Aims

- To discuss the medications used in the treatment of mental illnesses
- In particular, how they work; potential side-effects; relationship to street drugs; and the future for such medications
- With the hope that the presentation will provoke thought and discussion on the subject, and perhaps a different way at looking at drugs in society
The big picture is that medications are used and are effective but are often misunderstood or under-rated and even hated (CCHR)

That is not to say they are not misused or overused, but they are also greatly underused, particularly in certain clinical areas.
......it is time to rethink mental disorders, recognizing that these are *disorders of brain circuits* likely caused by developmental processes shaped by a complex interplay of genetics and experience.

Thomas R. Insel, MDPhilip S. Wang, MD, DrPH, JAMA, May 19, 2010
For 200 years, neurology and psychiatry were one thing

100 years ago a schism developed – psychiatrists went for things they thought were in an immaterial "mind"

Recent advances in neuroscience (genetics, new imaging, understanding of neurotransmitters, and effectiveness of medications) make this position untenable

mental illnesses/disorders are brain diseases
They are brain diseases that disrupt a person's thinking, feeling, mood, ability to relate to others, and daily functioning.

They can affect persons of any age, race, religion, or income.

They are not the result of personal weakness, lack of character or poor upbringing.

They are treatable.
Features are

A. A behavioral or psychological syndrome or pattern that occurs in an individual

B. That reflects an underlying psychobiological dysfunction

C. The consequences of which are clinically significant distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important areas of functioning)

D. Must not be merely an expectable response to common stressors and losses (for example, the loss of a loved one) or a culturally sanctioned response to a particular event (for example, trance states in religious rituals)

E. That is not primarily a result of social deviance or conflicts with society
Medications

- The theories behind and the evidence known is that medications work on the brain’s neurotransmitters and their receptors.

- They act by modulating neurotransmitters.

- Fascinating parallel between the animal brain and plants – the brain has receptors for opium and THC. There is a benzodiazepine receptor.
The medications

- Antipsychotics
- Mood stabilizers
- Antidepressants
- Anxiolytics
- Hypnotics
- Psychostimulants
- Anti-craving drugs (for addiction)
- Others – antihistamines, dopamine agonists
Antipsychotics
Indications/uses

- schizophrenia and other psychotic disorders
- mania
- psychotic depression
- Tourette’s syndrome
- augmentation of antidepressants & mood stabilizers
- aggression & impulsivity
- dementia
First generation – chlopromazine, haloperidol, fluphenazine, perphenazine, pimozide, thioridazine, trifluoperazine, etc

- Mostly block dopamine and histamine receptors
- Still effective at rapid control of behaviour
- Some recent research suggests new is not necessarily better
1950 Chlorpromazine synthesized as a sedating antihistamine
1952 Chlorpromazine reported to be beneficial in psychosis & mania
1958 Haloperidol developed
1962 Long-acting injectable fluphenazine developed
1970 Dopamine hypothesis of schizophrenia suggested
2005 CATIE trial shows positive outcome for perphenazine compared to newer antipsychotics

www.nimh.nih.gov/healthinformation/catie.cfm
Side-effects of 1st gen

- Extrapyramidal Effects (EPS)- dystonia (reversible), akathisia, Parkinsonism, tardive dyskinesia (irreversible)
- Amenorrhoea, galactorrhoea
- Anticholinergic effects
- Photosensitivity
- Lower seizure threshold (not haloperidol)
- Arrhythmias
- Agranulocytosis
- Neuroleptic malignant syndrome
Second/third Generation

- Block serotonin receptors
- Block dopamine receptors, but more loosely
- Also an effect on noradrenaline, histamine and acetylcholine receptors
- Have displaced 1st gen – seen as nicer drugs, less movement disorders, work on both negative and positive features
- But weight gain, diabetes, stroke
History

1990  clozapine introduced in US after long delay related to safety concerns
1994  risperidone
1996  olanzapine
1997  quetiapine
2000  ziprasidone
2003  aripiprazole
2004  ADA/APA consensus report on obesity & diabetes in those taking antipsychotics

http://care.diabetesjournals.org/cgi/content/full/27/2/596
Mood Stabilizers
Indications

