Functioning, Health Related Quality of Life and Relapse Prevention in Schizophrenia: Focus on Aripiprazole Maintena

Ofer Agid M.D.
Associate Professor of Psychiatry
The Centre for Addiction and Mental Health
Department of Psychiatry, University of Toronto, Canada

Disclosures: Professor Ofer Agid

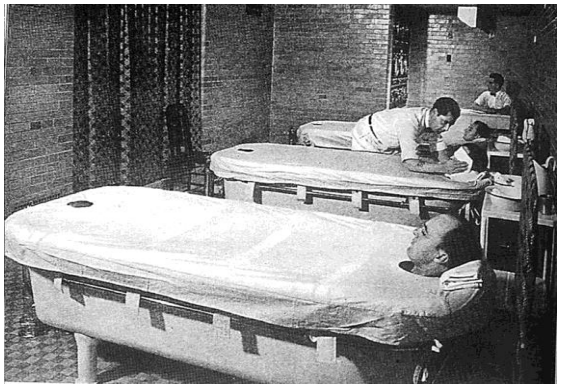
- I have an interest in relation with one or more organisations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships are summarised below:

Interest	Name of organisation
Research Contracts	Janssen-Ortho (Johnson & Johnson); Otsuka; Boehringer Ingelheim; Neurocrine Bioscience
Advisory board/Consultant	Janssen-Ortho (Johnson & Johnson); Otsuka; Lundbeck; Sumitomo Dainippon Pharma (DSP)
Speaking engagements	Janssen-Ortho (Johnson & Johnson); Lundbeck, Mylan Pharmaceuticals; Otsuka; HLS Therapeutics

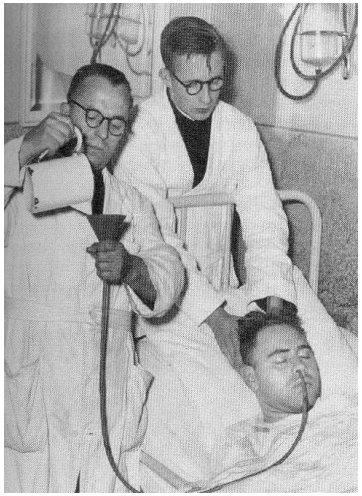
Outline

- A brief history of past treatments for schizophrenia
- Determine if schizophrenia is a progressive brain disease by re-examining the evidence
- Describe the consequences of relapse in schizophrenia across multiple dimensions
- The decline of functionality and HRQoL in schizophrenia – should we prioritize treatment goals differently?
- Subjective well-being, functionality and dopamine modulation.

Past treatments for schizophrenia



Artificial hibernation

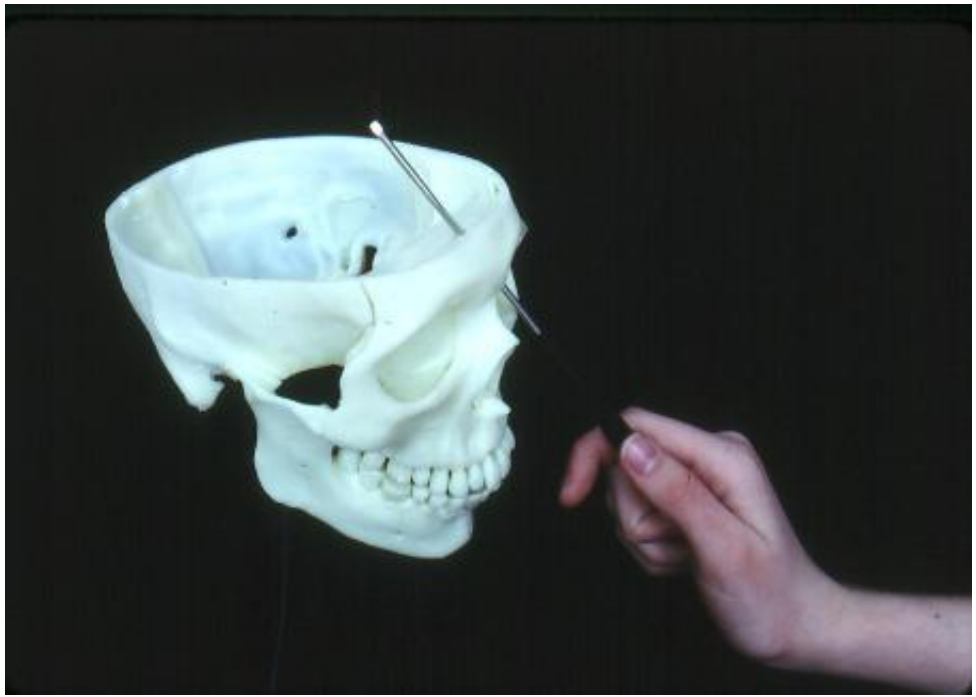


Insulin coma

Bathing therapy: lasting for days

Hahn WA. Creighton Law Rev. 1982-1983;16(3):719–42.

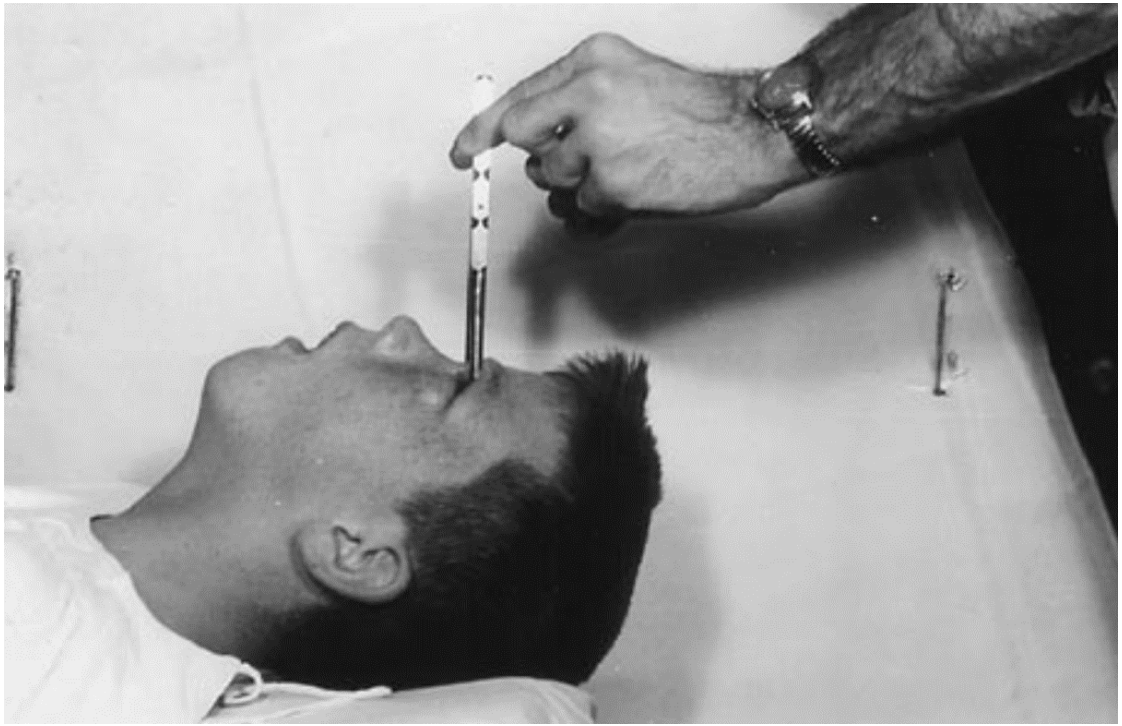
Frontal lobotomy



A metal probe inserted through the bony roof of the orbit (eye-sockets) enables access to the frontal lobes of the brain

Soares MS et al. Neuropsychiatr Dis Treat. 2013;9:509–15. doi: 10.2147/NDT.S35823. Epub 2013 Apr 15.

Frontal lobotomy

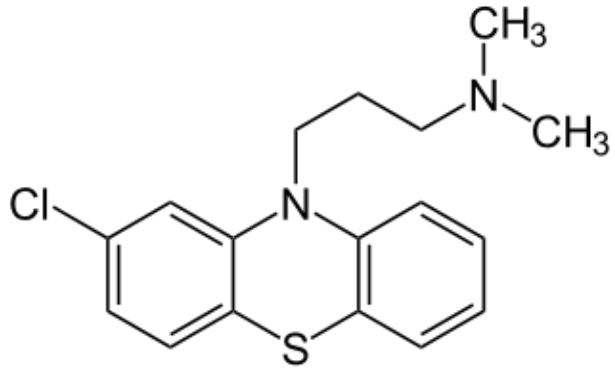


Egas Moniz (1874–1955)

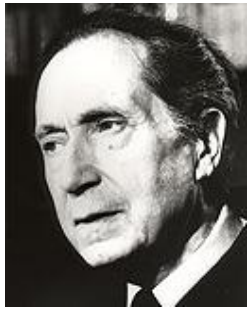
- Won the Nobel Prize in Physiology & Medicine 1949
- For his discovery of the therapeutic value of frontal lobotomy in psychoses

The Nobel Prize in Physiology or Medicine 1949. Available at https://www.nobelprize.org/nobel_prizes/medicine/laureates/1949/ (accessed April 2018).

