Augmented board & cares (Adult Residential Facilities) & apartments

Almost all have schizophrenia or schizoaffective disorder
Almost all are on an LPS conservatorship
Almost all are on polypharmacy (1-3 antipsychotics, + others)
Almost all come from locked settings where they’ve lived for 1+ yr
Many stay with us for 6+ months, some for years
MD appts q 2-3 wks, therapist appts ~wkly, MH rehab, med support
Ideally transition to “lower level of care”
Psynergy Programs, Inc.

Nueva Vista (Morgan Hill) Adult Residential Facility (ARF) – 70 beds
Cielo Vista (Greenfield) ARF – 40 beds
Nueva Vista Sacramento (Sacramento) ARF – 60 beds (+60 in 2yrs)
Vista de Robles (Sacramento) ARF – 54 beds (Oct 2019)
Vista Esperanza (Sacramento) RCFE (elderly) – 54 beds (spring 2020)
Tres Vista apartments (MH) – 4 apts, 8 beds
Tres Vista Sacramento (Sac) – 4 cottages, 16 beds (single rooms) (TBD)

Current total – 170 clients; will grow to ~ 358
Topics

• The term, diagnostic criteria, facts
• Risk factors / causes
• Treatments
• Drugs, caffeine, nicotine
• Recommended resources
Quick before-the-lecture summary

- Schizophrenia is an uncommon but costly and challenging illness
- Frustration & pessimism at times can seem the norm
  - Individually, within families, at institutional level
- New research is constantly finding new details in its origins
  - And new insights into treatments and possibly down the road, prevention
- Families matter: learn more, advocate, stay empathetic
The name

• 1896: Dementia praecox ("praecox" = "very early") (Emil Kraeplin)
• 1908-11: schizophrenia (Eugene Bleuler, swiss)
• Greek: “Schizo” = split, “phren” = mind (misnomer)
  • “Split” personality = Dissociative identity disorder (DID)
• Should the name be changed?
  • Mentally retarded -> Developmentally disabled
  • Manic depression -> Bipolar disorder
  • Multiple personality disorder -> DID
  • Dementia -> Neurocognitive disorder (DSM5)
Other names?

• Japan 2002: “Integration disorder”
  • inability to process information in their environment via the 5 senses; leading to hallucinations/delusions
  • Has led to decreased stigma, increased seeking treatment
  • Similar changes in South Korea, Hong Kong, Taiwan

• “Psychosis susceptibility syndrome”

  • Sommer IE, Kahn RS
  *Psychosis susceptibility syndrome: an alternative name for schizophrenia.*
  *Lancet Psychiatry.* 2014; 1: 111
Demographics / Facts

• Prevalence - 0.25-0.6 % - similar worldwide
• One of the top 15 leading causes of disability worldwide
• Estimated average potential life lost = 28 yrs (US)
  • Mostly due to co-occurring medical conditions, & under-detection and under-treatment of them
• ~ 5% die by suicide - highest risk in the early stages
• ~ 50% have co-occurring mental health disorders
• Males affected about equally to females
  • But onset is earlier in males
• ~ 20-30% treatment-resistant (failed 2 adequate antipsychotic trials)

Source – NIMH; Clozapine Handbook, Meyer
Schizophrenia vs Schizoaffective disorder

• Both are psychotic disorders

• Schizoaffective disorder: “schizophrenia + a mood disorder”
  • Bipolar type – at least one manic episode
  • Depressive type – only depressive episodes

• Schizoaffective usually has a better prognosis

• Treatment is similar
  • Mood stabilizers or antidepressants are used in both, but more often in schizoaffective

• Delusional disorder is another psychotic disorder
  • Better functioning overall; delusions are usually non-bizarre (had to be in DSM4; in DSM5, can be); least common
Other similar conditions

- Delusional disorder
- Schizotypal, paranoid, schizoid personality disorders
- Bipolar disorder, MDD with psychotic features
- Drug-induced psychosis (prescription, drugs of abuse)
- Secondary psychotic disorders
  - Huntington’s, Parkinson’s diseases, Alzheimer’s, strokes
Symptoms

• Positive symptoms
  • Hallucinations, delusions, disorganized speech & behavior
  • Symptom group that responds best to medication

• Negative symptoms
  • Avolition, anhedonia, social withdrawal, affect
  • Medications have very limited benefit; strong impact on daily functioning

• Cognitive symptoms
  • Poor attention & concentration, working memory, executive functioning, language, abstract thinking,
  • Some treatment approaches; strong impact on daily functioning

• Other
  • Anosognosia, alteration of senses, changes in emotions, movements and behavior, concrete thinking, neologisms
Delusions

• Grandiose, paranoid (persecutory), religious, jealousy
• Thought broadcasting / withdrawal / mind reading
Catatonia

- Catatonic excitement, stupor
- Still happens, but not nearly as common as pre-antipsychotic days (pre-1960s)

- Can treat catatonia with benzodiazepines, ECT, antipsychotics

https://www.psycom.net/schizophrenia/catatonic-schizophrenia/
Schizophrenia – DSM-IV

