MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

First-episode psychosis and schizophrenia

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose (recipient SELF; content SCHIZOPHRENIA):

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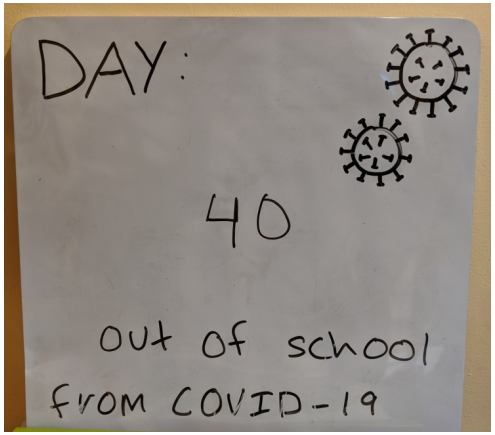
The return of social medicine

March 13, 2020



April 21, 2020

Rudolf Virchow

„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.

Outline

A. Broad treatment principles
   - Recovery orientation
   - Prevention orientation

B. New FDA drug approvals

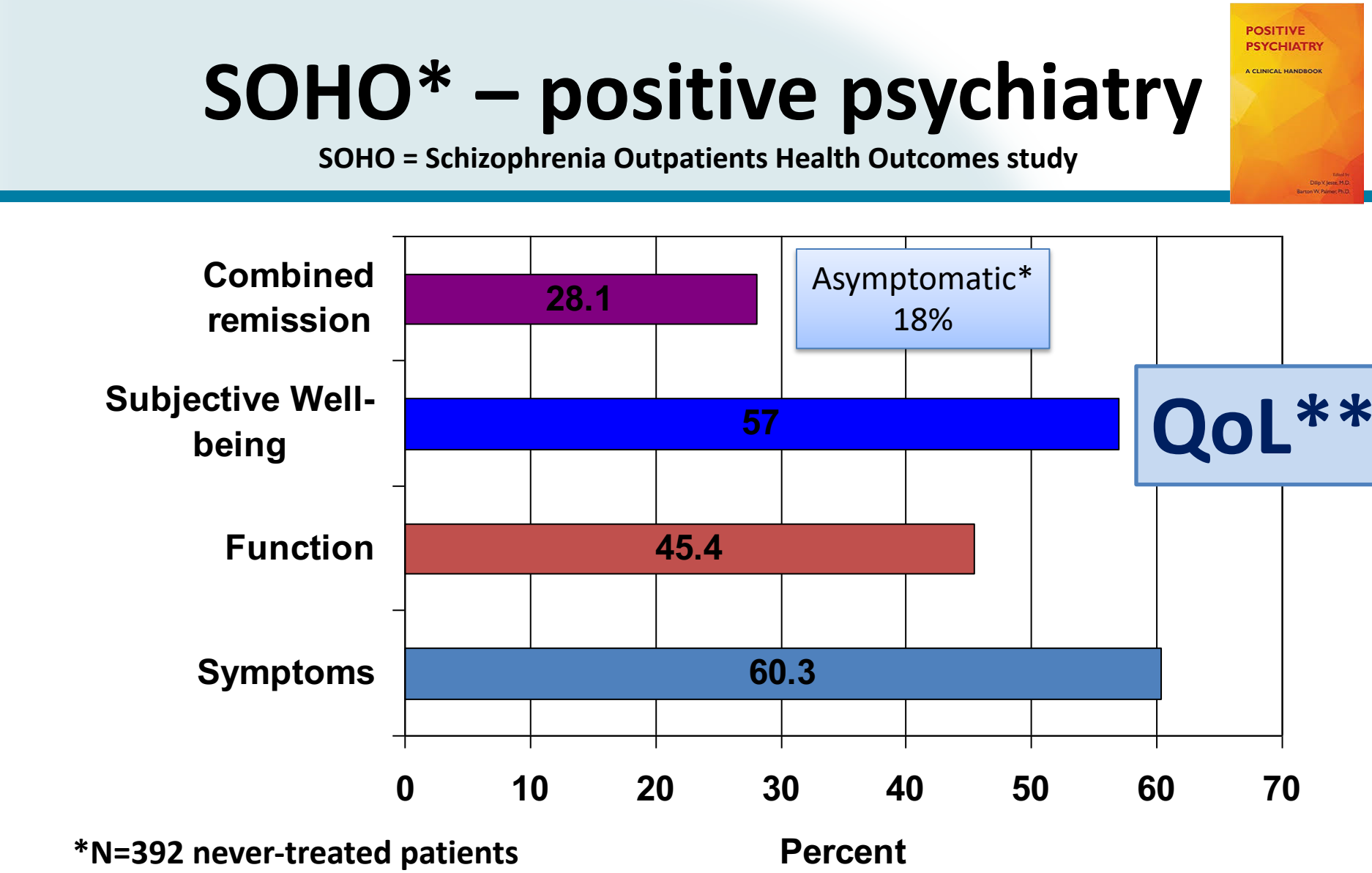
C. New stage-based insights
   - Prodromal phase
   - Acute psychosis
   - Post-psychotic/chronic phase

