What’s New in Psychopharmacology?
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Principles of Psychopharmacology

• What is Neurotransmission?
  – Anatomical
    • Neuron, Synapses
  – Chemical
    • 6 Neurotransmitters, Communication
  – Electrical
    • Excitation-secretion coupling

Neuron

Boerre, C.G., (n.d.) General Psychology: The Neuron
6 Key Neurotransmitters

- Serotonin (5HT)
- Norepinephrine (NE)
- Dopamine (DA)
- Acetylcholine (Ach)
- Glutamic Acid (Glutamate)
- Gamma-aminobutyric-acid (GABA)

Targets of Drug Action

- Receptors and Enzymes
  - Receptors are long chains of amino acids
  - Enzymes build up molecules and destroy molecules
- Agonists and Antagonists
  - Agonists are neurotransmitters that stimulate receptors
  - Antagonists block the actions of the agonists
  - Partial agonists are similar to but weaker than full agonists
Gene Expression

- Neurotransmission seeks to modify gene expression
- The human genome contains approximately 20,000 to 30,000 genes locate within 3 million pairs of DNA on 23 chromosomes.
- Genes modify behavior and behavior modifies genes.

Epigenetics

- Epigenetics is a system that determines if a gene is expressed or silenced
- Malfunctioning neuron are impacted by inherited genes
- Neurotransmission, genes, drugs and environment regulate which genes are expressed or silenced.
- Molecular mechanisms of epigenetics
  - Methylation, acetylation, phosphorylation

G-Protein-linked Receptors

- Major target of psychotropic drugs
- Agonists
- Antagonists
- Partial Agonists
- Inverse Agonists
Cytochrome P450 Enzyme System

- Pharmacokinetics
  - Absorb, distribute, metabolize and excrete
- Pharmacodynamics
- CYP 1A2, 2D6, 2C9, 2C19, 3A4
- CYP enzymes are polymorphic
- Genes for CYP Enzymes may be used to predict dosages

CYP A12

- Many antipsychotics and antidepressants are substrates for 1A2.
- Fluvoxamine is an inhibitor of 1A2
- Substrates of 1A2
  - Olanzapine, clozapine, zotepine, asenapine, duloxetine
- 1A2 and smoking

CYP 2D6

- Many antipsychotics and some antidepressant are substrates for CYP 2D6
- Several antidepressants are also inhibitors of 2D6
- Risperidone → paliperidone
- Venlafaxine → desvenlafaxine
- Asenapine is an inhibitor of 2D6
CYP 3A4

- Psychotropic drugs and HMG-CoA reductase inhibitors (statins)
- Many psychotropic drugs are weak inhibitors of CYP 3A4
- Nonpsychotic drugs that are powerful inhibitors of 3A4
- Combining a 3A4 inhibitor with aprazolam
- Combining a 3A4 inhibitor with certain statins
- Carbamezpine can induce 3A4

Schizophrenia Spectrum

- Symptoms > 6 months including at least 1 month of hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms
- Psychosis
  - Delusions and hallucinations, disorganized behavior, thought process, and distorted reality
  - Disorders include schizophrenia, substance induced psychotic disorders, schizoaffective disorders, and psychosis due to a general medical condition
Schizophrenia

• Affects 1% of the population
• Mortality rate 8 times greater than general population
• 25-50% attempt suicide (10% succeed)
• Life expectancy 20-30 years shorter than general population

Schizophrenia Phenotype

• Positive symptoms
  – Delusions
  – Hallucinations
  – Distortions or exaggerations in speech or behavior

• Negative symptoms
  – Apathy
  – Anhedonia
  – Cognitive blunting
  – Neuroleptic dysphoria

Dopamine Pathways in the Brain

https://upload.wikimedia.org/wikipedia/commons/a/a2/Overvi
ew_of_reward_structures_in_the_human_brain.png
Glutamate

- Schizophrenia and other psychiatric disorders
- Target of psychopharmacological agents
- Major excitatory neurotransmitter in the CNS

