



**MINERVA**  
NEUROSCIENCES, INC.

# **NEGATIVE SYMPTOMS OF SCHIZOPHRENIA**

**March 22, 2018**

# Forward-Looking Statement Safe-Harbor

This presentation contains forward-looking statements about Minerva Neurosciences which are subject to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts, reflect management's expectations as of the date of this presentation, and involve certain risks and uncertainties. Forward-looking statements include, but are not limited to: the benefits, efficacy and safety of our new formulations; the potential of the diagnosis and treatment of negative symptoms of schizophrenia; statements regarding our ability to successfully develop and commercialize our therapeutic products; our ability to expand our long-term business opportunities; our expectations regarding approval for our products by the U.S. Food and Drug Administration or equivalent foreign regulatory agencies; estimates regarding the market potential for our products; and future performance. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of the Company, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking statements. These forward-looking statements are based on our current expectations and may differ materially from actual results due to a variety of factors including, without limitation, whether any of our therapeutic products will advance further in the clinical trials process and whether and when, if at all, they will receive final approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies and for which indications; whether the results of future clinical trials of roluperidone (MIN-101) will be consistent with the results of past clinical trials; whether roluperidone will be successfully marketed if approved; whether our therapeutic product discovery and development efforts will be successful; our ability to achieve the results contemplated by our co-development agreements; the strength and enforceability of our intellectual property rights; our ability to raise additional capital to fund our operations on terms acceptable to us; and general economic conditions. These and other potential risks and uncertainties that could cause actual results to differ from the results predicted are more fully detailed under the caption "Risk Factors" in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2017, filed with the Securities and Exchange Commission on March 12, 2018. Copies of reports filed with the SEC are posted on our website at [www.minervaneurosciences.com](http://www.minervaneurosciences.com). Our audience is cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we disclaim any obligation to update any forward-looking statements, except as required by law.



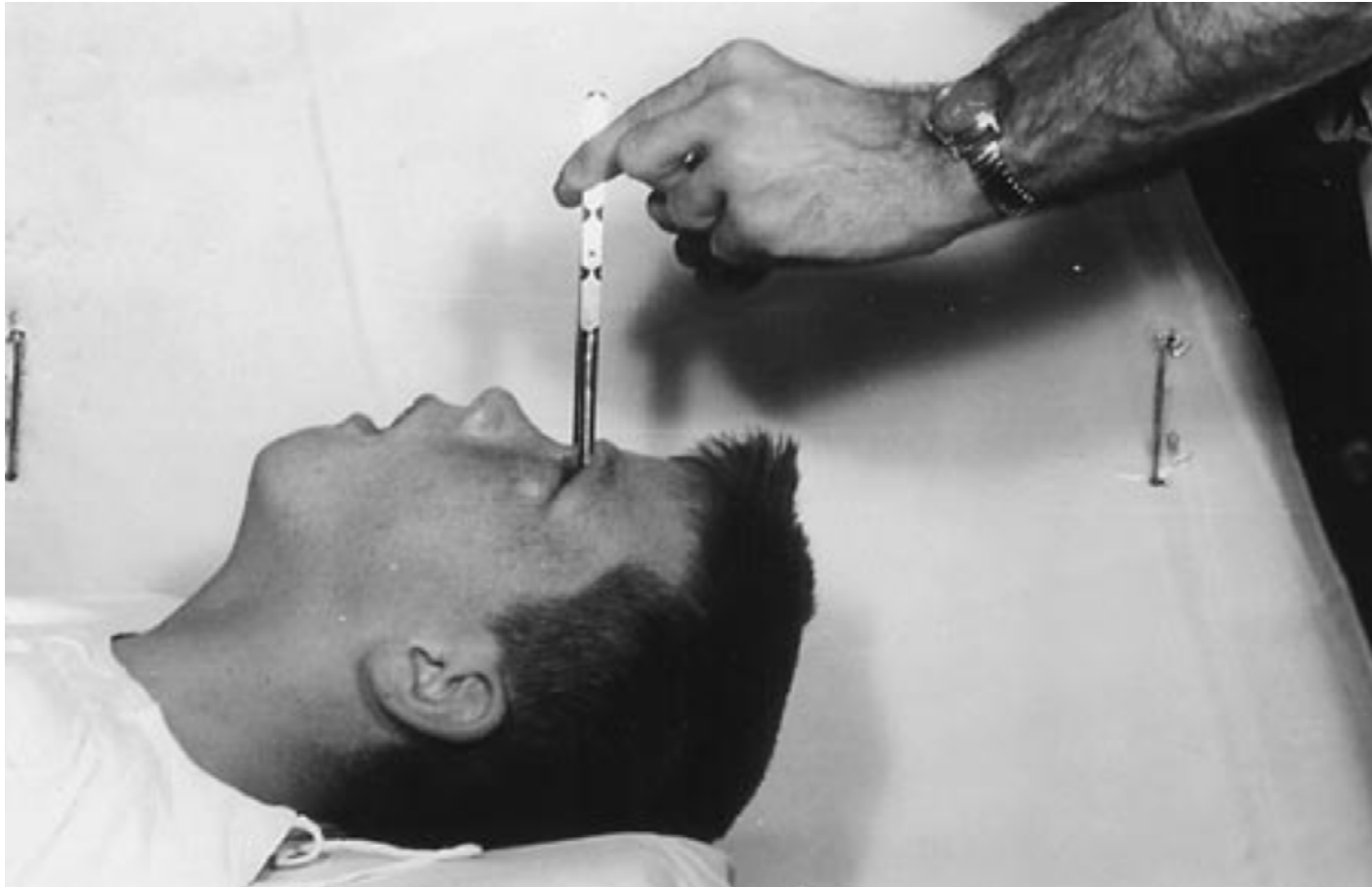


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# **Understanding the Neurobiology of Schizophrenia: From Receptors to Real Life**

Ofer Agid, M.D.  
Schizophrenia Program  
Centre for Addiction and Mental Health (CAMH)  
Associate Professor of Psychiatry  
Department of Psychiatry, University of Toronto

# 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



# 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

110<sup>e</sup> ANNÉE — 1952  
TOME DEUXIÈME

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

PUBLICATION PÉRIODIQUE  
PARAISANT 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.

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-propyl 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 joignons pratiquement 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 (tetranium), Specia (45-60 R.P.) et Ciba (C. 92-95) d'avoir bien voulu nous fournir des échantillons utiles à nos recherches.

Delay J, Deniker P, Harl JM. *Ann Med Psychol (Paris)* 1952



# Nobel Prize in Physiology & Medicine 2000

Arvid Carlsson



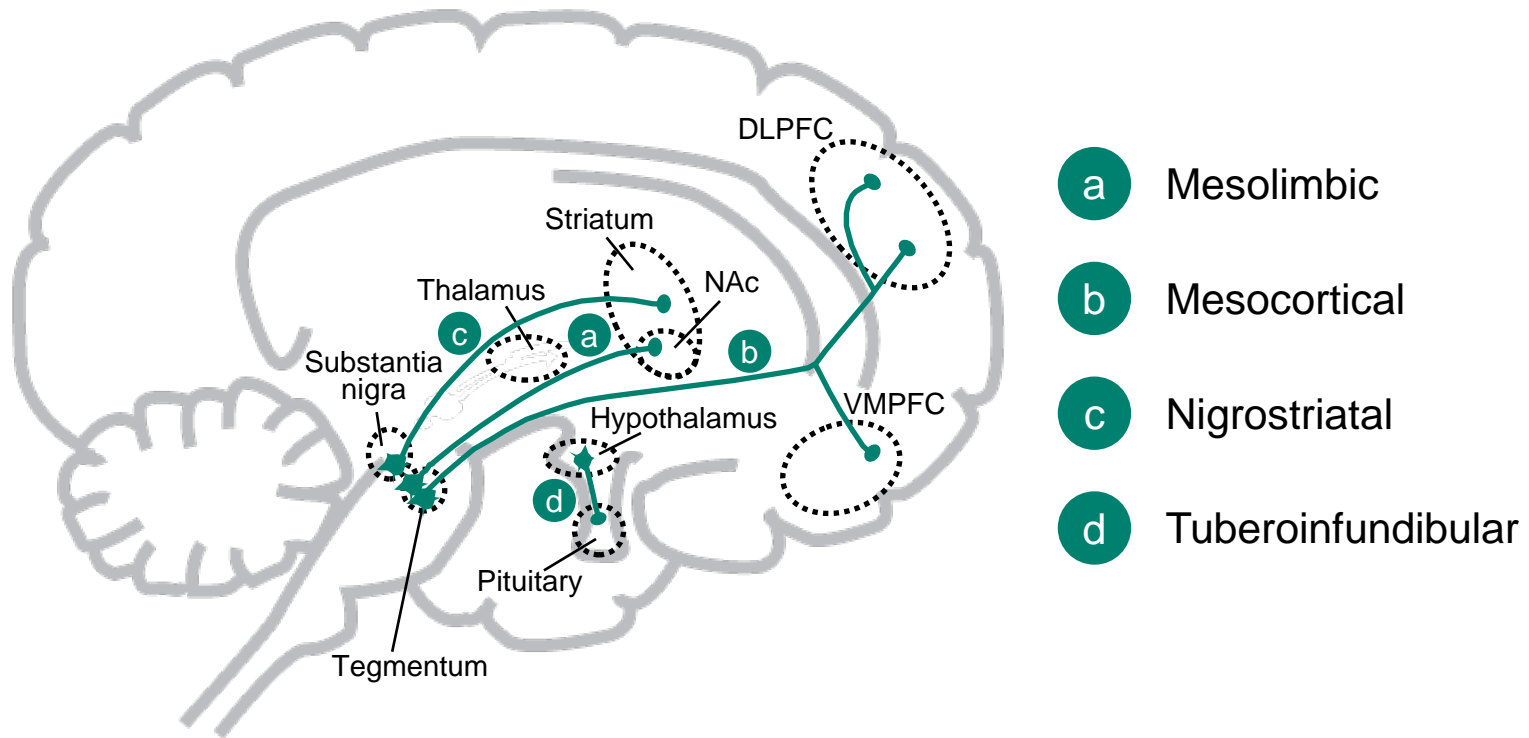
- Arvid Carlsson overturned conventional wisdom by showing that the chemical dopamine is an important neurotransmitter in the brain.
- Before, dopamine was presumed to be merely a precursor to a more important neurotransmitter, noradrenaline (norepinephrine).