D. Psychopharmacology during a pandemic

REVOVERY ORIENTATION

SOHO* – positive psychiatry

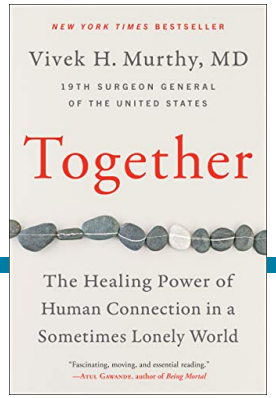
SOHO = Schizophrenia Outpatients Health Outcomes study



*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.

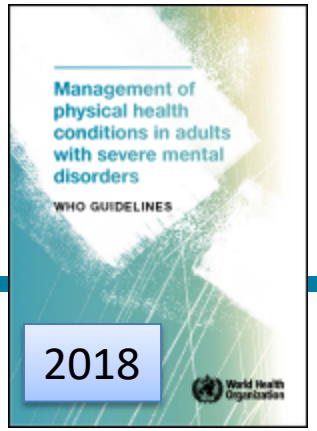
Life expectancy

- 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
- 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
  - No psychiatric treatment
- Improved medical care needed

Natural causes:	85%
Unnatural causes:	15%

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.

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]

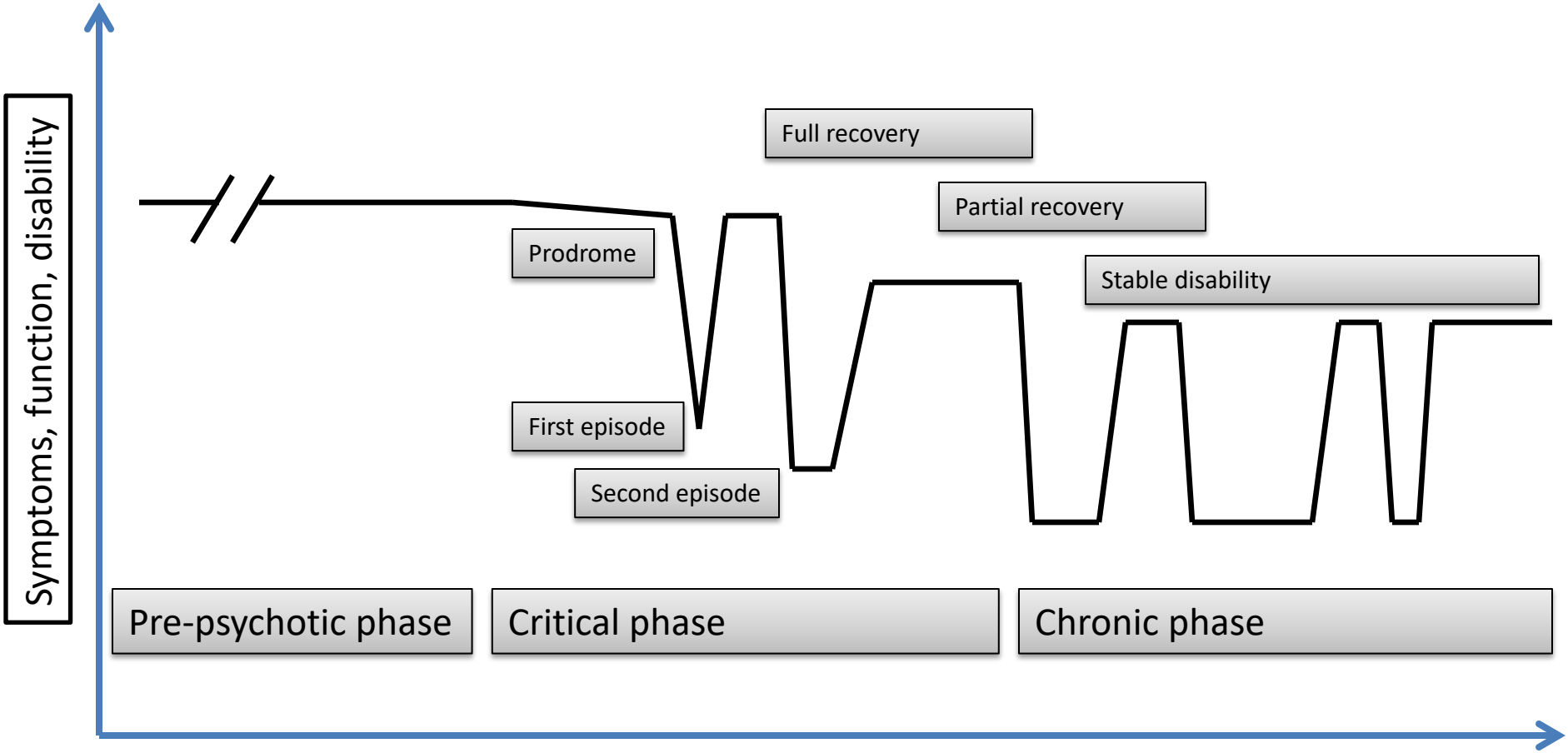
Smoking cessation

- 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]
- Varenicline
  - Efficacy: EAGLES trial[6]
  - Safety: removal of black box warning[7]
  - Initial treatment (American Thoracic Society 2020 Guideline)[8]

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.

www.mghcme.org

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
  - Phase-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]

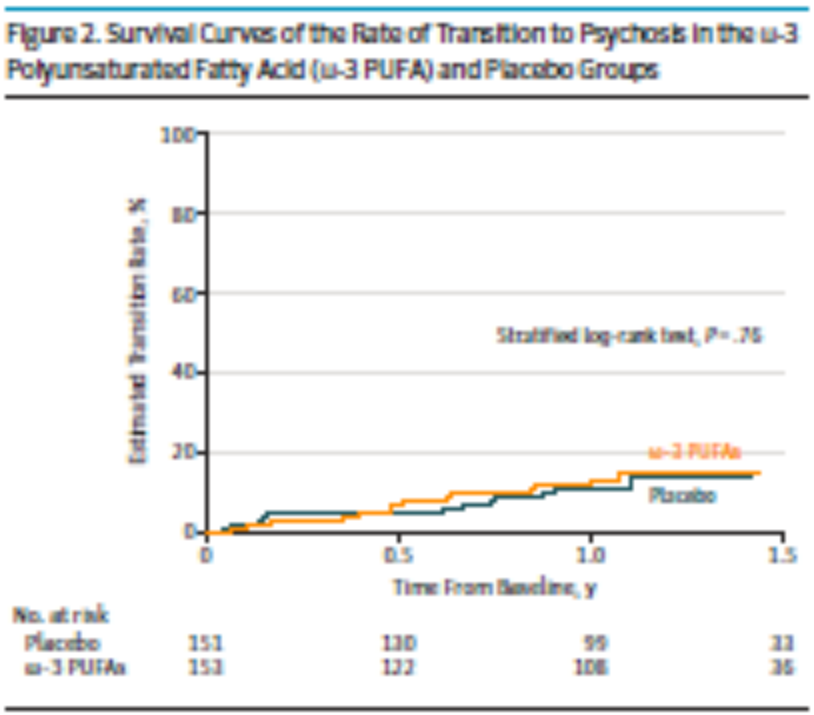
Clinical staging in psychiatry

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

Omega-3 fatty acids for indicated prevention

NEURAPRO = ?



