MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

# First-episode psychosis and schizophrenia

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# Disclosures

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# MGH PSYCHOSIS CLINICAL AND RESEARCH PROGRAM

North Suffolk Mental Health Association

# Outline

A. Broad treatment principles
   - Recovery orientation
   - Prevention orientation

B. New FDA drug approvals

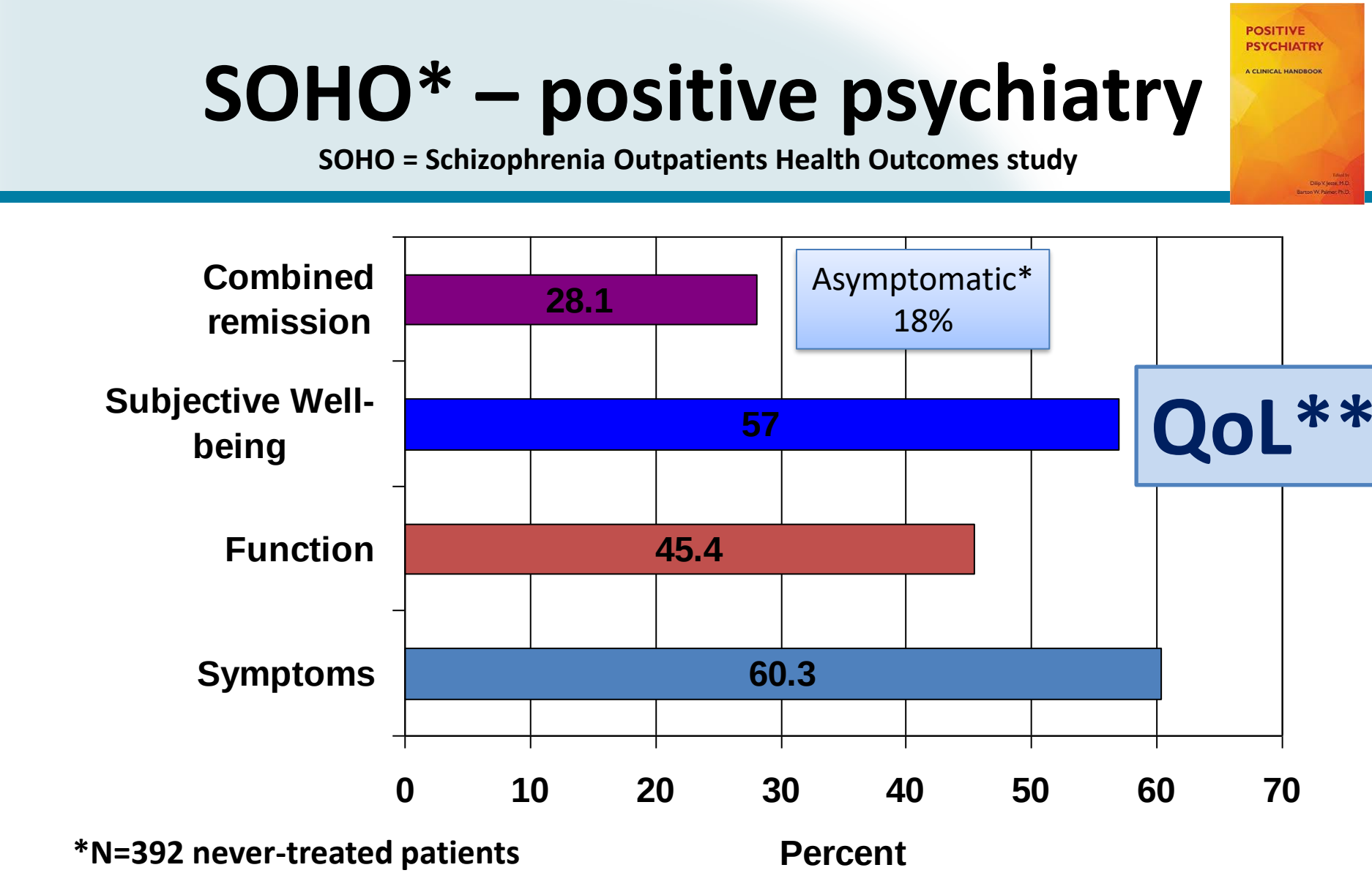
C. New stage-based insights
   - Prodromal phase
   - Acute psychosis
   - Post-psychotic/chronic phase

D. Reflections on outcome

# REVOVERY ORIENTATION

# SOHO* – positive psychiatry

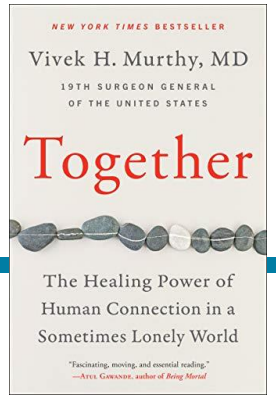
**SOHO = Schizophrenia Outpatients Health Outcomes study**



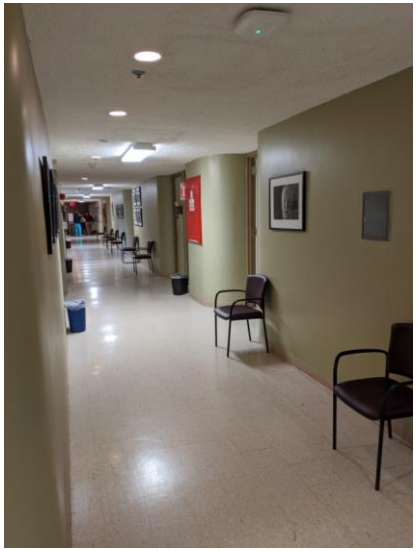

***N=392 never-treated patients**


Lambert M et al., Acta Psychiatr Scand. 2008;118:220.
MacBeth A et al. Early Interv Psychiatry. 2015;9:53.
*Schennach R et al. Schizophr Res. 2019; 209:185-192.
**Dong M et al. Psychiatr Q. 2019;90(3):519-532. [WHOQOL-BREF]

# Loneliness




- Increased mortality (HR 1.22)[1,2]
- Loneliness in SMI[3,4] "This has been my life all along."
  - Natural state of being for patients with schizophrenia
    - Negative symptoms [asociality – lack of social drive] may be protective
    - Impaired social cognition may contribute
    - Social determinants of health and stigma
  - Impairs quality of life
  - Exacerbated by social distancing
- Treatment
  - NB: self-treatment with alcohol[5]
  - Proactive outreach and accompaniment
  - Quality not quantity of social support



[1]Rico-Uribe LA et al. PLoS One. 2018 Jan 4;13(1):e0190033. [2]Holt-Lunstad J et al. Am Psychol. 2017 Sep;72(6):517-530.
[3]Michalska da Rocha B et al. Schizophr Bull. 2018 Jan 13;44(1):114-125.
[4]Eglit GML et al. PLoS One. 2018 Mar 22;13(3):e0194021. [5]Pettersen H et al. Int J Qual Stud Health Well-being. 2013 Dec 20;8:21968.
https://time.com/5833681/loneliness-covid-19/

# PREVENTION ORIENTATION

# Prevention in psychiatry

- **Primary prevention**
  - Universal prevention
    - Whole population
      - Reducing bacterial maternal infections[1]
      - Folate supplementation[2]
  - Selective prevention
    - More susceptible subgroup, still symptom free
- **Secondary prevention – "early intervention"**
  - Indicated prevention
    - Already showing signs of illness
      - Omega-3 fatty acids NOT effective[3]
      - Psychosocial support
- **Tertiary prevention – minimize disability**
  - Relapse prevention
    - Antipsychotics clear effective
      - Omega-3 fatty acids plus alpha-lipoic acid NOT effective[4]
- **Medical prevention in schizophrenia**