- Schizophrenia and Other Psychotic Disorders
- 5 subtypes – Paranoid, Disorganized, Catatonic, Undifferentiated, Residual
  - Subtype = the predominant symptom at the time of evaluation
- Made distinction between bizarre and non-bizarre delusions
  - Need 1 month of 2 “active symptoms” (hallucinations, delusions, disorganized speech, disorganized or catatonic behavior, negative symptoms) unless delusions are bizarre or hallucinations are running commentary and/or 2+ voices conversing.
Schizophrenia – DSM5

- Schizophrenia *Spectrum* and Other Psychotic Disorders

- Ditched the subtypes
  - Symptoms often changed from one subtype to another
  - Patients often present with symptoms of overlapping subtypes
  - Some are now “specifiers” – eg catatonia (which can happen in MDD and Bipolar dis)

- Ditched the bizarre vs non-bizarre
  - What’s considered “bizarre” can be vague and fairly subjective, & its removal reduces cultural bias

- Of the active symptoms, need 2, and one of them needs to be hallucinations, delusions, or disorganized behavior
DSM5 Criteria

• A. 2 or more of the following must be present for a significant portion of time during a 1-month period
  • Delusions, hallucinations, disorganized speech, catatonia or other grossly abnormal psychomotor behavior; negative symptoms
• B. Significant decreased function at work, in interpersonal relations, or in self-care
• C. At least 1 month of active symptoms unless successfully treated, and at least 6 mo. Of all symptoms (prodromal, active, and residual)
  • (<1 mo, brief psychotic disorder; <6 mo, Schizophrreniform disorder)
• D. Doesn’t meet criteria for Schizoaffective disorder, and sx of psychosis are not caused by substance abuse.
Age at Onset

Early-onset schizophrenia
(<13 yrs)

Late-onset schizophrenia
(40+ yrs)

Very late-onset schizophrenia
(60+ yrs)

The onset of schizophrenia depends on gender. Males typically develop the disorder earlier than females. Based on Gor and colleagues (2005).

https://slideplayer.com/slide/12737074/
Onset of symptoms

- Cannabis: brings out symptoms 3-6 yrs earlier
  - Depending on frequency of use and potency of the cannabis used

- Schizophr Res. 2016 Jan; Cannabis use is associated with 3 years earlier onset of schizophrenia spectrum disorder in a naturalistic, multi-site sample (N=1119).

- Schizophrenia Bulletin, Dec 2013; Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users
The cannabis effect

Schizophrenia Has Three Symptom Domains: (1) Positive Symptoms, Which Fluctuate Over Time, (2) Negative Symptoms, & (3) Cognitive Impairment, with the Latter Two Persisting and Causing Lifelong Disability

Course of the illness

https://seekingalpha.com/article/4159000-minerva-neurosciences-nerv-negative-symptoms-schizophrenia-slideshow
Risk of dementia?

• Cognitive symptoms as part of the illness do become more noticeable with aging – can present as a “non-progressive dementia”

• But there is *also* an increased risk for *progressive* dementia, eg Alzheimer’s – why?
  • Could the brain problems in Schizophrenia itself cause later dementia?
  • Many Alzheimer’s risk factors are present in schizophrenia patients
    • Eg High blood pressure, obesity, high cholesterol, cerebrovascular disease, substance abuse, diabetes,
  • Could there be a common cause of the two conditions?
  • Could antipsychotics increase the risk of dementia?
  • All (but #2) are unknowns.

Schizophrenia and risk of dementia: a meta-analysis study. *Neuropsychiatric Dis Trtmt* 2018
Dementia – multiple types / causes

- Lewy body known for visual hallucinations & delusions, even moreso than Alzheimer’s
- Frontotemporal – often behavioral changes, disinhibition before memory
- Also Parkinson’s dementia, AIDS-d, Huntington’s-d
- None are conclusively linked to schizophrenia, but each has similar features to schizophrenia

http://www.dfwsheridan.org/types-dementia
BUT - Only way to confirm type – is at autopsy

• On autopsy, neurofibrillary tangles and amyloid plaques = Alzheimer’s
• Post-mortem studies have generally *not* found an increased incidence of Alzheimer’s disease pathology in people with schizophrenia
• = Most people with schizophrenia and moderate to severe cognitive impairment do not have Alzheimer’s disease (the most common cause and type of dementia)

• So bottom line – we’re not really sure what’s going on.

https://pdfs.semanticscholar.org/f037/4b34ab85268346fe605ee264421fd26716b6.pdf
“Insight”

• What is insight?
  • Awareness of having an illness
  • Recognizing the signs and symptoms of that illness
  • Attributing consequences and deficits to the illness
  • Understanding the need for treatment of the illness

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4140620/;
Anosognosia – lack of insight

• A=without; noso=disease; gnosia=knowledge
• 1st used to describe neurological deficits (1914)
  • Unawareness of left hemiplegia (paralysis), right hemisphere lesions
• = the inability to identify the presence of deficits characteristic of an illness as well as their magnitude, progression, and how they limit daily life
  • ~50-90% of those with schizophrenia
  • 50+% of Alzheimer’s (~40% at time of dx)
  • Stroke (right hemisphere)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4140620/
Anosognosia – lack of insight

• What causes it? Theories:
  • “clinical model” = a primary symptom of the psychotic process
    • The psychosis itself convinces you you’re fine
  • “psychological denial model” = a coping mechanism to preserve emotional well-being by protecting against distress
    • Too distressing to admit there’s a serious problem
  • “neuropsychological model” = inadequate neurocognition caused by brain deficits
    • Brain wiring/chemistry abnormalities

• Not all-or-none (exists on a continuum), and can fluctuate over the course of the illness
Anosognosia – lack of insight

- Lower volume size of these areas correlates with poorer awareness of illness (Cooke et al, Schizophrenia Research, 2008)
- Many studies though point to mainly issues with the frontal lobes

What causes Schizophrenia?