1.4 g omega-3 FA (840 mg EPA/560 mg DHA

STUDY DESIGN

- Ultra-high risk patients
- Intervention: omega-3 PUFA x 6 months
- All participants received Cognitive Behavioral Case Management

RESULTS

- N=304 randomized
- ¼ lost to follow-up
- 6-month transition rates (CAARMS):
  - Placebo 5.1% (=15)
  - PUFA 6.7% (=17)
- 12-month transition rates:
  - Placebo 11.2%
  - PUFA 11.5%
- No effect of adherence (40%!)

Similar trajectories of improvement for all subgroups

McGorry PD et al. JAMA Psychiatry. 2017;74(1):19-27.
Editorial: Kane JM and Correll CU. JAMA Psychiatry. 2017;74(1):11-2.
Hartmann JA et al. Behavior Res Ther. 2020;124:103527.

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

Early intervention: reducing duration of untreated psychosis (DUP)

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

TIPS
TIDLIG OPPDAGELSE OG BEHANDLING AV PSYKOSER
Stavanger University Hospital
Stavanger Hospital Trust

[1]Perkins et al. 2005, [2]Marshall et al. 2005, [3]Melle et al. 2004, 2008; [4]Larsen et al. 2011 [5]Joa et al. 2008
[6]Lloyd-Evans et al., Br J Psychiatry 2011;198:256.
[7]Jonas KG et al. Am J Psychiatry. 2020;177(4);327-334. [8]Goff DC et al. Am J Psychiatry. 2020;177(4):288-290.

Phase-specific care: RAISE trial

RAISE = Recovery After an Initial Schizophrenia Episode

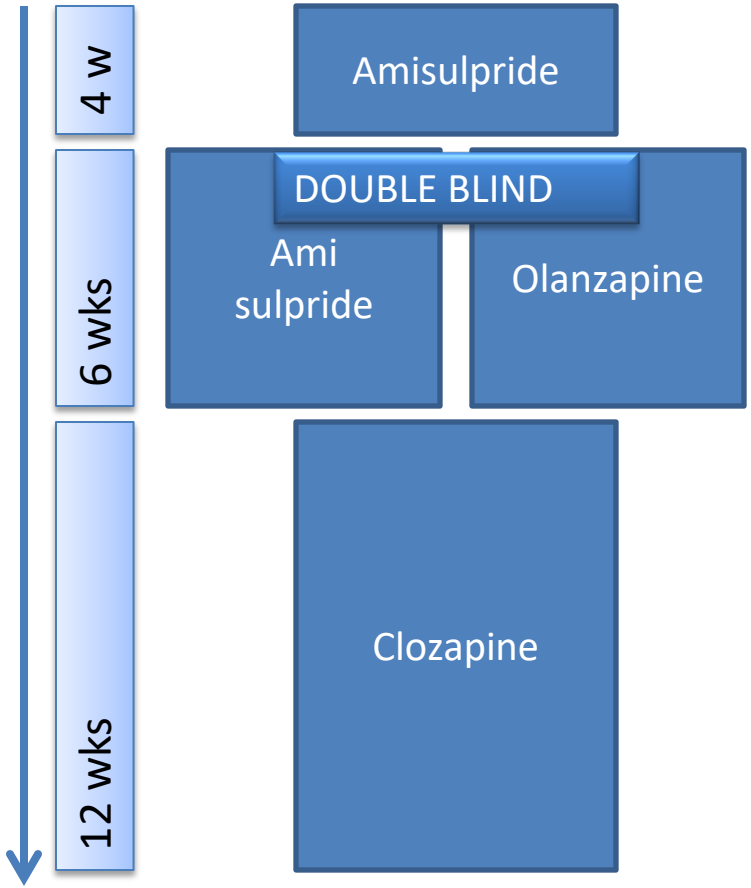
- Goal
  - Develop early-intervention system in real world of fragmented US healthcare system
- NAVIGATE
  - Cluster randomization of 34 clinics in 21 states of NAVIGATE versus community care (CC)
  - Core services: family education, resilience training, supported employment/education, medications[1]
  - 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.

www.mghcme.org

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]

[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. CNS Spectr. 2020;25(2):293.

