Neurotransmitters in Health and Disease

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Neurotransmitters in health and disease

- **General** theory is that many neurological disorders may be due to:

….. a deficiency of a transmitter,

….. an excess of a neurotransmitter, or

….. an imbalance between neurotransmitters

- Neurotransmitters are located in all three nervous systems: the Central Nervous System (CNS), the Peripheral Nervous System (PNS), and the Enteric Nervous System (ENS, or GI tract)
- One neurotransmitter is also located in platelets (serotonin)--☺--the name, serotonin, was derived from it's ability to constrict the blood vessels (sero=serum, tonin=tonic/tone)(1948); actually the Italians first found it in the ENS and named it enteramine (1933)

NEUROTRANSMITTERS—the list I'll be touching on today

- **Indolamines**

…Serotonin (5-hydroxytryptamine, or 5-HT)—the most ubiquitous of all neurotransmitters; CNS (~3%), Enteric Nervous System (~92-95%), blood platelets (~2%)—numerous functions—makes you happy, boosts self esteem, bolsters confidence ("the confidence" molecule), controls aggressive/impulsive behaviors; too much? Anxiety; nausea, vomiting

…Melatonin—CNS (pineal gland) – sleep/wake cycle of our biological clock; (infants produce the most serotonin vs. elderly produce the least)—the pineal gland shrinks in size with aging and melatonin levels plummet; sundowning may be caused by a disrupted "clock"… try melatonin in patients with sundowning—try 3 mg in the late afternoon (Lammer)

NEUROTRANSMITTERS—the list I'll be touching on today

- Acetylcholine—located in all 3 nervous systems
- In the CNS – cognitive function—mentation (90% depleted in late Alzheimer's disease)
- In the PNS (via the vagus nerve (X) primarily) – neuromuscular transmission, slows the heart down, bronchoconstriction, constricts the pupils, stimulates salivation, loosens the bladder sphincter
- In the ENS (enteric) – triggers peristalsis in the GI tract (excitatory), tightens the lower esophageal sphincter

NEUROTRANSMITTERS-- the list I'll be touching on today

- **Catecholamines**—in all 3 nervous systems: CNS, PNS, and ENS

  Dopamine (DA)—numerous functions including the reward system (oooohhh that feels good—let's do it again…and again), movement in the basal ganglia/striatum, vomiting in the TVC, sex drive; inhibitory in the GI tract—LES and peristalsis;

  Epinephrine (E)—fight/flight response

  Norepinephrine (NE)—energy in the CNS, appetite in the hypothalamus, aggression in the limbic system, alert

NEUROTRANSMITTERS—the list I'll be touching on today

- **GABA (gamma-amino-butyric acid**)"your "mother"— inhibitory in the prefrontal cortex; calms you down; plays a major role in keeping dopamine in check in the basal ganglia
- **Glutamate**— **excitatory** transmitter; excess glutamate triggers neuronal hyperexcitability (seizures); glutamate also triggers brain-derived growth factor and boosts neuronal connections

NEUROTRANSMITTERS

- So we'll be talking about everything from depression to dementia, self-esteem to sleep disorders, sex to seizures, anxiety to addiction, marijuana to movement disorders, and irritable people to irritable bowels…
- All of the above are associated with either an excess, a deficiency or an imbalance of various neurotransmitters in the three nervous systems

Chuckle.

- ***The statistics on mental disorders is that one out of every four persons are suffering from some form of mental illness.***
- ***Think of your three best friends – if they're ok then it's you.***

Receptors for neurotransmitters—back to Pharmacology 101

- In order for any neurotransmitter to do it's job, it has to have a specific receptor (s) to interact with
- Does the transmitter BOOST that receptor? If so, it will generally boost the function and action of that transmitter
- Does the transmitter block that receptor? If so, it will usually block the function of the neurotransmitter
- Drugs influence transmitters and receptors—some drugs boost receptors (known as agonists) and some drugs block receptors (known as antagonists) and some are partial boosters and blockers of receptors…(known as partial agonist/antagonists)

EXAMPLE: Serotonin Receptors…(17 at last count)

- Chemical name? 5-Hydroxytryptamine (5-HT)
- 7 different types of receptors with subtypes
- 5-HT $_{1,}$ 5-HT $_{2}$ 5-HT $_{3,}$ 5-HT $_{4,}$ 5-HT $_{5,}$ 5-HT $_{6,}$ 5-HT $_{7}$
- Subtypes—5HT $_{1A, 1B…}$ 5-HT $_{2A, 2B, 2C…}$
- Yada, yada, yada…

Famous serotonin <u>agonists</u> of 5-HT$_{2A}$

- LSD (“Lucy in the sky with diamonds” (Lysergic acid diethylamide)(acid, blotter, microdot), “magic” mushrooms, mescaline, PCP (angel dust) are famous 5-HT$_{2A}$ agonists causing the release of excess serotonin and dopamine—resulting in schizophrenic- like effects—hallucinations, psychosis
- Drugs that block 5-HT$_{2A}$ receptors are used to block hallucinations, psychosis—clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and more…FGA and SGA

Famous serotonin <u>antagonists</u> of 5-HT$_{2A}$ and 5-HT$_{2C}$

- Drugs that block the 5-HT $_{2C}$ receptor contribute to weight gain, and increase the susceptibility to insulin resistance, type 2 diabetes, and hyperlipidemia
- The second generation atypical antipsychotics (SGAs), Clozaril (Clozapine) and Olanzapine (Zyprexa) block the 5-HT $_{2c}$ receptor
- clozapine (20% or more weight gain over time); olanzapine (30% of patients gain at least 7% of their initial weight)
- Need to monitor weights (BMI) monthly x 3 months) and cholesterol (12 weeks, 1 year, 5 years) when patients are taking these SGAs

