zerit™)
- Primarily eliminated by the kidneys
- CNS Penetration 10-40% (AZT 60%)

Non-Nucleoside Reverse Transcriptase Inhibitors

- Includes
  - Delavirdine (Rescriptor™)
  - Efavirenz (Sustiva™)
  - Etravirine (Intelence ™)
  - Nevirapine (Viramune™)
  - Rilpivirine (Edurant™)
- Many interactions possible due to CYP450 metabolism: substrates, inhibitors, and inducers
- Mental status changes possible
- CNS penetration varies
  - Nevirapine > Efavirenz > Etravirine

Considerations with Sustiva™

- Most severe side effects occur during first month
- May subside by the end of 4-6 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:
  - Atazanavir (Reyataz™)
  - Darunavir (Prezista™)
  - Fosamprenavir (Lexiva™)
  - Indinavir (Crixivan™)
  - Lopinavir/ritonavir (Kaletra™)
  - Nelfinavir (Viracept™)
  - Ritonavir (Norvir™)
  - Saquinavir (Invirase™,Fortovase™)
  - Tipranavir (Aptivus™)
- Poor-Moderate CNS penetration
- Many serious drug interactions possible, especially involving CYP450

Newer Inhibitors

- Entry
  - Maraviroc (Selzentry ™)
  - Moderate-good CNS penetration
  - May cause insomnia (initiating and maintaining sleep)
  - Substrate of CYP3A
- Fusion
  - T-20, Enfuvirtide (Fuzeon™)
    - subcutaneous injections
    - peptide; metabolism likely not an issue
    - Poor CNS penetration
- Integrase Strand-Transfer
  - Raltegravir (Isentress ™)
  - Moderate-good CNS penetration
  - May cause insomnia
  - Metabolism primarily involves glucuronidation (metabolism, and acts as a strong inducer)

CNS Penetration-Effectiveness

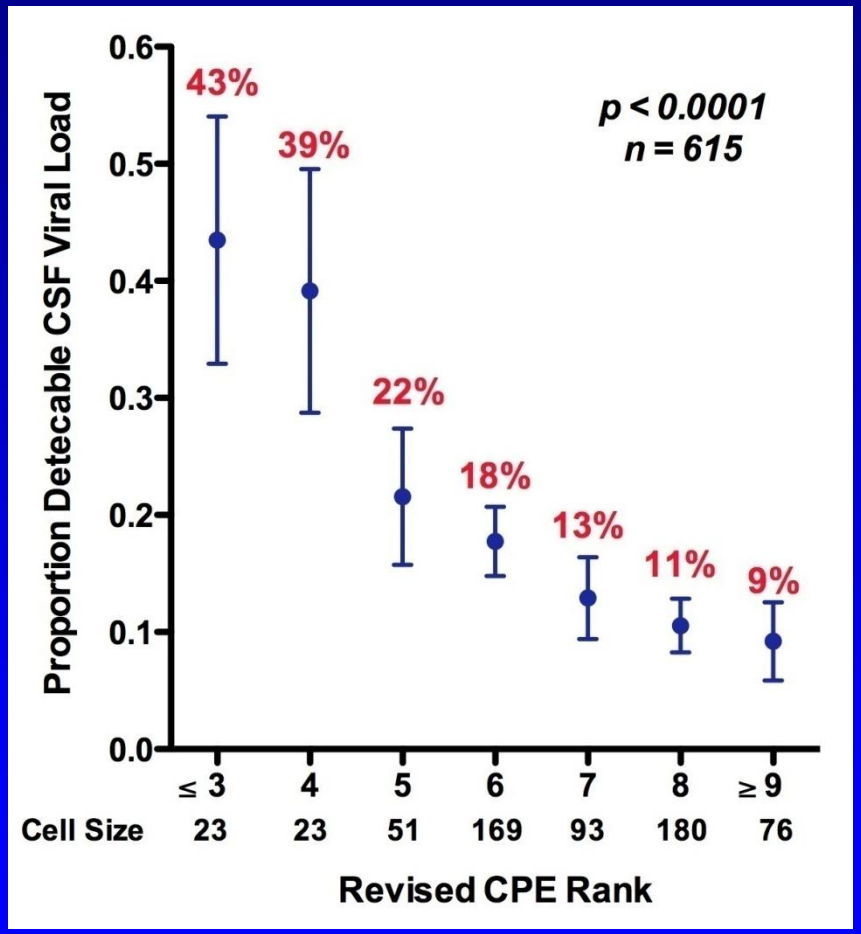
- Antiretrovirals have variable CNS penetration abilities
- Psychiatric assessments may become increasingly important in the selection of antiretrovirals in those patients who are experiencing cognitive dysfunction

