2015 Update on Psychotropics

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Learning Objectives

Upon completion of this session, participants shall be able to:

- Review the different classes of psychotropic medications.
- Discuss how to appropriately select, use and monitor psychotropic medications.
- Review the psychotropic drug pipeline.

Treatment of psychiatric disorders

- Common sense lifestyle interventions
- Psychotherapy
- Medication

Categories of psychotropics

- **Antidepressants**
- **Antipsychotics**
- **Mood stabilizers**
- **Dementia treatments**
- Sedative/hypnotics
- Other sleep medications
- Stimulants

Similarities among categories of psychotropics

- Decreased dosing in elderly
  - Think *one-half*
- Useful, necessary, but far from perfect

Differing mechanisms among categories of psychotropics

- Reuptake inhibitors
- Enzyme inhibitors
- Agonists
- Partial agonists
- Antagonists

Antidepressants: similarities

- Delayed therapeutic effect
  - Usually 3-6 weeks with range of 2-8 weeks for *beginning* of improvement
  - Stimulants are the exception
- Sexual side effects (nearly universal)
- *Choose your preferred mechanism and (mostly mild) side effects*, as old and new agents are generally equally efficacious.

Categories of antidepressants

- Tricyclic Antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Wellbutrin/bupropion (an NDRI)

Categories of antidepressants

- Remeron/mirtazapine (serotonin antagonist)
- nefazodone (was Serzone, mostly 5-HT2A antagonist)
- trazodone (similar, discussed later)
- Viibryd/vilazodone (NEW! SRI + 5-HT1A partial agonist)
- New serotonin receptor modulator i.e. Brintellix (vortioxetine)

Old antidepressants: advantages

- TCAs, especially amitriptyline (Elavil) and nortriptyline (Pamelor), have been shown effective in the treatment of neurogenic pain syndromes.

- MAOIs may have superior efficacy in more chronic depression when neurovegetative features are not prominent.

Old antidepressants: disadvantages

- MAOIs should be used with caution
  - Hypertensive crisis
  - Serotonin syndrome
- TCAs are older, but still useful
  - Anticholinergic (red as a beet, etc.)
  - Antihistaminic (sedative)
  - Antiadrenergic (positional low BP)
  - Cardiac effects may prolong QT interval

Safer MAOIs?

- Selective MAO Type B inhibition
  - selegiline (Eldepryl) selective at less than 10-15 mg/d
  - EmSam patch at 6mg or less

SSRIs

- fluoxetine (Prozac)
- sertraline (Zoloft)
- paroxetine (Paxil)
- fluvoxamine (Luvox)
- citalopram (Celexa)
- escitalopram (Lexapro)

SSRIs: Similarities

- Generally very well-tolerated and safe
- Remain first line for depression
- All effective… None clearly superior
- Safe
- Sexual dysfunction

SSRIs: Disadvantages

- Sexual dysfunction
- Weight gain (preceded by weight loss)
- Initial exacerbation of anxiety
  - May give benzodiazepine for first 1-4 weeks with explicit expectations about taper
- Discontinuation syndrome
  - Severity inversely proportional to half-life
- Vivid dreams

SSRIs: Disadvantages

- Cytochrome P450 interactions
  - All inhibit 2D6
  - Most inhibit 3A3/4, some (Prozac, Paxil) more than others (Zoloft, Celexa, Lexapro)
- Sedation (most prominently paroxetine) or activation (most prominently fluoxetine)
- Increased suicide risk in children and adolescents, adults

SNRIs

- Effexor (venlafaxine)
- Pristiq (desvenlafaxine, venlafaxine's metabolite)
- Cymbalta (duloxetine)
- Fetzima (levomilnazopram)

SNRIs

- NE and serotonin reuptake inhibition
  - but, unlike TCAs, not antihistaminic, only somewhat anticholinergic (except latter at high doses)
- Activation
- Can cause significant increase in BP, so think twice in patients with borderline hypertension
- Other side effects are like those of SSRIs
- Effexor has stubborn discontinuation syndrome (worse than SSRIs)

bupropion (Wellbutrin)

- NE and some dopamine reuptake inhibition
- Mild stimulant-like effect
- Some evidence shows less propensity to cause switching into manic states in bipolar patients
- Doesn’t help with anxiety like serotonergic agents do
- Absent sexual side effects (unique among antidepressants)
- Can cause seizures
- Increases BP

mirtazapine (Remeron)

- Complex antagonistic effects on NE and serotonin axes
- Sedation
- Prominent weight gain (may can be useful in elderly)
- Orthostasis
- Rare cases of bone marrow suppression and agranulocytosis (1/1000)

vilazodone (Viibryd)

- Complex mechanism:
  - SRI
  - 5-HT1A partial agonist (also found in buspirone and Abilify)
  - Name connected to nefazodone and trazodone, but those are 5-HT2 antagonists instead

vilazodone (Viibryd)