Weight gain risk from the atypical anti-psychotics

- Weight gain risk is primarily in first 6 months of taking the drug and is not dose-related--The likelihood that a certain medication will cause weight gain or other side effects varies from person to person.
- Clozapine (Clozaril)—High
- Olanzapine (Zyprexa)—H
- Quetiapine (Seroquel)—Medium
- Paliperidone (Invega)—M
- Risperidone (Risperdal)—M
- Aripiprazole (Abilify)—Low
- Lurasidone (Latruda)—L
- Ziprasidone (Geoden)—L
- (Haddad P. Antipsychotic Medications and Weight Gain. Brit Assoc Psychopharm, March 31, 2017)

How to negate the weight gain and secondary diabetes

- Start the patient on Metformin 500 mg/day* (Glucophage) along with the atypical antipsychotics to negate the weight gain and subsequent diabetes and hyperlipidemia (Wu)
- Actually start with 500 mg to reduce GI side effects; titrate up to 1000 mg

Drugs and Serotonin Receptors

- Drugs that affect serotonin either boost the receptors or block the receptors…agonists or antagonists
- 5-HT_{1A}—boosting this receptor makes you happy (SSRIs)
- 5-HT_{2A-} sexual dysfunction and insomnia (SSRIs)
- 5-$HT_{1B, 1D, 1F}$—if you boost these receptors vasoconstriction will occur as well as the blockade of neuropeptides released from trigeminal nerve endings that mediate migraine pain; the “triptans” interact with these receptors are used in the treatment of acute migraine headaches

Serotonin--Happy and positive self-esteem

- With just the right amount of serotonin individuals experience clear thinking and increased self-confidence along with social success; the brain balances aggressiveness with assertiveness—leaders and achievers; enough aggression is allowed to surface so that they can be assertive

Serotonin plays a role in impulsive eating disorders such as bulimia nervosa

- Boosting serotonin improves impulse control—helps control eating disorders including:
- Bulimia (be aware of girls with Type 1 diabetes and bulimia)
- Binge-eating disorder
- Fluoxetine (Prozac)
- Paroxetine (Paxil)

Nausea, vomiting, gastric motility, gastric hypersensitivity—5-HT_3 receptors

- Serotonin is released from the duodenum and interacts with the 5-HT_3 receptors to induce nausea; serotonin and the 5-HT_3 receptors in the CTZ (chemoreceptor trigger zone) in the brainstem induces vomiting
- 5-HT_3 antagonists – the "setrons"—ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet), palonesetron HCl (Aloxi)(long-acting)
- Chemotherapy (many types), anesthesia, trigger serotonin release from these areas--post-anesthesia N & V, chemotherapy-induced N & V, migraine headaches and N & V
- Side effect of constipation due to slowing of gastric motility

Serotonin and Irritable bowel syndrome (IBS)

- Defined as pain or discomfort occurring in association with altered bowel habits over 3+ months
- Brain-bowel connection
- Too little serotonin? Constipation-predominant--IBS-C
- Too much serotonin? Diarrhea-predominant—IBS-D
- Some individuals have a "mixed" IBS
- Treatment?

Irritable bowel syndrome (IBS)—some treatments based on serotonin excess or deficiency

- SSRIs for IBS-C – boost serotonin receptors in the bowel, increasing GI motility
- Tricyclics for IBS-D (amitryptyline)(anti-cholinergic effects)—slows intestinal motility
- Loperamide (Imodium) for IBS-D
- Ondansetron (Zofran)(5-HT_3 blocker) for IBS-D
- Viberzi (eluxadoline) for IBS-D—(doesn't work on serotonin) (boosts mu {opiate} receptors) to slow GI motility, decreases GI hypersensitivity

Serotonin and Premenstrual dysphoric disorder (PMDD)

- More women are admitted to psychiatric units in the week immediately prior to menses that any other week.
- SERIOUSLY???
- In one study, 47% of admissions occurred during this week (The Carlat Psychiatry Report, February 2014; Targum SD, et al, *J of Affect Disorders*, 1991;22(1-2):49-53)

PMDD—3-8% of women

- PMS? 80% of women—"I'm a little more moody the week before my period, but it's not a big deal."
- PMDD— "I will *kill* you if you make another sound…" is a severe form of PMS that includes mood swings, depressed mood, irritability, and other emotional and physical symptoms that are wicked enough to interfere with life, work, and relationships. PMDD—occurs exclusively during the luteal phase (one to two weeks before menses). It has been described as "hell on earth."

