



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

*EMA EFPIA Workshop on
Dose-Exposure-Response relationship estimation and dose finding.*

Dosing: Examples from Antipsychotics

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Public Declaration of transparency/interests*

Interests in pharmaceutical industry	NO	Currently	Last 2 years	More than 2 years but less than 5 years ago	More than 5 years ago (optional)
Direct interests:					
Employment with a company	X				
Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
Indirect interests:					
Principal investigator	X				
Investigator	X				
Individual's Institution/Organisation receives a grant or other funding	X				
CME Courses				X	

***Luca Pani**, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (26.01.2012) and published in the Italian Government Official Journal on 20.03.2012 according to 0044 EMA/513078/2010 on the handling of the conflicts of interest for scientific committee members and experts



Schizophrenia Symptoms & Signs



Louis Wain

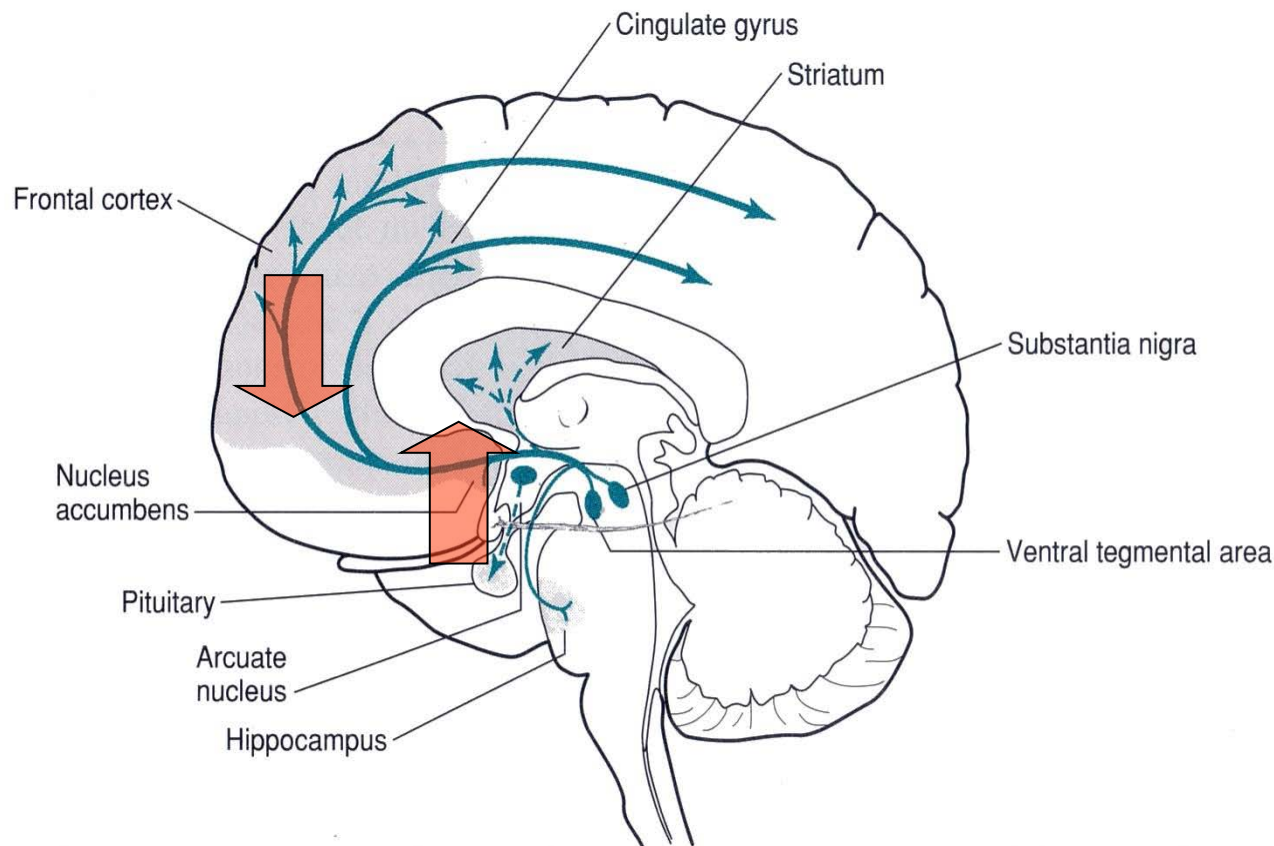
Positive symptoms
Bizarre behavior
Negative symptoms
Poverty of speech
Affective flattening
Low energy, inactivity
Cognitive symptoms
Impaired attention
Poor concentration

Social withdrawal
Slow thinking
Anhedonia
Poor memory
Hyperactivity
Catatonia
Delusions
Hallucinations

Reduced initiative & motivation
Disorganized speech and thinking
Difficulty understanding
Difficulty expressing thoughts
Difficulty integrating thoughts, feelings and behavior
Working memory deficit
Disorganized thinking

