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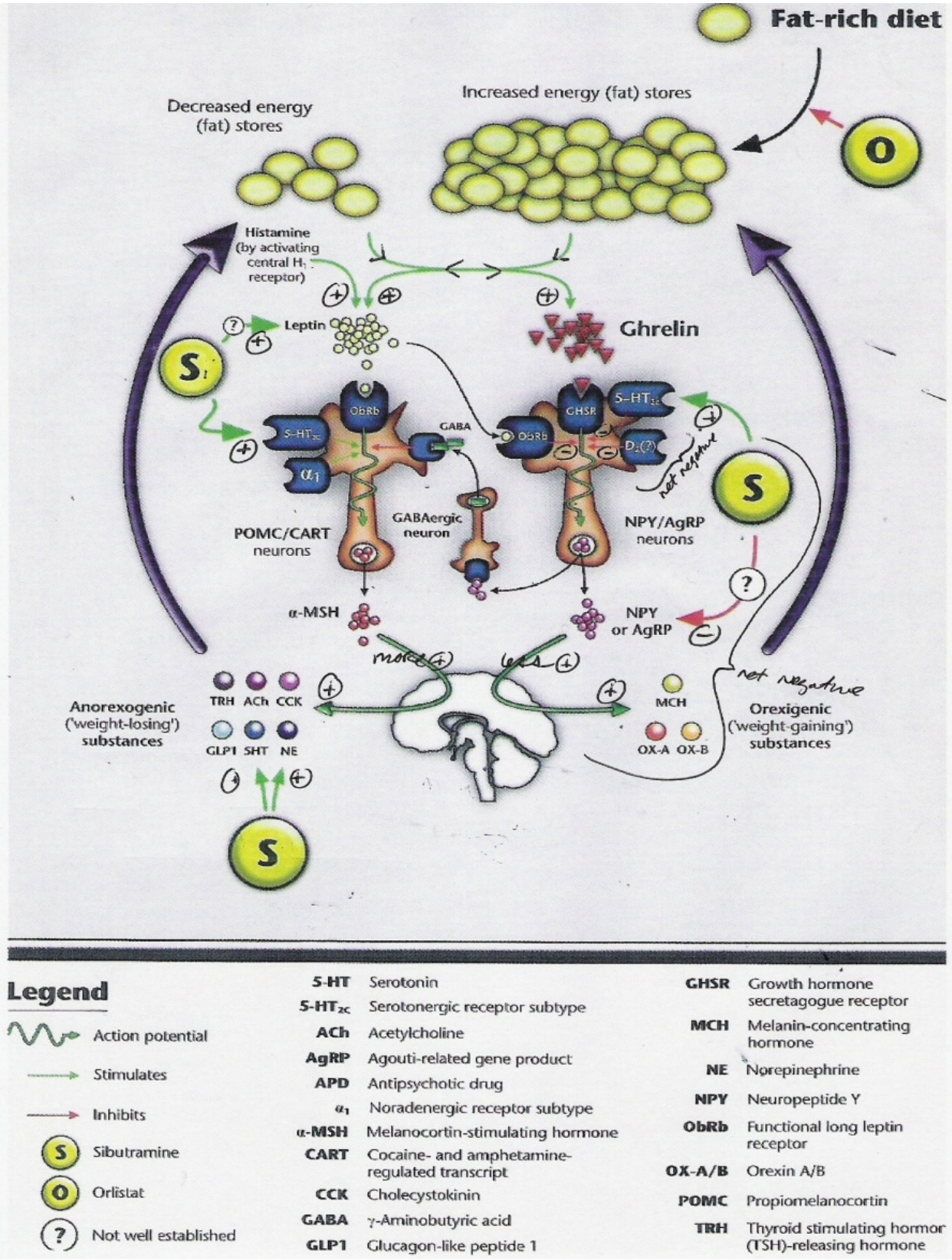
Managing Side Effects

Weight



Legend

- Action potential
- Stimulates
- Inhibits
- S — Sibutramine
- O — Orlistat
- ? — Not well established

5-HT	Serotonin
5-HT_{2C}	Serotonergic receptor subtype
ACh	Acetylcholine
AgRP	Agouti-related gene product
APD	Antipsychotic drug
α_1	Noradenergic receptor subtype
α-MSH	Melanocortin-stimulating hormone
CART	Cocaine- and amphetamine-regulated transcript
CCK	Cholecystokinin
GABA	γ-Aminobutyric acid
GLP1	Glucagon-like peptide 1
GHSR	Growth hormone secretagogue receptor
MCH	Melanin-concentrating hormone
NE	Norepinephrine
NPY	Neuropeptide Y
ObRb	Functional long leptin receptor
OX-A/B	Orexin A/B
POMC	Propiomelanocortin
TRH	Thyroid stimulating hormone (TSH)-releasing hormone