Menstrual cycle and mood disorders

- Drop in progesterone one to two weeks before menses, and this drop triggers menstruation.
- When the progesterone levels drop, the allopregnanolone levels also fall.
- In the healthy brain, progesterone is converted into allopregnanolone, which binds to the GABA-A receptor—the same receptor that benzodiazepines and alcohol bind to—and acts as a powerful anxiolytic that decreases anxiety and depression
- Women with PMDD are much more sensitive than others to this drop in progesterone and allopregnanolone, and this sensitivity causes the mood symptoms of PMDD (premenstrual dysphoric disorder)
- (Griffin L and Mellon S, *Proceedings Natl Acad Sci USA* 1999;96(23):13512-7)

Treatment of PMDD

- SSRIs—accelerate the conversion of progesterone to allopregnanolone
- Low-dose SSRIs—fluoxetine (Prozac/Sarafem 10-20 mg), sertraline/Zoloft (25-50 mg), and paroxetine/Brisdelle increase the enzyme needed for the conversion by 10-30 fold
- Mechanism works within several hours to several days
- Oral contraceptives "flatten out" the hormonal fluctuations, keeping the body's hormone levels consistent without any peaks or troughs)—the patient takes the exact same dose of estrogen and progesterone every day (no placebo week for most women)
- Takes 2 cycles to see if oral contraceptives work
- It only takes several hours to several days for SSRIs

Theories of Depression

- Neurotransmitter deficiencies are still the "main" theory…serotonin, norepinephrine, and dopamine—and the drugs we use to replace these transmitters work ~60% of the time
- But WAIT...there's more...depression causes dendrites to shrink and messages can't transmit across synapses—
- NEW MOA: releasing **glutamate** increases BDNF (brain-derived neurotrophic factor) – causing dendrites to sprout new spines…Ketamine is the new wonder drug in research for **treatment-resistant depression**
- Ketamine quickly releases releases glutamate

Ketamine for severe depression

- IV ketamine (Ketalar) (a cousin of angel dust/PCP; used by anesthesiologists and veterinarians for pre-op anesthesia) infusion for 40 minutes
- **Not FDA approved –** but is being used as a fast-acting "miracle" drug for severe depression
- Boosts glutamate in the brain
- Pop-up ketamine clinics for patients with refractory depression—studies showing a statistically significant response and improvement on various depression scales within 24 hours; response rates ranged from 40-70%
- Ketamine may work for as many as 60% of treatment-resistant patients. Some patients go into remission within a day and can remain free from depression for up to 10 days.
- Nasal ketamine has just been approved (March 2019)(esketamine/Spravato)

Ketamine for severe depression

- Dissociative effects during infusion (floating, hallucination) are positively associated with a treatment response
- relapse rates as high as 55% to 89% in the month following treatment; no maintenance strategy has been discussed

The SSRI's (selective serotonin reuptake inhibitors)…

- 1987—the first selective serotonin reuptake inhibitor was released and we all know that drug as fluoxetine, Prozac (Lilly) (longest t½) favored in patients who need a little "activation"… may cause insomnia, anxiety, weight loss; long half-life; can give Prozac weekly
- Not a good choice for older patients
- **REMEMBER THE RULE IN GERIATRIC PHARMACOLOGY—*Never give a drug with a half-life longer than their life!!***

The SSRI's (selective serotonin reuptake inhibitors)…

- Sertraline (Zoloft)(1992)—shortest t½; excellent choice for elderly depressed patient; may also be useful for mild irritability and aggression; OCD (6+ years), panic disorder, PTSD, PMDD, social anxiety

The SSRIs (or SRIs) have many clinical uses

- Citalopram (Celexa)—MDD (dose reduction due to prolonged QT interval)
- escitalopram (Lexapro, Cipralex)—major depressive disorder, generalized anxiety disorder (GAD), OCD, Body dysmorphic disorder, kleptomania-- little, if any, drug interactions; **excellent choice**
- Paroxetine (Paxil, Pexeva)—**most** anticholinergic effects, tremor at higher doses; weight gain, constipation, drug interactions
- SSRIs most effectively treat ANXIETY (except fluoxetine)

(APRIL 2016, Carlat Psychiatry Report)(Medication Fact Book for Psychiatric Practice, 4th edition, 2018)

Serotonin helps to modulate pain pathways in the brainstem …along with norepinephrine

- SNRIs—Duloxetine/Cymbalta—major depressive disorder and peripheral neuropathy; also used for generalized anxiety disorder
- Also approved to reduce the treatment-related joint pain caused by aromatase inhibitors in women with ER+ breast cancers (NCI, January 4, 2017)

SNRIs (Serotonin Norepinephrine Reuptake Inhibitors)

- venlafaxine (Effexor) (also a mild inhibitor of dopamine re-uptake)
- desvenlafaxine (Pristiq) –the active metabolite of venlafaxine; less drug interactions

Pure N.E. booster

- Mirtazepine (Remeron)--PURE N.E. booster—happy, (norepinephrine in appetite center increases weight gain)
- **Possible use for treatment methamphetamine use disorder; 30 mg/day vs placebo
- Men w/ mirtazapine had decreased meth use and decreased sexual risk

St. John's Wort

- Boosts serotonin
- Decreases cortisol
- Efficacy = sertraline (Zoloft)
- Lots of interactions with prescription drugs—generally makes the drugs less effective
- Teenage girls, depression, combined oral contraceptives

Moving on to the neurotransmitter dopamine…

- Neurotransmitter located in the central nervous system (primarily the striatum), the peripheral nervous system (one of the catecholamines), and the enteric nervous system
- Dopamine has 5 receptors—D1 – D5
- D1 and D2 are the most ubiquitous of the dopamine receptors, and clinically the most important

For example:

- Boosting D2 receptors gives your energy, makes you feel good; too much? Psychosis and hallucinations…SOOOOOOOOOOO
- Blocking D2 receptors decreases psychosis and hallucinations in patients with schizophrenia and in patients on drugs that cause psychosis and hallucinations (**the main goal of first generation and second generation antipsychotic drugs)**
- The FGA (first generation anti-psychotics) -- haloperidol/Haldol, chlorpromazine/Thorazine, stelazine, and more
- The SGA – clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), aripiprazole (Abilify), and more

