Overview of Anxiety and Depression

Major Depressive Disorder (MDD)
- American Psychiatric Association definition:
  - Minimum of five depressive symptoms (depressed mood, having a loss of interest/pleasure in hobbies/activities, significant changes in appetite, weight, sleep, psychomotor activity, loss of energy or fatigue, feelings or worthlessness, diminished ability to concentrate, or suicidal ideation)
  - Symptoms occur daily for at least two weeks, and are newly presented/clearly worsened prior to the onset of the episode
  - Depressive episodes must significantly impair social or occupational functioning and must not be attributed to substance abuse or better explained by other psychological disorders (schizophrenia, bipolar, etc)
- MDD affects ~17.3M people in the US annually (7.1% of population)
- Treatment is up to 80% effective yet only 33% of depressed people seek/receive treatment

Anxiety Disorders (AD)
- Feelings of intense irrational fear/panic that are difficult to control, coupled with dizziness, trembling, nausea, sweat, rapid heartbeat
- Diagnosis: Three or more symptoms (restlessness, fatigue, inability to concentrate, irritability, muscle tension, sleep disturbance) majority of days for three months
- Most common mental disorder, affects nearly 30% of adults at some point in their lives. ADs often progress into depression
- Variants of anxiety disorder:
  - panic disorder, obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), phobias, and general anxiety disorder (GAD)
- Treatment often includes both talk therapy and medication (anxiolytics)

Included in this GM:
- Overview of anxiety and depression
- Mechanism of action of selected drugs
- Brief history of antidepressants/anxiolytics
- Major drug classes in this field
- Atypical antidepressants
- Non-pharmaceutical treatments
- Investigational drugs

Not included in GM:
- Complete summary of all depression/anxiety treatments
- Other antipsychotics (for schizophrenia, bipolar, etc.)
- In-depth coverage of biology/mechanism of action for each drug
- Medical advice or diagnosis...

Glossary of Abbreviations:
- MDD: Major Depressive Disorder
- TRD: Treatment Resistant Depression
- (G)AD: (General) Anxiety Disorder
- GABA: gamma amino butyric acid
- MAOI: Monoamine Oxidase Inhibitor
- TCA: Tricyclic Antidepressant
- BDZ: Benzodiazepines
- SSRI: Selective Serotonin Reuptake Inhibitor
- SNRI: Serotonin/Norepinephrine Reuptake Inhibitor

Proposed Mechanisms of Action for Antidepressants/Anxiolytics

Antidepressants (also can act as anxiolytics):
- MAOIs: inhibits monoamine oxidase (MAO) enzyme, which degrades monoamine neurotransmitters (structures above), increasing available serotonin, norepinephrine, and dopamine
- TCAs: Non-specifically prevents reuptake of neurotransmitters
- SSRIss/SNRIs: Prevent reuptake of specific neurotransmitters

Anxiolytics:
- BDZs: (anxiolytic) act as a sedative; enhance binding at gamma aminobutyric acid (GABA) receptor, increasing function of GABA and slowing brain function
Prior to the 1960s, the concept of “biological psychiatry” was non-existent. Since pre-WWII, psychoanalysis had little to do with psychiatry (as practiced in mental institutions). Freudian mentality: mental illness could be healed by insight into previous distress that caused it, eschewing the use of drugs. Psychiatrists used drugs as means to sedate and restrain patients.

**Amphetamine**: the first antidepressant? Although not developed as an antidepressant, amphetamine was used as such in 1930s through 1950s

**Condensed timeline** (see Amphetamines GM, Harwood 2020)

1927: Gordon Alles reports “feeling of well-being” from amphetamine
1935: Benzedrine reported to enhance “pep” and “energy-feeling”
1936: Market with neurologists and psychiatrists increased in part due to studies of psychiatrist Abraham Myerson (Professor of Clin. Psych. Harvard Medical School).
   - Myerson considered an authority on depression, author of The Nervous Housewife (1920) and When Life Loses Its Zest (1925)
   - Referred to depression as ‘anhedonia’ (lack of pleasure)
   - Myerson’s treatment regimen: wholesome diet, moderate exercise, no heavy introspection, break insomnia patterns with sedatives
1937: Clinical trial for amphetamine. Neurasthenics (depressed patients) improved but anxious patients became more anxious. Benzedrine at first is only approved or use in psychiatric institutions
1939: Benzedrine approved for “mild depression”
1940s: Marketed as anti-depressant
1960s: Tricyclic antidepressants (TCAs) reinforced biological understanding and drug treatment of minor psychiatric conditions, concept of “biological psychiatry” is born

Rasmussen’s Journal of the History of Medicine, 2006
Antidepressant and Anxiolytic Drugs

Monoamine Oxidase Inhibitors continued

1. SOCl2
2. NaN3
3. HCl

Vardanyan & Hruby’s *Synthesis of Essential Drugs* Name step 2?