**We need to talk about prevention**

**Healy C and Cannon M. Am J Psychiatry. 2020;177(4):285-287.**

**Going upstream for psychosis prevention**

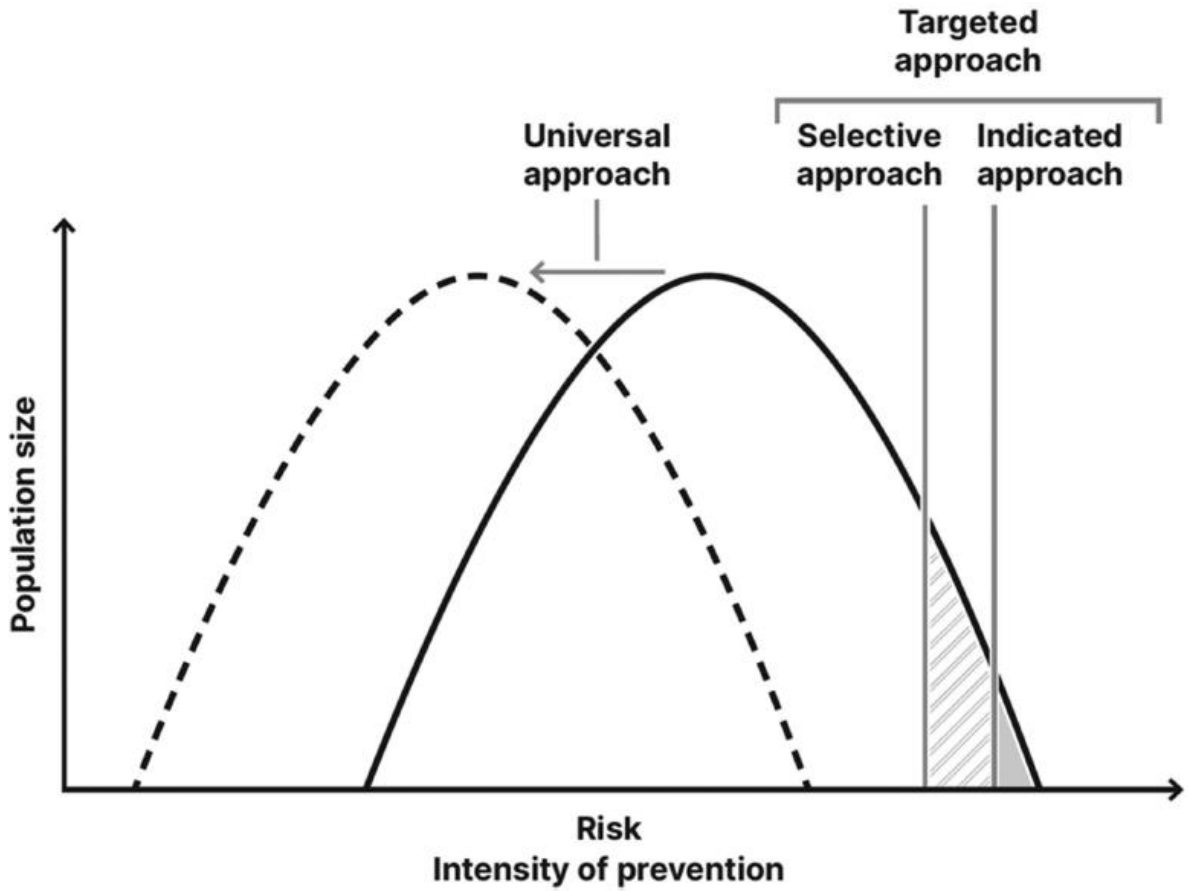
**Anglin DM et al. JAMA Psychiatry. 2020;77(7):665-666.**

**Mental health starts with physical health**

**Gates J et al. Lancet Psychiatry 2015;2:726.**

**Brown AS and McGrath JJ. Schizophr Bull 2011;37:257.**
**[1]Lee YH et al. Am J Psychiatry. 2019;177(1):66-75. [2]Roffman JL. Biol Psychiatry. 2019;84(1):4-6.**
**[3]McGorry PD et al. JAMA Psychiatry. 2017;74(1):19-27. [4]Emsley R et al. Schizophr Res 2014;158(1-3):230-5.**
**Fusar-Poli P et al. World Psychiatry. 2021;20:200-221.**

# Types of prevention




Fusar-Poli P et al. World Psychiatry. 2021;20:200-221.

# Life expectancy

- Greatly decreased compared to general population
  - 10- to 25-year reduced life expectancy
  - Two main medical causes
    - Cardiovascular disease
    - Cancer
  - Illicit drug use contributes significantly

| | |
|---|---|
| Natural causes: | 85% |
| Unnatural causes: | 15% |

- Main reasons for excess mortality
  - Poor "lifestyle choices" (diet, exercise, smoking)
  - Iatrogenic morbidity (antipsychotics)
  - Late diagnosis and poor treatment of medical illness
  - High risk of suicide and accidents
    - Suicide risk highest in young adults, particularly if suicidal symptoms and substance use
  - No psychiatric treatment
- Improved medical care needed

**Laursen TM. Curr Opin Psychiatry. 2019;32(5):388-93. Meta-analysis**
**Olfson M et al. JAMA Psychiatry 2015;72(12):1172-81.**
**Vermeulen JM et al. Schizophr Bull. 2019;45(2):315-29.**
**Taipale H et al. World Psychiatry. 2020;19(1):61-8.**
**Olfson M et al. JAMA Psychiatry. 2021;78(8):876-885. Life span Medicare cohort study**

# Beyond monitoring: need for action


- Physical health monitoring (screening) *alone* does not improve mortality
- Improving physical health through intervention[1]
  - Psychiatric stability
  - Dietary and exercise interventions
  - Choice and duration of antipsychotic prescribing
  - Pharmacological support for smoking cessation
  - Screening for health conditions
- Correct (*standard*) medical treatment saves lives[2]

[1]Ilyas A et al. Br J Psychiatry. 2017;211:194-96.
[2]Kugathasan P et al. JAMA Psychiatry. 2018;75:1234-40.
Ward MC and Druss BG. JAMA Psychiatry. 2019;76(7):759-60. [JAMA Network Insights]

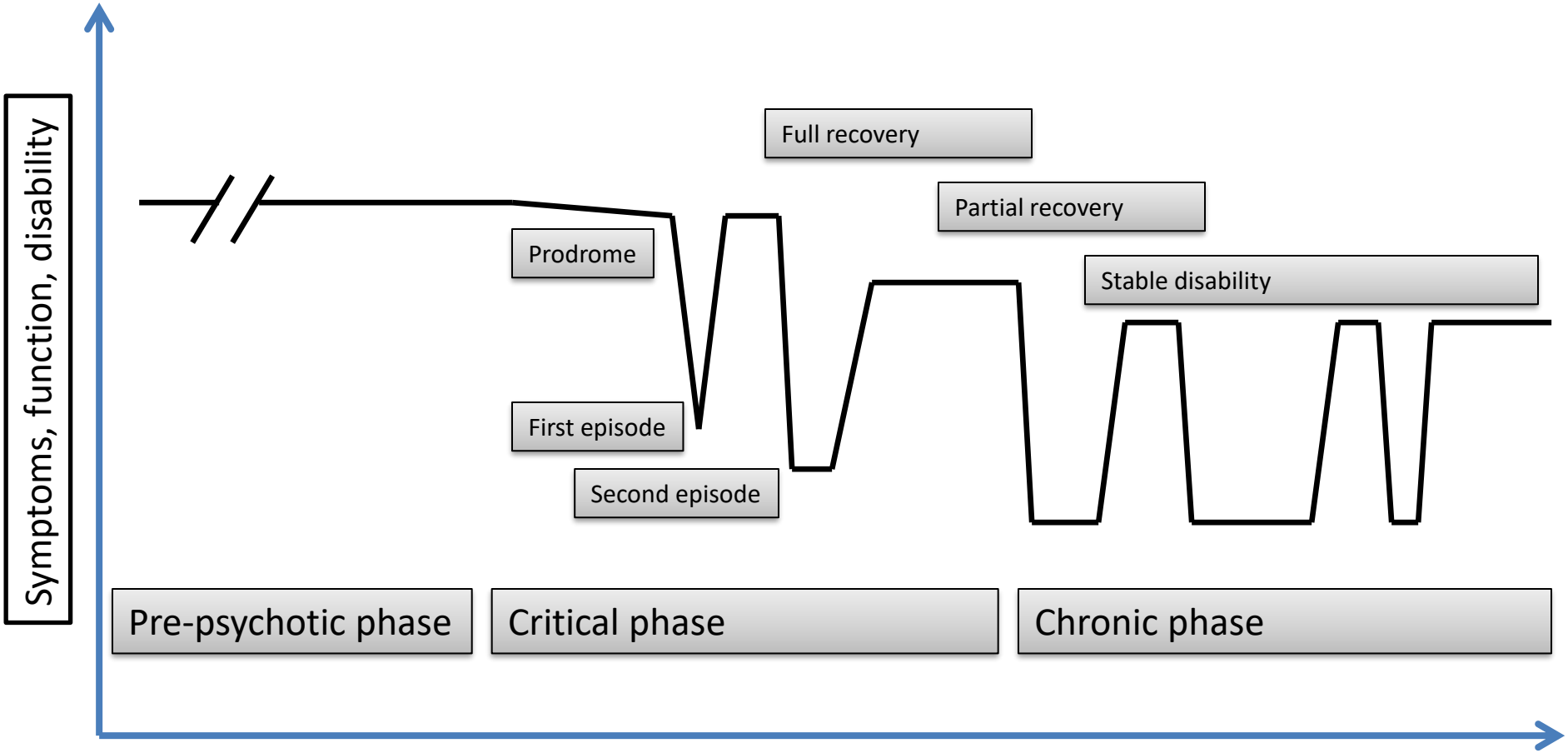
# Smoking cessation

- Prevalence remains high
  - 62% in a sample of research patients[1]
  - Smoking affects, among other things, quality of life[2]
- Address smoking in schizophrenia
  - Cardiovascular and cancer mortality[3]
  - Cognitive benefits from quitting[4]
    - Improved processing speed (digit symbol coding)
- Smoking cessation principles[5]
  - HANDS 3 trial (multi-facetted, sustained care); Brown RA et al. JAMA Psychiatry. 2021 May 5;e210707.
- Varenicline
  - Efficacy: EAGLES trial[6]
  - Safety: removal of black box warning[7]
  - Initial treatment (American Thoracic Society 2