Dopamine is involved in a wide variety of clinical conditions including:

- Pleasure, energy, and reward—
- If it feels good—let's do it again! And again…and again…and why not? AGAIN!! (reinforcement)
- Substance use disorders involve boosting dopamine in the reward system of the brain
- Cocaine and methamphetamine release the most dopamine

Excess dopamine can lead to substance use disorders (addiction)

- Nicotine, alcohol, opiates (morphine and codeine) and opioids (semisynthetics—heroin, oxycodone, etc) and synthetics (methadone, fentanyl, carfentanil), methamphetamine, cannabis, gambling, sex, food

Fentanyl/carfentanil abuse is the newest opioid nightmare—Fentanyl is 50-100 times more potent than morphine; carfentanil is 10,000 times stronger than morphine)

- 1960s– Fentanyl entered medical use as a general anesthetic known as Sublimaze); 1990s started being used for palliative use (patch, lollipops, dissolving tablets, sublingual)
- By 2012 – it became the widely used synthetic opioid in medicine;
- Today? More Fentanyl overdoses than any other drug
- Carfentanil—elephant tranquilizer—lacing heroin/cocaine with this incredibly potent opioid is even more DEADLY than Fentanyl…
- Take PRINCE for example (2016)...

Addiction and dopamine

- Addictive drugs can release two to 10 times the amount of dopamine that natural rewards do, (crystal meth vs. mashed potatoes) and they do it more quickly and more reliably.
- Once a person becomes addicted, brain receptors become overwhelmed.
- The brain responds by producing less dopamine (the person requires MORE of the addicting substance to get the same high)
- The brain may also eliminate dopaminergic cells and/or receptors all together (methamphetamine is notorious for this permanent change)

Drugs to treat methamphetamine addiction

- Many changes in the brain secondary to chronic meth use are ***irreversible***—loss of dopamine receptors and the neurons in the pleasure centers of the brain; neurons do NOT regenerate in this area (greater than 50% loss of permanent dopamine production—extreme DA depletion in meth addicts—tremors, PD)
- Mirtazapine (Remeron)(30 mg/day) to boost norepinephrine (gives you energy)
- Clinical trials—testing vaccine that binds to meth in blood and prevents it from crossing the BBB

(NIDA, drugabuse.gov, accessed July 8, 2014)

Early exposure to drugs and alcohol…

- More and more evidence points to "when" you started addictive behaviors and the increased risk of lifelong addictions
- Robert Downey, Sr. gave Jr. drugs and marijuana at age 6—thinking it was "cute"…
- *"I'm allergic to alcohol and drugs—I break out in handcuffs.* – Robert Downey, Jr.

Why are substance use disorders most likely to begin under the age of 25?

- Adolescents become addicted faster and with lower doses of addictive agents
- The dopamine-reward system is developing at this time with NO input from the prefrontal cortex (the ability to determine whether the reward is worth the risk)
- In general, trying an addictive substance before the age of 18 makes teenagers **6x** more likely to develop an addictive disorder later in life than those who wait until they're 21

Early exposure to drugs, nicotine, marijuana, and alcohol…

- "*The risk of marijuana abuse disorder is highest among children and adolescents—especially marijuana use prior to the age of 18.*" (9% of marijuana users develop marijuana abuse disorder. However, the overall number is 17% if marijuana is started before the age of 15)
- Danovitch I. June 2014, Carlat Report, Psychiatry
- 33% of teenagers **younger than 14** years who initiate substance use will develop substance use disorder in their lifetimes. (Sussman S, Lisha N, Griffiths M. Prevalence of the addictions: a problem of the majority or the minority? *Eval Health Prof*. 2011;34(1):56)

However, it's NOT just teenagers smoking cannabis…

- Cannabis was the rage back in the late 1960s
- People are now in their mid-to- late 60s and still smoking cannabis—swearing that they're going to get a really good job one day
- 1960s/70s—low THC content—5%)
- Today's THC? 20%, 30%

Adolescents and cigarettes

- 4 cigarettes as a 13-year-old can trigger addiction to nicotine
- 90% start smoking before age 19; 99% before age 25

Another teenage addiction? LOVE! "I'm in love and it's the real thing..."

- A dopamine tsunami…
- Obsession with boyfriends or girlfriends… "OMG, I'm so, like, in love with Tyler Schmyler... I'm going to marry him/her one day..."
- RIIIIIIIGHT...butterflies, texting,
- obsession is putting it mildly...
- *He'll be here in 15 minutes to pick me up...(*heart is pounding, I can hardly breathe..)
- AND NOW?

Dopamine plays a role in movement…in the basal ganglia

- Too much dopamine? Too much movement—examples: Huntington's chorea, "crack dancing", dopamine super-sensitivity with anti-psychotic drugs—tardive dyskinesias
- Too little dopamine? Too little movement—examples: Parkinson's disease, Parkinsonism from drugs that block dopamine

Imbalance between dopamine and acetylcholine=Parkinson's disease or Parkinsonism

- TOO LITTLE dopamine in the basal ganglia causing unopposed acetylcholine
- Parkinson's disease—loss of dopamine producing cells in the movement area of the brain known as the striatum (which includes the basal ganglia)—bradykinesia, rigidity, postural instability, tremor (usually unilateral to start)
- Drug-induced is known as Parkinsonism (bilateral sx, onset within weeks/months of starting drug