• Many many factors involved:
  • Genetics
  • Biological
  • Developmental
    • excessive pruning of synapses
    • Adverse childhood experiences (ACE) (probably more association than causation)
Structural differences
- larger ventricles
- smaller hippocampi
- less grey matter

*Structural imaging*
= *CT, MRI*

picture taken of the brain during 1 moment

https://www.webmd.com/schizophrenia/ss/slideshow-schizophrenia-overview
Functional imaging

- Pictures taken over time (examining the *functioning* of the brain)
- Functional MRI (fMRI)
- PET
- SPECT
- *Many* areas of the brain light up differently in schizophrenia patients (depending on the task during the test)

https://www.clinicaladvisor.com/home/topics/mood-disorder-information-center/schizophrenia-a-clinical-overview/

https://www.sciencemag.org/
Genetics of Schizophrenia

- Heritability of schizophrenia is high
  - but not quite as high as in bipolar disorder and ADHD

![Heritability estimates for various psychological disorders](image)

**Figure 13.9**
Genetics of Schizophrenia

• 2014 finding: 100+ genes likely involved – unknown how many you need to get schizophrenia
  • largest genomic study of any psych disorder, analyzed genomes of >100,000
• 2016 finding: One of most common genes involved seems to be on chromosome 6, for the “C4” (complement component 4) gene

• What do C4 and the other complement proteins do?
• How could changes in the C4 gene increase the risk of schizophrenia?
“Complement factors” like C4 help tag pathogens (bugs) for removal by the immune system.

- There’s a complicated “Complement cascade” in which the complement proteins work together.
- Complement factors have a similar role in the brain.
  - Clearance of cellular material that has been tagged for elimination: *synaptic pruning*.
Synapse

- where one neuron connects to another neuron
- Most psychiatric medications work on the chemicals in the synapse
- You don’t grow new neurons over time – your brain just changes the connections between them
What is “synaptic pruning” and why do we care?

• the normal elimination of connections between neurons that occurs during development
• Excessive synaptic pruning can lead to various brain disorders
• It’s a fairly recent discovery that complement factors are involved in synaptic pruning
  • And “malfunctioning” (or overfunctioning) complement factors, like C4, might then cause too much synaptic pruning
  • So - Abnormal (high) amounts of C4 proteins can increase one’s risk of developing schizophrenia
    • Different versions of the gene account for how much C4 is produced

Recommend watching:
Four common structural variants of the C4 gene (C4A/C4B loci):

1. Any of the four C4 alleles transcribed and translated into C4 proteins
2. C4 proteins distributed to dendrites and synapses at the end of the axon
3. Greater C4 protein expression increases synaptic pruning within the neuronal circuit
Inflammation & immune system

Definitely playing a role seeing how many associated autoimmune disorders there are

https://www.psychiatrictimes.com/cme/inflammation-immune-function-and-schizophrenia-overview/page/0/2
Neurotransmitters involved in Schizophrenia

• #1: Dopamine (later slides)
• #2: Serotonin
• To a lesser extent:
  • Glutamate
  • GABA

Paternal age

• Multiple studies confirm
• Possibly due to mutations in sperm cell DNA with aging

http://www.schizophrenia.com/prevention/older.htm; 2001 study
Seasonal birth – winter & spring

Sunlight? Vitamin D? Viral exposure? Maternal illness?

http://www.schizophrenia.com/prevention/season.html
Adverse childhood experiences

- Association vs causation?
- Definitely strong association (++studies)
- But twin studies in particular show that no ACEs are needed to develop schizophrenia

https://www.advokids.org/adverse-childhood-experience-study-aces/
Treatment / Management

so many options
so many underutilized
can be so hard to convince the person to get help
can be so hard to convince the person to stay well/adherent

-> but persist!
## Treatments

<table>
<thead>
<tr>
<th>Biological</th>
<th>Non-biological</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Psychopharmacology (medications)</td>
<td>• Psychotherapy (individual, group, family)</td>
</tr>
<tr>
<td>• Neurostimulation (ECT, TMS)</td>
<td>• Mental health &amp; vocational rehabilitation</td>
</tr>
</tbody>
</table>
Psychopharmacology of Schizophrenia

- Sometimes we’ll pick 1 medication
- Some will end up taking / requiring 1 or more of each class

• Antipsychotics
• Mood stabilizers
• Antidepressants
• Sedatives/hypnotics
• Medication-assisted Treatment (MAT) for substance use
  • Nicotine, alcohol, opiate use disorders
• Sometimes, mild stimulants
Antipsychotics aren’t just used in psychosis:

- Mood disorders (bipolar disorder, major depressive disorder)
- Anxiety disorders (PTSD, GAD [generalized anxiety d/o])
- Tic disorders (Tourette’s)
- Autism spectrum (for aggression, agitation)
- Dementia (aggression, agitation, psychosis)
- Delirium
- Refractory hiccups (chlorpromazine)
Antipsychotics