- Treat and prevent bipolar disorder (manic-depressive disorder)
- Many used to treat various seizure disorders, migraines, chronic pain syndromes, aggression, impulsivity, anxiety disorders, augmentation of antidepressants and antipsychotics
1949- lithium recognized as antimanic (Cade, Australia)
1966- French researchers demonstrate valproate’s efficacy in treating mania
1978- significant studies demonstrate lithium’s efficacy in bipolar disorder
1980- studies demonstrate effectiveness of carbamazepine in bipolar disorder
1990’s- lamotrigine investigated for mood stabilizing properties
1990’s- most newer approved anticonvulsants are investigated for mood stabilizing properties
2003- lamotrigine approved for bipolar I maintenance
- only mood stabilizer without significant anticonvulsant properties
- Not sure how it works
- up to 70% response rate
- demonstrated effectiveness in reducing suicidality
- less effective in rapid cycling and mixed bipolar states
- full clinical effect may take up to 1-2 months
- serum levels guide dosing
- excreted through the kidneys
Side-effects

- fine tremor, weight gain, nausea
- increased thirst and urination
- more severe toxicities include coarse tremor, gait instability, vomiting, diarrhea, confusion
- increased risk of toxicity with fluid or salt restriction, hot weather/sweating, use of anti-inflammatory drugs, ace inhibitors & angiotensin receptor blockers, diuretics
- may cause kidney and thyroid dysfunction so regular monitoring of creatinine, BUN and TSH are necessary
- females are at much greater risk of lithium related thyroid dysfunction
Carbamazepine (Tegretol)- features

- used in acute mania and bipolar maintenance
- more effective than lithium in rapid cycling & mixed states
- less effective in bipolar related depression

side effects

- GI: nausea, constipation, diarrhea, appetite loss
- CNS: sedation, dizziness, unsteadiness, confusion
- benign rashes common, catastrophic rashes rare
- many possible serious abnormalities in CBC
Valproate -
- can be dosed rapidly to treat acute mania
- more effective than lithium in rapid cycling & mixed states
- used by some to treat aggression and impulsivity in other psychiatric disorders
- approved for migraine prophylaxis

Side effects
- nausea, weight gain, unsteadiness (ataxia), hair loss, tremor
- liver dysfunction, decreased platelets (thrombocytopenia)
- pancreatitis (rare but potentially serious)
- polycystic ovary disease suggested by some reports
- ammonia levels can be increased particularly in those rare individuals with genetic metabolic deficits
- drug-drug interactions by various mechanisms with numerous other anticonvulsants, aspirin and others
Newer mood stabilizers

Lamotrigine (Lamictal)
- Minimally sedating unlike most other mood stabilizers
- Appears to be especially effective in treated bipolar depression but unproven to treat mania
- Rashes – start slowly.

Oxcarbazepine (Trileptal)
- Used primarily in combination with other mood stabilizers although efficacy not clearly substantiated

Topiramate (Topamax)
- Research questions its use as a mood stabilizer although scattered reports suggest possible benefit

Levatiracetam (Keppra)
- Efficacy in bipolar disorder unsubstantiated although scattered reports suggest possible benefit
Antidepressants
Indications

- Major Depression and Dysthymia
- OCD
- Anxiety Disorders
- Addiction esp nicotine
- Chronic pain
- Eating disorders
- Sleep disorders esp TCAs and mirtazepine
- Migraine
- Enuresis (TCAs)
History

1952- First MAOI found with antidepressant properties in process of looking for an antituberculosis drug
1958- imipramine (TCA) failed investigation as antipsychotic but found to have antidepressant properties.
1960’s- multiple other TCA’s developed and placed into use
1988- Prozac (SSRI) introduced
1992-98- Other SSRIs introduced
2006- Transdermal selegilene (MAOI) patch approved to treat depression
MAOIs (eg phenelzine)

- Inhibit MAO so levels of serotonin, noradrenaline and dopamine increase
- Effective antidepressants
- But dietary restrictions
  - Many cheeses, chocolate, soybeans, hot dogs, dry sausage, caffeine, beer, wine, pickles, olives, … etc.
- Drug-drug interactions
  - Multiple prescribed and over-the-counter medications can be potentially lethal. Serotonin syndrome with SSRIs & many others.
TCAs (amitriptyline, nortriptyline etc)