CNS Penetration-Effectiveness Ranks 2010

	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

Letendre et al, 17th CROI 2010, Abstract 172

Estimation of CNS Penetration-Effectiveness
Better Penetration = Lower CSF Viral Loads



Values on the x-axis represent the sum total of CPE scores of each component HIV antiretroviral. E.g., if patient is on tenofovir, emtricitabine, and efavirenz, their score would be 1+3+3 = 7

Letendre S, et al. CROI 2010. Abstract 172

Other HIV-related medications to consider

- Antifungals (e.g,.itraconazole)
  - very potent 3A4 inhibitors
- IFN-α + Ribavirin (Hepatitis C treatment)
  - mental status changes probable
- 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

HIV-Associated Neurocognitive Disorders (HAND)

- Asymptomatic Neurocognitive Impairment (ANI)
- Mild Neurocognitive Disorder (MND)
- HIV-associated Dementia (HAD)
- Diagnosis is no longer made by symptoms, but rather by impairment defined by results of standardized neuropsychological testing

Asymptomatic Neurocognitive Impairment

- ANI is defined by performance at least 1.0 SD below the mean in at least two cognitive areas (attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory, including learning and recall, simple motor skills *or* sensory perceptual abilities)
- No abnormality in daily functioning

Mild Neurocognitive Disorder

- Acquired impairment in cognitive functioning, involving at least two ability domains at least 1.0 SD below the mean. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):
  - a) Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
  - b) Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.

HIV-Associated Dementia

- Acquired cognitive abnormality in two or more cognitive domains at least two standard deviations below the mean, or
- Impairment in at least one cognitive domain greater than 1.0 standard deviation below the mean and impairment within one other domain that is greater than or equal to 2.5 standard deviations below the norm
- Acquired abnormality in motor performance and/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

Screening for HAND

- May be appropriate when the gold standard (full neuropsychological testing) is unavailable or difficult to obtain
- Accepted screening tools include
  - International HIV Dementia Scale
    - N. Sacktor, et. al. Johns Hopkins University
  - HIV Dementia Scale (Original or Modified)
    - Johns Hopkins University
  - Montreal Cognitive Assessment (MOCA)
    - www.mocatest.org

Treatment for HAND

- Immune reconstitution with antiretrovirals remains the mainstay of treatment for HIV-related cognitive disorders
- Symptomatic treatments useful for comorbid depression, agitation, anxiety, insomnia
- Neurotransmitter manipulation has been explored in HIV-related cognitive dysfunction
    - Antidepressants (MAO type B inhibitors, SSRIs)
    - Mood stabilizers (lithium, valproic acid)
    - Stimulants
    - Others (acetylcholinesterase inhibitors, antioxidants, peptide T)

Lithium and HIV

- Prevents gp120-induced HIV neurodegeneration in vitro
- Lithium at 300 mg/day in a small open-label study led to overall improvement in neuropsychological performance (especially executive functioning and information processing)
- Caution when administered with tenofovir, as GFR may be reduced by this antiretroviral

