Psychopharmacology for Medically Ill Patients

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Recognize & Treat – What to Use

- Psychiatric illness may interact with other illness
- Psychiatric medication and interaction with other medication
- Should psychiatric medication be stopped with other illness?
- Is there evidence based psychiatric treatment?

The format

- Make the information relevant to primary care providers to have solid “take away” information to apply everyday
- Major Depressive Episodes to be the example to foster discussion
- Offer evidenced reasoning and references for treatment
- Periodic updates from DSM IV to DSM V regarding depressive disorders
Evidence Based Diagnosis & Treatment of Major Depressive Episode

- Depressed mood & Anhedonia constitute the two most important symptoms of a depressive episode
- Suicidal thoughts or behaviors are the most worrisome symptoms
- Major depressive episode symptoms to be clinically significant must cause distress or impairment in social, occupational or other important aspects of the patient’s life

DSM-V Specifiers

- One of the hardest diagnosis determinations of mood episodes is to distinguish between primary depressive episodes and ones as direct physiological consequence of a general medical condition
- Cognitive impairment that can occur as part of a Major Depressive Episode can be so severe that it mimics a neurocognitive disorder
- Thought blocking can be so severe it mimics dementia
- Depression can present with catatonia

How Does the DSM - V differ from DSM - IV in classification of mood disorders?

- DSM-IV included all mood disorders in a single section; DSM - V places depressive and bipolar mood disorder in separate sections
- Premenstrual Depressive Disorder is included in the “depressive disorders” chapter of DSM - V but not included in the “mood disorders” chapter of DSM - IV
- PMDD after 20 years of research was confirmed as a specific treatment responsive form of depressive disorder that begins sometime following ovulation and remits within a few days of menses and has a marked impact on functioning
DSM-V Specifiers

DSM-V added the specifiers to allow more ability to explain the type of depressive episode. Part of rating the depression is to deconstruct the syndrome and utilize medications more suited to that symptom cluster. The ability to do pharmacogenetic testing to pick the best drug with maximum ability for the patient to metabolize is in the future at a clinical level. It is necessary to classify the depressive episode as mild, moderate or severe in presentation. It is important to note whether the episode is first, recurrent or relates from stopping their medication too early in the treatment process.

• With anxious mood - (nervousness, worry, jitteriness)
• With mixed features - (anxiety & depression)
• With melancholic features - (loss of pleasure)
• With atypical features - (weight change, hypersomnia, leaden)
• With mood – congruent psychotic features - (delusions/hallucinations)
• With mood – incongruent psychotic features
• With catatonia - (totally withdrawn)
• With peripartum onset - (during and or post partum)
• With seasonal pattern - (associated with available sunlight)

Use of Antidepressants in Medically Ill Patients - Considerations

• Drug – Drug interaction
• Pharmacokinetics - (absorption, distribution, metabolism, excretion)
• Sexual side effects - (libido, orgasm, erection)
• Alarthnia - (feeling of needing to move constantly)
• Hypoaesthesia - (low sodium)
• Serotonin syndrome - (altered consciousness, GI symptoms, autonomic disturbance, neurological signs – tremor, myoclonus, incoordination, and muscle rigidity)
Major Depression & Other Illness

- Cardiovascular disease
- Pulmonary disease
- Renal disease
- Endocrine disease
- Thyroid
- Cancer
- Neurological illness

Depressive disorder surprise question?

- How do individuals with substance/medication-induced depressive disorders differ from individuals with major depressive disorder who do not have a substance use disorder?
  - They are more likely to be female
  - They are more likely to have graduate school education
  - They are more likely to be male
  - They are more likely to be white
  - They are less likely to report suicidal thoughts/Attempts
  - (DSM-V, self-exam questions; test questions for diagnostic criteria, Muskin, Philip, M.D.)

Which of the following statements about prevalence of major depressive disorder in the USA is true?