Chlorpromazine (Largactil®/Thorazine®)



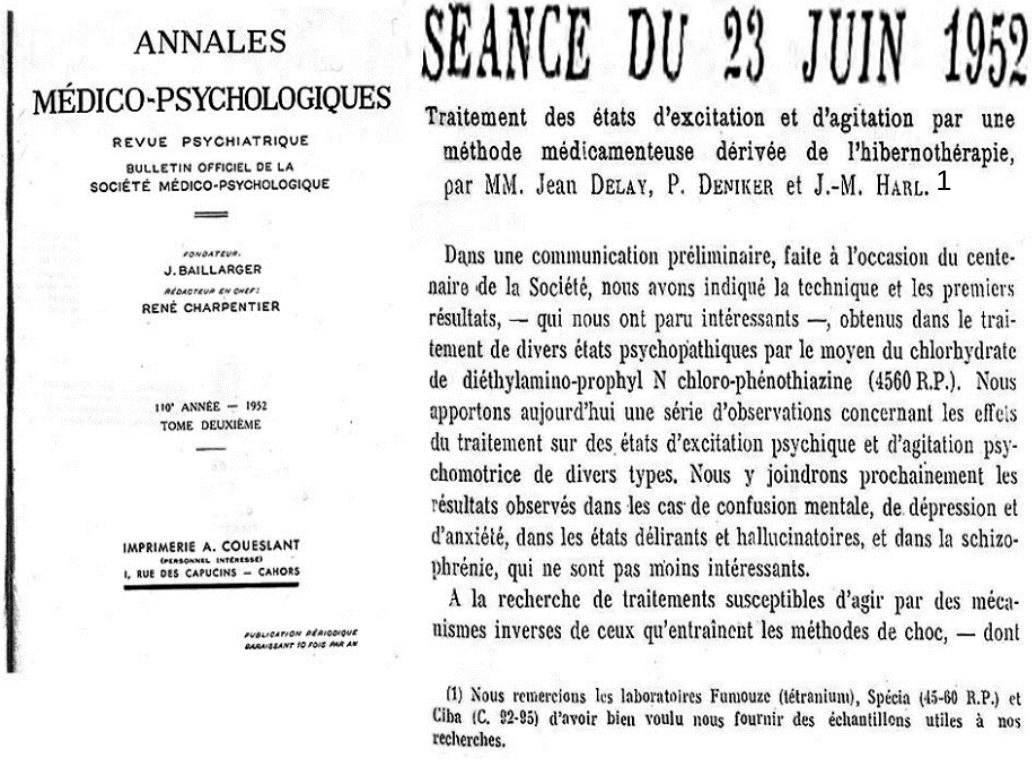
Henri Laborit



Jean Delay

Pierre Deniker

First report of antipsychotic treatment



ANNALES

MÉDICO-PSYCHOLOGIQUES

REVUE PSYCHIATRIQUE

BULLETIN OFFICIEL DE LA SOCIÉTÉ MÉDICO-PSYCHOLOGIQUE

FONDATEUR:
J. BAILLARGER

RÉDACTEUR EN CHEF:
RENÉ CHARPENTIER

110e ANNÉE — 1952
TOME DEUXIÈME

IMPRIMERIE A. COUESLANT
(PERSONNEL INTÉRESSÉ)
1, RUE DES CAPUCINS — CAHORS

PUBLICATION PÉRIODIQUE
PARAISSANT 10 FOIS PAR AN

SEANCE DU 23 JUIN 1952

Traitement des états d'excitation et d'agitation par une méthode médicamenteuse dérivée de l'hibernothérapie, par MM. Jean DELAY, P. DENIKER et J.-M. HARL. [1]

Dans une communication préliminaire, faite à l'occasion du centenaire de la Société, nous avons indiqué la technique et les premiers résultats, — qui nous ont paru intéressants —, obtenus dans le traitement de divers états psychopathiques par le moyen du chlorhydrate de diéthylamino-prophyl N chloro-phénothiazine (4560 R.P.). Nous apportons aujourd'hui une série d'observations concernant les effets du traitement sur des états d'excitation psychique et d'agitation psychomotrice de divers types. Nous y joindrons prochainement les résultats observés dans les cas de confusion mentale, de dépression et d'anxiété, dans les états délirants et hallucinatoires, et dans la schizophrénie, qui ne sont pas moins intéressants.

A la recherche de traitements susceptibles d'agir par des mécanismes inverses de ceux qu'entraînent les méthodes de choc, — dont

(1) Nous remercions les laboratoires Fumouze (tétranium), Spécia (45-60 R.P.) et Ciba (C. 92-95) d'avoir bien voulu nous fournir des échantillons utiles à nos recherches.

"…within 3 days chlorpromazine alleviated hallucinations and stopped internal voices…" [2]

1. Delay J et al. Ann Med Psychol. 1952;110:267–73; 2. Agid O et al. J Psychiatry Neurosci. 2006;31:93–100.

Mechanism of action of antipsychotics: The beginning of the “receptor era”

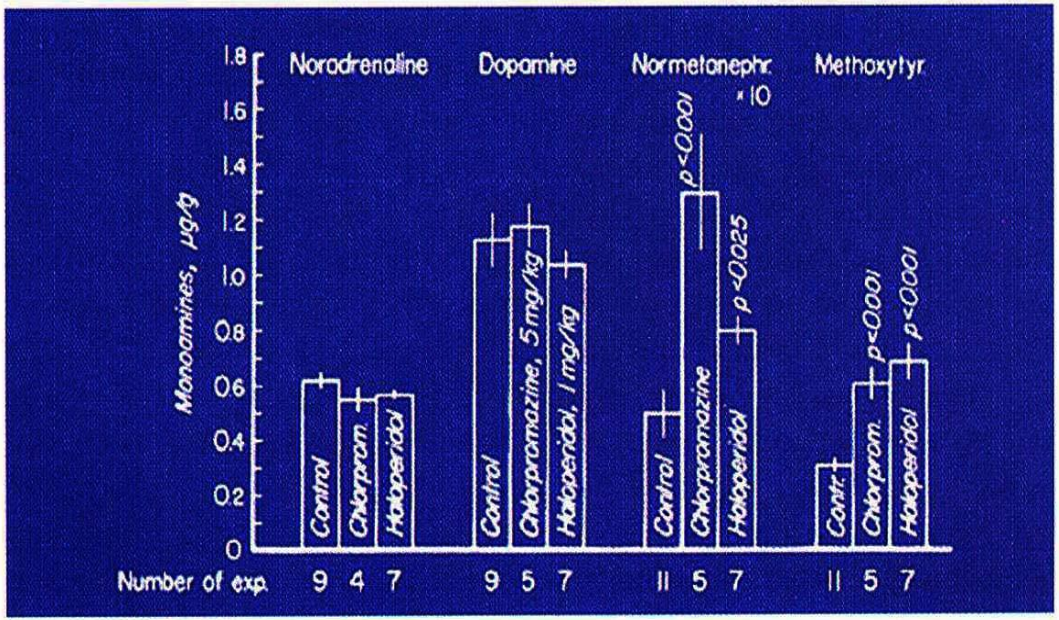


Figure 14. Accumulation of of the basic catecholamine metabolites normetanephrine and 3-methoxytyramine, enhanced by treatment with major neuroleptic agents following monoamine oxidase inhibition. From Carlsson and Lindqvist 1963.

Image from Arvid Carlsson - Nobel Lectures: Physiology or Medicine 1996-2000. Editor Hans Jörnvall, World Scientific Publishing Co., Singapore, 2003.

Nobel Prize in Physiology & Medicine 2000

Arvid Carlsson

- Arvid Carlsson overturned conventional wisdom by showing that the chemical dopamine is an important neurotransmitter in the brain
- Before, dopamine was presumed to be merely a precursor to a more important neurotransmitter, noradrenaline (norepinephrine)[1]

Snyder SH. Proc Natl Acad Sci USA. 2011;108(47):18869–71. doi: 10.1073/pnas.1114346108. Epub 2011 Nov 21.

IS SCHIZOPHRENIA A NEUROPROGRESSIVE DISORDER?

The myth of schizophrenia as a progressive brain disease

- Minority of patient show the incremental loss of function characteristic of neurodegenerative illnesses
- MRI studies demonstrate decreases in brain tissue volumes that are explicable by effects of substance abuse, and other secondary factors
- Patients show cognitive deficits that does not appear to deteriorate over time

MRI, magnetic resonance imaging

Zipursky et al. *SCZ Bull* 2013.

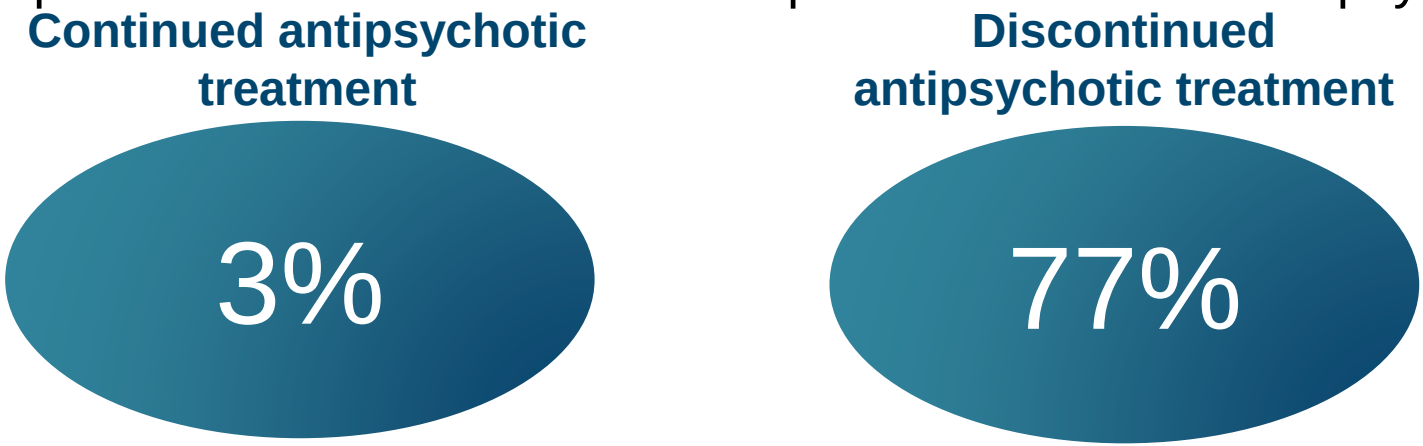
Long-term outcome of schizophrenia

Studies Investigating Long Term Outcome of Adherent Patients with Schizophrenia

0

Risk of symptom recurrence declines with maintenance treatment

Recurrence rates at 1 year in patients with schizophrenia achieving symptomatic remission from a first episode of non-affective psychosis

