Dipartimento di Scienze del Farmaco e della Salute
Università di Catania
IRCSS Oasi Troina, Italy
INSERM, Neurocentre Magendie,
Universitè de Bordeaux

Terapia con i LAI di seconda generazione nella prevenzione delle ricadute psicotiche: aspetti neurobiologici e farmacologici

Filippo Caraci

Catania 4-12-20

Neuropsychiatric Disease and Treatment

Dovepress

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ORIGINAL RESEARCH

Targets, attitudes, and goals of psychiatrists treating patients with schizophrenia: key outcome drivers, role of quality of life, and place of long-acting antipsychotics

Andrea de Bartolomeis[1]
Andrea Fagiolini[2]
Marco Vaggi[3]
Claudio Vampini[4]

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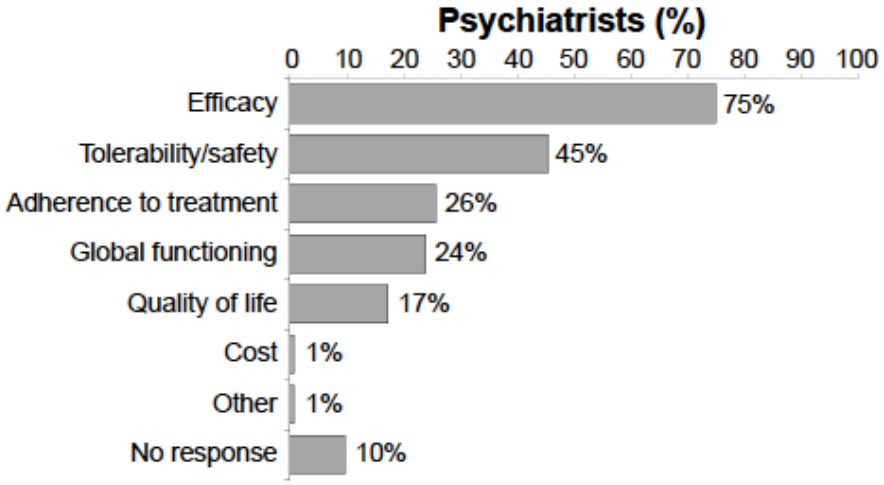

Figure 2 Suggested parameters to be considered when evaluating the success of an antipsychotic therapy in patients with schizophrenia.
Notes: Responses to the question "Which parameters do you consider when evaluating the success of antipsychotic therapy in patients suffering from schizophrenia?" Percentage of the total number of times the specific domain has been reported in answering this open-ended unsolicited question by the 709 respondents.

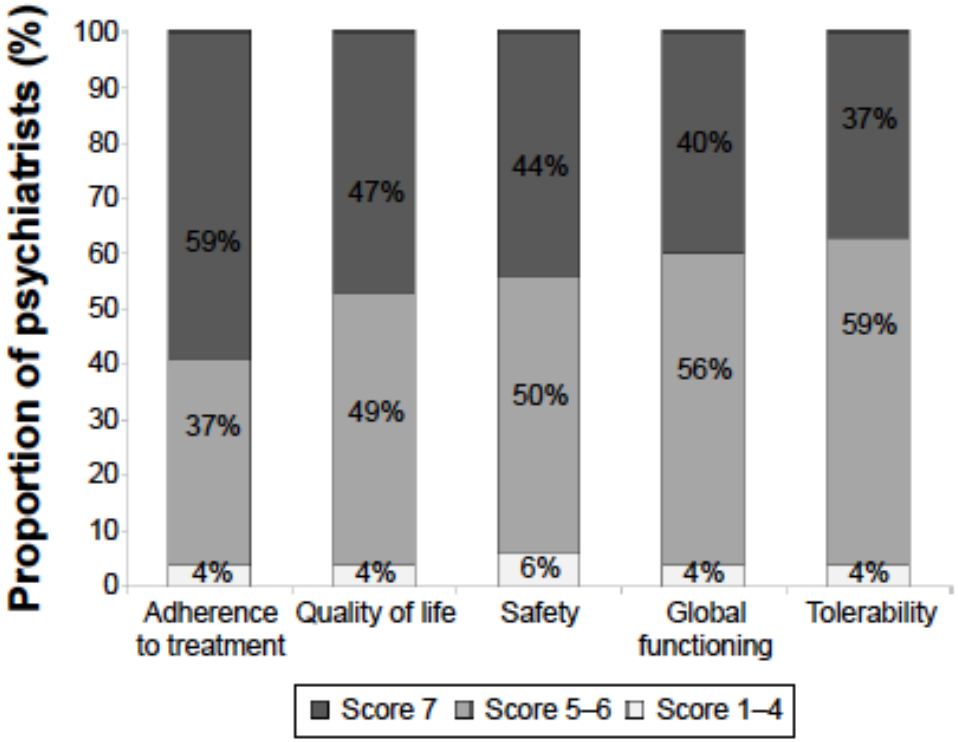

Figure 3 Domains of importance of preset responses when assessing treatment success rated from 1 (not important) to 7 (of utmost importance) by psychiatrists treating patients suffering from schizophrenia.

Notes: Responses to the question "How important do you think are the following items, except for the therapeutic efficacy, when assessing the success of an antipsychotic therapy in a patient with schizophrenia?" Percentage of responses mentioning the specific domain from a cohort of 709 respondents.

Quali altri fattori considerare nella scelta dei LAI?

Quanto possono contare gli aspetti neurobiologici ed una valutazione del decorso longitudinale della schizofrenia nella scelta del LAI ?

Altering the course of schizophrenia: progress and perspectives

NATURE REVIEWS | DRUG DISCOVERY

Mark J. Millan[1], Annie Andrieux[2], George Bartzokis[3], Kristin Cadenhead[4], Paola Dazzan[5], Paolo Fusar-Poli[5], Jürgen Gallinat[6], Jay Giedd[7], Dennis R. Grayson[8], Markus Heinrichs[9], René Kahn[10], Marie-Odile Krebs[11], Marion Leboyer[12], David Lewis[13], Oscar Marin[14], Philippe Marin[15], Andreas Meyer-Lindenberg[16], Patrick McGorry[17], Philip McGuire[18], Michael J. Owen[19], Paul Patterson[20], Akira Sawa[21], Michael Spedding[22], Peter Uhlhaas[20], Flora Vaccarino[23], Claes Wahlestedt[24] and Daniel Weinberger[25]

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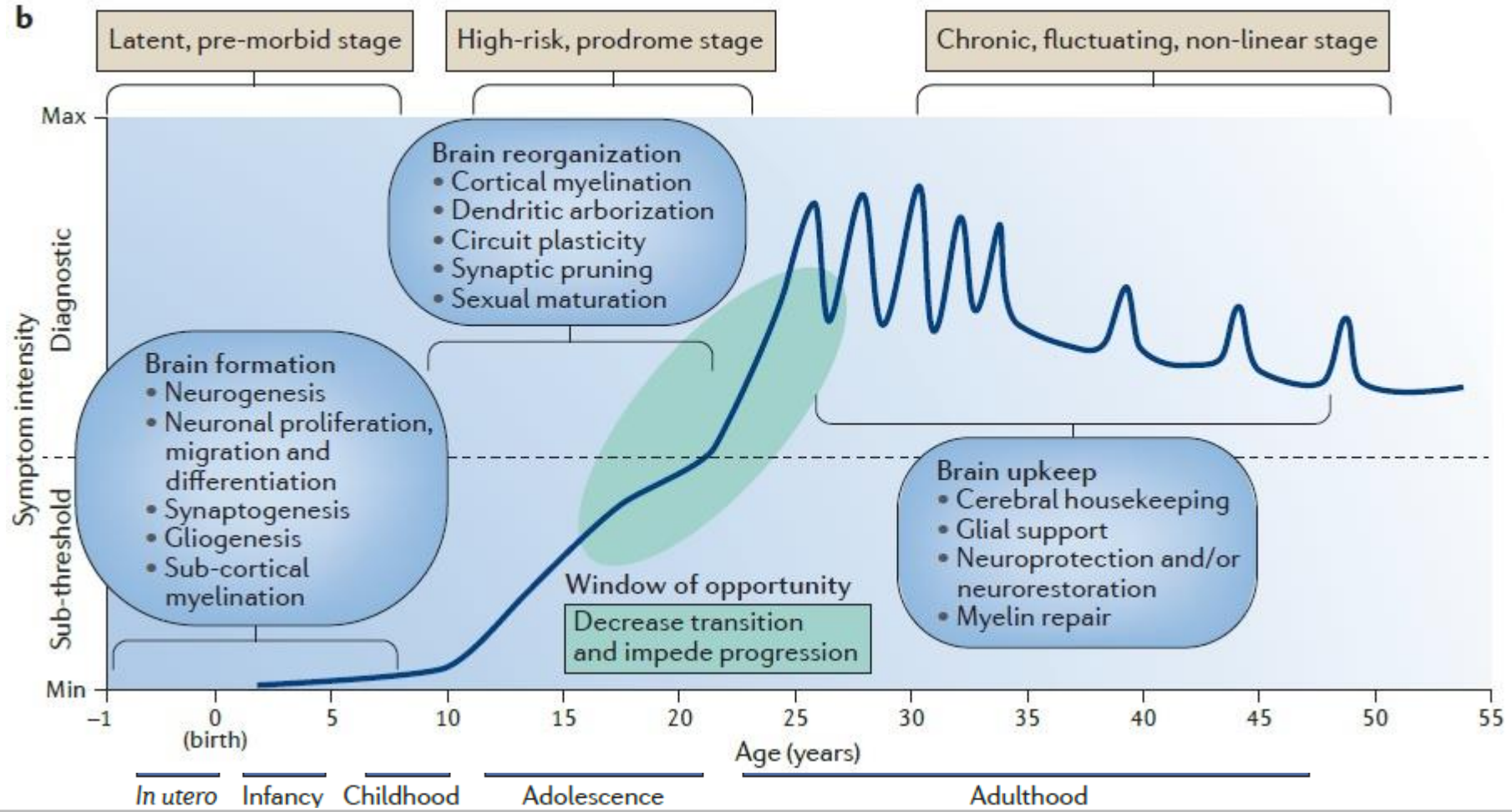
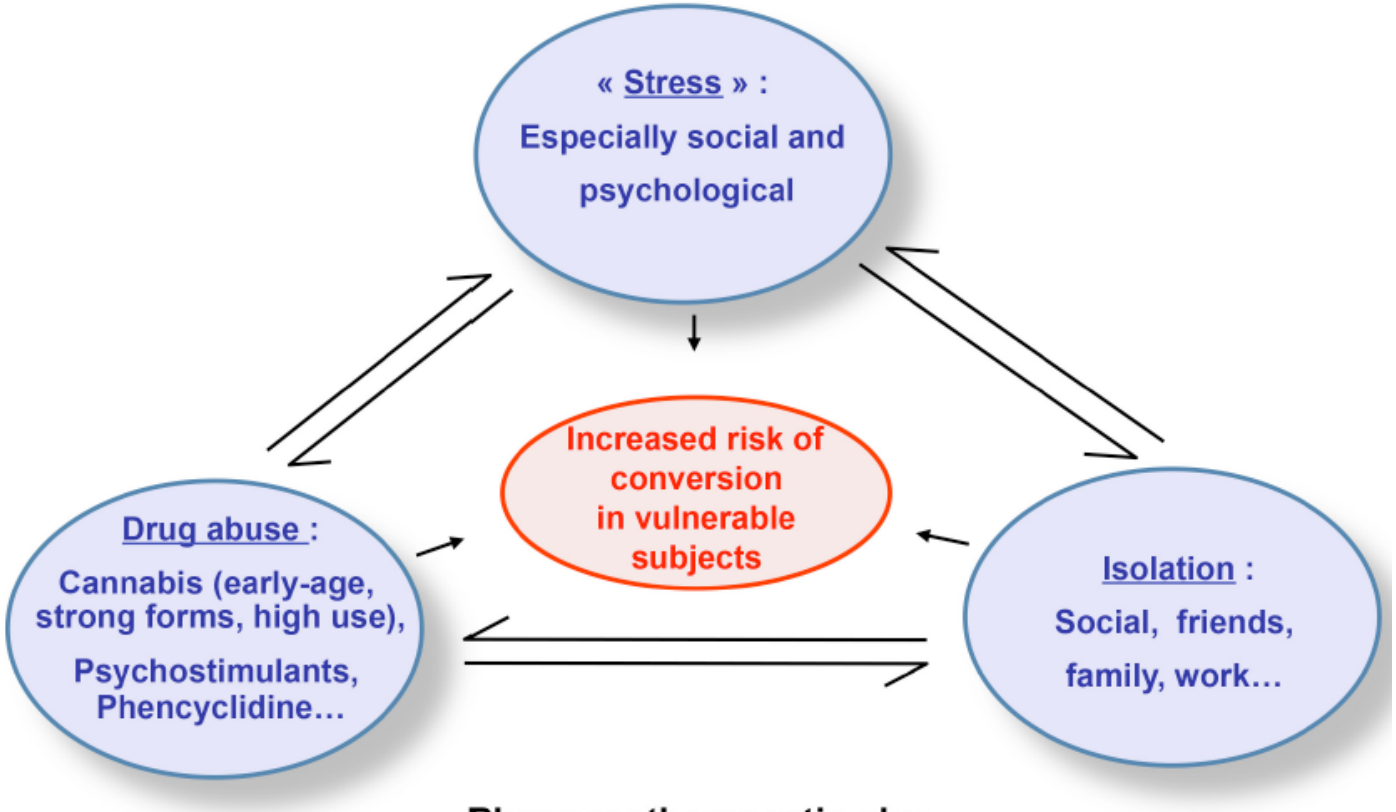
doi:10.1038/nrd.2016.28
Published online 4 Mar 2016



A 'triad' of interacting risk factors favouring transition to schizophrenia in young vulnerable individuals



