Combination Therapy in Psychiatry

Psychotropic Combinations: Drug Interactions and Adverse Effects

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Learning Objectives

1. Discuss the controversy of combination therapy (i.e., polypharmacy) with psychotropic medications for efficacy and safety in children/adolescents, adults, and geriatric patients.
2. Recognize duplication of therapy for antidepressants, antipsychotics, anxiolytics (e.g., benzodiazepines), and anticholinergic-antihistamine agents.
3. Differentiate between pharmacokinetic and pharmacodynamic drug interactions.
5. Describe situations when combination therapy may be appropriate for a specific psychiatric disorder or patient.
Polypharmacy
Do we know what we are doing?

The term polypharmacy generally refers to
the use of multiple medications

- The term is used when too many forms of medication are used by a patient, more drugs are prescribed than clinically warranted, or even when all prescribed medications are clinically indicated but there are problems with drug interactions
- Furthermore, a portion of the treatments may not be evidence-based and used off-label
- The common result of polypharmacy is increased drug interactions, adverse drug reactions, and higher costs
Polypharmacy

- Long-term use of multiple drugs (drug cocktails)
- Poorer outcome due to iatrogenic changes in neurotransmitters and receptor sensitivity
- Poorer response to medications = treatment resistant
- Chronically mentally ill and unable to work
  - 1 out of 15 US young adults now has a “serious mental illness” and is taking psychotropics
    - Treatment-refractory disorders

Whitaker (2010)

National Trends in Polypharmacy

- A recent significant increase in polypharmacy involving antidepressants, antipsychotics, and sedative-hypnotics
  - Minimal evidence to show efficacy with combinations
  - May have poorer clinical outcome
  - Increased off-label prescribing
  - Increased risk of drug-drug interactions and adverse effects
  - Significant impact on cost of care

Patients at Risk for Polypharmacy

- Women > men
- Older adults and elderly
  - Higher rates in ages 45-64 compared to younger ages
  - > 50% of older adults take 5 or more pills a day
  - 2 million are at risk for drug interactions
- Psychiatric disorders
  - Multiple diagnosis increase risk
- Concurrent medical conditions
- Multiple physicians/prescribers
- Multiple pharmacies filling prescriptions
- Recently hospitalized patients
- Medicaid/Medicare > private insurance

Psychotropic Medications

- Increased polypharmacy
  - **Antidepressants** – widely prescribed drug category
    - Combining two antidepressants (e.g., SRI + bupropion or mirtazapine)
  - **Atypical antipsychotics** – used in non-psychotic disorders
    - Adding atypical to antidepressants (direct marketing with aripiprazole) and quetiapine for sedation
  - **Anticonvulsants** – added to drug therapy for agitation, impulsivity and weight loss (topiramate)
    - Gabapentin, lamotrigine, topiramate, oxcarbazepine, carbamazepine, valproate

Prescription Patterns in US

- Growth of managed care and increased role for primary care physicians and nurse practitioners for prescribing psychotropics
  - Most adults treated with antidepressants and anxiolytics are seen by a general practitioner
    - GP: 65% anxiolytics, 62% antidepressants, 52% stimulants, 37% antipsychotics, 22% antimania
- Multiple specialists involved with prescribing
- Significant increase in costs of drugs
  

Is Polypharmacy Rational and Safe?

- Lack of systematic research
- Drug development is usually by itself versus either a placebo and/or a comparator agent
- The combination of two drugs is virtually never studied
  - Usually drug-drug pharmacokinetic interaction studies in healthy young volunteers
- Lack of federal research funding to study combination therapy or long-term use
Reasons for Polypharmacy

- To treat comorbid illnesses
- To treat an adverse effect produced by the primary drug
- To provide acute treatment while waiting for the delayed effect of another medication
- To treat intervening phases of an illness
- To boost or augment the efficacy of the primary treatment

Karow & Lambert (2003); Preskorn & Lacey (2007)

Criteria for Rational Combination Therapy in Psychiatry

- Knowledge that the combination has a positive effect on the pathophysiology or pathoetiology of the disorder
- Convincing evidence that the combination is more effective, including more cost-effective, than monodrug therapy
- The combination should not pose significantly greater safety or tolerability risks than monotherapy

Preskorn & Lacey (2007)
Criteria for Rational Combination Therapy in Psychiatry

- Drugs should not have pharmacokinetic or pharmacodynamic drug interactions.
- Drugs should have mechanisms of action that are likely to interact in a way that augments response.
- Drugs should have only one mechanism of action.

Preskorn & Lacey (2007)

Criteria for Rational Combination Therapy in Psychiatry

- Drugs should not have opposing mechanisms of action.
- Each drug should have simple metabolism.
- Each drug should have an intermediate half-life.
- Each drug should have linear pharmacokinetics.

Preskorn & Lacey (2007)
Polypharmacy

- Mono-drug therapy: ideal
- Two drug combinations: commonly needed to treat adverse effects or for pharmacodynamic reasons
- Three drug combinations: may be necessary in some rare situations
- Four drug combinations: first consider that three drugs are not working
  - Adherence, adverse effects, drug interactions

Why Polypharmacy Continues?