- Stimulants
- Dopamine agonists
  - See amantadine above
- Topamax
  - Multiple positive RCT's; average loss in one study 5 lbs
  - 15% risk of paresthesias (numbing/tingling in extremities)
  - McElroy et al, 2007: RCT Topamax vs. silbutramine in patients with bipolar disorder (and weight gain associated with medications); average weight loss 6 lbs with Topamax vs. 9 lbs with silbutramine; discontinuation rates were the same (>50%)
- Metformin
  - General
    - Biguanide used to treat diabetes
    - Reduces glucose production, increases sensitivity to insulin, increases glucose uptake by skeletal muscle
    - An antihyperglycemic agent; if used alone, it does not cause hypoglycemia
    - Beneficial effect on serum lipids
    - Reduction in weight in patients with type II diabetes
  - Evidence in psychiatry
    - Randomized, placebo-controlled trial of metformin for the treatment of weight gain induced by antipsychotic medication in young people with autism spectrum disorder: open-label extension (Handen et al, 2017)
      - 16 week open-label extension of the study below (Anagnostou et el, 2016)
      - Those who took placebo in initial study lost weight on metformin
      - Those who took metformin in initial study maintained weight loss
      - Side effects
        - Abdominal pain, upper abdominal pain, dyspepsia or discomfort 13-39%
        - Constipation 0-9%
        - Diarrhea 37-61%
        - Flatulence 7-18%
        - Nausea or vomiting 20-43%
        - Fatigue 13-21%
        - Irritability 17-31%
        - Confusion 3-5%
        - Dizziness 3-7%
        - Headache 17-36%
        - Somnolence 0-9%
        - Tremor 3-9%
        - Aggression 3-18%
        - Anger 0-14%
        - Anxiety 4-14%
        - Insomnia 6-25%
        - Cough 7-23%
        - Rash 3-14%
    - Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder: A Randomized Clinical Trial; Evdokia Anagnostou, Michael G Aman, Benjamin L Handen, Kevin B Sanders, Amy Shui, Jill A Hollway, Jessica Brian, L Eugene Arnold, Lucia Capano, Jessica A Hellings, Eric Butter, Deepali Mankad, Rameshwari Tumuluru, Jessica Kettel, Cassandra R Newsom, Stasia Hadjiyannakis, Naomi Peleg, Dina Odrobina, Sarah McAuliffe-Bellin, Pearl Zakroysky, Sarah Marler, Alexis Wagner, Taylor Wong, Eric A Macklin, Jeremy Veenstra-VanderWeele; *JAMA Psychiatry 2016 August 24*
      - **Importance:** Atypical antipsychotic medications are indicated for the treatment of irritability and agitation symptoms in children with autism spectrum disorder (ASD). Unfortunately, these

medications are associated with weight gain and metabolic complications that are especially troubling in children and with long-term use.
        - **Objective:** To evaluate the efficacy of metformin for weight gain associated with atypical antipsychotic medications in children and adolescents with ASD (defined in the protocol as DSM-IV diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified), aged 6 to 17 years.
        - **Design, Setting, and Participants:** A 16-week, double-blind, placebo-controlled, randomized clinical trial was conducted at 4 centers in Toronto, Ontario, Canada; Columbus, Ohio; Pittsburgh, Pennsylvania; and Nashville, Tennessee. In all, 209 potential participants were screened by telephone, 69 individuals provided consent, and 61 participants were randomized to receive metformin or placebo between April 26, 2013, and June 24, 2015.
        - **Interventions:** Metformin or matching placebo titrated up to 500 mg twice daily for children aged 6 to 9 years and 850 mg twice daily for those 10 to 17 years.
        - **Main Outcomes and Measures:** The primary outcome measure was change in body mass index (BMI) z score during 16 weeks of treatment. Secondary outcomes included changes in additional body composition and metabolic variables. Safety, tolerability, and efficacy analyses all used a modified intent-to-treat sample comprising all participants who received at least 1 dose of medication.
        - **Results:** Of the 61 randomized participants, 60 participants initiated treatment (45 [75%] male; mean [SD] age, 12.8 [2.7] years). Metformin reduced BMI z scores from baseline to week 16 significantly more than placebo (difference in 16-week change scores vs placebo, -0.10 [95% CI, -0.16 to -0.04]; P = .003). Statistically significant improvements were also noted in secondary body composition measures (raw BMI, -0.95 [95% CI, -1.46 to -0.45] and raw weight, -2.73 [95% CI, -4.04 to -1.43]) but not in metabolic variables. Overall, metformin was well tolerated. Five participants in the metformin group discontinued treatment owing to adverse events (agitation, 4; sedation, 1). Participants receiving metformin vs placebo experienced gastrointestinal adverse events during a significantly higher percentage of treatment days (25.1% vs 6.8%; P = .005).
        - **Conclusions and Relevance:** Metformin may be effective in decreasing weight gain associated with atypical antipsychotic use and is well tolerated by children and adolescents with ASD.
    - Jarskog et al, 2013: double blind, RCT in overweight outpatients with schizophrenia or schizoaffective disorder, 16 week study, -6.6 pounds with metformin vs. -2.2 pounds with placebo; also: improved BMI, triglycerides, and hemoglobin A1c; improvements significant by 4 weeks and improving each week through 16 weeks
    - Correll et al, 2013 (editorial)
    - Hoffman, et al, 2012: more helpful than amantadine at minimizing weight gain from Zyprexa (1.4 pound weight gain with metformin added to Zyprexa vs. 6 pound weight gain with Zyprexa alone)
    - Baptista et al, 2007: metformin for Zyprexa-related weight gain—3 pound weight loss and a small decrease in BMI vs. no change with placebo
    - Klein et al, 2006: 16 week double blind, placebo-controlled trial in 39 youth initiating atypical antipsychotic therapy whose weight had increased by more than 10% during less than 1 year of treatment: weight stabilized in those on metformin (which, given normal growth in youth, resulted in a relative weight loss) while those on placebo continued to gain ~0.68 pound per week
- Doses studied are often 1000-1500 mg/day, divided 2-3 times-a-day (maximum daily dose 2000 mg), taken with meals to minimize gastrointestinal side effects; in kids, 850 mg two times-a-day is a common dose
- Available in 500 mg, 850 mg, and 1000 mg pills and in 750 mg extended release XR) pills
- Should be used with caution in those with kidney problems, congestive heart failure, liver disease, or excessive alcohol consumption
- Side effects:
    - Diarrhea
    - Stomach upset
    - Risk of lactic acidosis
        - 3 cases of lactic acidosis for every 100,000 patients who take the medication for a year