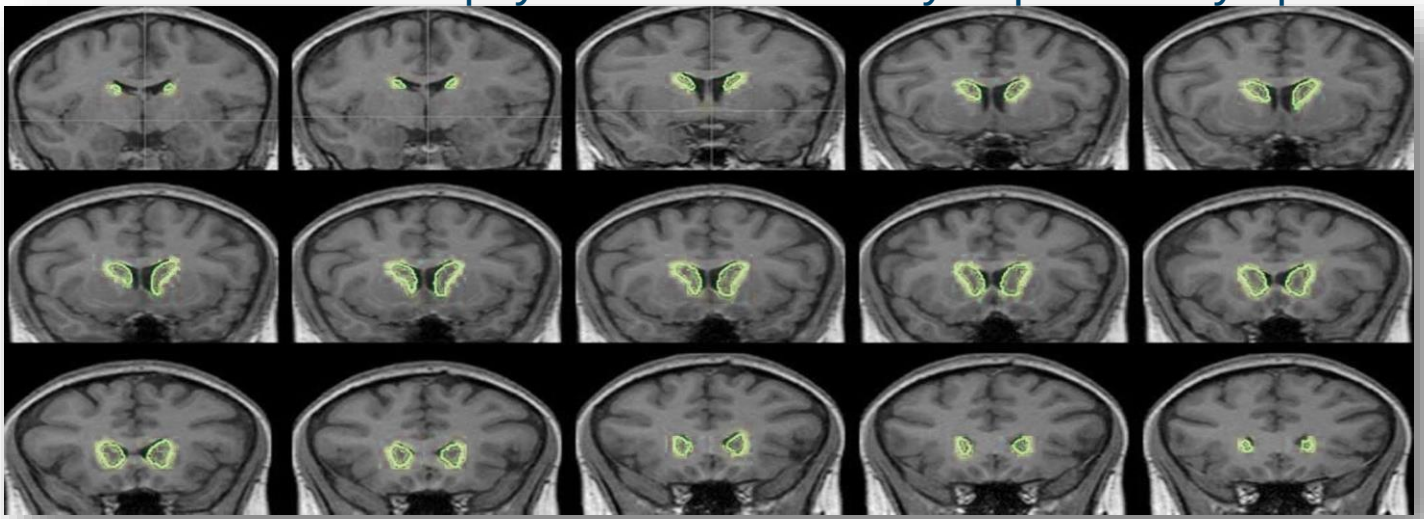


Highlights a need for effective maintenance treatment initiated early in the disease course

Zipursky RB, et al. *Schizophr Res* 2014;152:408–414.

The neurotoxic effect of untreated psychosis

Caudate volume was significantly associated with
duration of untreated psychosis and severity of positive symptoms

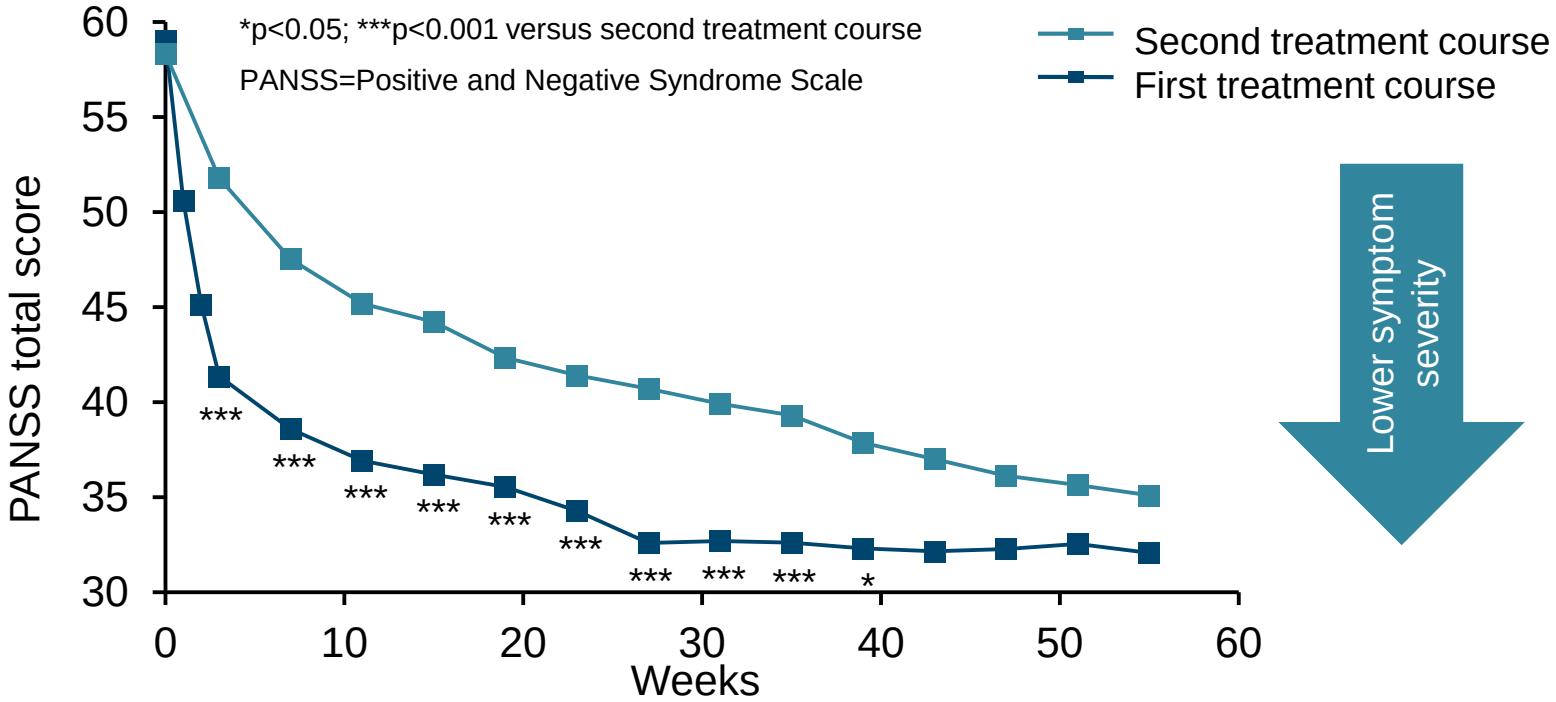


Coronal slices showing the caudate nucleus tracings (in green)

For duration of untreated psychosis, relative caudate nucleus volume -0.266, p=0.022; for severity of positive symptoms (highest vs. lowest quartile for psychotic symptom severity), t=-2.02, df=58, p=0.048.

Crespo-Facorro B, et al. *Schizophr Res* 2007;91(1-3):87-96.

Treatment response declines with each relapse – BPRS total score

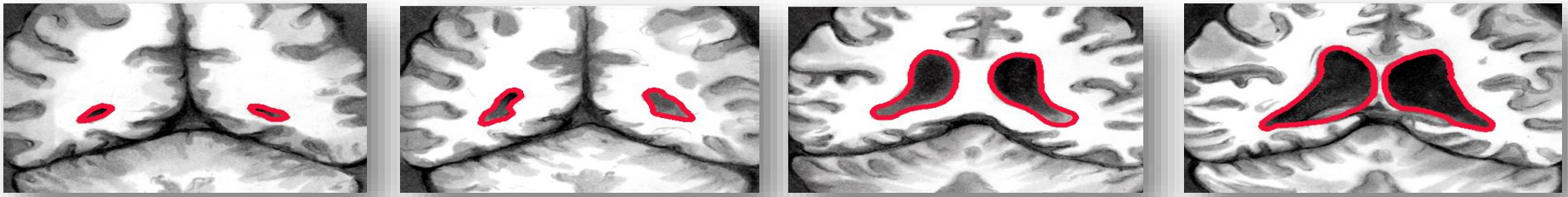


BPRS, Brief Psychiatric Rating Scale

Agid O, et al. *Neuropsychopharmacology* 2014;39: S373–S374; Zipursky R, et al. Poster at ACNP 2014.

Multiple relapses may lead to continuing neurodegeneration

- Deterioration in schizophrenia is at least partly the result of neurodegeneration



- Many patients who stop treatment and then relapse fail to regain prior level of function
- Early adequate and sustained intervention is, therefore, the key to improving outcome

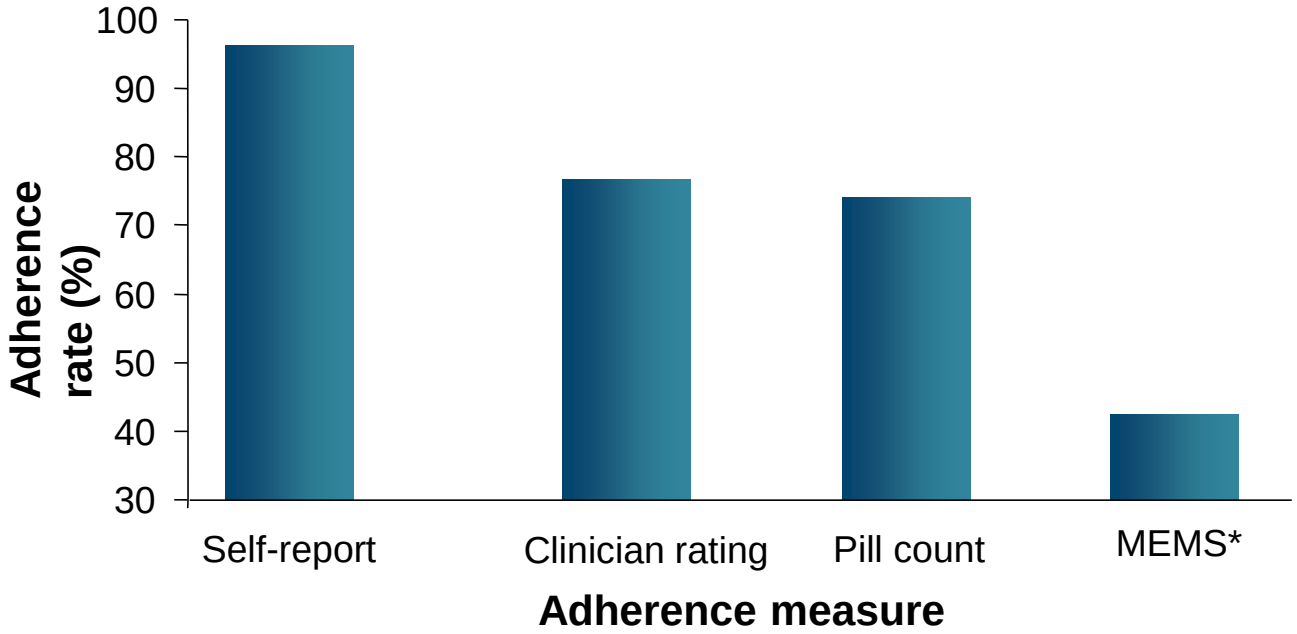
Lieberman JA, et al. *J Clin Psychiatry* 1996;57 Suppl 9: 5–9; Sheitman BB, et al. *Psychiatric Res* 1998;32:143–150.

Medication Event Monitoring System (MEMS®)

Micro-electronic circuit registers times when the closure is opened/closed

Remington G, et al. *Schizoph Res* 2007;90(1-3):229-37.