**Needed**
Opt-out stance
Maintenance treatment

[1]Dickerson F et al. Psychiatr Serv. 2018;69:147-153. [2]Vermeulen J et al. Lancet Psychiatry. 2019;6(1)23-34.
[3]Olfson M et al. JAMA Psychiatry 2015;72(12):1172-81. [4]Vermeulen JM et al. Am J Psychiatry. 2018;. 175(11):1121-8. [5]Cather C et al. CNS Drugs. 2017;31(6):471-81. [6]Anthenelli RM et al. Lancet. 2016;387(10037):2507-20. [EAGLES trial]
[7]www.fda.gov/downloads/Drugs/DrugSafety/UCM532262.pdf [8]Leone FT et al. Am J Respir Crit Care Med. 2020 Jul 15;202(2):e5-e31.

# Typical course of schizophrenia




Freudenreich O. Psychotic Disorders. Springer 2020.

# Clinical staging in psychiatry

| STAGE | Definition | Clinical features |
|---|---|---|
| 0 | Asymptomatic subjects | Not help seeking<br>No symptoms but risk |
| 1a | "Help-seeking" subjects with symptoms | Non-specific anxiety/depression<br>Mild-to-moderate severity |
| 1b | "Attenuated syndromes" | More specific syndromes incl. mixed<br>At least moderate severity |
| 2 | Discrete disorders | Discrete depr/manic/psych/mixed sy<br>Moderate-to-severe symptoms |
| 3 | Recurrent or persistent disorder | Incomplete remission<br>Recurrent episodes |
| 4 | Severe, persistent and unremitting illness | Chronic deteriorating<br>No remission for 2 years |

**Hickie IB et al. Early Interv Psychiatry. 2013;7(1):31-43.**
**See editorial: Shah JL. JAMA Psychiatry. 2019;76(11):1121-3.**

# Staging model of treatment

Treatment as prevention

- Rational for staging
  - Avoid progression to disease stages where only amelioration is possible
  - Better response to treatments in early stages
  - Earlier treatments are less aggressive
- Principles
  - Early intervention to treat patients as early as possible in the disease course
  - Stage-specific care that tailors the interventions to the patient's needs
  - Stepped care that adjusts treatment intensity based on response
- Works best for "transdiagnostic psychiatry" in early stages

**McGorry PD and Nelson B. World Psychiatry. 2019;18(3):359-360.**
**Shah JL et al. World Psychiatry. 2020;19(2):233-242. [International Consensus Statement]**

# Early intervention: reducing duration of untreated psychosis (DUP)

- Prolonged DUP[1,2]
  - Poorer response
  - Worse outcome including for cognition[3]
- DUP can be reduced[4]
  - Clinical advantage at baseline, 2-year[4] and 5-year f/u[5]
  - *Sustained* information campaign is key[6]
- Focus on outliers[7]
- Role of lead-time bias[8,9]

[1]Perkins et al. 2005, [2]Marshall et al. 2005; [3]Stone WS et al. JAMA Psychiatry. 2020;77(11):1116-1126.
[4]Melle et al. 2004, 2008; [5]Larsen et al. 2011 [6]Joa et al. 2008; [7]Lloyd-Evans et al., Br J Psychiatry 2011;198:256.
[8]Jonas KG et al. Am J Psychiatry. 2020;177(4);327-334. [9]Goff DC et al. Am J Psychiatry. 2020;177(4):288-290.
Clinical umbrella review: Howes OD et al. World Psychiatry 2021;20(1):75-95.

# Stage-specific care: RAISE trial

**RAISE = Recovery After an Initial Schizophrenia Episode**

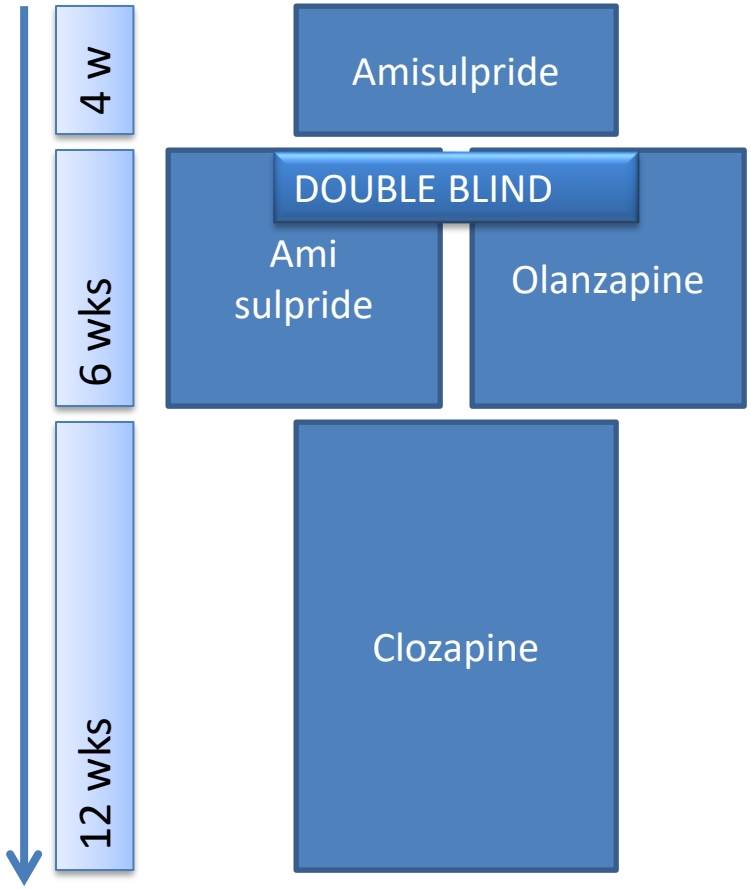
- Goal
  - Develop early-intervention system in real world of fragmented US healthcare system
- NAVIGATE
  - Cluster randomization of 34 clinics in 21 states of NAVIGATE versus community care (CC)
  - Core services: family education, resilience training, supported employment/education, medications[1]
  - N=404
- Results
  - Team-based, multi-component NAVIGATE improved primary outcome variable (QoL) more than CC[2]
  - Effects were better for those with shorter DUP (median 74 weeks)[3]
  - Improved QOL if more perceived autonomy support[4]

**QoL = Quality of Life**


**[1]Mueser KT et al. Psychiatr Serv. 2015;66(7):680-90.**
**[2]Kane JM et al. Am J Psychiatry. 2016;173(4):362-72.**
**[3]Addington J et al. Psychiatr Serv. 2015;66(7):753-6.**
**[4]Browne J et al. Psychiatr Serv. 2017;68(9):916-922.**

# Stepped care: early use of clozapine

**OPTiMiSE = Optimization of Treatment and Management of Schizophrenia in Europe**




- Good overall *remission* rate after 10 weeks of treatment
  - 2/3 of patients
- 56% responded in four weeks to amisulpride
- No added benefit from switching to olanzapine
- Some benefit from switching to clozapine (25%) but not as good as responders

**Leucht, S et al. Schizophr Bull. 2015;41:549-58.**
**Kahn RS et al. Lancet Psychiatry. 2018; 5(10):797-807.**

# Stage-specific care

## Stage 1 (Clinical high-risk)

- **High index of suspicion (functional decline, withdrawal, distress)**
- **Offer needs-based psychosocial care**
- **Treat identifiable comorbidities; avoid antipsychotics**

## Stage 2 (first-episode psychosis)

- **Reduce duration of untreated psychosis**
- **Use low doses of antipsychotics to minimize side effects**
- **Offer coordinated specialty care**
- **Offer LAIs and clozapine if no symptomatic remission in 3-6 months**

## Stage 3 and 4

- **Retain optimistic stance**
- **Focus on quality of life and vocational rehabilitation**
- **Pay attention to physical health**

https://www.psychiatrictimes.com/view/stage-specific-treatment-of-psychotic-disorders