        - Increased risk in those with kidney problems, congestive heart failure, liver disease, or excessive alcohol consumption
        - If present it is fatal in 50% of cases
        - Can occur in diabetes, unrelated to or in the absence of metformin
        - Defined by elevated blood lactic acid, decreased blood pH, electrolyte disturbances, and increased lactate
    - Meridia
    - Chromium
    - Biotin
    - Carnitine

FATIGUE/NUMBNESS/LACK OF ENERGY AND MOTIVATION

- Bromocriptine 2.5-5 mg/day
- Pramiprexole
- Ropirinole
- Amantadine
- ?Abilify 2.5-15 mg/day
- Wellbutrin
- Stimulants
- **Provigil** (modafinil)
  - In US since 1998, in France for several years prior
  - Approvable letter (to treat ADHD) from FDA in 2005 but RELEASE DELAYED DUE TO RISKS OF DANGEROUS RASH AND OTHER RISKS (see below)
  - Promotes wakefulness, focus
  - No evidence of abuse; no evidence of withdrawal
  - Mechanism:
    - it increases histamine in the cortex (by increasing firing of histaminergic neurons in the hypothalamus)
    - it's actions appear to be dependent on alpha 1b adrenergic receptors as well as dopamine reuptake transporters.
    - also activates orexin neurons in the hypothalamus (though this may be result of wakefulness)
    - also appears to increase serotonin, dopamine, and norepinephrine release in the cortex.
    - releases dopamine in the limbic cortex as well but to a more limited extent (and thus there is no apparent abuse liability)
    - it may block GABA action
  - Evidence of efficacy
    - Children
      - Greenhill, Biederman, et al, 5/06, RCT, DB, placebo-controlled study of modafinil film-coated tablets in children with ADHD; 9-week study; 200 children ages 7-17; dose range 170-425 mg/day
        - 52% response rate versus 18% with placebo
        - Side effects
          - Insomnia 28% (vs 7% with placebo)
          - Headache 22% (vs 9% with placebo)
          - Decreased appetite 18% (vs 3% with placebo)
          - Abdominal pain 12% (vs 4% with placebo)) or nausea or diarrhea
          - Weight loss 5% (vs 1% with placebo)
          - Nervousness or anxiety
          - Not associated with drug high or withdrawal or tolerance.
          - No effect on sleep architecture.
          - Rash (in youth)
            - 12/933 (1.3%) with likely definitive dangerous rash (erythema multiforme or Stevens Johnson syndrome (SJS)) OR early prodromal rash OR suggestive dangerous rash, 1 of which was thought to be definitive SJS (though child was on an antibiotic medication as well).
            - No reports of SJS among 36,000 children prescribed the drug off-label between 2002-2005.
          - Rates similar (for medication vs. placebo) for infection, cough, pharyngitis, rhinitis, vomiting, emotional lability, nervousness, accidental injury, fever, tiredness, nausea
      - Side effects in the one-year open-label continuation phase of the studies in the Biederman review:
        - Insomnia 27% (vs. 4% with placebo)
        - Headache 20% (vs. 13% with placebo)
        - Decreased appetite 16% (vs. 3% with placebo)
        - Abdominal pain 10% (vs. 3-8% with placebo)
        - Nervousness 5% (vs. 4% with placebo)