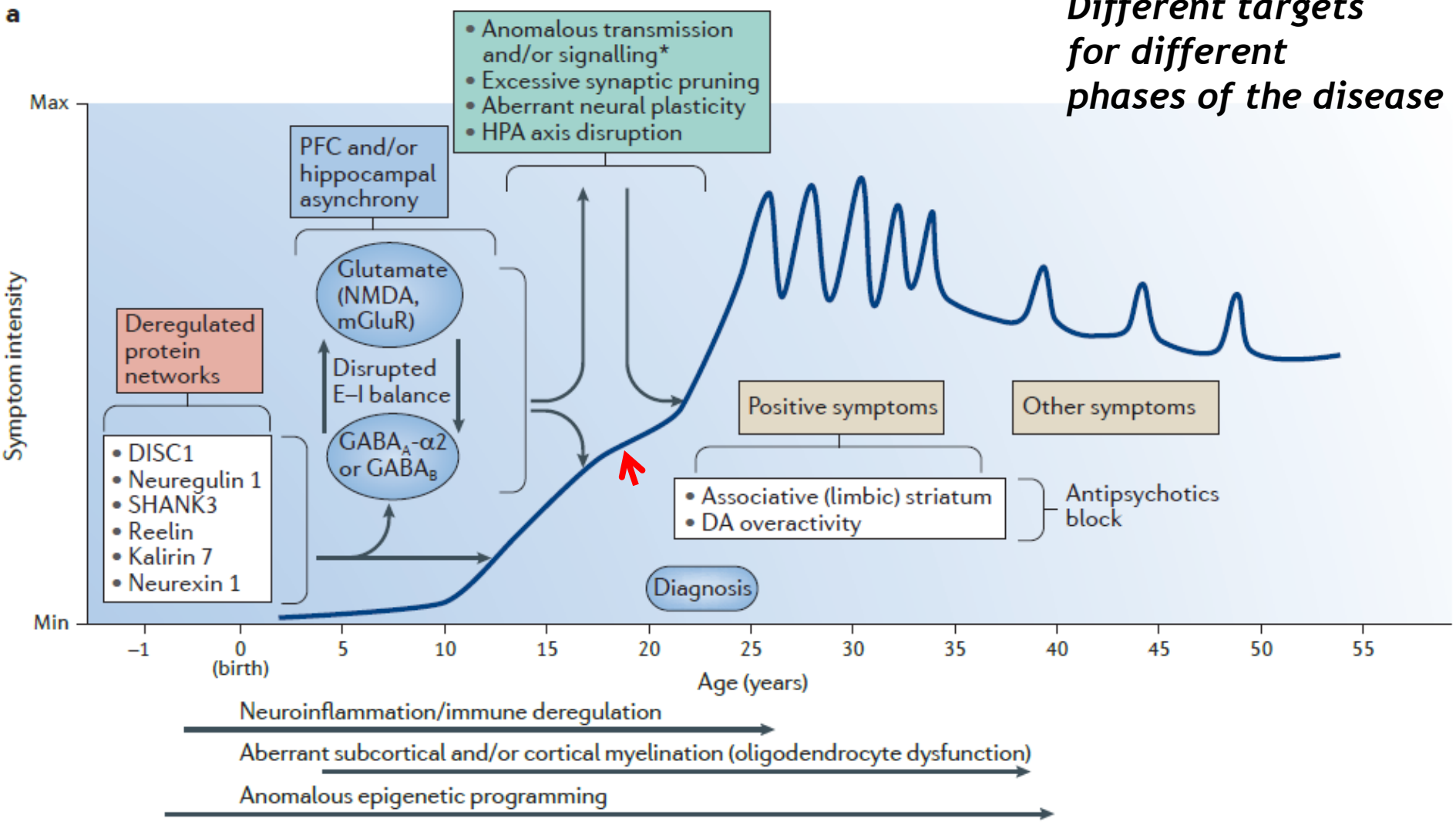
Pharmacotherapeutic plus

psychosocial and cognitive-behavioural strategies

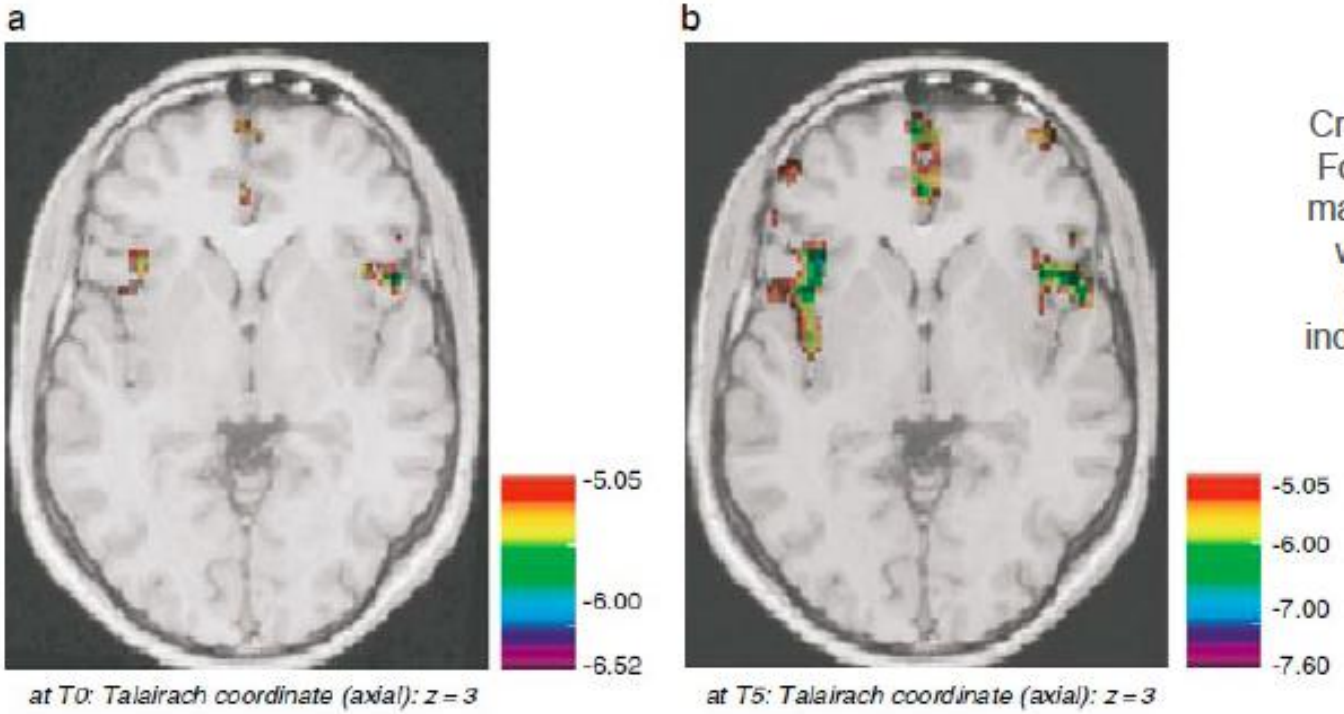
for alleviation

Core pathophysiological mechanisms in schizophrenia: potential targets for course-altering intervention

Different targets for different phases of the disease



Focal Gray Matter Changes in Schizophrenia : A 5-Year Follow-Up Study I



Cross-sectional analysis: Focal decreases in gray matter density in patients with schizophrenia as compared to healthy individuals at baseline (a) and follow-up (b).

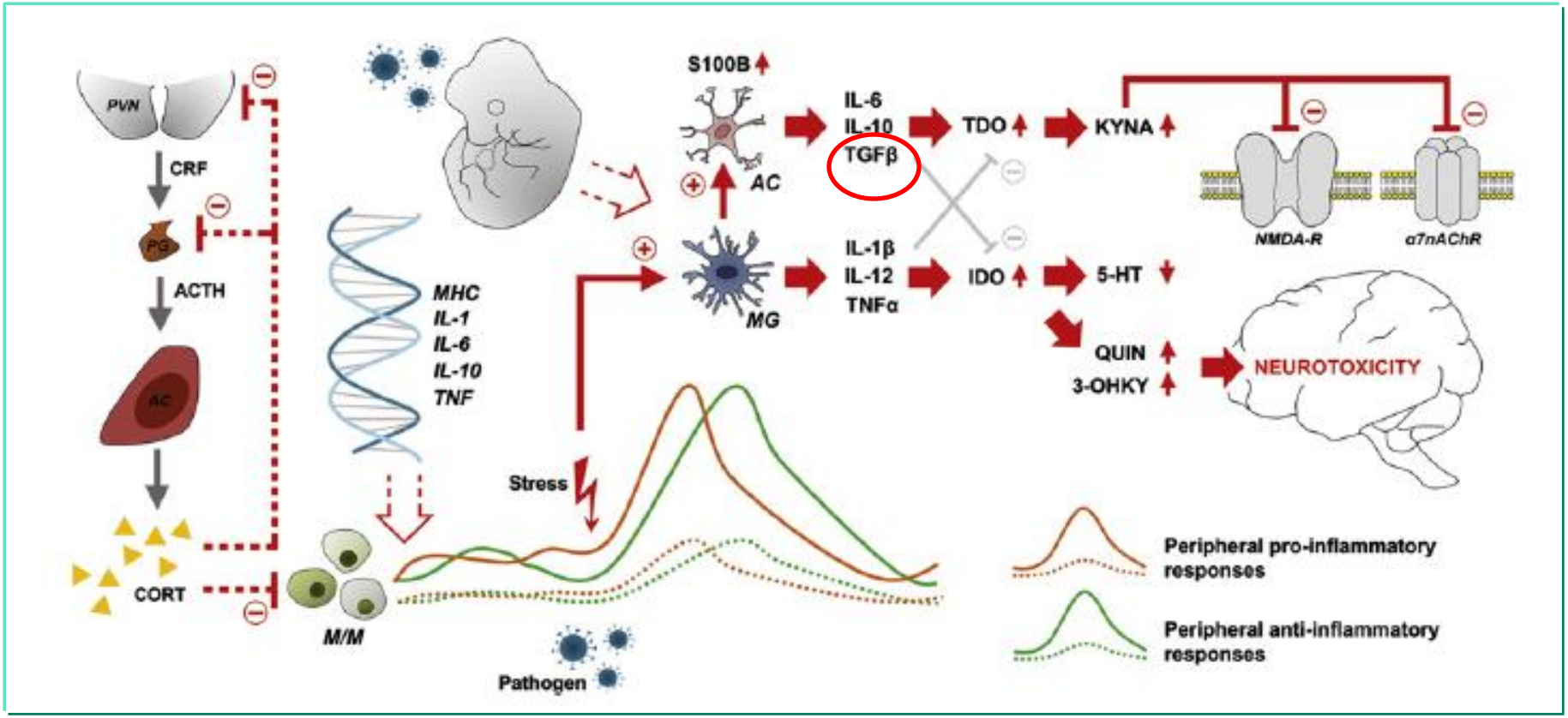
- Over the 5-year interval, excessive decreases in gray matter density were found in patients as compared to healthy individuals
- Progression in left frontal density loss appeared to be related to an increased number of psychotic episodes

van Haren et al. Neuropsychopharmacology 2007;32:2057–2066

Pharmacology & Therapeutics 132 (2011) 96–110

Inflammatory processes in schizophrenia: A promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond

Urs Meyer [a,*], Markus J. Schwarz [b], Norbert Müller [b]

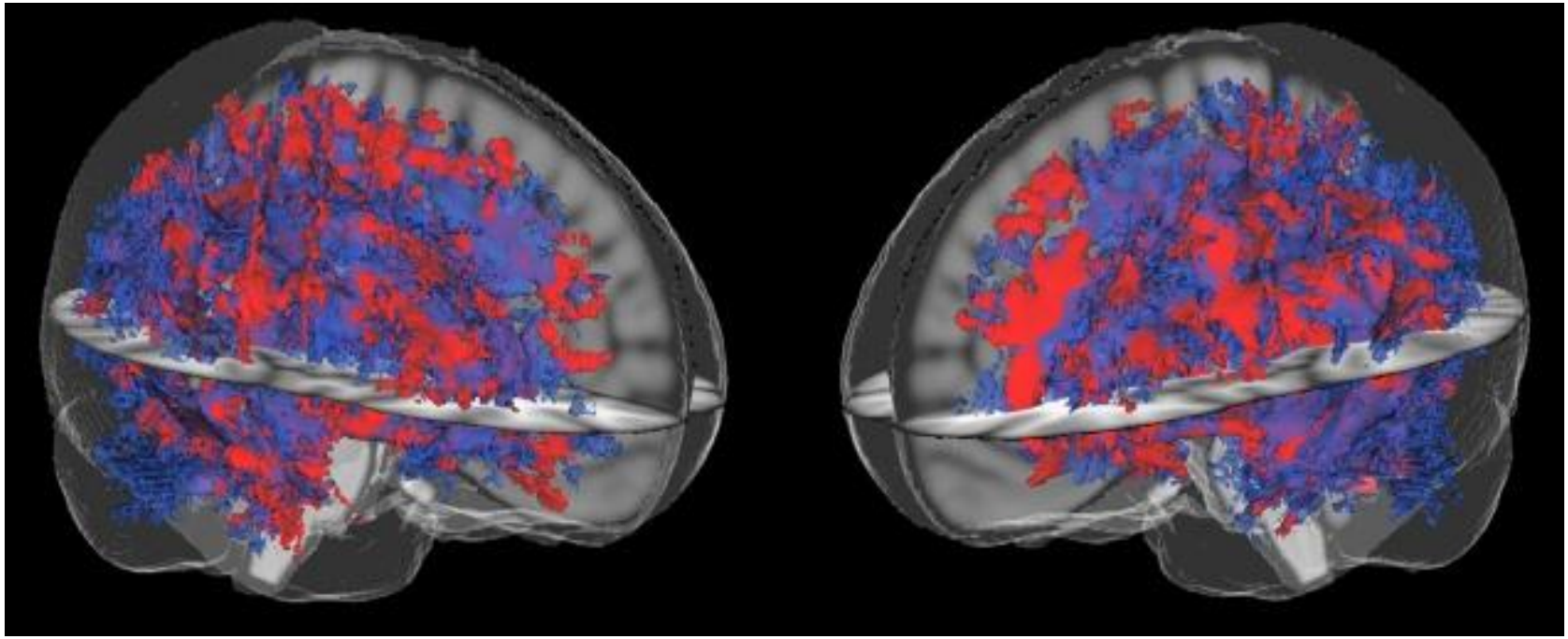


Neuroinflammation leads to axonal degeneration in an early phase of schizophrenia's pathogenesis

Excessive Extracellular Volume Reveals a Neurodegenerative Pattern in Schizophrenia Onset

