MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Clinical Approaches to Treatment Resistance in Schizophrenia

3RD INTERNATIONAL PSYCHOPHARMACOLOGY:
DEPRESSION & SCHIZOPHRENIA
May 16, 2021

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Disclosures

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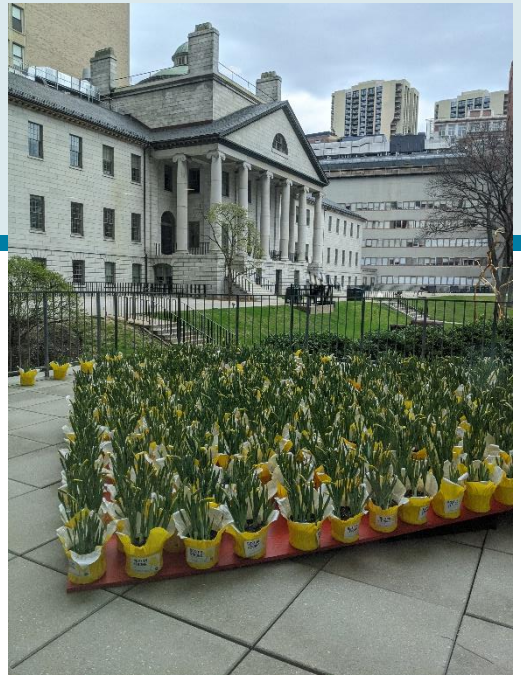
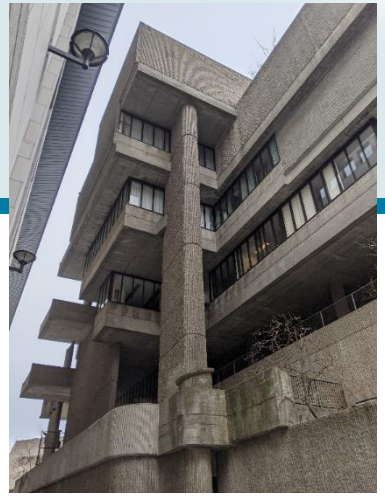
Outline

1. Treatment-resistant schizophrenia (TRS)
   - ✓ Biology
   - ✓ Diagnosis
2. Prevention
   - ✓ Stage-specific care
3. Treatment
   - ✓ Clozapine trial
   - ✓ Augmentation strategies
   - ✓ Medical care
4. Reflections: prognosis
   - ✓ Psychosocial support
   - ✓ Humanism



