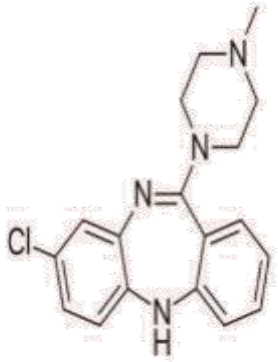
החלמה ותקווה במחלות פסיכיאטריות מורכבות



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Disclosure

- The talk is sponsored by Lundbeck

על מה נדבר

- בעיית האבחנות בפסיכיאטריה
- שיקום והחלמה במחלות מורכבות
- תרופות אנטיפסיכוטיות

Schizophrenia & Inflammation

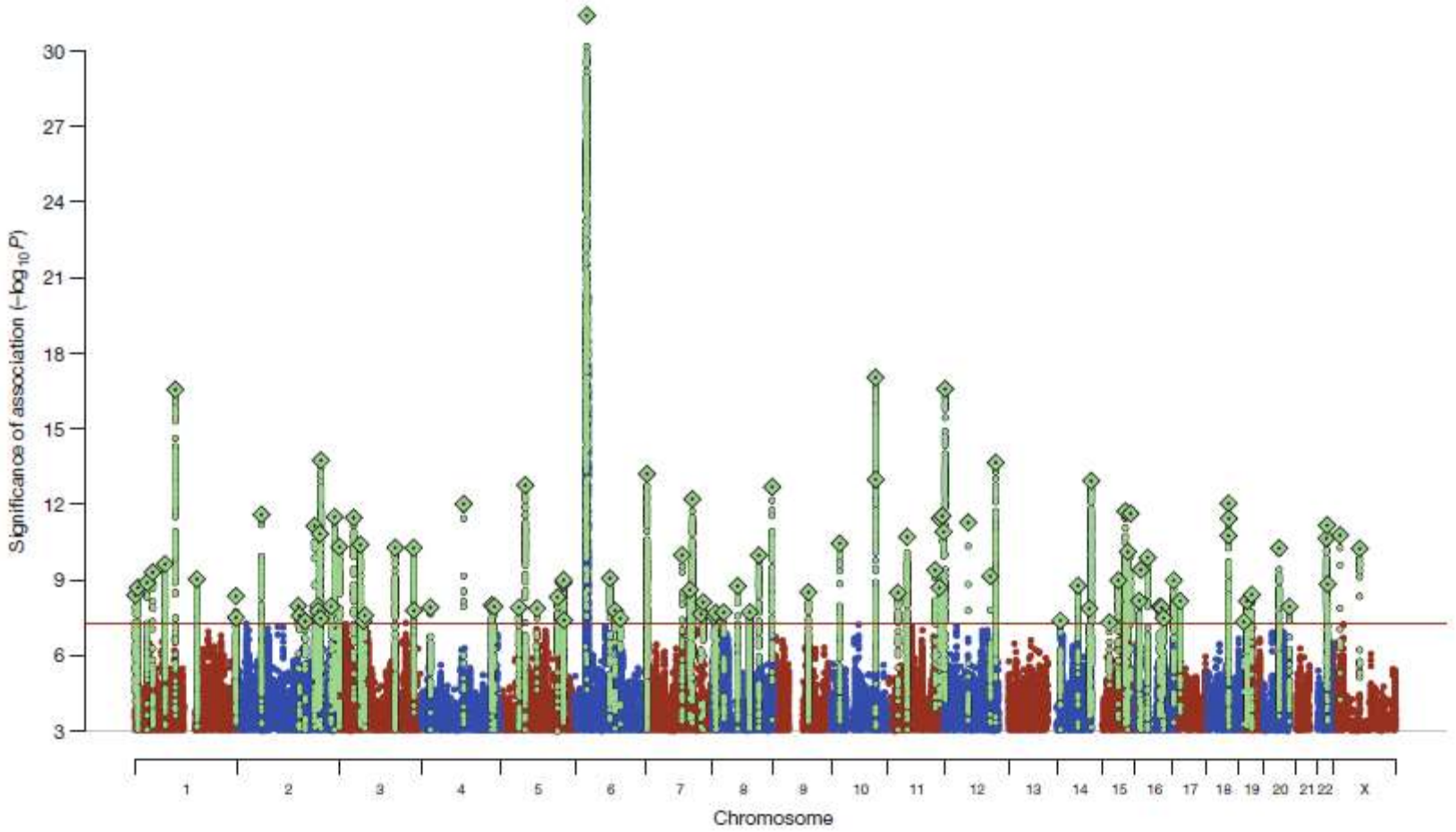


Figure 1 | Manhattan plot showing schizophrenia associations. Manhattan plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). The *x* axis is chromosomal position and the *y* axis is the significance ($-\log_{10} P$; 2-tailed) of association derived by logistic regression. The red line shows the genome-wide significance level (5×10^{-8}). SNPs in green are in linkage disequilibrium with the index SNPs (diamonds) which represent independent genome-wide significant associations.

Nature, 7/2014

ARTICLES
https://doi.org/10.1038/s41591-021-01475-7
nature medicine

Check for updates

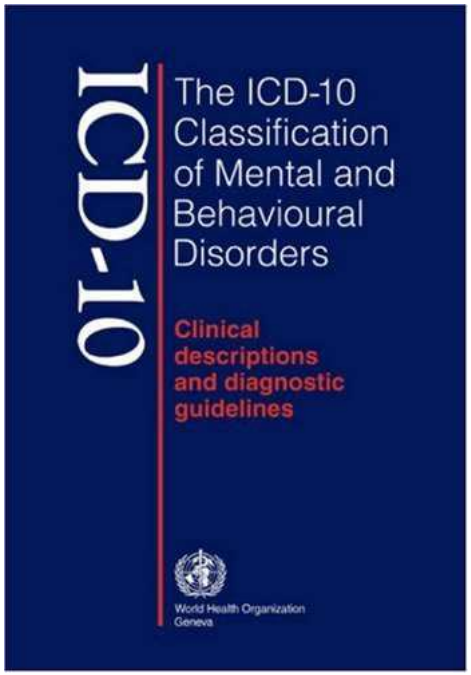
Prognostic value of polygenic risk scores for adults with psychosis

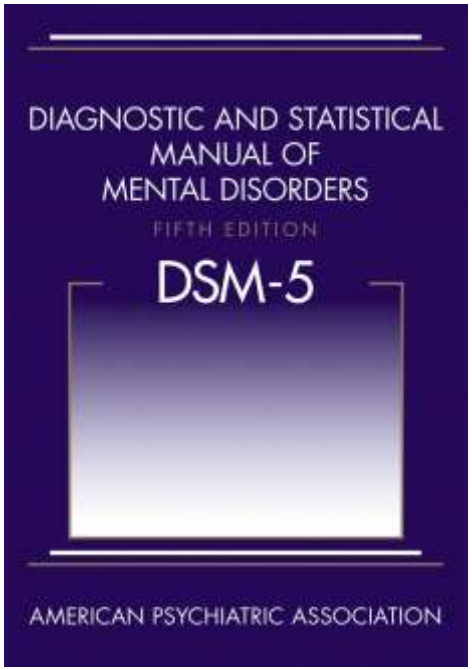
Isotta Landi[1,2,3,4] ✉, Deepak A. Kaji[1,2,3], Liam Cotter[1,2,3,4], Tielman Van Vleck[3,4,5,6], Gillian Belbin[5,7], Michael Preuss[6], Ruth J. F. Loos[6], Eimear Kenny[2,5,7], Benjamin S. Glicksberg[2,3,4], Noam D. Beckmann[2,3], Paul O'Reilly[2], Eric E. Schadt[2,8], Eric D. Achtyes[9,10], Peter F. Buckley[11], Douglas Lehrer[12], Dolores P. Malaspina[1,2], Steven A. McCarroll[13,14], Mark H. Rapaport[15,16], Ayman H. Fanous[17,18], Michele T. Pato[17], Carlos N. Pato[17], Tim B. Bigdeli[17,18], Girish N. Nadkarni[3,4,5,6] and Alexander W. Charney[1,2,3] ✉

Polygenic risk scores (PRS) summarize genetic liability to a disease at the individual level, and the aim is to use them as biomarkers of disease and poor outcomes in real-world clinical practice. To date, few studies have assessed the prognostic value of PRS relative to standards of care. Schizophrenia (SCZ), the archetypal psychotic illness, is an ideal test case for this because the predictive power of the SCZ PRS exceeds that of most other common diseases. Here, we analyzed clinical and genetic data from two multi-ethnic cohorts totaling 8,541 adults with SCZ and related psychotic disorders, to assess whether the SCZ PRS improves the prediction of poor outcomes relative to clinical features captured in a standard psychiatric interview. For all outcomes investigated, the SCZ PRS did not improve the performance of predictive models, an observation that was generally robust to divergent case ascertainment strategies and the ancestral background of the study participants.