- Lack of integrated medical and prescription records
- Marketing of drugs without pharmacodynamic /pharmacokinetic and combination studies
- Easy to start a medication and difficult to stop medications (withdrawal syndrome)
- Rush to prescribe without seeking the causes of the patient’s symptoms
Combination Therapy is Here to Stay

“The negative connotation of polypharmacy will fade as combination therapies become the new standard of care.” – Henry A. Nasrallah, M.D. (2010)

- Although psychiatrists commonly combine psychotropic medications, researchers malign the practice as “not evidence-based”.
- Research is finally catching up with clinical practice...the evidence is that many patients with severe psychiatric disorders, 2 drugs are better than 1.

Long-Term Use of Psychotropic Medications


- Do psychotropic medications increase the likelihood that people will be chronically ill?
- Do psychotropic medications make long-term changes in the brain and worsen outcomes?
  - Why is polypharmacy (multiple drug combinations) so common now? Does it cause long-term changes in the brain and worsen outcomes?
Unipolar Depression

- Antidepressants may only be beneficial in very severe depression
  - Minimal benefit for mild or moderate symptoms
- Mixing two different types of antidepressants
  - SRI, SNRI, and NDRI + mirtazapine or trazodone
  - Antidepressants + lithium and/or thyroid (T3)
- Antidepressants now being combined with atypical adjuncts (e.g., aripiprazole and quetiapine) for treatment resistant patients


Antipsychotic Prescribing in Unipolar Depression

- Conventional antipsychotics may cause depression
- Atypical antipsychotics have not been found to be effective in either unipolar or bipolar depression
  - Quetiapine is approved but only compared to placebo
- Up to 40% of people on antipsychotics have no symptoms of psychosis

Refractory Mood Disorders

- Increasing number of medications are being required to achieve the same degree of improvement in patients with refractory mood disorders.
- Sequential pharmacology (using a series of medications)
- Add-on approaches
- No controlled studies of late- or early-polypharmacy strategies or outcomes
- No evidence-based algorithms


Treatment-Refractory Depression

- STAR*D Trial
  - The use of monotherapy in the treatment is often not enough and cause the patient to be frustrated
  - “Despite the relatively small literature, augmentation and combination strategies provide clinicians with an armament of tools that must be used to provide relief not only from the depression, but also from residual symptoms and treatment-emergent side effects”

Combining Antidepressant Medications

- Single antidepressant – only 50-75% response rate and ~25-30% full remission
- Many patients do not receive an adequate monotherapy trial (dose and duration) before progressing to polypharmacy.
- The use of two or more medications does not appear to improve efficacy using the CGI.
- Women more likely to receive concomitant SSRI therapy than men.
  

Initial Polypharmacy for Depression

- Blier et al. 2010 reported that initial antidepressant combinations may double remission rates using HAMD-D ≤7 in 6 wks.
  - Fluoxetine (N=28): 25% remission rate
  - Fluoxetine + mirtazapine (N=25): 52% remission rate
  - Venlafaxine + mirtazapine (N=26): 56% remission rate
  - Bupropion + mirtazapine (N=26): 46% remission rate
6-Week Trial (N=105)

- Response rates were not significantly different between groups
- Time to sustained response (14-15 days) was not different between groups
- Some measures did not reach statistical significance (e.g., Montgomery-Asberg Depression Rating Scale, CGI Scale)
- No placebo group
- Editorial: These results provide justification for combining antidepressant medications, especially mirtazapine with other agents

Rush (2010)

6-Month Trial (N=66)

Blier et al. 2010

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relapsed during 6 mo.</th>
<th>Relapsed during 1st mo.</th>
<th>Drop Out</th>
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</thead>
<tbody>
<tr>
<td>Fluoxetine + Placebo (N=15) no change in therapy</td>
<td>27%</td>
<td>13%</td>
<td>33%</td>
</tr>
<tr>
<td>Fluoxetine + Mirtazapine (N=16) changed to fluoxetine</td>
<td>56%</td>
<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>Venlafaxine + Mirtazapine (N=18) changed to mirtazapine</td>
<td>50%</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Bupropion + Mirtazapine (N=17) changed to mirtazapine</td>
<td>24%</td>
<td>12%</td>
<td>29%</td>
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</tbody>
</table>
Mirtazapine

- Sedative effects - improves sleep
  - Less likely to use benzodiazepines or sleeping medications
- Increased appetite and weight gain
  - Improved nutrition and protein intake to make neurotransmitters
- Less likely to cause sexual dysfunction
- HAM-D rating scale is sensitive to changes in sleep and weight, thus drugs like mirtazapine will improve HAM-D scores

Mirtazapine

- Antagonist: 5-HT2A & 2C & 3, histamine 1, muscarinic, alpha-1 & 2
- Adverse Effects
  - Somnolence (54%)
  - Increased appetite (17%) and weight gain (12%; weight gain of > 7% in 8% of adults); increased cholesterol and triglycerides
  - Agranulocytosis, neutropenia
    - Similar to clozapine, olanzapine, quetiapine
- Drug Interactions
  - Substrate: 1A2, 2D6, 3A4 (major)
  - Inhibits: 1A2, 3A4 (minor)
Trazodone