        - No withdrawal or rebound effects
        - Mild decreases in weight from baseline for up to 3 months, then an increase in weight of 0.7 kg by month 12.
        - No significant changes in vital signs, weight, or height.
    - Biederman review of 3 randomized trials in youth aged 6-17 yo with ADHD (?overlaps with specific studies below)
        - 423 subjects receiving Provigil, 215 receiving placebo
        - Two nine-week studies, doses of 170-425 mg
        - One seven-week study, 340 mg/day
        - Safe and effective
    - 2005: multi-site, double-blind, placebo-controlled study in pediatric ADHD suggests efficacy.
    - Biederman, 2003 (partially funded by Cephalon): four week study of 248 children with ADHD demonstrated safety and efficacy
    - Swanson, 2003: four week study of 48 children demonstrated safety and efficacy
    - Rugino, 2003: positive safety and efficacy
    - Rugino, 2001: positive safety and efficacy comparable to Dexedrine
    - Fletcher, 2000: positive single site controlled study
    - 2000: failed multisite controlled trial
- Adults
    - ADHD
        - Turner, 2004: positive
        - Taylor, 2000: positive; equivalent in efficacy to Dexedrine
        - Overall potency in ADHD appears less than stimulants, Strattera, or atypical antipsychotics.
    - Depression
        - Promotes wakefulness in patients with depression
    - Cognitive side effects of chemotherapy
    - Schizophrenia
        - Pierre et al, 2007: improved global symptoms and functioning but not negative symptoms specifically
        - Improved cognitive function in schizophrenia (mixed results in Hunter et al, 2006)
- Side effects and risks in adults
    - headache
    - infrequent insomnia
    - infrequent anxiety
    - abdominal pain
    - loss of appetite
    - cough, fever
    - runny nose
- Pharmacology
    - induces 3A4 enzyme; can theoretically lower birth control
    - half-life 15 hours, time to max 2-4 hours
    - rebound sleepiness is minimal
- Nuvigil (armodafinil)
    - Single-isomer formulation of Provigil
    - Has longer half-life than Provigil
    - 150-250 mg/day
    - four multicenter double-blind studies demonstrating safety and efficacy (in sleep apnea), one of which:
        - 196 patients (aged 18-65 years) randomized to receive armodafinil 150 mg (n = 65), armodafinil 250 mg (n = 67), or placebo (n = 64) once daily for 12 weeks
        - statistically significant improvements in memory, attention, and fatigue
        - most common adverse events in patients receiving armodafinil were headache, nausea, and dizziness
    - Side effects
        - Headache 15% at 150 mg and 21% at 250 mg and in 7-8% of placebo

- Nausea
- Insomnia
- Dizziness
- Anxiety

POOR CONCENTRATION

- **Stimulants**
- **Wellbutrin**
- **Atypical antipsychotics** (they block dopamine receptors but increase dopaminergic function in the frontal cortex via blockade of serotonin 2a receptors).
- **Strattera**
- ?**Provigil**?
- **Nicotine** patch
- **Dasotraline:** dopamine and norepinephrine reuptake inhibitor
- **Centanafidine:** triple reuptake inhibitor
- **Edivoxetine:** norepinephrine reuptake inhibitor
- **Mazindol:** dopamine and norepinephrine reuptake inhibitor
- **SPN810 (molindone):** D2 blocker
- **SPN812:** norepinephrine reuptake inhibitor
- **AZD3480** (aka TC-1734)
    - Partial nicotinic agonist
    - Highly selective for alpha4/beta2 nicotinic receptors
    - Studied in 24 non-smoking adults with ADHD (5 mg/day vs. 50 mg/day vs. placebo); (2013)
        - 50 mg/day > placebo
        - Benefit was similar to average benefit from stimulants
        - More effective than non-stimulant treatments for ADHD
- **Rhodiola rosea**--do not take with consultation by psychiatrist
    - may increase norepinephrine, dopamine, and serotonin; boosts transport of tryptophan and 5-HTP into brain; may inhibit breakdown of serotonin (by blocking COMT)
    - may boost brain ATP and creatine
    - may help concentration, memory, thinking, energy; may have antidepressant efficacy (data minimal)
    - dose range: 100-600 mg/day
        - for cognition: 150 mg/d or 150 mg twice-a-day
        - for depression: 300-450 mg/d (split twice-a-day)
        - give 20 minutes before meals; start 150 mg in the AM and increase by 150 mg every 7 days
    - side effects:
        - excess stimulation
        - vivid dreams
        - rare sedation
        - rare hypersexuality
        - rare agitation with increased blood pressure
        - mild gastrointestinal distress
        - risk of serotonin syndrome
    - brands: Rosavin—www.2ameriden.com; Arctic root—www.adaptogen.com