Diagnostic system (nosology)

- DSM V and ICD 10
- Based on phenomenology only





Problems with current Diagnostic Systems

- No biological markers
- Categorical
  - Loss of subthreshold symptoms
  - Loss of cross-diagnostic symptoms
- Non-specific treatments
- Excessive co-morbidity of disorders
- Marked heterogeneity of mechanisms and reification of disorders
- the DSM and ICD categories do not map well onto emerging findings from genetics, systems neuroscience and behavioral science

Challenges in Mental Health Research

- The brain is the most complex organ in the body
- Mental illnesses involve highly complex interactions of genetic factors and experience
- The brain cannot be studied directly with the facility we have for more accessible organs, limiting progress based on pathology.

The result

"It becomes very difficult to translate research from basic studies, either in animal models or in humans, to a systematic understanding of pathology or to systematic treatments directed at mechanisms"

Cuthbert & Insel, BMC Medicine 2013

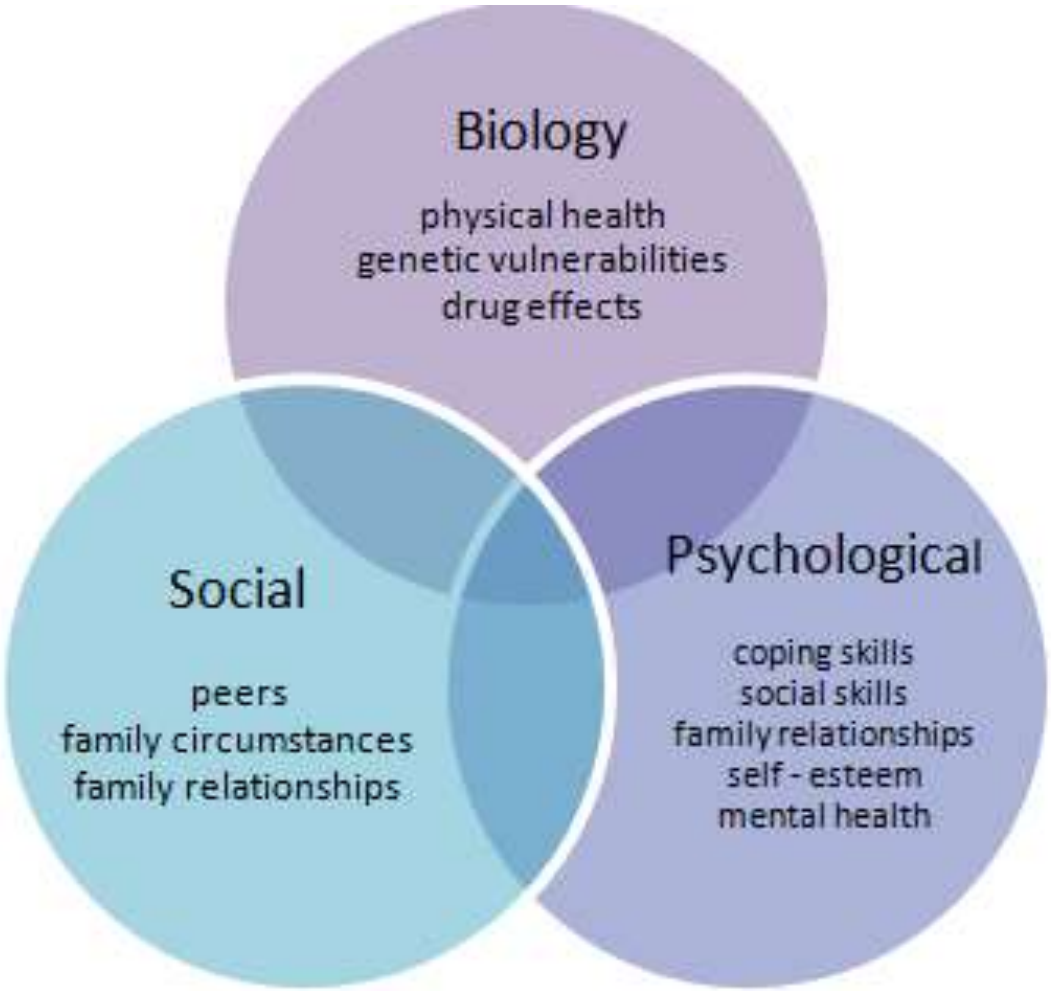
Complex psychosis

Refers to a primary diagnosis of a psychotic illness (this includes schizophrenia, bipolar affective disorder, psychotic depression, delusional disorders and schizoaffective disorder) with severe and treatment-resistant symptoms of psychosis and functional impairment.

People with complex psychosis usually also have 1 or more of the following:

- cognitive impairments associated with their psychosis
- coexisting mental health conditions (including substance misuse)
- pre-existing neurodevelopmental disorders, such as autism spectrum disorder or attention deficit hyperactivity disorder
- physical health problems, such as diabetes, cardiovascular disease or pulmonary conditions.

NICE guidelines 8.2020 www.nice.org.uk/guidance/ng181


Biology
physical health
genetic vulnerabilities
drug effects
Social
peers
family circumstances
family relationships
Psychological
coping skills
social skills
family relationships
self - esteem
mental health

Integrative care model – Stake holders

Community Support Networks

HEALTH SERVICES AND DELIVERY RESEARCH

VOLUME 3 ISSUE 5 FEBRUARY 2015
ISSN 2050-4349

Improving community health networks for people with severe mental illness: a case study investigation

Vanessa Pinfold, Daryl Sweet, Ian Porter, Cath Quinn, Richard Byng, Chris Griffiths, Julie Billsborough, Doyo Gragn Enki, Ruth Chandler, Martin Webber, John Larsen, John Carpenter and Peter Huxley