- Side effects:
  - Sedation
  - GI side effects
  - Less weight gain
  - Less sexual dysfunction

Antidepressant pipeline

- Amifitadine (EB-1010): an SNDRI
- Edivoxetine (LY-2216684): an SNRI
- Drugs with Ketamin-like effects
  - Rapastinel (Glyx-13)
  - Esketamine
- Antipsychotics

Antipsychotics

- First generation (neuroleptics)
  - Everything before clozapine
  - Potency range (low to high)
- Second generation (atypical antipsychotics)

Antipsychotics: Similarities

- More effective for positive than negative symptoms of psychosis
- All have a black box warning in demented elderly
- All are mood stabilizers
- All (or nearly all) are associated with weight gain/diabetes/lipid changes… the "metabolic syndrome"
- Tardive dyskinesia (nearly all)

Low potency neuroleptics

- Example: Thorazine (chlorpromazine)
- Anticholinergic
- Sedating
- Cause more weight gain
- Cause dizziness

High potency neuroleptics

- Example: Haldol (haloperidol), Prolixin (fluphenazine)
- More extrapyramidal side effects
- Less sedation, weight gain and dizziness

Mid potency neuroleptics

- Examples: Navane (thiothixine), Trilafon (perphenazine)
- Side effects are a milder mix of both high and low potency side effects

Atypical Antipsychotics

- Differ by “power”
- Differ by side effect profile

Side effect differences among atypical antipsychotics

- Extrapyramidal side effects
- Risk of tardive dyskinesia
- Sedation
- Weight gain/DM/metabolic syndrome

Atypical Antipsychotics

- Clozaril (clozapine)
  - Gold standard
  - No TD, but most sedation and weight gain
  - Agranulocytosis (need for weekly to monthly monitoring)
- Risperdal (risperidone)
  - Most TD among atypicals
  - Less sedation and weight gain

Atypical Antipsychotics

- Zyprexa (olanzapine)
  - #2 to clozapine for overall “power”
  - Also #2 for weight gain, sedation, metabolic syndrome
- Seroquel (quetiapine)
  - Sedation with less weight gain
- Geodon (ziprasidone)
  - Less sedation and less weight gain
  - High risk of prolonged QT interval

Atypical Antipsychotics

- Abilify (aripiprazole)
  - Little sedation and less weight gain
  - Dose dependent akathisia (restlessness), especially when increased quickly
- Invega (paliperidone)
  - Active metabolite of risperidone

NEW Atypical Antipsychotics

- Saphris (asenapine)
  - Sublingual, twice daily (5-10mg)
  - Approved for schizophrenia and BPAD
  - Affected by medications that alter CYP450
  - Can decrease sense of taste

NEW Atypical Antipsychotics

- Fanapt (iloperidone)
  - Approved for schizophrenia
  - Needs slow titration to avoid orthostasis
  - Less sedation but more weight gain than Geodon
  - Genetic markers may predict treatment response (and risk of long QT)

NEW Atypical Antipsychotics

- Latuda (lurasidone)
  - Approved for schizophrenia, Bipolar disorder and Bipolar depression
  - Once daily dosing (40-80mg)
  - High 5-HT7 receptor binding, which may predict better cognitive function
  - Affected by medications that alter CYP450
  - Watch for akathisia and parkinsonism (EPS)
  - Weight gain similar to Geodon

Antipsychotic pipeline: Group II metabotropic glutamate receptor agonists

- Decreases NMDA receptor activity presynaptically
- May have antipsychotic and anti-anxiety properties without causing sedation

Antipsychotic pipeline

- Rexulti (Brexpiprazole)
  - Dopamine D2 receptor partial agonist
  - More potent 5HT1A antagonist and better side effect profile than Abilify
  - Up to 3 mg for depression and 4 mg for schizophrenia
  - FDA approved July 10, 2015 as an adjunct for depression and as a treatment for schizophrenia
- Bitopertin
  - Glycine reuptake inhibitor (GRI)
  - Enhances NMDA receptor activity
  - Roche not moving forward

Mood Stabilizers

- Lithium
- Lamictal (lamotrigine)
- Depakote (divalproex, valproic acid)
- Tegretol (carbamazapine)
- Trileptal (oxcarbazapine)
- Neurontin (gabapentin)
- Topamax (topiramate)

Lithium

- Still the top mood stabilizer
- Common effect on thyroid
- Generally gradual effect on kidneys
- Narrow therapeutic window and high risk of toxicity (hydration is key!)
- Cheap as heck

Lamictal (lamotrigine)

- Main medication for bipolar depression
- Mostly favorable side effect profile
- Potential for rash and potentially fatal Stevens-Johnson Syndrome

Dementia Treatments: Current Medications

- Acetylcholinesterase inhibitors
  - Aricept (donepezil)
  - Razadyne (Galantamine)
  - Exelon (Rivastigmine)
- NMDA receptor antagonist
  - Namenda (memantine)