INSOMNIA

- General
  - The circadian (daily) alerting system increases in the AM (e.g., 9 am) throughout the day, with a transient plummet around 3 pm, and a slow decrease from around 5-7 pm to the nadir in the middle of the night
  - The circadian sleep system increases throughout the day as well, peaking at 10-12 pm, reaching a nadir in the morning (e.g., 9 AM).
  - The ventrolateral preoptic (VLPO) area of the hypothalamus appears responsible for the control of deep sleep; it is an area rich in GABA receptors. It's activity is tightly coordinated with the raphe nucleus (the main center of serotonergic neurons) and the locus ceuruleus (the main center of noradrenergic neurons)
  - The suprachiasmatic nucleus (SCN) in the hypothalamus appears to be responsible for maintaining circadian rhythyms; it is rich with melatonin receptors.
  - Prevalence of persistent insomnia in adults: 9-18%
  - Hyperarousal in Clients with Insomnia
    - Overactivation of hypothalamic-pituitary axis (HPA; the cortisol stress response system) and higher cortisol levels
    - Overactivation of the sympathetic nervous system
    - Increased metabolic rate
    - Increased EEG arousal and brain metabolism
    - Evidence of increased cognitive arousal during sleep
    - Functional neuroimaging changes
    - The circadian rhythm of body temperature is often delayed so that the daily peak in adults with insomnia occurs 2-4 hours later than the peak in folks without insomnia.
- Sleep Hygeine
  - Do
    - Awaken same time every AM
    - Increase exposure to bright light during the day
    - Establish daily activity routine
    - Exercise regularly in the AM and/or afternoon
    - Set aside a worry time
    - Establish a comfortable sleep environment
    - Maintain regular bedtime and wake time
    - Do something relaxing prior to bedtime
    - Use bed for sleep and intimacy only (or possibly reading)
    - Try a warm bath
    - No media within 1 hour or more of sleep time, including phones, iPads, etc
    - Cognitive behavioral therapy
      - Stimulus control
      - Sleep restriction therapy
      - Sleep education and hygiene
      - Cognitive therapy
      - Arousal reduction/relaxation training
    - With kids, above and:
      - Graduated extinction
      - Positive bedtime routines
      - Scheduled awakenings
      - Bedtime fading
      - Bedtime pass
      - Monster spray
      - Reinforcement/sleep fairy
  - Avoid
    - Naps
    - Alcohol
    - Caffeine, nicotine, and other stimulants
    - Exposure to bright light during the night

        - Exercise within 3 hours of bedtime
        - Heave meals or drinking within 3 hours of bedtime
        - Using your bed for things other than sleep (or sex)
        - Browsing internet, doing emails/work in bed
        - Napping (unless a shift worker)
        - Watching the clock
        - Trying to sleep (get out of bed if not sleeping after 20 minutes)
        - Noise
        - Excessive heat/cold in room
- Psychological and Behavioral Treatments
    - Stimulus control therapy (getting out of bed if not sleeping in 20 minutes)
    - Relaxation therapies (biofeedback, guided imagery, progressive muscle relaxation)
    - Restriction of time in bed (to time actually asleep and increase as sleep efficiency improves)
    - Cognitive therapy (to dispel unrealistic and exaggerated notions about sleep)
    - Paradoxical intention (try to stay awake)
    - Sleep hygiene education
    - Cognitive behavioral therapy (combination of above)
- Melatonergic agents
    - General
        - Trials up to 6 months have not shown significant changes in safety parameters
        - Side effects:
            - Next day sedation
            - Vivid dreams/nightmares
            - Rise in prolactin
            - Decrease in FSH
            - No weight gain
    - Rozerem (ramelteon, TAK-375)
        - Selective melatonin-1 and 2 receptor agonist (which are located only in the suprachiasmatic nucleus (SCN) in the brain which serves as the brain's clock); ramelteon is more specific to melatonin-1 and 2 receptors than the natural hormone melatonin; no measurable affinity to other receptors.
        - By activating the melatonin-1 and 2 receptors in the SCN, ramelteon dampens the alerting signal generated by the SCN as an individual's need for sleep increases
        - discovered in Japan in 1996; > 100 pre-clinical studies; 43 clinical studies involving > 4,200 patients.
        - FDA-approved 2005 for insomnia characterized by difficulty with sleep onset; approved for long-term use; available 8/05
        - Recommended dose is 8 mg taken 30 min prior to bedtime; range 4-64 mg/pm; half-life of 1.2 hours; t-max 0.3 hours; high fat foods will delay absorption, 1A2 metabolism; 8 mg tabs
        - Not directly sedating
        - Side effects and risks
            - no adverse effects on alertness or ability to concentrate in the morning
            - minimal side effects (rates of headache same as placebo, more likely to cause sleepiness than placebo)
            - dizziness
            - fatigue
            - ?increased prolactin/decreased testosterone?
            - was safe and effective in geriatric clients (with no more likelihood of side effects than with younger adults)
            - safe and effective in clients with COPD and sleep apnea
            - associated with decreased testosterone levels and increased prolactin levels in adults (which could affect menstrual cycles, sexual functioning, lactation)
            - avoid with fluvoxamine (due to decreased metabolism of ramelteon)
    - Melatonin
        - 17 studies involving 284 subjects; 15 studies in insomnia