- The 12-month prevalence is 17%
- Females and males have equal prevalence at all ages
- Females have increased prevalence at all ages
- The prevalence in 18 to 29 year olds is 3 times higher than that in 60 year olds
- The prevalence in 60 y/o's is 3 times higher than that in 18 to 29 years olds
### Cardiovascular disease overview

- 20% of individuals with recent acute myocardial infarction have clinical depression
- Untreated depression in recent MI patients increases the risk of a serious to fatal repeat event 4-5 times more likely than treated depression (Taylor et al. 2005)
- SSRI's may be cardio-protective due to SSRI-mediated serotonergic activity that may have positive anti-inflammatory effect on platelet function (makes them “less sticky” less likely to form clot to re-infarct) (Joynt and O'Connor 2005)
- SSRI's, bupropion, & mirtazapine have safest cardiac profile and TCAs have highest risk for adverse events

### CARDIOVASCULAR - specifics

- Pharmokinetic changes in heart disease
- R. side failure = hepatic congestion, gut wall edema - decreased absorption
- L. side failure = Dec. hepatic Arterial Bls. flow, decreased phase 1 hepatic metabolism – reduced elimination of parent drug
- L. side failure = elimination – decreased renal artery blood flow, decreased glomerular filtration rate – reduced elimination of water soluble molecules (example: lithium toxicity)

### CARDIOVASCULAR – caution first

- Adverse Effects of Psychotropic Drugs (Mackin 2008)
- Antidepressants
  - Bupropion - hypertension
  - SNRI - hypertension
  - SSRI - reduced heart rate, occasional clinically significant sinus bradycardia, or sinus arrest
  - Stimulants - hypertension, tachycardia, tachyarrhythmias
  - Tricyclics - orthostatic hypotension
CARDIOVASCULAR-caution

- Mood Stabilizers
- Lithium - sinus node dysfunction
- Carbamazepine - type 1A anti-arrhythmic effects; antioventricular block
- Mirtazapine - orthostatic hypotension (van Melle et al. 2007)
- TCAs - hypotension, orthostatic hypotension, type 1A antiarrhythmic effects: slowed conduction through AV node and HIS bundle, heart block, QT prolongation, ventricular fibrillation

CARDIOVASCULAR

- Hierarchy of Drug Choice (combined studies available evidence July 2009)
- Citalopram, escitalopram, and sertraline seemed to be the first line treatments for depression with heart disease
- The relative absence of CYP interactions associated with citalopram and escitalopram and to lesser degree sertraline was cited as an advantage over other meds in this summary
- Patients that fail on these medications might logically be offered mirtazapine, bupropion, venlafaxine or duloxetine with attention to blood pressure response
- Medications should be started low dose and RO EKG response along with physical examination and laboratory results reassessed before increasing the dose that must go to a therapeutic dose to be effective in treatment of depression
- Bupropion is the only antidepressant associated with weight loss and may need to be considered in cardiac patients that need to lose weight

Trazadone it's own slide

- Late 1970's called Desyrel
- Not very effective stand alone antidepressant
- Used for sleep in combination with SSRIs started late 1980's
- Very variable dose from 50 – 400 mg / 24 hours
- Usually low risk of severe side effects and may be used long periods of time
Trazadone – more!!

- Adverse effects: orthostatic hypotension, priapism, suicidality, SIADH, withdrawal seizures if high dose and abrupt, platellet abnormal bleeding, arrhythmia, syncope, tremor, arthralgia, nausea, sexual dysfunction, anemia, nasal congestion, abdominal discomfort are a few of the main minor and major
- Inhibits serotonin reuptake, antagonizes alpha-1 adrenergic and serotonin 5 - H1/H2 receptors
- Half life 3-6 hours, first phase and 5-9 h second phase, urine 75% excretion, 1 % unchanged, feces 20% excretion