# New FDA drug approvals

- 2017: Valbenazine[1]
  - Approved for tardive dyskinesia (TD)
  - VMAT-2 inhibitor
- 2017: Deutetrabenazine[2]
  - Approved for Huntington's disease and TD
  - VMAT-2 inhibitor
- 2017: Proteus sensor for aripiprazole
- 2017: Aripiprazole lauroxil long-acting injectable
  - 2-month dosage
- 2018: Aripiprazole lauroxil long-acting injectable
  - New initiation regimen
- 2018: SC risperidone long-acting injectable
- 2019: Transdermal patch asenapine [brand name Secuado]
- 2019: Lumateperone [brand name Caplyta]
- 2021: Olanzapine plus samidorphan [brand name Lybalvi]

**[1]Freudenreich O and Remington G. Clin Schizophr Relat Psychoses. 2017;11(2):113-119.**
**[2]Anderson KE et al. Lancet Psychiatry. 2017;4(8):595-604.**

FDA approval October 15, 2019

# Asenapine patch

- Transdermal patch[1]
- Efficacy
  - 6-week, placebo-controlled phase-3 trial[2]
- Dosing
  - Once-a-day patch 3.8mg/24hr, increase after one week to 5.7 or 7.6mg/24 hrs
- Drug interactions
  - CYP1A2 and UGT1A4 substrate; weak CYP2D6 inhibitor
  - QTc prolongation
  - Orthostatic hypotension
- Side effects
  - EPS, weight gain; rash at application site (10%)
- Patient selection
  - Dysphagia
  - Can be used in mild-to-severe renal impairment
  - Can be used in mild-to-moderate hepatic impairment
  - Easy visibility of patch in controlled settings

Dose conversion
3.8mg/24hr = 5 mg bid SL
7.6mg/24hr = 10 mg bid SL

**[1]Citrome L et al. J Clin Psychiatry. 2019;80(4):18nr12554.**
**[2]Citrome L et al. J Clin Psychiatry. 2020;82(1):20m13602.**
**Suzuki K et al. J Clin Psychopharmacol. 2021;41(3):286-294. [Pharmacokinetics]**

FDA approval December 23, 2019

# Lumateperone

**Brand name CAPLYTA, from Intra-Cellular Therapies; ITI-007 in clinical trials**

- FDA-approved for schizophrenia in adults; not studied in geriatric patients
- MOA
  - Includes antagonism for 5-HT2A >>> (post-synaptic) D2 receptors[1]
  - Only 40% D2 occupancy
  - Also binds to serotonin transporter; D1; others; low muscarinic and histaminergic[2]
- Dosing: 42 mg once daily with food
- Metabolism: very complex; 3A4 and UGT (VPA!) clinically relevant
- Clinical assessment
  - Effectiveness established in 2 trials for 42 mg; failed at lower and higher doses (narrow therapeutic window)[3]
  - Somnolence (24% vs 10%); nausea (9% vs 5%), dry mouth (6% vs2%). EPS rates similar
  - Long-term experience needed to judge relative position vis-à-vis metabolic liability but may be favorable[4]
  - Insignificant QTc increase


[1]Vanover KE et al. Neuropsychopharmacology. 2019;44(3):598-605.

[2]Kumar B et al. Drugs Today. 2018;54(12):713-9.

[3]Correll CU et al. JAMA Psychiatry. 2020;77(4):349-358. [Phase 3 trial]

[4]Edwards JB et al. CNS Spectr. 2021;26(2):152. [Pooled analysis] Correll CU et al. Schizophr Res. 2021;229:198-205

FDA approval Jun 1, 2021

# Samidorphan/olanzapine (ALKS 3831)

**Brand name Lybalvi, from Alkermes; ALKS 3831 in clinical trials**

- ALKS 3831 = samidorphan + olanzapine
  - Samidorphan[1]
    - 3-carboxamido-4-hydroxynaltrexone
    - Potent mu-opioid receptor antagonist
- Dosing
  - Olanzapine 5/10/15/20 mg + samidorphan 10 mg
- Drug-drug interactions
  - Opiates
    - Accidental overdose
    - Opiate withdrawal
- Side effects
  - See olanzapine
  - See drug-drug interactions with opiates

**NOT FOR PEOPLE WHO ARE TAKING OPIATES!**

[1]Turncliff R et al. Clin Ther. 2015;37(2):338-48. Silverman BL et al. Schizophr Res. 2018;195:245-251. [Phase I, PoC]
[2]Potkin SG et al. J Clin Psychiatry. 2020;81(2):61-9.
[3]ClinicalTrials.gov Identifier: NCT02694328. [4]Brunette MF et al. J Clin Psychiatry. 2020;81(2):22-9.
[5]Pathak S et al. J Clin Psychiatry. 2020;81(2):19m12731.

# New stage-based insights

| | GOALS | KEY QUESTION |
|---|---|---|
| **Prodromal Phase** | Prevent psychosis<br>Prevent schizophrenia? | Treat with antipsychotic? |
| **Acute Psychosis** | Keep DUP short<br>Achieve initial response and early positive symptoms remission | Which antipsychotic?<br>Problem: early non-response (positive Sx) |
| **Post-psychotic Phase** | Achieve sustained remission<br>Recovery and QOL<br>Prevent morbidity | Treat for how long?<br>Problems: early relapse and residual Sx (adherence); risk-benefit |

# PRODROMAL PHASE

# Prodromal schizophrenia

DSM-5 Attenuated Psychosis Syndrome (APS)*

- Prodrome can only be diagnosed in retrospect
  - Transition risk for putatively prodromal patients not 100%[1]
    - 18% after 6 months
    - 22% after 1 year
    - 29% after 2 years
    - 36% after 3 years
- Transition risk prediction in its infancy
  - No Framingham risk score (yet) for selective or indicated prevention
  - Low positive predictive value of positive symptoms (less than 2%)[3]
  - Polygenic risk score enhances prediction (somewhat)[4]
- Majority will not convert (stage 2) but is help-seeking[5]
  - "Probably at risk but certainly ill"
  - Heterogeneous neurocognitive trajectories[6]
- Increasing appreciation of social determinants of health risk factors
  - Example, deprived environments and cognitive development[7]

**PLEIOTROPIC**

**BROAD SYNDROME OF MENTAL DISTRESS**

[1]Fusar-Poli P. Arch Gen Psychiatry. 2012;69(3):220-9. [2]Lin A et al. Am J Psychiatry. 2015;172(3):249-58.
[3]Livny A et al. Am J Psychiatry. 2018;175(4):351-8. [4]Muarry GK et al. JAMA Psychiatry. 2021;78(2):210-219. [Clinical Review]
[5]Iorfino F et al. JAMA Psychiatry. 2019;76(11):1167-75. Fusar-Poli P et al. JAMA Psychiatry. 2020;77(7):755-764.
[6]Gold JM et al. JAMA Psychiatry. 2021;78(8):827-828. [7]Lewis G et al. JAMA Psychiatry. 2020;77(7):729-736.
*Salazar de Pablo G et al. JAMA Psychiatry. 2020;77(3):311-320. Corcoran CM et al. JAMA Psychiatry. 2021;78(8):821-822.

# Early intervention CHR guidance

**IEPA=International Early Psychosis Association[1]**

**EPA = European Psychiatric Association[2]**

- Assess and treat syndromes (anxiety, depression)
- Benign interventions to delay conversion[1,2]
  - CBT should be first-line treatment
  - Integrated psychological interventions (EDIPPP)[3]
  - Omega-3 fatty acids ineffective;[4] NAC?; minocycline?
- Use of antipsychotics
  - Low-dose second-generation antipsychotic
  - If severe symptomatology
  - *Not* long-term for primarily preventive purpose
- Note: do not treat for pseudo-ADD with stimulants[5,6,7]


[1]Br J Psychiatry Suppl. 2005 Aug;48:s120.
[2]Schmidt SC et al. Eur Psychiatry 2015;30:388.
[3]McFarlane et al. Schizophr Bull 2015;41:30.
[4]McGorry PD et al. JAMA Psychiatry. 2017;74(1):19-27.
[5]Freudenreich O et al. Am J Psychiatry 2006;163:2019.
[6]MacKenzie LA et al. Pediatrics 2016;137:1.
7Moran LV et al. NEJM. 2019;380(12):1128-38.