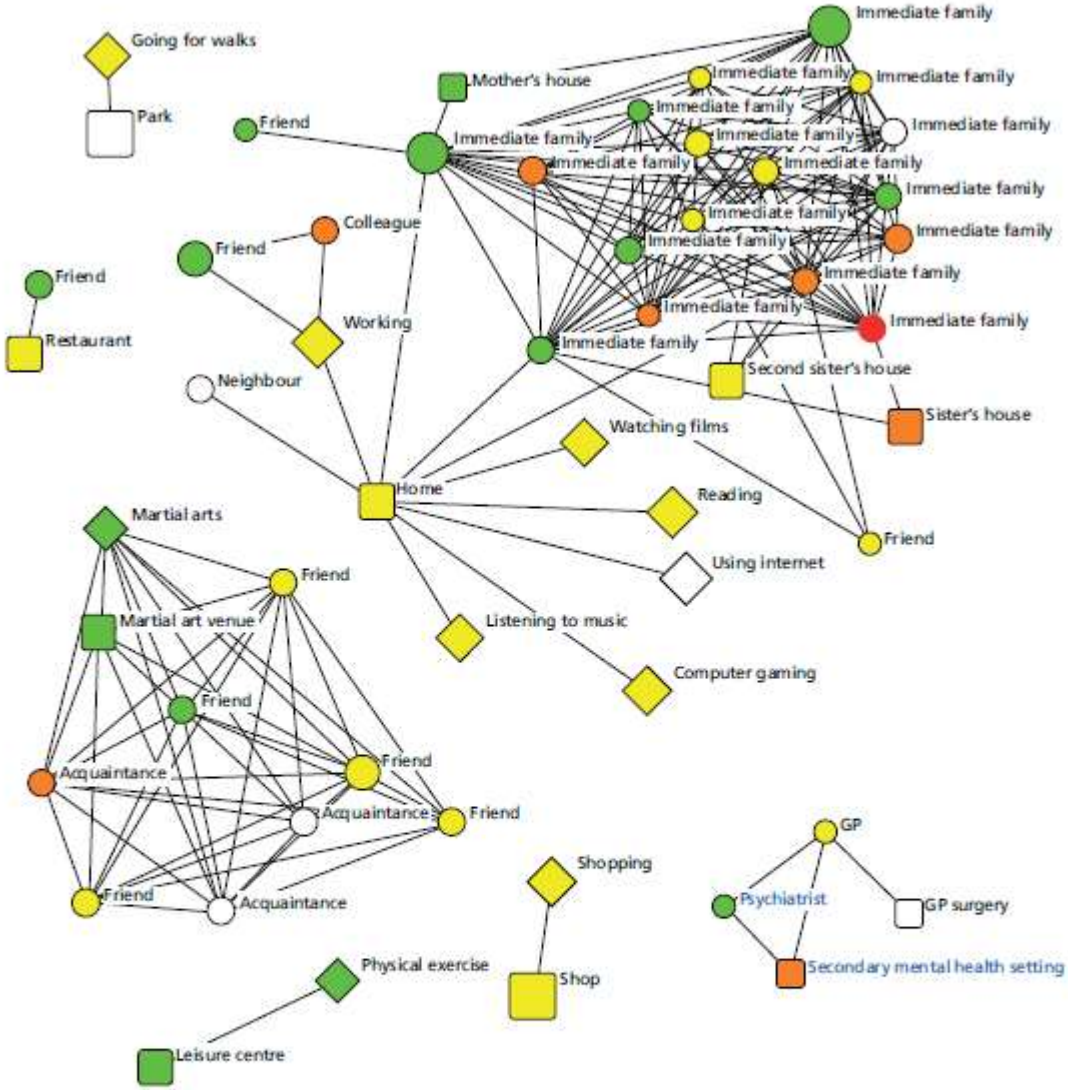
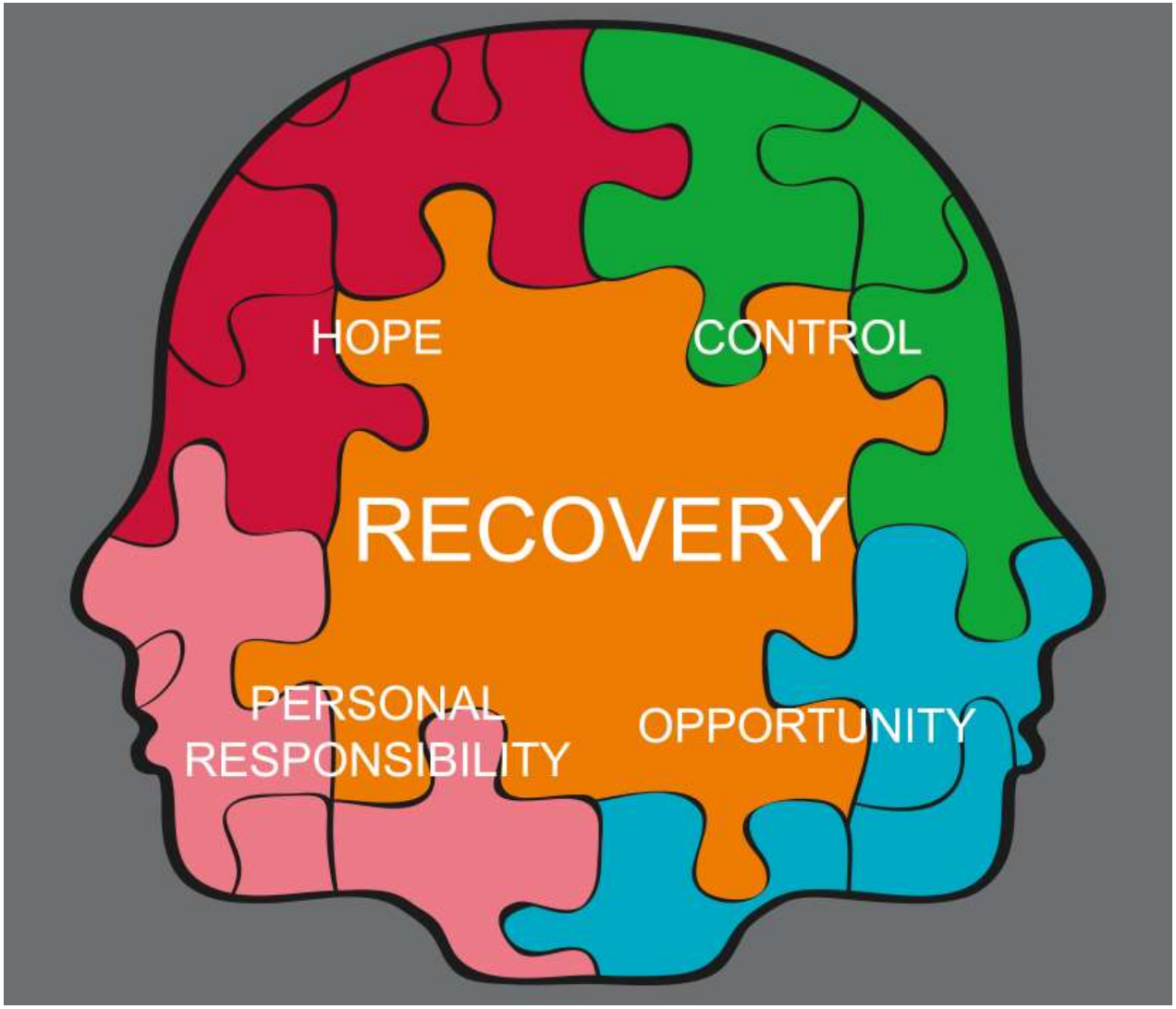


FIGURE 10 An example diverse and active network (SUL29). Shape of node: type of node. Circle = person, square = place, diamond = activity. Colour of node = well-being impact. Red = very negative, orange = negative, white = neutral, yellow = positive, green = very positive. Size of node: frequency. Larger nodes = more frequently interacted with social ties/activities engaged in/places connected to. Colour of text: mental health network. Blue text = mental health nodes, black = other. Note: These diagrams have been anonymised, including changing of place names where they were too specific. Where social ties and activities were not attached to places this was because they were not interacted with or done in any specific location. Similarly activities without connections to people were those that were done alone. The participant was not located in these diagrams in order to reduce complexity of diagrams but they were connected to everything within them.