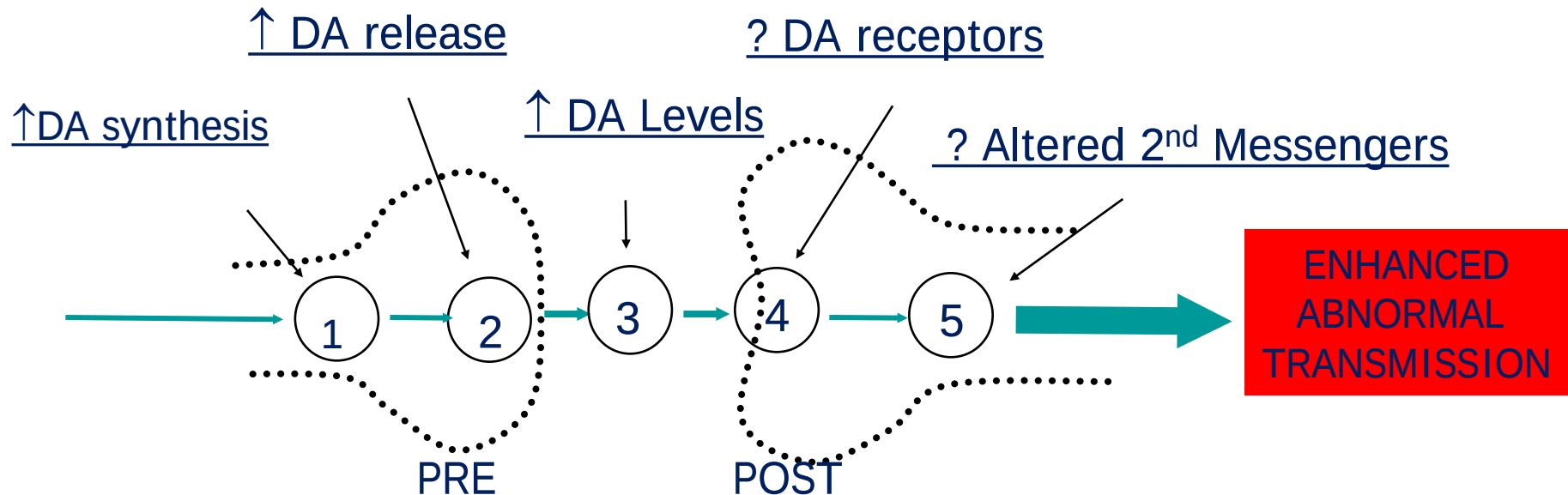


Dopamine in Schizophrenia & Antipsychotic Action



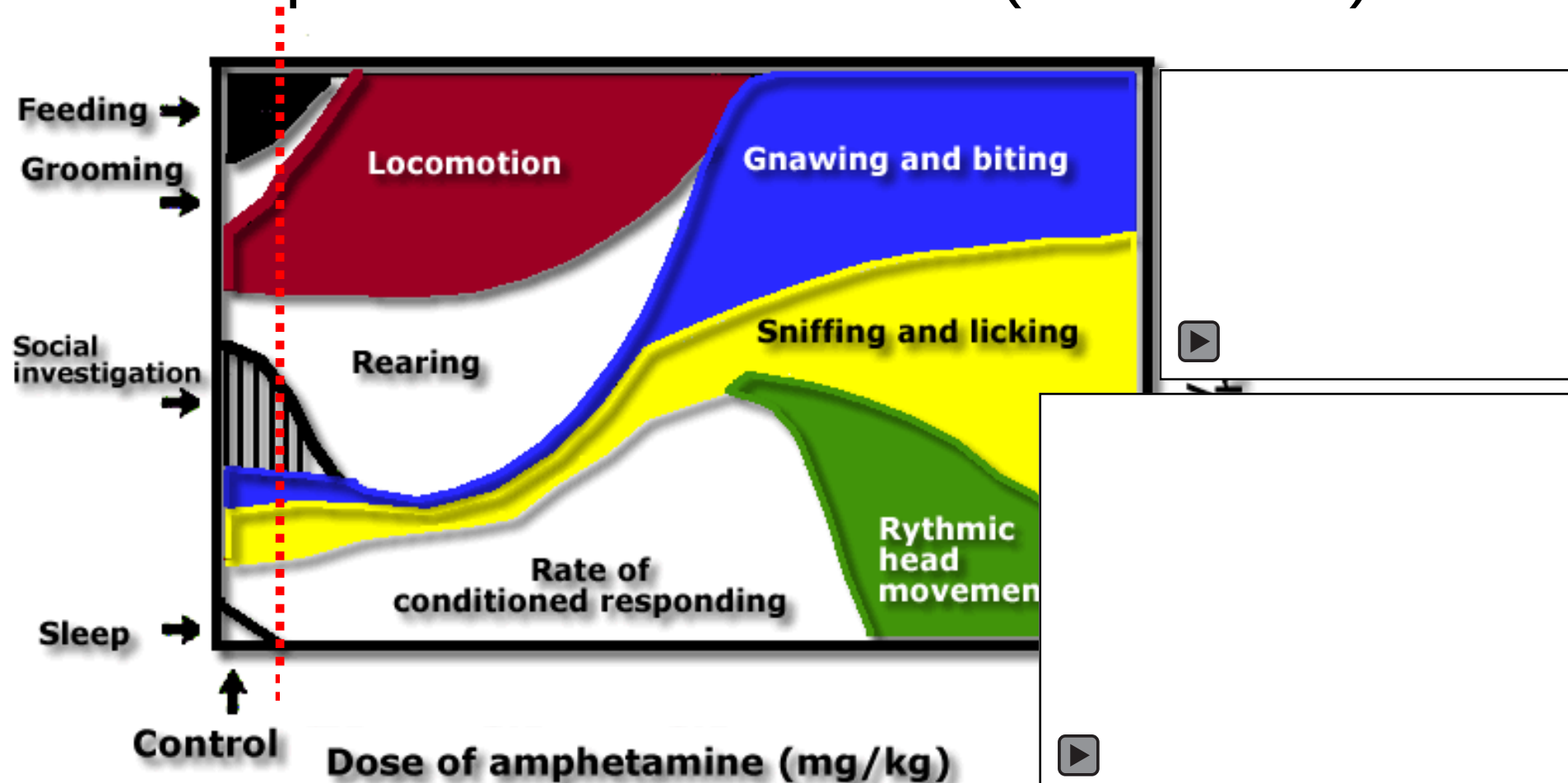
Both hypofunctioning prefrontal DA projections and hyperfunctioning mesolimbic DA system in schizophrenia