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)
  - 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[3]
  - 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]ASCP 2020: Abstract 3002348. Presented May 30, 2020.

New stage-based insights

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

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

PRODROMAL PHASE

Prodromal schizophrenia

DSM-5 Attenuated Psychosis Syndrome (APS)*

- Prodrome can only be diagnosed <u>in retrospect</u>
  - 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 <u>in its infancy</u>
  - 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 <u>help-seeking</u>[5]
  - "Probably at risk but certainly ill"
- Increasing appreciation of social determinants of health risk factors
  - Example, deprived environments and cognitive development[6]

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]Perkins DO et al. Am J Psychiatry. 2020;177(2):155-163.
[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]Lewis G et al. JAMA Psychiatry. 2020;77(7):729-736. *Salazar de Pablo G et al. JAMA Psychiatry. 2020;77(3):311-320.

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]
  - Commercialization leading to potent THC products[2]
  - Destabilizes early course schizophrenia via reduced adherence[3]
  - 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]Murray RM and Hall W. JAMA Psychiatry. 2020;77(8):777-8.
[3]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)dzSF
  - 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

[1]Leucht S et al. Am J Psychiatry. 2020;177(4):342-353.

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.**

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 symptomts
- 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. 2019 (in press). [4]Brown HE et al. JAMA Psychiatry. 2020;77(7):766-767. [5]https://www.psychiatrictimes.com/view/prescribing-hope-for-recovery

Long-acting injectable antipsychotics

Drug	Dose strengths	Dose (IM) & Frequency	Notes
Haloperidol decanoate [HALDOL DECANOATE]	Vials 50mg/ml Vials 100mg/ml	50 - 200 mg monthly Other dose intervals are possible	Initiation: overlap with oral antipsychotic Loading dose strategy possible Maintenance dose equals 20 x oral dose
Fluphenazine decanoate [PROLIXIN DECANOATE]	Vials 25mg/ml	6.25 - 25 mg every 2 weeks Other dose intervals are possible	Initiation: overlap with oral antipsychotic
Risperidone microspheres [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 Main release of drug occurs 3 weeks after injection 50 mg every two weeks corresponds to 4 mg/d oral (50 mg is highest IM dose]
Risperidone long-acting suspension [PERSERIS]	90 mg, 120 mg	90 or 120 mg monthly subcutaneously	For subcuaneous use 90 mg corresponds to 3 mg/d oral 120 mg corresponds to 4 mg/d oral
Paliperidone palmitate [INVEGA SUSTENNA] [INVEGA TRINZA]	39 mg, 78 mg, 117 mg, 156 mg, 234 mg 273 mg, 410 mg, 546 mg, 819 mg	39-234 mg monthly 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 156 mg monthly corresponds to 9 mg/d oral Every 3 months dose can be used after 4 months of monthly injections 546 mg corresponds to 9 mg/d oral
Olanzapine pamoate [ZYPREXA RELVPEVV]	150 mg, 210 mg, 300 mg, 405 mg	150 or 300 mg every 2 weeks 405 mg monthly	No overlap with oral antipsychotic (higher initiation doses) Monitor for 3 hours of observation for post-injection delirium/sedation syndrome (PDSS)* 300 mg monthly corresponds to 10 mg/d oral
Aripiprazole monohydrate [ABILIFY MAINTENA]	Vials 200 mg/ml	160mg- 400mg monthly	Initiation: 2 week overlap with oral antipsychotic 300 mg corresponds to 10 mg/d oral; 400 mg to 15 mg/d
Aripiprazole lauroxil [ARISTADA]	441 mg, 662 mg, 882 mg, 1064 mg	441,662,882 mg every 4 weeks 882 mg every 6 weeks 1064 mg every 2 months	Initiation: 3 week overlap with oral antipsychotic or with initiation regimen Inject rapidly due to non-Newtonian fluid characteristics Only lowest dose of 441 mg dose can be given in deltoid 441 mg monthly corresponds to 10 mg/d oral 662 mg monthly or 1064 mg every two months corresponds to 15 mg/d oral 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]
- Can be life-saving[2]
  - 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
  - Maintaining frequent clinical contact may be a valid psychosocial relapse prevention treatment[3]
  - Breakthrough symptoms (hospitalization) still high: 30% incidence[4]
- You and you team may be the biggest barrier![5]
  - In finished PRELAPSE trial, early-phase patients accept LAI[6]