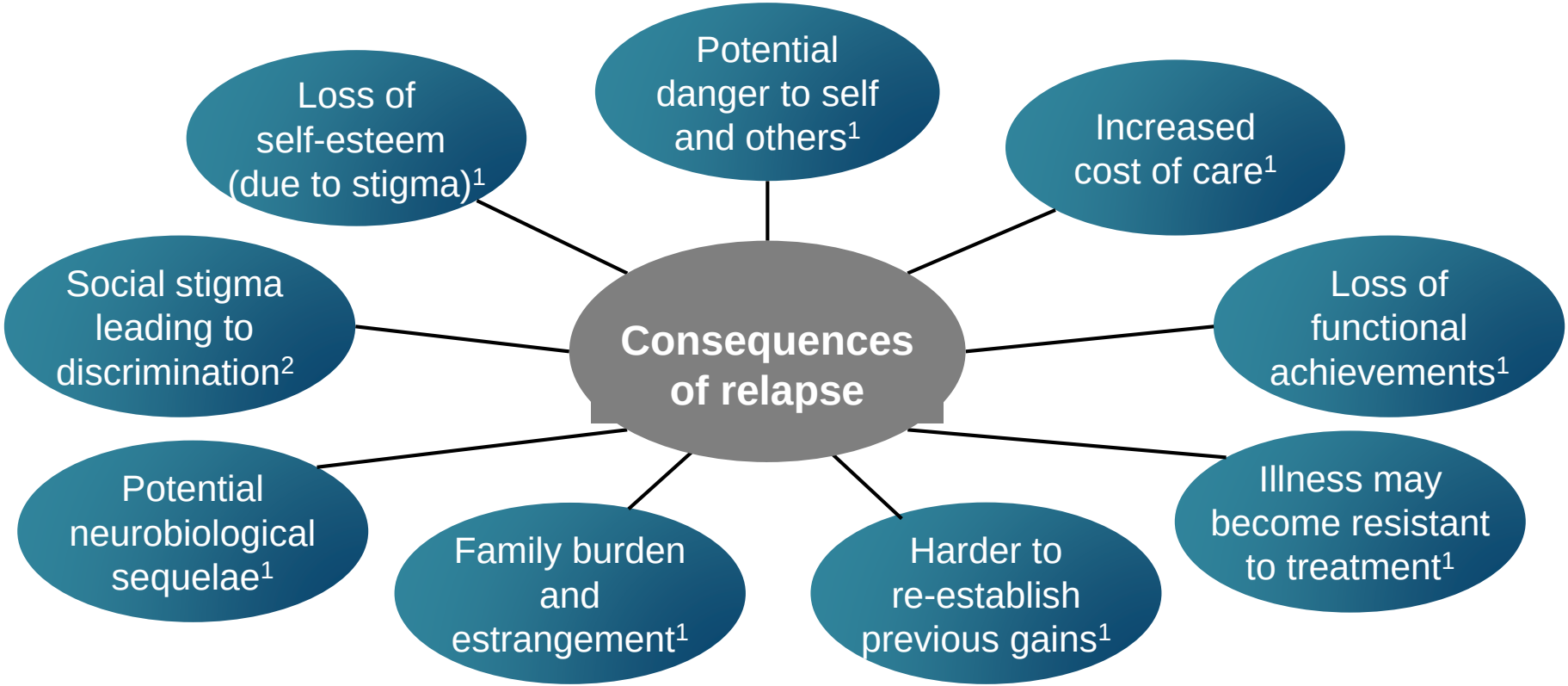
Adherence to treatment among outpatients with schizophrenia



*Medication Event Monitoring System (MEMS®)

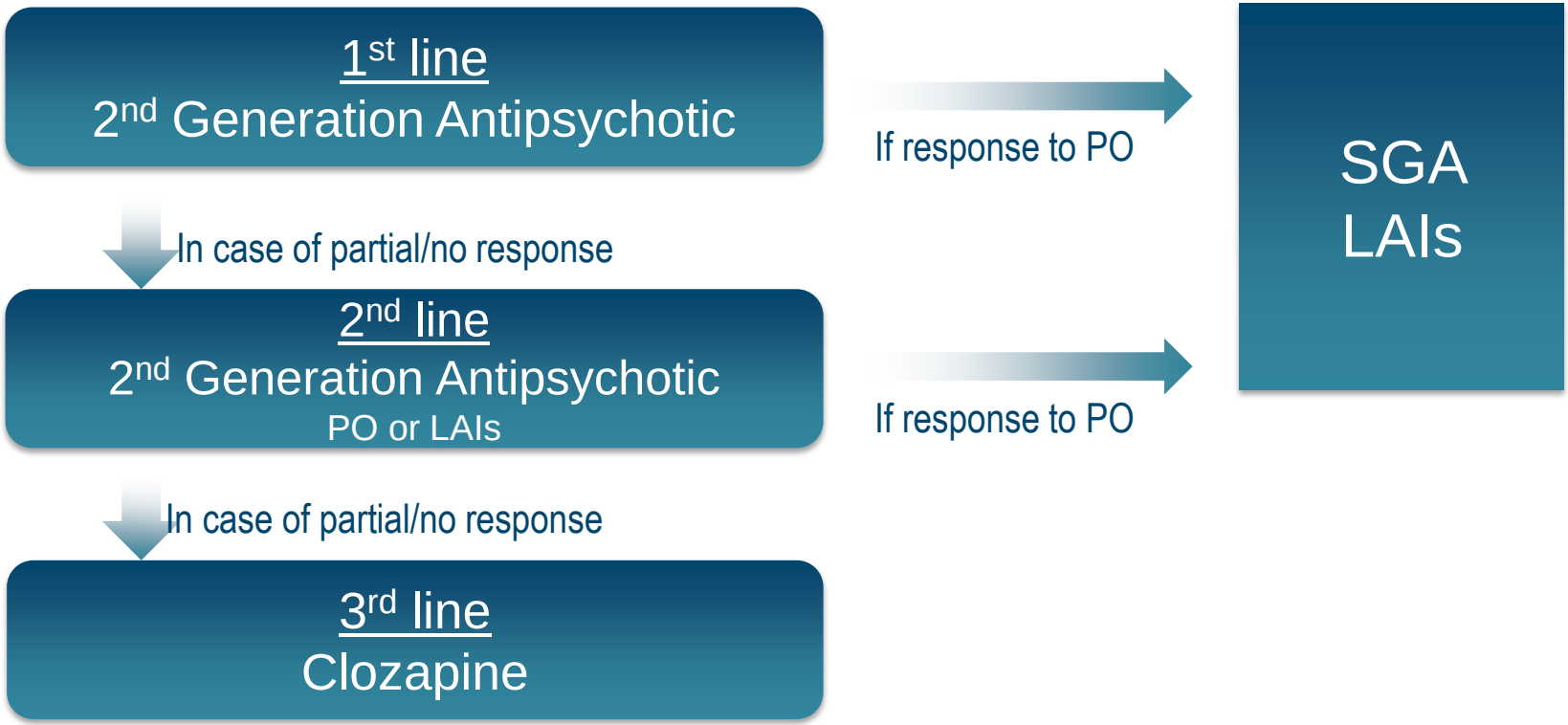
Remington G, et al. *Schizoph Res* 2007;90(1-3):229-37.

The high cost of relapse



1. Kane JM. *CNS Spectr* 2007;12(10 suppl 17):21–26; 2.Thornicroft G, et al. *Lancet* 2009;373:408–415.

Treatment algorithm for schizophrenia



SGA LAI, second-generation antipsychotic long-acting injectables. PO, *per os*

Agid, O., et al. Journal of Clinical Psychiatry, 2011 Nov; 72(11): 1439-1444.

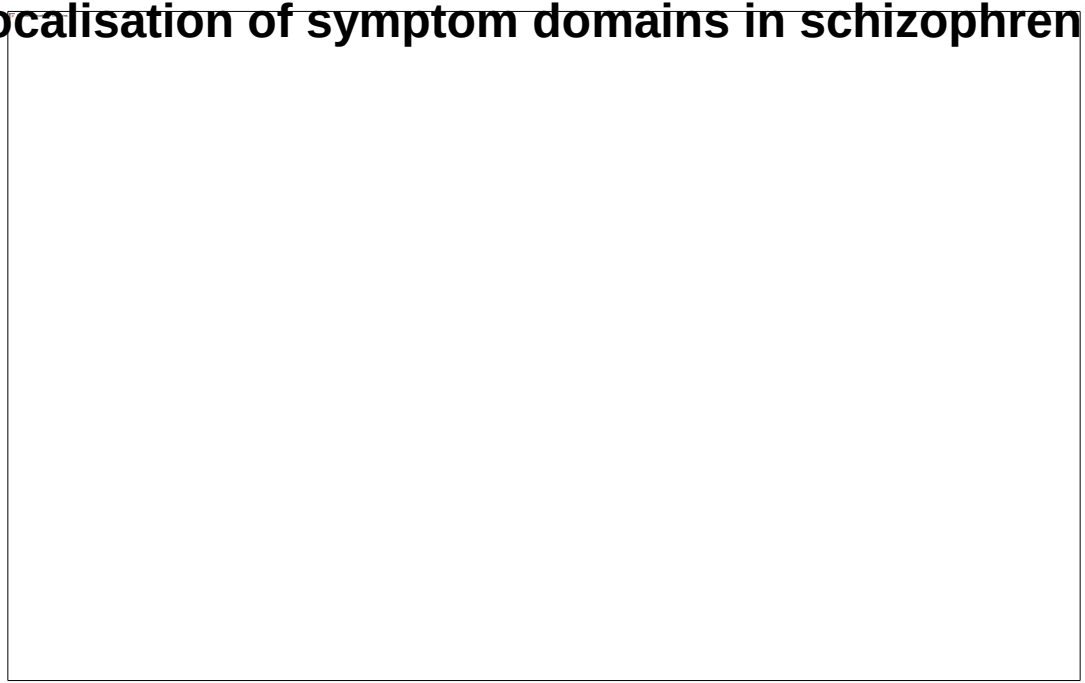
The logic of long-acting injectable antipsychotic therapy in schizophrenia

- Psychotic relapses are probably neurotoxic with progressive brain tissue loss[1]
- Antipsychotics reverse acute psychosis and prevent relapses[2]
- Nonadherence is very high among persons with schizophrenia which leads to frequent psychotic relapse and further neurodegeneration[3]
- Antipsychotics might induce neurotrophins and neurogenesis and help regenerate brain tissue and functioning[4]
- Long-acting injectable antipsychotics exert better protection from relapses than oral antipsychotics[5]

Andreasen NC, et al. *Am J Psychiatry* 2013; 170(6):10.1176/appi.ajp.2013.12050674. 2. Leucht S, et al. *Lancet* 2012; 379(9831):2063-71. 3. Alvarez Jimenez et al. *Schizophr Res* 2012;139(1-3):116-28. 4. Hunsberger et al. *Dialogues Clin Neurosci* 2009;11(3):333-348. 5. Brissos et al. *Ther Adv Psychopharmacol* 2014;4(5):198–219.