“SOCIAL”
Psychiatric rehabilitation - definition

A whole systems approach to **recovery** from mental illness that maximizes an individual’s **quality of life** and **social inclusion** by encouraging their **skills**, promoting **independence** and **autonomy** in order to give them **hope** for the future and leads to successful community living through appropriate **support**. (Killaspy et al, 2005)

The objective of treatment

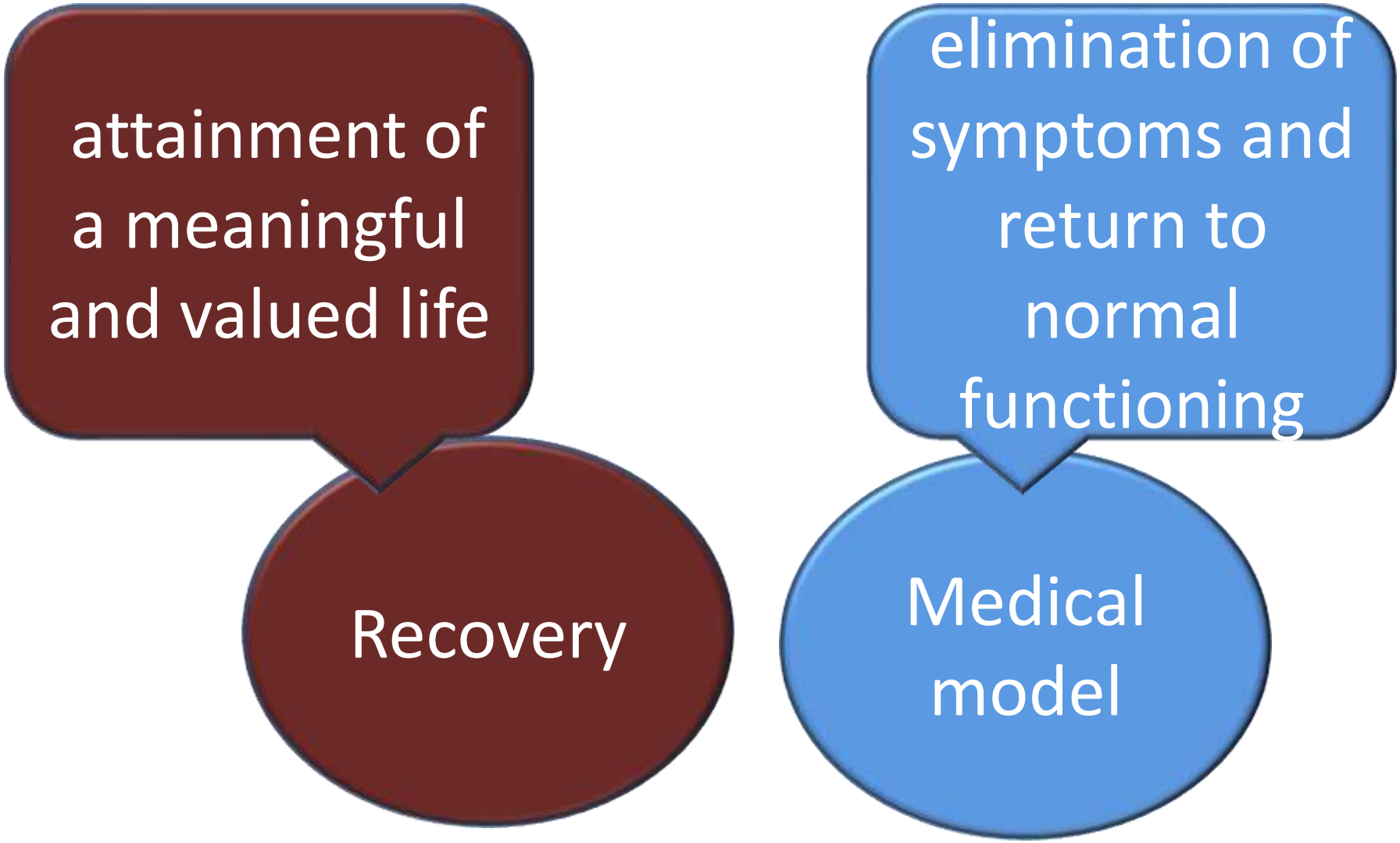


Recovery - definition

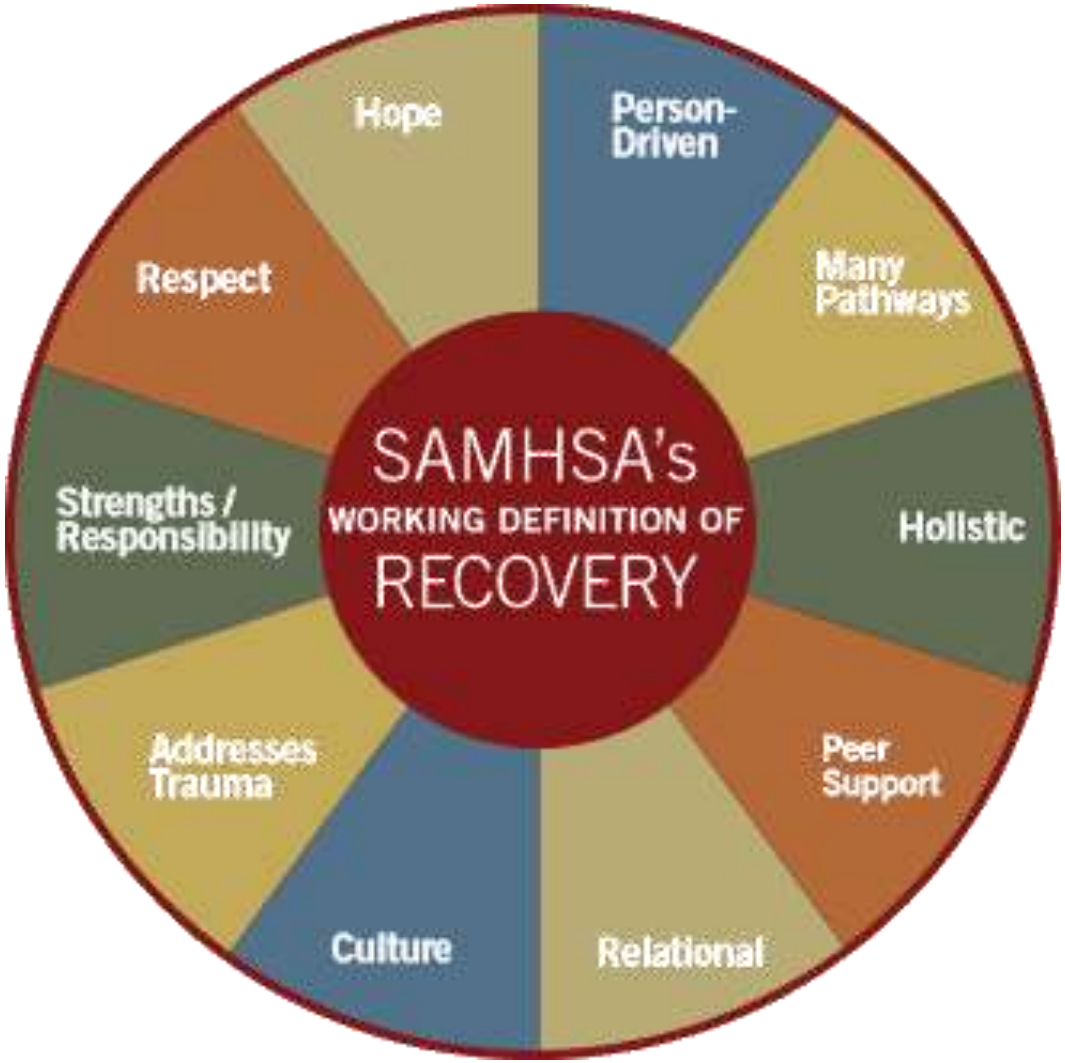
"Mental health recovery is a journey of healing and transformation enabling a person with a mental health problem to live a meaningful life in a community of his or her choice while striving to achieve his or her full potential."