# **Dopaminergic Pathways in the Brain**

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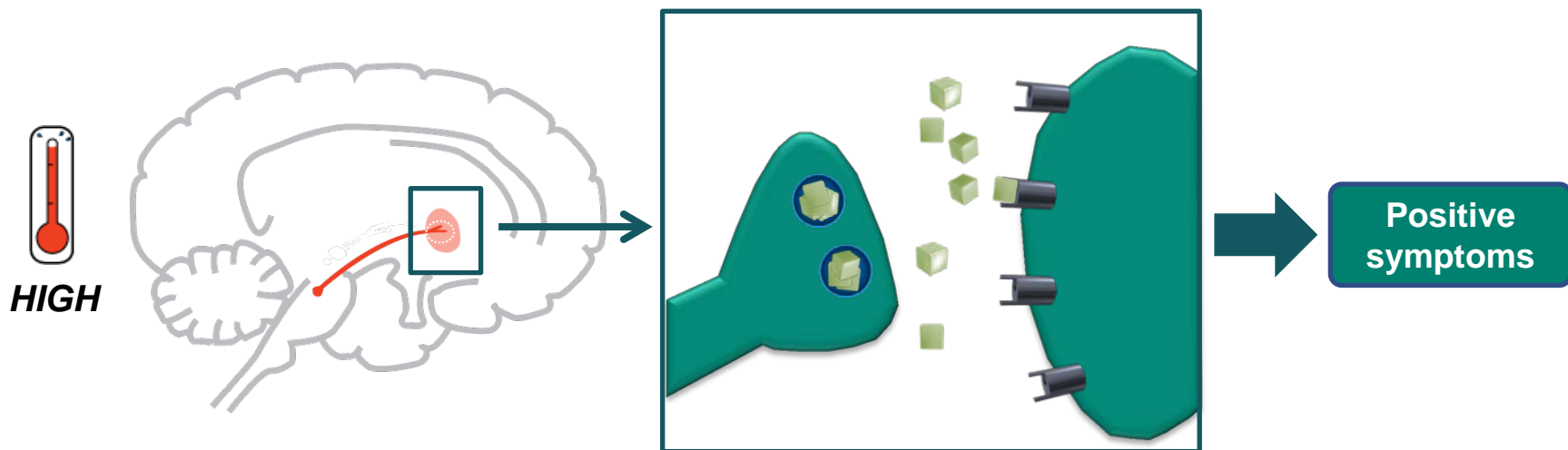
# Dopaminergic Pathways in the Brain



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

Stahl. Stahl's Essential Psychopharmacology. 4<sup>th</sup> edition, 2013, Cambridge University Press

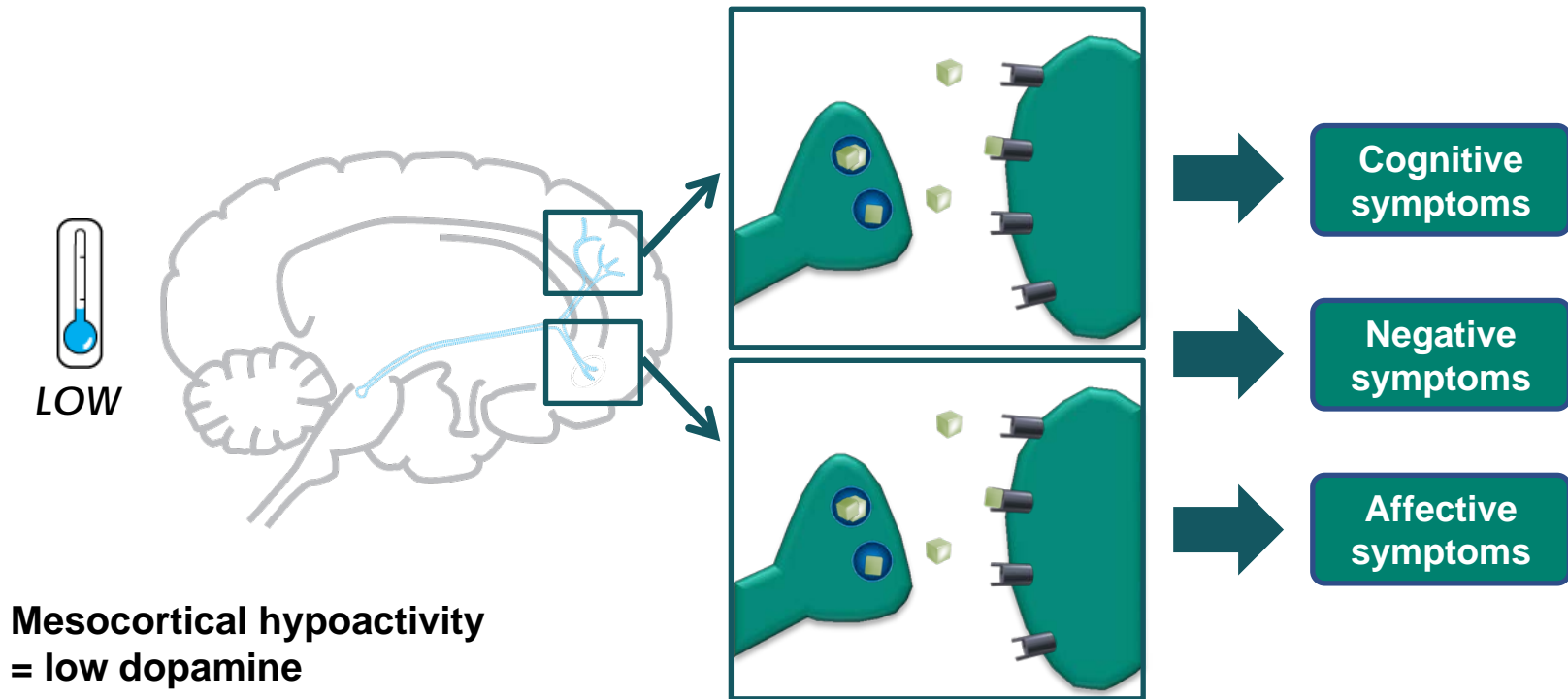
# The Mesolimbic Dopamine Hypothesis of Positive Symptoms of Schizophrenia



**Mesolimbic hyperactivity  
= excessive dopamine**

Stahl. Stahl's Essential Psychopharmacology. 4<sup>th</sup> edition, 2013, Cambridge University Press

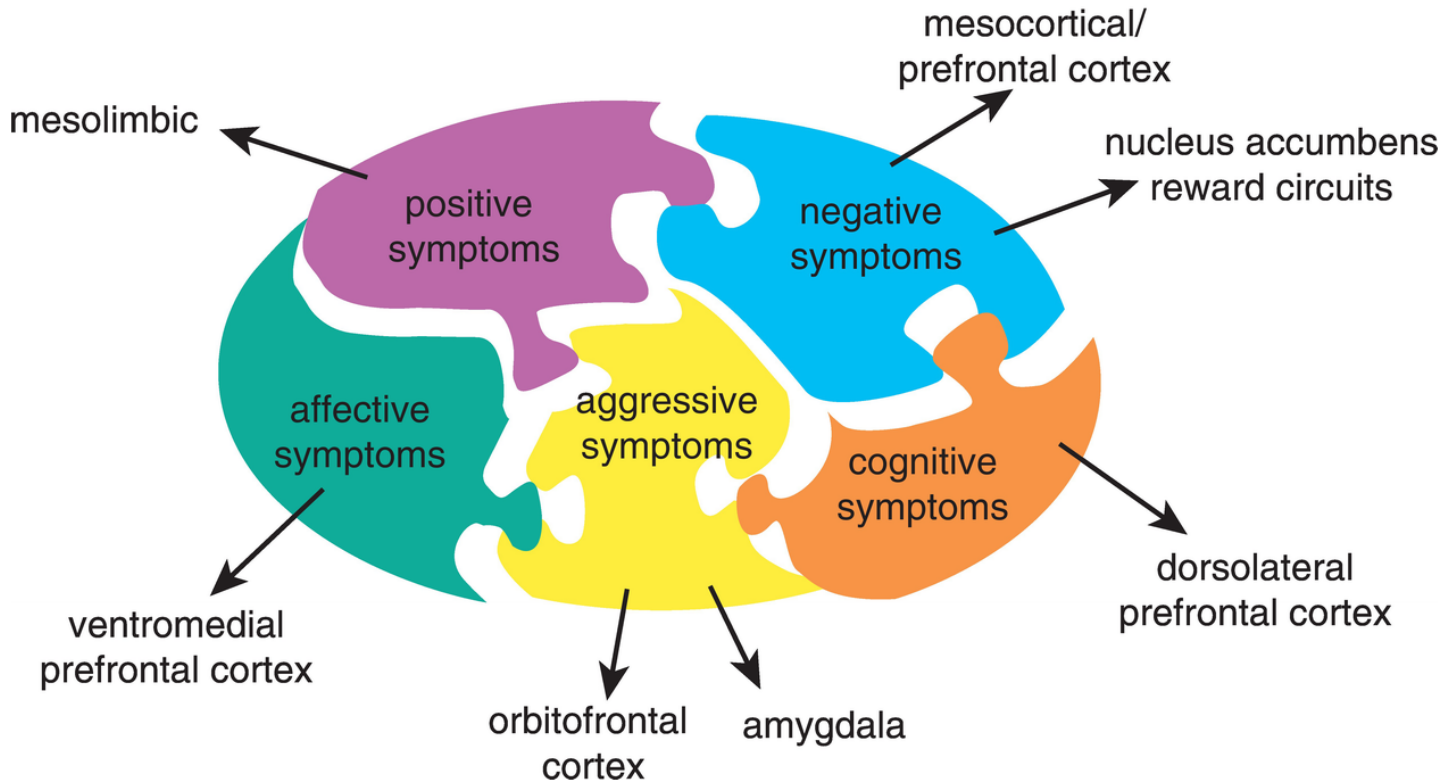
# The Mesocortical Dopamine Hypothesis of Cognitive, Negative and Affective Symptoms of Schizophrenia



Stahl. Stahl's Essential Psychopharmacology. 4<sup>th</sup> edition, 2013, Cambridge University Press

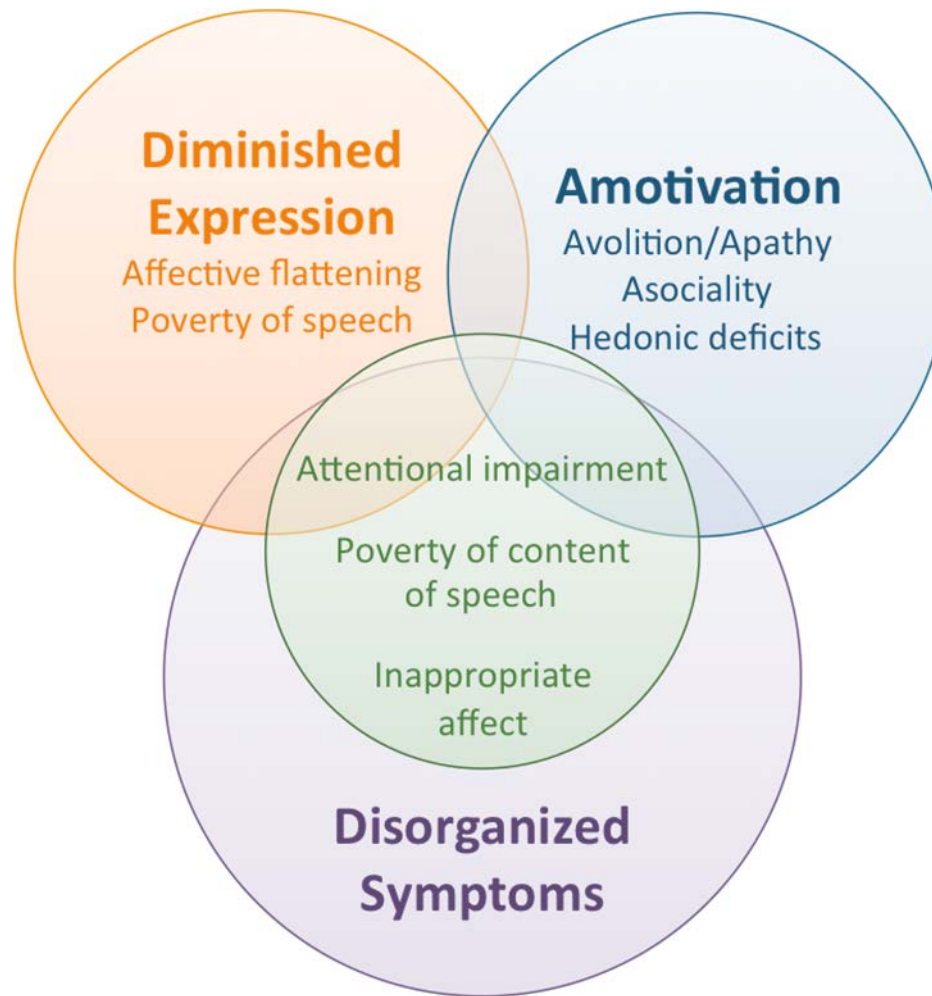


# Schizophrenia as a Heterogeneous Group of Disorders with Different Onsets, Presentations, Treatment Response, Trajectories and Outcomes