- **Mechanism of action**
  - Norepinephrine, serotonin, histamine, muscarinic (cholinergic) and α-adrenergic receptor activity although in differing ratios
  - Anticholinergic activity leads to many of the side effects of these drugs

- **Indications & off-label uses**
  - Depression and similar spectrum of disorders as SSRIs
  - Especially helpful with chronic pain and depression secondary to medical conditions such as AIDS
  - enuresis, narcolepsy, premature ejaculation, insomnia, migraine prophylaxis, OCD

- **Blood levels:** May be obtained to monitor dose effectiveness
TCA side-effects

- Drug-drug interactions (DDI)
  - Multiple significant interactions in each direction with potentially serious consequences

- Side effects (SE)
  - Anticholinergic SE include: dry mouth, constipation, blurred vision and urinary retention
  - Cardiac arrhythmias and conduction changes
  - Orthostatic hypotension
  - Sedation
  - Weight gain

- Cautions
  - Overdose is frequently fatal
  - Pts with bipolar d/o may be pushed into mania or rapid cycling
**Mechanism of action**

- Inhibit serotonin reuptake so increase synaptic serotonin levels
- Many SSRIs affect other receptors especially at high doses
- Clinical effect usually takes weeks so mechanism goes beyond simply increasing synaptic serotonin levels
- Several serotonin (5-HT) receptor subtypes
Side effects

- Decreased sex drive and impaired sexual function tend not to resolve with time
- Nausea, diarrhea, anorexia, vomiting
  - all increase with dose and can resolve with time
- Weight gain (esp. paroxetine) after initial GI effects
- Headache, dizziness, anxiety (esp. fluoxetine), rash, insomnia, sedation, sweating, vivid dreams, tremor, dry mouth (esp. paroxetine), bruising, ↑ prolactin
Cautions

- Suicidal ideation and ↑ suicide risk especially with children early in tx but significant debate
- Serotonin syndrome (SSRI + MAOI, possibly lithium, others)
  - diarrhea, tremor, sweating, restlessness, hyperreflexia
  - progression of symptoms if untreated ►►►
  - disorientation, rigidity, fever ►► coma, seizures ►► death (approximately 10% mortality rate)
- Many medications/substances have serotonin activity:
  - tramadol, fentanyl, pethidine, sumatriptan,
  - St John’s Wort, MDMA (ecstasy), LSD, many others…
Other antidepressants

- **SNRIs** – venlafaxine, duloxetine and Pristiq are both serotonin and norepinephrine reuptake inhibitors – like TCAs
- **Bupropion (Zyban)** has dopamine and noradrenaline activity (only approved for smoking cessation in Australia)
- **NARIs** – noradrenaline only – mianserin, reboxetine, Strattera
- **mirtazapine**
  - Complex serotonin, NA (α2) & histamine activity
  - Receptor activity changes with changes in dose
  - Sedation & weight gain especially at lower dose
Anxiolytics
Anxiety Disorders

- Generalized Anxiety Disorder (GAD)
- Panic Disorder
- PTSD
- OCD
- Social Anxiety Disorder (SAD)
Drugs for anxiety disorders

- Barbiturates
- Benzodiazepines
- Antidepressants, especially SSRIs and SNRIs
- Mood stabilizers esp pregabalin
- Beta blockers
- Antihistamines
- Buspirione
- Alcohol - SAD
- MDMA (Ecstacy) - PTSD
Since 1957

Own receptor (why?) increases GABA (inhibitory) activity

Indications/uses include anxiety, panic, mania, seizures, phobias, insomnia, alcohol withdrawal, muscle spasm, agitation, catatonia, akathisia, IV sedation

Side effects

- sedation, cognitive impairment, anterograde amnesia
- disinhibition in susceptible individuals
Abuse and dependence

- Risk of abuse is small in individuals who are not abusing other substances: no effect on dopamine, benzo receptor
- Withdrawal symptoms and physical dependence are not in themselves problematic if reductions are done gradually to minimize symptoms
- Symptoms of “withdrawal” may represent breakthrough of the underlying anxiety disorder
- Needing to increase the dose (tolerance) not generally an issue at therapeutic doses
Since 1957 (Ritalin)