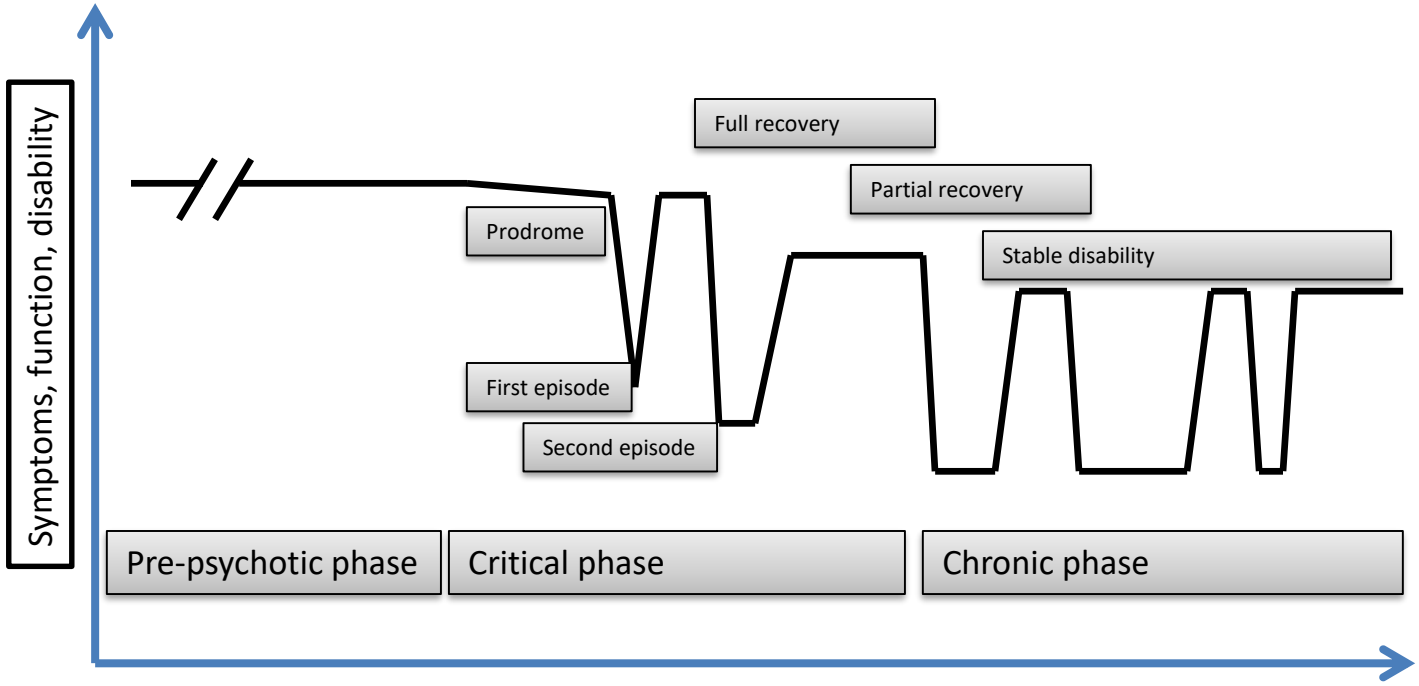
Massachusetts General Hospital
Boston, Massachusetts



Erich Lindemann Mental Health Center
Boston, Massachusetts

TREATMENT-RESISTANT SCHIZOPHRENIA

Typical course of schizophrenia



Freudenreich O. Psychotic Disorders. Springer 2020.

Scope of the problem

20-30% of patients with schizophrenia have limited response to first-line antipsychotics.

At least 10% of patients with schizophrenia have no response to clozapine.

The tragedy of life is what dies inside a man while he lives – the death of genuine feeling, the death of inspired response, the death of the awareness that makes it possible to feel the pain or the glory of other men in oneself.

-Albert Schweitzer, 1875-1965

Siskind D et al. Can J Psychiatry. 2017;62(11):772-777.

Biology of treatment-resistance

- Heterogeneous pathophysiology and biotypes
  - "The group of treatment-resistant schizophrenias"[1]
- Time course[2]
  - Resistance from the "get-go"
  - Evolving over time and related to relapse
- Mechanism[3]
  - Dopamine supersensitivity[4]
  - Neurotransmitters other than dopamine
  - Inflammation

[1]Kinon BJ. Front Psychiatry. 2019;9:757.
[2]Howes OD et al. Am J Psychiatry. 2017;174(3):216-229.
[3]Potkin SG et al. npj Schizophrenia (2020) 6:1.
[4]Chouinard G et al. Psychother Psychosom 2017;86:189–219.

Treatment-resistant schizophrenia (TRS)

- Consensus guidelines on diagnosis and terminology developed by TRRIP Working Group
  - Clinical sub-specifiers for positive, negative, cognitive symptom domains
  - Time-course (i.e., early, medium, late onset)
  - Ultra-treatment resistant (i.e., clozapine)
- Minimum requirements for TRS:
  - Current symptoms
    - Symptom threshold at least moderate severity (rating scale!)
    - Symptom duration at least 12 weeks
    - Functional impairment at least moderate (rating scale!)
  - Adequate treatment
    - At least two trials of at least 6 weeks of at least 600 CPZ-EQ
    - At least 80% adherence

TRRIP = Treatment Response and Resistance in Psychosis

Howes OD et al. Am J Psychiatry. 2017;174(3):216-229. Campana M et al. Schizophr Res. 2021;228:218-226. Kane JM et al. J Clin Psychiatry. 2019 Mar 5;80(2). pii: 18com12123. [Clinical Guidance]

PREVENTION


breakfast
conven. breakfast
potatoes
gluten free
Scott
Brighty

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.