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

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

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.

Psychopharmacology during a pandemic

March 5, 2020

March 21, 2020

April 21, 2020

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Contributors to poor outcomes

- Unresponsive biology

Health disparities in society are magnified during COVID-19.

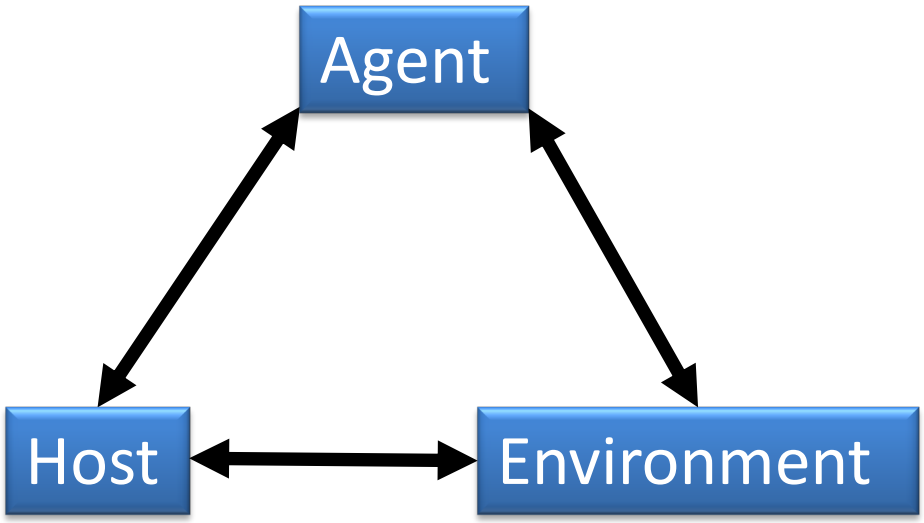
- **Time spent psychotic, in hospitals, or idle at home**
- **Poor access to treatment and no care**
- **Substandard psychiatric care**
- **Poor engagement in ongoing care and poor adherence**
- **Substance use**
- **Comorbid medical disorders**
- **Multiple social determinants of health**

Zipursky RB. J Clin Psychiatry. 2014; 75 Suppl 2:20-4.
Bartels S et al. Psychiatric Serv. 2020 (in press).

“Tragic” epidemiologic triad of SMI and COVID-19

Psychiatric illness
-Negative symptoms
-Cognitive difficulties

Medical comorbidities
-Obesity
-Smoking
-Lung disease
-Metabolic syndrome



Freudenreich O et al. Current Psychiatry. 2020 (in press)

Priorities

- Preventing spread
  - Stay up-to-date
  - Speak up and be involved
- Preventing medical mortality
  - Smoking cessation
  - Continue to address medical comorbidities during COVID-19!
- Preventing disengagement and psychiatric crises
  - Assure treatment to prevent relapse
    - Essential treatments: antipsychotics for schizophrenia
      - Special considerations: clozapine and long-acting injectable antipsychotics
  - Provide support to mitigate effects of social isolation
  - Preserve care access and continuum of care

Sine qua non
Keep people engaged in care.

Treatment as prevention!

http://psychnews.org/update/5b13.html
Zhou J. Am J Psychiatry. 2020;177(7):574-5.

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 (in press).