The Journal of Neuroscience, November 28, 2012 • 32(48):17365–17372 •

Ofer Pasternak,[1] Carl-Fredrik Westin,[2] Sylvain Bouix,[1] Larry J. Seidman,[4,6] Jill M. Goldstein,[1,3,4] Tsung-Ung W. Woo,[5] Tracey L. Petryshen,[6,7,8] Raquelle I. Mesholam-Gately,[4] Robert W. McCarley,[4,9] Ron Kikinis,[2] Martha E. Shenton,[1,9] and Marek Kubicki[1]

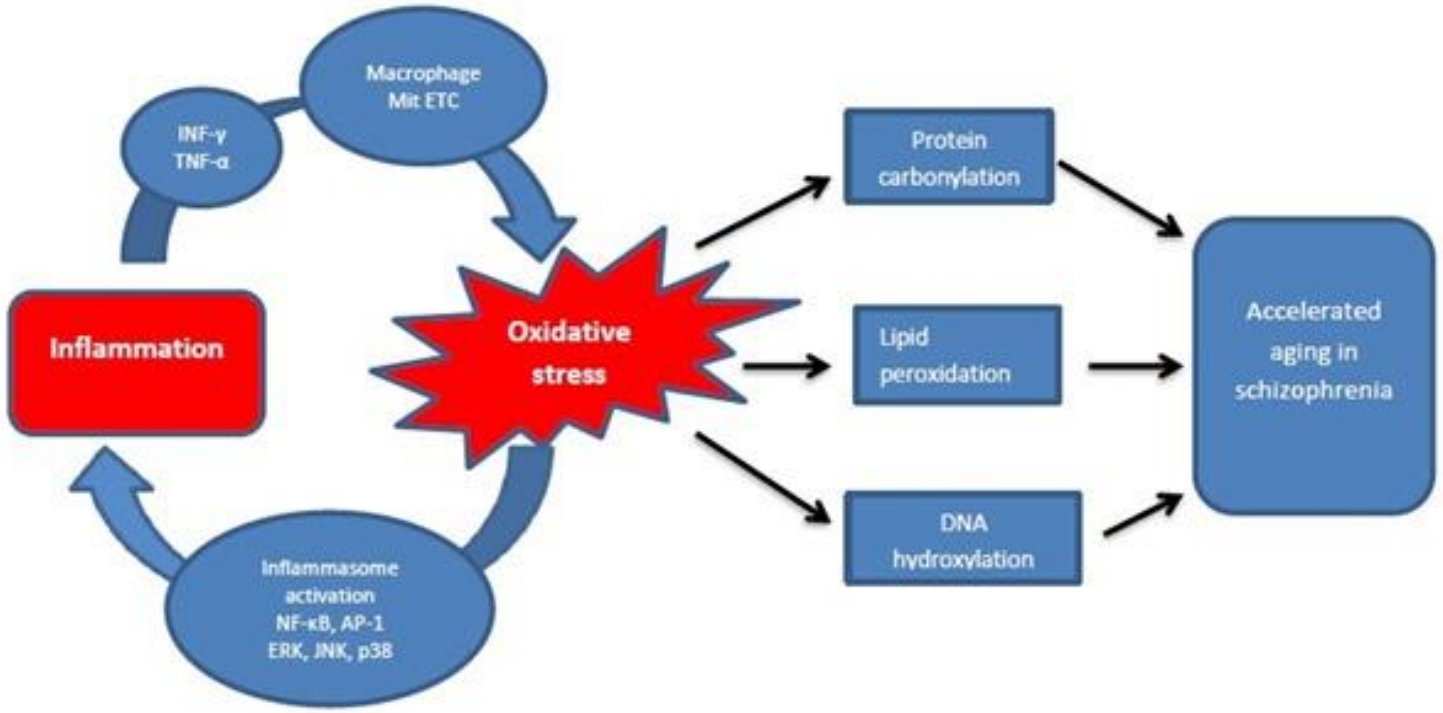


Excessive extracellular volume is a surrogate biomarker for neuroinflammation and can be separated out by MRI (DTI) to reveal axonal degeneration in prefrontal cortex

Inflammation and oxidative stress in schizophrenia

- Inflammation and oxidative stress may reciprocally induce each other via a positive feedback loop

- The feedback loop involves the induction of increased production of ROS by proinflammatory cytokines (INF-γ and TNF-α) in macrophages/microglia



Olaoluwa O. Okusaga (2013) Aging Dis **5**:256-62. doi: 10.14336/AD.2014.0500256.

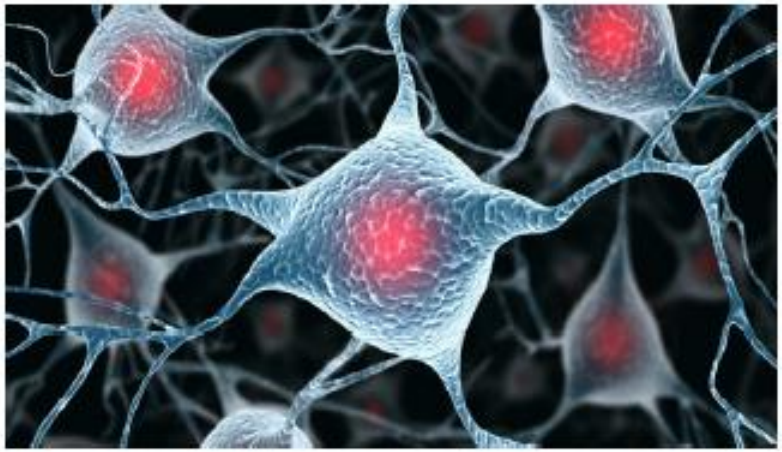
Consequences of Relapse

Psychosocial[1]

- Risk of self-harm and harm to others
- Relapse may:
  - Jeopardize interpersonal relationships
  - Interrupt employment or educational status
  - Diminish personal autonomy
  - Contribute to stigma

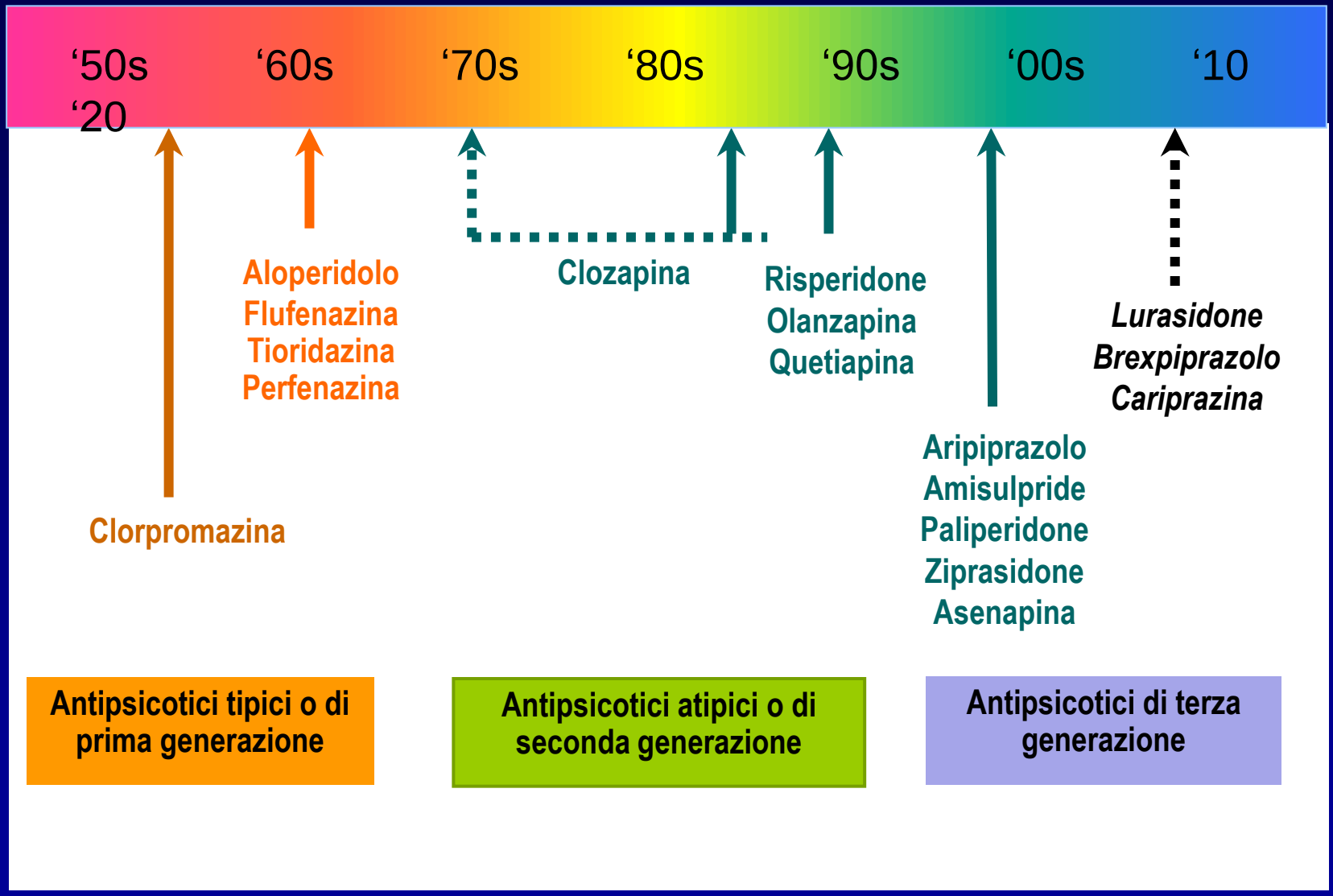
Biological[2]

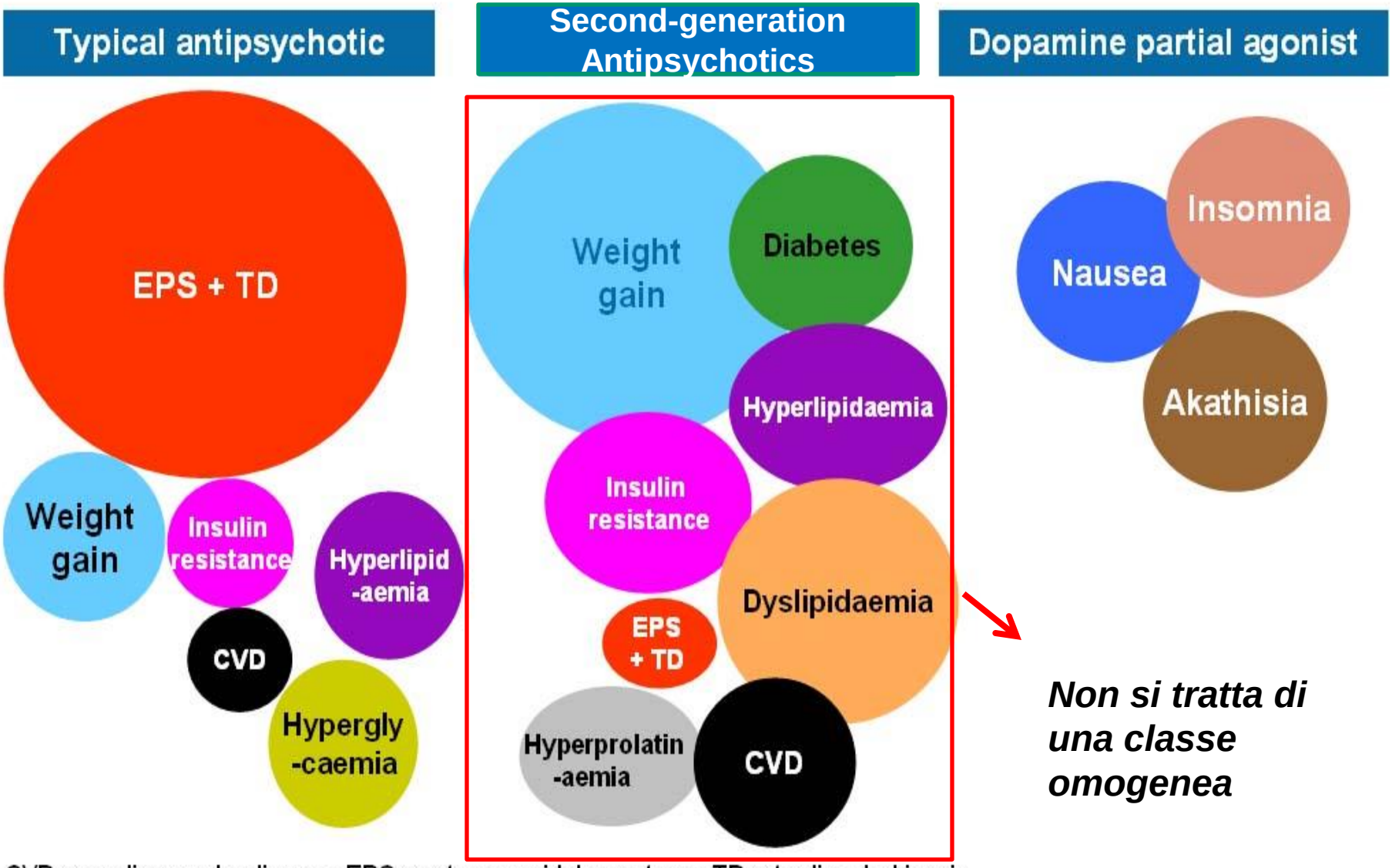
- Is psychosis neurotoxic?