Dementia Treatments: Pipeline medications

Compound	Company	Mechanism of Action
MK-8931	Merck	BACE1 inhibitor
AZD3293	AstraZeneca/Lilly	BACE1 inhibitor
JNJ 54869111	Janssen	BACE1 inhibitor
NB360	Novartis	BACE1 inhibitor
PQ912	Probiodrug	Glutaminyl Cyclase Inhibitor
CAD106	Novartis	Active immunotherapy
Bapineuzumab	Pfizer / Janssen	Monoclonal Antibody
Gantenerumab	Roche	Monoclonal Antibody
Crenezumab	Roche/Genentech	Monoclonal Antibody
Solanezumab	Lilly	Monoclonal Antibody
BAN2401	Eisai/BioArtic/Biogen	Monoclonal Antibody
Aducanumab	Biogen	Monoclonal Antibody
ACI-35	AC Immune/Janssen	anti-tau vaccine
AAD- vac1	AXON Neuroscience	anti-tau vaccine
Lu AE58054	Lundbeck	5-HT6 Receptor Antagonist
Encenicline	Forum	α7-nAChR agonist

Dementia Treatments: Symptomatic Agents

Compound	Company	MOA	Phase
Encenicline (EVP-6124)	Forum	α7 NNR agonist	3
Idalopirdine (Lu AE58054)	Lundbeck / Otsuka	5HT6 antagonist	3
MK-7622	Merck	Muscarinic M1 positive allosteric modulator	2
RVT-101	Roivant Sciences	5-HT6 antagonist	2
PF-05212377 (SAM-760)	Pfizer	5-HT6 antagonist	2
SUVN-502	Suven	5-HT6 antagonist	1
Brexpiprazole (OPC-34712) *	Lundbeck / Otsuka	D2 dopamine partial agonist	3
AVP-923 *	Avanir / Otsuka	Dextromethorphan / quinidine	2
ELND005 **	Transition Therapeutics	Myo-inositol reducer	2
Pimavanserin ***	Acadia	5-HT2A inverse agonist	2

Alzheimer's Pioneering Research at PMI

- Lundbeck's Lu AE58054
  - Phase 3 trials
- Forum Pharmaciutical's Encenicline
  - Developed to treat both Alzheimer's disease and schizphrenia
- Toyoma's T-817MA
  - Currently in its Phase 2 trials
  - Oral neurotropic agent

Lundbeck's Lu AE58054

- Phase 2 trials showed statistically significant improvement for patients with AD
- Phase 3 trials has goal of 3000 patients, and began in 2013
- Lu AE58054 is a 5-HT6 Receptor antagonist
  - Targets the activity of modulates activity o several neurotransmissions

Clinical Development of Encenicline: Phase 3

Patient population	Patients with mild to moderate Alzheimer's Disease aged 55-85 years, currently receiving stable treatment or previously treated with an acetylcholinesterase inhibitor
Doses	Two doses of encenicline (EVP-6124) or placebo
Duration of treatment	6 months, plus blinded extension (up to 1 year)
Number of patients randomized	Total: ~ 790 per study (~ 263 subjects per group)- Total 1580 across both parallel studies
Geographic location	US, Western Europe, Asia/Pacific, Latin America, others (~190 centers)
Co-primary end points	ADAS-Cog-13 and CDR-SB
Secondary end points	• ADAS-Cog-11(derived from ADAS-Cog-13) • DAD (activities of daily living; caregiver interview) • NPI (psychiatric and behavioral symptoms; caregiver interview) • MMSE (cognitive assessment based on subject interview and performance) • COWAT (cognitive assessment based on subject performance)

Toyama's T-817MA

- Ages 55-85
- neurotropic agent wishing to slow down the onset of AD
- Inclusion Criteria:
  - Diagnosis of mild to moderate AD
  - On Aricept, Exelon or Namenda
  - Living in the community
- Exclusion Criteria:
  - Clinically significant Cardiac, hepatic or renal impairment
  - Non-Alzheimer's dementia
  - Taking drugs besides those mentioned above

Medications with psychiatric side effects

- Levaquin (levofloxacin)
- Steroids (oral or injected)
- Narcotic pain medications
- Muscle relaxants
- Parkinson's medications

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- **Dementia treatments**
- Sedative/hypnotics
- Other sleep medications
- Stimulants

Sedative/hypnotics

- Little used: chloral hydrate, meprobamate, barbiturates
- Benzodiazepines
  - Similar mechanism (GABA receptor agonists)
  - Differences in potency
  - Differences in onset of action
  - Differences in half-life

Other sleep medications

- Trazodone
- Neurontin (gabapentin)
- Melatonin
- Rozerem
- Belsomra (suvorexant)

Stimulants

- Classic stimulants
  - Slow release versions preferable because of reduction in peaks and abuse potential
- Provigil (modafinil)
- Nuvigil (armodafinil)

Done!

- Thanks for your attention.
- Ask questions.
- Go get ’em!