Neurodevelopment and Genetics

- Nature vs Nurture
- Epigenetics
- Identical twin studies
Antipsychotic Agents

- Conventional
  - Neuroleptics
  - Typical
  - Classical
  - First Generation
- Atypical
  - Second Generation

Conventional

- Chlorpromazine (Thorazine)
- Fluphenazine (Prolixin)
- Haloperidol (Haldol)
- Loxapine (Loxitane)
- Perphenazine (Trilafon)
- Pimozide (Orap)
- Thioridazine (Mellaril)
- Thiothixene (Navane)
- Trifluoperazine (Stelazine)

Chlorpromazine (Thorazine)

- Blocks Dopamine 2 receptors
- Weight gain
- Heat exposure
- Photosensitivity
- Sensitivity to Phenothiazines
- Pregnancy Risk Category C
- Advantages:
  - Available in intramuscular formulation for use in emergencies
  - Positive symptoms
  - Aggression or violence
  - Sedative action
Fluphenazine (Prolixin)

- Blocks Dopamine 2 receptors
- Prolactin elevation
- Worsening of negative or cognitive symptoms
- Agranulocytosis
- Anticholinergic side effects
- Pregnancy Risk Category C
- Other side effects:
  - Akathisia, Priapism, extrapyramidal symptoms (EPS), parkinsonism, tardive dyskinesia, tardive dystonia, sedation
- Advantages:
  - Available in intramuscular formulation for use in emergencies
  - Positive symptoms
  - Aggression or violence
  - Less risk of sedation

Haloperidol (Haldol)

- Blocks Dopamine 2 receptors
- Weight gain
- Anticholinergic side effects
- Pregnancy Risk Category C
- Other side effects:
  - Akathisia, galactorrhea, amenorrhea, extrapyramidal symptoms (EPS), parkinsonism, tardive dyskinesia, tardive dystonia, dizziness
- Advantages:
  - Intramuscular formulation for use in emergencies
  - 4 week depot long acting injectable
  - Low cost
  - Positive symptoms
  - Aggression or violence

Perphenazine (Trilafon)

- Blocks Dopamine 2 receptors
- Weight gain
- Anticholinergic side effects
- Pregnancy Risk Category C
- Do not use with known liver disease or blood dyscrasias
- Other side effects:
  - Akathisia, galactorrhea, amenorrhea, extrapyramidal symptoms (EPS), parkinsonism, tardive dyskinesia, dizziness, sexual dysfunction
- Advantages:
  - Less risk of sedation and orthostatic hypotension
  - Use for treatment resistant patients
  - Augmentation in patients with poor response to atypicals
  - Positive symptoms
  - Aggression or violence
Atypical Antipsychotics

- Aripiprazole (Abilify/Maintena/Discmelt)
- Asenapine (Saphris)
- Brexpiprazole (Rexulti)
- Cariprazine
- Clozapine (Clozaril, Fazaclo)
- Iloperidone (Fanapt)
- Lurasidone (Latuda)
- Olanzapine (Zyprexa, Zydis/Relprev)
- Paliperidone (Invega/Quetiapine/Trinsha)
- Quetiapine (Seroque/IR/XR)
- Risperidone (Risperdal/Consta/MR‐Tab)
- Ziprasidone (Geodon)
- Zotepine

Other Clinical Actions

- Antidepressant actions
- Antimanic actions
- Anxiolytic actions
- Sedative actions
- Cardiometabolic actions
  - The metabolic highway

Clozapine (Clozaril, Fazaclo)

- Serotonin SHT 2A-dopamine D2 antagonists (SDA)
- The Gold Standard for efficacy in Schizophrenia
- Approved for treatment-resistant schizophrenia and reduction of risk in recurrent suicidal behavior
- Usual Dose range: 300-450mg/day
- Benefits
  - Treatment efficacy
  - Treatment-resistant schizophrenia
  - Aggressions and violence
  - Reduces risk of suicide in schizophrenia
  - Mood stabilizing
- Special considerations
  - Risk of developing agranulocytosis
  - Frequent blood work required
  - Reduces seizure threshold
  - Stomatitis
  - Weight gain, flu like symptoms
  - Sedation
  - Cardiometabolic risk
Olanzapine (Zeprexa, Zydis, Relprevv)