National Consensus Statement on Mental Health Recovery
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Treatment goal



- Recovery
  - Empowerment
  - Responsibility
  - Person centered
  - Holistic
  - Non-linear
  - Peer support
  - HOPE !!!



Services


Intensive Case Management
For populations with mild to moderate MH/SUD needs
Mobile Crisis Services
Including peer-based crisis support
Assertive Community Treatment
For high-need MH/SUD populations
Psychosocial Rehabilitative Services
Supported employment, skill building, community support
Evidence-based, trauma-informed, motivational approach to engagement and service provision
Guiding Principles:
Choice, Harm Reduction, Recovery-Oriented, Community Integration
Substance Use Services
Example: Medication-assisted treatment for opioid dependence
Nonemergency Medical Transportation
Medication Services
Medication management and reconciliation
Individual and Group Therapy
Examples: Integrated dual disorders, illness self-management and recovery
Peer Support Services

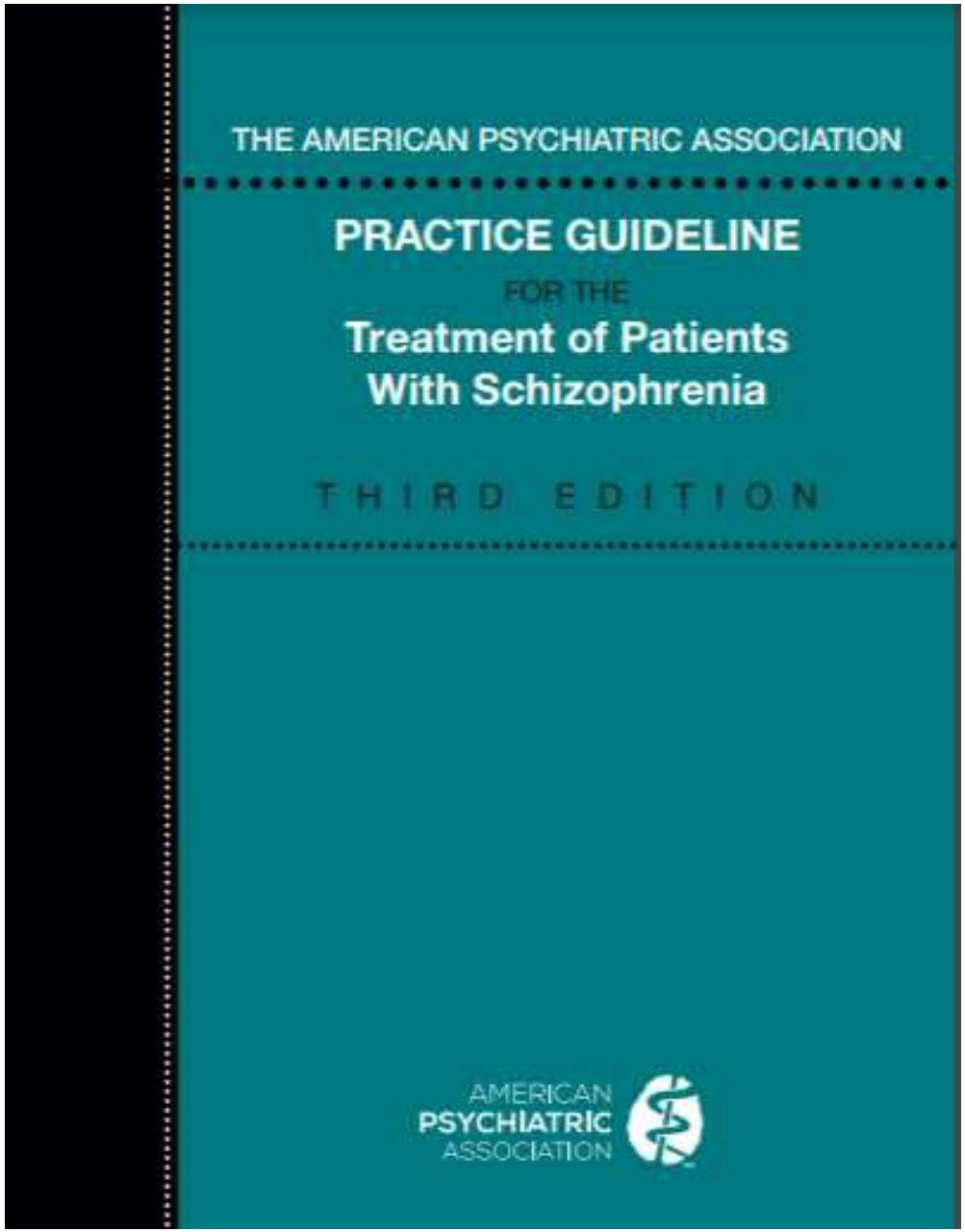
WHAT IS THE PLACE OF DRUGS IN PSYCHOSIS ?

Symptoms reduction

Caution of SE

Symptom control - Medications

- Symptom reduction should be a tool
- Symptoms are barriers on the road to recovery
- Informed use of pharmacotherapy
- Risk management
- Shared decision making
- LAI


THE AMERICAN PSYCHIATRIC ASSOCIATION
PRACTICE GUIDELINE
FOR THE
Treatment of Patients
With Schizophrenia
THIRD EDITION
AMERICAN
PSYCHIATRIC
ASSOCIATION

The authors of the guideline determined each final rating, as described in the section "Guideline Development Process," that is endorsed by the APA Board of Trustees. A *recommendation* (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of the intervention clearly outweigh harms. A *suggestion* (denoted by the numeral 2 after the guideline statement) indicates greater uncertainty: although the benefits of the statement are still viewed as outweighing the harms, the balance of benefits and harms is more difficult to judge, or the benefits or the harms may be less clear. With a suggestion, patient values and preferences may be more variable, and this can influence the clinical decision that is ultimately made.

Each guideline statement also has an associated rating for the *strength of supporting research evidence*. Three ratings are used: *high*, *moderate*, and *low* (denoted by the letters A, B, and C, respectively). These ratings reflect the level of confidence that the evidence for a guideline statement reflects a true effect based on consistency of findings across studies, directness of the effect on a specific health outcome, precision of the estimate of effect, and risk of bias in available studies (Agency for Healthcare Research and Quality 2014; Balshem et al. 2011; Guyatt et al. 2006).

Pharmacotherapy

4. APA *recommends* **(1A)** that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.*
5. APA *recommends* **(1A)** that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with an antipsychotic medication.*
6. APA *suggests* **(2B)** that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.*
7. APA *recommends* **(1B)** that patients with treatment-resistant schizophrenia be treated with clozapine.*
8. APA *recommends* **(1B)** that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.*
9. APA *suggests* **(2C)** that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.*
10. APA *suggests* **(2B)** that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.*
11. APA *recommends* **(1C)** that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.
12. APA *suggests* **(2C)** the following options for patients who have parkinsonism associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, or treating with an anticholinergic medication.
13. APA *suggests* **(2C)** the following options for patients who have akathisia associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, adding a benzodiazepine medication, or adding a beta-adrenergic blocking agent.
14. APA *recommends* **(1B)** that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2).