- Sedative effects – improves sleep
- Antagonist: 5-HT2A, histamine 1, muscarinic, alpha-1

Adverse Effects
- Dizziness, sedation, headache, confusion, decreased concentration, fatigue, incoordination, nausea, blurred vision

Drug Interactions
- Substrate: 2D6 (minor), 3A4 (major)
- Inhibits: 2D6 (moderate), 3A4 (weak)

Drug Combinations

- Venlafaxine (Effexor)
  - 5-HT, NE, DA reuptake inhibitor (with higher doses)
  - Substrate: CYP 2D6, 3A3/4
  - Inhibitor/Inducer: NA

- Mirtazapine (Remeron)
  - Presynaptic alpha\textsubscript{2} adrenergic antagonist: ↑ NE release
  - 5-HT\textsubscript{2A,2C,3} antagonist
  - Histamine\textsubscript{1} antagonist
  - Alpha\textsubscript{1} adrenergic antagonist
  - Muscarinic antagonist
  - Substrate: CYP 1A2, 2C9, 2D6, 3A4
  - Inhibitor/Inducer: NA
Drug Combinations

- Fluvoxamine (Luvox)
  - 5-HT Reuptake Inhibitor
  - Substrate: CYP 1A2,
  - Inhibitors: CYP 1A2, 2C9, 2C19, 2D6, 3A4
- Mirtazapine (Remeron)
  - Presynaptic alpha$_2$ adrenergic antagonist: ↑NE release
  - 5-HT$_{2A,2C,3}$ antagonist
  - Histamine$_1$ antagonist
  - Alpha$_1$ adrenergic antagonist
  - Muscarinic antagonist
  - Substrate: CYP 1A2, 2C9, 2D6, 3A4
  - Inhibitor/Inducer: NA

Bipolar Disorder

- Several combination studies
  - Lithium + valproate vs. monotherapy
    - Open label studies
  - Mood stabilizer + atypical antipsychotics
  - Two mood stabilizers
- Most medications have been approved only for acute mania or short-term maintenance, not for depressive episodes
- Despite lack of studies, polypharmacy is common in long-term maintenance treatment

Bipolar Disorder

- **Antipsychotics**
  - Atypicals marketed for acute mania
  - Few long-term studies for efficacy in maintenance therapy – may cause depression
- **Antidepressants**
  - Monotherapy contraindicated in Bipolar Type I
  - Recommendations for SSRIs or bupropion
- **Bipolar Depression**
  - Fluoxetine + olanzapine (Symbyax)
  - Quetiapine (Seroquel)

Hellewell JSE (2006), Thase (2005)

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Fluoxetine + Olanzapine

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Olanzapine</th>
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<tbody>
<tr>
<td>Serotonin</td>
<td>SRI = ↑ 5-HT activity = ↓ DA release</td>
<td>5-HT2A/2C Antagonist = ↓ 5-HT activity = ↑ DA release</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>NRI (minor) = ↑ NE activity</td>
<td>Alpha-1 Antagonist = ↓ NE activity</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Antagonist: DA1-4, H1, Muscarinic1-5</td>
</tr>
<tr>
<td>Substrate (CYP)</td>
<td>2C9 (major), 2D6 (major)</td>
<td>1A2 (major)</td>
</tr>
<tr>
<td>Inhibits (CYP)</td>
<td>1A2 (moderate), 2D6 (strong), 2C19 (moderate)</td>
<td>* Fluoxetine decreases metabolism of olanzapine and ↑ blood levels</td>
</tr>
</tbody>
</table>

* Fluoxetine decreases metabolism of olanzapine and ↑ blood levels
**Rapid Cycling Bipolar**

- Antidepressants may induce a manic episode or start rapid cycling and mixed states in some patients.
  - 20-40% of bipolar patients may be susceptible to antidepressant-induced mania (e.g., strong genetic load, disorder beginning in adolescents or young adulthood)
  - TCAs >>> SSRIs/SNRIs>>>bupropion

Goldberg & Truman (2003)

**Schizophrenia**

- Patients have an increased use of nicotine, caffeine, and substances such as cocaine, methamphetamine, and cannabis
- High rates of non-adherence with therapy
- More than a third of patients with chronic schizophrenia receive > 2 antipsychotics
  - Up to 50% have received antipsychotic polypharmacy during treatment
  - Few controlled studies with combining two antipsychotics

Antipsychotic Polypharmacy

- Little is known about the efficacy and safety of antipsychotic combination therapy
  - Increasingly common in treatment of schizophrenia and schizoaffective disorder
- Increased rates of combining antipsychotics with antidepressants, mood stabilizers, and CNS stimulants – up to 90% of patients
- Use of excessive (high) doses above recommended range.
- Very expensive to combine atypical antipsychotics.
  - Refractory: clozapine +/- atypical antipsychotic