- Serotonin 5HT 2A-dopamine D2 antagonist (SDA)
- Higher doses → greater efficacy
- Sedation
- Benefits
  - Higher doses → greater efficacy
  - Effective for mood symptoms
  - Oral disintegrating form, acute intramuscular injection and long-acting depot
- Special considerations
  - Weight gain
  - Greater metabolic risks
  - Dyslipidemia (elevated fasting triglycerides)
  - Diabetes (hyperglycemia)
  - Neuroleptic malignant syndrome NMS

Quetiapine (Seroquel/IR/XR)

- Serotonin-dopamine antagonist (SDA)
- Immediate Release (IR)
  - Hypnotic effect
- Extended Release (XR)
  - Hangover effect
- Antidepressant effect in bipolar depression
- Benefits
  - Hypnotic effect
  - Antidepressant effect
  - Mood stabilizer
- Specials Considerations
  - Weight gain
  - Increase fasting triglycerides and insulin resistance

Asenapine (Saphris)

- Serotonin-Dopamine antagonism
- Antipsychotic and antimanic actions
- Sublingual form
- BID administration
- Benefits
  - Can be used as rapid acting oral PRN
  - Targets (+) and (-) 5HT, cognitive Sx's, Aggressive Sx's, and unstable mood.
  - Less significant for weight gain
- Considerations
  - Sedation, dizziness, oral ulcers, EPS, increase risk for diabetes and dyslipidemia, orthostatic hypotension Type 1 hypersensitivity (anaphylaxis, angioedema, swollen tongue, difficulty breathing
  - Life threatening
  - Avoid rapid discontinuation. Taper over 2-4 weeks.
  - Not recommended if hepatic impairment
Zotepine (Lodopin, Zoleptil)

- Available in Japan and Europe, not in USA
- Serotonin–dopamine antagonist
- Considerations
  - Increased risk of EPS, prolactin elevation, weight gain, sedation, burred vision, constipation
  - May prolong QT interval
  - 75-300mg/day in three divided doses

Risperidone (Risperdal/Consta/M-Tab)

- Serotonin–dopamine antagonist (SDA)
- Approved for Schizophrenia ages 13 and up, acute mania, autism related irritability ages 5-16, acute/mixed mania ages 10 and up and bipolar maintenance
- Benefits
  - Available in long-term depot, orally disintegrating tablets, and liquid formula.
  - Aggressive symptoms
  - Behavioral Sx’s in children and adolescents
  - Agitation and aggression in dementia/elderly
- Considerations
  - Hyperprolactinemia
    - Gynecomastia, Galactorrhea
  - Weight gain, sedation, increase risk of diabetes and dyslipidemia, EPS, sexual dysfunction

Paliperidone (Invega/Sustenna/Trinsa)

- Serotonin–dopamine antagonist (SDA)
- Active metabolite of Risperidone
- Dosing is once daily.
- Tends to be better tolerated than risperidone
- Approved for Schizophrenia (ages 12 and over)
- Benefits
  - Sustena-Depot formulation every 4 weeks
  - Trinsa- a 3 month injection
- Considerations
  - Weight gain, elevated prolactin, metabolic changes, insulin resistance, Diabetes, dyslipidemia, QT prolongation, TD
### Ziprasidone (Geodon)
- **Serotonin-dopamine antagonist (SDA)**
- **Approved for Schizophrenia, acute agitation in schizophrenia, acute/mixed mania, and bipolar maintenance**
- **BID dosing with food**
- **Benefits**
  - Im formulation for rapid use in emergency situations
  - Psychosis and bipolar d/o refractory to treatment
  - Aggressive Sx’s
  - Lowered cardiac metabolic risk
- **Considerations**
  - Low or no propensity for weight gain, dyslipidemia, insulin resistance

### Iloperidone (Fanapt)
- **Serotonin-dopamine antagonist (SDA)**
- **Approved for Schizophrenia**
- **Benefits**
  - Low incidence of EPS, low incidence of dyslipidemia
  - For treatment resistant/refractory cases
- **Considerations**
  - Weight gain, sedation, dizziness, hypotension, tachycardia
  - Increased risk for diabetes and dyslipidemia
  - QTc warning