• First-generation antipsychotics (FGA) ("typical antipsychotics")
  • Haloperidol (Haldol)
  • Fluphenazine (Prolixin)
  • Perphenazine (Trilafon)
  • Chlorpromazine (Thorazine)
  • Trifluoperazine (Stelazine)
  • Loxapine (Loxitane)
Antipsychotics

- Second-generation antipsychotics (SGA) ("atypical antipsychotics")
  - Clozapine (Clozaril, Fazaclo)
  - Risperidone (Risperdal, Risperdal Consta)
  - Quetiapine (Seroquel, Seroquel XR)
  - Olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv)
  - Ziprasidone (Geodon)
  - Aripiprazole (Abilify, Abilify Maintena, Aristada)
  - Paliperidone (Invega, Invega Sustenna, Invega Trinza)
  - Iloperidone (Fanapt)
  - Asenapine (Saphris)
  - Lurasidone (Latuda)
  - Brexpiprazole (Rexulti)
  - Cariprazine (Vraylar)
“Atypical” APs – what makes them atypical?

- Clinical properties
  - Reduced chance of extrapyramidal side effects (EPS) including TD

- Chemical properties
  - Receptors affected: serotonin as well as dopamine
    - There’s a huge variation between the atypicals (eg risperidone has a higher affinity for dopamine receptors, ie binds more tightly to it, than does quetiapine (Seroquel), and is more likely to cause Parkinsonian side effects as a result; Seroquel has a higher affinity for acetylcholine and histamine receptors than does Risperdal, and is more likely to cause sedation, weight gain, blood pressure changes...)
  - Serotonin = “5-HT”; receptor most blocked by SGAs is 5-HT2A
Antipsychotics – how do they work in SZ?

• Blocking excessive dopamine activity
  • There’s not *too much* dopamine – too much dopamine nerve cell firing

• Basis of the “dopamine hypothesis” of schizophrenia
  • There’s 4 dopamine “pathways”
  • Blocking dopamine activity in each pathway leads to different effects – some wanted, some unwanted
  • We don’t have a way to selectively *pick* which dopamine pathway we want to affect – so instead we find antipsychotics that do *more* than just block dopamine
    • Essentially the difference between FGAs and SGAs
1. Dopamine is stored into synaptic vesicles via the VMAT2 and stored until its release into the synapse.
2. Dopamine released during neurotransmission acts on 5 types of postsynaptic receptors (D1-D5).
3. The presynaptic D2 autoreceptor acts as a negative feedback mechanism regulating the release of dopamine from the pre-synaptic neuron.


https://psychscenehub.com/psychinsights/the-dopamine-hypothesis-of-schizophrenia/
Four Dopamine Pathways & Schizophrenia

1) Mesolimbic (SCZ - increase in DA causes positive symptoms)
2) Mesocortical (SCZ – DA hypoactivity: negative & cognitive & affective symptoms)
3) Nigrostriatal (Drugs - EPS & TD drug side effects)
4) Tuberohypophyseal (Drugs - hyperprolactinemia side effects)

http://tmedweb.tulane.edu/pharmwiki/doku.php/rx_of_schizophrenia
Dopamine Pathways Relevant to Schizophrenia Symptoms

[Diagram showing overactivity of the mesolimbic pathway leading to positive symptoms and mesocortical pathway dysfunction leading to negative and cognitive symptoms]

https://www.youtube.com/watch?v=9ah8pNwP8hQ
Dopamine blockers aren’t necessarily needed - enter Pimavanserin (Nuplazid)
Pimavanserin (Nuplazid)

• The first-ever non-dopaminergic antipsychotic
  • Serotonin – inverse agonist of 5-HT2A receptors & 5-HT2C receptors

• 2016: FDA-approved for Parkinson’s disease psychosis
  • No affinity for dopamine receptors, so ideal for Parkinson’s dz
    • Antipsychotics tend to make parkinsonian symptoms worse

• May work for schizophrenia:
  • Open label studies show it’s effective
  • May be more effective for negative symptoms than other antipsychotics
  • July 2019 study – added to another antipsychotic, improvement compared to placebo but not statistically significant
Methods of administering medications
Medicine routes:

• Oral – tablet / capsule, dissolvable tablet (ODT), liquid
• Intramuscular (IM)
  • Fast-acting injectable
  • Long-acting injectable (LAI)
• Intravenous (Haldol)
  • Only in hospitals, on a heart monitor, mostly for delirium

• (some psych medications come in a patch form – no antipsychotic though)
Oral Dissolvable/Disintegrating tablets (ODT)

- **Clozapine ODT – Fazaclo**
- **Olanzapine ODT – Zyprexa Zydis**
- **Risperidone ODT – Risperdal M-tab**
- **Aripiprazole ODT – Abilify Discmelt**
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Liquid antipsychotics

- Abilify oral solution
- Risperdal oral solution
- Versacloz (clozapine) oral solution

Can administer directly from pipette, or mix with beverage (water, coffee, OJ, milk; not grapefruit juice). Have to be careful measuring

- Chlorpromazine (Thorazine) oral solution & syrup
- Fluphenazine (Prolixin) oral solution
- Haloperidol (Haldol) oral solution
Even a pill with a chip?! Abilify MyCite ($$$)