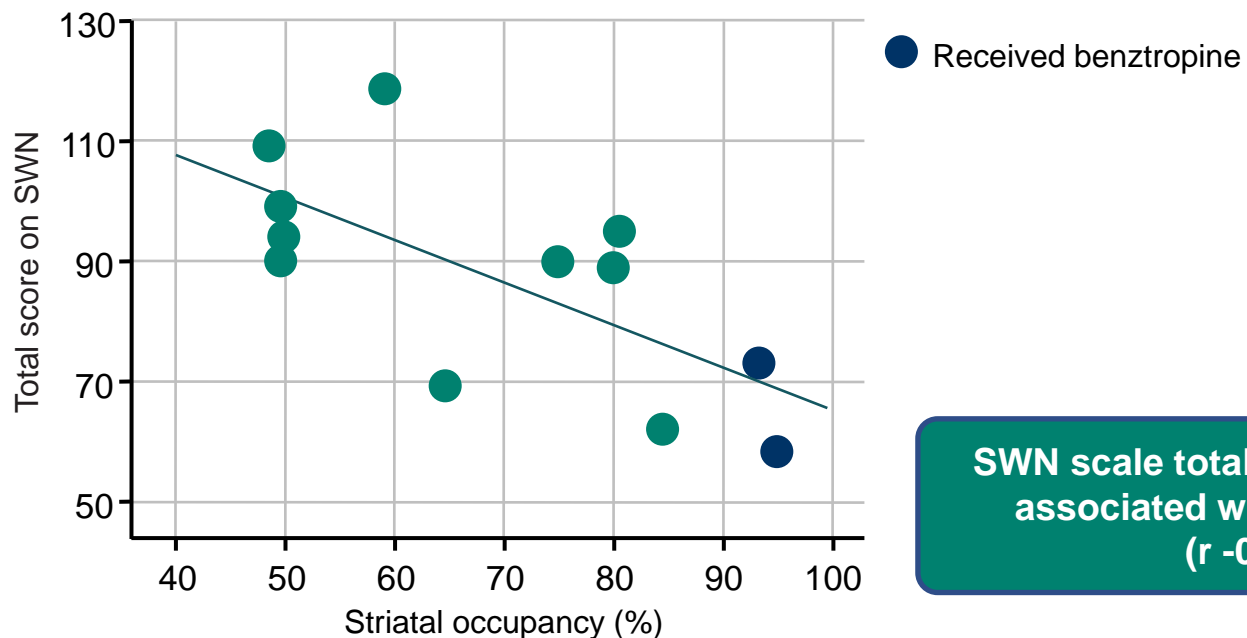
Stahl. Stahl's Essential Psychopharmacology. 4<sup>th</sup> edition, 2013, Cambridge University Press

# The Negative Symptom Domain in Schizophrenia



Mueser et al. 1994; Sayers et al. 1996; Kelley et al. 1999; Peralta & Cuesta 1999; Kimhy et al. 2006; Foussias & Remington 2010; Messinger et al. 2011; Liemburg et al. 2013; Strauss et al. 2013; Fervaha et al. 2014.

# Relationship Between Striatal Dopamine Blockade and Total Score on the Subject Well-being Under Neuroleptics (SWN) Scale



**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).

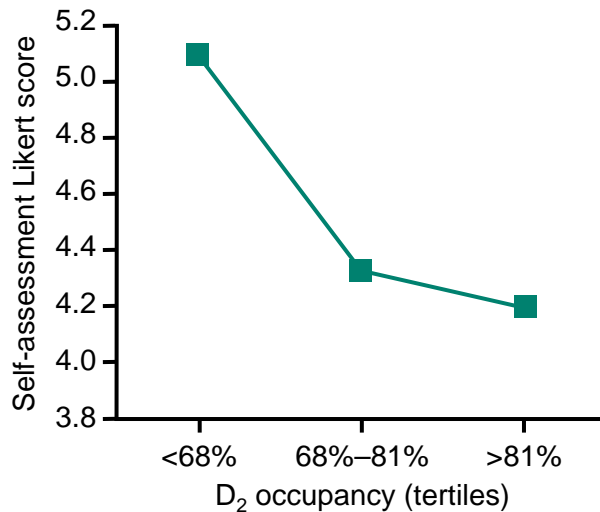
Subjective experiences, and striatal dopamine D<sub>2</sub> receptors (determined with [<sup>11</sup>C]raclopride PET scans) were evaluated after 2 weeks of continuous antipsychotic treatment

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

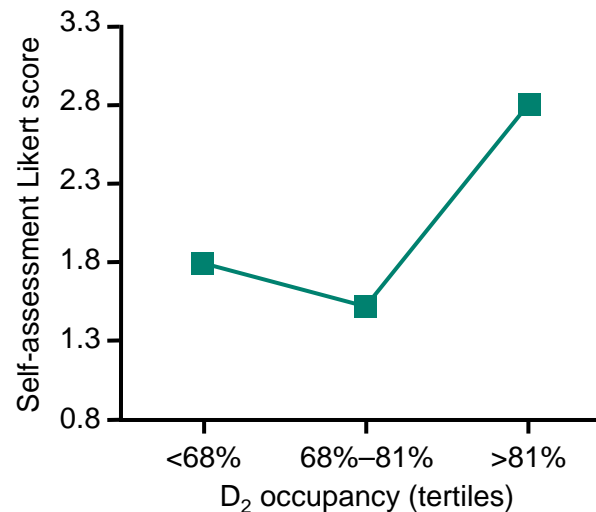


# Tight-binding Agents and Their Influence on Emotional Experience

## Positive affect



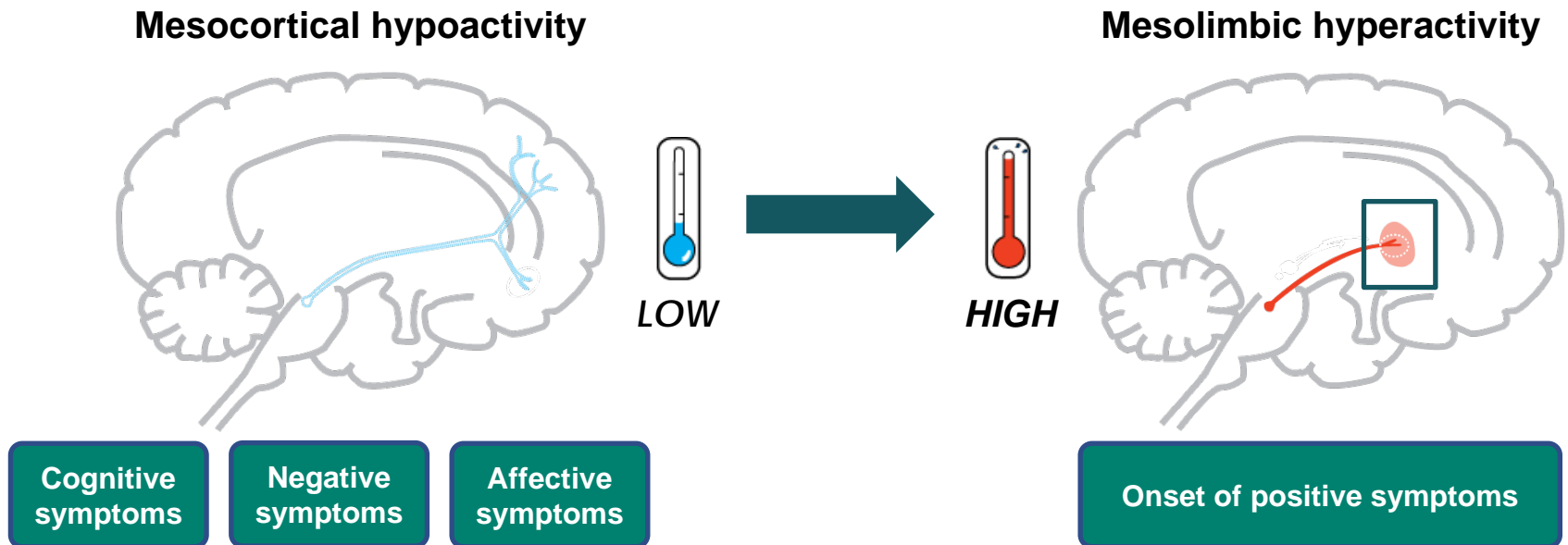
## Negative affect



- There was a significant effect for D<sub>2</sub> receptor binding estimates on positive affect ( $\chi^2_2=6.42$ ,  $p=0.04$ ). 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<sub>2</sub> receptor occupancy (>81%)
- Additionally, D<sub>2</sub> occupancy was significantly related to negative affect ( $\chi^2_2=29.48$ ,  $p=0.0001$ ), with a significant increase in negative affect in the highest D<sub>2</sub> receptor occupancy

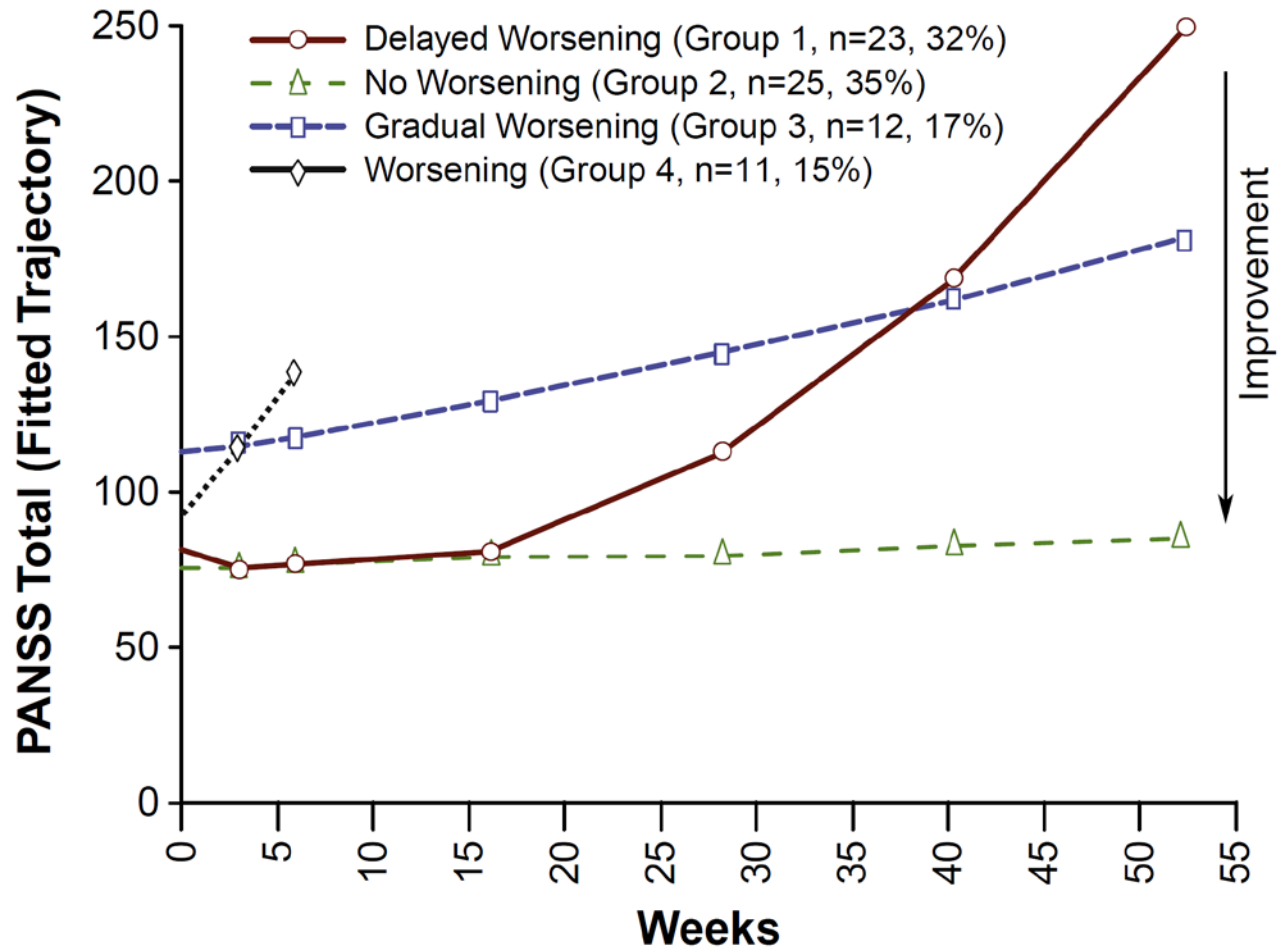
Lataster et al. J Clin Psychiatry 2011;72(10):1397–1404