### Lurasidone (Latuda)
- **Serotonin-dopamine antagonist (SDA)**
- **Approved for Schizophrenia and Bipolar depression**
- **Benefits**
  - Little or no weight gain or dyslipidemia
  - Little or no sedation
  - No QTc prolongation
  - Antidepressant effect
  - Rapid onset without needed dosage titration
  - May be taken once a day.
- **Considerations**
  - Taken with food
  - Sedation, Akathisia, Nausea
  - Increased risk for diabetes and dyslipidemia
Aripiprazole (Abilify/Maintena/Discmelt)

- Dopamine receptor partial agonist
- Approved for Schizophrenia (ages 13 and up) and acute/mixed mania (ages 10 and up), depression, autism related irritability (ages 6-17), acute agitation with Schizophrenia and Bipolar d/o.
- Benefits
  - Available in IM short term formulation, orally disintegrating tablet, and liquid formulation
  - Approved for child and adolescent groups
  - Reduced EPS
  - Not generally sedating
  - Lower metabolic risk
    - Low propensity for weight gain
    - Low association with dyslipidemia, elevated triglycerides or insulin resistance
- Considerations
  - Akathisia, dizziness, insomnia, orthostatic hypotension, constipation, N/V
  - May be activating or cause mild agitation

Brexipiprazole (Rexulti)

- Serotonin-dopamine activity modulator
- Approved for Schizophrenia and as adjunctive treatment for depression.
- Benefits
  - Low incidence of EPS
  - Once daily dosing
- Consideration
  - Weight gain, headaches, insomnia, nausea, dizziness, anxiety
  - Akathisia

Cariprazine (Vraylar)

- Dopamine partial agonist
- For Schizophrenia, acute bipolar mania, bipolar depression and treatment resistant depression
- Once a day dosing
- Dyspepsia, drowsiness, vomiting
- Metabolic changes
- Extrapyramidal symptoms
- Decrease in blood counts
- Orthostatic Hypotension, syncope
- Seizures
- Avoid getting overheated
- Dysphagia
Others

- Sulpride
- Amisulpride
- Sertinole
- Perospirone

Switching antipsychotics

- With aripiprazole, amisulpride, and paliperidone ER immediate stop is possible
- With risperidone, ziprasidone, iloperidone and lurasidone, begin new agent gradually titrating over 2 weeks
- Quetiapine
- Risperidone
- Aripiprazole

Treatment Resistance

- Treatment Resistant Psychosis
- Maximize dose
- Consider Clozapine
- Use caution with high dose monotherapy or antipsychotic polypharmacy.
  - Augment atypical with conventional
  - Give 2 atypicals together
  - May have intolerable side effects
Violence and Psychiatric Emergencies

- Violence
  - Pharmacodynamic failure
    - More time needed for efficacy
    - Higher doses
    - Augment
- Psychiatric Emergencies
  - non-violent crisis intervention
  - Rapid tranquilization
  - Offer oral medication
  - Rapid acting IM injection

Associated lab work

- Clozapine
  - CBC before treatment, weekly for 6 months, biweekly 6-12 months, then every 4 weeks after that.
  - Weigh and track BMI
- EKG, CBC, TFT, LFT, lipid profile, Chemistry panel, prolactin level, therapeutic drug level
- Weigh and track BMI and waist circumference

Future Pharmacological Treatment

- Glutamatergic treatments
- Glycine agonists
- Prodromal treatments
Depression

- Monoamine hypothesis of depression
- Symptoms of Depression
  - Depressed mood
  - Apathy
  - Anhedonia
  - Weight changes
  - Appetite changes
  - Sleep disturbances
  - Psychomotor agitation or retardation
  - Low energy
  - Feelings of guilt or worthlessness
  - Diminished concentration
  - Thoughts of death
### Classes of Antidepressants