1. Kane. J Clin Psychiatry 2007; 68(suppl 14):27–30
2. Wyatt. Schizophr Bull 1991;17:325–351

Sviluppo cronologico dei farmaci antipsicotici





Non si tratta di una classe omogenea

CVD = cardiovascular disease; EPS = extrapyramidal symptoms; TD = tardive dyskinesia

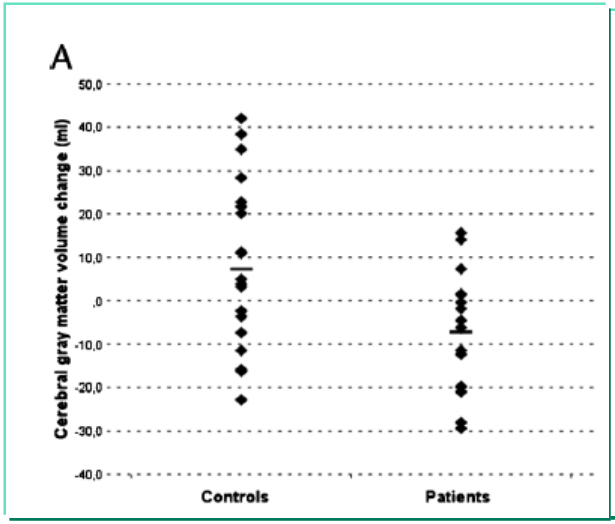
Lieberman J *et al*. *Pharmacol Rev* 2008;60:358–403; Young A *et al*. *Br J Psychiatry* 2009;194:40–8; Daniel D *et al*. *J Psychiatr Pract* 2007;13:170–7

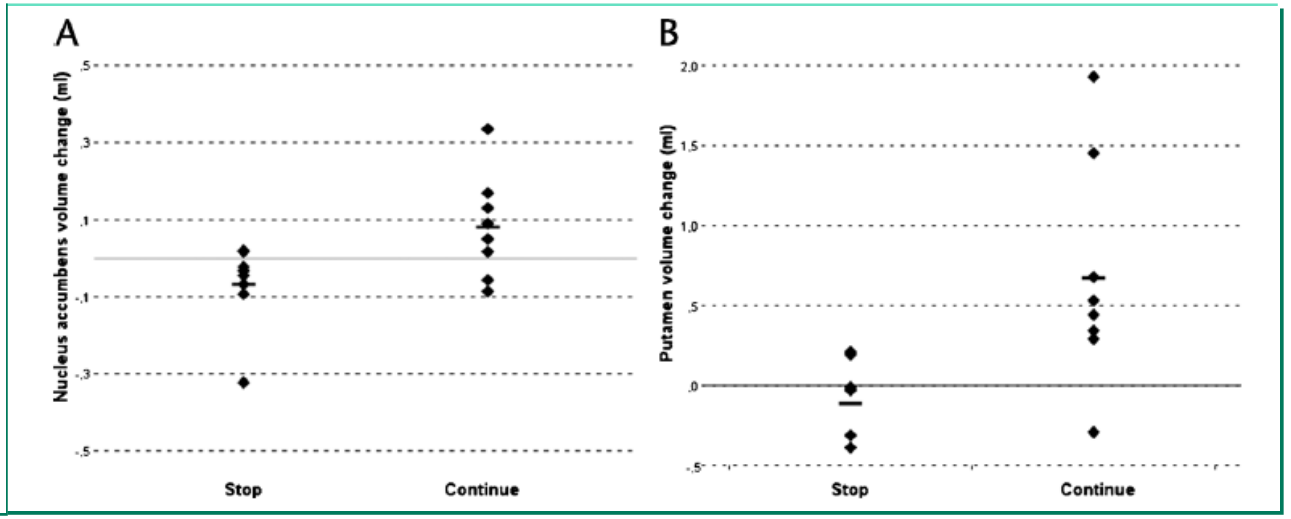
Brain Volume Changes After Withdrawal of Atypical Antipsychotics in Patients With First-Episode Schizophrenia

Geartsje Boonstra, MD, MSc,† Neeltje E.M. van Haren, PhD,* Hugo G. Schnack, PhD,* Wiepke Cahn, MD, PhD,* Huibert Burger, MD, PhD,†‡ Maria Boersma, MSc,* Bart de Kroon, MSc,* Diederick E. Grobbee, MD, PhD,† Hilleke E. Hulshoff Pol, PhD,* and René S. Kahn, MD, PhD**

(*J Clin Psychopharmacol* 2011;31: 146–153)

Gray matter | **Nucleus accumbens** | **Putamen**





This study examined the effect of discontinuation of atypicalantipsychotic medication on brain volume change during a 1-year interval in remitted and stable patients with first-episode Schizophrenia

Decreases in the nucleus accumbens and putamen volumes during the interval in patients who discontinued antipsychotic medication

Secondary prevention in schizophrenia ?

Archival Report

Biological Psychiatry

The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-analysis and Meta-regression of Longitudinal Magnetic Resonance Imaging Studies

Antonio Vita, Luca De Peri, Giacomo Deste, Stefano Barlati, and Emilio Sacchetti

ABSTRACT

BACKGROUND: Deficits in cortical gray matter (GM) have been found in patients with schizophrenia, with evidence of progression over time. The aim of this study was to determine the role of potential moderators of such changes, in particular of the amount and type of antipsychotic medication intake.

METHODS: Longitudinal magnetic resonance imaging studies comparing changes in the volume of cortical GM over time between patients with schizophrenia and healthy control subjects published between January 1, 1983, and March 31, 2014, were analyzed. Hedges' *g* was calculated for each study and volume changes from baseline to follow-up were analyzed. Meta-regression statistics were applied to investigate the role of potential moderators of the effect sizes.

- Eighteen studies involving **1155 patients with Schizophrenia** (SCH) and **911 healthy control** subjects were included

Vita A. et al. - Biological Psychiatry September 15, 2015; 78:403–412

Biological Psychiatry

The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-analysis and Meta-regression of Longitudinal Magnetic Resonance Imaging Studies

- A significantly high **loss of total cortical GM volume** in patients with SCH was **related to cumulative antipsychotic intake** during the interval between scans
- **More progressive GM loss correlated with higher mean daily** antipsychotic intake in patients treated with at least one **first-generation antipsychotic**
- **Less progressive GM loss correlated with higher mean daily** antipsychotic intake in patients treated only with **second-generation antipsychotics**

Vita A. et al. - Biological Psychiatry September 15, 2015; 78:403–412

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Studies included in quantitative synthesis (meta-analysis) (n = 24)

Schizophrenia Research 208 (2019) 1–7

Neuroprotective effects of the second generation antipsychotics

Alexander T. Chen [a], Henry A. Nasrallah [b,*]

CATIE AND CUTLASS studies did not investigate any differential neuroprotective or neurotoxic effects across the ***FGAs*** and ***SGAs***

Table 1
SGAs included and their proposed mechanisms of neuroprotection.

SGAs represented in included studies	SGA mechanisms of neuroprotection
Aripiprazole	Attenuate brain damage after ischemic stroke
Clozapine	Decrease TNF-α and nitric oxide release in the presence of interferon-γ
Lurasidone	Increase BDNF
Olanzapine	Increase NGF
Paliperidone	Increase oligodendrocyte regeneration and myelin repair
Perospirone	Increase OPC differentiation into mature oligodendrocytes
Quetiapine	Neurogenesis
Risperidone	Prevent cortical grey matter loss
Ziprasidone	Prevent myelin breakdown and oligodendrocyte loss
	Protect against cell death related to NMDA receptor dysfunction
	Protect against glutamate toxicity
	Protect against oxidative stress
	Reverse altered/weakened antioxidant defense
	Reverse dendritic changes

SGAs are associated with multiple neuroprotective properties via 14 different molecular mechanisms,

Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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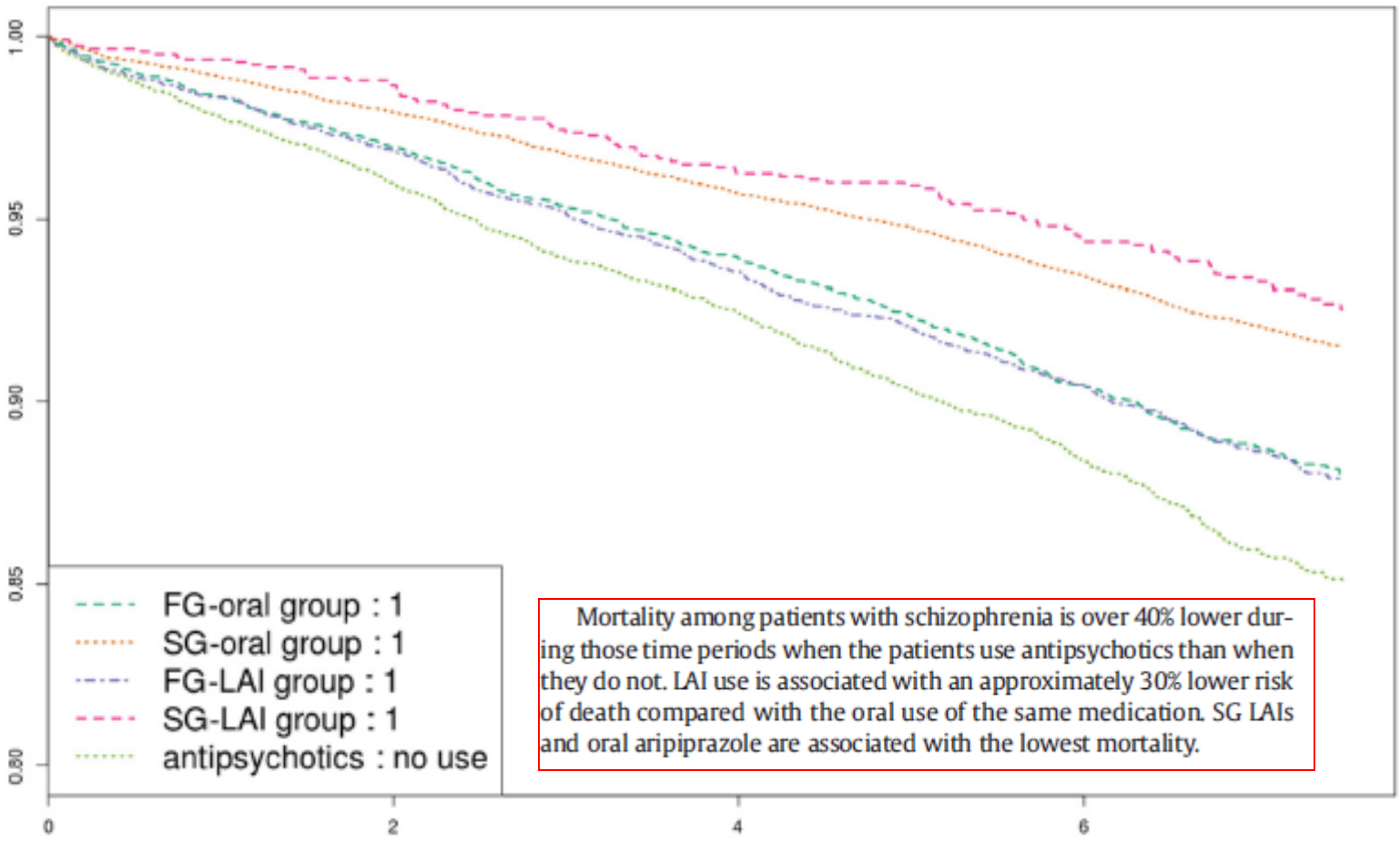


Mortality among patients with schizophrenia is over 40% lower during those time periods when the patients use antipsychotics than when they do not. LAI use is associated with an approximately 30% lower risk of death compared with the oral use of the same medication. SG LAIs and oral aripiprazole are associated with the lowest mortality.

Triple advantages of injectable long acting second generation antipsychotics: Relapse prevention, neuroprotection, and lower mortality

Schizophrenia Research 197 (2018) 69–70

Henry A. Nasrallah

Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine, Saint Louis, MO, USA

It is particularly interesting to note that the cohort of non-first episode patients (followed for 7 years) in this analysis were severely ill, with high rates of drug abuse and suicidal tendency. It could imply that using ***SGA-LAI in first episode schizophrenia (FES) may have a disease-modifying effect on symptoms, functional outcome, and mortality*** in the following reasons:

• High remission rates in FES patients with reduced response to SGA-LAI after an interval of oral therapy (-16%) (Emsley et al. 2008);

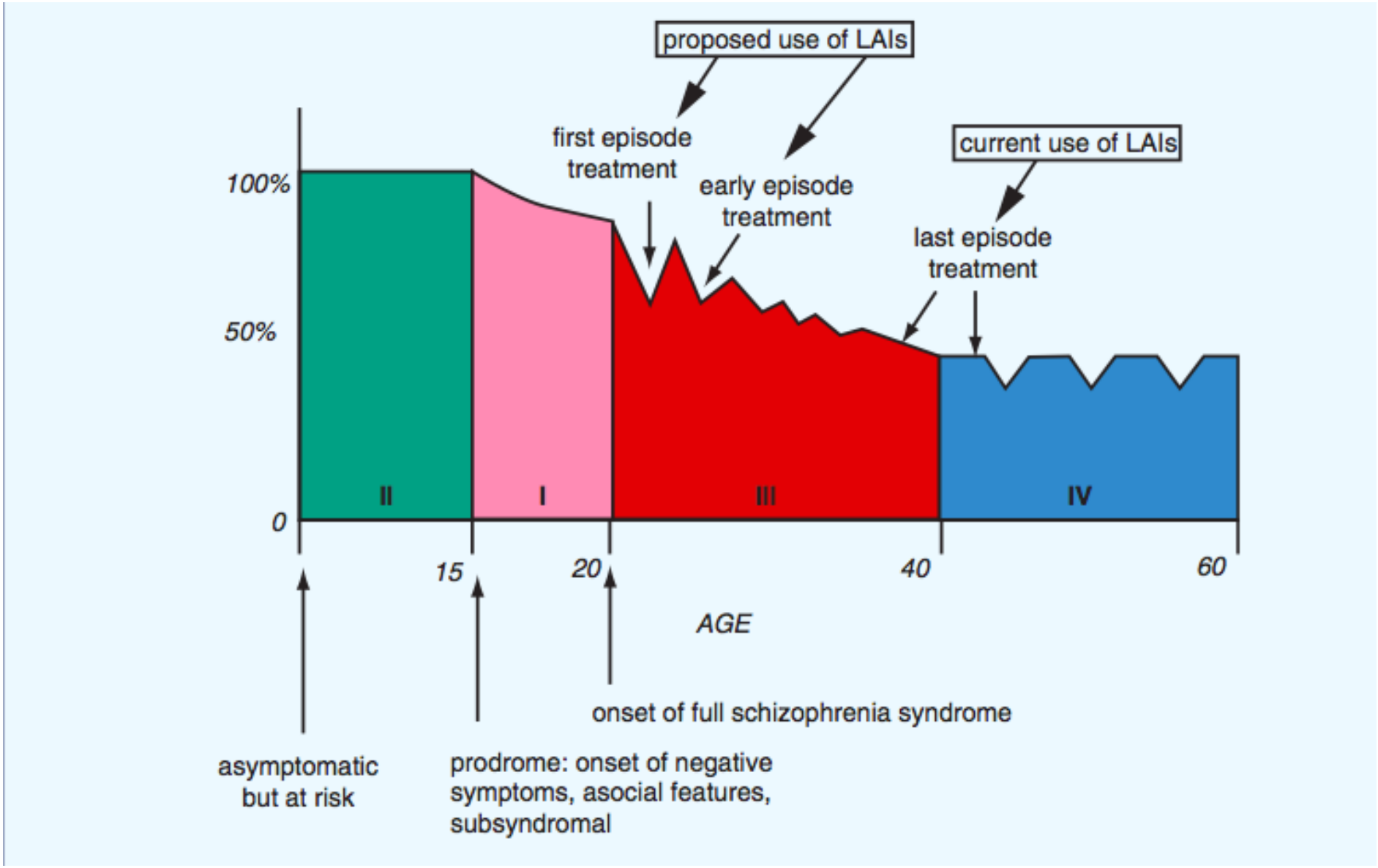
•Brain volume continues to decrease in schizophrenic patients receiving FGA but not SGA (Vita et al., 2015).