# Too Little Dopamine, or Too Much?



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

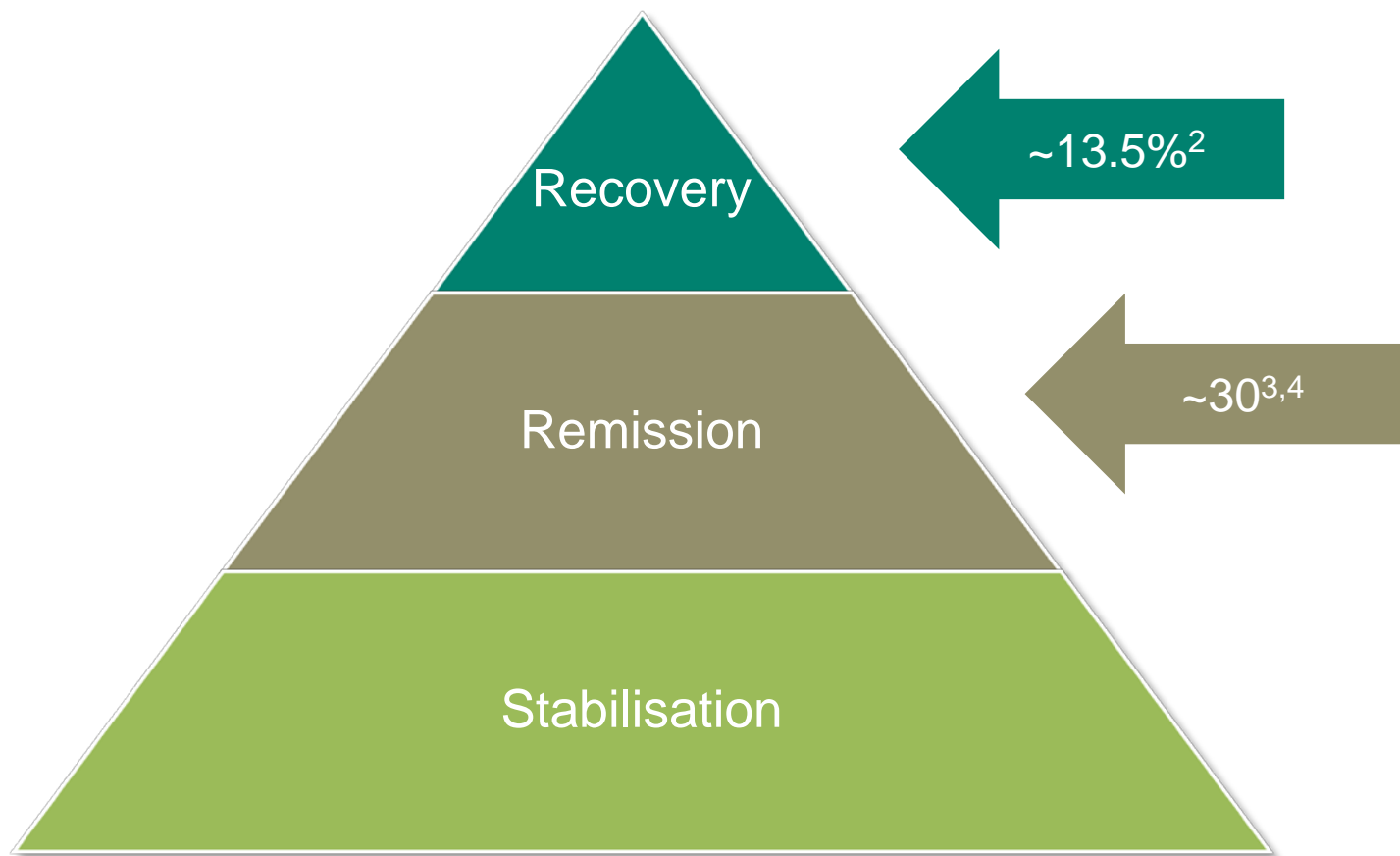
# Group Placebo Response Trajectories in One-Year Trial: PANSS Total Score



Potkin, Agid et al. SCZ Res. 2011: 32(2-3):108-13.



# Our Treatment Goals in Schizophrenia Have Changed<sup>1</sup>, but How Successful are We Today?



1. Remington et al. CNS Drugs 2010;24(1):9–20; 2. Jääskeläinen 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

# Summary

- Schizophrenia is a complex, multi-domain and perhaps the most devastating disorder of mankind.
- While treated as one illness, it is probably a heterogeneous group of disorders differentiating in etiology, course, response to treatment and outcome.
- There is no current treatment for schizophrenia; the only available medications are antipsychotics.
- The dopamine hypothesis presents the complexity of treating schizophrenia and the double edge sword of dopamine blockade.
- While recovery and functioning are the ultimate goals of treatment, more than sixty years of antipsychotic treatment have not brought us closer to achieving these goals.
- There is a lack of efficacy of all current treatment options for negative symptoms with minimal effect size across pharmacological and behavioral interventions.



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# **Regulatory Perspective on the Development of Drug Therapies for Residual Symptoms in Schizophrenia**

Thomas Laughren, M.D.

Director, Laughren Psychopharm Consulting, LLC



## Topics for Discussion

- A shifting focus from schizophrenia as a broad target of drug development to phases of the illness and specific symptom constructs within phases
  - Early vs late schizophrenia
  - Prodromal, acute, residual schizophrenia
  - Positive symptoms, negative symptoms, cognitive impairment, depression, aggression, etc.
- Alternative models for treating schizophrenia
- Alternative designs for studying potential treatments for schizophrenia

# Conventional Thinking About Schizophrenia

- Chronic, essentially life-long condition
- Prodromal Phase: Progressive deterioration in social/academic/vocational functioning with both negative symptoms and cognitive impairment
- Active Phase: First and usually recurring acute psychotic episodes with prominent positive symptoms, requiring treatment with a D2 blocker (all current antipsychotics)
- Residual Phase: With management of positive symptoms, patients enter a residual phase with prominent negative symptoms and cognitive impairment, and substantial functional impairment
- Usual treatment recommendation: Keep patients on D2 blockers indefinitely (due in part to lack of alternative treatments)

## More Recent Focus on Residual Phase Symptoms (Cognitive Impairment and Negative Symptoms)

- MATRICS program targeting cognitive impairment
  - NIMH funded: Academia, Industry, Regulatory
  - Resulted MATRICS Battery and guidelines for registration trials targeting cognitive impairment
  - Preferred design: adjunctive trial to usual antipsychotic with agent with different pharmacology
  - Led to regulatory acceptance of legitimacy of targeting cognitive impairment in schizophrenia
- Parallel effort to gain acceptance of targeting negative symptoms
  - Not as formal a program, but some NIMH assistance in facilitating this effort
  - Supported work on developing new rating instruments
  - Papers published on consensus views in support of this concept, including regulatory acceptance
  - Preferred design: again, adjunctive trial to usual antipsychotic with agent with different pharmacology

## Usual Design for Either Cognitive Impairment or Negative Symptoms

- Residual phase patients with minimal positive symptoms
- Taking an antipsychotic and considered stable
- Attempt to exclude patients with secondary residual symptoms (depression, EPS, prominent positive symptoms)
- Adjunctive design: added-on new drug with different pharmacology than antipsychotic or added-on placebo
- Patients selected for either cognitive impairment or negative symptoms at some threshold level
- Functional co-primary measure if targeting cognitive impairment, not if negative symptoms
- 3-6 months duration



# Brief History of Failures in Programs Targeting Either Cognitive Impairment or Negative Symptoms

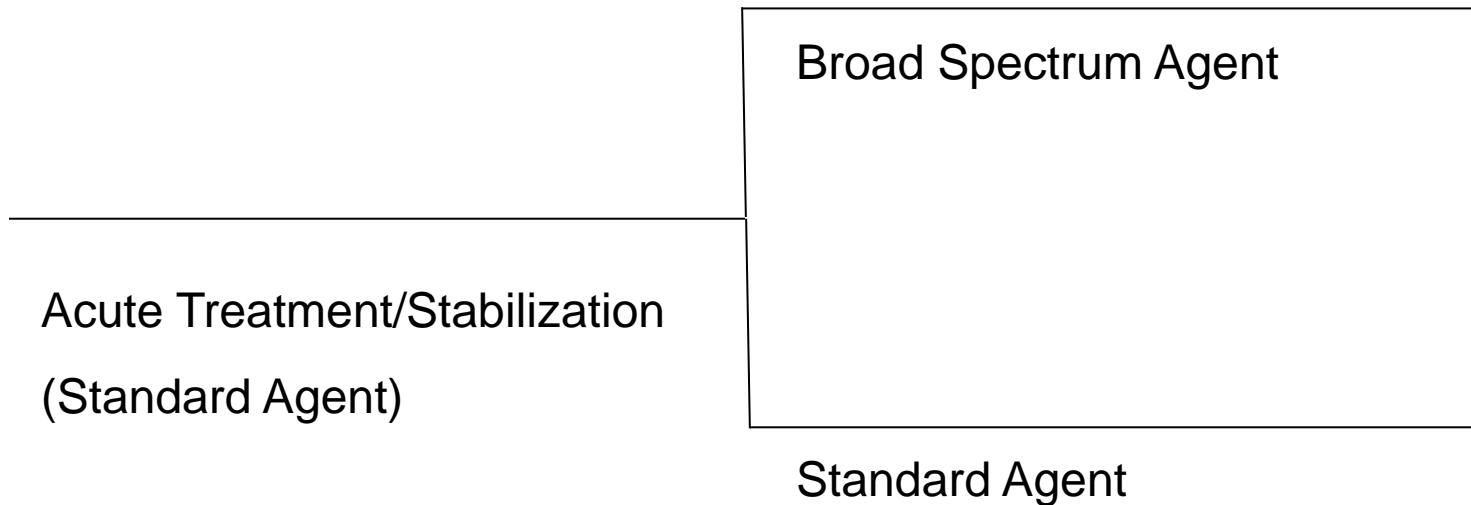
- Covers a roughly 10 year period
- Includes drugs with a variety of mechanisms
- Similar mechanisms used to target both cognitive impairment and negative symptoms
- All used adjunctive design in residual phase patients
- Some promising phase 2 data, but most have not made it to phase 3
- None of the phase 3 programs have succeeded