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]

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

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
- Treatment of choice: long-acting injectable antipsychotics

Relapse prevention is key goal of schizophrenia care

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

TREATMENT

Establishing TRS – clinical approach

Assumption: correct diagnosis of schizophrenia

Persistent symptoms …

- ✓ Characterize cross-sectional symptom cluster profile
- ✓ Characterize disability

… despite adequate treatment

- ✓ Rule-out pseudo-resistance: substance use and poor adherence
- ✓ Establish adequacy of prior treatment with first-line antipsychotics (history review)
- ✓ Consider your own prospective LAI trial

Common reasons for non-response

"Pseudo-resistance"

- Diagnosis incorrect
- ***Substance use***
- Insufficient dose
- Insufficient duration
- Unusual genetic metabolism
- Drug interactions
- ***Insufficient adherence***

True biological non-response

- Treatment-resistance to usual treatments
- Target symptom not responsive to selected intervention

***1 in 3 TRS patients have subtherapeutic drug levels.**

Based on: Freudenreich O et al. Facing Serious Mental Illness. MGH Psychiatry Academy, 2021.
***McCutcheon R et al. Acta Psychiatr Scand. 2018;137(1): 39–46.**

Stepped care for TRS

Treatment-resistant schizophrenia

- Two failed antipsychotic trials

Clozapine trial

- Timely and optimal clozapine trial

Clozapine augmentation

- Judicious use of add-on treatments

https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Clozapine TDM

- Clozapine metabolism
  - Main P450 enzyme1A2
  - Large inter-individual variability between dose and drug level
  - Literature is based on clozapine levels, not active moiety
    - Norclozapine has 10% activity of clozapine
- Therapeutic drug monitoring (TDM)
  - Substantial research into clozapine TDM
  - For routine outpatient care
    - 200 to 300 ng/mL sufficient for most
  - For refractory psychosis:
    - Upper limit of efficacy is not established. Target 450 ng/mL
    - Higher dose/blood level increases seizure risk

Freudenreich O. Current Psychiatry. 2009 March;8(3):78. [Pearls]
Schoretsanitis G et al. J Clin Psychiatry. 2020 May 19;81(3):19cs13169. [Consensus statement]

TRS and clozapine – dirty little secrets

- Clozapine efficacy is limited
  - Spectrum of response
    - Rarely restitutio ad integrum
    - Partial response (average 25% symptom reduction) is typical[1]
    - Ineffective in perhaps as many as 50% of patients with TRS[2]
  - Not effective for negative or cognitive symptoms which drive functional impairments
  - Not effective if risk for (partial) non-adherence is high
- Medical disease burden is high
  - Diabetes, hyperlipidemia, intestinal obstruction[3]
  - Underappreciated: aspiration pneumonia[4]

[1]Siskind D et al. Can J Psychiatry. 2017;62:772-777. [2]Porcelli S et al. Neuropsychopharmacol. 2012;22:165-182.
[3]Stroup TS et al. Am J Psychiatry. 2016;173:166-73. [4]De Leon H et al. World Psychiatry. 2020;19(1):120-1.

Clozapine augmentation

- ECT has good efficacy for TRS
  - One half to two thirds of patients improve if ECT us added[1]
  - Is this truly an augmentation strategy?
- Medication augmentation strategies are limited[2,3]
  - Aripiprazole
    - Clozapine plus aripiprazole prevents hospitalizations
    - Improves metabolic profile
  - SSRI antidepressants
    - For demoralization, dysphoria, depression, negative symptoms
  - Topiramate[4]
    - Benefit for psychopathology and weight

[1]Lally J et al. Schizophr Res. 2016;171(1-3):215-224. [2]Correll CU et al. JAMA Psychiatry. 2017;74(7):675-84.
[3]Wagner E et al. Schizophr Bull. 2020;46(6):1459-1470. [Expert Consensus TRRIP Working Group]
[4]Correll CU et al. J Clin Psychiatry. 2016;77(6):e746-56.