Schizophrenia as heterogeneous group of disorders with different onsets, presentations, treatment response, trajectories and outcomes

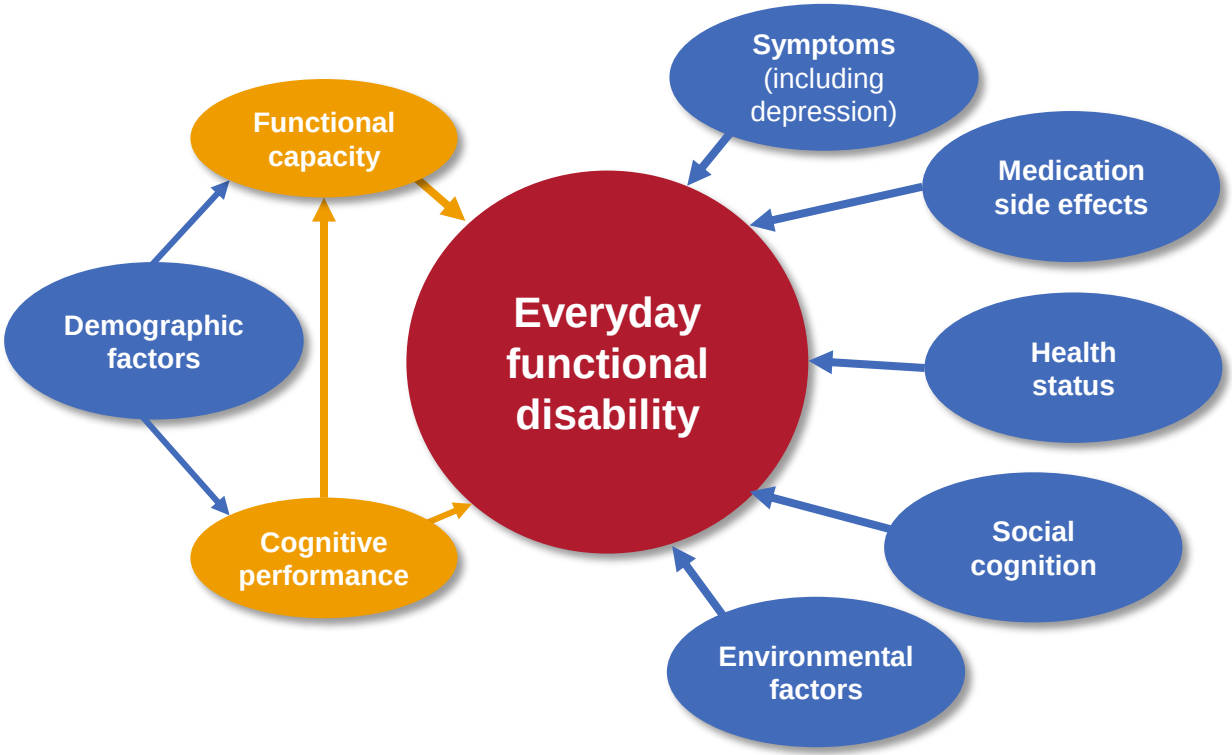
Localisation of symptom domains in schizophrenia



Stahl. Stahl's Essential Psychopharmacology. 4th edition, 2013, Cambridge University Press (Chapter 4 – Online version)
Lehoux C et al. The Five-Factor Structure of the PANSS: A Critical Review of its Consistency Across Studies. Clin Schizophr Relat Psychoses. 2009;3(2):103-110.

The decline of functionality and HRQoL in schizophrenia, and treatment goals

A variety of factors contribute to functional impairment in patients with schizophrenia



Adapted from: Harvey & Strassnig. World Psychiatry 2012;11(2):73–79

Recovery is the ultimate long-term treatment goal

Recovery:
Enduring symptom remission and restored social and occupational functioning

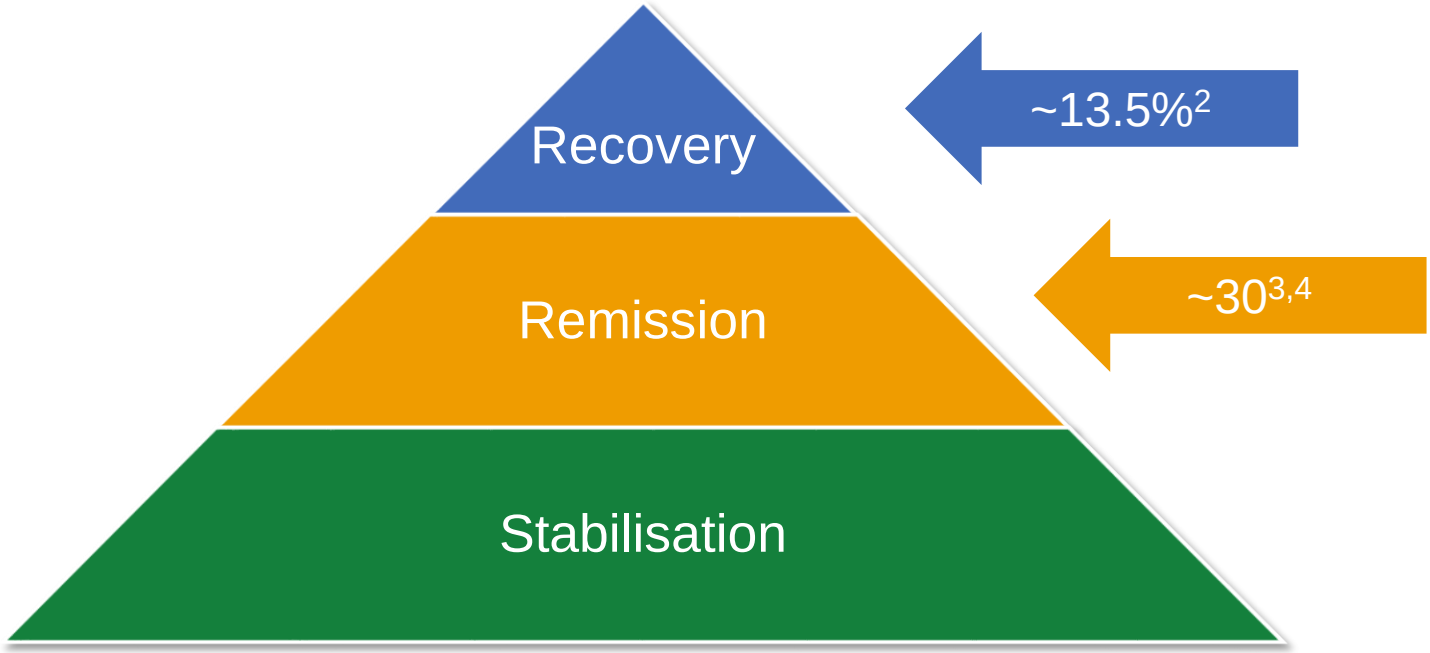
- That is, symptom remission, adequate vocational functioning, independent living, peer relationships, for at least 2 years[1]

Functional remission:

- “Multiple domains of everyday functional activities where adequate performance on a day-to-day basis is required for normal functioning... These include productive activities, residential and self-maintenance activities, and social relationships”[2]

1. Liberman et al. Int Rev Psychiatry 2002;14(4):256–272; 2. Harvey & Bellack. Schizophr Bull 2009;35(2):300–306

Our treatment goals in schizophrenia have changed[1] – but how successful are we today?



1. Remington et al. CNS Drugs 2010;24(1):9–20; 2. Jääskelainen et al. Schizophr Bull 2013;39(6):1296–1306;
3. Meesters et al. Schizophr Res 2011;126(1–3):237–244; 4. Boter et al. Schizophr Res 2009;115(2–3):97–103

HRQoL is a measurable concept

Quality of life measurement in schizophrenia

- Numerous scales are available[1]
  - Disease-specific scales may be more sensitive than generic scales[1]
  - Subjective scales and objective scales are both important components of the QoL construct in schizophrenia[2]
- The **Quality of Life Scale** (Heinrichs et al., 1984)[3] is the most widely used[1]
  - A 21-item semi-structured interview to assess QoL in relation to deficit symptoms and impaired functioning[3]
  - Total score and four subscores[3]
  - 45 minutes[3]

QoL=quality of life

1. Karow et al. Dialogues Clin Neurosci 2014;16:185–195;
2. Awad & Voruganti. Pharmacoeconomics 2012;30(3):183–195; 3. Heinrichs et al. Schizophr Bull 1984;10(3):388–398

Clinician-rated scale – Heinrichs–Carpenter Quality of Life Scale (QLS)

Rater	Clinician			
Domains	Interpersonal relations	Instrumental role	Intrapsychic foundations[a]	Common objects and activities
Purpose	To examine a patient's social experience	To assess a patient's work functioning	To assess a patient's sense of purpose and motivation	To evaluate a patient's level of participation in the community
Items	1. Household 2. Friends 3. Acquaintances 4. Social activity 5. Social network 6. Social initiative 7. Withdrawal 8. Sociosexual	9. Occupational role 10. Work functioning 11. Work level 12. Work satisfaction	13. Sense of purpose 14. Motivation 15. Curiosity 16. Anhedonia 17. Aimless inactivity 20. Empathy 21. Emotional interaction	18. Commonplace objects 19. Commonplace activities
Scoring	Each item is rated on a 7-point scale, ranging from 0 (severe impairment) to 6 (normal or unimpaired functioning); higher scores indicate a better quality of life and functioning			

[a]The items within the 'Intrapsychic foundations' domain are considered to be the building blocks for interpersonal and instrumental role functioning