Parkinson's disease

- Imbalance between dopamine and acetylcholine—too little dopamine with a relative excess of acetylcholine
- Earliest signs with 60% loss of dopamine—anosmia, constipation, REM sleep disorder
- By the time the ***movement disorder*** of Parkinson's disease is diagnosed the area of the basal ganglia that produces dopamine (substantia nigra) has lost 80% of the neurons
- Symptoms of rigidity, bradykinesia (slowness of movement*), slowness of thought, and the loss of spontaneity of movement** are due to dopamine deficiency (the tremor is due to unopposed acetylcholine), and postural instability

Postural instability and the "righting" reflex—Cats have the best righting reflex

Pharmacologic treatment of Parkinson's disease

- Provide the missing neurotransmitter
- Levodopa or L-dopa with carbidopa (Sinemet)—gold standard of treatment to replace dopamine
- Lots of drugs used today for PD

Excess dopamine—excess movement—chorea (rapid, jerky movements), tardive dyskinesia, athetosis (slow, writhing movements) – all known as extrapyramidal movements (EPS)

- 30% of all patients on neuroleptic drugs will develop tardive dyskinesia

Treatment of Huntington's chorea/tardive dyskinesia

- Tetrabenazine (Xenazine)(drug first synthesized for schizophrenia 50 years ago—approved for chorea in 2009); depletes neurotransmitters serotonin, norepinephrine and especially dopamine in the basal ganglia and reduces the involuntary movements (Medical Letter, January 2009)
- Valbenazine/Ingrezza (April 2017)
- Deutetrabenazine/Austedo (June 2017)
- *add gingko biloba to valbenazine or deutetrabenazine for a greater response

Other treatments for tardive dyskinesia

- Deep brain stimulation: Invasive treatment--effective in suppressing many of the hyperkinesias in tardive dystonia and other dyskinesia syndromes.
- (Bhidayasiri R et al. Evidence-based guideline: Treatment of tardive syndromes—Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013 Jul 30;81:463)

Dopamine plays a role in sexual function

- The Selective Serotonin Reuptake Inhibitors (SSRIs) for depression decrease dopamine in the area of the limbic system responsible for sexual desire and sexual function
- SSRIs may cause anorgasmia, delay in orgasm, loss of libido
- up to 60% of patients taking an SSRI may experience this problem

Benefit of SSRIs for men with premature ejaculation

- One of the side effects of the SSRIs is to significantly delay the achievement of orgasm in both male and female patients (which is annoying most of the time),
- But, it's a perfect treatment for premature ejaculation

Drugs that boost dopamine can boost sexual function

- Bupropion (Wellbutrin) 75 mg TID boosts dopamine and can be used for SRI-induced sexual dysfunction as well as for depressed patients with diminished libido
- Amantadine (Symmetrel), 100 mg TID, also boosts dopamine and may counteract the sexual side effects of the SRIs
- Drugs that treat the dopamine deficiency of Parkinson's disease (bromocriptine (Parlodel), pramipexole (Mirapex), ropinirole (Requip); Amantidine (Symmetrel)) stimulate dopaminergic receptors and can also boost dopamine in the area of sexual function—"sexual pests"

Excess dopamine triggers vomiting in the TVC (true vomiting center) of the brainstem

- Dopamine blockers like metoclopramide (Reglan) work in the TVC to block dopamine and reduce vomiting

Attention Deficit Hyperactive Disorder (ADHD) and dopamine

- The "attention" area in the frontal lobe is HYPOfunctioning …most of the drugs used for ADHD are stimulants—to boost the release of catecholamines (dopamine, norepinephrine) in the attention area of the frontal lobe
- Treatment works!! Lack of treatment = risk of impaired outcomes

ADHD treatment—amphetamine-based drugs for ADHD boost norepinephrine and dopamine

- FDA-approved amphetamine-based drugs such as
- dextroamphetamine (Dexedrine, Dextrostat),
- amphetamines (Adderall, Adderall XR);
- methamphetamine HCl (Desoxyn)
- lisdesamfetamine (Vyvanse)
- *the amphetamine-based drugs are twice as potent as the methylphenidate-based drugs
- (Zuvekas S et al, *Am J Psych* 2012;169(2):160-166); Polanczyk G et al. *Am J Psych* 2007;164(6):942-8)

ADHD treatment--Stimulant ADHD drugs—methylphenidate-based drugs

- Methylphenidate-based drugs—
- Ritalin; Ritalin SR (sustained release), Ritalin LA (long acting);
- long-acting methylphenidate (Concerta), patch (Daytrana); Metadate ER, Metadate CD, Methylin (oral)
- Dexmethyphenidate—Focalin, Focalin XR
- (Zuvekas S et al, *Am J Psych* 2012;169(2):160-166); Polanczyk G et al. *Am J Psych* 2007;164(6):942-8)
- Non-stimulant – atomoxetine – Strattera (24 hours)(norepinephrine reuptake inhibitor—not a controlled substance; less effective than methylphenidate)

Drugs for psychosis

- *"Why is it that when we talk to God we're said to be praying, but when God talks to us we're schizophrenic?"* -- Lily Tomlin

Drugs that block dopamine receptors (D2) are used to treat psychotic symptoms

- First generation antipsychotics—Thorazine (chloropromazine), Haldol (haloperidol), Mellaril (thioridazine), fluphenazine (Prolixin), Trilafon (perphenazine), thiothixene (Navane)—blocked both D1 receptors as well as the D2 receptors
- D2 receptors are the key targets, (psychosis/hallucinations). Need to block at least 65% of D2 receptors for antipsychotic efficacy; (greater than 70% blockade increases S.E.)
- D1 receptor blockade caused the side effects of the first generation drugs—tardive dyskinesia and galactorrhea (inhibit dopamine in the hypothalamus and increase PRL {prolactin} release)—resulting in breast milk production