Pimavanserin

SSIA = Selective Serotonin Inverse Agonist

5-HT2A inverse agonist

- Mechanism of action[1]
  - Antagonist/inverse agonist at serotonin 5HT2A receptors
  - Less potent antagonist/inverse agonist at 5HT2C receptors
- 2016 FDA-approval for psychosis in Parkinson's disease (Nuplazid)[2,3]
- Clinical case series (N=10) for TRS[4]
- Phase III 6-week add-on trial in (somewhat) TRS (Acadia's ENHANCE-1)[5]
  - Negative results for psychosis (PANSS total score)

[1]Stahl SM. CNS Spectr. 2016;21:271-5. [2]Cummings J et al. Lancet. 2014;383(9916):533-40.
[3]Mathis MV et al. J Clin Psychiatry. 2017; 78(6):e668-e673. [4]Nasrallah HA et al. Schizophr Res. 2019;208:217-220.
[5]ClinicalTrials.gov Identifier: NCT02970292.

Non-pharmacological augmentation

- Target psychiatric comorbidities[1]
  - Agoraphobic avoidance, worry, self-esteem, insomnia
  - Dimensions of psychopathology
    - Affective symptoms
    - Negative symptoms
    - Cognitive symptoms
- Tools
  - Third-wave psychotherapies
  - Psychosocial rehabilitation
  - Exercise[2]

Ancillary CBT for:
✓Residual psychosis
✓Negative symptoms
✓Depression

[1]Freeman D et al. Schizophr Res. 2019;211:44-50.
[2]Girdler SJ et al. Psychopharmacol Bull. 2019;49(1):56-69. [review]

"However beautiful the strategy*, you should occasionally look at the results."**

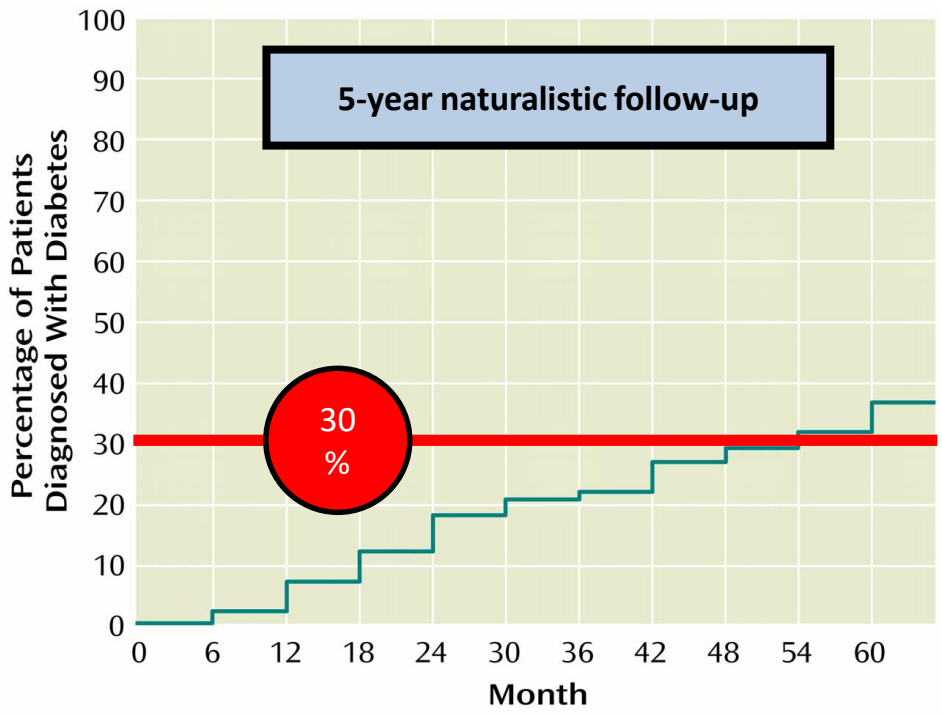
-Sir Winston Churchill

*** = what your clinic does**
**** = how your patient is doing**

Haas LF. JNNP 1996;61(5):465.