Stimulants and HIV

- Methylphenidate (30 mg/day) shown effective in HIV-related cognitive slowing
- Dextroamphetamine also seen effective in overall health in those with HIV-related cognitive dysfunction
- Very few case-controlled trials

GALANTAMINE AND HIV

- Used in treating Alzheimer's dementia by inhibiting acetylcholinesterase
- Giunta et al. looked at methods of modulating the immunological activation of brain mononuclear phagocyte cells. This process, called the microglia inflammatory mechanism, is implicated in the sequelae of HIV-associated dementia (HAD)
- Because microglial cells express the same or a similar anti-inflammatory regulation response as the peripheral nervous system by way of acetylcholine, researchers theorized that they could identify and use a cholinesterase inhibitor to treat or prevent HAD
- The researchers reported that galantamine was effective in modulating microglia inflammation, (Giunta, et al, 2005), however HIV-galantamine clinical trials since then have not been published
- Donepezil also an acetylcholinesterate inhibitor with limited effect and use in HIV-associated dementia

Memantine and HIV

- Antagonist of the NMDA receptor
- Safe and well tolerated in HIV+ subjects with cognitive impairment, however no significant differences in cognitive performance
- Shown through magnetic resonance spectroscopy to ameliorate neuronal metabolism (and thus help stabilize or prevent neuronal injury); may prove to be an important component in future HIV clinical trials

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
- Hepatitis C Co-infection
  - Treatment may last for one year; mental status changes are common
  - Consider use of prophylactic antidepressants

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, lamotrigine, 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

- Modafinil 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; medications include 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 two weeks 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. Three 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