# Cannabis guidance

US Surgeon General's Advisory:
Marijuana use and the developing brain

- Clear down-sides
  - Component risk factor for 12% of schizophrenia[1]
    - Increased population attributable risk fraction from 2% to 6-8%[2]
  - Commercialization leading to potent THC products[3]
  - Destabilizes early course schizophrenia via reduced adherence[4]
  - Effects on adolescent brain (cognition)
- CBD oil (brand name Epidiolex) (Schedule V)
  - 2018 FDA-approved for Lennox-Gastaut and Dravet syndrome
  - Off-label prescribing
  - Minimal research regarding CBD

**Pierre JM. Curr Psychiatry. 2019;18(5):13-20. Brunette MF et al. Psychiatr Serv. 2018;69(11):1181-3.**
**[1]Di Forti M et al. Lancet Psychiatry. 2019;6(5):427-36. [2]Hjorthøj C et al. JAMA Psychiatry. 2021 (in press).**
**[3]Murray RM and Hall W. JAMA Psychiatry. 2020;77(8):777-8. [4]Schoeler T et al. Lancet Psychiatry. 2017;4(8):627-33.**
https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/advisory-on-marijuana-use-and-developing-brain/index.html

# ACUTE PSYCHOSIS

**“Der Ball ist rund und das Spiel dauert 90 Minuten.”**

**- Sepp Herberger**

# First-episode work-up: neuroimaging

- No consensus
  - Disadvantages
    - False-positive results
    - CT scan means radiation exposure
  - Unlikely discovery of secondary psychosis in young adults without neurological abnormalities
    - EPIP sample chart review 1998-2016: 380 CT scans, 92 MRIs; age 20
    - CT scan with 4.7% incidental findings (#1 arachnoid cysts)
    - MRI scan with 11.1% incidental findings
- Clinical guidance
  - Clear indication if intracranial pathology suggested
  - CT sufficient for mass or hemorrhage and urgent intervention
  - MRI scan is more sensitive and prone to incidental findings but may (in future) be better course predictor (cortical thinning)

**EPIP = Early Psychosis Intervention Program (EPIP) in Calgary, AB**

**Andrea S et al. J Clin Psychiatry. 2019;80(6):18m12665.**

# Synaptic autoantibodies

- Most important for psychiatry: NMDAR
- Triggers
  - Tumors, viral triggers (HSV)
- Phases
  - Prodromal, psychiatric, classic neurological, recovery
- Polypmorphous psychopathology
- Severe sleep disturbance
- Diagnosis
  - CSF abnormal; MRI normal, EEG abnormal
  - CAVE: Seronegative presentations![2]
  - CAVE: Methodology really matters![3]
  - Clinical screening criteria[4]
- Treatment
  - Prolonged immunotherapy (problem: poor penetration BBB)
  - Benzodiazepines; antipsychotic poorly tolerated

Very few have AB in CSF in established schizophrenia including TRS.[1]
FEP = up to 5%

Anti-NMDA receptor encephalitis is a clinical diagnosis.

**Graus F et al. Lancet Neurol. 2016;15(4):391-404. [Diagnostic Guideline]**
**[1]Kelleher E et al. Schizophr Res. 2020 (in press). [2]Lavasani S et al. Psychosomatics. 2020;61(3):288-295.**
**[3]Hoffmann C et al. JAMA Psychiatry. 2020;77(3):322-325. [4]Warren N et al. J Psychiatr Res. 2020;125:28-32.**

# Substance-induced psychosis

- Danish population-based registry study[1,2]
  - 20-year follow-up
  - N=6,778
  - Majority alcohol, cannabis, amphetamines
  - 32.2% of patients converted to schizophrenia or bipolar disorder
    - Substantial differences in conversion rates between substances
      - Almost 50% if cannabis-induced psychosis
    - Half converted within 3 years to schizophrenia
    - The younger the patient, the higher the conversion risk
- Implications
  - 50% of cannabis induced psychosis will become schizophrenia
  - Longer-term follow-up and treatment needed to prevent schizophrenia?
  - Will legalization of cannabis increase psychosis incidence?[3]
- "…drug-precipitated disorder in highly vulnerable individuals"[4,5]

[1]Starzer MSK et al. Am J Psychiatry. 2018;175(4):343-50.
[2]Ghose S. Am J Psychiatry. 2018;175(4):303-4. [Editorial] [3]Murray RM and Hall W. JAMA Psychiatry. 2020;77(8):777-8.
[4]Kendler KS et al. Am J Psychiatry. 2019;176(9):711-9.
[5]Tandon R and Shariff SM. Am J Psychiatry. 2019;176(9);683-4. [Editorial]

# Antipsychotic choice

- Efficacy[1,2]
  - Antipsychotics not equivalent
    - Clozapine ES 0.88
    - Olanzapine ES 0.59
    - Risperidone ES 0.56
  - Overall efficacy for rest
    - ES 0.33 to 0.50
- Avoid haloperidol in first-episode patients[3]
- Partial agonist antipsychotics
  - No higher risk for psychiatric hospitalization when switching to aripiprazole[4]

**Choose wisely**


[1]Smith RC et al. Psychopharmacology. 2019;236(2):545-59.
[2]Leucht S et al. Lancet. 2013;382(9896):951-62. Huhn M et al. Lancet. 2019;6736(19):1-13.
[3]Zhu Y et al. Lancet Psychiatry. 2017;4(9):649-705. [network meta-analysis]
[4]Montastruc F et al. JAMA Psychiatry. 2019;76(4):409-17.

# Antipsychotic dosing

- More is not necessarily better
  - Neuroleptic threshold for first-generation antipsychotics
  - Lower dose range for first-episode patients
  - Very few studies have established possible benefit for high-dose approach (olanzapine)
  - TDM for outliers
- Dose-response meta-analysis[1]
  - Approved dose ranges based on initial estimates from animal studies often too high
  - 95% effective dose (ED95) based on data
    - Table 1 with ED95 (calculated optimal dose), equivalence doses, minimum effective dose, maximum dose
- Use standard (acute stabilization) dose for maintenance[2]

[1]Leucht S et al. Am J Psychiatry. 2020;177(4):342-353.
[2]Hojlund M et al. Lancet Psychiatry. 2021;8:471-486.

# TDM – Potential benefits

- Consensus statement
- Informed decision regarding root causes of treatment complications
  - Poor response to antipsychotics (25% of patients)
    - Pseudo-refractoriness (non-adherence) vs. refractoriness*
  - Poor tolerability of antipsychotics (15% of patients)
    - Slow elimination vs. high drug sensitivity
- Identifies patients at higher relapse risk[1]
- Indications
  - Non-response at therapeutic doses
  - Uncertain drug adherence
  - Suboptimal tolerability
  - Pharmacokinetic drug-drug interactions

***1 in 5 TRS patients have non-detectable drug level.**

**Schoretsanitis G et al. J Clin Psychiatry. 2020;81(3):19cs13169. Predmore Z et al. Psychiatr Serv. 2018;69:12-4.**
**[1] Melkote R et al. Schizophr Res. 2018; 201:324-328. [CATIE sample]**
*** McCutcheon R et al. Acta Psychiatr Scand. 2018;137(1): 39–46.**

# German Schizophrenia Guideline 2019

- There are a multitude of guidelines[1]
- Revised, national guidelines on schizophrenia[2]
  - Large efforts, with many stakeholders
  - Comprehensive
    - 7 modules
    - Challenging clinical situations
- Notable recommendations
  - Diagnosis
    - Include MRI in first-episode work-up
  - Treatment
    - Indeterminate duration of maintenance treatment after first-episode of psychosis
    - Physical health monitoring is part of psychiatric care

**DGPPN = Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde**

**[1]Keating D, et al. BMJ Open 2017;7:e013881. [2]Available at www.awmf.org, including in English**

# Post-Psychotic/ Chronic phase

**Nach dem Spiel ist vor dem Spiel.**

**- Sepp Herberger**

# Treatable comorbidities

- Substance use
  - Common, course-destabilizing
  - Alcohol use disorders
    - Post-hoc analysis of CATIE[1]
      - Olanzapine better than other antipsychotics
    - Negative trial: ALKS 3831 = samidorphan + olanzapine
- Psychiatric comorbidities[3]
  - Agoraphobic avoidance, worry, self-esteem, insomnia
  - Dimensions of psychopathology
    - Negative symptoms
    - Cognitive symptoms
      - Cog rem (active therapist, structured, integrated with rehab)[4]
- Medical comorbidities

**[1]Pathak S et al. J Clin Psychiatry. 2020;81(2):19m12731.**
**[2]Brunette MF et al. J Clin Psychiatry. 2020;81(2):22-9.**
**[3]Freeman D et al. Schizophr Res. 2019;211:44-50.**

# Cost of relapse in schizophrenia

- Relapse has **psychosocial toxicity**
  - Loss of job
  - Derailed education
  - Criminal problems
  - Suicide
  - Loss of reputation
- Relapse might be biologically harmful[1]
  - Emergent treatment non-response in 16%
- Sustained remission is basis for accrued treatment benefits over time

**Relapse prevention is key goal of schizophrenia care**



[1]Emsley R et al. J Clin Psychopharmacol. 2013;33(1):80-3.