Pulmonary Disease

- MDD can be as high as 47% in asthma patients while 20% average in general public
- Treatment of depression in asthma can lead to better compliance in their asthma medicine regimen leading to positive outcome with mental health and pulmonary disease. (Brown et al. 2005)
- Antidepressants have a therapeutic effect on respiratory capacity and asthma symptoms via anti-inflammatory effect
- SSRIs and TCA’s are first line treatment options in individuals with anxiety and/ or depression in addition to respiratory complications secondary to pulmonary disease. (Levenson 2005)
- Bupropion was effective in treatment of anxiety and depression in asthma patients without exacerbating asthma symptoms (Brown et al. 2007)

Put it in perspective slide - ? med

- Adverse effects (black box) inc. risk of serious and potentially fatal CV thrombotic event, MI, and stroke & risk increases more the patients use the medication, risk of serious GI bleed, ulcer, stomach or intestine perforation
- Common side effects – nausea, dyspepsia, headache, dizziness, ALT, AST elevation, fluid retention, ecchymosis, tinnitus, constipation
- Serious side effects – HTN, CHF, renal papillary necrosis, nephrotoxicity, hepatotoxicity, bronchospasm, Steven – Johnson syndrome, aplastic anemia, thrombocytopenia, anaphylaxis
Key Clinical Points-Pulmonary

Up to 47% of asthma patients compared to 20% of general public may have depression and that can lead to poor compliance of their asthma regimen causing morbidity and sometimes fatal results (Brown et al. 2005).

In a study by Nascimento et al. 2005 a trial of SSRI's with panic disorder subjects displayed higher forced expiratory lung volume and forced expiratory flow leading to greater lung function on the SSRI protocol for the panic attacks due to anti-inflammatory effect of SSRI's.

Asthma and SSRI Treatment

- In a randomized study of 90 subjects with asthma receiving citalopram or placebo, the citalopram patients had greater remission of depression and reduced asthma symptom severity (Brown et al. 2007).
- SSRI's and carefully TCA's are considered first line treatment options in individuals with anxiety and/or depression in addition to respiratory complications secondary to pulmonary disease (Levenson 2005).

Renal Disease

- SSRI's are the most common antidepressants associated with inappropriate antidiuretic hormone secretion causing hyponatremia and usually occurs in first 2-4 weeks of taking the medication - rare.
- Most common causes of SIADH include malignant tumor, postoperative pain, prolonged nausea and pharmacological agents such as SSRI's.
- Patient risk factors (older age, female gender, comorbid medical conditions, hypertension).
- Medications associated with SIADH: antihypertensives, diuretics, SSRI's with inhibitory effects on cytochrome P450: fluoxetine, fluvoxamine, paroxetine.
Management of antidepressants with end-stage renal disease

- SSRI's - generally safe, start at low dose and titrate conservatively
- Special considerations: paroxetine potential for elevated levels with renal impairment
- Sertraline shown at times to prevent hemodialysis related hypotension
- Venlafaxine, decreased elimination in renal insufficiency and ESRD
- Imipramine potential for elevated levels of metabolites and lowered seizure threshold
- TCA - generally safe, monitor for toxicity - can obtain blood levels of the TCA
  *(Baghdady et al. 2009)*

Diabetes and Depression Differential

- Differential diagnostic consideration in diabetes with psychiatric symptoms include:
  - Prior history of psychiatric disorder
  - Acute mood and cognitive effects of hyperglycemia and hypoglycemia
  - Cognitive and behavioral impairment resulting from CNS microvascular disease
  - Common comorbidities and their treatments that can cause neuropsychiatric symptoms (cardiovascular, renal disease, etc.)
  - Remember the situation is likely to be a combination of all or part of the symptoms
  - A trial of antidepressants may be diagnostic

Thyroid Disorders

- 40% of patients with hypothyroidism have depression
- 12-50% of patients with depression have some level of hypothyroidism *(Carvalho et al. 2007)*
- Profound hypothyroidism can produce psychosis (myxedema madness), delirium and catatonia
Cancer Patients

- Major depressive disorder found in 5-42% of cancer patients.
- Several anticancer drugs have had serious drug interactions with antidepressants such as selective serotonin receptor regulators such as tamoxifen and SSRIs.
- Both flurazepam and paroxetine have been shown to have strong inhibitory effects on CYP2D6 metabolism that can reduce the efficacy of tamoxifen in the fight against breast cancer.
- TCAs in combination with tamoxifen can prolong QTc and may cause torsades de pointes.
- Combination of citalopram with topoisomerase inhibitors such as irinotecan can increase the likelihood of having thrombomylsis.