Concomitant Medications

- No controlled studies that show concomitant psychotropic medications improve the outcome in schizophrenia after the acute phase.
  - Polypharmacy is far more common than monotherapy
    - Antipsychotic + benzodiazepine + antidepressant + mood stabilizer
    - Two or more antipsychotics (e.g., clozapine + risperidone)
  - Need to change prescribing practices

Off-Label Use of Atypical Antipsychotics

- **Clinical Uses**
  - Sedation
  - Dementia-agitation and behavioral disorders
  - Depression
  - OCD
  - PTSD
  - Personality disorders
  - Tourette’s syndrome
  - Autism

- **Adverse Effects**
  - Mortality in dementia
  - Cardiovascular changes
  - Cerebrovascular accidents
  - EPS
  - Prolactin increase
  - Sedation
  - Weight gain
  - Diabetes
  - Metabolic syndrome

Quetiapine

- Marketed for schizophrenia, bipolar disorder, bipolar depression, depression
- Off-label: anxiety disorders, insomnia, agitation/aggression, impulsivity, autism
- Polypharmacy highest with quetiapine compared to risperidone or olanzapine in patients with schizophrenia
- Annual cost: quetiapine > olanzapine > risperidone

Aripiprazole

- Pharmacology
  - Partial agonist/antagonist on D2 and D3 and 5-HT1A receptors
  - Partial antagonist at 5-HT2A
- Often added to other antipsychotic drugs
  - Reports of worsening of psychosis and mania
- Marketed for augmenting antidepressants for treatment resistant depression
  - Direct marketing
  - Increased use in ADHD and bipolar disorder

Adjunctive Aripiprazole

- Adding aripiprazole to other antipsychotics has not been shown to improve outcome.
  - ↓ Hyperprolactinemia induced from risperidone
    - used to decrease prolactin levels
  - Half-life of 75 hrs (steady-state of 14-16 days)
    - Metabolized by CYP2D6 – possible drug interactions
  - Dopamine receptor occupancy reaches a plateau at doses above 10 mg/d
Sparshatt et al (2010)
Anxiety Disorders

- Antidepressant + atypical antipsychotic
  - SRI/SNRI + serotonin antagonist
- Antidepressant + benzodiazepines
  - SRI/SNRI + GABA augmentation
- Antidepressant + buspirone
  - SRI/SNRI + serotonin partial agonist/antagonist

Benzodiazepines

- Commonly added with other psychotropic agents
- CNS depressant effects
  - Decreased respiratory drive
  - Cognitive and motor impairment
- Tolerance and dependence
- Withdrawal syndrome
Elderly Population

- A nationwide problem due to multiple diseases, medications, and prescribers
  - 12.4% of US population in 2000 and 19.6% in 2030
  - 5-15% with dementia
  - > 50% take 5 or more medications/pills a day
  - 2 million are at risk for drug interactions
  - Polypharmacy common in hospitalized patients

Polypharmacy issues
- Pharmacodynamic interactions
  - Duplication of therapy or opposite mechanism of action
- Pharmacokinetic interactions
  - Reduced renal and liver functioning, protein binding, etc.

Aparasu et al (2005)

Elderly Population

- Marketing of atypical antipsychotics as safer and more effective
  - Antipsychotics have an increased risk of mortality in older adults with dementia
- Use of anticonvulsants for agitation (e.g., gabapentin, valproate, oxcarbazepine)
- Use of SRIs + aspirin/NSAID/warfarin = ↑bleeding risk
Beta-Blockers in the Elderly

- Causes fatigue, decreased energy, sexual dysfunction
- Prescription database found patients taking beta-blockers had higher rates of receiving a concurrent antidepressant than other cardiovascular or diabetic medications.
- Studies have found no difference in the incidence of depression
- Use the lowest dose and titrate up slowly

Muzyk and Gagliardi (2010)

Parkinson’s Disease

- Dopamine augmentation strategies
  - Levodopa + carbidopa (Sinemet)
    - + MAOI (rasagiline, selegiline)
    - + COMT (entacapone)
    - + DRI (bupropion)
    - + DA agonist (pramipexole, ropinirole)

- Decreased dopamine (DA) activity
  - SRI: serotonin at 5-HT2A decreases DA release
  - Antipsychotics: block post-synaptic DA receptors
Pediatric Population

- Psychiatric polypharmacy is common and increasing in the pediatric population
  - Prior to 1980, very few youth were medicated
  - Now: high rates of ADHD, mood disorders, behavioral disorders due to DSM diagnosis
    - 23-42% are receiving polypharmacy regimens
    - Increased prescribing of atypical antipsychotics
      - Nonpsychotic disorders and off-label indications
    - Black box warnings: CNS stimulants, atomoxetine, antidepressants
  - Only short-term and open-label trials with combination therapies

Attention-Deficit/Hyperactivity Disorder

- 1990 – 1 million diagnosed with ADHD
- 2007 – 1 in 23 children in US taking stimulants
- 2010 – 3.5 million in US taking stimulants
  - US – children consume 3 times the quantity of stimulants taken by the rest of the world’s children combined
  - Epidemic in bipolar disorder diagnosis may be iatrogenic due to giving children stimulants or antidepressants
  - First episodes of mania in older adolescents and young adults may be due to SSRI prescribing