Psychosocial Interventions

15. APA *recommends* **(1B)** that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a coordinated specialty care program.*
16. APA *recommends* **(1B)** that patients with schizophrenia be treated with cognitive-behavioral therapy for psychosis (CBTp).*
17. APA *recommends* **(1B)** that patients with schizophrenia receive psychoeducation.*
18. APA *recommends* **(1B)** that patients with schizophrenia receive supported employment services.*
19. APA *recommends* **(1B)** that patients with schizophrenia receive assertive community treatment if there is a history of poor engagement with services leading to frequent relapse or social disruption (e.g., homelessness; legal difficulties, including imprisonment).*
20. APA *suggests* **(2B)** that patients with schizophrenia who have ongoing contact with family receive family interventions.*
21. APA *suggests* **(2C)** that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.*
22. APA *suggests* **(2C)** that patients with schizophrenia receive cognitive remediation.*
23. APA *suggests* **(2C)** that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.*
24. APA *suggests* **(2C)** that patients with schizophrenia be treated with supportive psychotherapy.*

Special Article

Psychotherapy and Psychosomatics

Psychother Psychosom 2017;86:189–219
DOI: 10.1159/000477313

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Published online: June 24, 2017

Antipsychotic-Induced Dopamine Supersensitivity Psychosis: Pharmacology, Criteria, and Therapy

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Charles-Siegfried Peretti[g] Nobuhisa Kanahara[h] Masayuki Takase[i]
Masaomi Iyo[h, i]

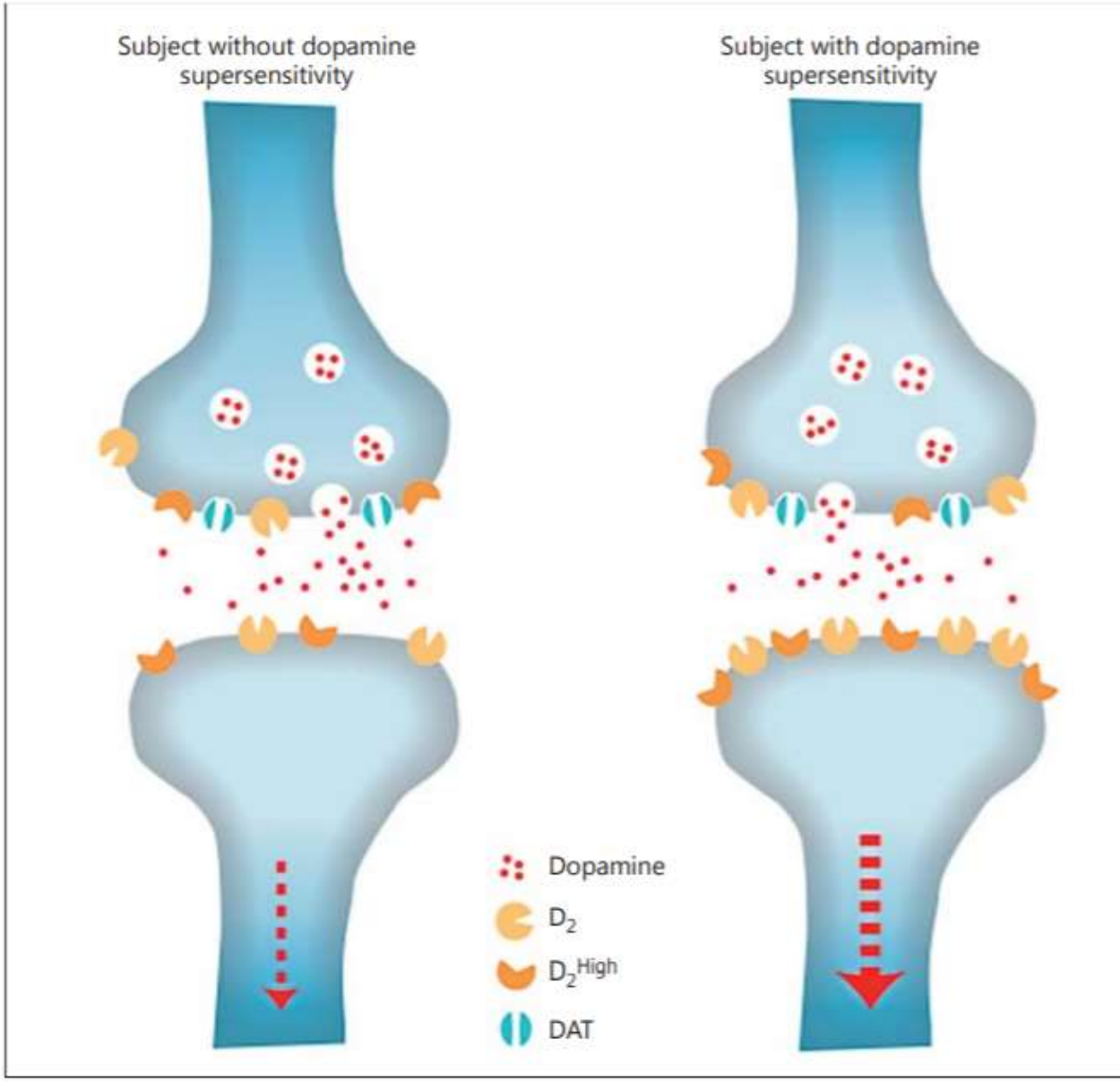

Fig. 1. Theoretical model illustrating the ability of chronic treatment with antipsychotic medication to induce dopamine supersensitivity. It is proposed that with chronic antipsychotic treatment (synapse on the right), there are increases in the numbers of dopamine D_2 receptors (D_2) and D_2 receptors in a high-affinity state for dopamine (D_2^{High}) in the striatum, without significant changes in presynaptic dopamine release, synthesis, or reuptake. In turn, the D_2 receptor upregulation enhances D_2-mediated dopamine signaling, shown by the red arrows, thus producing a state of supersensitivity to dopamine agonist stimulation. The functional consequences of this dopamine supersensitivity would include antipsychotic treatment failure, supersensitivity-related psychosis, and movement disorders (see text). DAT, dopamine transporter.

Schizophrenia Bulletin
doi:10.1093/schbul/sbab017

MAJOR REVIEW

A Method for Tapering Antipsychotic Treatment That May Minimize the Risk of Relapse

Mark Abie Horowitz*[,1,2], Sameer Jauhar[3], Sridhar Natesan[3], Robin M. Murray[3], and David Taylor[3,4]