# Non-adherence

**NNT = 3**

- Antipsychotics are highly effective to prevent relapse[1]
- The reality of first-episode psychosis[2]
  - One fifth not using services
  - Majority not using antipsychotics following first episode
- Non-adherence as system failure
  - Team-based prescribing[3]
- Patient-centered solutions[4]
  - Medication as a tool
  - Shared decision making
  - Family engagement
- Prescribing hope for recovery[5]

[1]Leucht S et al. Lancet 2012;379: 2063-2071. [2]Gilmer TP et al. Schizophr Bull. 2020;46(1):91-97. [3]Plowman RS et al. Acad Med. 2020;95(8):1186-90. [4]Brown HE et al. JAMA Psychiatry. 2020;77(7):766-7. [5]https://www.psychiatrictimes.com/view/prescribing-hope-for-recovery

# Long-acting injectable antipsychotics

| Drug | Dose strengths | Dose (IM) & Frequency | Notes |
|---|---|---|---|
| Haloperidol decanoate<br>[HALDOL DECANOATE] | Vials 50mg/ml<br>Vials 100mg/ml | 50 - 200 mg monthly<br>Other dose intervals are possible | Initiation: overlap with oral antipsychotic<br>Loading dose strategy possible<br>Maintenance dose equals 20 x oral dose |
| Fluphenazine decanoate<br>[PROLIXIN DECANOATE] | Vials 25mg/ml | 6.25 - 25 mg every 2 weeks<br>Other dose intervals are possible | Initiation: overlap with oral antipsychotic |
| Risperidone microspheres<br>[RISPERDAL CONSTA] | 12.5mg, 25 mg, 37.5 mg, 50 mg | 12.5-50 mg every 2 weeks | Initiation: 3 week overlap with oral antipsychotic<br>Main release of drug occurs 3 weeks after injection<br>50 mg every two weeks corresponds to 4 mg/d oral (50 mg is highest IM dose] |
| Risperidone long-acting suspension<br>[PERSERIS] | 90 mg, 120 mg | 90 or 120 mg monthly<br>subcutaneously | For subcuaneous use<br>90 mg corresponds to 3 mg/d oral<br>120 mg corresponds to 4 mg/d oral |
| Paliperidone palmitate<br>[INVEGA SUSTENNA]<br><br>[INVEGA TRINZA] | 39 mg, 78 mg, 117 mg, 156 mg, 234 mg<br><br>273 mg, 410 mg, 546 mg, 819 mg | 39-234 mg monthly<br><br>273-819 mg every 3 months | Loading dose of 234 mg [deltoid!] to initiate (no oral overlap needed), 2nd dose one week later, the monthly<br>156 mg monthly corresponds to 9 mg/d oral<br>Every 3 months dose can be used after 4 months of monthly injections<br>546 mg corresponds to 9 mg/d oral |
| Olanzapine pamoate<br>[ZYPREXA RELVPEVV] | 150 mg, 210 mg, 300 mg, 405 mg | 150 or 300 mg every 2 weeks<br>405 mg monthly | No overlap with oral antipsychotic (higher initiation doses)<br>Monitor for 3 hours of observation for post-injection delirium/sedation syndrome (PDSS)*<br>300 mg monthly corresponds to 10 mg/d oral |
| Aripiprazole monohydrate<br>[ABILIFY MAINTENA] | Vials 200 mg/ml | 160mg- 400mg monthly | Initiation: 2 week overlap with oral antipsychotic<br>300 mg corresponds to 10 mg/d oral; 400 mg to 15 mg/d |
| Aripiprazole lauroxil<br>[ARISTADA] | 441 mg, 662 mg, 882 mg, 1064 mg | 441,662,882 mg every 4 weeks<br>882 mg every 6 weeks<br>1064 mg every 2 months | Initiation: 3 week overlap with oral antipsychotic or with initiation regimen<br>Inject rapidly due to non-Newtonian fluid characteristics<br>Only lowest dose of 441 mg dose can be given in deltoid<br>441 mg monthly corresponds to 10 mg/d oral<br>662 mg monthly or 1064 mg every two months corresponds to 15 mg/d oral<br>882 mg monthly corresponds to 20 mg/d oral (highest IM dose) |

Oral test dose required for all antipsychotic if patient has never been exposed to IM antipsychotic
*See REMS website for olanzapine pamoate

# Long-acting injectable antipsychotic medications

- Relapse risk 20 to 30% lower for LAI compared to oral[1]
  - 56% reduction in mirror image studies[2]
- Can be life-saving[3]
  - 30% lower risk LAI compared to oral antipsychotic
- Shared decision-making should be based on facts
  - LAI gives real-time, accurate information about adherence
  - Avoids family conflict
- Best if employed as part of comprehensive care program
  - Frequent clinical contact as valid psychosocial relapse prevention[4]
  - Breakthrough symptoms (hospitalization) still high: 30% incidence[5]
- You and you team may be the biggest barrier![6]
  - In finished  PRELAPSE trial, early-phase patients accept LAI[7]

[1]Tiihonen J et al. JAMA Psychiatry. 2017 Jul 1;74(7):686-693.
[2]Kishimoto T et al. Lancet Psychiatry. 2021;8(5):387-404. [3]Taipale H et al. Schizophr Res. 2018; 197:274-280.
[4]Buckley PF et al. Psychiatr Serv. 2016(12);67:1370-72. [5]Rubio JM et al. Psychol Med. 2019; 13:1-12.
[6]Robinson DG et al. Psychiatr Serv. 2020;71(4):337-342. [7]Kane JM et a. J Clin Psychiatry. 2019;80(3):18m12546.

# LAIs update

- Early use of LAIs
  - PRELAPSE trial[1]
  - Better efficacy in patients with shorter illness duration[2]
  - Lower risk of death, reduces suicide risk by half[3]
- Use of LAIs to reduce arrests/incarcerations
  - Post-hoc analysis of PRIDE study[4]
    - Monthly LAI paliperidone palmitate
  - Focus on Black/African American patients

**High mortality risk from suicide in first 5 years after diagnosis.**
-Kurdyak P et al. Schizophr Bull. 2021;47(3):864-74.


[1]Kane JM et al. JAMA Psychiatry. 2020;77(12):1217-1224.
[2]Kim S et al. J Clin Psychiatry. 2021;82(1):20m13446.
[3]Huang CY et al. 2021 May 3;4(5):e218810.
[4]Bell Lynum K et al. J Clin Psychiatry. 2021;82(2):20m13356.

# LAI use during COVID-19

Ideally, patients should be seen as infrequently as medically prudent *in-person* during this public health emergency, to limit the possibility of exposure (both patients and staff)

- Outpatient clinic
  - Have a plan how to continue giving injections
    - Make a spread sheet (population-based management)
    - Who can do it and where?
    - Every patients needs to have an individual plan: stay, switch LAIs, switch to oral
  - Develop optimal mixture between in-person contact and telepsychiatry
  - Plan on resuming metabolic monitoring
- Inpatient setting
  - Consider initiating LAI during hospitalization
  - Plan to give patient injection on day of discharge
- Emergency room
  - May be an option but only *if everything else fails*

Harm reduction approach for patients unlikely to be adherent after discharge

Reduce changes of gap in antipsychotic coverage during transition of care

**Schnitzer K et al. Current Psychiatry. 2021;20(2):8-13.**
**https://smiadviser.org/knowledge_post/what-are-clinical-considerations-for-giving-lais-during-the-covid-19-public-health-emergency**

# Not everyone gets better with first-line antipsychotics

- Move to clozapine[1]
  - Refractoriness
  - Aggression and self-injury
- Risks of not prescribing clozapine
  - Accruing psychosocial toxicity
  - "End-stage" brain disease with poor function
  - Polypharmacy
  - Higher mortality[4]

**Over 80% of refractory patients are refractory from the start.[2]**

**Clozapine has real-world effectiveness for relapse prevention.[3]**


[1]Warnez S and Alessi-Severini S. BMC Psychiatry. 2014;14:102.
[2]Demjaha A et al. Psychol Med. 2017;47(11):1981-9.
[3]Tiihonen J et al. JAMA Psychiatry. 2017;74(7):686-93.
[4]Tiihonen J et al. Lancet. 2009;374(9690):620-7.

# Clozapine news

(Re-)enroll and (re-)certify in new Clozapine REMS
DEADLINE: November 15, 2021
https://www.newclozapinerems.com/home

**Good for survival**
**FIN 20 study**
Vermeulen JM et al. Schizophr Bull. 2019;45(2):315-29.
Taipale H et al. World Psychiatry. 2020;19(1):61-8.

- Effectiveness
  - Excellent for relapse prevention[1]
  - Clozapine augmentation strategies are limited[2]
  - Clozapine plus aripiprazole prevents hospitalizations[3]
  - Best clinical efficacy for all patients, **not limited to TRS**[4]
- Safety
  - Diabetes, hyperlipidemia, **intestinal obstruction**[5]
  - Underappreciated: **aspiration pneumonia**[6]
  - Feasible to continue during chemotherapy[7]
  - Utility of clozapine to norclozapine ratio?[8]

[1]Tiihonen J et al. JAMA Psychiatry. 2017;74(7):686-93. [2]Correll CU et al. JAMA Psychiatry. 2017;74(7):675-84.
[3]Tiihonen J et al. JAMA Psychiatry. 2019 [Epub ahead of print]. [4]Mizuno Y et al. Neuropsychopharmacology. 2020;45(4):622-631.
[5]Stroup TS et al. Am J Psychiatry. 2016;173:166-73. [6]De Leon H et al. World Psychiatry. 2020;19(1):120-1.
[7]Grainger BT et al. Eur J Haematol. 2019 (in press). [Review] [8]Costa-Dookan KA et al. Expert Opin Drug Saf. 2020 Jan;19(1):43-57.