Whitaker (2010)
Attention-Deficit/Hyperactivity Disorder

- Long-term use of CNS stimulants
  - Emotionally flat, lack emotional expressions, less interactive, devoid of humor, passive, submissive, socially withdrawn
  - Stimulants do not produce long-lasting improvements in aggression, conduct disorder, educational achievement and job functioning

Whitaker (2010)

Attention-Deficit/Hyperactivity Disorder

- Stimulants can induce psychotic and manic episodes → bipolar diagnosis with rapid cycling or mixed states
  - Hallucinations: visual and tactile involving insects, snakes, and worms
  - Daily cycles of arousal and dysphoria
- Combination therapies common
  - CNS Stimulants induced insomnia
    - Clonidine or guanfacine
  - ADHD + bipolar disorder
    - CNS stimulant or atomoxetine + mood stabilizer or antipsychotics
  - Methylphenidate + atomoxetine
    - Additive adverse effects reported

Major Depressive Disorder

- Prevalence of mood disorders has increased during the past 20 years in children in US.
  - 1988 –1 in 250 children < 18 yrs taking an antidepressant (Prozac marketed)
  - 2002 – 1 in 40 children < 19 yrs
- Increased polypharmacy: 23-42%
- Risk of mania or manic-like symptoms / hostility
- Risk of suicidality – black box warning
- Long-term: apathy, lack of motivation, lethargy, flatness, cognitive decline

McIntyre & Jerrell (2009), Whitaker (2010)

Pediatric Bipolar Disorder

- Rare before drugs used: 1 in 10,000
  - Unmasking of disorder with CNS stimulants and antidepressants (started in late 1980’s)
  - By 1990’s – bipolar epidemic erupted
    - Five fold increase in diagnosis from 1996 to 2004 in hospitalized children
    - Poorer outcome: significant emotional, academic, and social impairment
- FDA approved: lithium, risperidone, aripiprazole
  - Commonly prescribed multiple psychotropic medications (mean = 3.0 ± 1.6)

Atypical Antipsychotics

- Increased use in children for ADHD, bipolar disorder, insomnia with stimulants, aggression and disruptive behavior (not psychosis)
  - Significant weight gain, metabolic abnormalities, sedation, and increased prolactin levels
  - Topiramate used for weight reduction but no improvement in reducing symptoms of mania

Topiramate

- Used off-label for weight reduction caused by atypical antipsychotics
- Not effective for bipolar disorder
- Causes cognitive clouding, psychiatric changes, sedation, paresthesias, dizziness, ataxia, metabolic acidosis, and kidney stones
- Must titrate doses up and down (withdrawal with abrupt discontinuation)
Optimizing Drug Therapy

- Deciding if a drug is indicated or needed
  - Selecting the best drug, dose, and schedule
  - Assessing for drug interactions and potential adverse effects
  - Getting rid (tapering/stopping) unnecessary drugs
- Monitoring for effectiveness and toxicity
- Avoiding combination therapy if possible

How to Improve Outcomes

- Know the patient very well before starting drug therapy
- Develop a treatment plan
- Educate the patient and family
- Choose the right medication and dose based on the disorder, age, renal/liver function, and drug interactions
- Ensure adherence
- Use the fewest prescriptions possible
How to Improve Outcomes

- Tailor all treatment to the patient’s needs: ease of administration, dosing, and financial issues
- Know the drug well for adverse effects, dosing, and drug interactions
- Always consider the patient’s viewpoint
- Have a high level of suspicion for any changes in disease state or changes in symptoms or behavior

Why Psychotropic Medications May Not Work

- Neurotransmitters
  - Synthesis, storage, release, reuptake
  - Receptor “open” for binding
- Drugs that counter-act or increase/decrease blood levels of each other
  - Pharmacodynamic and/or pharmacokinetic drug interactions
- Hormone deficiency states
  - Aging process
- Substance Use/Abuse
Neurotransmitter Synthesis

- **L-tryptophan** → serotonin → (darkness) melatonin
  - Dairy, eggs, meat, poultry, fish
  - Serotonin modulates (or decreases) dopamine release
  - Inhibitory/calming effects
- **Phenylalanine** → tyrosine → dopamine → norepinephrine → epinephrine
  - Kidney beans, beets, peas, soybeans, almonds, barley, oats, grains, eggs, dairy products, meats
  - Excitatory/energizing effects
- **Glucose** → glutamate/glutamic acid → GABA
  - Inhibitory effects

Important Factors

- **Nutrition**: regular intake of complete proteins (i.e., essential amino acids), vitamins/minerals, and complex carbohydrates are important for mood, sleep, energy and appetite regulation
  - Every 3-4 hours for adults
- **Exercise/movement/touch** is important to release neurotransmitters
- **Sleep** is important to make and store neurotransmitters for the next day
  - Maximum REM sleep = 8 hours
- **Hormones** important for mood regulation and cognition (thyroid, estradiol, testosterone, etc)
Important Factors Related to Brain Functioning