Dopamine and positive symptoms

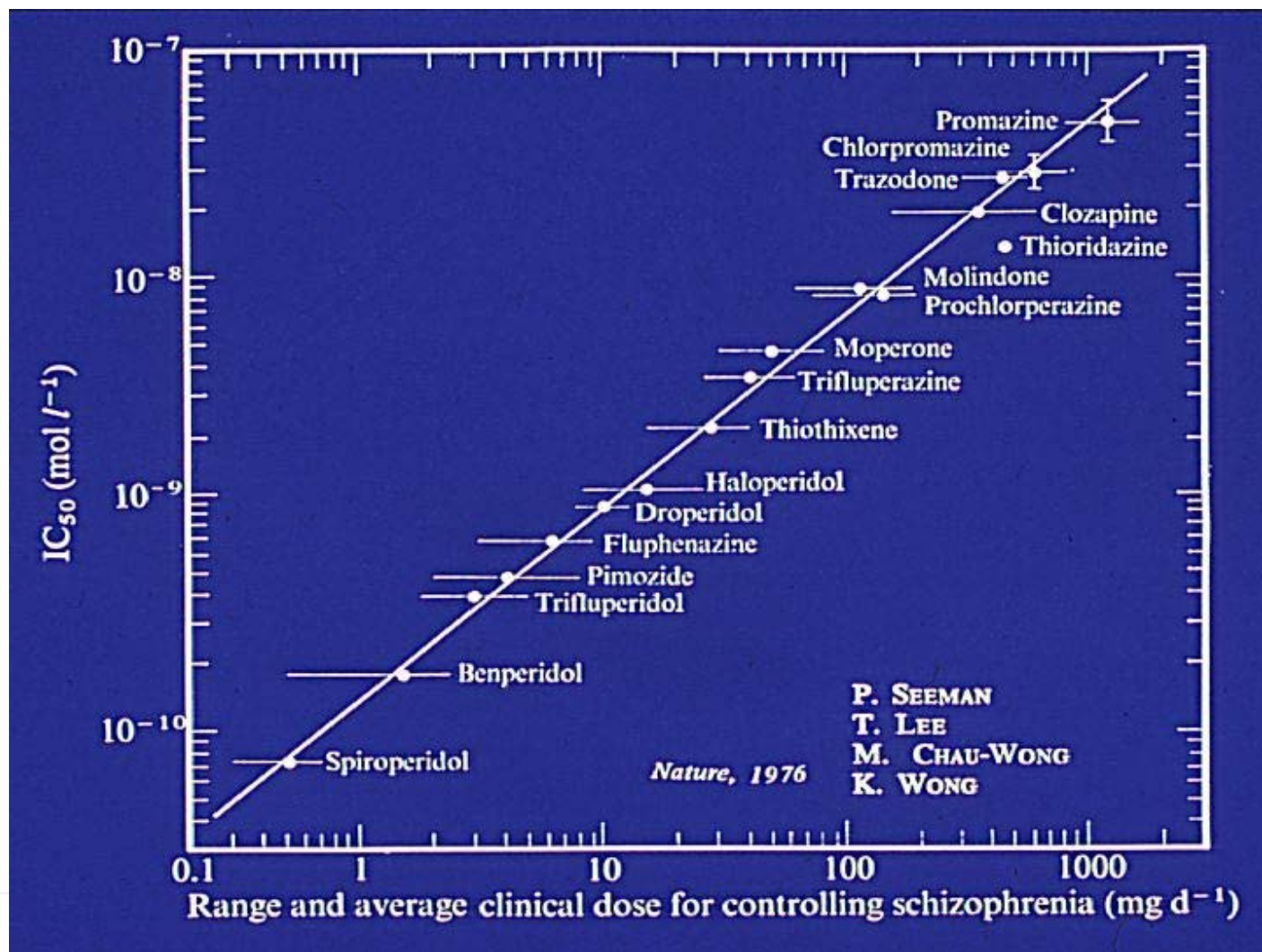


- Not Exclusive
- Not Primary
- Relates more to the state of psychosis-in-schizophrenia