# Alternative Models for Thinking about Treating Residual Symptoms

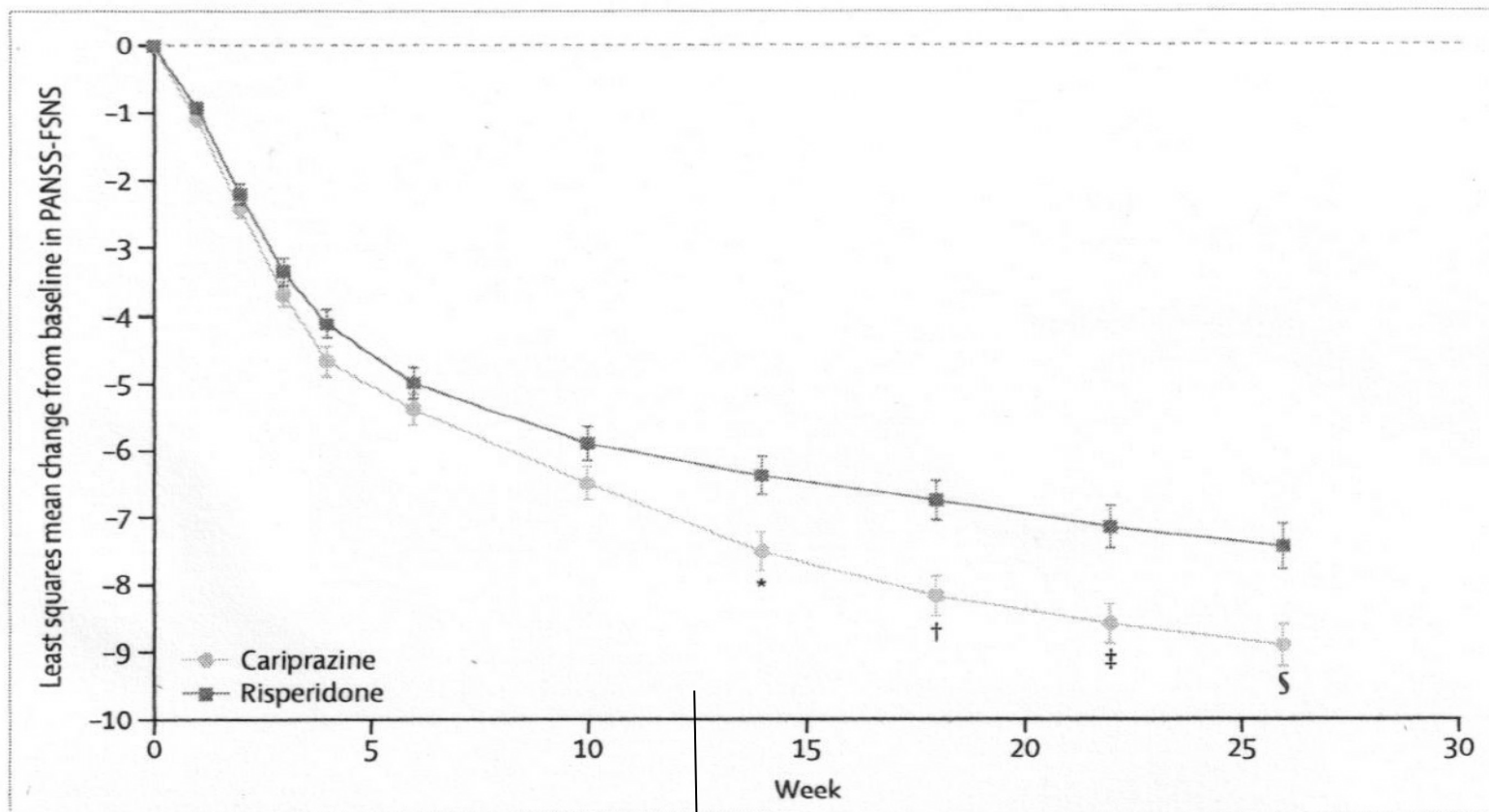
- Broad Spectrum Antipsychotics
  - Drugs that treat both positive symptoms and residual phase symptoms (either negative symptoms or cognitive impairment, or both)
  - Switching design
  - What claim do you get for a positive study?
- Prominent negative symptom subtype of schizophrenia that does not require D2 blocker maintenance treatment
  - Should permit a monotherapy study (negative symptom drug vs pbo)
  - How to identify such patients?
  - Do these drugs also prevent relapse to positive symptoms to allow longer-term management of these patients?

# Proposed Design for Study of “Broad Spectrum” Agent During Residual Phase of Schizophrenia

- Achieve optimal control/stability for positive symptoms with standard antipsychotic agent in acutely psychotic patients (open)
- Randomize (during residual phase) to:
  - Continuation of standard agent
  - Switch to broad spectrum agent



# Cariprazine Study



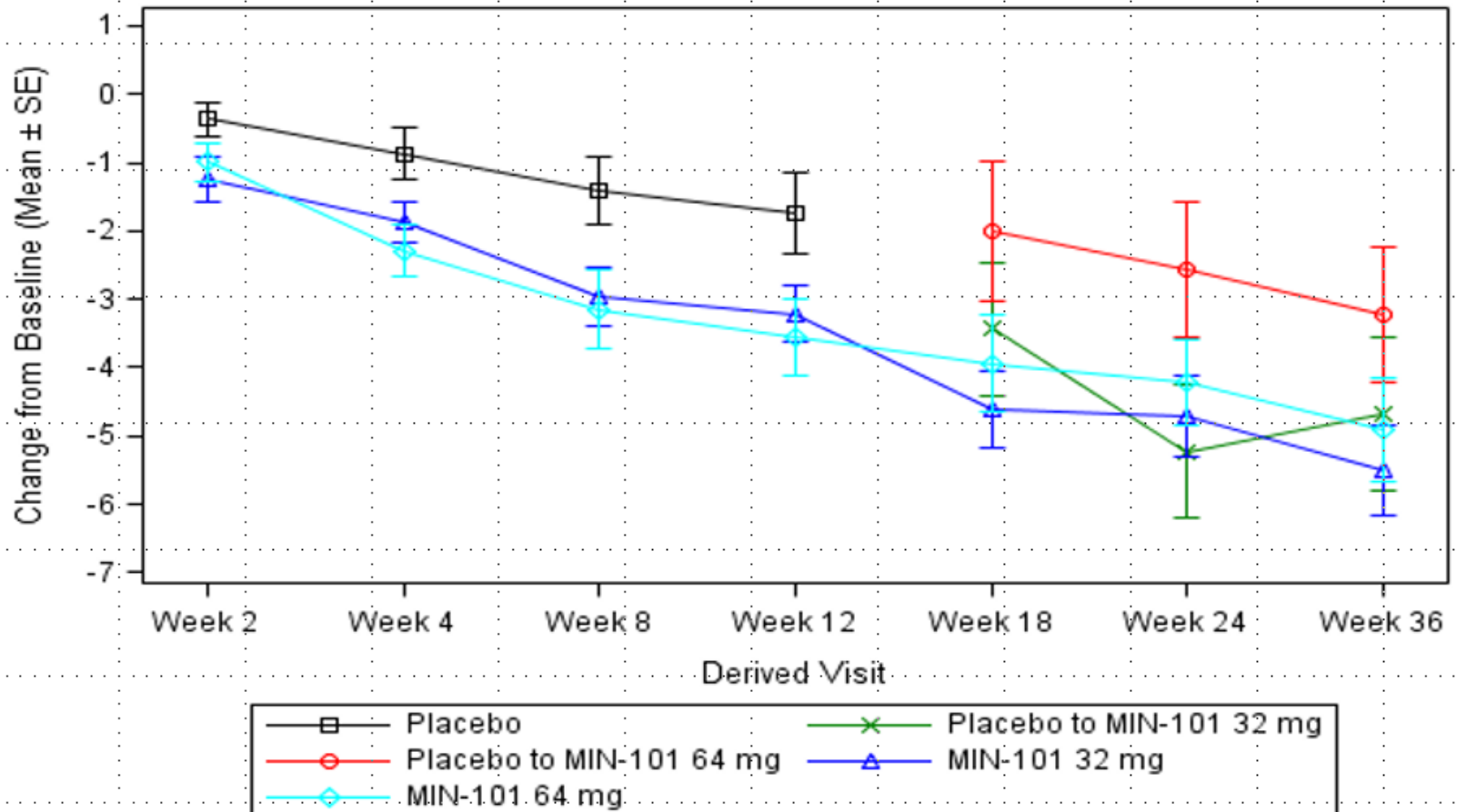
**Figure 2: Mean change from baseline to week 26 in PANSS-factor score for negative symptoms**  
p=0.0092 for the overall treatment effect of cariprazine versus risperidone. PANSS-FSNS=Positive and Negative Syndrome Scale factor score for negative symptoms. \*p=0.0079. †p=0.0011. ‡p=0.0016. §p=0.0022.

# Is There a Prominent Negative Symptom Subtype of Schizophrenia That Does Not Require D2 Blocker Maintenance Treatment?

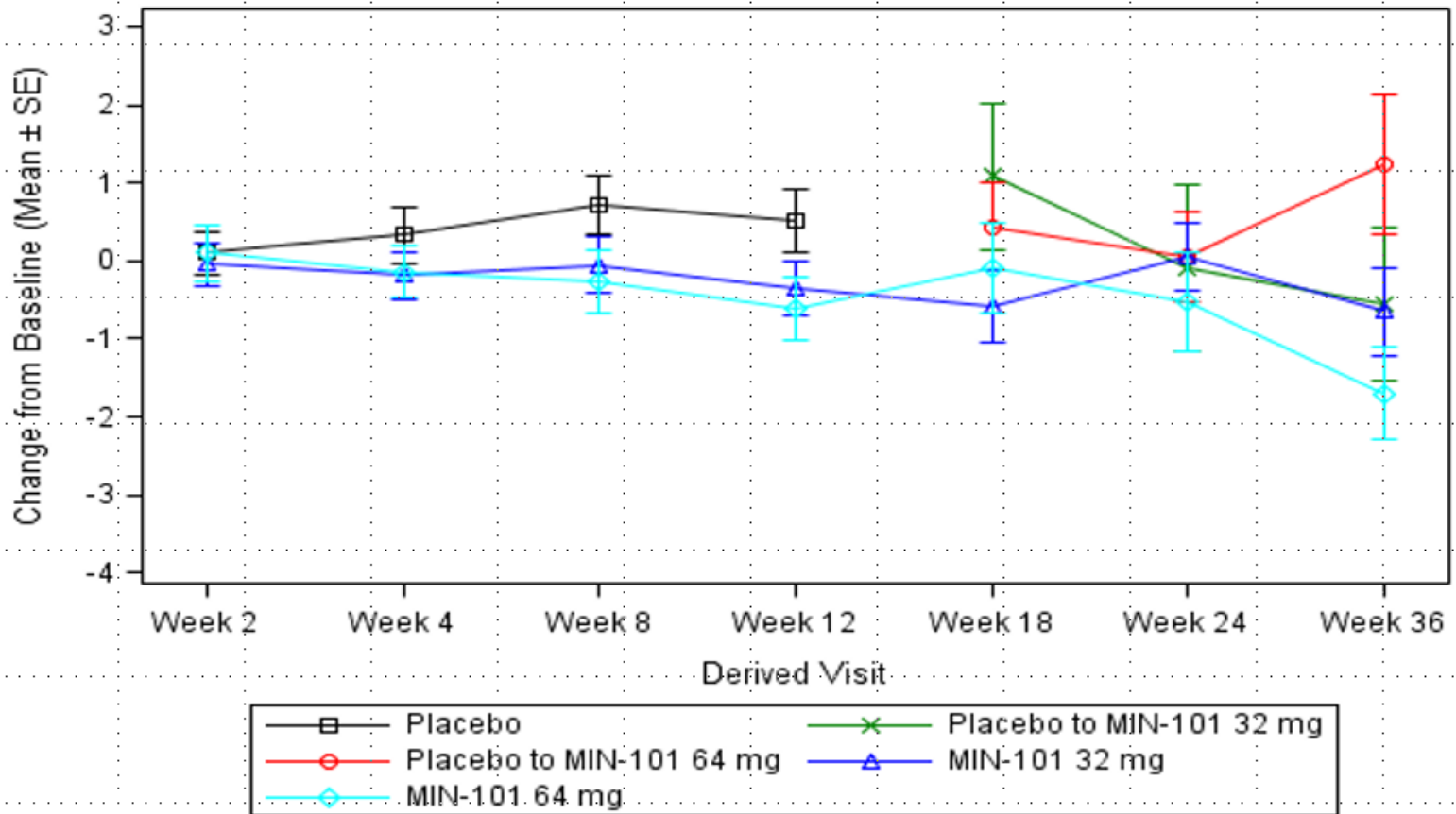
- Conventional wisdom argues for continuous and life-long maintenance treatment of chronic schizophrenic patients on drugs that have as part of their pharmacology at least some D2 blockade
  - Atypical antipsychotics are preferred, but all have D2 blockade (or partial agonism)
- There are, however, some opposing views and data:
  - Some have argued for a subtype of schizophrenia who have brief and infrequent psychotic exacerbations but persistent and severe negative symptoms (Bobes et al, 2010).
  - Some emerging literature arguing for such a subgroup of patients who do not need D2 maintenance (Hafner, et al, 2013; Harrow et al, 2012; Harrow et al, 2014; Wunderink et al, 2013; Wils et al, 2016).
  - Some academics and clinicians have argued for a more flexible approach in treating this population, and of course many patients themselves simply choose not to accept a lifetime of D2 blockade