The need to focus on mortality

ELMHC clozapine cohort



Henderson DC et al. Am J Psychiatry. 157(6):975-981.

Greatly decreased life expectancy

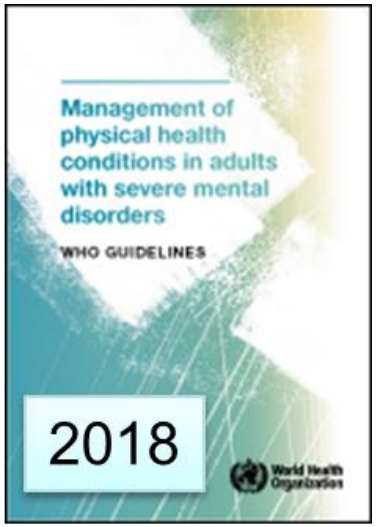
Natural causes: 85%
Unnatural causes: 15%

Two main medical causes:
#1 Cardiovascular disease
#2 Cancer

Laursen TM. Curr Opin Psychiatry. 2019;32(5):388-93. Meta-analysis
Olfson M et al. JAMA Psychiatry 2015;72(12):1172-81.

Proactive medical management

- Iatrogenic complications
- But: worst outcomes in untreated patients with schizophrenia[1,2]
- Iatrogenic complications
- Proactive (preventive) treatment
  - Metformin[3]
  - Behavioral interventions[4]



[1]Vermeulen JM et al. Schizophr Bull. 2019;45(2):315-29.
[2]Taipale H et al. World Psychiatry. 2020;19(1):61-8.
[3]Siskind DJ et al. PLoS One. 2016;11(6):e0156208. [meta-analysis]
[4]Ward MC and Druss BG. JAMA Psychiatry. 2019;76(7):759-60. [JAMA Network Insights]

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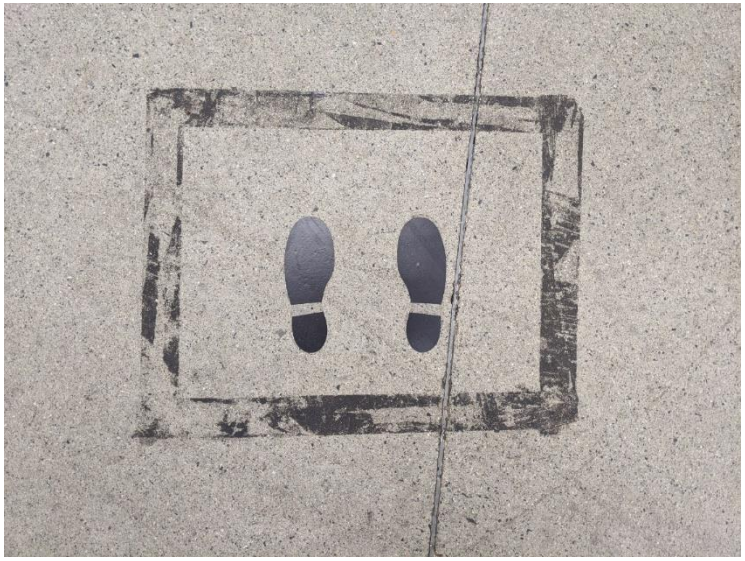


Contributors to poor outcomes

- 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. Psychiatr Serv. 2020;71(10):1078-1081.
Kinon BJ. Front Psychiatry. 2019;9:757.
***Nasrallah HA. Curr Psychiatry. 2021;20(3):14-16;28. [Editorial]**