- Digital ingestion tracking system
  - The ingestible sensor first permitted for marketing by FDA in 2012
- Aripiprazole tablet with a sensor – FDA approved Nov 2017
  - Ingestible sensor embedded in the pill that records that the med was taken
  - Sends a message from the sensor to a wearable patch; patch transmits the info to an app, so can be tracked by a smartphone
- Can also then access the info through a web-based portal (for caregiver/MD)
Short-acting injectables

- Used as-needed in hospitals, locked settings
  - Not used usually in board-and-cares
- Typically ~15-20 min minimum onset
- Usually for severe agitation / aggression
- Usually when refusing oral medication

- Olanzapine (Zyprexa), ziprasidone (Geodon), risperidone (Risperdal), Haloperidol (Haldol), aripiprazole (Abilify), chlorpromazine (Thorazine), fluphenazine (Prolixin)
  - Not: Seroquel, Invega
Long-acting injectables (LAI)

Muscle: Deltoid (shoulder), Gluteal (rear)

Needle size: 1-inch for shoulder; 1.5-2 inch for gluteal - also depends on weight / body size

Injection site pain/reactions – usually mild
Long-acting injectables (LAIs)

First-generation antipsychotics came first:
- Fluphenazine decanoate (Prolixin decanoate) (1970s)
- Haloperidol decanoate (Haldol LA) (1980s)
- Drug dissolved in an oil-based solution
Long-acting injectables (LAIs)

• Abilify Maintena - every 4 wks (powder for reconstitution) (2013)

• Aristada (aripiprazole lauroxil) – every 4 wks, 6 wks, 8 wks
• Invega Sustenna – every 4 wks
• Invega Trinza – every 3 months
• Zyprexa Relprevv – every 4 wks
• Risperdal Consta – every 2 wks
• Perseris (risperidone) – every 4 wks
Long-acting injectables (LAIs)

- Abilify Maintena - every 4 wks
- **Aristada (aripiprazole lauroxil) – every 4 wks, 6 wks, 8 wks**
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Long-acting injectables (LAIs)

- Abilify Maintena - every 4 wks
- Aristada (aripiprazole lauroxil) – every 4 wks, 6 wks, 8 wks
- **Invega Sustenna** (paliperidone palmitate – every 4 wks) (2006)
  - Invega Trinza – every 3 months
  - Zyprexa Relprevv – every 4 wks
  - Risperdal Consta – every 2 wks
  - Perseris (risperidone) – every 4 wks

![Dose conversion from INVEGA* to INVEGA SUSTENNA*](image)

<table>
<thead>
<tr>
<th>INVEGA* extended-release tablet (daily)</th>
<th>INVEGA SUSTENNA* Injection (once monthly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>39-78 mg³</td>
</tr>
<tr>
<td>6 mg</td>
<td>117 mg</td>
</tr>
<tr>
<td>9 mg</td>
<td>156 mg</td>
</tr>
<tr>
<td>12 mg</td>
<td>234 mg</td>
</tr>
</tbody>
</table>
Long-acting injectables (LAIs)

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Long-acting injectables (LAIs)

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• Invega Sustenna – every 4 wks
• Invega Trinza – every 3 months

• **Zytrexa Relprevv** – olanzapine pamoate
  - every 4 wks – powder for reconstitution (2009)

  • The “special” one d/t risks
  • Have to wait 3 hrs at the clinic

• Risperdal Consta – every 2 wks
• Perseris (risperidone) – every 4 wks
Long-acting injectables (LAIs)

- Abilify Maintena - every 4 wks
- Aristada (aripiprazole lauroxil) – every 4 wks, 6 wks, 8 wks
- Invega Sustenna – every 4 wks
- Invega Trinza – every 3 months
- Zyprexa Relprevv – every 4 wks

- Perseris (risperidone) – every 4 wks (2018)
Convincing someone to take an LAI

• “It’s the newest technology”
• “Smooth and consistent drug level”
• “One less pill to take”
• “It’s just like getting a flu shot”
• “Wouldn’t it be nice to not have to convince people you’re taking your medication regularly?”
• “Wouldn’t you like to lower the chance of going back to hospital?”
What’s “too much medication”?

Patient A – doing well

• Abilify Maintena injection
• Trazodone (sleep)

Patient B – doing well

• Clozapine ODT
• Risperdal Consta injection
• Lorazepam (anxiety)
• Celexa (antidepressant)
• Lithium (mood stabilizer)
• Depakote (mood stabilizer)
• Seroquel as-needed (PRN)
Combining medications

• Avoid it if possible, but often necessary.
• Sometimes clozapine can take the place of 2-3 medications
• Watch for drug interactions:
  • One medication that can interact with the action or metabolism of another
• Watch for combining side effects:
  • Sedating effects of one add to the sedating effects of another
• Sometimes drug interactions are *purposeful*:
  • eg Clozapine + fluvoxamine (Luvox) – Luvox increases clozapine’s blood level
• Typical practice in schizoaffective disorder
  • antipsychotic + mood stabilizer/antidepressant is usual practice
Clozapine (Clozaril, Fazaclo) — what’s the big deal?

• Been around for a long time
  • Discovered in Switzerland in 1956
  • Only a few yrs after discovery of the 1st AP, chlorpromazine
  • Fell out of use in mid-70s; came back ~ 1995

• Most effective antipsychotic
• Most life-saving antipsychotic
• Most “dangerous” antipsychotic
• Most underused antipsychotic
Clozapine (Clozaril, Fazaclo) — what’s the big deal?