# Negative Symptoms (5-Factors)



# Positive Symptoms Scale



# Regulatory Perspective on Negative Symptoms as Target for Drug Development

- “Negative symptoms of schizophrenia” is recognized as an unmet need and is an acceptable target for drug development
- No regulatory endorsement yet of any specific primary endpoint for these trials
  - However, Marder NSFS is widely used in negative symptom trials and has wide acceptance in the community of experts in this area
- Trials of 3-6 months duration are acceptable (FDA has endorsed a number of ph 3 programs of this duration)
- Monotherapy design is acceptable
  - Explicit in EMA guidance
  - Implicit for FDA (no formal guidance)
  - Placebo arm is required
- Position on need for positive control not clear as yet
  - No standard of care for negative symptoms (nothing approved as yet)



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# **Negative Symptoms: Therapeutic Shortcomings and Real-World Impact**

Michael Davidson, M.D.  
Chief Medical Officer  
Minerva Neurosciences, Inc.

# Content

- What are the shortcomings of currently available treatments for schizophrenia?
- What are negative symptoms and what are the functional impairments related to negative symptoms?
- Does the typical patient seen in daily clinical practice have negative symptoms?
- Are negative symptoms manifested beyond schizophrenia?



# Shortcomings of Current Treatment

## Systematic Review and Meta-Analysis of Recovery in Schizophrenia (1940 onwards)

Table 1. Recovery Percentages in Subpopulations

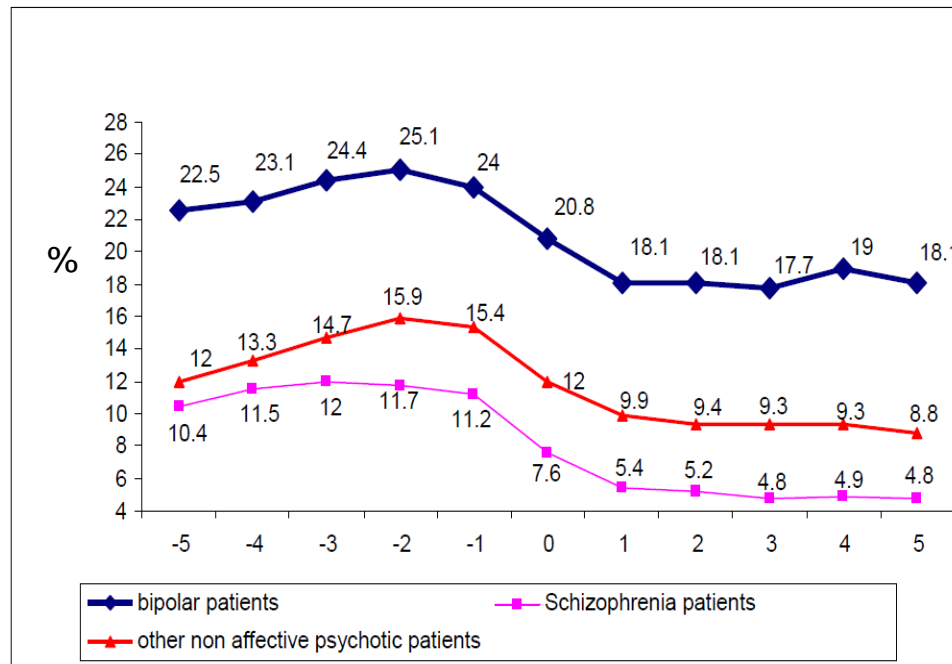
	Number of Studies	Median% <sup>a</sup>	IQR <sup>b</sup>	Statistical Test <sup>c</sup>
Sex	24			$t = 1.08, P = .293$
Males	12	12.9	10.0–19.4	—
Females	12	12.1	7.5–29.0	—
Midpoint of the collection of the sample <sup>d</sup>	48			$t = -0.38, P = .704$
Before 1941	11	13.0	6.4–20.0	—
1941–1955	5	17.7	13.0–19.7	—
1956–1975	11	16.9	16.3–32.4	—
1976–1995	19	9.9	5.8–19.0	—
After 1996	2	6.0	3.9–8.1	—
Economic index of the site <sup>e</sup>	50			$t = -2.93, P = .005$
Low or lower-middle	5	36.4	16.7–37.0	—
Upper-middle	5	12.1	10.0–31.8	—
High	40	13.0	7.7–19.0	—
First-episode vs not first-episode samples	46			$t = -0.18, P = .857$
First-episode sample	30	16.6	9.0–20.4	—
Not first-episode sample	16	11.1	6.0–22.5	—

The proportion of individuals with schizophrenia who met recovery is 13.5% and appears not to have increased across time. There is no evidence to suggest that we are “getting better” at getting our patients better.

Jääskeläinen et al. Scz Bull 2013

# Economic Impact of Lack of Recovery

## Percentage of Patients Making Minimal Wages after 1<sup>st</sup> hospitalization



*Rates of employment in the general population in the western world ~ 50%-60%*

Davidson et al Scz Bull 42(2):443-447, 2016

# What are Negative Symptoms in Schizophrenia and How Can You Function with Such Symptoms?

Subdomain	Clinical symptom term †	Clinical symptoms or behaviors
Dysfunction of communication	Alogia	Poverty of speech, e.g. talks little, uses few words; abnormal prosody of speech
Dysfunction of affect	Blunted affect	Reduced range of expressed emotions, and self-reported emotions (feels numb or empty inside, recalls few emotional experiences, good or bad)
Dysfunction of socialisation	Asociality	Reduced social drive and interaction, e.g. few friends, little interest in spending time with others, little sexual interest
Dysfunction of capacity for pleasure	Anhedonia	Reduced ability to anticipate or recall pleasure from previous hobbies or activities of interest
Dysfunction of motivation	Amotivation (or Avolition)	Reduced desire, motivation, persistence, e.g. reduced ability to undertake and complete everyday tasks; may have poor personal hygiene

† The Clinical symptoms terms are found in DSM-5 and are terms are from a NIMH-supported consensus meeting of schizophrenia experts

Stahl SM & Buckley PF. Acta Psychiatr Scand 2007;115:4–11

# What do Negative Symptoms Look Like in Clinical Practice? Is the Trial Patient the Patient You See in Daily Clinical Practice?

- Single 37 y/o male, first hospitalized for acute psychosis while in college.
- Because he never regained social and vocational functioning, treatment was tried with almost every antipsychotic drug.
- He occasionally did odd jobs but for the last 3 years he lives on disabilities.
- He has few acquaintances but no friends and spends most of the time watching TV.
- In the past he was bothered by a loud, scary voice telling him several times per day: “*stupid stand-up*”, “*move faster*” but lately he learned to ignore the voice, which does not scare him anymore.
- About 2 years ago he got into a loud argument with a neighbor, and when the police found out that he is a mental patient he was taken to the psychiatric hospital, where he spent a week.
- He attends the community mental health clinic, where he receives a prescription of antipsychotic medication.
- Because the medication makes him feel *heavy* and *slow*, he takes it only every third day instead of daily. He once confessed this to his psychiatrist, who told him he should take the medication every day, but he didn't seem concerned.

# Potential Cumulative Prevalence of Negative Symptoms Beyond Schizophrenia

▪ Idiopathic Parkinson	0.3% *
▪ Apathy post Major depression	3%
▪ Apathy in Alzheimer Disease	1%
▪ Apathy Frontal dementia	0.01%
▪ NS in mental retardation	0.5%
▪ Apathy post-brain trauma	0.01%
▪ Apathy post-CVA	0.3%
▪ NS in autism spectrum	1.2%
▪ NS in schizophrenia	0.7%
▪ Ns in schizophrenia spectrum	1%
▪ NS in premorbid schizophrenia	1%
▪ NS in drug abuse	0.3%

**~10 % of the general population? \*\***

\* Approximate percentage of affected individuals in the general population not based on empirical data

\*\* About 10% of the healthy general population has mild manifestation of negative symptoms Werbeloff et al PLOS 2015

**Are negative symptoms, apathy, and mild cognitive impairment the common pathway reaction to developmental or acquired brain insult?**