Heinrichs et al. Schizophr Bull 1984;10(3):388–398

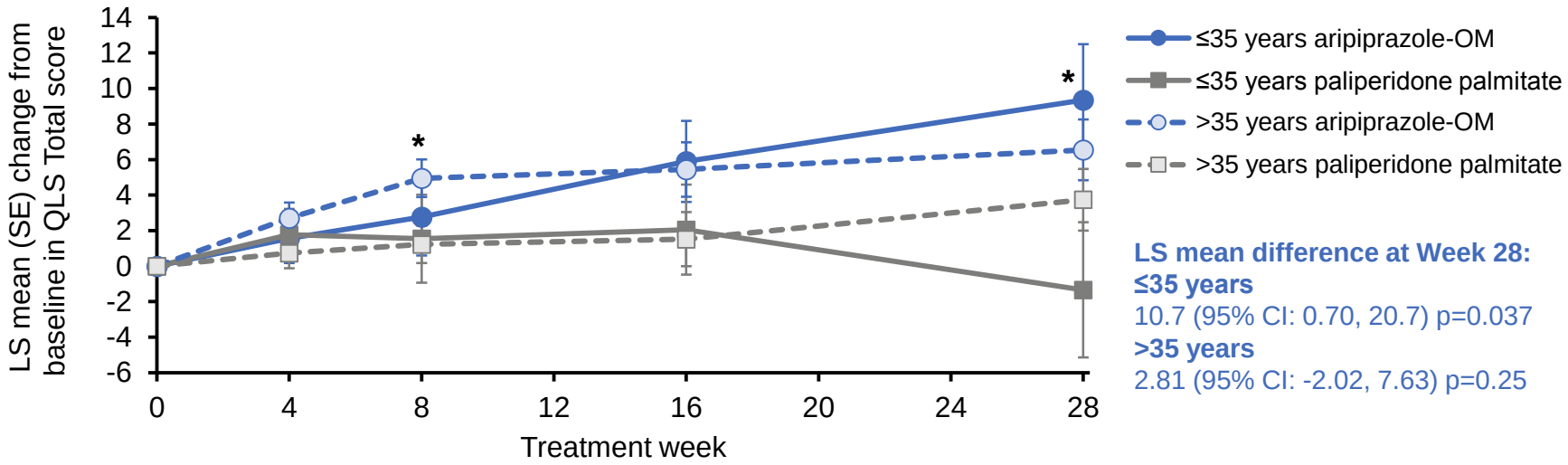
QLS uses and interpretation

- The QLS[1] has been used:
  - In psychopharmacological treatment trials for schizophrenia[2]
  - In a naturalistic setting trial to measure effectiveness, e.g., as primary endpoint in the CUtLASS 1 study[3]
  - As primary or secondary endpoint, e.g., the CATIE study[4-6]
- An MCID has been estimated for the QLS, aiding the interpretation of antipsychotic treatment effects and long-term patient HRQoL outcomes in schizophrenia[2]
  - **QLS Total MCID = 5.3 points**

CATIE=Clinical Antipsychotic Trials of Intervention Effectiveness study; CUtLASS=Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study; MCID=minimal clinically important difference

1. Heinrichs et al. Schizophr Bull 1984;10(3):388–398; 2. Falissard et al. Int J Methods Psychiatr Res 2016;25(2):101–111;
3. Jones et al. Arch Gen Psychiatry 2006;63(10):1079–1087; 4. Swartz et al. Am J Psychiatry 2007;164(3):428–436;
5. Phillips et al. J Clin Psychiatry 2006;67(9):1397–1403; 6. Witte et al. Curr Med Res Opin 2012;28(3):315–323

QUALIFY study: age-stratified change from baseline in QLS Total score



LS mean difference at Week 28:
≤35 years
10.7 (95% CI: 0.70, 20.7) p=0.037
>35 years
2.81 (95% CI: -2.02, 7.63) p=0.25

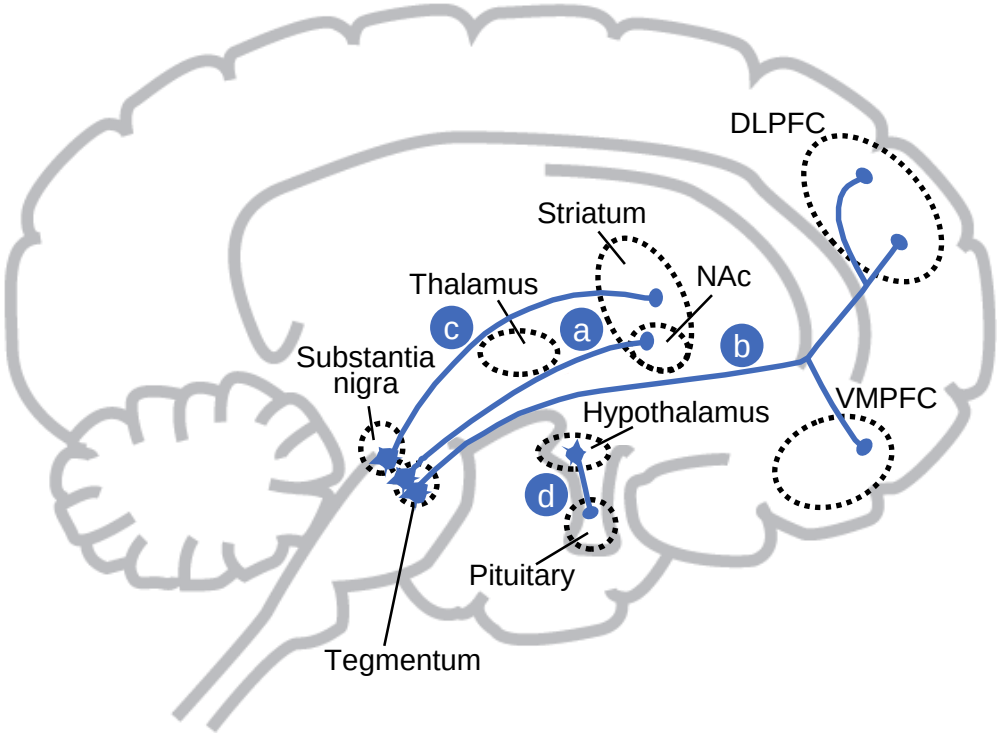
Greater improvements with aripiprazole-OM versus paliperidone palmitate were consistently demonstrated younger patients

*p<0.05 versus PP, within age stratum; FAS, MMRM; mean baseline QLS Total score (FAS): ≤35 years AOM (n=41) 67.2, PP (n=37) 64.5, >35 years AOM (n=95) 65.4, PP (n=95) 62.2; AOM=aripiprazole once-monthly; CI=confidence interval; FAS=full analysis set; LS=least squares; MMRM=mixed model for repeated measures; PP=paliperidone palmitate; QLS=Quality of Life Scale; SE=standard error

Naber et al. Schizophr Res 2015;168(1–2):498–504; Naber et al. Poster 160 at NEI 2015

The dopaminergic basis of functional outcomes

Dopaminergic pathways of the brain

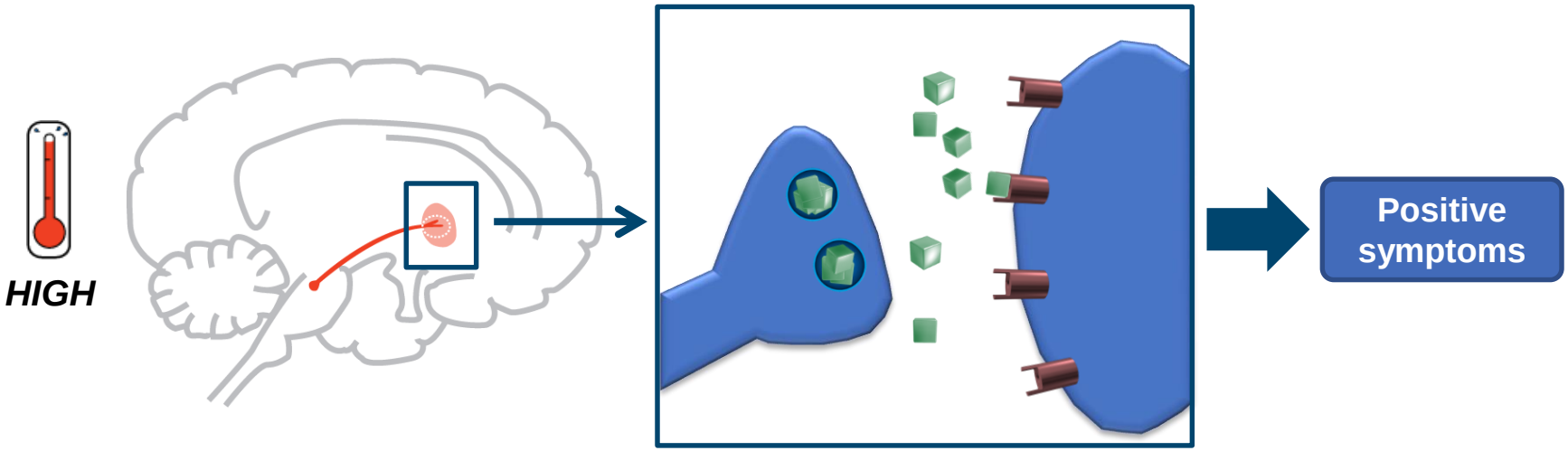


- a Mesolimbic
- b Mesocortical
- c Nigrostriatal
- d Tuberoinfundibular

DLPFC=dorsolateral prefrontal cortex; NAc=nucleus accumbens; VMPFC=ventromedial prefrontal cortex

Stahl. Stahl's Essential Psychopharmacology. 4th edition, 2013, Cambridge University Press