• FDA-indicated for:
  • Treatment-resistant Schizophrenia
  • Recurrent suicidal behavior in schizophrenia/ schizoaffective disorder who are at chronic risk of suicide (2002)

• One of least likely antipsychotics to cause tardive dyskinesia (TD) & extrapyramidal side effects (EPS)
  • Often used to treat tardive dyskinesia – the only AP to do so

• ~60% of treatment-resistant schizophrenia pts improve
  • But ~ 40% do not

Source – Clozapine Handbook, Meyer & Stahl
Clozapine (Clozaril, Fazaclo) — what’s the big deal?

• Clozapine-tx’d pts have decreased mortality from all-causes
  • Mortality rate ratios ~ 40% lower than other antipsychotics (while continuously taking it)

• Uniquely effective in schizophrenia pts w/ psychogenic polydipsia

• Proven efficacy in treating bipolar disorder

• Prior to pimavanserin, the antipsychotic with strongest efficacy and tolerability in Parkinson’s disease psychosis

• Significant benefit on impulsive aggression and violence
  • Anti-aggression effect is independent of antipsychotic effect (eg beneficial for Antisocial Personality disorder)

Source – Clozapine Handbook, Meyer & Stahl
Clozapine – why so effective? Not sure.

https://www.slideshare.net/ramijames/clozapine
Clozapine – woefully underutilized

- Rx % by state, 2006-09 (Medicaid)
- Overall ~ 4.8% of schizophrenia pts
- Least commonly used in deep south – 2% in Louisiana
- Most commonly rx in New England, & highest in South Dakota (16%)

Clozapine – why so underutilized?

• It’s generic – so no “caretaker / manager” to defend and push it

• Prescriber: fears of its risks
• Patient/client: Dislike of getting frequent lab work
• Both: Frequent side effects

• Not tried it? Ask for it. Your prescriber refuses? -> CureSZ
CureSZ Foundation

• Founded in 2016
• Can log onto their website and find a prescriber on their panel who lives closest to them, for another opinion

Comprehensive Understanding via Research and Education into Schizophrenia

www.curesz.org
Clozapine (Clozaril, Fazacllo) – risks

• Agranulocytosis
• Seizures
• Cardiac (myocarditis, risk of arrhythmia)
• Severe constipation, ileus

• Metabolic side effects (wt gain, lipids, diabetes)
• Sialorrhea (drooling)
Clozapine (Clozaril, Fazaclo) – risks

• Problematic but not as concerning:
  • Metabolic side effects (wt gain, lipids, diabetes)
  • Sialorrhea (drooling)
Clozapine (Clozaril, Fazaclo) – risks

• **Agranulocytosis** – recognized fear since ~ 1975
  • WBCs are also known as “granulocytes”
  • = ANC (absolute neutrophil count) <500
  • ~ 0.8 to 1.3% of clozapine patients
  • Can be fatal if not detected early and clozapine stopped
  • Usually occurs in the first 6 months

• Neutrophils are a type of white blood cell
  • Make up 40-60% of all our WBCs
  • First to arrive on the scene during a bacterial infection
Clozapine (Clozaril, Fazaclo) – risks

• Agranulocytosis
  • Everyone on clozapine is enrolled in the ClozapineREMS national program
  • Pharmacies will not dispense clozapine without updated labs / approval from ClozapineREMS
• Clozapine REMS needs the ANC measured:
  • Weekly for the first 6 months
  • Every 2 wks for the next 6 months
  • Every month thereafter
Clozapine (Clozaril, Fazaclo) – risks

• Frequent labwork can be a pain, and deterrent to taking clozapine

• Devices now exist that remove need for needles, and involve just a fingerstick
  • Athelas’ device – FDA-approved 2019
The next generation of immune monitoring.

Neutrophils, Lymphocytes, Platelets, WBCs, Morphology, and Cell Activation all within minutes from a fingerprick of blood.

The Athelas One for WBC and NEUT% is now FDA Cleared for point-of-care indications.

RESEARCH AND ADVISORS FROM

Stanford  UCSF  USCU University of Southern California
Clozapine risks - Seizures

• All antipsychotics increase risk of seizures
  • Clozapine’s increased risk is a little higher than the others
• Risk of seizures seems to go up with higher dose
• Usually generalized tonic-clonic type; can be myoclonic
• Higher risk: clozapine level >1000 ; dose 600+ mg/d
  • Usual level we aim for is 350-1000
  • 600+ mg/d ~ 4% risk; 300-600 mg/d ~ 2.5% risk; <300 mg ~ 1%
Clozapine risks - Seizures

• If higher risk, often we add an anti-seizure (anticonvulsant)
  • Many of which are mood stabilizers and can even enhance the antipsychotic’s efficacy
    • Eg Lamotrigine (Lamictal), valproate (Depakene/Depakote)
    • Usually avoid carbamazepine (Tegretol) as it has lots of drug interactions and can also drop the white blood cell count.
    • Neurologists often use Keppra (levetiracetam) – low side effects, low drug interactions, but not really mood stabilizer nor “boosts” the antipsychotic

• Experts conclude: If a seizure has happened on clozapine, does *not* mean clozapine should be stopped.
Clozapine interacts with cigarettes