Some notes on haloperidol—a first generation antipsychotic

- Haloperidol has a faster onset vs. the atypicals
- Used for the treatment of delirium--PO is optimal; IM or IV optional
- 0.25 to 1.0 mg followed by a repeat dose q 20 to 30 minutes until patient is manageable. Maximum does should not exceed 3-5 mg
- Significantly more efficacious in the reduction of the mania scale score at week 1 vs. olanzapine/Zyprexa and ziprasidone/Geodon
- No significant differences between Haldol and aripiprazole/Abilify, quetiapine/Seroquel and risperidone/Risperdal
- Benzodiazepines for acute delirium from alcohol withdrawal
- Goikolea JM, et al. *Eur Neuropsychopharmacol* 2013; 23(4):305-16. Doi:10.1016/j.euroneuro.2012.05.017

"Atypical" or 2nd generation antipsychotics (SGA)

- **The atypical antipsychotics were discovered to reduce the EPS of the first antipsychotics**
- Newer "atypical antipsychotics"—also block serotonin receptors (5-HT2A) but ***only*** D2 receptors – the major area responsible for hallucinations
- Patients no longer feel as if they are hearing the voices of 40 radio stations—the volume is softer, speed is slower, things are making more sense, voices and visions don't always disappear but can allow people with schizophrenia to hold jobs and have families

Can you believe?

- The definition of "atypical" was linked initially with differences in the way these drugs affected how rats climbed up poles when on these drugs as compared to the older 1st generation pole-climbing activities
- (Costall B et al. *Br J Pharmacol* 1978;63(2):381P-382P)

"Atypical" antipsychotics

- Clozapine (Clozaril)('89), treatment resistant schizophrenia
- olanzapine (Zyprexa)('96)- schizophrenia, bipolar mania, bipolar maintenance
- risperidone (Risperdal)('93)—schizophrenia, bipolar mania, irritability in autism (5-16 yo.)
- quetiapine (Seroquel)('97)—schizophrenia, bipolar mania, maintenance
- ziprasidone (Geoden)('01)—schizophrenia, bipolar mania, agitation in schizophrenia (IM only)
- aripiprazole (Abilify)('02)—all of the above and more; Tourette's, irritability in autism
- olanzapine + fluoxetine = Symbyax (approved for depressive episodes associated with bipolar disorder);

Atypical antipsychotics

- paliperidone (Invega)('06)—schizophrenia, schizoaffective disorder
- lloperidone (Fanapt)('09)--schizophrenia
- Asenapine (Saphris)('09)—schizophrenia, acute manic and mixed episodes of bipolar disorder
- Lurasidone (Latuda) ('10)—schizophrenia, bipolar depression
- Brexipiprazole (Rexulti ('15)—schizophrenia, depression adjunct
- Cariprazine (Vraylar)('15)—schizophrenia, bipolar mania, mixed episodes
- Pimavanserin (Nuplazid)('16)—psychosis in PD (doesn't worsen motor symptoms w/ dopamine blockade—just blocks 5-HT_{2A} receptors)

Endocannabinoid (EC) system

- The EC system is found in throughout the central nervous system from the cortex to the basal ganglia to the brainstem, the limbic system, and the spinal cord, explaining why it affects so many different body functions.
- Cannabinoids exert their influence by regulating how cells communicate—how they send, receive, or process messages. Cannabinoids act like a type of "dimmer switch," slowing down communication between cells.
- The endogenous cannabinoids (natural neurotransmitters in this system) are anandamide and 2- AG (arachidonoyl glycerol) – binding to the CB1 cannabinoid receptors in the brain

Cannabis

- Tetrahydrocannabinol (THC) is a partial agonist of CB1 and CB2 receptors. It is psychoactive and produces the euphoric effect.
- Cannabidiol (CBD) has a weak affinity for CB1 and CB2 receptors and appears to exert its activity by enhancing the positive effects of the body's endogenous cannabinoids.
- There are at least 113 cannabinoids isolated from cannabis

The effects of cannabinoids on the various areas of the nervous system are as follows:

- Amygdala—regulates emotions, fear, anxiety. THC can cause panic, paranoia, and psychosis.
- Basal ganglia—the area of the brain that assist in planning, starting a movement and stopping a movement. THC can slow reaction time. This is a particular problem when driving.
- Brain stem—CRTZ (Chemoreceptor Trigger Zone) and the TVC (True Vomiting Center). THC has potent anti-nausea effects. However, too much cannabis can have the opposite effects and trigger hyperemesis.
- Cerebellum—motor coordination and balance. THC contributes to problems with balance and coordination.
- Hippocampus—learning new information, forming memories and "bringing back" those memories. THC can cause impaired memory and learning.

The effects of THC on the various areas of the nervous system are as follows:

- Hypothalamus—the specific nucleus known as the appetite center—THC is well-known to trigger "the munchies." There's not a cheezo-wheezo-whizzo-boom-boom munchie that is spared when a cannabis user has the munchies.
- Cerebral cortex—area of complex thinking, sensory phenomenon, and voluntary movement. THC use results in altered thinking, judgment, sensation and movement.
- Nucleus accumbens—the area of dopamine release and "woo-hoo" this feels fabulous. THC use results in euphoria.
- Spinal cord—the pathways of transmission of pain to the cerebral cortex. THC alters pain sensitivity and reduces the "interpretation of pain" in the cerebral cortex. This is the basis for the use of THC in chronic pain syndromes and may also be the reason the THC use is associated with a reduction in opioid use (by 63% in one study).