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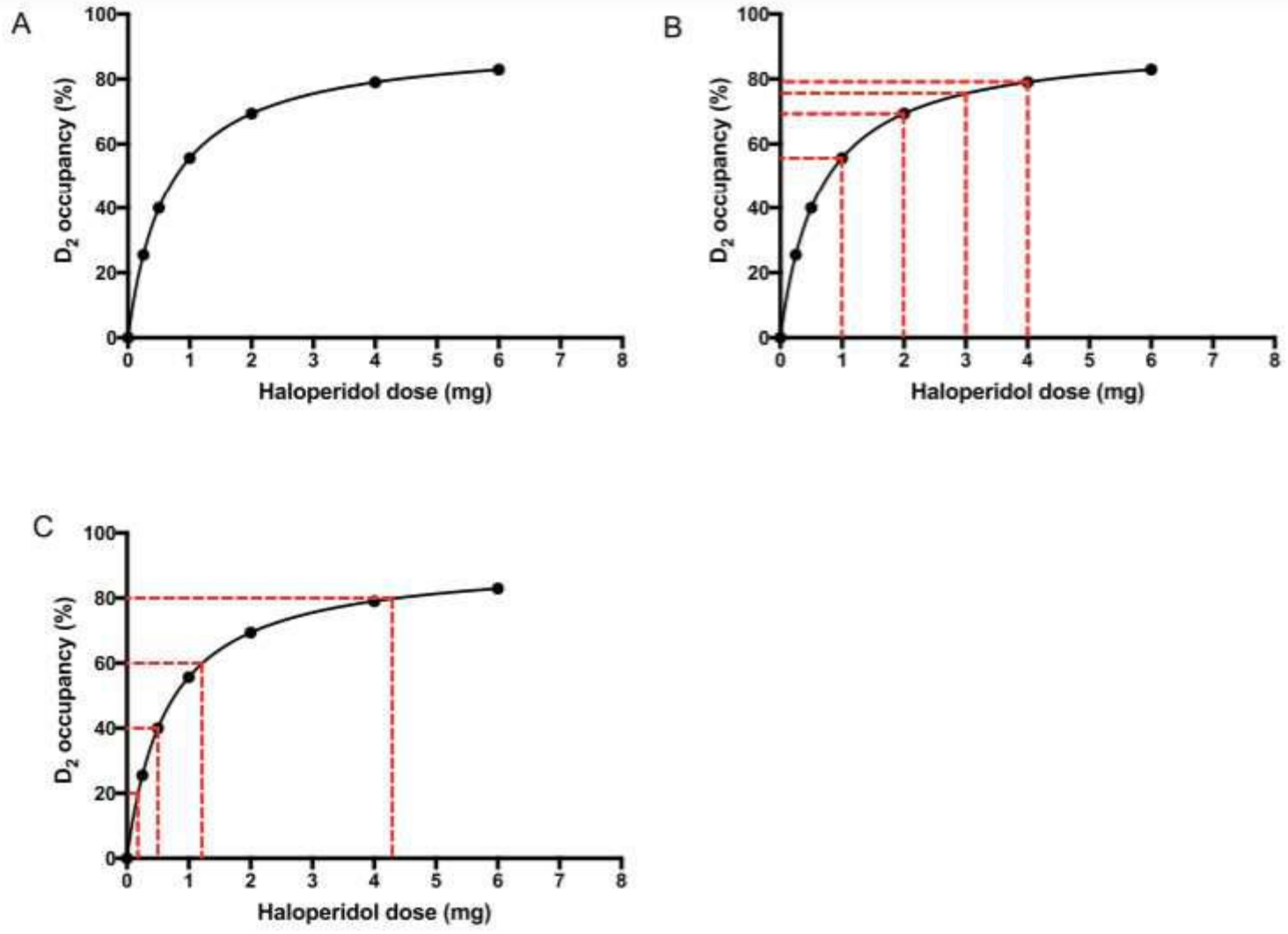
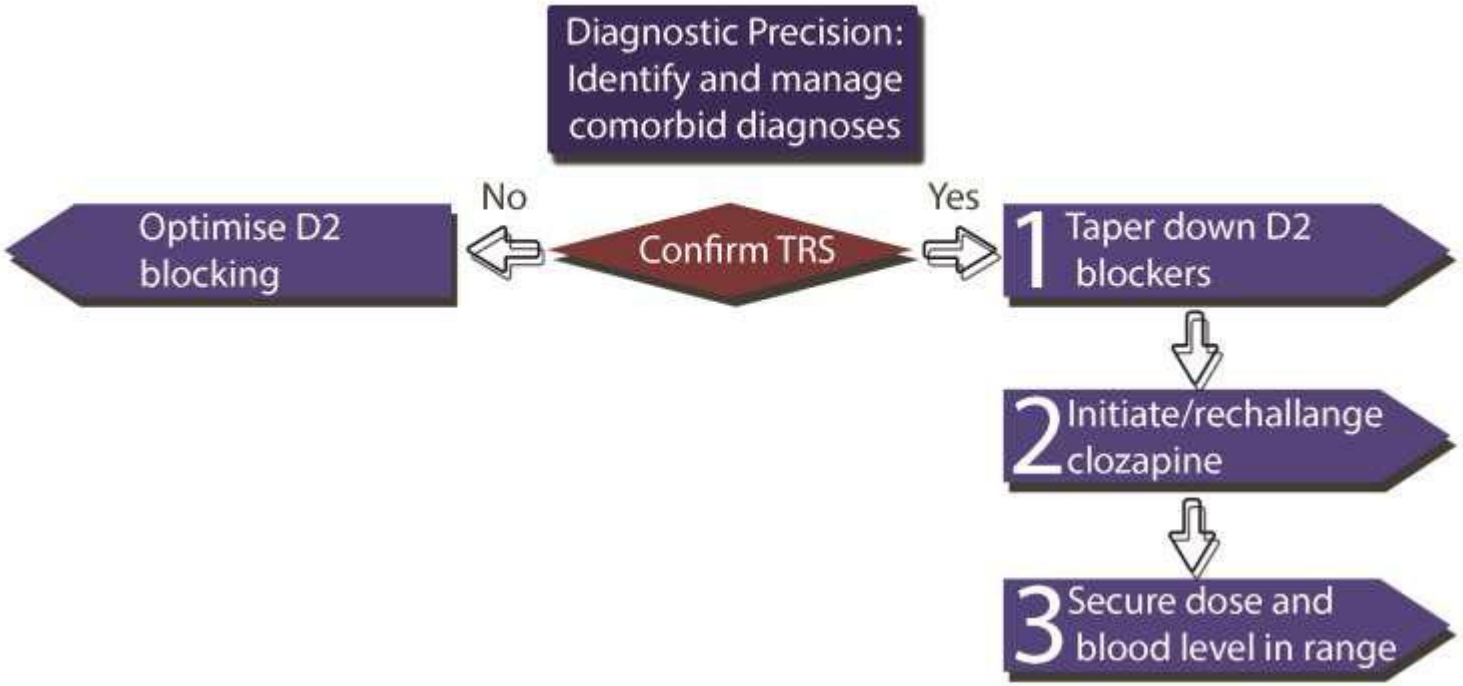
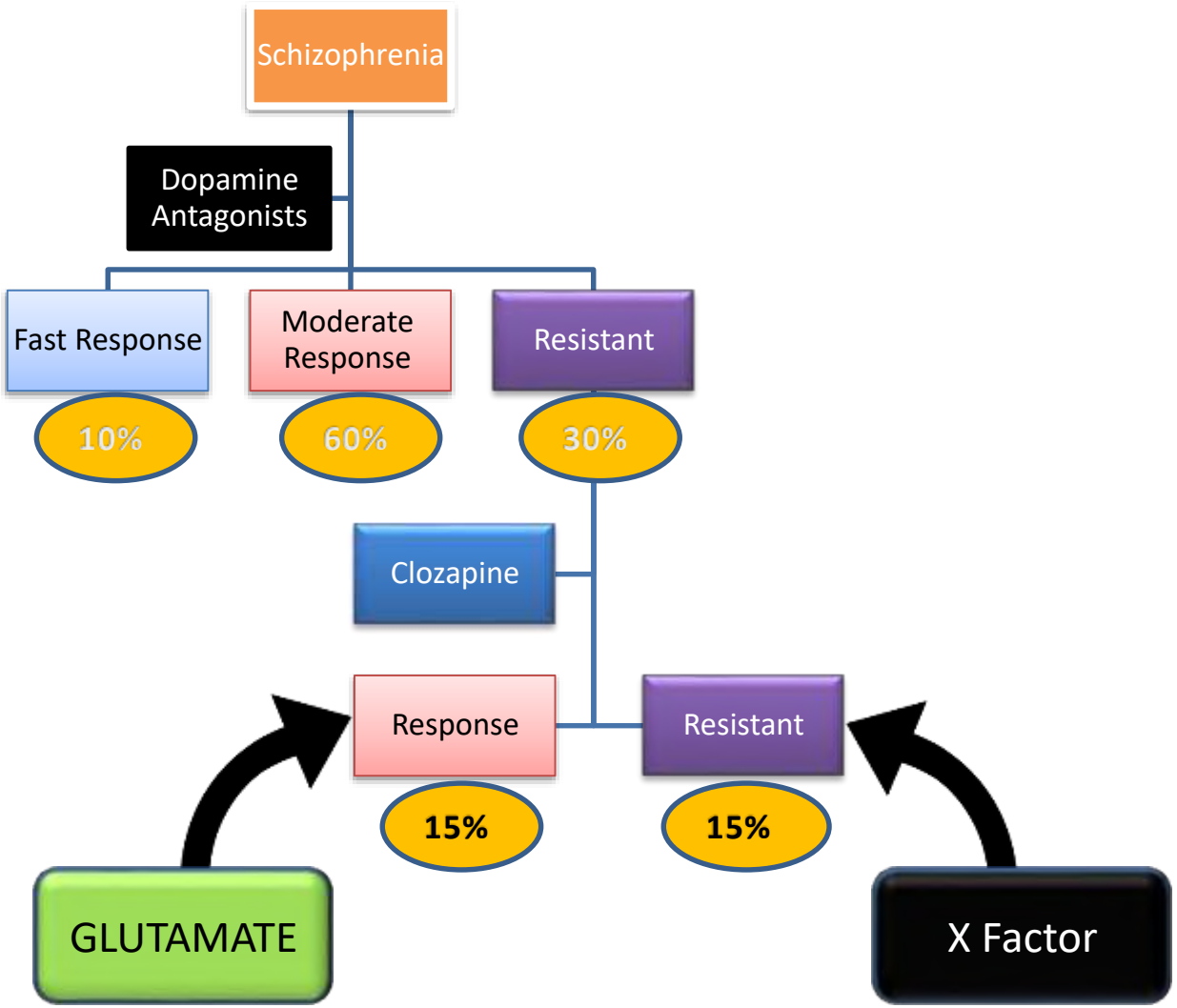