# Clozapine use during COVID-19

- Consensus statement on the use of clozapine during the COVID-19 pandemic[1]
  - REC #1: Criteria for up to 90-day clozapine supply
  - REC #2: Evaluate for any new infection
  - REC #3: Consider reducing clozapine dose during infection
- Consistent with FDA guidance[2]
- Endorsed by many states including MA and countries
- Pay attention to differential diagnosis![3]

[1]Siskind D et al. J Psychiatry Neurosci. 2020 Apr 3;45(4):200061. doi: 10.1503/jpn.200061.
[2]https://www.fda.gov/media/136317/download
[3]Dotson S et al. Psychosomatics. 2020; 61(5):577-578.

# Aggression prevention

- Dangerous triad of psychosis, young male, sociopathy
- RTC
  - Clozapine > olanzapine > haloperidol
  - Conduct disorder

Consider clozapine for prevention of violence in patients with psychosis, particularly if conduct disorder is present

**Krakowski M et al. Am J Psychiatry. 2021;178(3):266-274.**
**Faay MDM and Sommer IE. Am J Psychiatry. 2021;178(3):218-220. [Editorial]**

# APA Schizophrenia Guideline, 3rd ed

- Assessment and treatment plan
- Psychopharmacology
  - Clozapine for TRS, suicidality, or aggression
  - LAIs as a good choice if preferred or if adherence poor or uncertain
  - VMAT-2 inhibitors as treatment of choice for TD
- Psychosocial interventions
  - Coordinated specialty care for first-episode patients

https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841

# REFLECTIONS

# The return of social medicine



**„Die Medizin ist eine soziale Wissenschaft, und die Politik ist nichts weiter als Medizin im Großen.“**

- Rudolf Virchow, 1821-1902

**Waitzkin H. Social Medicine. 2006;1:5-10.**

# Contributors to poor outcomes

- Unresponsive biology

- Time spent psychotic, in hospitals, or idle at home
- Poor access to treatment and no care
- Substandard psychiatric care
- Poor engagement in ongoing care and poor adherence
- Substance use
- Comorbid medical disorders
- Multiple social determinants of health

Health disparities in society are magnified during COVID-19.

**Zipursky RB. J Clin Psychiatry. 2014; 75 Suppl 2:20-4.**
**Bartels S et al. Psychiatr Serv. 2020;71(10):1078-1081.**

# The shocking reality…

Risk factors for mortality from COVID-19

#1 Age

#2 Diagnosis of schizophrenia

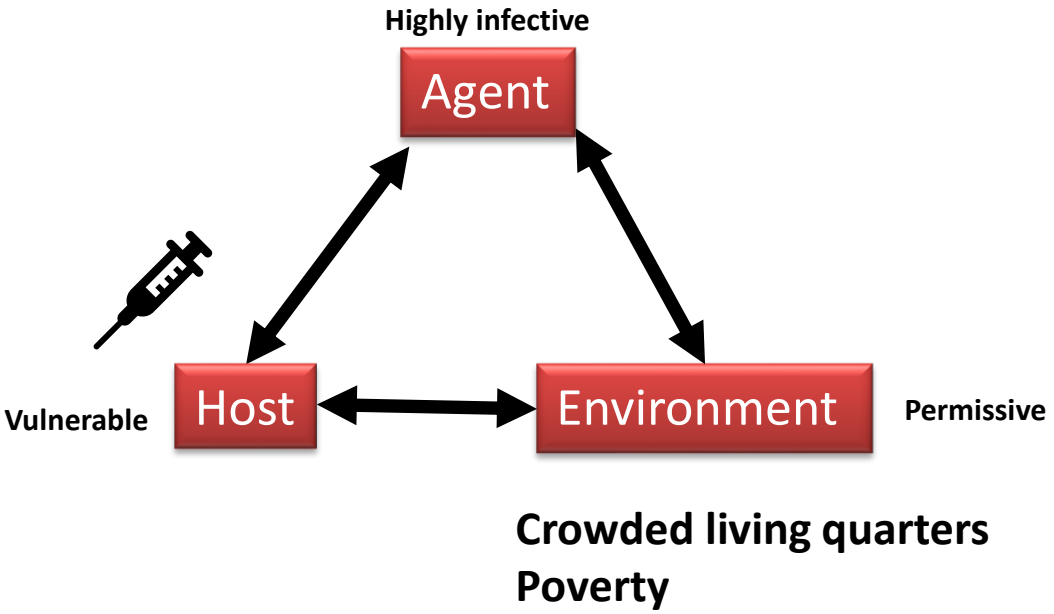
Nemani K et al. JAMA Psychiatry. 2021;78(4):380-386.
Vai B et al. Lancet Psychiatry. 2021 (in press).

**OR = 2.0**

# “Tragic” epidemiologic triad of SMI and COVID-19

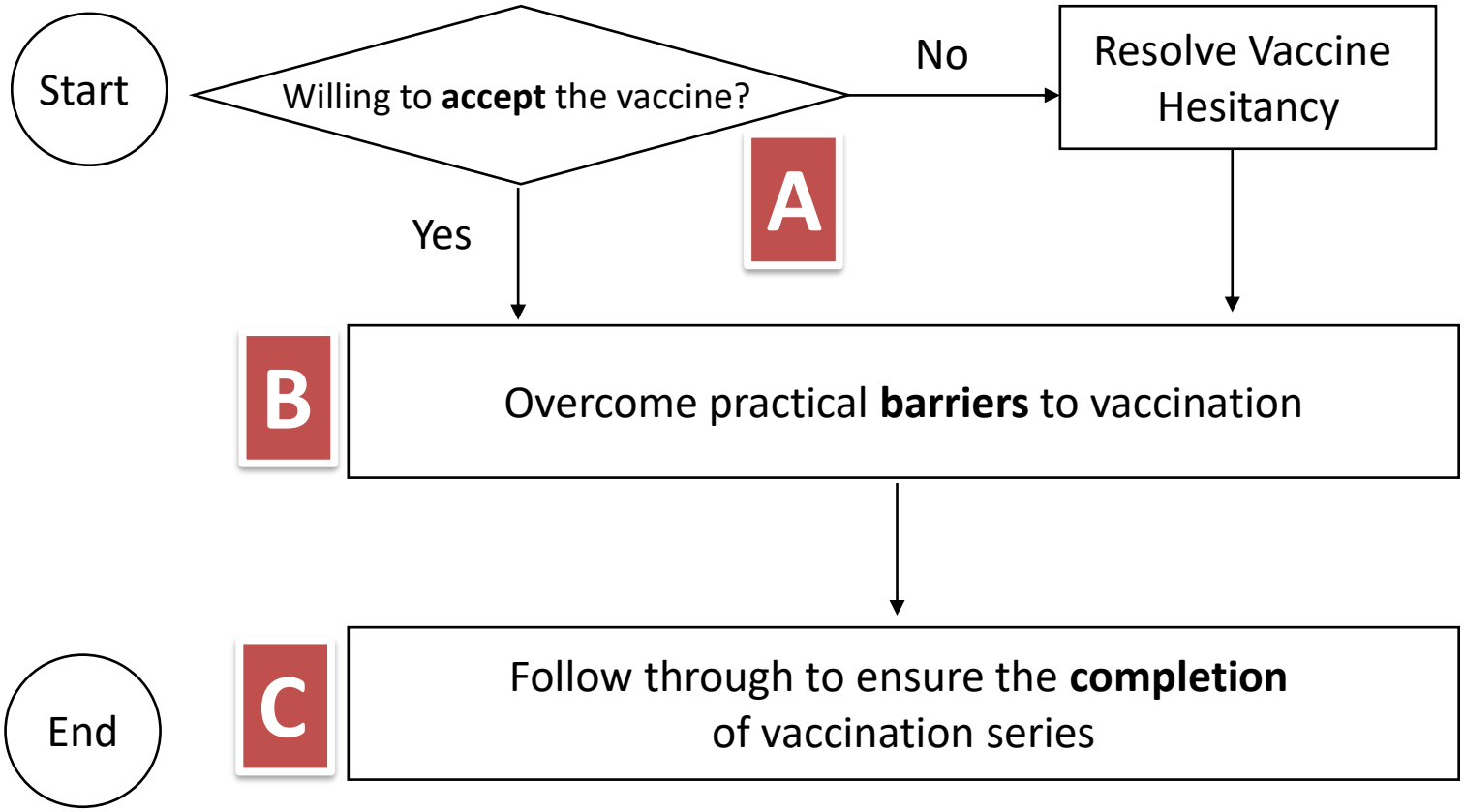
**Psychiatric illness**
-Acute psychosis/mania
-Disorganization
-Negative symptoms
-Cognitive difficulties

**Medical comorbidities**
-Obesity
-Smoking
-Lung disease
-Diabetes




Freudenreich O et al. Current Psychiatry. 2020;19(9):24-39.