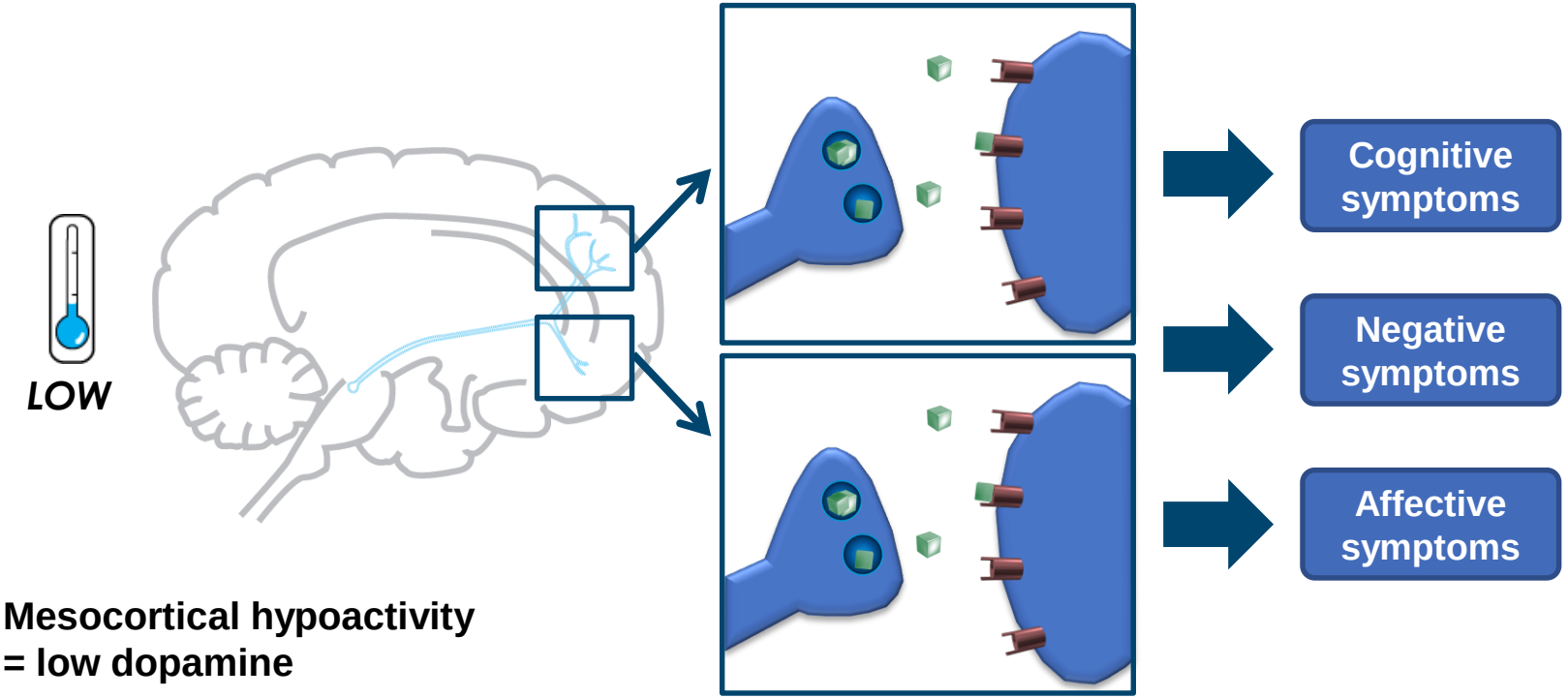
The mesolimbic dopamine hypothesis of positive symptoms of schizophrenia



Mesolimbic hyperactivity
= excessive dopamine

Stahl. Stahl's Essential Psychopharmacology. 4th edition, 2013, Cambridge University Press

The mesocortical dopamine hypothesis of cognitive, negative, and affective symptoms of schizophrenia

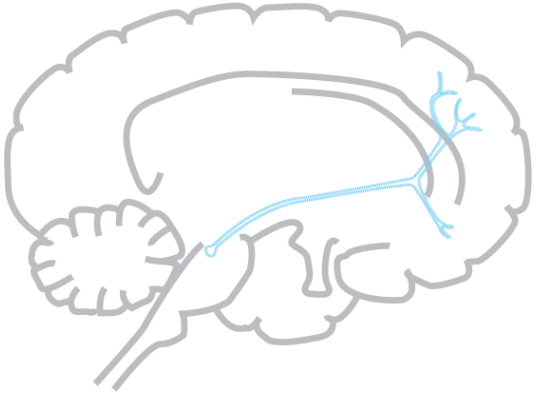


Mesocortical hypoactivity
= low dopamine

Stahl. Stahl's Essential Psychopharmacology. 4th edition, 2013, Cambridge University Press

Too little dopamine, or too much?

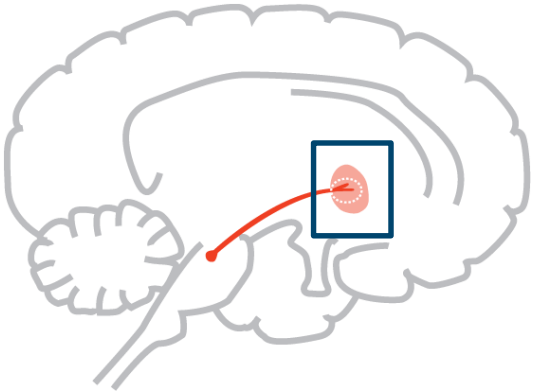
Mesocortical hypoactivity



LOW

HIGH

Mesolimbic hyperactivity



Cognitive symptoms

Negative symptoms

Affective symptoms

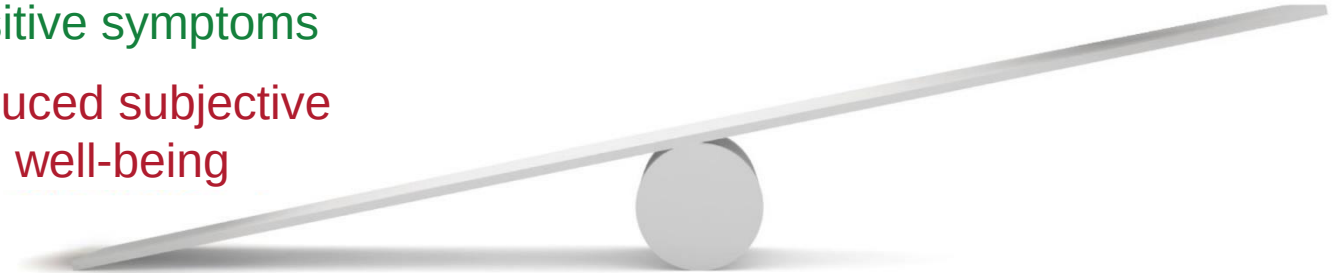
Onset of positive symptoms

Remington et al. Expert Rev Neurother 2011;11(4):589–607;
Stahl. Stahl's Essential Psychopharmacology. 4th edition, 2013, Cambridge University Press

A trade-off in treatment?

Few residual positive symptoms

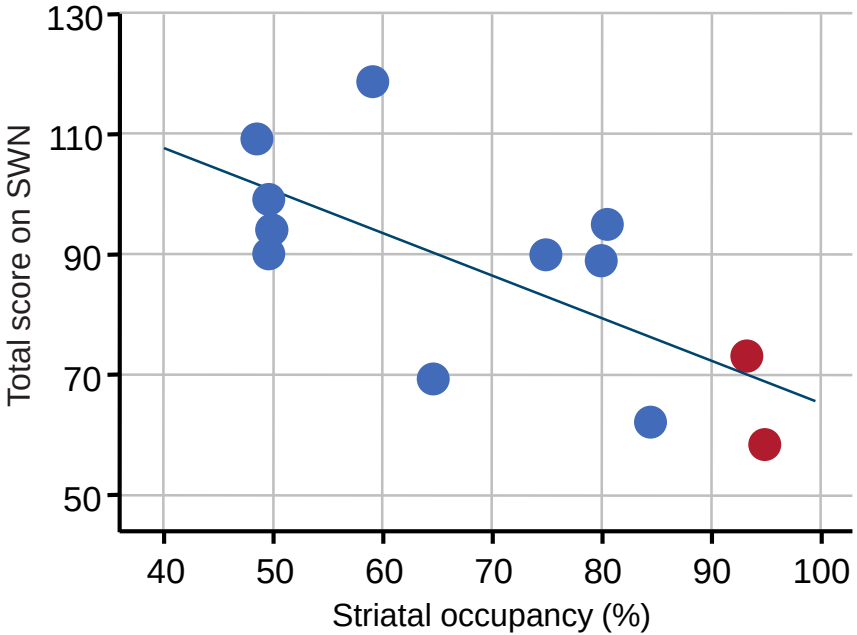
Reduced subjective well-being



Some residual positive symptoms

Better subjective well-being

Relationship between striatal blockade and total score on the SWN



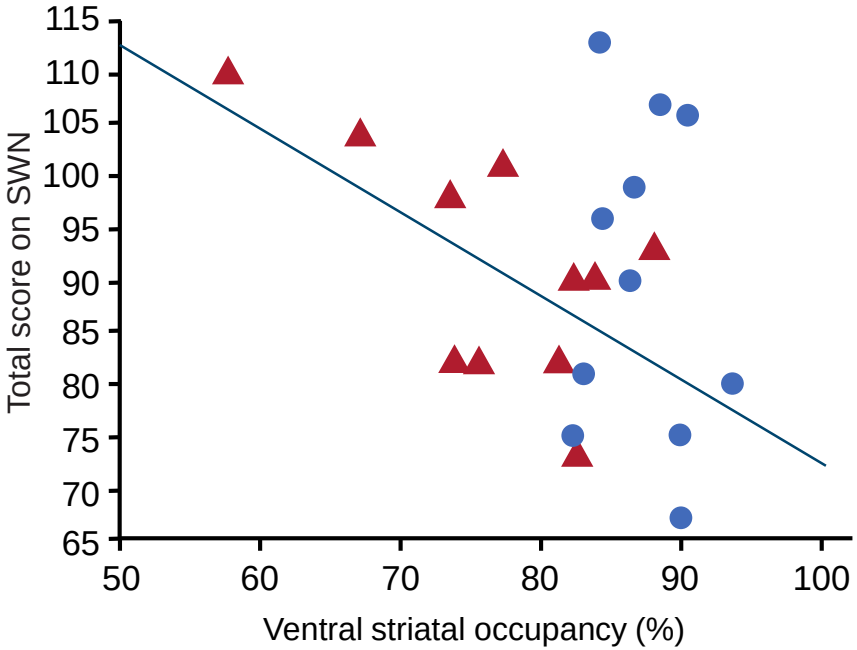
SWN scale total score was significantly associated with striatal occupancy (r -0.66, p=0.01)

SWN=Subjective Well-Being Under Neuroleptics Scale

Patients with recent-onset psychosis (N=12) were randomly assigned to olanzapine (2.5 or 15 mg/day) or risperidone (1 or 4 mg/day). Subjective experiences, and striatal dopamine D_2 receptors (determined with ([^{11}C]raclopride PET scans) were evaluated after 2 weeks of continuous antipsychotic treatment