A
B
C
D2 occupancy (%)
Haloperidol dose (mg)
0
20
40
60
80
100
0
1
2
3
4
5
6
7
8



Krivoy A, et al, J Clin Psychiatry 2019


Schizophrenia
Dopamine Antagonists
Fast Response
Moderate Response
Resistant
10%
60%
30%
Clozapine
Response
Resistant
15%
15%
GLUTAMATE
X Factor

Optimize clozapine treatment - pharmacokinetics

- Metabolism in the liver
- Excreted in the kidney
- Main metabolite - norclozapine
- Therapeutic blood monitoring (TDM)
- Adherence

- Moderating factors:
  - Gender
  - Age
  - Body weight
  - Fast metabolizers (CYP 1A2, 3A4)
  - Smoking
  - Fever
  - Other drugs (Fluvoxamine)
  - Caffeine

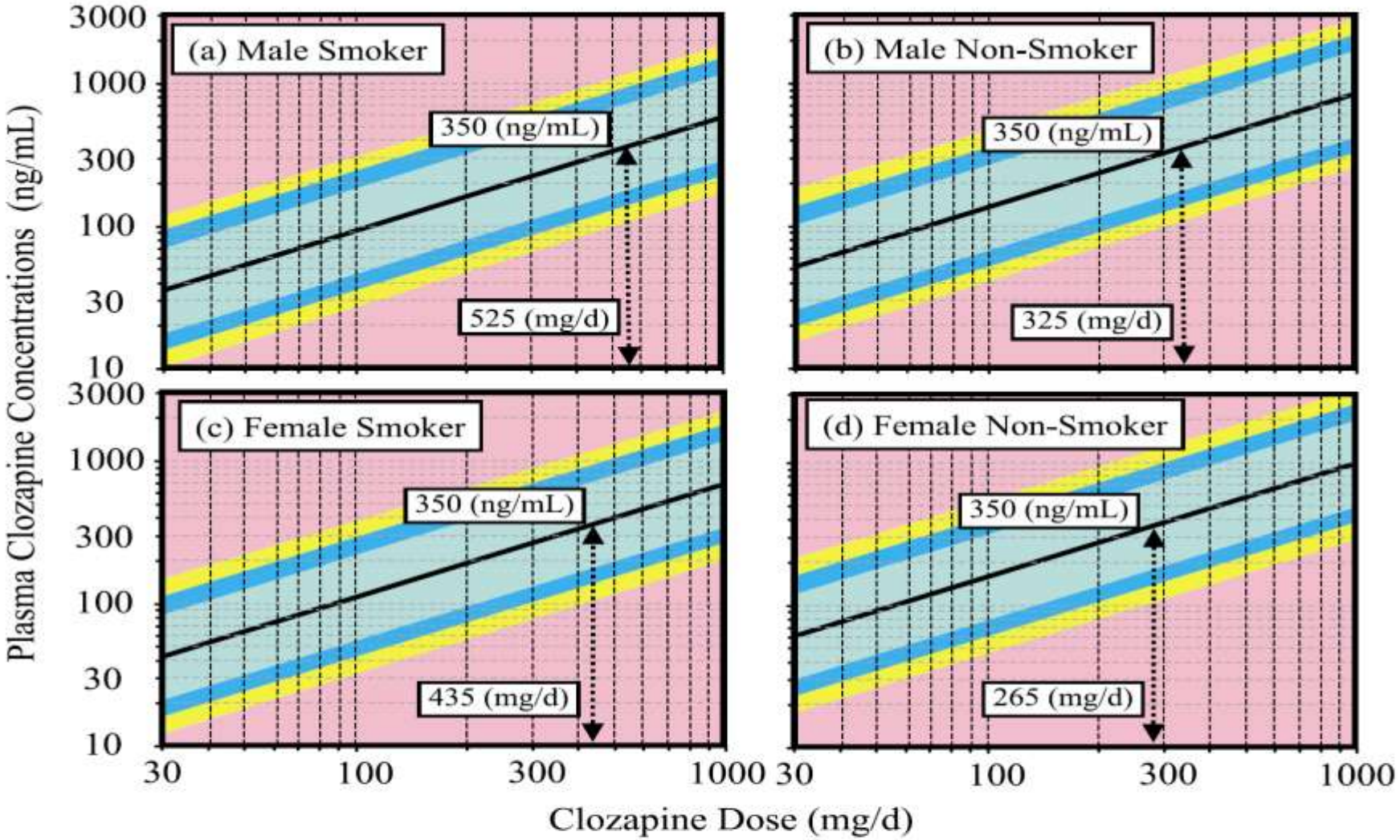


FIGURE 1. Nomograms showing the likelihood of observed plasma clozapine trough concentration for a given daily dose in a 40 year old patient with an average weight of 80 kg (male) or 70 kg (female) and a clozapine/norclozapine MR of 1.32. (a) Male Smoker, (b) Male Nonsmoker, (c) Female Smoker, (d) Female Nonsmoker. The broken arrows show the daily doses that provide the highest likelihood of the plasma clozapine concentration 350 ng/mL. (from this nomogram no likelihood can be estimated for different doses associated with specific clozapine concentrations, ie, the likelihood estimation works only in the vertical direction and not in the horizontal direction).

Key:

- Green area = 50% of patients;
- Green & Blue areas together = 75% of patients;
- Green & Blue & Yellow areas together = 95% of patients;
- Pink area = less than 5% of patients

Rostami-Hodjegan A et al,

J Clin Psychopharmacol 2004

TDM in Israel – 2 labs !!

- Rambam
  - Cost 398 ILS
  - EDTA tube – purple cap -(10 ml)

- Carmel (Clalit Health Services)
  - Cost 133 ILS (covered by HMO)
  - Red cap tube (6 ml)
  - Circulate and process
  - Freeze -20C°

ארגונים שחשוב להכיר בישראל

- לשמ"ה
  - עמיתים מומחים
- עוצמה
- ISPS
- ISPRA
  - Navigate
- אנוש
  - מיל"ם
  - ידע מניסיון חיים
  - בית הספר הארצי לשיקום

לסיכום

- האם יש דבר כזה "סכיזופרניה" ? – הנזק עולה על התועלת ?
- הייעוד הוא החלמה = הצלחות גדולות יותר
- גישה למחלות נפשיות מורכבות היא רב מימדית כאשר הטיפול התרופתי ממוקד בהפחתת סימפטומים
  - מינון מינימלי אפקטיבי
  - ניהול תופעות לוואי
  - הפחתת סטיגמה
- גישה אופטימית ומלאת תקווה – אתגר למשפחה ולצוות המטפל !