1. Grignard
2. HCl

1st Generation TCAs: tertiary amine chain inhibit serotonin and norepinephrine reuptake
2nd Generation TCAs: secondary amine chain selective for inhibition of norepinephrine reuptake
- Dangers: cause arrhythmia/cardiac arrest at high doses
- Largely replaced by SSRIs


Tricyclic Antidepressants (TCAs)
- Nonselective inhibitors of neurotransmitter reuptake
- Affect norepinephrine and serotonin receptors in brain, but also interact with other receptor sites (histamine, acetylcholine, and epinephrine) leading to side effects such as dry mouth, disorientation/dizziness, irregular heart rate
- Serendipitous discovery of TCAs from antischizophrenic activity of chlorpromazine
- Explored by Swiss psychiatrist Roland Kuhn in 1950s at Ciba-Geigy
- Amine side chain key to activity

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See GPCR Drug GM, Barton 2019

- imipramine only available antidepressant for years following withdrawal of iproniazid
- Drawback: numerous side effects and narrow therapeutic window (can lead to overdose)
Antidepressant and Anxiolytic Drugs

Benzodiazepines (BDZs)
- BDZs act as modulators on GABA\(_A\) receptor
- GABA: inhibitory neurotransmitter, blocks brain signals, decreases CNS activity
- Binding of GABA to receptor produces anxiolytic effect
- Side effects: drowsiness, confusion, dizziness
- High risk of abuse and dependency

Antidepressant and Anxiolytic Drugs

Azapirones
- Serotonin receptor agonist
- No tendency for addiction/abuse, but long onset of action
- Suggested combination therapy: azapirone and BDZ
- Most famous in this class of anxiolytics: buspirone (BuSpar) 1986 BMS

Route from original patent

Selective Serotonin Reuptake Inhibitors (SSRI)
- Used for treatment of simultaneous depression and anxiety
- First antidepressant drug class rationally designed to target one specific neurotransmitter
- Safe alternative to TCAs, BDZs, MAOIs, but not without side effects:
  - anorgasmia, erectile dysfunction, decreased libido (but can be used to treat premature ejaculation)
  - sleep disorders: insomnia or excessive sleep
  - gastrointestinal discomfort
  - abrupt discontinuation can lead to withdrawal symptoms (vertigo, electric shock sensation)
- First discovered at Eli Lilly in 1970, findings from seminal work:
  - MAOIs effective because they elevate concentrations of amine neurotransmitters
  - diphenhydramine (an antihistamine) is a weak antidepressant; blocks reuptake of norepinephrine and serotonin

OPPI 2008, 40, 391-394

name?

Azapirones not approved in US:
Nat Rev Drug Discov. 2013, 12, 667–687

gepiron (Travivo) BMS
- Development began in 1986
- Rejected multiple times
- Favorable review from FDA in 2016 but still not approved

sertraline (Zoloft) Pfizer
1992 for MDD, 1996 for OCD

paroxetine (Paxil) GSK 2001
Antidepressant and Anxiolytic Drugs

Fluoxetine synthesis: selected examples


1. CH$_2$O, HNMe$_2$
2. B$_2$H$_6$, THF

1982 Racemic

Fluoxetine

1988 asymmetric

NaH

Catalopram/Escitalopram synthesis and impurity synthesis


Citalopram (Celexa), racemic mixture, (S)-(+) ent.

Lundbeck 1998, 2002

Citalopram

Escitalopram (Lexapro), (+)-(+)

★Kalcat C8030-type Raney Ni

Significant impurities observed in cyclization step (0.5%)

Both were synthesized; use of tosyl suppresses formation

Other SSRIs

vilazodone (Viibryd)

US 2011 Merck/Forest Labs
- Only for MDD not GAD

fluvoxamine (Luvox)

Solvay (now Abbott), 1994 (US)
- Primarily for OCD but also MDD and anxiety disorders
- Candidate for prevention of breathing problems caused by COVID-19

Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)

- Simultaneous inhibition of both serotonin and norepinephrine reuptake
- Used for treatment of simultaneous depression and anxiety
- Designed to interact with more than one receptor site
- Does not interact with histaminic and cholinergic-adrenergic receptors and avoids adverse events such as dry mouth, hypotension, and sedation