Foussias et al, 2013





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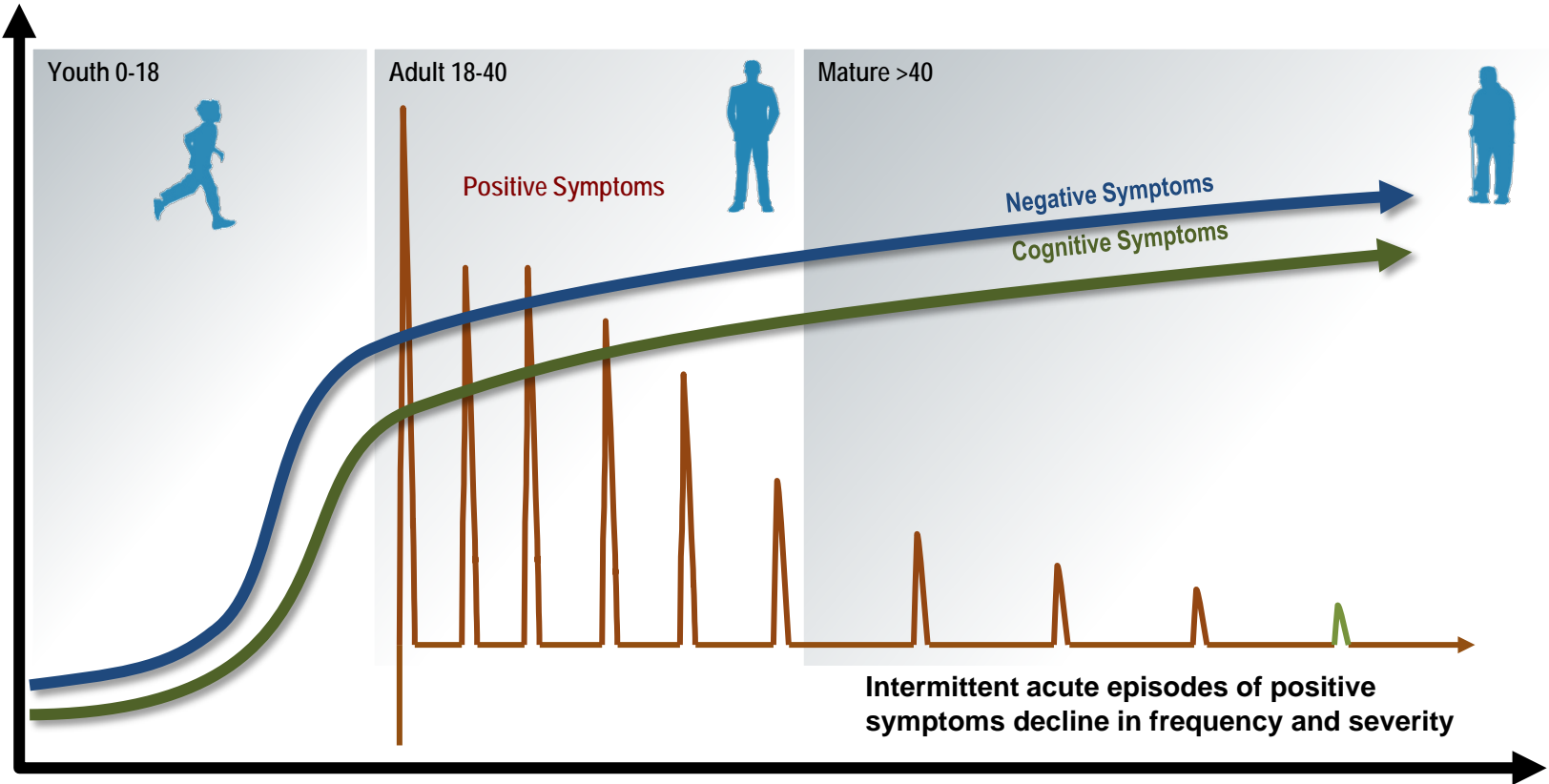
## **Defining Patients Who Can Benefit From Monotherapy with Roluperidone (MIN-101)**

Remy Luthringer, PhD  
Executive Chairman and CEO  
Minerva Neurosciences Inc.  
March 22, 2018

# Current Rx Approach Assumes “*One Size Fits All;*” Can We Do Better?

- The DSM phenomenological definition of schizophrenia includes a heterogeneous population of individuals with **biologically diverse** diseases.
- Even the same individual, throughout life, has diverse phenomenological disease presentations, consistent with a **biologically dynamic** disease.
- *Does a **subgroup** of patients who can benefit from Rx with drugs **without** significant affinities for DA receptors **exist**, and can they be **identified**?*

# Schizophrenia Has Three Symptom Domains: (1) Positive Symptoms, Which Fluctuate Over Time, (2) Negative Symptoms, & (3) Cognitive Impairment, with the Latter Two Persisting and Causing Lifelong Disability



# Which Patients Can Benefit from Treatment Without Dopamine (DA) Blocking Drugs, and How to Select Them for Clinical Trial?

- Is it essential to have a **ceiling on total positive symptoms sub-score** or certain specific psychotic symptoms, such as delusions, conceptual disorganization, or hallucinations?
- If not, what symptoms or scale items should have an upper threshold in monotherapy trials without DA blockers?
- Is it essential to have a **minimum negative symptoms sub-score** or on specific items?
- What duration of stability is enough, and is it essential to demonstrate it prospectively?
- Does age matter?

## Main Inclusion Criteria MIN-101 Phase 2b

- DSM-5 schizophrenia criteria
- Baseline score  $\geq 20$  on the 7 PANSS negative symptoms sub-scale
- Symptomatically stable with persistent negative symptoms for 3 months, as judged by the Principal Investigator
- Age 18-60



### ***Ceiling based on agitation/hostility rather than psychosis***

- **A score <4 (only mild or less) on the PANSS:**

- P-4 excitement/hyperactivity

- P-6 suspiciousness/persecution

- P-7 hostility

- G-8 uncooperativeness

- G-14 poor impulse control

# What Did We End up with at Baseline?

TABLE 1. Characteristics of Patients With Schizophrenia Treated With MIN-101 or Placebo

Variable	Placebo (N=83)		MIN-101				Overall (N=244)			
			32 mg/day (N=78)		64 mg/day (N=83)		Total (N=161)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	40.0	10.2	39.8	10.2	40.6	10.6	40.2	10.4	40.2	10.3
BMI	26.0	4.5	25.3	4.5	25.6	4.3	25.4	4.4	25.6	4.4
	N	%	N	%	N	%	N	%	N	%
Male	48	57.8	41	52.6	48	57.8	89	55.3	137	56.1
Antipsychotic at screening										
None	1	1.2	5	6.4	6	7.2	11	6.8	12	4.9
Depot	6	7.2	4	5.1	3	3.6	7	4.3	13	5.3
Oral second-generation	58	69.9	53	67.9	56	67.5	109	67.7	167	68.4
Oral first-generation	18	21.7	16	20.5	18	21.7	34	21.1	52	21.3

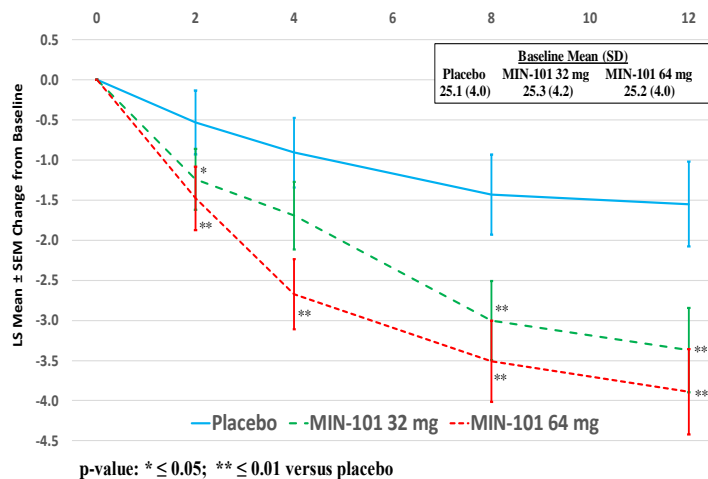
TABLE 2. Baseline Clinical Measures for Patients With Schizophrenia Treated With MIN-101 or Placebo

Measure	Placebo (N=79)		MIN-101				Total (N=155)		
			32 mg (N=76)		64 mg (N=79)		Total (N=155)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
PANSS									
Total score	80.2	10.7	81.2	9.8	79.7	11.1	80.4	10.5	
Negative score	26.5	3.8	27	3.7	26.8	3.8	26.9	3.7	
Positive score	14.2	3.0	14.6	3.3	13.9	3.3	14.3	3.3	
General psychopathology score	39.5	7.1	39.5	6.4	39.1	7.3	39.3	6.9	
PANSS five-factor model									
Negative score	31.5	4.7	31.7	4.2	31.4	4.3	31.6	4.2	
Positive score	10.4	2.9	10.5	3.0	10.2	2.9	10.3	3.0	
Dysphoric mood score	10.9	3.3	10.6	3.2	10.7	3.2	10.6	3.2	
Activation score	12.6	2.8	12.6	2.6	12.1	2.7	12.4	2.6	
Autistic preoccupation score	18.0	2.9	18.3	2.9	18.1	3.3	18.2	3.1	
Clinical Global Impressions, severity score	4.1	0.7	4.2	0.6	4.1	0.7	4.2	0.6	
Brief Negative Symptom Scale	47.3	9.0	47.3	9.4	47.1	9.6	47.2	9.5	
Brief Assessment of Cognition in Schizophrenia, composite T-score	17.5	18.2	16.9	20.3	18.3	18.7	17.7	19.4	
Calgary Depression Scale for Schizophrenia	2.2	3.2	2.2	3.0	2.0	2.5	2.1	2.8	

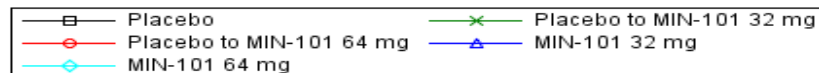
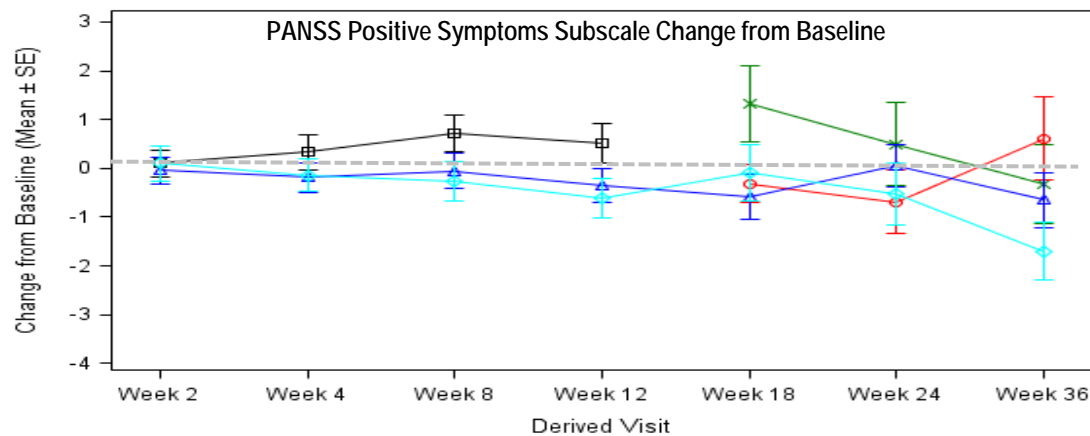
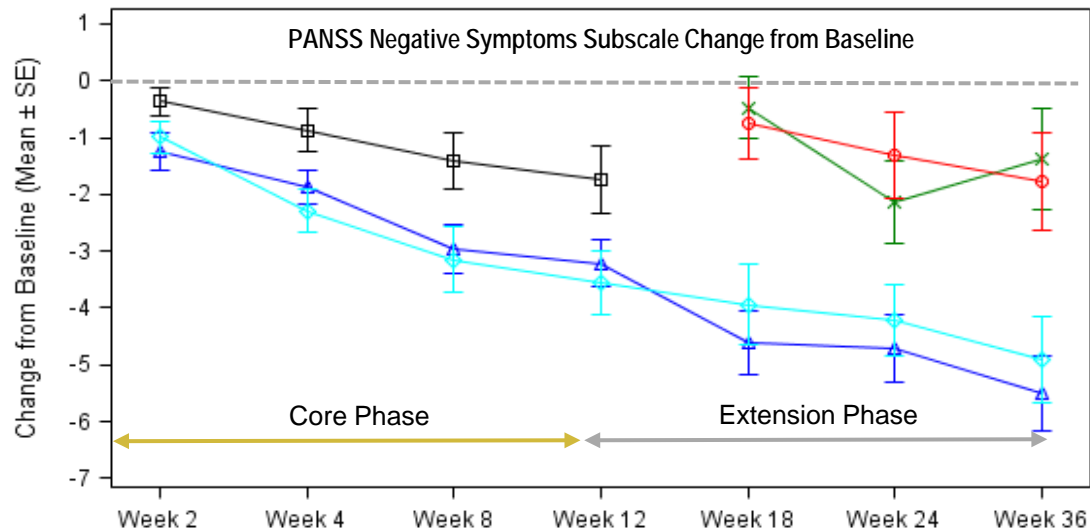
# Phase 2b Study Showed Specific Improvements in Negative Symptoms over 12 and 36 Weeks and Maintained Stable Positive Symptoms