Research: thinking outside the box

- Lu AF35700
  - Predominant D1 vs. D2 receptor antagonist
    - Profile comparable to clozapine
    - High occupancy 5-HT2A and 5-HT6 serotonin receptors
  - Nightfall for DayBreak [ClinicalTrials.gov Identifier: NCT02717195]
    - No difference in PANSS total score[1]
- Non-dopaminergic drugs
  - SEP-363856[2]
    - Mechanism of action: TAAR-1 agonism
  - Sodium benzoate augmentation[3]
    - Mechanism of action: DAAO inhibitor
- Targeting neurocircuits
  - Transmagnetic stimulation[4] and transcranial direct current stimulation[5]

TAAR-1 = Trace amine-associated receptor 1
DAAO = D-amino acid oxidase

[1]https://investor.lundbeck.com/news-releases/news-release-details/lundbeck-updates-clinical-phase-iii-study-lu-af35700-treatment
[2]Koblan KS et al. N Engl J Med. 2020;382(16):1497-1506. Goff DC. N Engl J Med. 2020;382(16):1555-1556. [Editorial]
[3]Lin CH et al. Biol Psychiatry. 2018;84(6):422-432.
[4]Brady RO et al. Am J Psychiatry 2019;176(7):512–520. [5]da Costa L et al. JAMA Psychiatry. 2020;77(2):121-129.

Xanomeline

- Muscarinic agonist
  - *Orthosteric* muscarinic acetylcholine receptor (mAChR) agonist
    - M1/M4-preferring; M5 antagonist
  - Effective for treatment of schizophrenia[1]
  - Schizophrenia subtype: low cortical M1 receptor density[2]
  - Poor tolerability due to dose-limiting peripheral action: early trials with patch in DAT
- Co-formulated with trospium as KarXT
  - Trospium (brand name Sanctura) = FDA-approved peripheral muscarinic antagonist for overactive bladder; 20 mg bid
  - Met primary endpoint in Phase II trial, with improved tolerability[3]
- Potential treatment targets
  - Schizophrenia: psychosis, negative symptoms, cognition
  - Alzheimer's disease: psychosis, cognition
  - Analgesic

[1]Shekhar A et al. Am J Psychiary. 2008 Aug;165(8):1033-9.
[2]Dean B et al. Schizophr Bull. 2018 Apr; 44(Suppl 1): S70–S71. Hopper S et al. Int J Neuropsychopharmacol. 2019;22(10):640-650.
[3]Brennan SK et al. N Engl J Med 2021;384:717-26.

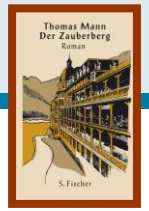
Rudolf Virchow

„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.

Plus ça change, plus c'est la même chose



1924

1995

VIEWPOINT

Improving Long-term Psychiatric Care
Bring Back the Asylum

Dominic A. Sisti, PhD
Department of Medical Ethics and Health Policy, Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

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Department of Medical Ethics and Health Policy, Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

Ezekiel J. Emanuel, MD, PhD
Department of Medical Ethics and Health Policy, Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

Sisti DA et al. JAMA 2015;313:243.

reflection

On *Asylums: Essays on the Social Situation of Mental Patients and other Inmates*, by Erving Goffman

Nick Bouras

BJPsych The British Journal of Psychiatry (2014) 205, 423–424. doi: 10.1192/bjp.bp.114.151704

Editorial

Can there be false hope in recovery?

Patrick W. Corrigan

Summary
Although hope is key to recovery, might the course of some people's mental illness be so severe that false promise is offered? This paper unpacks considerations and, after a critical analysis, concludes hope is still central to healing and personal well-being.

Declaration of interest
None.