- Average reduction in sleep latency: 4 minutes; average increase in sleep efficiency: 2.2%; average increase in total sleep time: 12.8 minutes.
- Recent short-term study in children with ADHD positive
- Take roughly 2-3 hours before sleep when possible
- Plasma peak level about 1 hour post-dosage
- Minimal effects on sleep architecture
- Half-life is about 45 minutes
- Dose range 0.2 -10 mg/pm (more common range 3-10 mg/pm, 2-3 hours before desired sleep time)
- Pediatric studies
    - Van Gailswick, 2010
        - Advanced sleep onset by about 1 hour
        - Increased sleep onset latency by about 35 minutes
    - Melatonin in ADHD plus autism spectrum disorder (Smits, 2001, 2003; Van der Heljden, et al, 2006, 2007; Weiss, 2006; Nir, et al, 1996; Kulman, et al, 2000; Pasivronan, 2003, 2004; Gerstang, 2006; Giannotti, et al, 2006; Andersen, 2008; Wasdell, 2006; Bream, 2009; Wright 2011
        - Shortens sleep onset latency
        - 1-6 mg/day
- Side effects
    - Headache
    - Abdominal cramps
    - Headache
    - Dizziness
    - Irritability
    - Vasoconstriction
    - Low heart rate/hypotension
    - Pruritis
    -
    - No weight gain (may protect against "metabolic syndrome")
    - May have beneficial effects on thrombus growth, cholesterol levels, and blood pressure
- Risks (which are not fully studied so not certain)
    - Inhibits secretion of GnRH/LH/FSH
    - May suppress the hypothalamic/pituitary/gonadal axis and could trigger precocious puberty upon d/c
    - May cause gonadal suppression
    - May cause infertility
    - ?reduced seizure threshold
    - Suspected risks of myocardial infarction, or stroke, but not at all clear
    - Evidence of protecting against and possibly increasing risk of cancer
- Tasimelteon
    - MT1 and MT2 agonist
- Piromelatine
    - MT 1 and MT2 agonist
    - 5HT1a and 5HT1D agonist
    - 5HT2B antagonist
- Agomelatine
    - MT1 and MT2 agonist
    - 5HT2C antagonist
    - Also treats major depression
    - Pecenak et al, 2013
        - Open label, 8 week, multicenter, 111 patients with moderate to severe depression
        - 25-50 mg/day
        - Safe and effective (with no hepatotoxicity (though this risk is reported elsewhere)

        - 14.1% responded in first 233k
        - 74.5% responded by study completion
    - Enol-3-IPA: melatonin agonist/lipocortins synthesis antagonist
    - PD66735 (LY-156735): synthetic melatonin
- Non-benzodiazepine GABA-receptor agonists
    - General
        - Side effects: drowsiness, dizziness; rare withdrawal symptoms: insomnia, muscle cramps, seizures
        - Take on empty stomach for faster onset
        - Dose about 50% lower in women
    - Ambien (zolpidem)
        - 2.5-10 mg/PM; Half-life 2-4 hours
        - Addictive at doses above 10 mg; 36 cases in world 1966-2002 (Hajak)
        - Tabs: 5 mg and 10 mg; now comes generic
        - 2011: Sublimox, orally dissolving tablet of zolpidem, approved in Canada
    - Ambien CR
        - modified-release formulation that incorporates both immediate- and controlled-release preparations to improve sleep maintenance while maintaining the same elimination half-life as the standard preparation
        - with higher blood level 3-6 hours postdose to maximize middle of the night coverage while minimizing morning sedation)
        - 6.25 and 12.5 mg tablets.
    - Sonata (zaleplon)
        - Half-life1-2 hours
        - Short half-life allows middle of the night dosing
        - Dose range 10-20 mg/night
        - Extended release form in progress
    - Lunesta (eszoplicone)
        - Enantiomer of zoplicone which is available in Europe
        - 22 cases of dependence 1966-2002 (Hajak)
        - Studied for up to 6 months in 788 patients. A total of 24 clinical studies involving more than 2,700 adult patients; more than 60 pre-clinical studies; some research up to 12 months use.
        - Dose range 1-2 mg/pm for falling asleep, 2-3 mg for staying asleep
        - No evidence of tolerance
        - Adverse effects include unpleasant taste and headache
        - Available in 1-, 2-, and 3-mg tablets.
    - Indiplon
        - under investigation
        - IR form (1-1.5 hour elimination half-life allowing middle of the night dosing): 20 mg/pm
        - MR form: 30 mg/pm. GABA-A receptor modulator
        - No evidence of next-day residual effects
        - No evidence of withdrawal or rebound upon abrupt discontinuation.
- Other GABAergic agents
    - Suvorexant
        - Targets orexin system
        - 30-40 mg/pm; 2030 patients with primary insomnia
        - Sleepiness and headache most common side effects
        - Next day sleepiness 10% (vs 3% in placebo)
    - Gaboxadol
    - Gabatril (tiagabine)
    - Neurontin (gabapentin)
    - Depakote
    - Vigabatrin—inhibits GABA transaminase
    - Topamax—acts on GABA at ion-gated channels
    - Pregabilin (Lyrica)
    - Ocinaplon , GABAa receptor modulator