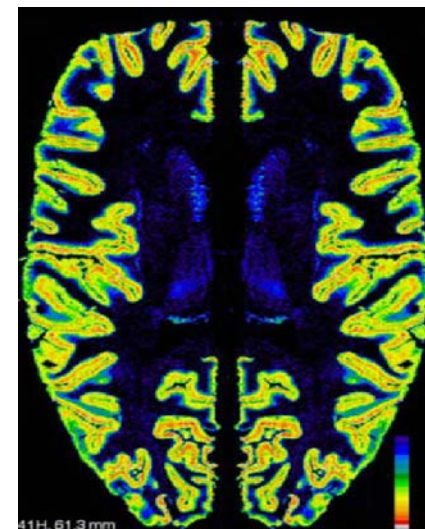
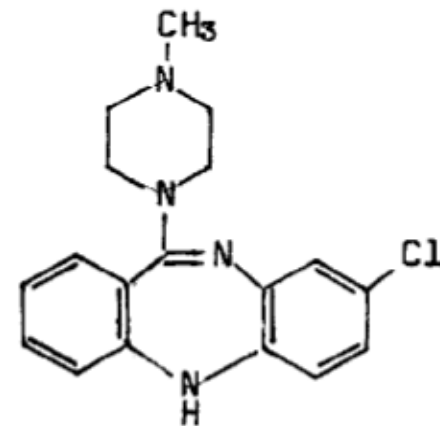
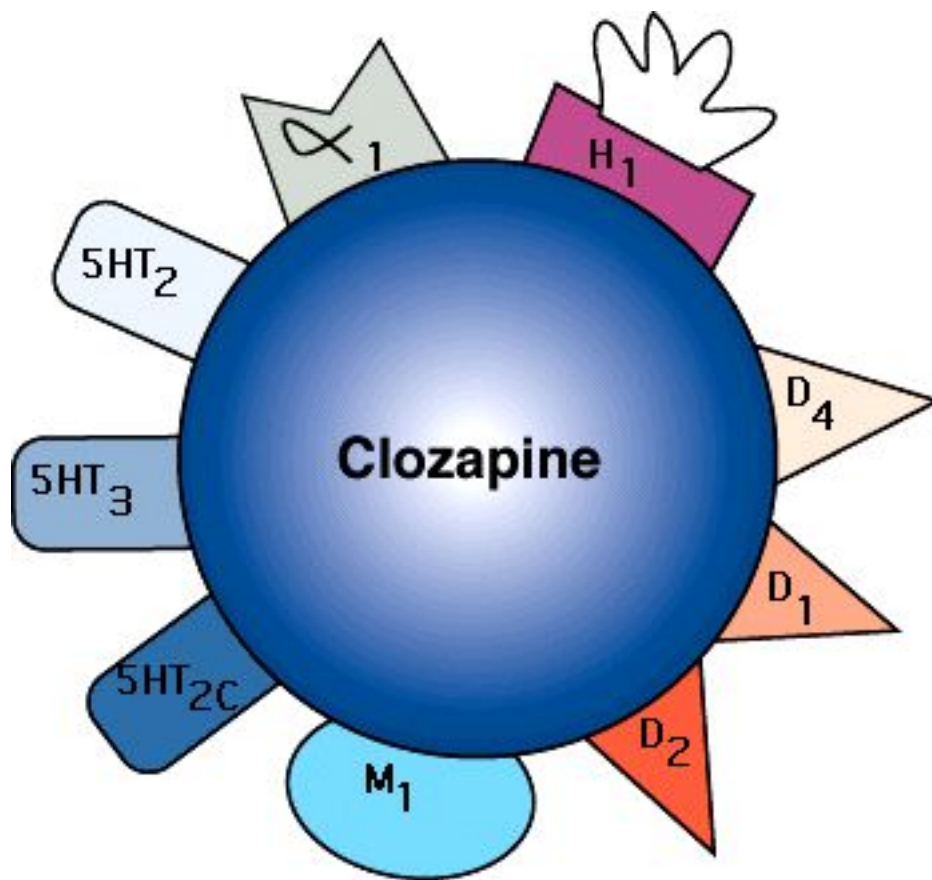
The inverse relationship between level of dopamine and behaviour (rat models)



D₂ affinity predicts antipsychotic efficacy and extrapyramidal side effects (EPS)

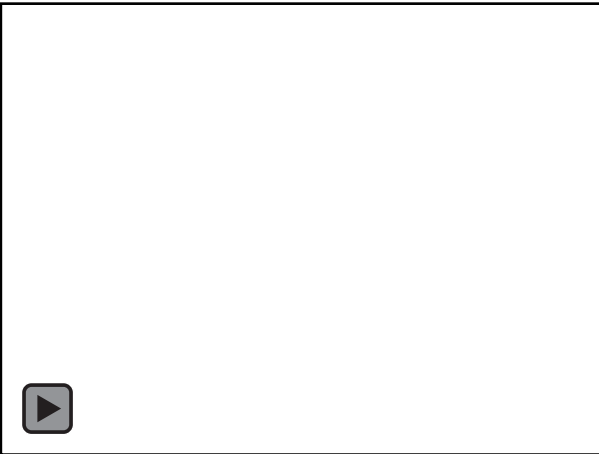


Until this molecule arrived

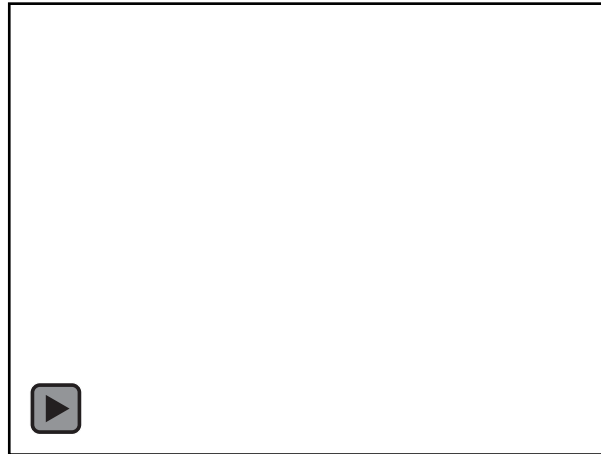


Effect of DRD2 blockade on animal models

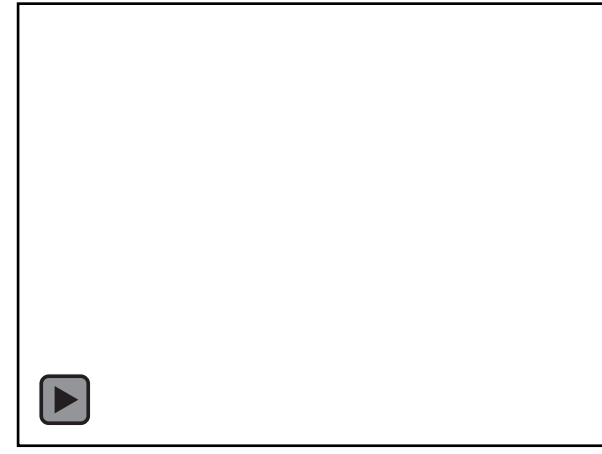
The Bar Test



Vehicle



Haloperidol (0.5 mg/kg)