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. 2020 (in press).
https://smiadviser.org/knowledge_post/what-are-clinical-considerations-for-giving-lais-during-the-covid-19-public-health-emergency

Supportive psychotherapy during COVID-19

- Education
  - Risk and risk perception
  - Terms and how to apply them
- Manage anxieties
  - Use pharmacotherapy as support
    - Dose adjustment: not the time for low-dose approach
      - Helpful to have TDM
    - Judicious use of ancillary psychotropics
  - Use proactive crisis intervention, before a crisis
    - More frequent contacts (MD, social work, psychologists)
    - Use telepsychiatry
- Problem-solving and concrete help
  - Filling out forms

Social distancing =
Physical distancing
NOT: emotional distancing

Telehealth and SMI

Telemedicine is currently STANDARD OF CARE unless contact is needed.

- Facts
  - MGH Psychiatry went from less then 5% telehealth to almost 100% telehealth in a few weeks
  - Regulatory barriers (reimbursement, licensure, privacy) were removed
- Benefits
  - Often surprisingly easy for both sides, regardless of type of patient
  - Patients quite thankful for contact from clinic
  - More convenient: you literally meet patients where they are at
  - More economic and efficient
- Downsides
  - You cannot use all your senses to evaluate patients
  - Not all patients have access to telehealth (**digital divide**)
  - Some psychiatric procedure require in-person contact (ECT, LAIs, blood work)
  - Privacy and other regulatory concerns like consent
  - Long-term effectiveness unclear

https://ps.psychiatryonline.org/editorschoice/considerations-for-telepsychiatry-service-implementation-in-the-era-of-COVID-19
Torous J et al. JMIR Ment Health. 2020 Mar 26;7(3):e18848. Shalev D and Shapiro PA. Gen Hosp Psychiatry. 2020 Apr 3;64:68-71.
https://smiadviser.org/wp-content/uploads/2020/04/How-to-Prepare-for-a-Video-Appointment.pdf

Concrete steps for working with SMI patients during COVID-19

- Educate and address concerns
  - Clarify risk and correct misperceptions
    - Prevent unhelpful action (hoarding that would lead to shortages)
    - Advise limited media exposure
  - Provide tailored materials
- Model coping in the face of adversity
- Model correct approach to infection control
  - Correct mask wearing
- Monitor alcohol use
- Push for smoking cessation
- Plan for the fall
  - Flu shots
  - Resume routine health care
  - Get workflows in order for essential medications (LAIs, clozapine)
- Plan for the worst
  - Get contact information in order
  - Crisis plan (Psychiatric Advance Directive [PAD])
  - Discuss end-of-life care

Get smart yourself!

Don't forget the individual patient for focus on public health
✓Engage the patient, not just the disease
✓Explain, keep it simple, clarify, advise
✓Maintain clinical contact

Disillusionment

What will our new normal feel like?

"It was the first winter that you realized that this is going to last, this is your life. And somehow you live. Just like people are adapting to the situation now."

Velibor Bozovic recalls the 1990s siege of Sarajevo

Deliberate resilience building

- Deliberate resilience building – not innate and fixed
- Embrace "toughness"
- Emphasize shared mission and camaraderie
- Counteract helplessness
  - Make infection control a ritualized practice
- Avoid the victim narrative
  - Embrace post-traumatic growth mindset
- Pay attention to self-care for endurance
  - Rest, nutrition, exercise
- Practice self-compassion
  - Self-kindness, common humanity, and mindfulness

Per aspera ad astra

https://www.resilienceandprevention.com/healthcare-providers

Pfefferbaum B and North CS. NEJM. April 13, 2020.

Rosenberg AR. JAMA Pediatr. April 14, 2020. [Deliberate resilience building]

Chen Q et al. Lancet Psychiatry. 2020;7(4):e15-e6. *Lisa Rosenbaum. NJEM. April 1, 2020.

Albert Camus

‘This whole thing is not about heroism. It’s about decency. It may seem a ridiculous idea, but the only way to fight the plague is with decency.’

‘In general, I can’t say, but in my case I know that it consists in doing my job.’

- Doctor Bernard Rieux

https://www.nytimes.com/2020/03/19/opinion/sunday/coronavirus-camus-plague.html

Thank you!