Cannabis

- Smoking a joint—effects observed almost immediately—remember: smoking any substance (crack, nicotine, cannabis) hits the brain in seconds
- Oral ingestion (edibles)—30 – 60 minutes; delayed effects so people think they didn't ingest enough…and take another dose... inadvertently consuming more THC than they intended to.

Shouldn't add to brownies for the medicinal effect--☺

Cannabis—other effects

- Excess THC (taking too much, high potency, inexperience) may cause anxiety, fear, distrust, or panic.
- Acute psychosis may occur, including hallucinations, delusions, and a loss of the sense of personal identity.
- These temporary reactions are distinct from longer-lasting psychotic disorders, such as schizophrenia.
- RISK of developing psychotic disorder--(FH—1st degree relative—parent or sibling—1/10 chance; no FH? 7/1000 chance)

Cannabis and the brain…

- Heavy marijuana use as a teenager increases the risk of a decline in IQ scores
- Largest drop with heaviest use—up to 5.75 IQ points
- Anti-motivational syndrome is another short term ***and*** long-term effect…controversial
- Breast development in teenage boys who are daily smokers
- Urine testing—cannabis may be excreted for 3 **weeks** after last use; longer if used heavily

Medical Cannabis

- The most evidence for the use of medical cannabis include N & V, alterations in appetite (HIV wasting, cancer cachexia), muscle spasticity (MS, CP), as an anticonvulsant, and analgesic effects.
- CBD oil has been touted as the cure-all, be-all, go-to for everything. NEED MORE RESEARCH.
- But…

CBD oil for severe seizure disorders in children

- Cannabidiol, a non-psychoactive compound derived from cannabis, has been shown to be particularly effective in some children with a severe seizure disorder (Dravet's syndrome. Cannabidiol **(Epidiolex**) reduced the median number of seizures that children experienced per month by about 50 percent, while placebo reduced median monthly seizures by about 5 percent.
- "We now have solid, rigorous scientific evidence that in this specific syndrome, cannabidiol is effective at reducing seizures," neurologist and lead author Orrin Devinsky of New York University Langone Medical Center told *STAT*.

Cannabis for pain

- A University of Michigan June 2016 study published in the *Journal of Pain* provides some compelling data. Cannabis:
- Decreased side effects from other medications
- Improved quality of life
- **Reduced use of opioids (on average) by 64%**
- When considering cannabis to treat chronic pain, the adage 'less is more' rings true. Patients seem to find more relief in **indica** strains which are higher in THC than most sativa or hybrid strains. What has been found is that these strains can be highly effective in **low to moderate** doses, but could actually make pain worse in higher doses.
- Important -- start low, and titrate up as appropriate.

Why not try Botox for depression?

- Study—patients with major depressive disorder who had not responded to usual antidepressant therapy were given a single dose (consisting of 5 injections) of Botox in the area of the face between and just above the eyebrows
- Control group was given placebo injections
- Depressive symptoms in Botox group decreased 55% after six weeks; Placebo group? 0%
- Theory? Prevents facial muscles from registering negative emotions
- Botox decreases the feedback from the facial muscles to the brain resulting in less activation of the amygdala and other structures involved in depression; OR it may be due to its cosmetic effect, more positive social feedback to a happier face

(Magid M et al, *J Clin Psych* 2014;75(8);837-44)

What else can you do to make you happy? Hang around with people that make you happy! Mirror neurons

Don’t hang around negativity—it’s also contagious

- Bad attitudes and negative attitudes are contagious—
- Mirror neurons

Exercise

Let's talk about your MOM—GABA (gamma-amino-butyric-acid)

- She is "inhibitory"…
- NO, NO, NO
- She calms the brain down
- Executive functions—slow down, think before acting, don't choose risky behaviors

Benzodiazepines— "Mother's little helpers"

- Benzodiazepines (anti-anxiety drugs)—first introduced in the '60s Librium (chlordiazepoxide) w/ slogan— "Whatever the diagnosis—Librium")
- They work on the GABA-BZ receptor;
- Cause sedation, reduce anxiety; muscle skeletal relaxation; anticonvulsant effects
- 1966 Rolling Stones song "Mother's Little Helper" —"She goes running for the shelter of a mother's little helper…"

Benzodiazepines

- Indicated for anxiety disorders: panic disorder, generalized anxiety disorder (GAD), phobias, obsessive-compulsive disorder, or post-traumatic stress disorder (PTSD)
- Two main types of drugs are used to treat anxiety—SSRIs (as mentioned—except fluoxetine) and benzodiazepines (BZs)
- BZs 10-30 minutes—can be taken PRN, or on a regular basis (SSRIs take 2-4 weeks)

Anxiolytics/hypnotics— "zolams and zepams"

Benzodiazepines— "zepams" and "zolams"
Diazepam—Valium (20-100 h)
Flurazepam—Dalmane (40-114)
Quazepam—Doral (25-115)
Clonazepam—Klonapin (18-50 h)
Lorazepam—Ativan (10-20)
Oxazepam—Serax (5 -20)
Temazepam—Restoril (10-40)
Aprazolam—Xanax (6 – 20)
Triazolam—Halcion (2.5)
chlordiazepoxide (Librium)—not a zepam or zolam; long-half life like diazepam

Treatment for panic disorders/generalized anxiety

- For long-term treatment of panic/generalized anxiety—use SSRIs (paroxetine/Paxil; sertraline/Zoloft; citalopram/Celexa; SNRI—venlafaxine/Effexor)—take longer to work; start with 50% of dose used for depression
- If BZ's are used for a long period of time side effects become a problem—physical and psychological dependence, withdrawal symptoms with abrupt discontinuation, reduced alertness, drowsiness, physical fatigue, impaired physical coordination, and memory loss
- Side effects are magnified with alcohol use

Rodney Dangerfield

- *"I went to the doctor because I'd swallowed a bottle of sleeping pills. My doctor told me to have a few drinks and get some rest."* Rodney Dangerfield.