Clozapine (20 mg/kg)

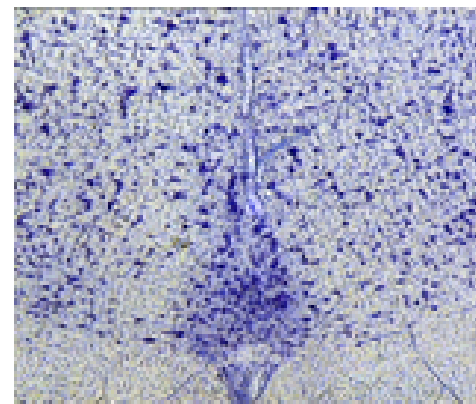
The ideal Second Generation Antipsychotic (SGA)

- Absence of TD
- No PRL elevation
- Active on L-DOPA positive symptoms without inducing EPS
- Active in most of SZ resistant patients
- Improves primary or secondary negative symptoms
- Improves working and semantic memory
- Holds its effect in the long term (*i.e.* > 52 weeks)
- Shows superior compliance and adherence
- Decreases the hospitalization rate

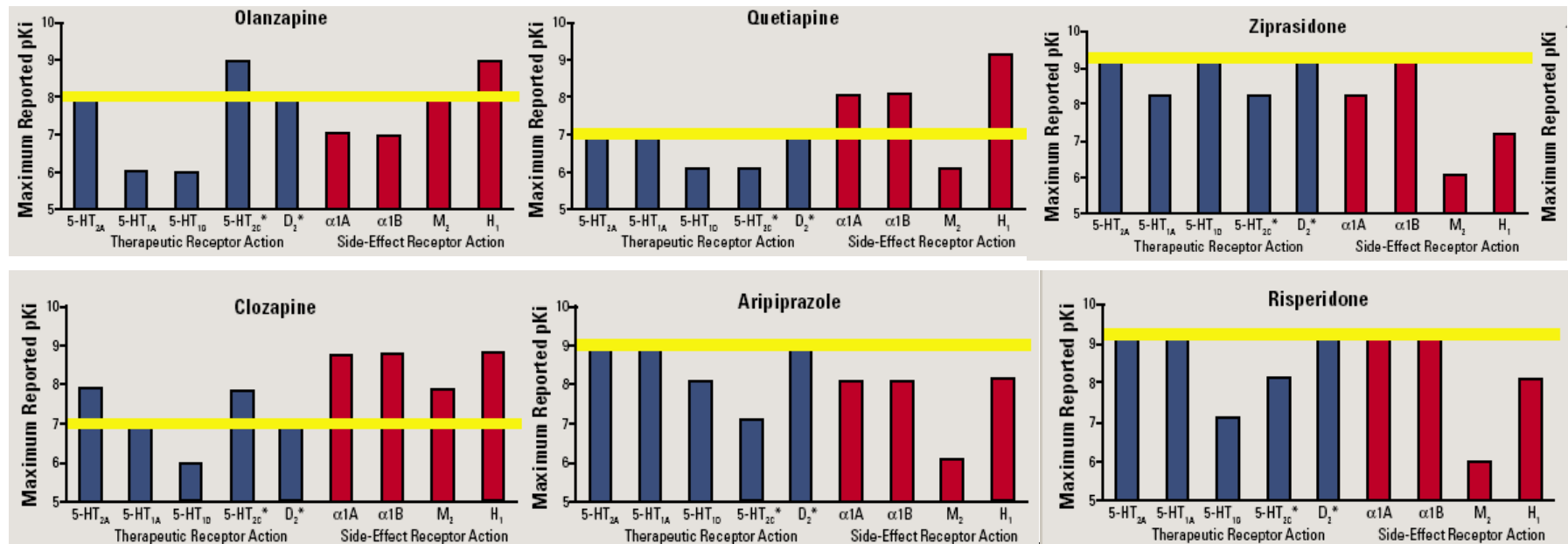


Strategical development of a new SGA

- Try to block more selectively the dopamine receptors
- Try to block less the dopamine receptors
- Try to partially agonise the dopamine receptors
- Try block receptors other than those for dopamine
- Try to block receptors with a differential brain regional distribution (*i.e.* PFC)
- Explore other dosages and/or change the PK (delivery techniques)



Result: Binding Dissimilarities (all Antagonism)