•The LAI-SGA paliperidone palmitate has the lowest mortality in this study (with therapeutic doses lower than oral doses), beyond being a neuroprotective SGA (Gasso et al., 2012) and an adherence- ensuring LAI that reduce the risk of neurotoxic psychotic relapse compared to oral antipsychotics

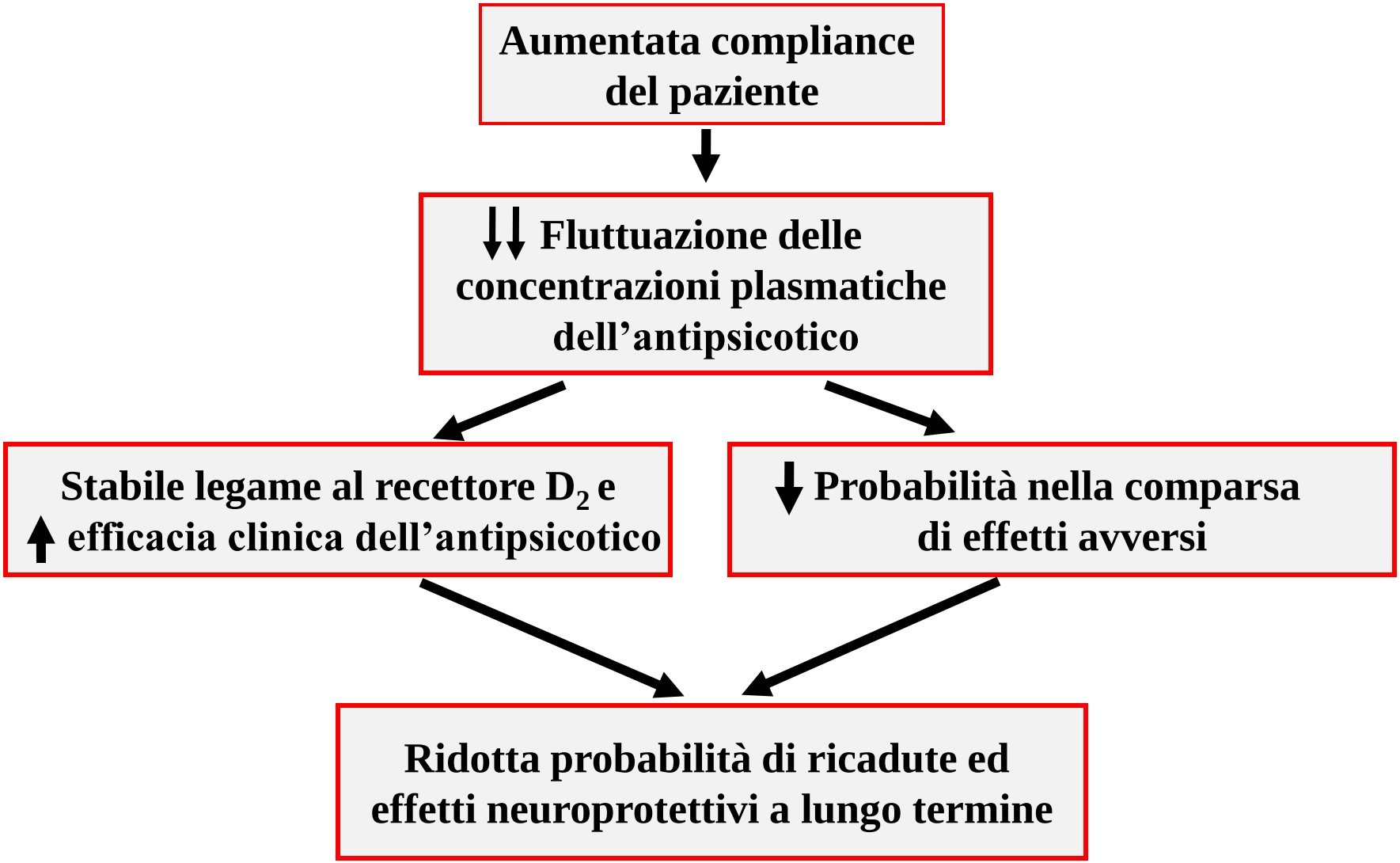
•Future studies with another neuroprotective *SGA-LAI (Aripiprazole) are needed.*

Second generation LAI antipsychotics: shall the last be first?

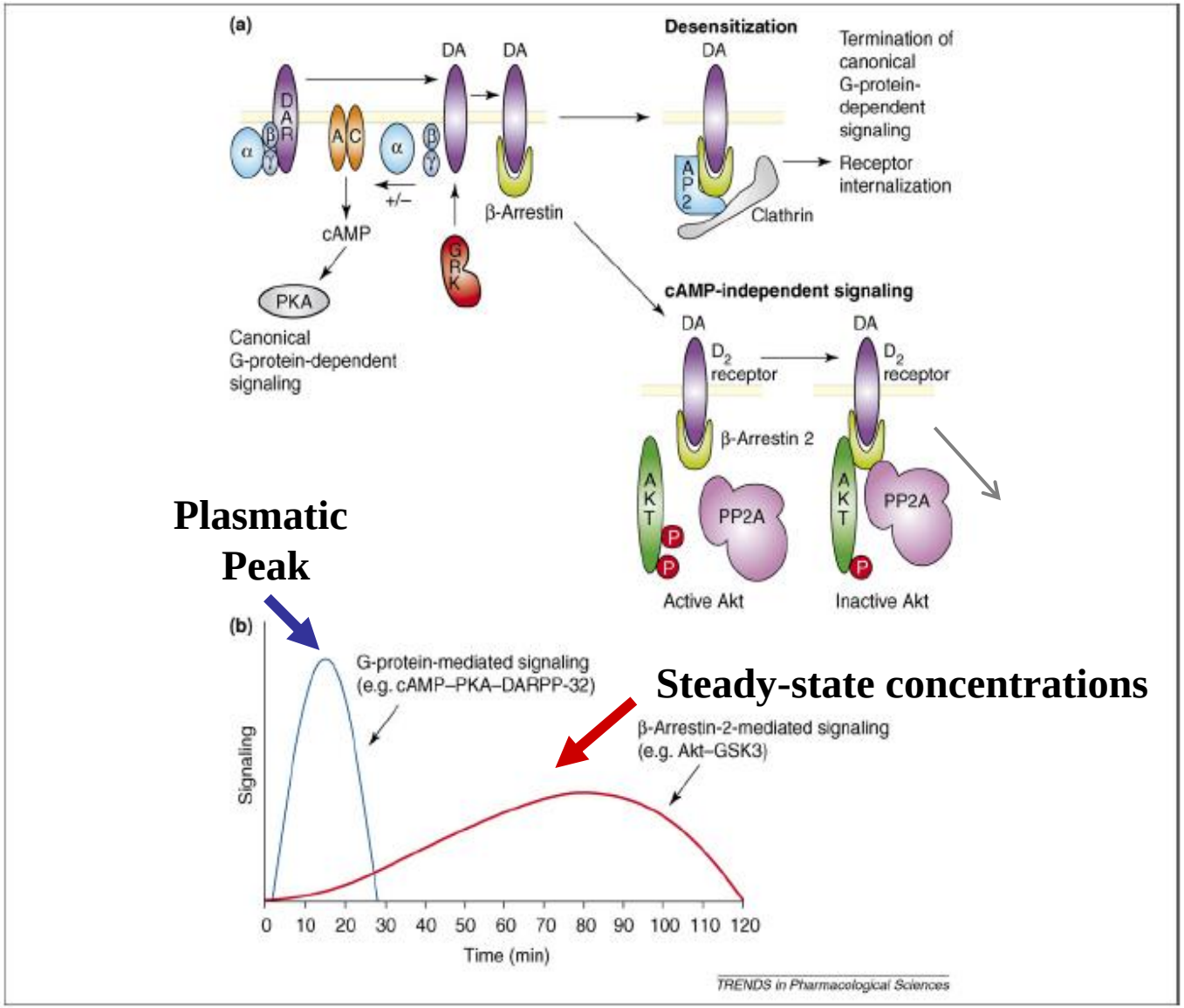
Stephan M. Stahl, CNS Spectrum, 2014



Effetti di un'aumentata compliance sulle concentrazioni plasmatiche e sull'efficacia clinica di un antipsicotico



Può una differente farmacocinetica determinare una diversa risposta farmacodinamica degli antipsicotici ?



Effetti di una formulazione LAI sui processi di mielinizzazione:

Possibili strategie di prevenzione secondaria nella fase iniziale della schizofrenia

Formulazione long-acting

↓

Maggiore stabilità delle concentrazioni plasmatiche dell'antipsicotico

↓

Stabile legame al recettore D_2

↓

Costante e Continua Inibizione della GSK-3β

⇩

Prevenzione dei processi di demielinizzazione nella fase iniziale di malattia e ↑ tassi di remissione

Bartzokis 2012

Antipsychotic drugs in mechanisms of Neurodegeneration/neuroprotection

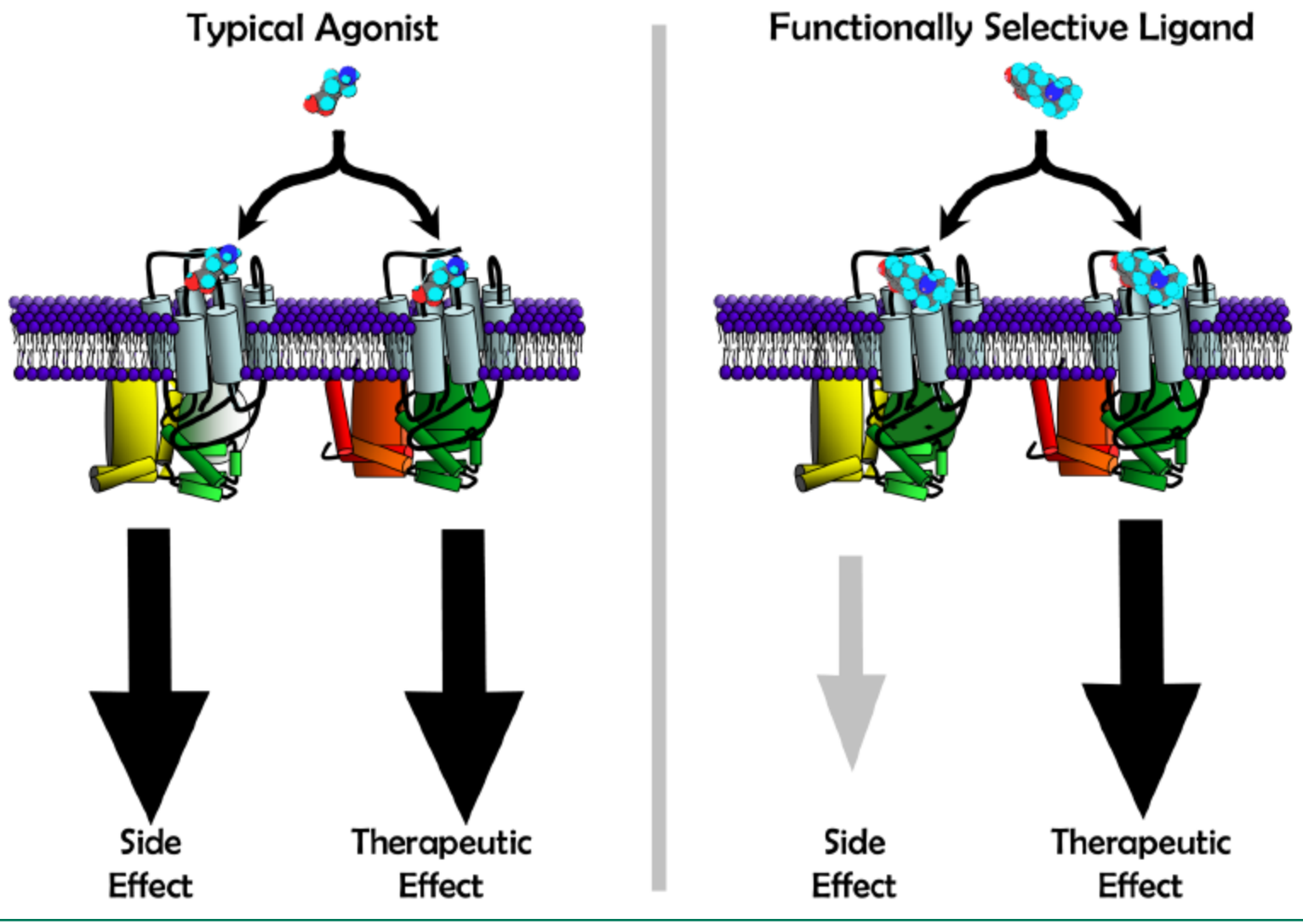
1. *Classical vs. Atypical*

2. *Oral vs. LAI*

Third generation antipsychotic drugs: partial agonism or receptor functional selectivity?

Curr Pharm Des. Author manuscript; available in PMC 2011 January 1.

Richard B. Mailman and **Vishakantha Murthy**



Il concetto"innovativo" di selettività funzionale in neuropsicofarmacologia

Implicazioni per la pratica clinica

- Ligands could induce an essentially limitless number of conformational states of a target receptor, which could cause markedly different effects on receptor signaling partners (Mailman et al.2012).
- Functional selectivity means that a drug may have different actions at different signaling pathways mediated by the same receptor (e.g., a ligand could be an agonist at one pathway and an antagonist at another).
- Drugs that are functionally selective will have different intrinsic activity on different signaling pathways (agonist, partial agonist, antagonist, or inverse agonist)
- Functionally selective ligands induce unique conformational states of a receptor that are distinct from those caused either by the endogenous ligand (e.g. dopamine) or by"classic" antagonists (e.g. neuroleptics).