- Adequate diet (protein) and regular meals (q3-4 hours) to make neurotransmitters
  - L-tryptophan $\rightarrow$ serotonin $\rightarrow$ melatonin
  - Tyrosine/Phenylalanine $\rightarrow$ dopamine $\rightarrow$ norepinephrine $\rightarrow$ epinephrine
  - Glucose $\rightarrow$ Glutamate $\rightarrow$ Glutamic acid $\rightarrow$ GABA

- Vitamin and mineral intake / deficiencies
  - Vitamin B6, B12, folate
  - Iron
  - Vitamin D and calcium

- Essential fatty acids

Important Factors Related to Brain Functioning

- Hormone status
  - Estradiol - MAOI and increases neurotransmitters
  - Progesterone – binds to GABA$_A$ receptors
  - DHEA $\rightarrow$ Testosterone $\rightarrow$ Estradiol $\rightarrow$
    Estrone $\rightarrow$ Estriol

- Thyroid status
  - Hypothyroidism: decreased metabolism
  - Hyperthyroidism: increased metabolism
Deprivation of REM Sleep

- Less synthesis of serotonin and norepinephrine = anxiety and depression
- Daytime sleepiness = narcolepsy
- Fatigue, low energy, cognitive impairment
- Increase in appetite = weight gain
- Increase in irritability, aggression and fighting
- Increase in cortisol and stress hormones = worsening of immune functioning

Important Factors Related to Brain Functioning

- Caffeine
  - Augments DA activity and high doses block GABA effects (increased risk of seizures)
- Nicotine (smoking cigarettes)
  - Nicotine augments DA activity
  - Smoking induces CYP 1A2 enzymes and increases metabolism of some psychotropics
- Alcohol
- Stimulants
- Marijuana
- Opioids
Drug Interactions

Important Factors Related to Drug Interactions

- **Protein Binding**
  
  *Displacement interactions for highly protein bound drugs*
  
  - Protein bound to albumin = inactive drug
  - Non-protein bound = free (and active) drug

- **Receptor Binding**
  
  *The displacement of drugs from their receptor sites (pharmacological interaction)*
  
  - Agonist
  - Antagonist
Important Factors Related to Drug Interactions

- Liver Metabolism (CYP isoenzymes)
  - Majority of drugs must be metabolized in the liver to be eliminated from the body

- Renal Clearance
  - A few drugs are excreted through the kidneys and do not require liver metabolism (e.g., lithium, gabapentin (Neurontin))
Serotonin

- ↓ activity (receptor antagonist)
  - Buspirone (if high 5-HT)
  - Cyproheptadine (2A, 2C)
  - Mirtazapine (2A, 2C, 3)
  - Nefazodone (2A)
  - Trazodone (2A)
  - Aripiprazole (2A)
  - Asenapine (2A)
  - Clozapine (2A)
  - Olanzapine (2A, 2C)
  - Paliperidone (2A)
  - Quetiapine (2A)
  - Risperidone (2A)
  - Ziprasidone (2A)

- ↑ activity (e.g., reuptake inhibitor, MAOI)
  - Buspirone (if low 5-HT)
  - Clomipramine (+NE)
  - Citalopram
  - Duloxetine (+NE)
  - Escitalopram
  - Fluoxetine (+NE)
  - Fluvoxamine (+NE)
  - Milnacipran (+NE)
  - Paroxetine (+NE, anticholinergic)
  - Sertraline (+DA)
  - Venlafaxine (+NE & DA)
  - MAOIs (+NE & DA)
  - L-Tryptophan

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![Diagram of the serotonin system](image-url)
Norepinephrine

- ↓ activity
  - Beta-Blockers
    - Atenolol
    - Nadolol
    - Propranolol
  - Alpha-2 Agonists
    - Clonidine
    - Guanfacine

- ↑ activity
  - Reuptake Inhibitors
    - Desipramine
    - Bupropion (+DA)
    - Venlafaxine (+ 5-HT & DA)
    - Amphetamines
  - NE Releasing Agents
    - Amphetamines
    - MAOIs (+ 5-HT & DA)
  - Alpha-2 Antagonists
    - Yohimbine
    - Mirtazapine
  - NE Precursor: PA/Tyrosine
Dopamine

- ↓ activity
  - DA Antagonists
    - Antipsychotics
      - D1
      - D2
      - D3
      - D4
    - Metoclopramide
    - Antiemetics
  - ↑ 5-HT2A activity

- ↑ activity
  - 5-HT2A Antagonists
  - DA Precursor
    - Levodopa, Tyrosine, Phenylalanine
  - DA Agonist
    - Apomorphine, Bromocriptine, Pramipexole, Ropinirole
  - DA Releasing
    - Amphetamine
  - DA Reuptake Inhibitor
    - Methylphenidate,
    - Bupropion (+ NE)
  - MAOIs and COMT Inhibitors
  - Nicotine and caffeine

Double Boosts of CNS Stimulant Effects

- ↑ NE Activity
  - Reuptake Inhibitor
    - Atomoxetine
    - Bupropion (+DA)
    - Desipramine
    - Duloxetine
    - Venlafaxine
    - Milnacipran
  - NE Releaser
    - Mirtazapine
    - Yohimbine
  - MAOI