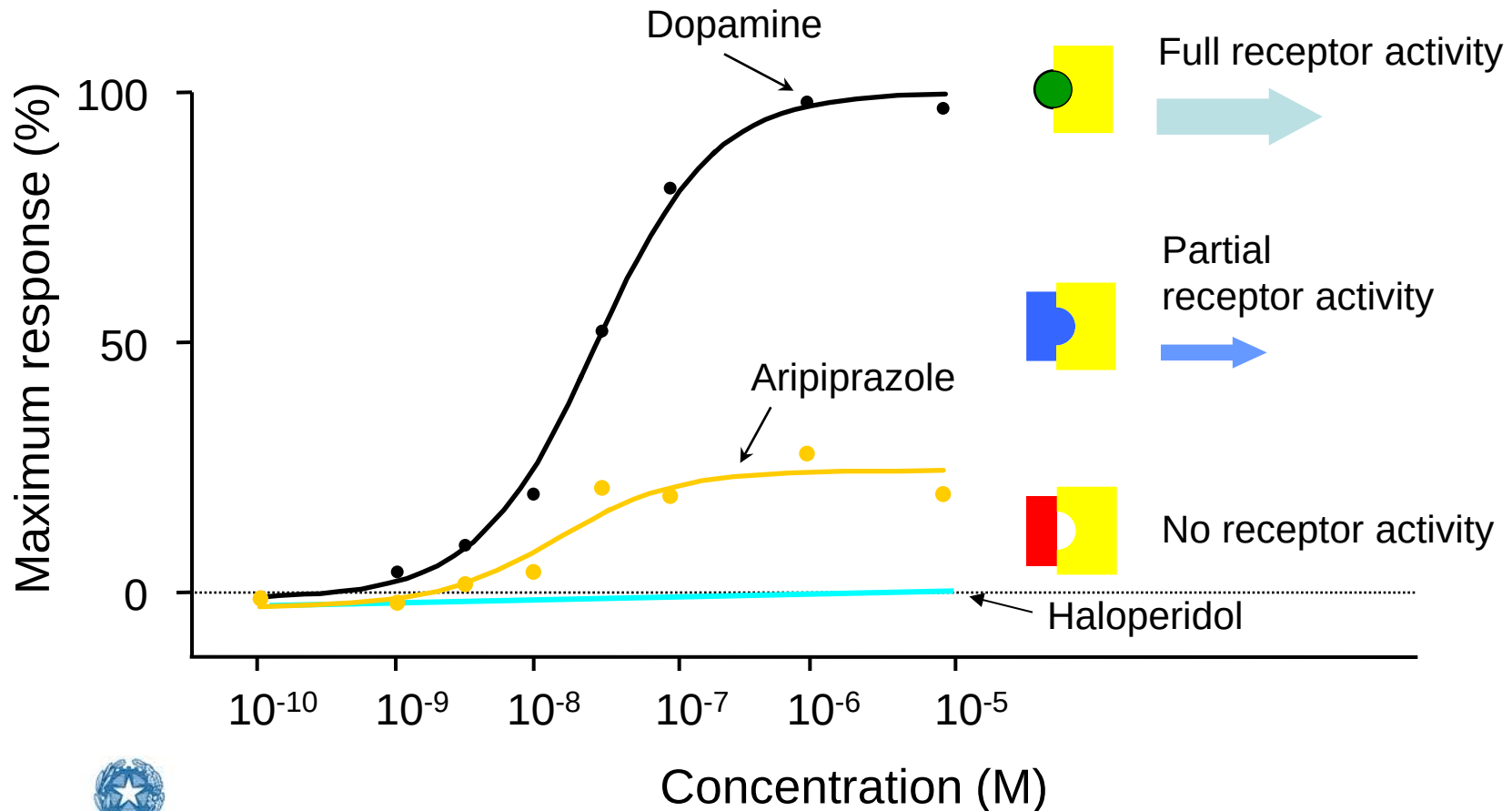


yellow line indicates D₂ affinity level for each drug

- Second generation antipsychotics (SGAs) have a unique set of binding affinities for receptors
- Receptors may induce therapeutic effects or side-effects
 - e.g. 5-HT_{2C} and D₂ receptors may induce both therapeutic effects and side-effects