Now we have your attention about cancer patients - what can be done?

- Depression has a median point prevalence of 24% in cancer patients.
- SSRIs may not be as effective as one would like in depression but in studies have shown to help with lessening feelings of general distress.
- Mirtazapine (Remeron) has been shown in a 6 week trial of oncology patients with somatic and psychiatric complaints at dose 7.5mg - 30mg/day to improve depression, anxiety and insomnia compared to imipramine or other medication control (Cathcartan et al. 2008).
- Sustained release bupropion (100-300mg/day) was effective in an open-label trial for depressive symptoms in cancer patients where fatigue was the primary issue (Mons et al. 2006).

Review of Psychotic Depression
(ref. Anthony Rothschild, MD)

- Major depression with psychotic features
- 14% of major depression (ECA study)
- 18.3% of major depression (European study)
- Inpatient settings:
  - 45% of depressed adolescents
  - 24% - 53% of depressed patients
Psychotic Depression & Mortality

- Patients with psychotic depression have a two-fold greater risk of death than do patients with severe, non-psychotic major depression (41% vs 20% dying within 15 years after hospital admission).
- Most of the later deaths were not from suicide but medical causes.
- Risk of completed suicide 5 x higher than nonpsychotic depression (Roose et al., 1983).
- More likely to use violent methods to suicide than patients with nonpsychotic depression (Iconcino et al., 1994).

Diagnostic Issues Psychotic vs Nonpsychotic Depression

- Increased paranoia
- Increased hopelessness
- Increased hypochondriasis
- Increased anxiety
- Increased early and middle insomnia

Psychotic Depression

- In addition to the previous symptoms other psychotic symptoms can present and at times make it hard to distinguish from psychotic disorder.
- Hallucinations may be present but are usually a theme of negative messages to the patient or commanding self-harmful behavior.
- Delusional behavior is negative such as the neighbors that were friends are now plotting to have patient thrown out of the neighborhood.
- Psychotic depression in geriatrics can be a precursor to dementia as seen in some studies.
Treatment of Psychotic Depression

- Treatment must be a combination regimen and kept in place for an extended period and if medication stopped many times the disorder will resume.
- Flint and Rifat, 1998 – 47% relapse rate in 2 yr. follow-up with nortriptyline monotherapy.
- Meyers et al., 2001 – 15% relapse rate on nortriptyline monotherapy, 33% on nortriptyline + perphenazine at 26 – week follow-up.
- Rothschild et al., 2003 – 27% relapse when perphenazine tapered after 4 months of fluoxetine + perphenazine (Trilafon).

Understanding Antidepressant Nonresponse

- Diagnosis
- Drug selection
- Dosage/ adherence
- Duration of therapy
- Disabilities/ complexity/ comorbidities

Thyroid Function & Depression

- Hypothyroid can cause depressive symptoms
- Subclinical hypothyroidism is associated with lessened antidepressant response
- Depression may warrant better than normal thyroid function
- Do not argue with endocrinologists or your friendly internist “we know they do not have clinical hypothyroidism” we do not plan to “suppress their thyroid for no reason with supplement”
- We are talking about treating resistive depression and if a patient has depression slow to respond to first line therapy despite “doing things right” and he has a TSH >4-6 consider low dose supplement.
Thyroid Augmentation

- 11 published studies
- T3 preferred over T4 (Cytomel over Synthroid)
- 25-50 Ug/day of T3
- Safe and easier to implement than lithium supplement
- Women have a better response to supplement with T3 than men