- Theanine
  - Amino acid
  - Lyon, et al, 2011
    - 93 boys with ADHD (some treated with stimulants, some not)
    - 200 mg twice-a-day
    - Sleep efficiency significantly improved
    - Somewhat improved likelihood of awakening after sleep onset
    - No change in sleep onset latency or total sleep time
  - Also, in schizophrenia
    - 400 mg/day
    - improves negative symptoms of schizophrenia and improves anxiety
    - increases inhibitory neurotransmitters
    - modulates 5-HTP and dopamine
    - increases BDNF
    - may be neuroprotective
- Valerian
  - Extract of Valeriana officinalis
  - Several potentially active components, including valerinic acid, other sesquiterpenes, valepotriates
  - May reduce sleep latency and improve total sleep time
  - Extracts of 2-3 mg taken 1-3 times-a-day in a tincture or tea
  - Side effects
    - Sedation, drowsiness
    - Unsteadiness
    - Dizziness
    - Overdoses: cramping, tremor, unsteadiness, confusion
  - Mechanisms of action of valerenic acid (derived from valerian root):
    - inhibition of GABA catabolism
    - binds to GABA receptors
    - 5HT1a receptor activity
    - actions on adenosine receptors
- Serotonin 2a blockers
  - Trazodone
    - Inhibits serotonin reuptake
    - Decreases adrenergic sensitivity
    - Antihistamine side effects → sedative properties
    - Onset of action 30-120 minutes
    - 25-100 mg 30-120 minutes before bedtime
    - Peak level reached within 2 hours
    - Metabolized by 2D6
    - Half-life of 7-8 hours (biphasic: 3-6 hours and 5-9 hours)
    - →
      - improved sleep continuity
      - increases slow wave sleep
      - decreased REM sleep
    - Side effects
      - Sedation
      - Orthostatic hypotension
      - Fast heart rate
      - Dry mouth
      - Constipation
      - Blurred vision
      - Priapism in 1/6000 men
      - Worse anxiety if combined with a 2D6 inhibitor (due to build-up of mCPP)
  - Remeron

- Alpha-2agonist
- 5HT2 antagonist
- Sedating at 7.5-15 mg/day
- Improved sleep onset latency and less waking up after sleep onset
- Increase sleep duration
- Esmirtazepine maleate (Org-50081)
- Doxepin
  - Histamine-1 antagonist
  - Half-lie 15 hours (31 hours for metabolite)
  - Dose: 3-6 mg
  - Side effects: somnolence, nausea
  - Contraindicated in severe urinary retention, narrow angle glaucoma, MAOI within previous 2 weeks
- Amitriptyline
- Seroquel
  - 25-100 mg improves sleep induction and continuity and increases total sleep time, sleep efficiency, % stage 2 sleep, and subjective sleep quality
- Eplivanserin (SR 46349): increases slow wave sleep
- M-100907
- Clonidine (especially for PTSD-related sleep problems)
  - Rapid absorption
  - Onset within 1 hour
  - Peak effects 2-4 hours
  - →
    - increase in slow wave sleep
    - decrease in REM sleep
  - Pediatric studies (data not high quality)
    - Prince, et al, 1996
      - improvement
      - adverse effects in 31%
    - Wilens, et al, 1995
      - rapid onset (30 minutes)
      - all night duration
      - improvement
      - no adverse effects
    - Ming, et al, 2008
      - parent reported improvements
  - Side effects
    - hypotension (rebound hypertension)
    - anticholinergic
    - irritability
    - dysphoria
    - tolerance
    - parasomnias
    - risk of overdose
- Prazosin (especially for PTSD-related sleep problems)

- Other agents
  - Tricyclic antidepressants
  - ?Buspar
  - Prazosin
    - Helps reduce PTSD-related nightmares
    - Raskind et al, 2013: 15 week, RCT, up to maximum dose of 5 mg/midmorning and 20 mg/pm; average dose 15.6 mg; effective; blood pressure did not change
  - Suvorexant