Two Generations of venlafaxine synthesis

*OPRD 2011, 15, 1392–1395*

venlafaxine

Effexor

Wyeth 1993

desvenlafaxine (Pristiq)

2008 Pfizer
hydroxy analog of venlafaxine

levomilnacipran (Fetzima)

2013 Forest Labs, MDD
racemate: milnacipran (Savella)
Cypress Biosciences
- MDD in France 1996
- Approved for MDD in other countries, but not for fibromyalgia
- Only approved for fibromyalgia in US
- NDA filed in 2001 but delayed due to cGMP violations
- MDD, GAD, fibromyalgia

MDD, GAD, fibromyalgia

1. CNBr, benzene
2. KOH, H$_2$O glycol, 130 °C

HO

CF$_3$

NaOH, MeOH reflux

5-cyanophthalide

G1: LDA
G2: NaOMe, MeOH

G1: Rh/I$_2$O$_3$
G2: H, Ra-Ni*

G1&G2:
HCHO, HCOOH

* Name?
**Antidepressant and Anxiolytic Drugs**

**Atypical Antidepressants**

**bupropion** (Wellbutrin) 1985 GSK
- Dual reuptake inhibitor of dopamine and norepinephrine (NDRI), only NDRI on market
- Significantly lower rates of sexual disfunction (SD) than other antidepressants
- Can alleviate SD/treat SSRI-induced SD (off label)
- Used as anti-obesity and smoking cessation aid
- Side effects: can lead in increase in anxiety and lowers threshold for seizures

![Chemical structure of bupropion HCl]

**agomelatine**
2009 Servier
- melatonin receptor agonist
- approved in EU and AUS but not US
- no significant advantage over other antidepressants

One-pot Synthesis: (from freshman chem lab curriculum…)

**Alternate Indications for Antidepressants**

- Eating disorder treatment: fluoxetine for bulimia nervosa
- bupropion and several SSRIs for binge eating disorder
- Smoking cessation: bupropion
- Chronic pain management: duloxetine
- Migraine prevention: TCAs
- SNRIs for comorbid migraine/MDD

**Purported Natural Remedies for MDD/GAD**

- Effective:
  - Vitamin B9: (dosed as folate/folic acid)
    - reduction of depression in concert with SSRIs
  - Vitamin D: significant decrease in depressive symptoms
  - Xiaobuxin-Tang: (Chinese herbal decoction) efficacy in rats
- Some efficacy:
  - Aromatherapy: in combination with massage
    - temporarily improved mood
  - Meditation: shown to reduce symptoms of MDD and GAD
  - Zinc: moderate effect on depressive symptoms
  - Omega-3: small to moderate positive effects

- Adverse effects:
  - Kava extract: (Piper methysticum)
    - superior to placebo
    - hepatotoxicity issues
  - Valerian, St. John's wort, passionflower:
    - widely used but effectiveness/safety not guaranteed
    - St. John's wort shown to have negative interactions with several drugs including pharmaceutical antidepressants

- No proven efficacy:
  - Acupuncture
  - Melatonin
  - Ginger
  - Green tea
  - Magnesium

**Pharmacology, Biochemistry and Behavior** **2008**, 89, 572–580

**Adverse effects:**

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**Other Drugs**

- Lithium (dosed as Li₂CO₃)
  - Approved for bipolar in 1970
  - MOA not fully understood, but impacts neurotransmission through inhibition of excitatory signaling
  - Effective in augmentation of antidepressants for TRD

- **hydroxyzine** (Atarax)
  1956 Pfizer
  antihistamine
- **modafinil** (Provigil)
  1998 Cephalon
  sleep disorder drug shown to treat MDD
- **pregabalin** (Lyrica)
  2004 Pfizer
  antiepileptic, fibromyalgia approved for GAD in EU

**Off-Label Anxiety/Depression drugs:**

- **hydroxyzine**
  - Approved for panic disorder in 1970
  - used to reduce anxiety in concert with SSRIs
- **propranolol** (Inderal)
  1965 ICI (now AstraZeneca)
  - 1988 Nobel Prize in Medicine for treatment of coronary artery disease and hypertension
  - Used for performance anxiety and PTSD
- **modafinil** (Provigil)
  1998 Cephalon
  sleep disorder drug shown to treat MDD

**Sleep disorder treatment:**

doxepine

**Urinary incontinence:**

duloxetine

**Hives:**
doxepine

**Premature ejaculation:**

SSRIs

**ADHD:**

TCAs for second line treatment

**Eating disorder treatment**:

- fluoxetine for bulimia nervosa
- bupropion and several SSRIs for binge eating disorder