Drugs with "gaba" in their name

- Gabapentin – Neurontin--The "Swiss-Army Knife" of neurology; Approved for use in 1994 as an anticonvulsant; In 1996, research on other clinical uses began to appear in the literature; "off label" use for neuropathic pain in the late 1990s
- Used for many chronic neuropathic pain syndromes (post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome); used for sedation & dizziness
- Pregabalin – Lyrica (2nd generation)—approved for the treatment of neuropathies (DM, Shingles) and fibromyalgia (150 mg of Lyrica TID) + benefit in as early as one week—greatest benefit with highest doses; Side effects--sleepy, dizzy; adjunctive Rx for seizure disorders (no drug-drug interactions…wow; excreted through kidney)

Seizures—anti-convulsants and GABA

- Gabapentin (Neurontin) and pregabalin (Lyrica)—increase inhibitory effects of GABA – Neurontin was originally released as an anticonvulsant
- Topiramate (Topamax)—increase inhibitory effects of GABA and blocks excitatory effects of glutamate
- Valproic acid—Depakote, Depakene, Depacon, Stavzor—boosts GABA

GABA and dopamine in chronic alcoholics

- Dopamine/GABA relationship: Dopamine is like a toddler-run, run, run; gives you energy; GABA keeps dopamine in check
- Chronic alcoholics have decreased dopamine—no energy
- Alcohol takes the place of GABA
- When alcoholics don't have access to booze, dopamine "rebounds" in about 3-5 days
- Causes the DTs (delirium tremens)

Alcohol withdrawal syndrome—the DTs

- Medical emergency with sx of hallucinations, confusion, disorientation, generalized seizures and pronounced autonomic activity due to dopamine rebound
- Tachycardia, hypertension, hyperthermia, tachypnea, tremors

How do you treat the DTs?

- The GABA-BZ (benzodiazepine) receptor—boosting the GABA receptor with BZ's during alcohol withdrawal puts the brakes on dopamine rebound; benzodiazepines "act" like GABA
- RX: Lorazepam (Ativan)—1 mg initial dose (range 2-4 mg); diazepam (Valium)—5 mg initial dose (10-20 mg range), chlordiazepoxide (Librium)—25 mg is initial dose (50-100 mg range); oxazepam (Serax)—15 mg is initial dose (10-30 mg range)

Norepinephrine

- Gives you energy (CNS), Boosts mood (CNS)
- Lack of CNS norepinephrine = anhedonia (the lack of interest in day-to-day activities)
- Drugs that boost norepinephrine make you happy and give you energy (amitriptyline/ Elavil; Prednisone and euphoria; mirtazepine/Remeron); SNRIs (with serotonin)
- Drugs that block norepinephrine have the opposite effect– lipid-soluble beta blockers (propranolol, timolol, metoprolol, carvedilol) -**anhedonia**
- Boosting NE in the appetite center—Prednisone, mirtazepine
- Fight-flight response and aggression
- **Weight gain as a side effect of drugs that boost norepinephrine**

Bibliography

- Alati R, et al. "In Utero Alcohol Exposure and Prediction of Alcohol Disorders in Early Adulthood: A Birth Cohort Study, *Archives of General Psychiatry* (September 2006); 63 (9); 1009-16.
- Bailey BN et al. Prenatal exposure to binge drinking and cognitive and behavioral outcomes at age 7 years. *Am J Obstet Gynecol* 2004 Sep;191:1037-43.
- Bigal ME, Walter S. Monoclonal antibodies for Migraine: Preventing Calcitonin-Related Gene Activity in *CNS Drugs,* Vol.28, No. 5:389-895; May 2014
- Bigal ME, Walter S, Rapoport AM. *British J Clin Pharm, Vol 79 (6):886-895, June 2015*

Bib

- FDA February 26, 2009. Metoclopramide and Tardive Dyskinesia
- Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. J Clin Psychiatry 2000;61(Suppl 4):10-14.
- Loebal A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: A randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2013; published online October 30; doi:10, 1176/appi.ajp.2013.12070984.

Bibliography

- Glial cells, GABA, and Glutamate. The Carlat Psychiatry Report, December 2009.
- Berner LK, Kriston L. St John's wort for major depression. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.:CD000448. DOI:10.1002/14651858.
- Gazzaniga MS. Smarter on Drugs. *Scientific American Mind.* November 21, 2005.
- Lammers M, Ahmed A. Melatonin for Sundown Syndrome and Delirium in Dementia: Is It Effective? *J Am Geri Soc.* 14 Jun 2013
- Nicolaou KC, Montagnon T. Molecules that Changed the World. Wiley.

Bibliography

- Porter R, Madness: A brief history. 2002. Oxford University Press.
- Wu R-R, Zhao J-P, Jin H, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA.* 2008;299:185-193
- Wu R-R et al. Metformin for treatment of antipsychotic-induced amenorrhea and weight gain in women with first-episode schizophrenia: A double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 2012 Jun 15.