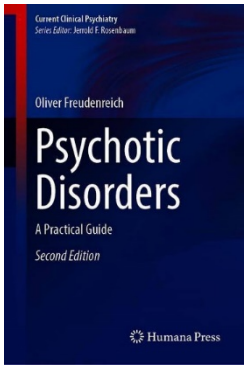
Website

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

Articles

Freudenreich O et al. COVID-19 and patients with serious mental illness. Current Psychiatry. 2020 (in press)

Book



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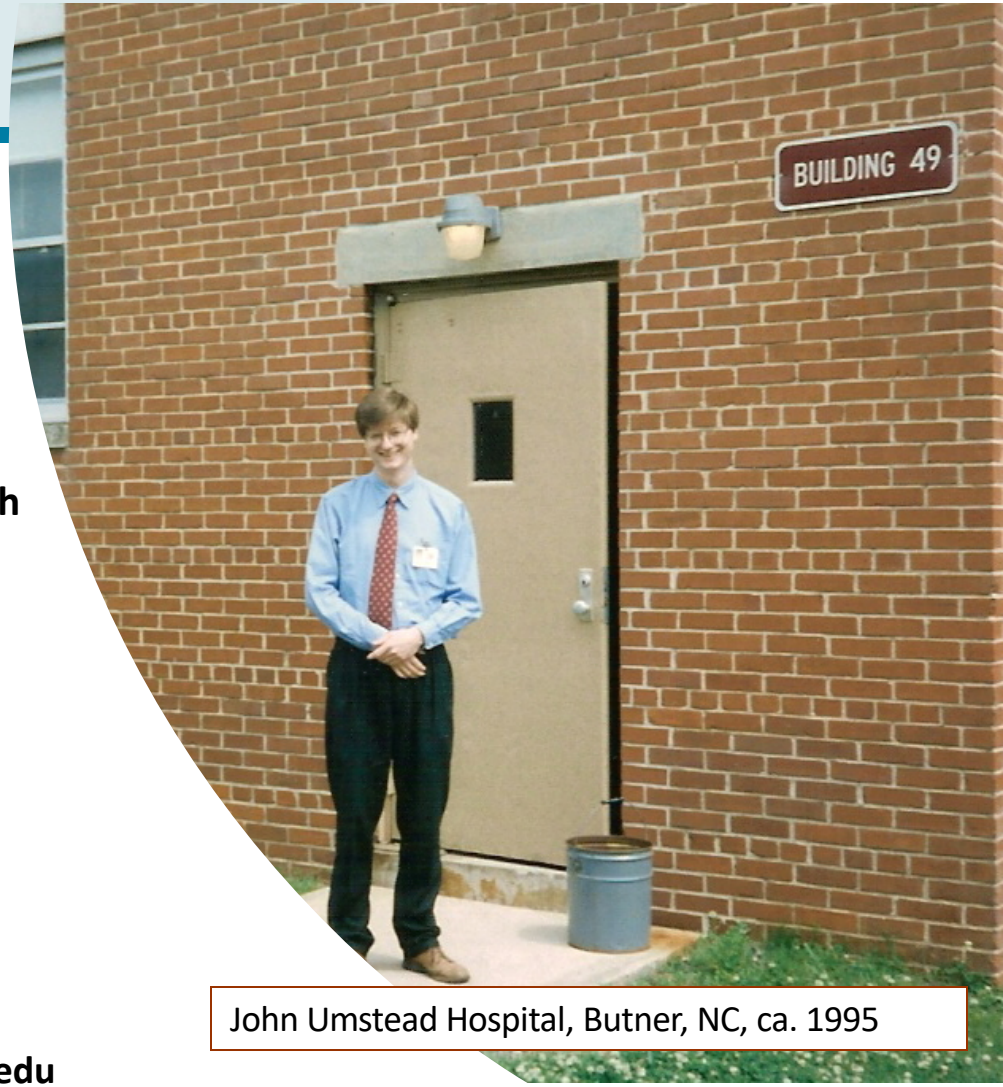

John Umstead Hospital, Butner, NC, ca. 1995