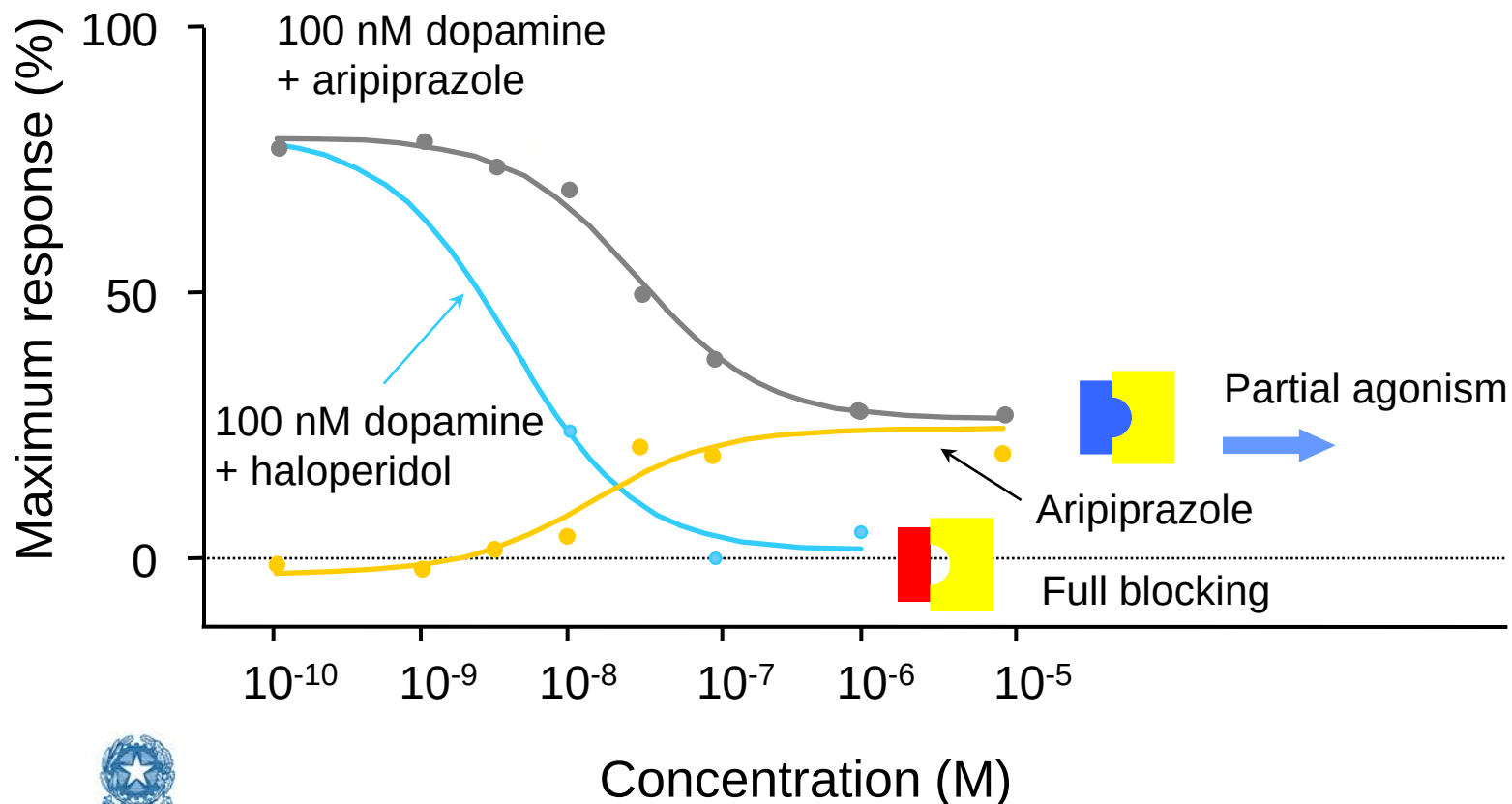
Agonist and antagonist effects

(Cloned Human D2 Receptors)



Competing with dopamine

(Cloned Human D2 Receptors)