• Cigarette smoking (the hydrocarbons, not nicotine) lowers the clozapine blood level
  • Just 7-8 cigs/day can drop the level by ~30%
  • Induces liver enzyme CYP450 1A2 (ie the 1A2 enzyme is “sped up” and chews up the clozapine more quickly)
  • Reverse also applies when someone quits smoking (eg when hospitalized)
Clozapine interacts with **caffeine**

- Caffeine though mildly increases the clozapine level
  - Caffeine is also metabolized through 1A2 – so it competes w/ clozapine
  - But caffeine also indirectly increases dopamine activity, which then increases psychotic symptoms
  - Drinking several cups of coffee daily will usually have a negative net effect on symptoms, despite slightly increasing clozapine level.
Managing side effects of common meds

- Weight gain, increased risk of diabetes, high cholesterol (lipids)
- Drooling (sialorrhea)
- Sedation
- Extrapyramidal symptoms (EPS)
- Tardive dyskinesia
- Urinary incontinence / bedwetting
- Restlessness (akathisia)
Weight gain

- Olanzapine = clozapine, > quetiapine > risperidone > others’
  - Usually by increasing appetite.
- Measure/track weights monthly initially, then every 3-6 mo
- If gaining weight, need to intervene:
  - Assess diet & exercise – change lifestyle
  - Assess whether the right medication / right dose / combination
  - Weight loss medication
Managing Weight gain

• Weight loss medications
  • **Metformin** (a diabetes medication) (many MDs won’t rx unless pre/diabetic)
  • Contrave (bupropion / naltrexone) – bupropion stimulating, pro-dopamine (risky)
  • Topiramate (Topamax) – cognitive side effects

• We usually stay away from those that are more risky:
  • Phentermine (Lomaira, Adipex-P)
  • Amphetamines (Adderall, Dexedrine, Vyvanse) & methylphenidate (Ritalin)
Urinary incontinence / bedwetting

- Drink less fluids after dinner
- Timed bathroom checks during the night / using an alarm
- Wearing Depends at night
- Medication options:
  - **Oxybutynin** (used for overactive bladder)
  - Desmopressin (DDAVP) – used in children for bedwetting; quite useful – but need to monitor sodium levels (can drop)
Somnolence (sedation)

• Take most of medication at bedtime
• More exercise during the daytime
• Be careful with caffeine
  • Indirectly can increase dopamine levels and can worsen symptoms
  • Separate from its activating / “revved-up” effects
• Medication treatments can be used with caution:
  • Bupropion (Wellbutrin) – can worsen psychosis, increased risk of seizure
  • Modafinil (Provigil) – can worsen psychosis
  • Stay away from amphetamines (much more likely to worsen psychosis)
Other bothersome side effects:

**Drooling** (sialorrhea)

- Direct-to-the-mouth options are best:
  - Atropine 1% drops – sublingually (under the tongue), or dissolved in water, swish and spit
  - Ipratropium bromide (Atrovent) spray under the tongue
- Oral pill (“systemic”) options also exist:
  - Glycopyrrolate tablets
  - Benztropine (Cogentin) tablets
  - Tricyclic antidepressants (e.g. amitriptyline)
Extrapyramidal symptoms (EPS)

• 1st described in 1952 after chlorpromazine (Thorazine) caused Parkinson’s disease-like symptoms

• What does “extrapyramidal” mean?
  • Nerves concerned w/ motor activity that descend from the cortex to the spine and are not part of the pyramidal system
    • Nerves that mostly involve/cause “involuntary” actions/movements
  • “pyramidal system” = nerves descending from pyramidal cells of the cortex
    • Nerves that mostly involve/cause “voluntary” actions/movements

• So basically – extrapyramidal symptoms are abnormal muscle movements that are involuntary (not doing them on purpose)
Spinal column cut horizontally:

Motor and descending (efferent) pathways (red)
- Lateral corticospinal tract
- Anterior corticospinal tract

Sensory and ascending (afferent) pathways (blue)
- Dorsal Column Medial Lemniscus System
  - Gracile fasciculus
  - Cuneate fasciculus
- Spinocerebellar Tracts
  - Posterior spinocerebellar tract
  - Anterior spinocerebellar tract
- Anterolateral System
  - Lateral spinothalamic tract
  - Anterior spinothalamic tract
- Spino-olivary fibers

Extrapyramidal Tracts
- Rubrospinal tract
- Reticulospinal tracts
- Olivospinal tract
- Vestibulospinal tract
Extrapyramidal symptoms (EPS)

Common with first-gen antipsychotics (FGAs)

• Can happen w/ SGAs, usually at higher doses (or in elderly)
  • Risperidone most likely; clozapine least likely

• Includes:
  • Dystonia (sustained muscle contraction)
  • Akathisia (restlessness; acute, tardive)
  • Parkinsonism (tremor, stiffness/rigidity, shuffling)
  • Dyskinesia (repetitive movements; acute, tardive)
Akathisia

• Inner sense of restlessness, can be quite uncomfortable
  • Pacing, rocking back and forth, feeling compelled to move
• Other than antipsychotics:
  • Antidepressants (SSRIs in particular)
  • Anti-nausea meds: metoclopramide, prochlorperazine
• Treatment:
  • Stop or lower the dose of the medication that’s causing it, if possible
  • Propranolol (Inderal), a beta-blocker – s/e of low heart rate, dizziness
  • Benztropine (Cogentin) – s/e of dry mouth, constipation
  • Benzodiazepines, eg Lorazepam (Ativan) – s/e of sedation, risk falls
  • Amantadine, clonidine
Tardive Dyskinesia