- ↑ DA Activity
  - DA agonist
    - Pramipexole
  - Reuptake Inhibitor
    - Bupropion (+NE)
    - Methylphenidate
  - DA Releaser
    - Amphetamines
  - 5-HT2A antagonist
    - Nefazodone
    - Trazodone
    - Mirtazapine
  - MAOI
  - Nicotine and caffeine
## Double Boosts of CNS Depressant Effects

- **↑ GABA Activity**
  - $\text{GABA}_A$: Benzodiazepine
  - Zolpidem/Zaleplon
  - $\text{GABA}_B$: Baclofen
  - $\uparrow$ GABA Synthesis: Gabapentin (?)
  - $\uparrow$ GABA Availability: Divalproex Sodium

- **↓ Glutamate Activity**
  - Inhibits Release: Lamotrigine (+ inhibits Na channels)
  - Blocks Activity: Topiramate (+ inhibits Na channels)

## Sedation, Confusion, Anergy

- **CNS Effects**
  - Benzo + Benzo
  - Benzo + Non-Benzo Hypnotic (e.g., Ambien)
  - Benzo + another sedative-hypnotic or mood stabilizer (e.g., Depakote, Tegretol, Lamictal, Neurontin)
  - Gabapentin, pregabalin
  - Antihistamines
  - Alpha-2 agonists
  - Beta blockers
Non-Response to SRIs

- SRI + trazodone or mirtazapine or atypical antipsychotic
  - SRI’s - increase 5-HT to act at the 5-HT2A receptor
    - May increase EPS because of reduction in presynaptic DA release
  - Trazodone, nefazodone, mirtazapine, and atypicals block the 5-HT2A receptor

Non-Response to NRI or CNS Stimulant

- DA/NE augmenting agents + agent that decreases DA/NE
  - Bupropion, duloxetine or venlafaxine
    - Antipsychotic
    - Alpha-2 agonist
    - Beta-blocker
  - Atomoxetine
    - Alpha-2 agonist
    - Beta-blocker
  - Methylphenidate or amphetamine
    - Antipsychotic
    - Alpha-2 agonist
    - Beta-blocker
Antihistamine/Anticholinergic

- Multiple anticholinergic/antihistamine agents
  - Hydroxyzine
  - Diphenhydramine
  - Benztropine
  - Tricyclic antidepressants
  - Low potency typical antipsychotics
  - Atypical antipsychotics

Pharmacokinetic Drug Interactions
Cytochrome P450 Isoenzymes

- Responsible for the oxidation of many drugs
  - Substrate - requires metabolism through the CYP 450 isoenzymes
  - Inducer - stimulates or induced liver enzymes to be more active and increases metabolism (decreases serum concentrations of drugs)
  - Inhibitor - reduces or inhibits liver enzymes to not be active and decreases metabolism (increases serum concentrations of drugs)

Cytochrome P450 Isoenzymes: Ethnic Variations

- CYP 1A2 Drug metabolism
- CYP 2A6 Nicotine metabolism
- CYP 2C19 Drug metabolism
- CYP 2D6 Drug metabolism
- CYP 2E1 Alcohol metabolism
- CYP 3A3/4 Drug metabolism
CYP 2D6 Substrates

- **Antipsychotics**
  - Aripiprazole (Abilify), haloperidol (Haldol), perphenazine (Trilafon), phenothiazines, thioridazine (Mellaril), olanzapine (Zyprexa), risperidone (Risperdal)

- **Antidepressants**
  - Amitriptyline (Elavil), desipramine (Norpramin), duloxetine (Cymbalta), imipramine (Tofranil), nortriptyline (Pamelor), trazodone (Desyrel), fluoxetine (Prozac), paroxetine (Paxil), venlafaxine (Effexor)

- **Opiates**
  - Codeine, dextromethorphan, hydrocodone, meperidine, methadone, morphine, oxycodone, pentazocine

- **Other**
  - Amphetamines, ACE inhibitors, atomoxetine (Strattera), beta-blockers, tramadol (Ultram)

CYP 2D6 Inhibitors

- **Antipsychotics**
  - Clozapine (Clozaril), haloperidol (Haldol), fluphenazine (Prolixin), perphenazine (Trilafon), pimozide (Orap), thioridazine (Mellaril)

- **Antidepressants**
  - Bupropion (Wellbutrin), duloxetine (Cymbalta), fluoxetine and norfluoxetine (Prozac), paroxetine (Paxil)

- **Antihistamines**
  - Diphenhydramine (Benadryl), chlorpheniramine, hydroxyzine (Atarax, Vistaril)

- **Other**
  - Cimetidine (Tagamet), methadone
CYP 1A2 Substrates

- **Antipsychotics**
  - Clozapine (Clozaril), fluphenazine (Prolixin), haloperidol (Haldol), olanzapine (Zyprexa), thiothixene (Navane)

- **Antidepressants**
  - Amitriptyline (Elavil), duloxetine (Cymbalta), imipramine (Tofranil), fluvoxamine (Luvox)