**Smoking cessation**:

- bupropion

**Chronic pain management**:

- duloxetine

**Migraine prevention**:

- TCAs
- SNRIs for comorbid migraine/MDD

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**Pharmacology, Biochemistry and Behavior** **2008**, 89, 572–580
Antidepressant and Anxiolytic Drugs

**Investigational Drugs**

- **Veranamine**
  - Recently isolated natural product
  - In vivo antidepressant activity and selective affinity for serotonin receptors

- **psilocybin**
  - Very recently (JAMA Psychology, November 2020), demonstrated to have antidepressant activity in TRD patients
  - 2020 update (20 g scale):
    - Improvements to yield and purity of Int A
    - Determination of critical process parameters (CPPs) and in-process controls (IPCs)
    - Recrystalization identified
  - Synthesis *2020*, 52, 688–694

**N-Methyl-D-Aspartate (NMDA) Receptor Antagonists**

- NMDA receptors: ligand-gated cation channels activated by glutamate
- Possible mechanism of action of antagonists (such as ketamine):

  - **lanicemine**
    - AstraZeneca
    - Failed to meet endpoint, terminated in 2013
  - **memantine** (Namenda)
    - 2013 Merz alzheimer’s treatment
    - Low-to-moderate NMDA receptor blockade
    - Ineffective against MDD
  - **rislenemdaz**
    - Cerecor (acquired from Merck)
    - Under development for TRD
    - Failed in Ph II in 2016
  - **rapastinel**
    - Allergan
    - Partial agonist at glycine-binding site on NMDA receptor
    - FDA’s breakthrough therapy designation in 2014, failed during Phase III

- **psilocybin**
  - Magic Mushrooms
  - U.S. Patent 4,826,860
  - 1995 Rhone-Poulenc-Rorer ALS drug
  - Unsuccessful in trials for TRD
  - Under development for GAD

**Clinical Trial Failures**:

- **riluzole** (Rilutek)
  - 1995 Rhone-Poulenc-Rorer ALS drug
  - Under development for GAD

- **veranamine**
  - C&EN 2020 Volume 98, Issue 3
**Antidepressant and Anxiolytic Drugs**

**Ketamine:** “Special K”
- Approved as an anesthetic in 1970, commonly prescribed off label for MDD

**Esketamine:**
- Recently approved for TRD,
- 4X antidepressant effect of racemate
- NMDA-type glutamate receptor antagonist
- Exact mechanism of action is unknown

Synthetic approaches to ketamine

**Original Route (Stevens Method)**

\[
\text{Cl} \quad \text{CN} \quad \text{MgBr} \quad \text{THF} \quad \text{then NH}_2\text{Cl} \quad \text{Br}_2 \quad 66\% \quad \text{or NBS} \quad 77\%
\]

**Mechanism?**

yield not reported

\[
\Delta \quad \text{ketamine}
\]

\[
\Delta \quad 73\%
\]

**New Route**
- Improved yields, avoids use of Br₂

\[
\text{Cl} \quad \text{Br} \quad \text{Mg} \quad \text{THF} \quad 82\% \quad \text{acetic ionic liquid} \quad 97\%
\]

**Synthesis of Esketamine**
- Previous enantiospecific syntheses: lack of efficient method for the installation of the α-tertiary amine center
*Org. Lett.* **2019**, 21, 6575–6578

**Unsuccessful strategy:**

Name?

Reason for failure?

**Allyl cyanate/isocyanate rearr.**

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Endocannabinoids
Relevant GM: Cannabinoids, Harwood 2020
- THC is anxiogenic, but effect is diminished when co-administered with CBD
- CBD given alone has anxiolytic properties, particularly under circumstances or in response to stimuli which normally provoke anxiety, but still a need for large scale placebo-controlled studies

-cannabidiol (CBD)
-tetrahydrocannabinol (THC)

- Previously, interest in studying cannabinoid receptor CB1 agonists, but rimonabant when used for anti-obesity lead to depression, anxiety, and suicidal ideation

-rimonabant (Acomplia)
inverse CB1 receptor agonist
Approved in 2006 (EU)
Withdrawn in 2008

“Mental pain is less dramatic than physical pain, but it is more common and also more hard to bear. The frequent attempt to conceal mental pain increases the burden: it is easier to say “My tooth is aching” than to say “My heart is broken.”
C.S. Lewis, The Problem of Pain