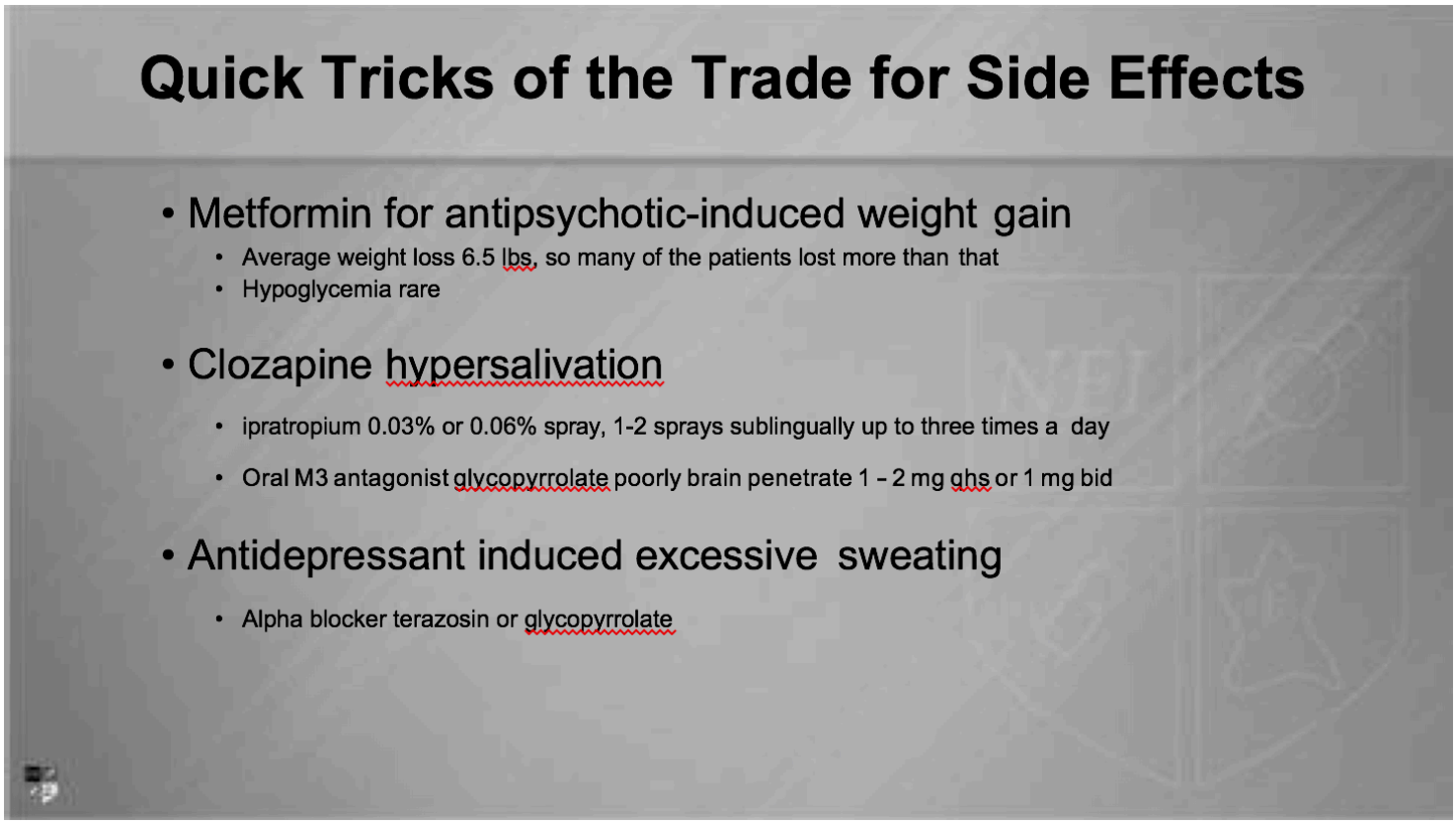
Nausea

- Remeron
- Zofran (ondansetron); very expensive
- Anzemer (dolasteron); very expensive

Hypoactive Sexual Desire Disorder

- Flibanserin
    - 5HT1a post-synaptic agonist
    - 5HT2a antagonist
    - 100 mg/HS
    - FDA-approved for generalized, acquired HSDD in premenopausal women
    - 50% of women respond
    - Stop if no effect after 8 weeks
    - Requires REMS registration at www.addyirems.com
    - Safe and effective in post-menopausal women, but not yet approved
    - Adverse effects
        - General:
            - 67% with adverse effects vs. 56% placebo
            - 7% severe adverse effects vs. 5% placebo
            - 13% discontinuation due to adverse effects vs. 6% placebo
        - Specific

• Dizziness	11.4% flib	2.2% plac
• Somnolence	11.2%	3.1%
• Nausea	10.4%	3.7%
• Fatigue	9.2%	5%
• Insomnia	4.9%	2.4%
• Dry mouth	2.4%	0.9%



Quick Tricks of the Trade for Side Effects

- Antipsychotic induced akathisia
  - Propranolol 20 mg bid day one, then 40 mg bid, up to 360 mg/day if tolerated
  - NOT cardioselective beta blockers like metoprolol
  - NOT anticholinergics
  - Secret weapons are 5HT2A antagonists like mirtazapine and cyproheptadine

Quick Tricks of the Trade for Side Effects

- Lithium induced diabetes insipidus
  - First reduce dose if possible and/or change to single bedtime dose
  - Next add KCl 20 mEq/day or amiloride 10 mg bid
  - Next cautiously add hydrochlorothiazide 25 mg once or twice a day
  - Then dry amiloride plus hydrochlorothiazide
  - Finally, consider indomethacin 50 mg three times a day