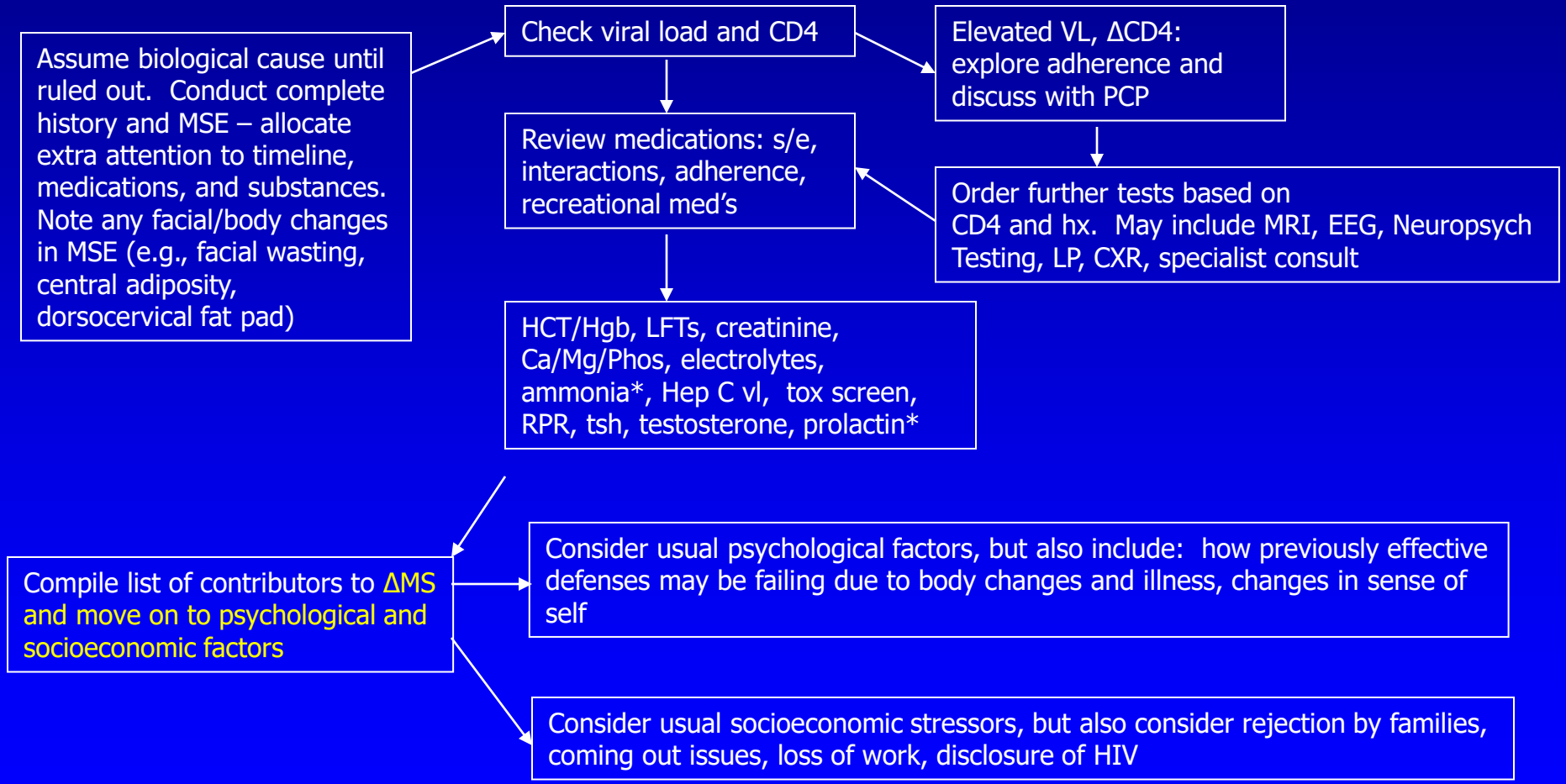
Garlic Capsules

Milk Thistle

Cat's Claw (Uña de Gato)

Psychiatric Assessment and Management

Algorithm in Approaching ΔMS in HIV/AIDS



*when applicable

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 HAND and delirium in the differential
  - Maximizing HIV antiretrovirals for CNS penetration
    - Consider CPE scoring system
  - Assure adherence to antiretrovirals
  - Stimulants (e.g., methylphenidate 5 milligrams twice daily) may be useful in some cases

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 to older typicals 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 those are contributing to the mood change

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)
  - Protease inhibitors may lead to a 3-10 fold increase in plasma concentration of methamphetamine

Review Questions

1) What is lipodystrophy?

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5) Primary care MD approaches you, "I want to start Charlie on efavirenz." What would you advise this doctor?

- **A. Efavirenz has no proven benefit in an HIV regimen**
- **B. Efavirenz may lower the concentration of medications metabolized by CYP3A4**
- **C. Efavirenz may cause neuropsychological changes**
- **D. All of the above**
- **E. B and C**

Answers

1) C. Lipodystrophy may be recognized by fat loss in the face and limbs, and fat gain in the abdomen (visceral), breasts, and dorsocervical area ("buffalo hump").

2) D. The CD4 count, in part, gives one an idea of the strength of the immune system and its ability to fight off fungal, viral, and parasitic infections. Due to a generalized compromise of the immune system, the HIV-positive patient also has a weakened ability to fight off bacterial infections.

3) E. Lorazepam, temazepam, and oxazepam concentrations are not elevated by 3A4 inhibitors. Alprazolam concentrations may increase when administered with potent 3A4 inhibitors.

4) C. In those with HIV, methamphetamine has been shown to impair cognitive function and cause structural changes in the brain. The drug causes these changes whether smoked, injected, "snorted," or ingested orally/anally. Concentrations of methamphetamine can increase dramatically in the presence of some HIV antiretrovirals. As with amphetamines, methamphetamine is a stimulant and not a depressant.

5) E. Efavirenz is a medication effective for many patients as part of their antiretroviral combination therapy. It may induce some cytochrome P450 enzymes (including 3A4), thus lowering the concentrating of medications metabolized by 3A4. One of the common side effects of efavirenz is neuropsychological changes, including mood and vestibular-like changes (e.g., dizziness) which may either persist or be self limiting.