Mizrahi et al. Am J Psychiatry 2007;164(4):630–637

Relationship between striatal blockade and total score on the SWN



- No significant correlation between SWN score and D_2 occupancy value at the ventral striatum with partial agonist-treated patients
- As expected, there was a negative association between D_2 occupancy in the ventral striatum and SWN in patients treated with antagonist antipsychotics

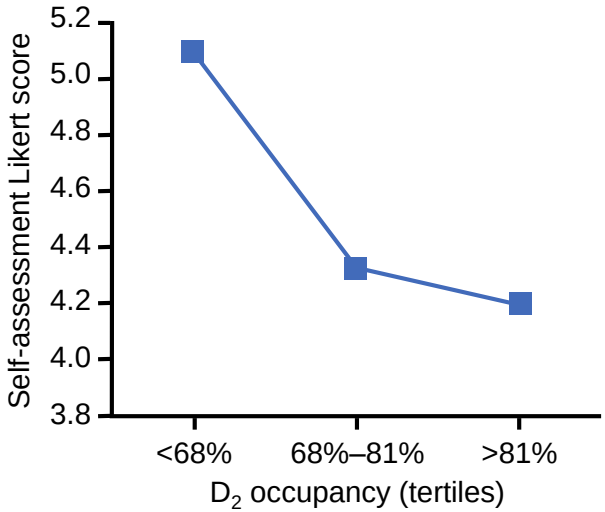
SWN=Subjective Well-Being Under Neuroleptics Scale

Association between SWN score and [^{11}C]raclopride D_2 occupancy in partial agonist-treated (aripiprazole; ●) vs. full antagonist antipsychotic-treated (risperidone or olanzapine; ▲) patients

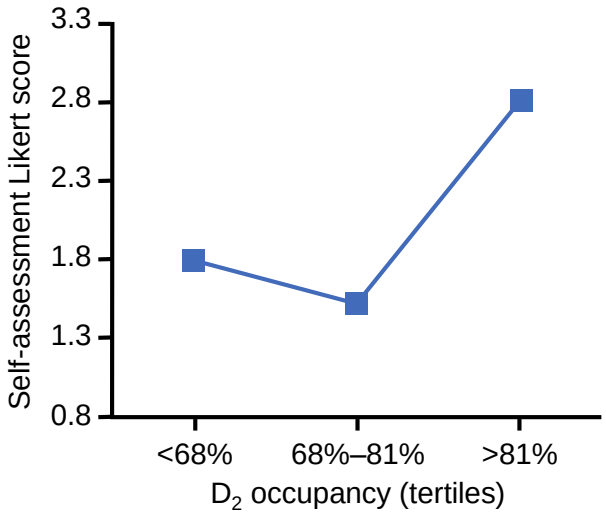
Mizrahi et al. Int J Neuropsychopharmacol 2009;12:715–721

Tight-binding agents and their influence on emotional experience

Positive affect



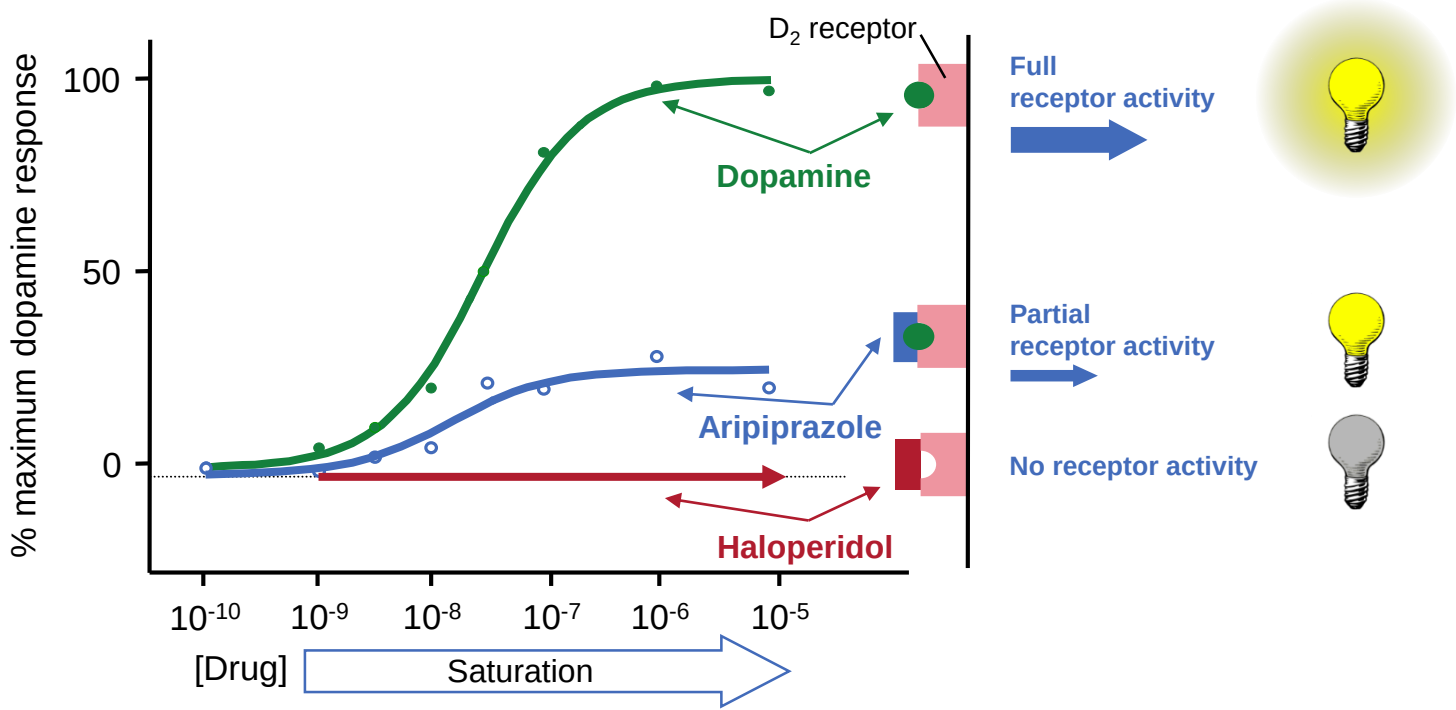
Negative affect



- There was a significant effect for D_2 receptor binding estimates on positive affect (χ^2_2=6.42, p=0.04). There was a clear decrease in positive affect in the middle occupancy group (range 68%–81%) and an even larger decrease in the group with the highest D_2 receptor occupancy (>81%)
- Additionally, D_2 occupancy was significantly related to negative affect (χ^2_2=29.48, p=0.0001), with a significant increase in negative affect in the highest D_2 receptor occupancy

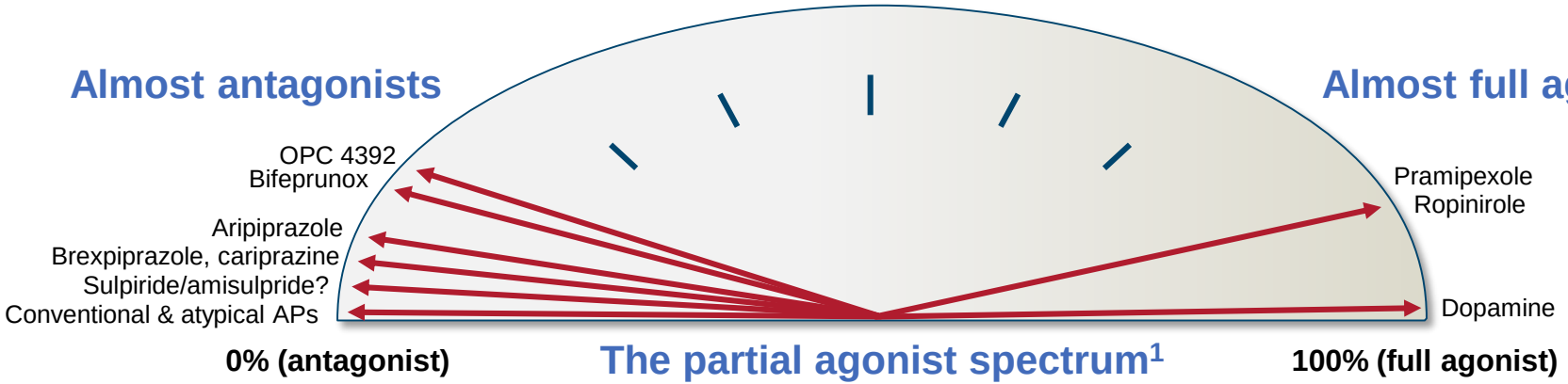
Lataster et al. J Clin Psychiatry 2011;72(10):1397–1404

‘Third generation’ antipsychotics – dopaminergic partial agonists



Schematic based on: Jordan et al. Prog Neuropsychopharmacol Biol Psychiatry 2007;31(2):348–356

A balancing act at the D_2 receptor



Full antagonist:
- ✓ Efficacy on positive symptoms[1]
- × Low subjective well-being[2]
- × Risk of cognitive impairment[3]
- × Risk of EPS and prolactin elevation

Partial agonist:
- ✓ Efficacy on positive symptoms[1]
- ✓ Positive effect on quality of life[4]
- ✓ Low EPS and prolactin effects[1]

Full agonist:
- × Lack efficacy on positive symptoms[1]
- × Nausea[1]
- ✓ No EPS[1]

AP=antipsychotic

1. Stahl. Stahl's Essential Psychopharmacology. 4th edition, 2013, Cambridge University Press; 2. Mizrahi et al. Am J Psychiatry 2007;164(4):630–637;
3. Sakurai et al. Schizophr Bull 2013;39(3):564–574; 4. Naber et al. Schizophr Res 2015;168(1–2):498–504

Conclusions

- Long-acting injectable antipsychotics exert better protection from relapses than oral antipsychotics
- Schizophrenia is associated with a decline in HRQoL and functionality
- Long-term treatment goals in schizophrenia – recognised by treatment guidelines – include improving HRQoL and functionality
- HRQoL in schizophrenia can be assessed with rating scales, but improvement may lag behind symptomatic improvement
- Antipsychotics can improve HRQoL; the degree of improvement may be related to antipsychotic activity at the D_2 receptor
- Prioritising the treatment of patient functioning and HRQoL, over the treatment of symptoms, may improve overall outcome for a subset of patients