Pharmacology 212, DOI 10.1007/978-3-642-25761-2_3,

Kevin N. Boyd and Richard B. Mailman

Pharmacology 212, DOI 10.1007/978-3-642-25761-2_3,

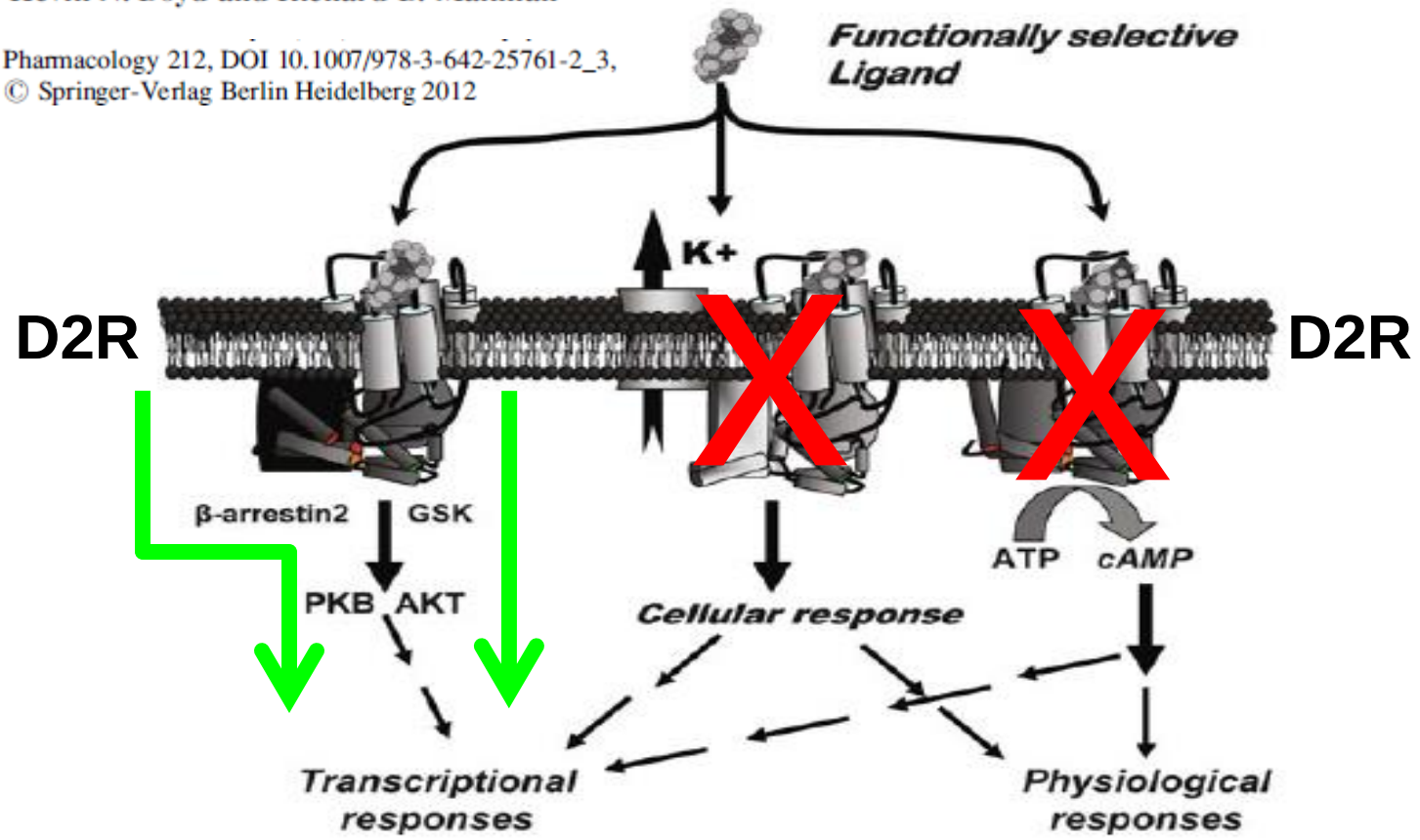
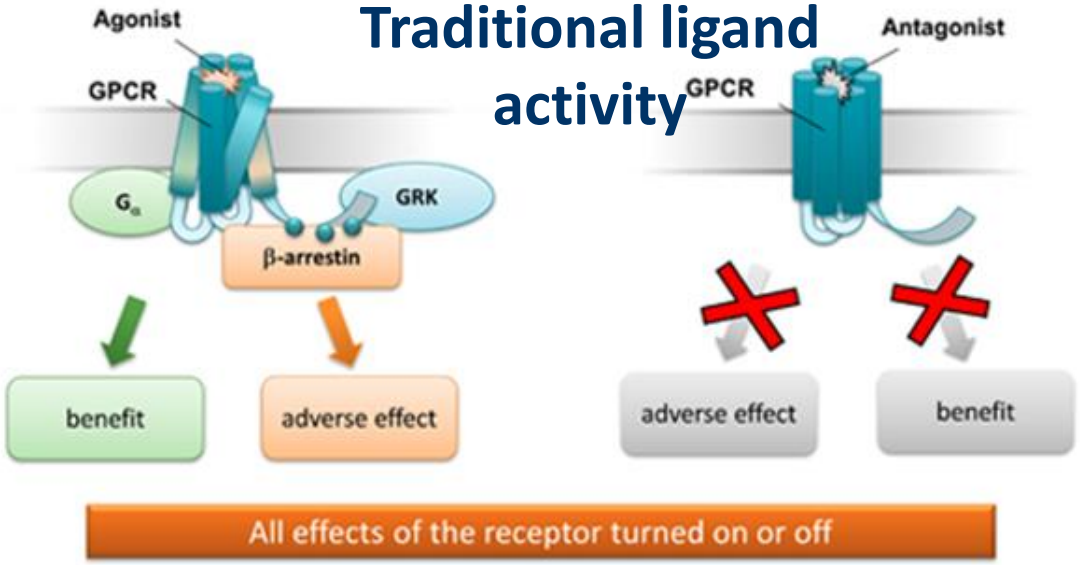


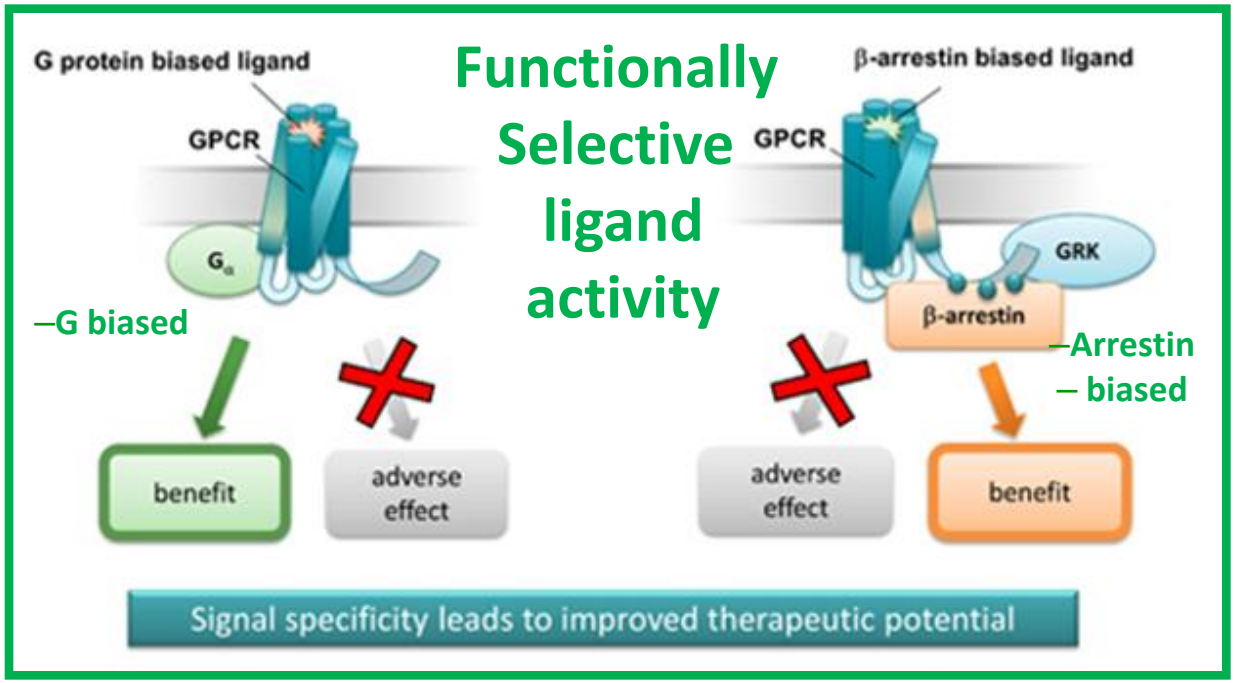
Fig. 1 The implications of functional selectivity at the dopamine D_2 receptor are illustrated in this *cartoon*. Functionally selective drugs, unlike dopamine, might differentially affect both canonical and noncanonical signaling pathways. This could result in differential acute effects, which is illustrated by the *center* and *right-hand* aspects of the figure. For example, a ligand would cause differential effects on mediators of acute action (e.g., the dopamine-induced hyperpolarization of a cell mediated via inward-rectifying potassium channels and acute actions of cAMP) as well as the longer term effects of drugs. Thus, changes in transcription initiated by cAMP on mechanisms like CREB could be altered by some drugs in a different manner than receptor-initiated changes in transcription initiated by β-arrestin2/Akt



Il potenziale degli *antipsicotici dotati di selettività funzionale*

↓

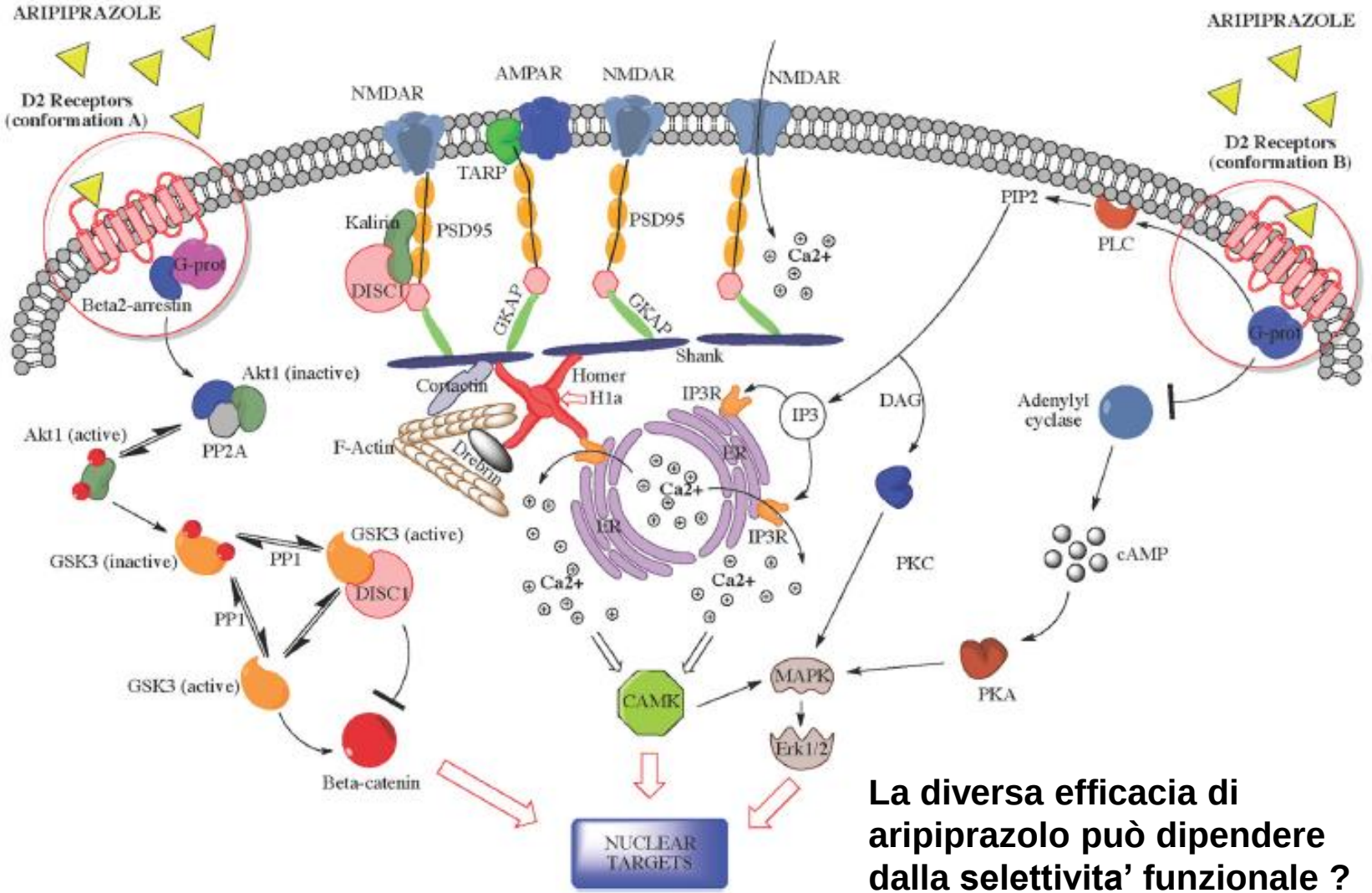
Maggiore efficacia e Minori effetti avversi



Update on the Mechanism of Action of Aripiprazole: Translational Insights into Antipsychotic Strategies Beyond Dopamine Receptor Antagonism

CNS Drugs (2015) 29:773–799
DOI 10.1007/s40263-015-0278-3

Andrea de Bartolomeis[1] · Carmine Tomasetti[1] · Felice Iasevoli[1]



La diversa efficacia di aripiprazolo può dipendere dalla selettivita' funzionale ?