# Operation Warp Speed alone is insufficient



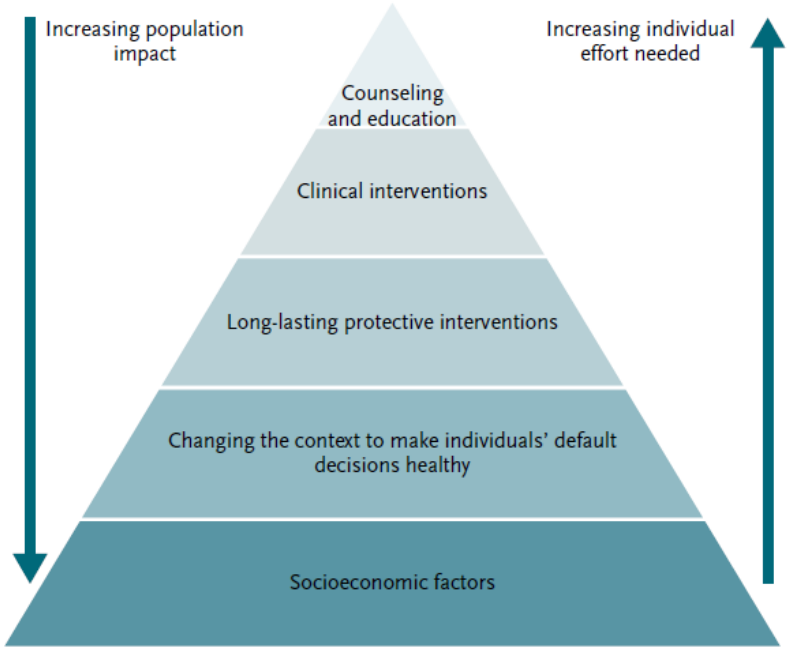

**Freudenreich O et al. Current Psychiatry. 2021;20(3):48-9.**
**Lim C et al. Current Psychiatry. 2021;20(8):10-38.**

## Preventive care (vaccinations) as legitimate role for mental health

- COVID-19 vaccination uptake public health priority[1]
  - Enlist mental health staff to overcome barriers
  - Make vaccinations a problem point in EMR
    - Clozapine Clinic at FTC achieved 85% vaccination rate[2]
- Broaden vaccination efforts beyond COVID-19
  - Annual flu vaccine
- View vaccination equity as part of larger effort to reduce health disparities AND GET INVOLVED[3]

**[1]Warren N et al. JAMA Psychiatry. 2021;78(6):589-590.**
**[2]Poster accepted for presentation at Annual ACLP meeting 2021**
**[3]https://www.psychiatry.org/File%20Library/Psychiatrists/APA-Guidance-Psychiatrists-Role-in-Equitable-Distribution-COVID-19-Vaccine.pdf**

# Health impact pyramid




**Shattuck Lecture: Frieden TR. NEJM 2015;373(18):1748-54.**

# Priorities during (post?) COVID

- Preventing spread of COVID-19
  - Stay up-to-date
  - Speak up and be involved (protect staff!)
  - Psychoeducation
  - Vaccination
- Preventing disengagement and psychiatric crises
  - Assure treatment to prevent relapse
    - Essential treatments: antipsychotics for schizophrenia
  - Provide support to mitigate effects of social isolation
    - Monitor for increased alcohol or drug use
    - Monitor for demoralization and suicidality
- Preventing medical mortality
  - Smoking cessation
  - Continue to address deferred medical care

Psychiatrists as vaccine ambassadors*

http://psychnews.org/update/5b13.html

**Kahl KG and Correll CU. JAMA Psychiatry. 2020;77(9):977-978.**
***Lim C et al. Current Psychiatry. 2021;20(8):10-38.**

# Thank you!

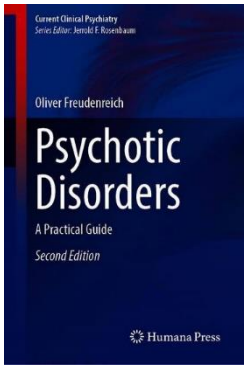
**Website**

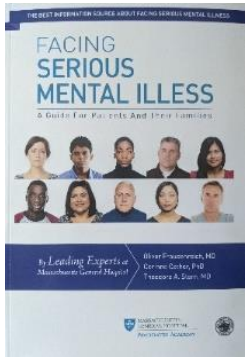
APA SMI Adviser project
https://smiadviser.org/

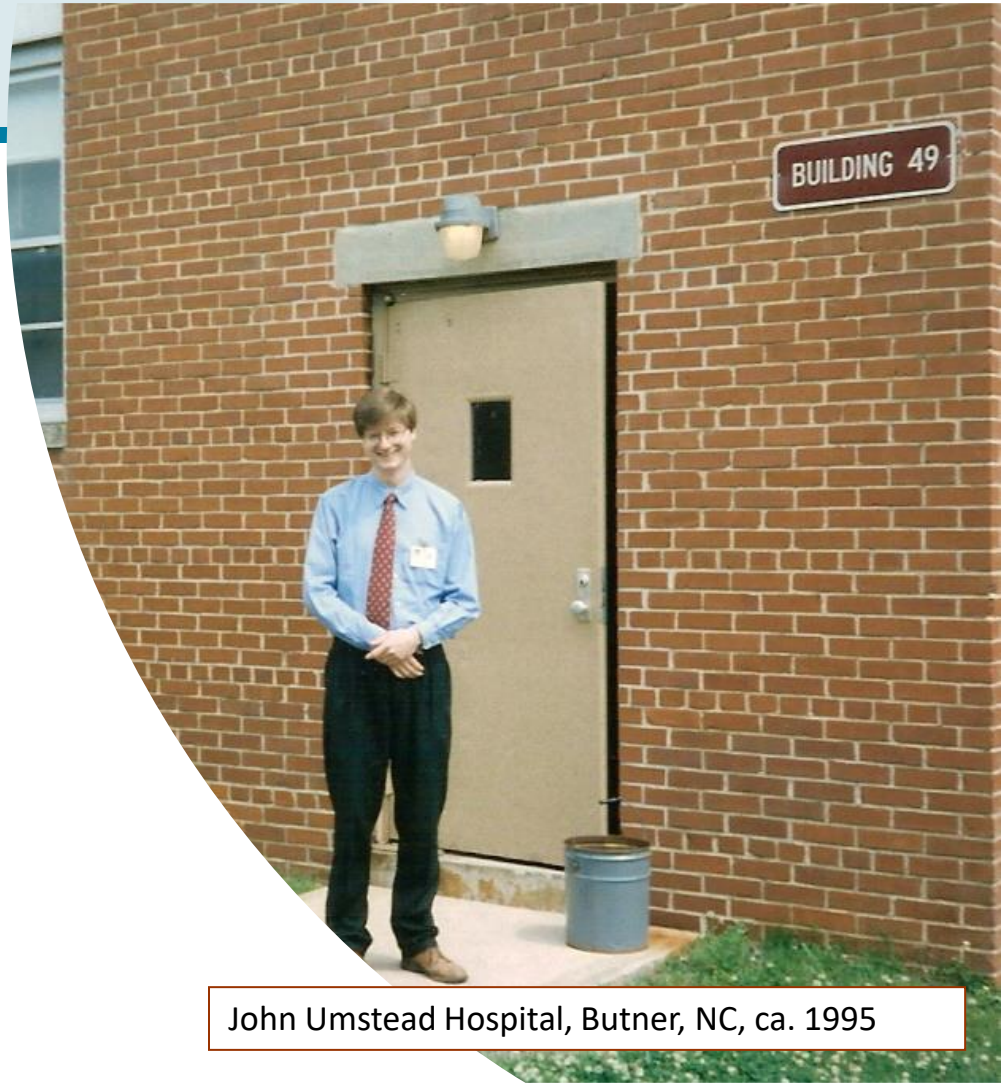
**Books**

Freudenreich, O. (2020). Psychotic disorders. A practical guide (2nd edition). Humana Press/Springer Verlag.

Freudenreich O et al. (2021). Facing serious mental illness. A guide for patients and their families. MGH Psychiatry Academy.




John Umstead Hospital, Butner, NC, ca. 1995

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