A third sobering lesson can be taken from the findings of Killaspy and colleagues' negative trial: if even well-resourced units with determined input from dedicated teams do not improve patients' functioning at the severe end of the disorder, perhaps we should shed our current orthodoxy that demonises the asylum function of psychiatric care, to provide a place of safety, refuge, and protection. Until we make a major therapeutic breakthrough, we should ensure that we do not keep cutting the number of long-stay beds in the hope that simply discharging patients into the community will improve outcomes. Good mental health care needs investment in all aspects. No amount of community investment will ever obviate the need for some hospital beds. If communities were all that therapeutic, people

"A battle for resources"
Singh S. Lancet Psychiatry 2015;2:3.

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
  - Proactive and preventive use of metformin
- 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]

Clinical Peals for Patients in Stage 3/4

- Retain an optimistic stance
- Focus on quality of life and rehabilitation
- Pay attention to physical health
- Forget “evidence-based medicine”
  - Compassionate use of experimental treatments
  - Offer time-limited trials and stop treatments that do not work
  - Judicious use of polypharmacy
- Conduct periodic treatment plan review
- Remember humanism in medicine

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

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/**

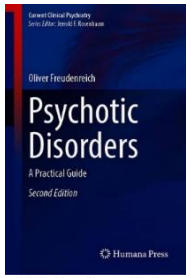
Journal article

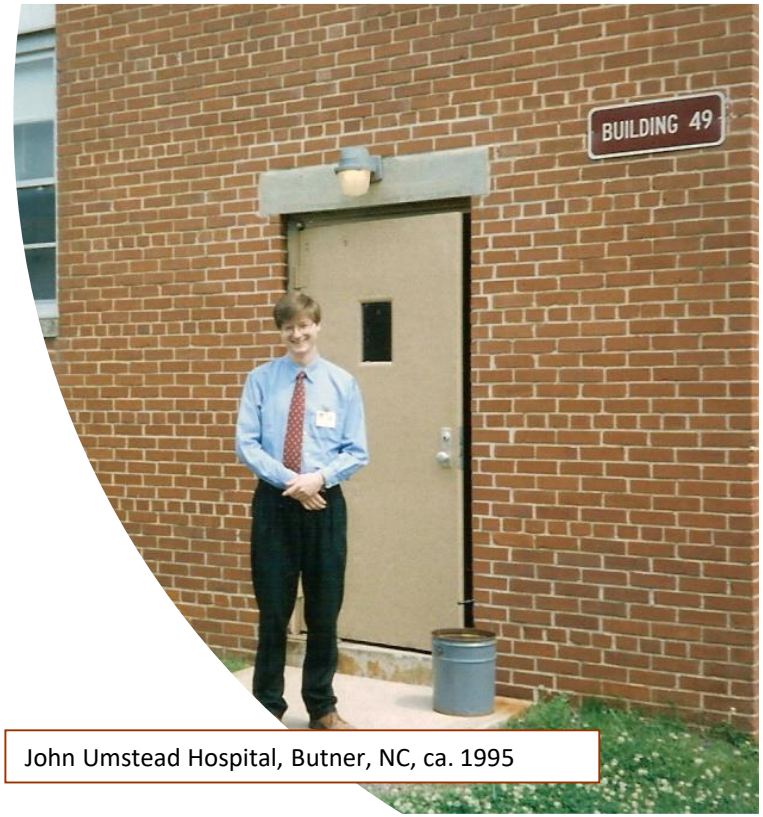
Kane JM et al. Clinical Guidance on the Identification and Management of Treatment-Resistant Schizophrenia. J Clin Psychiatry. 2019 Mar 5;80(2). pii: 18com12123.

Wagner E et al. Clozapine combination and augmentation strategies in patients with schizophrenia -recommendations from an international expert survey among the Treatment Response and Resistance in Psychosis (TRRIP) Working Group. Schizophr Bull. 2020;46(6):1459-1470.

Book

Freudenreich O. Treatment-resistant schizophrenia. In: Psychotic disorders. A practical guide (2nd edition). Humana Press/Springer Verlag. 2020; pp 157-170.





John Umstead Hospital, Butner, NC, ca. 1995

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