BJP British Journal of Pharmacology

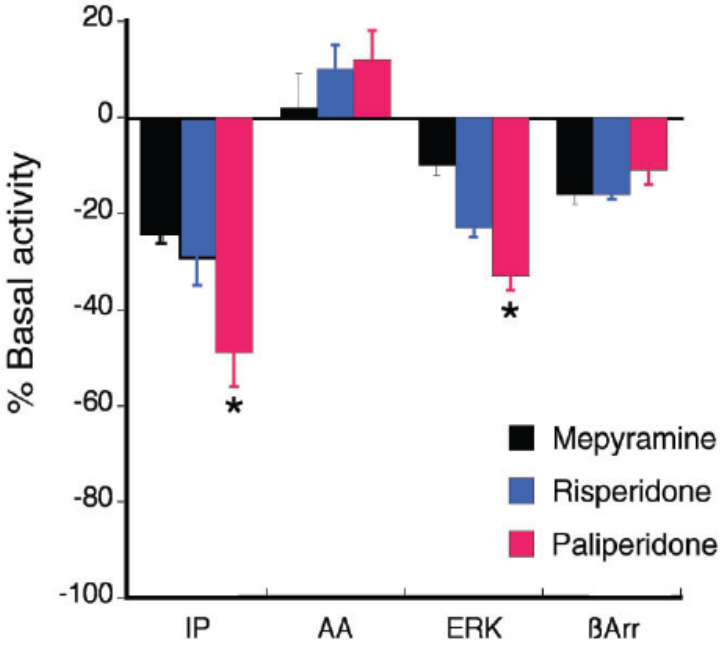
RESEARCH PAPER

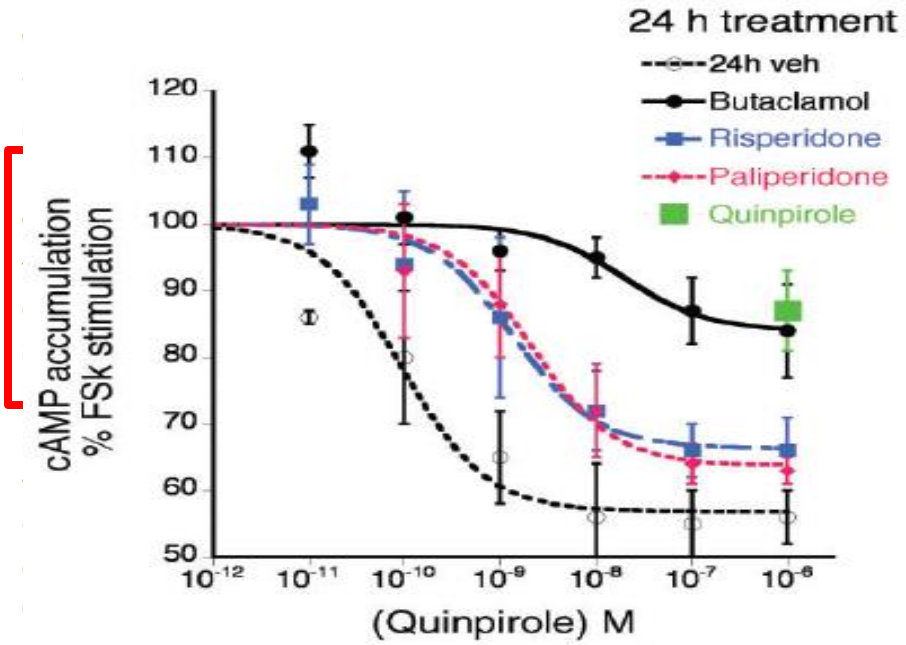
Received
13 March 2013
Revised
20 June 2013
Accepted
25 June 2013

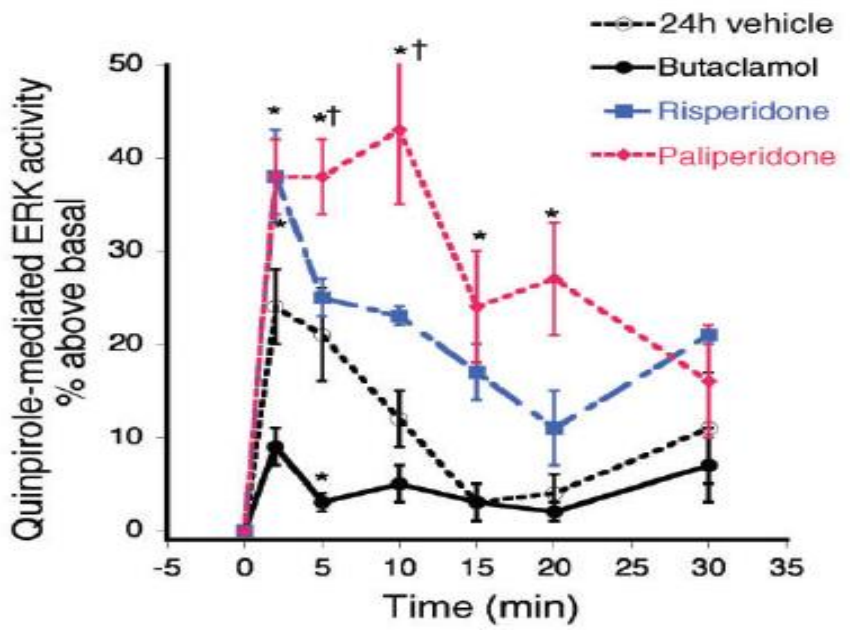
Signalling profile differences: paliperidone versus risperidone

W P Clarke, T A Chavera, M Silva, L C Sullivan and K A Berg

Department of Pharmacology, University of Texas Health Science Center, San Antonio, TX, USA







Long-Acting di seconda generazione

Vantaggi farmacocinetici o anche farmacodinamici ?

Migliorare la compliance

→ **Minore frequenza di somministrazioni**

Possibilità d'uso in pazienti non collaboranti

Migliorare il profilo farmacocinetico

→ **Rapido raggiungimento di concentrazioni efficaci (in acuto)**

Concentrazioni plasmatiche di equilibrio meno soggette a fluttuazioni (in cronico)

Migliorare il profilo farmacodinamico

→ **Interazione stabile con il recettore D_2**

Attivazione del signaling di AKT/beta arrestina

EXPERT REVIEWS

New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia

Expert Rev. Neurother. 13(7), 767–783 (2013)

Leslie Citrome

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citrome@cnsconsultant.com

Long-acting injectable (depot) antipsychotics are one approach in the management of individuals with schizophrenia. Since the introduction of risperidone long-acting injection in 2003, three additional second-generation antipsychotics have become available in a long-acting injectable formulation: paliperidone, olanzapine and aripiprazole. Although these different depot options can help with adherence and thus encourage better treatment outcomes, they differ in terms of specific indications, approved injection sites, needle gauge, injection volume, injection interval, requirements for oral supplementation, availability of prefilled syringes, storage needs and postinjection observation period, as well as potential drug–drug interactions and commonly encountered adverse reactions. After a review of the evidence base, guidance is offered on the appropriate selection among the long-acting injectable formulations of both first and

Long-acting antipsychotic therapy may be best suited for patients in the early stage of schizophrenia, when the most can be done before disease progression associated with poor adherence occurs

EXPERT REVIEWS

New second-generation long-acting injectable antipsychotics

Box 1. Guidance on the selection of a long-acting injectable antipsychotic.

Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine or aripiprazole?

- Switch to the corresponding LAI formulation using the dosing-conversion information contained in the product labeling. For patients receiving oral risperidone, consider using PLAI for convenience (no requirement for oral supplementation upon initiation, less frequent injections, supplied in prefilled syringes, smaller needle bore, lower injection volume, no requirement for refrigeration). For patients receiving oral fluphenazine or haloperidol, weigh the potential disadvantages of using concomitant oral anticholinergics for the management of motoric adverse effects – these agents add complexity to the regimen (an oral tablet/capsule) and anticholinergic agents can interfere with memory and other cognitive functions

Is the patient being treated acutely?

- Consider LAI antipsychotics that do not require oral supplementation and where the clinical trials have demonstrated acute efficacy – namely PLAI and OLAI

Are weight gain and metabolic adverse effects a concern for this individual patient?

- Consider ALAI, PLAI and RLAI among the second-generation LAI antipsychotics, in that order. Also consider first-generation LAI antipsychotics

Is prolactin elevation a clinical concern for this individual patient?

- Consider ALAI. Avoid PLAI, RLAI or first-generation LAI antipsychotics

Is cost the primary concern?

- The first-generation LAI antipsychotics may be the only option available. There remains a need to weigh the potential disadvantages of using concomitant oral anticholinergics for the management of motoric adverse effects – these agents add complexity to the regimen (an oral tablet/capsule) and anticholinergic agents can interfere with memory and other cognitive functions

Are any of the following people or entities not enrolled in the OLAI Patient Care Program: patient, prescriber, healthcare facility, pharmacy?

- OLAI cannot be used

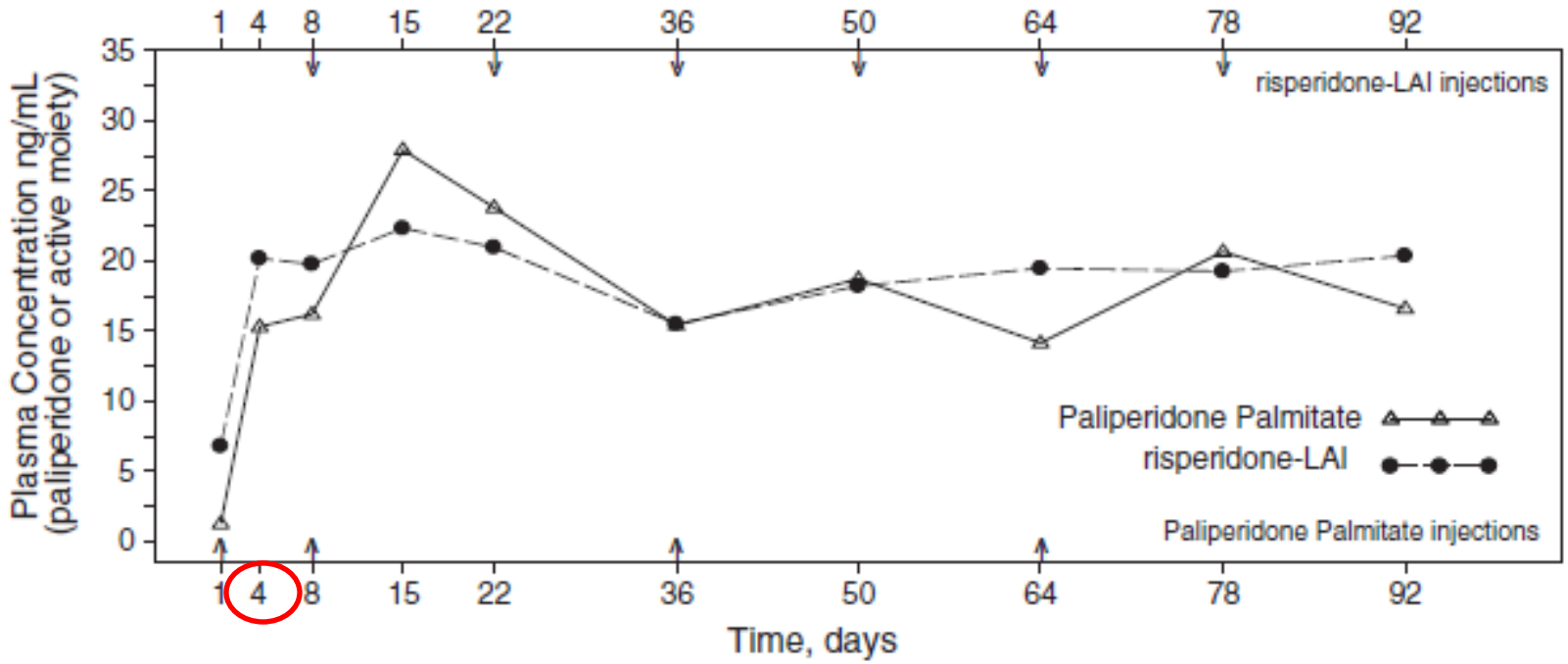
Antipsicotici LAI

Confronto dei parametri farmacocinetici

	Risperidone LAI	Paliperidone palmitato 1M	Paliperidone palmitato 3M	Olanzapina pamoato	Aripiprazolo LAI
T_{max} (giorni)	28-35	13-17	30-33	2-4	5-7
Emivita (giorni)	4-6	25-49	84-95 (deltoide) 118-139 (gluteo)	14-28	30-46
Tempo per steady-state	6-8 settimane	4-6 settimane	-	3 mesi	3-4 mesi
Enzimi metabolizzanti	CYP2D6 CYP3A4	Prevalente escrezione renale	*Prevalente escrezione renale*	CYP1A2 UGT1A4 CYP2D6	CYP2D6 CYP3A4
Metaboliti attivi	Paliperidone			-	Deidro-aripiprazolo

LAIs bypass the initial deactivating process by avoiding first-pass metabolism in the liver ➡ Increased bioavailability ➡ reduced dosage/month

Pharmacokinetic profile of Paliperidone palmitate



The initial dosing regimen

[two initial deltoid IM injections of 150 mg eq. on Day 1 and 100 mg eq. on Day 8] leads to therapeutic plasma concentrations (above 7.5 ng/ml) from day 4

Pandina et al. Prog. NeuroPsy&Biol 2011; Samtani et al. CNS drugs 2011

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journal homepage: www.elsevier.com/locate/schres

Pharmacokinetics, tolerability and safety of aripiprazole once-monthly in adult schizophrenia: An open-label, parallel-arm, multiple-dose study☆☆