- Dexamphetamine and methylphenidate
- Inhibit dopamine reuptake
- Causes increased attention span & concentration, decreased distractability, hyperactivity and impulsivity
- Used to treat ADHD, ADD, depression, narcolepsy
Non-stimulant treatments of ADHD

- **Modafinil**
  - poorly understood mechanism of action
  - used for sleepiness related to narcolepsy, obstructive sleep apnea, depression, multiple sclerosis
  - use for ADHD being investigated

- **Atomoxetine (Strattera)**-
  - recent caution about suicidal ideation
  - rare liver function impairment

- **Clonidine (Catapres)**
  - antihypertensive alpha 2 agonist
  - used for ADHD, substance (opioid) withdrawal, Tourette’s syndrome, others
Drug Dependence Medications
Use of medications in addiction

- Treatment of withdrawal symptoms
  - Benzodiazepines, anticonvulsants, clonidine
- Treatment of comorbid psychiatric disorders
  - Anxiety & depression are common (both primary & secondary etiologies)
  - SSRIs, mood stabilizers, BZ
- Prevention of relapse
  - Deterrents (disulfiram, naltrexone), control of craving
Craving control

- Opioids (esp methadone, buprenorphine, long-acting morphine)
- Acamprosate, naltrexone, ondansetron, topiramate, GHB
- Varenicline
- Nortriptyline
- Nicotine
- Zyban
- Dexamphetamine
Other drugs in mental illness
Other drugs used

- Clonidine – ADHD, opioid withdrawal syndrome, PTSD, Tourette’s syndrome
- Beta blockers – akithisia, tremor, performance anxiety, hyperarousal
- Calcium channel blockers – bipolar disorder
- Kava – anxiety
- St John’s wort – depression
- Cannabidiol – schizophrenia
- MDMA - PTSD
Examples of the complexity of drug use.
Receptor stimulation:

5-HT\textsubscript{1A}  
Anti-depressive, anti-anxiety, anti-obsession; anti-bulimia.

5-HT\textsubscript{2A}  
Behavioral activation, insomnia, anxiety, sexual dysfunction

5-HT\textsubscript{2C}  
Irritability, decreased appetite

5-HT\textsubscript{3}  
Nausea, headache and emesis
Receptor antagonism:

5-HT$_{2A}$  Reduces behavioral activation, improves sleep, reduces sexual sexual dysfunction

5-HT$_{2C}$  Reduces irritability and appetite; reduces cortisol?

5-HT$_3$  Reduces nausea, headache and emesis
Attitudes to drugs
That psychiatric drugs cause:
- Birth Defects
- Worsening depression
- Mania
- Psychosis
- Violence
- Homicide
- Suicide
- Death

www.youtube.com/watch?v=8ufOUHeS-ZY&feature=player_embedded
Relationship to street drugs
Which medications are used on the street and why?

Benzodiazepines – self-medication and intoxication
Anti-psychotics esp Seroquel – self medication, tranquility
Analgesics – self-medication, addiction, euphoria
Clonidine – tranquility
Psychostimulants – speed effect
Antidepressants – self-medication
Anti-convulsants – self-medication, relaxation.
Kava - relaxation
Which street drugs are or could be used in psychiatry?

Cannabidiol – psychosis
Other cannabinoids – pain
MDMA – PTSD
GHB – alcohol dependence syndrome
Psychostimulants – ADHD
Opioids - pain
The Future
More medications will be made available but there are many obstacles

- Reluctance to use current drugs eg topirimate, ondanstron, naltrexone and acamprosate in alcohol dependence
- Lack of regulatory approval to use drugs eg MDMA and GHB
- Lack of funds for research
Why lack of funds for research?

- Expensive – longer testing times required
- Stricter controls – eg placebo controlled trials of monotherapy insisted on
- Suspicion/antagonism to drug treatments in mental illness
- Drugs that increase quantity of life approved over those that improve quality
- PBS slow/resistant – a new statin goes straight on, but a new antidepressant (eg agomelatine) not on PBS yet
Mental illnesses are brain problems
There are many effective medications to treat these problems
There are barriers to their use and to the discovery of new ones.
The future lies in neuroscience
\textit{But,} advancement cannot take place without the centrality of the patient and a complete change in the way society, including health professionals, views their illnesses
Pain of mind is worse than pain of body.

Publilius Syrus
1st Century BC