Lithium Supplement

- Depressed patients have different responses to lithium
- Supplement to a lithium level of 0.4 – 0.6 lower than treatment of bipolar
- Allow 6 weeks to assess effect
- May continue long time
- Lithium has been proven to have some anti-suicide qualities
- Must monitor thyroid and kidney function with lithium supplement

Medications

- Tricyclic refers to the three rings in their structure (examples, amitriptyline, nortriptyline, clomipramine, imipramine, desipramine)
- Heterocyclic / atypical more complex ring (examples, amoxapine, maprotiline)
- TCAs are as effective as second generation antidepressants with reuptake inhibition
- TCA side effect profile consists of blurred vision, dry mouth, constipation, and urinary retention, sedation, weight gain, orthostatic hypotension, tachycardia and LETHAL OVERDOSE CONCERN
Medications

- Selective serotonin reuptake inhibitor (SSRI) – first released in 1987: fluoxetine, sertraline, paroxetine, citalopram, escitalopram
- SSRI’s: no more effective than TCA’s for re-uptake inhibition
- Severely ill patients safer to alleviate symptoms without the danger of lethal overdose using an SSRI
- SSRI side effects consist of: headache, dizziness, fatigue, insomnia, nausea, constipation, diarrhea, excessive sweating, sexual dysfunction (delayed orgasm or anorgasmia)
- Unlike TCA’s: SSRI’s do not cause cardiac conduction delay, and thus decreases their severe risk in overdose unlike TCA’s lethal cardiac conduction issues

SSRI’s

- Fluoxetine, paroxetine and to lesser degree sertraline inhibit the drug metabolizing enzyme cytochrome P450 (CYP) 2D6
- The inhibition is factor in compromised settings and can be with beta blockers and codeine along with other settings mentioned in other segments of the lecture

Stroke and Depression

- Post-stroke depression many times presents as a slow down of the rehabilitation that had been going well
- May be a withdrawal, irritability, low motivation, hopelessness
- When symptoms occur in a patient that has no other reason to be in this typical or atypical presentation of lethargy of recovery consider depression as one of the concerns
- Many stroke units screen throughout early recovery and rehabilitation for depression signs
Summary

- Diagnosis of depression - DSM - V
- Key points in treating patients with common medical illness for depression
- Discussion of antidepressants
- Psychotic depression - diagnosis and treatment
- Treatment supplement of resistive depression (supplements – lithium and thyroid)
- Last discussion of integrated care (psychiatry and primary care)

Integrated Care

- The idea that patients should be able to get a majority of their care under one big tent
- Psychiatry and primary care working hand in hand
- There is no consistent psychiatric rotation for residents in family medicine, internal medicine, or emergency medicine
- The subtle message is mental health must not be very important or it would have been a bigger deal in my training to take care of “sick people” – maybe they are not really sick?

Integrated Care

- If one doesn’t have a lot of familiarity with some issue it is easier to discount the issue
- In medicine we need to know about mental health disorders just like cancer, or heart disease and especially osteopathic medicine (we are the original whole body docs)
- Helping primary care to be more comfortable treating mental health makes for better medicine and patient care
Integrated Care

- It is a two-way street psychiatry needs more general medicine
- Many aspects of patient care are affected by the negative gap that exists in psychiatric exposure at the residency level for the young physician in primary specialties
- Primary care sees 80% of mental health patients
- Up to 70% of relapses of psychiatric illness post-hospitalization for another medical illness relapse due to their psychotropic meds being stopped in the hospital and not restarted on discharge thus they relapse in 2-3 months

Integrated Care Rural Oklahoma

- The future for rural Oklahoma primary care clinics is to integrate psychiatry by utilizing tele-psychiatry for integrating care and training
- Mental health centers are adding primary care clinic space to their facilities as chronic mentally ill patients die 25 years earlier than other patients due to a void of primary care
- There is hope let’s all remember we are on the same team to treat the whole patient and osteopathic medicine understands that better than anyone!
Thank you