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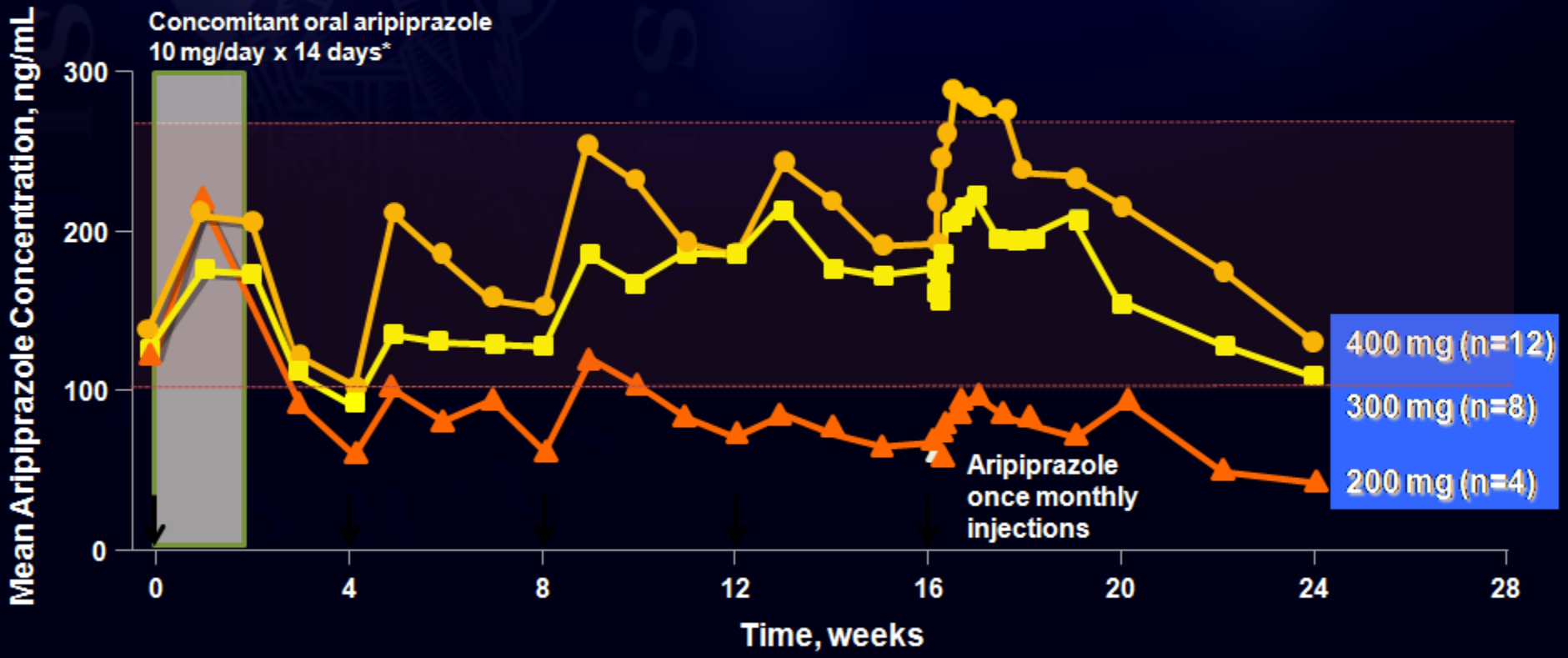
Schizophrenia Research 2013 150, 281-288DOI: (10.1016/j.schres.2013.06.041)

Pharmacokinetic Study of Aripiprazole Once Monthly

Phase 1b open-label study in patients with schizophrenia (N=41)



*After the first aripiprazole once monthly injection, continue treatment with oral aripiprazole or other oral antipsychotic for 14 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy.

Mallikaarjun, S., et al., Pharmacokinetics, tolerability and safety of aripiprazole once-monthly in adult schizophrenia: An open-label, parallel-arm, multiple-dose study, Schizophr. Res. (2013), http://dx.doi.org/10.1016/j.schres.2013.06.041

Novel emerging pharmacological entities: to achieve faster efficacy and significantly shorten or eliminate oral supplementation during the initiation phase

TABLE 5. Selected novel and emerging pharmacological treatments for schizophrenia targeting the amelioration of antipsychotic non-adherence and body weight gain

References	Total *N*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
Aripiprazole Lauroxil (AL) NanoCrystal® Dispersion (Aripirpazole Lauroxil $_{NCD}$; Aristada Initio)							
Walling et al. (2018)[100]	161	3 weeks	AL 441 mg/1-day ($n=39$) AL 882 mg/1-day ($n=41$)	AL 441 mg/21-days ($n=40$) AL 882 mg/21-days ($n=41$)	N/A	N/A	*Positive study*: The 1-day regime groups had comparable aripiprazole exposure to the corresponding 21-day group.
Risperidone ISM® (Doria®)							
https://clinicaltrials.gov/ct2/show/results/NCT03160521[114,115]	438	12 weeks	Risperidone ISM 75 mg/day ($n=$N/Av) Risperidone ISM 100 mg/day ($n=$N/Av)	Placebo ($n=$N/Av)	PANSS total	Risperidone ISM 75 mg vs. placebo $p<.0001$ Risperidone ISM 100 mg vs. placebo $p<.0001$	*Positive study*: Risperidone was significantly superior to placebo in PANSS total and CGI-S scores.
					CGI-S	Risperidone ISM 75 mg vs. placebo $p<.0001$ Risperidone ISM 100 mg vs. placebo $p<.0001$	
Perseris™ Risperidone (RBP-7000)							
Nasser et al. (2016)[109]	337	8 weeks	RBP-7000 90 mg/day ($n=111$) RBP-7000 120 mg/day($n=114$)	Placebo ($n=112$)	PANSS total	RBP-7000 90 mg vs. placebo $p=.0004$ RBP-7000 120 mg vs. placebo $p<.0001$	*Positive study*: RBP-7000 was significantly superior to placebo on the PANSS total, positive, and general score, as well as on the CGI-S. RBP-7000 was not superior to placebo on the PANSS negative subscale score.
					PANSS negative	RBP-7000 90 mg vs. placebo, $p=.186$ RBP-7000 120 mg vs. placebo, $p=.039$	
					PANSS positive	RBP-7000 90 mg vs. placebo, $p=.0003$ RBP-7000 120 mg vs. placebo, $p<.0001$	

Based on the in-situ formation of biodegradable matrices after the administration of a liquid carrier. Due to its special characteristics, therapeutic antipsychotic blood levels are achieved rapidly…

Krogmann et al. 2019 CNS Spectrum

Metabolizzatori rapidi

*CYP2D6*1/CYP2D6*2*

Metabolizzatori lenti (3-5% caucasici)

*CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6*

Metabolizzatori intermedi

*CYP2D6*10, CYP2D6*17, CYP2D6*41*

Metabolizzatori ultrarapidi (ca. 3-4% caucasici)

*CYP2D6*1 o 2xN (15-20% Etiopi, Algerini)*

***Inibitori CYP2D6 da evitare**:*

Chinidina, Celecoxib, Amiodarone, Terbinafina, Paroxetina, Fluoxetina, Bupropione, Duloxetina, Aloperidolo, Levomepromazina

Eur J Clin Pharmacol (2016) 72:175–184
DOI 10.1007/s00228-015-1965-1

PHARMACOGENETICS

Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol

Patteet Lisbeth[1] · Haufroid Vincent[2,3] · Maudens Kristof[1] · Sabbe Bernard[4,5] · Morrens Manuel[4,6] · Neels Hugo[1,7]

Purpose Therapeutic drug monitoring (TDM) of antipsychotics can aid in therapy optimization, explaining adverse effects or non-response. One reason for therapeutic failure or adverse effects is caused by genetic variations in the cytochrome P450 drug-metabolizing genes. The aim of this study was to evaluate the impact of CYP2D6 polymorphisms on steady-state serum concentrations of antipsychotics metabolized by CYP2D6, taking into account the co-medication with CYP2D6 inhibitors.

Results Overall, 6.1 % UM (n = 5), 25.6 % EM-f (n = 21), 46.3 % EM-s (n = 38), 1.2 % EM-s/EM-f (n = 1), 6.1 % IM (n = 5), and 14.6 % PM (n = 12) were found, taking co-administration of strong and moderate CYP2D6 inhibitors into account (phenoconversion). It was demonstrated that CYP2D6 polymorphisms affect the serum concentrations of aripiprazole (n = 18), haloperidol (n = 11), risperidone (n = 20), and zuclopenthixol (n = 6), while no influence was seen on the paliperidone serum concentrations (n = 31).

Table 1 Patient demographics and daily dose by analyte

Analyte	Sex	Number	No. of samples	Age		OR/LA/NM (n)	Dose (mg/day)	
				Median	Range		Median	Range
Aripiprazole	Male	11	18	36	21–66	OR (17)	15.0	5.0–30.0
	Female	7				LA (1)	14.3	
Haloperidol	Male	9	11	25	19–56	OR (4)	6.3	2.5–15.0
	Female	2				LA (7)	3.6	2.7–4.8
Paliperidone	Male	22	32	35	18–64	OR (9)	9.0	6.0–9.0
	Female	10				LA (22)	3.6	1.8–7.1
						OR + LA (1)	14.4	
Risperidone	Male	12	20	43	21–65	OR (9)	3	1.0–6.0
	Female	7				LA (7)	2.7	2.7–4.5
						OR + LA (4)	5.7	5.6–5.8
Zuclopenthixol	Male	4	6	36	30–54	OR (2)	–	15.0–60.0
	Female	2				LA (4)	16.7	16.7–33.3

Eur J Clin Pharmacol (2016) 72:175–184
DOI 10.1007/s00228-015-1965-1

Table 4 Median dose, concentration-to-dose ratios (C/D) and metabolite-to-parent ratios (M/P) of aripiprazole (ARI), dehydro-aripiprazole (DARI), haloperidol (HAL), reduced haloperidol (RHAL), risperidone (RIS), paliperidone (PAL) and zuclopenthixol (ZUC) according to CYP2D6

ARI (n = 18)	n	Dose (mg/day)	C/D ratio ARI (ng/mL/mg)	C/D ratio DARI (ng/mL/mg)	C/D ratio ARI + DARI (ng/mL/mg)	M/P ratio
PM	3	15.0 (14.3–20.0)	15.6 (10.2–19.0)	3.7 (3.6–5.2)	19.2 (13.9–24.2)	0.27 (0.23–0.36)
EM-s	9	15.0 (7.5–30.0)	12.3 (5.8–21.9)	6.3 (3.1–8.2)	20.4 (10.8–29.0)	0.43 (0.32–0.86)
EM-f	5 (4)[a]	15.0 (10.0–30.0)	10.1 (7.4–12.1)	5.0 (4.6–6.6)	16.0 (12.0–16.8)	0.55 (0.38–0.76)
UM	1	25.0	6.1	3.2	9.3	0.52
HAL (n = 11)	n	Dose (mg/day)	C/D ratio HAL (ng/mL/mg)	C/D ratio RHAL (ng/mL/mg)	C/D ratio HAL + RHAL (ng/mL/mg)	M/P ratio
PM	2	10.0 (5.0–15.0)	0.5 (0.4–0.6)	1.38 (1.27–1.49)	1.88 (1.67–2.09)	2.86 (2.48–3.25)
EM-s	5	3.6 (2.5–7.5)	0.4 (0.2–1.3)	0.16 (0.07–0.21)	0.58 (0.31–1.45)	0.32 (0.14–0.42)
EM-f	3	3.6 (2.7–4.8)	0.5 (0.4–0.5)	0.14 (0.10–0.19)	0.63 (0.57–0.69)	0.37 (0.22–2.76)
UM	1	4.8	0.4	0.11	0.49	0.28
RIS (n = 20)	n	Dose (mg/day)	C/D ratio RIS (ng/mL/mg)	C/D ratio PAL (ng/mL/mg)	C/D ratio RIS + PAL (ng/mL/mg)	M/P ratio
PM	4 (3)[a]	2.8 (2.7–5.8)	11.4 (6.4–13.8)	2.6 (2.1–4.4)	15.8 (8.6–16.3)	0.33 (0.19–0.38)
IM	2 (1)[b]	4.3 (4.0–4.8)	2.3 (0.3–4.3)	5.4[b]	9.7[b]	1.25[b]
EM-s	11 (10)[b]	3.6 (1.0–5.8)	3.0 (0.2–5.6)	6.7 (3.5–11.6)	8.8 (4.2–16.0)[b]	2.89 (1.55–23.60)[b]
EM-f	2	4.3 (3.0–5.6)	1.2 (1.1–1.2)	9.8 (5.8–13.7)	10.9 (6.9–16.0)	8.17 (5.20–11.14)
UM	1	5.6	0.9	7.5	8.4	8.25
PAL (n = 31)	n	Dose (mg/day)	C/D ratio PAL (ng/mL/mg)			
PM	4	4.1 (2.7–14.4)	9.6 (2.7–12.8)			
IM	3	5.4 (2.7–9.0)	6.9 (5.9–7.0)			
EM-s	11	3.6 (1.8–9.0)	5.9 (2.2–9.3)			
EM-f	11	6.0 (1.8–9.0)	8.8 (3.5–19.6)			
UM	2	4.8 (3.6–6.0)	4.2 (2.7–5.7)			

2011 CCNP Heinz Lehmann Award paper

J Psychiatry Neurosci 2013;38(3):152-63

Cytochrome P450–mediated drug metabolism in the brain

Sharon Miksys, PhD; Rachel F. Tyndale, PhD

Variation in brain CYP-mediated metabolism may be a contributing factor when plasma levels do not predict drug response

Table 1: Examples of central nervous system–acting substrates for 3 drug-metabolizing cytochromes P450[5,13–18]

Enzyme	CNS-acting drugs	Endogenous	Other drugs and toxins
CYP2B6	Bupropion, diazepam, ketamine, methadone, meperidine, nicotine, pentobarbital, phencyclidine, propofol, sertraline selegiline, tramadol	17-β estradiol, anandamide, arachidonic acid, estrone, serotonin, testosterone	3,4-methylenedioxy-amphetamine (ecstasy), chlorpyrifos, cyclophosphamide, DEET, efavirenz, ifosphamide, malathion, paraquat, parathion
CYP2D6	Amyltriptyline, brofaromine, clomipramine, codeine, citalopram, clozapine, desipramine, dextromethorphan, ethylmorphine, fluoxetine, fluvoxamine, haloperidol, hydrocodone, imipramine, mianserin, mirtazapine, nicergoline, nortryptaline, oxycodone, paroxetine, perphenazine, risperidone, tramadol, tranylcypromine, venlafaxine, zuclopenthixol	5-methoxytryptamine, anandamide, progesterone, tyramine	MPTP, parathion, tamoxifen
CYP2E1	Enflurane, felbamate, halothane, isoflurane, sevoflurane, trimethadione	17-β estradiol, arachidonic acid, estrone, prostaglandin	Acetaminophen, acetone, aniline, benzene, carbon tetrachloride, chloroform, chlozoxazone, ethanol, NNK, phenol, theophylline, trichloroethane

Changes in brain CYP metabolism can influence drug response, toxicity and drug-induced behaviours