- **Misc:**
  - Acetaminophen, caffeine, cyclobenzaprine
  - Estradiol, naproxen, propranolol, theophylline

CYP 1A2

- **Inducer**
  - Carbamazepine
  - Charbroiled foods
  - Cigarette smoke
  - Cruciferous vegetables (cabbage, Brussels sprouts, broccoli, cauliflower)

- **Inhibitor**
  - Grapefruit juice (+3A3/4 inhibitor)
CYP 1A2
Inhibitors and Inducers

- **Inhibitors**
  - Amiodarone, cimetidine, ciprofloxin, enoxacin, fluvoxamine, norfloxacin, ritonavir
  - Grapefruit juice (+ 3A3/4 inhibitor)

- **Inducers**
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - Charbroiled foods
  - Cigarette smoke
  - Cruciferous vegetables (cabbage, Brussels sprouts, broccoli, cauliflower)

CYP 3A3/4 Substrates

- **Antipsychotics**
  - Aripiprazole, clozapine, haloperidol, pimozide, quetiapine, risperidone, thioridazine, ziprasidone

- **Antidepressants/Mood Stabilizers**
  - Carbamazepine, citalopram, escitalopram, ethosuximide, mirtazapine, nefazodone, sertraline, tiagabine, trazodone, zonisamide

- **Benzodiazepines/Antianxiety/Hypnotics**
  - Alprazolam, buspirone, clonazepam, diazepam, midazolam, triazolam, zaleplon, zolpidem
CYP 3A3/4 Substrates

- Calcium Channel Blockers/Cardiovascular Agents
  - Amiodarone, amlodipine, atrovastatin, serivastatin, diltiazem, felodipine, lercanidipine, lidocaine, lovastatin, nifedipine, misoldipine, nitrendipine, nimodipine, quinidine, quinine, simvastatin, verapamil

- Antibiotics/Antifungals/Immune Modulators
  - Clarithromycin, cyclosporine, erythromycin, dapsone, indinavir, ketoconazole, nelfinavir, saquinavir, ritonavir, taxol, tamoxifen, vincristine
  - Alfentanil, astemizole, chlorpheniramine, cisapride, cocaine, codeine, estrogens, fentanyl, hydrocortisone, methadone, progesterone, falmeterol, terfenadine, testosterone, sildenafil

CYP 3A3/4 Inhibitors and Inducers

- Inhibitors
  - Fluoxetine, fluvoxamine, nefazodone, norfluoxetine, clozapine, haloperidol
  - Diltiazem, verapamil, gestodene
  - Erythromycin, itraconazole, ketoconazole, ritonavir
  - Grapefruit juice, corn

- Inducers
  - Carbamazepine, dexamethasone, felbamate, mesoridazine, oxcarbazepine, phenobarbital, phenytoin, rifampin, topiramate
  - St. John’s wort
Common Psychototropic Drug Interactions

- Inducers of CYP
  - Carbamazepine (Tegretol)
  - Oxcarbazepine (Trileptal)
  - St. John’s wort

- Inhibitors of CYP
  - Bupropion (Wellbutrin, Zyban)
  - Duloxetine (Cymbalta)
  - Fluvoxamine (Luvox)
  - Fluoxetine (Prozac)
  - Nefazodone (Serzone)
  - Paroxetine (Paxil)
  - Sertraline (Zoloft)
  - Clozapine (Clozaril)
  - Haloperidol (Haldol)

Assessment of Patients: How to Avoid Potential Drug Interactions and Adverse Effects
Assessment of Patients

- Questions to ask:
  - Take three or more prescribed medications?
  - Take dietary supplements, vitamins, or over-the-counter drugs?
  - Take homeopathic remedies or herbal medicines?
  - Use different pharmacies to fill your prescriptions?
  - Have more than one doctor giving you prescriptions?
  - Take medicine more than once a day?
  - Have trouble opening medicine bottles?
  - Have poor eyesight or hearing?
  - Live alone?
  - Sometimes forget to take your medications?
  - Have memory problems?

Ways to Avoid Drug Interactions and Adverse Effects

- Always read labels. They may tip you off to possible drug interactions.
- Use only one pharmacy to fill prescriptions.
- Learn your medications by name and what they are for.
- If you have more than one doctor, make sure each one knows what the other is prescribing.
- Make a list of all your medications including pill strength and dose, as well as herbal products, vitamins, homeopathic remedies, supplements and over-the-counter drugs. Update it after every doctor visit.

- Carry your medications list everywhere. Bring it every doctor visit, along with the pill bottles.

- Ask your primary caregiver or pharmacist to run your medication list through a drug interactions database to identify possible problems, especially if you’re on three or more drugs.

- Avoid combination products such as cold formulas. Ask your pharmacist to help you find a product just for the symptoms you’re experiencing - not for every possible symptom.

- Never take a new drug without asking your pharmacist about its side effects and interactions with other drugs.

- Get familiar with your medications. Learn about them from your physician or pharmacist, or learn from prescription drug books. Information available on-line may come from questionable sources.
References


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