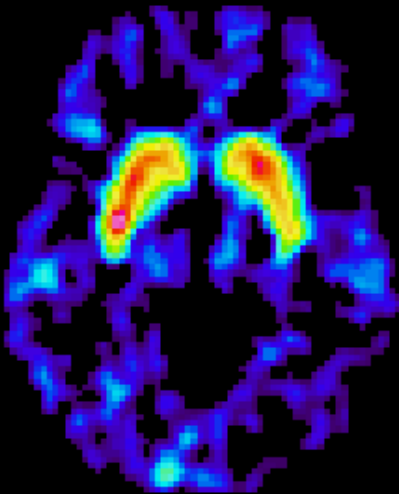


So Haloperidol blocks D_2but causes EPS

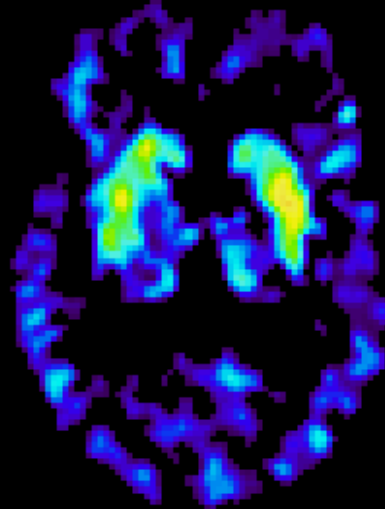
1 mg

2.0 mg

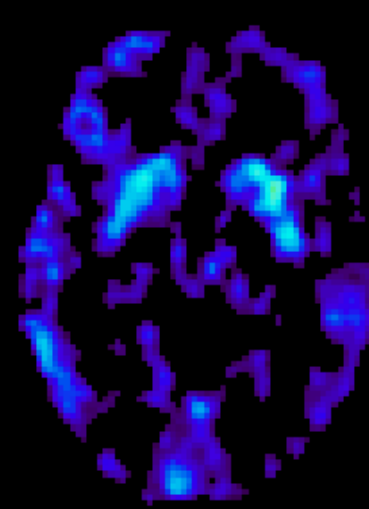
5.0 mg



~39% D_2 occupied
Little Efficacy
Minor EPS

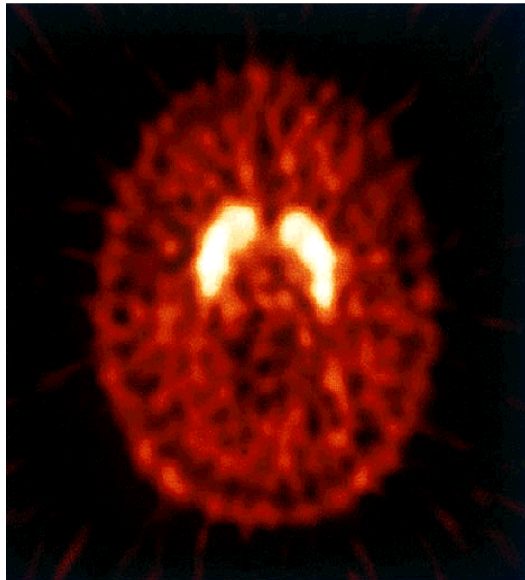


~74% D_2 occupied
Efficacy
Mild EPS

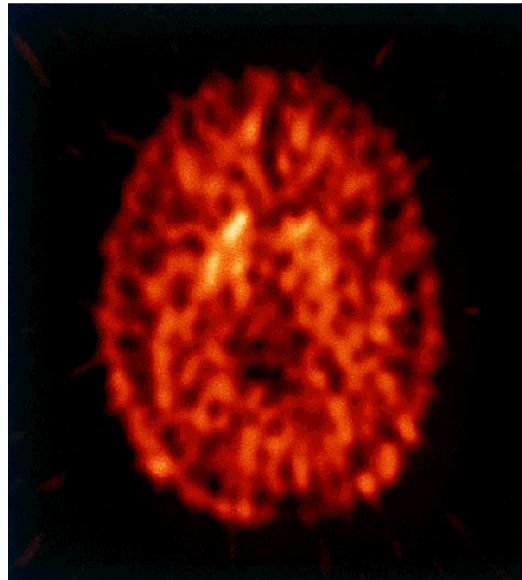


~86% D_2 occupied
Efficacy
Severe EPS

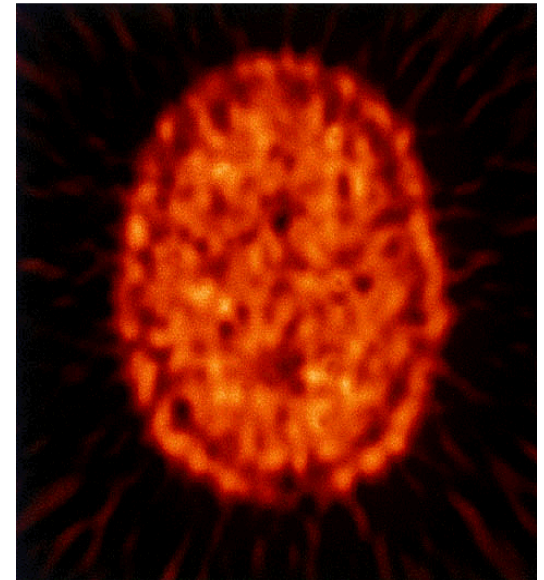
While D₂ partial agonism binding = no EPS



Before aripiprazole



Aripiprazole
2 mg/day
>65% D₂ occupancy
NO EPS



Aripiprazole
30 mg/day
>90% occupancy
NO EPS

Haloperidol dosage

- Moderate Symptomatology: 1.5-6.0 mg/die
- Severe Symptomatology: 9.0-15.0 mg/die
- In the elderly initial daily dosage ranging from 0.5 to 1.5 mg (0.25 to 0.5 mg, 2 or 3 times a day) should be employed. Upward adjustment of these doses should be made gradually; maximum and maintenance doses should be individualized
- Patients who remains severely disturbed or inadequately controlled may required dosage adjustment. Daily dosage up to 100 mg may be necessary in order to achieve optimal response. Infrequently, Haloperidol has been used in doses above 150 mg/die for severely resistant patients.



How about the SGA doses in real life!

- Risperidone (original dosing of 16 mg reduced to 2-4 mg)
- Olanzapine (original dosing of 10 mg increased to >30 mg)
- Quetiapine (original dosing of 75-300 mg increased to > 800 mg)
- Ziprasidone (average dose still often < 80 mg; > 50% of use is below 120 mg; while dose needs to be 120/160 mg for optimal efficacy)
- Aripiprazole (therapeutical range 10-30 mg; may consider 5 mg as starting dose in co-administration with potent inhibitors of CYP3A4 & CYP2D6; in slow cross-titration with other antipsychotics and in sensitive population)



Dosing and Efficacy in positive symptoms

- All first-line agents, by definition, should be effective in treating positive symptoms
- Although some patients respond to or tolerate one agent better than another, no agent has never proven superior to another in treating positive symptoms
- Dosing remains a critical issue in optimizing each agent but it should be studied early in the course of development taking into account the pathophysiology and the pharmacology.



500 years later still: "*Sola dosis facit venenum*"

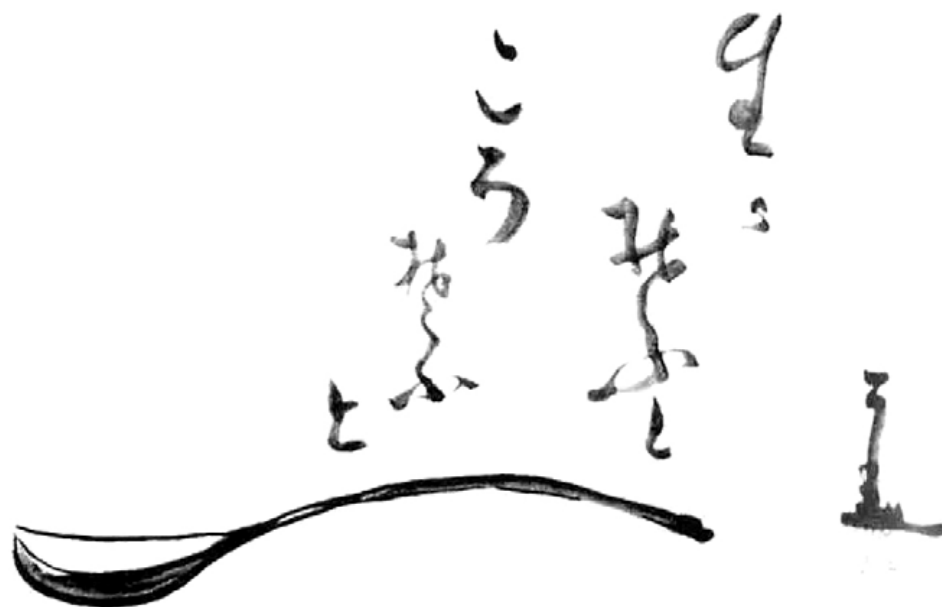


Theophrastus Bombastus von Hohenheim
Swiss physician and alchemist
(c. 1493-1541)



Agenzia Italiana del Farmaco

AIFA



Whether for life, whether for death –
it depends on the right spoon-measure.

Sengai (1750-1838), Japanese Zen
monk and calligrapher.
Idemitsu Museum, Tokyo.