• Consequence of long-term use of (usually first-generation) antipsychotics
  • Not a side effect of clozapine, and usually not of the SGAs
• Involuntary repetitive movements, often of tongue, facial muscles
• (Expensive) FDA-approved treatments (that are partially helpful) now exist:
  • **Ingrezza** (valbenazine)
  • **Austedo** (deutetrabenazine)
• Others:
  • Clozapine
  • tetrabenazine
Routine medical monitoring

• Everyone on antipsychotics should have:
  • (at least) annual labs: fasting glucose or HbA1c, fasting lipids
  • EKG within the first year
  • Their weight tracked – initially monthly, then every 3 months

• Lithium: thyroid (TSH), kidneys (GFR, Creatinine)
• Depakote: liver (LFTs), blood count (CBC)
Alternative / complementary medicines

- Omega-3 fatty acids (eg fish oil)
  - Yes, may have some benefits and is safe
- Ginko biloba
  - May have some benefits; rarely rx
- Multivitamins?
  - Probably not. If vitamin D or B deficient, rx vit D or B.
- CBD? .....  
  - THC, the other main ingredient in cannabis, is pro-psychotic
So what about “pure” CBD, no THC?

• CBD can be extracted from both hemp and marijuana plants

• 2nd most prevalent of the active ingredients in marijuana (after THC)

• FDA eased regulations in 2015, allowing CBD treatment trials

• Strongest scientific evidence is for several severe childhood epilepsy syndromes, which don’t usually respond to medications
  • FDA approved Epidiolex (CBD) June 2018 for these seizure conditions
• Cannabidiol (CBD) may have a future role
  • “findings suggest that CBD has beneficial effects in patients with schizophrenia. As CBD's effects do not appear to depend on dopamine receptor antagonism, this agent may represent a new class of treatment for the disorder.”
  • N=88 ; After 6 wks of treatment, cf placebo the CBD group had lower levels of positive symptoms, and were more likely to be rated improved by the treating MD; somewhat improved cognition and overall improved functioning.
According to a report from the World Health Organization, “In humans, CBD exhibits no effects indicative of any abuse or dependence potential.... To date, there is no evidence of public health related problems associated with the use of pure CBD.”
Neurostimulation treatments

• **ECT** (electroconvulsive therapy)
  • Very effective for severe depression, mania and catatonia
  • Not as effective for schizophrenia, but still useful for some & tried in some treatment-resistant cases

• **TMS** (transcranial magnetic stimulation)
  • Some benefit for hallucinations, cognition, mood symptoms
  • $$ (not covered by insurance)
Coping with voices

• Talking with others

• Vocalisation
  • The physical act of talking – using vocal cords in other ways, eg singing – interferes w/ the process that creates voices, reducing their intensity
    • Singing, humming, counting, talking, reading out loud, prayer, sub-vocal speech (talking quietly so that others can’t hear)

• Listening to music
  • Switching attention from voices in their head to sounds in the music; relaxation

• Wearing earplug
  • One ear ("monaural occlusion") – can be effective, while still being able to hear
AVATAR Therapy

• Invented by Julian Leff in 2008
• Have dialogue with a digital representation (avatar) of their presumed persecutor
• Sound of voice switches between what the patient’s persecutor sounds like in patient’s head, and the therapist’s actual voice
• Avatar responds by becoming less hostile and concedes power over the course of therapy
• In studies, 6 weekly 50-min sessions, 10-15 min involving face-to-face work w/ Avatar
• Better results than supportive counseling

https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(17)30427-3/fulltext
Recovery? Remission?

• Most with schizophrenia will not get *all* symptoms into remission (gone)
• So when treating with medication, when do you say “That’s enough, no more medication. We’ve done what we can.”
• My argument:
  • Don’t call someone “treatment-refractory”/”treatment-resistant” until a good trial of clozapine
    • Adequate duration (3+ months), adequate blood level (>350); whatever dose that requires
  • Do whatever possible to eliminate complications:
    • Substance use will usually worsen symptoms and reduce medication efficacy
    • Reduce stressors as much as possible
    • Therapy, mental health rehabilitation, family support
How do we define “recovery”? Should we?

• Patient A: has been out of hospital for 15 yrs, has a part-time job, lives independently

• Patient B: has been out of hospital for 1 yr, no employment, living in a board and care
  • But the first time staying out of hospital for more than 9 months; been out of jail for 15 yrs; been out of a locked setting finally

• Should we expect Patient A’s scenario to be the goal for all? (No)
• It’s a very “heterogeneous” disorder – presents very differently from patient to patient; what’s seen as “doing well” is also individual
  • Use “stable” and “functional”? 
Helpful resources

• You obviously already know about NAMI...

• CureSZ foundation (www.curesz.org)
  • Lots on clozapine & TD
• ClinicalTrials.gov
• Search Schizophrenia, your area, currently recruiting
• Eg 5 currently recruiting, mostly through Stanford
Thank you! 😊

Questions?

• Email: Mlilly@psynergy.org
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• Psynergy Programs, Inc – www.psynergy.org