Statistically significant improvements in the primary endpoint

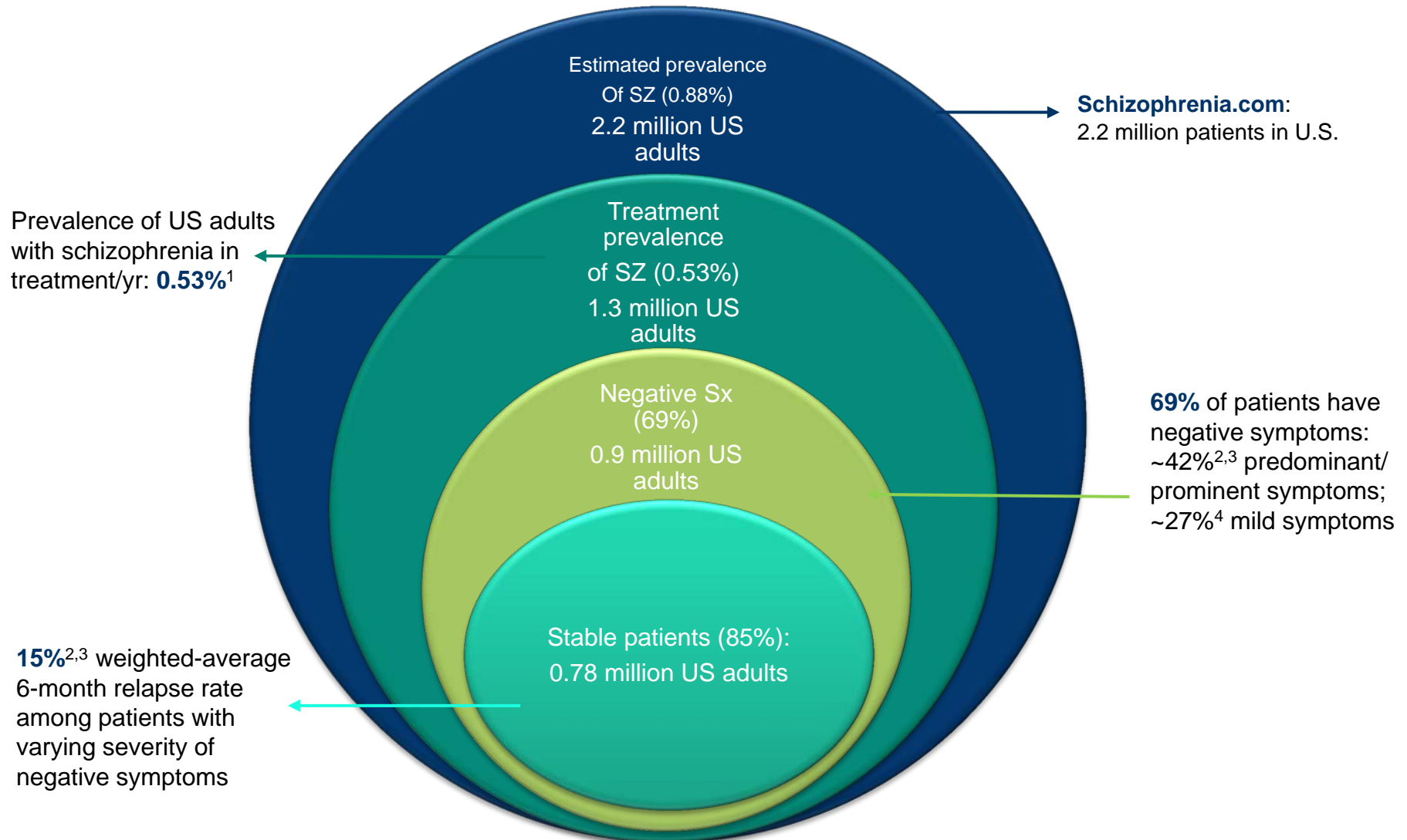
PANSS Negative Symptoms Factor Score (Marder) Change from Baseline (MMRM) (ITT Population)



## Extension



# 59% of Adult patients with Schizophrenia Who are Treated Have Negative Symptoms and Are Clinically Stable



1. Wu et al., Psychol Medicine 2006; 2. Millier et al., J Market Acc Health Policy, 2017; 3. Haro et al., Schizo Research 2015 ; 4. Nordstroem et al., J Social Psychiatry 2017

## Pathophysiological Rationale: Can the Mechanism of Action of MIN-101 Explain Observed Clinical Effects?

Receptor subtypes	Materials	Ki values, nmol/L
Serotonin 5-HT <sub>2a</sub>	Rat, cerebral cortex	7.5
	Human recombinant	5.2
Sigma <sub>2</sub>	Guinea pig, brain	8.2
Sigma <sub>1</sub>	Guinea pig, brain	253.8
A <sub>1</sub> adrenergic	Rat, brain	14.4

- ✓ **Specific Affinity for 5-HT<sub>2A</sub>,  $\sigma_2$ , and  $\alpha_1$ -adrenergic receptors**
- ✓ **No affinity (>1000 nM) for other receptors, including dopaminergic, muscarinic, cholinergic and histaminergic receptors**
- ✓ **No direct Dopamine binding**
- ✓ **The behavioral pharmacology package is consistent with an antagonistic effect for 5-HT<sub>2A</sub>,  $\sigma_2$ , and  $\alpha_1$ -adrenergic receptors**



# 5-HT<sub>2A</sub>, $\sigma_2$ , and $\alpha_1$ -adrenergic: the Relevant Scientific Literature

## 5HT2A:

1. Howland RH. Antidepressant, Antipsychotic, and Hallucinogen Drugs for the treatment of Psychiatric Disorders: A Convergence at the Serotonergic-2A Receptor. *J Psychosoc Nurs Ment Health Serv*. 2016; 54(7):21-4

## Sigma2:

1. Debonnel G, de Montigny C. Modulation of NMDA and dopaminergic neurotransmissions by sigma ligands: possible implications for the treatment of psychiatric disorders. *Life Sci*. 1996; 58(9): 721-34
2. Derbez AE et al., Sigma (2)-receptor regulation of dopamine transporter via activation of protein kinase C. *J Pharmacol Exp Ther*. 2002; 301(1): 306-14
3. Guo L, Zhen X. Sigma-2 receptor Ligands: neurobiological effects. *Curr Med Chem*. 2015; 22(8): 989-1003
4. Alon A et al., Identification of the gene that codes for the sigma2 receptor. *Proc Natl Acad Sci USA*. 2017; 114(27): 7160-7165

## Alpha 1:

1. Maletic V et al., The role of Norepinephrine and its alpha-Adrenergic Receptors in the Pathophysiology and Treatment of Major Depressive Disorders and Schizophrenia: A Systematic Review. *Front Psychiatry*. 2017; 8:42

# MIN-101 is Unique in the Late-Stage Schizophrenia Pipeline: a Monotherapy Targeting Negative Symptoms

	Phase 3 studies: Acute	Phase 3 studies: Maintenance & Sub-population studies	
Indications		Negative Symptoms, Treatment-resistance, Residual positive symptoms, and Niche populations	Long-Acting Injectables or Patch
	<p><b>Alkermes</b> <b>ALKS 3831</b> (Mu-opioid antagonist + olanzapine)</p> <p><b>Intra-Cellular Therapies</b> <b>ITI-007 (lumateperone)</b> (5-HT<sub>2A</sub> antagonist, D<sub>2</sub>/D<sub>1</sub> modulator, SSRI)</p>	<p><b>MINERVA NEUROSCIENCES</b> <b>MIN-101</b> (5-HT<sub>2A</sub> &amp; σ<sub>2R</sub> antagonist) <b>-Negative symptoms, monotherapy</b></p> <p><b>Lundbeck</b> <b>Lu AF35700</b> (D<sub>1</sub>, 5-HT<sub>2A</sub> &amp; 5-HT<sub>6</sub> antagonist) -Treatment-resistant, monotherapy study vs. risperidone and olanzapine</p> <p><b>ACADIA<sup>®</sup> Pharmaceuticals</b> <b>ACP-103 (pimavanserin)</b> (5-HT<sub>2A</sub> inverse agonist) -Residual positive symptoms, adjunctive use</p> <p><b>SyneuRx</b> <b>NaBen (sodium benzoate)</b> (D-amino acid oxidase inhibitor) <b>Three late-stage indications:</b> -Residual positive symptoms, adjunctive use -Adolescents, monotherapy -Clozapine refractory, adjunctive use</p>	<p><b>INDIVIOR</b> <b>RBP-7000</b> (once-monthly, SR risperidone)</p> <p><b>Braeburn pharmaceuticals</b> <b>Risperidone implant</b> (6 monthly, nonbiodegradable risperidone drug-eluting stent)</p> <p><b>NOVEN PHARMACEUTICALS, INC.</b> <b>HP 3070</b> (transdermal patch of asenapine)</p> <p><b>ATA ROW</b> <b>Risperidone ISM</b> (once-monthly IM risperidone)</p>

Source: Jan 2018; Cambridge Healthcare Research (CHR) Limited, [www.camhcr.com](http://www.camhcr.com); ClinicalTrials.gov

# Improving the Standard-of-Care in Schizophrenia

- Amotivation is negatively linked to dopamine (DA) blocking
- Can negative symptoms, and in particular amotivation and asociality, be improved in the context of blocking the DA-dependent motivation/reward brain circuits?
- Can a pharmacological intervention targeting negative symptoms overcome the DA blocking effect of antipsychotics if used adjunctively?
- Can we do better than the current treatment paradigm focused on DA blockade, and improve the standard-of-care to one that is more patient-centered, tailored to different disease phases and addressing underlying negative symptoms that drive poor outcomes?

# Does the Body of Clinical Trial Data Support Chronic Use of Antipsychotics?

- Randomized clinical trials (RCTs) showing superiority of antipsychotics as maintenance therapy are too short (mean of 6 months) to support guidelines for chronic long term use, and differences between drugs and placebo become smaller as lengths of studies increase.<sup>1,2</sup>
- "Functional unblinding" due to side-effects of antipsychotics increases the difference between drugs and placebo.<sup>3</sup>
- Criteria for relapse are highly weighted toward poor impulse control, rather than functional improvement reflecting real life outcomes.
- Should targeted, intermittent treatment with antipsychotics be reconsidered?

1.Howes et al *Arch Gen Psychiatry* 2012; 2.Moncrieff et al *Cochrane Database Syst Rev* 2004; 3.van Os and Howes *Lancet* 2012

# Is the Pendulum Swinging Back? Time for Reconsideration



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- Harrow M, et al 2012 Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. Psychological Medicine
- Harrow et al 2014 Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multi-follow-up study. Psychol Med.
- Morgan C, Lappin J, Heslin M, et al. 2014 Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. Psychol Med . Ten-year outcome study of an epidemiological sample of first-episode psychosis patients, reporting better-than-expected outcomes
- **Insel T. (2013) Post by Former NIMH Director Thomas Insel: Antipsychotics: Taking the Long View**
- Moncrieff J. (2015) Antipsychotic Maintenance Treatment: Time to Rethink? PLoS Med.
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- Wils RS, Gotfredsen DR, et al. (2016). Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis. Schizophr. Res.
- **Wunderink L, et al 2013 Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry.**
- Alvarez-Jimene, Mc Gorry 2016 Beyond Clinical Remission in First Episode Psychosis: Thoughts on Antipsychotic Maintenance vs. Guided Discontinuation in the Functional Recovery CNS Drugs
- **Murray RM, et al 2016 Should psychiatrist be more cautious about long term use of antipsychotics? Br J Psychiatry.**
- Moore TG and Furberg CD 2017 The Harms of Antipsychotic Drugs: Evidence from Key Studies Drug Saf





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# **NEGATIVE SYMPTOMS OF SCHIZOPHRENIA**

**March 22, 2018**