- Monoamine Inhibitors (MAOIs)
- Tricyclic Antidepressants (TCAs)
- Serotonin Selective Reuptake Inhibitors (SSRIs)
- Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- Serotonin Norepinephrine Dopamine Reuptake Inhibitors (SDNRIs)
- Selective Norepinephrine Reuptake Inhibitors (NRIs)
- Alpha-2 Antagonist
- Serotonin Antagonist/Reuptake Inhibitors (SARIs)

### Monoamine Inhibitors (MAOI’s)

- Dietary tyramine interaction
  - Hypertensive crisis
- Drug-drug interactions
  - Avoid cold medicines, anesthetics, serotonergic agents
  - Serotonin syndrome/toxicity
  - Drugs to avoid: SSRIs, SNRIs, Clomipramine, St John’s Wort, NMDA (Ecstasy), Cocaine, Methamphetamine, Meperidine, Tramadol, Methadone, Fentanyl, dextromethorphan
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Isocarboxazid (Marplan)
- Selegiline (EMSAM)
  - Transdermal patch or capsule

### Tricyclic Antidepressants (TCA’s)

- Clomipramine (Anafranil)
- Imipramine (Tofranil)
- Amitriptyline (Elavil)
- Nortriptyline (Pamelor)
- Protriptyline (Vivactil)
- Maprotiline (Ludiomil)
- Amoxapine (Asendin)
- Doxepine (Sinequan)
- Desipramine (Norpramin)
- Trimipramine (Surmontil)
- Dothiepin (Prothiaden)
- Lofepamine (Deprimyl)
- Tianeptine (Coaxil)
Serotonin Selective Reuptake Inhibitors (SSRIs)

- Fluoxetine (Prozac)
- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Fluvoxamine (Luvox)
- Citalopram (Celexa)
- Escitalopram (Lexapro)

Serotonin Norepinephrine Reuptake Inhibitors

- Duloxetine (Cymbalta)
- Milnacipran (Toledomin, Ixel, Savella)
- Venlafaxine (Effexor, Effexor XR)
- Desvenlafaxine (Pristiq)

Serotonin Norepinephrine Dopamine Reuptake Inhibitors (SDNRI's)

- Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban)
- Approved for MDD, seasonal affective d/o, and Nicotine addiction
- SE: Dry mouth, constipation, nausea, weight loss, anorexia, myalgia, insomnia, dizziness, headache, anxiety, tremor, tinnitus, HTN
- Risk of seizures, induction of mania, or activation of SI
Selective Norepinephrine Reuptake Inhibitors (NRIs)

- Reboxetine
  - Not approved in US
- Atomoxetine (Strattera)
  - Approved for ADHD in adults and children over 6
- Agomelatine
  - Not approved in US

Alpha-2 Antagonist

- Mirtazepine (Remeron)
  - Approved for MDD
  - Sedative effect
  - Does not affect the CYP450 system
  - Considerations: weight gain, increased appetite, hypotension, dry mouth, constipation, abnormal dreams, induction of mania, activation of SI, may lower white blood count, may increase cholesterol, may cause photosensitivity, sexual dysfunction
  - Dosage: 15-45mg at night

Serotonin Antagonist/Reuptake Inhibitors (SARIs)

- Trazodone (Desyrel, Oleptro)
  - Approved for Depression
  - Dosage 150mg-600mg
  - Priapism, sexual dysfunction
- Nefazodone
Complimentary Alternative Medicine

- L-methylfolate
- S-adenosyl-methionine (SAM-e)
- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)
- Deep brain stimulation (DBS)
- St. John’s Wort

Summary and Useful Tidbits

- ECT → Chlorpromazine → Fluphenazine → Thioridazine → Haloperidol → Clozapine
- EPS
- Hyperlipidemia
- CATIE
- Prolactin
- Clozapine
- Quetiapine
- Aripiprazole
- Superior efficacy of SGAs over FGAs?
  - Neuroleptic Malignant Syndrome (NMS)

Summary continued...

- SSRIs vs TCAs
- Mirtazapine
- Milnacipran
- Sertraline
- Medical complications of SSRIs & SNRIs
- Vortioxetine (Brintellix)
- Pregnancy
References

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- RxWiki, For patients, By pharmacists (n.d.) http://www.rxwiki.com/cariprazine

Thank you!