Università degli Studi di Messina

Dipartimento di Medicina Clinica e Sperimentale

Sezione di Farmacologia

ANALOGIE E DIFFERENZE FRA GLI ANTIPSICOTICI ATIPICI

Edoardo Spina


BIKINI


VESPE
E VINCERE
ULTRAS
GIUSTIZIA
PER

Classi terapeutiche omogenee: mito o realtà?

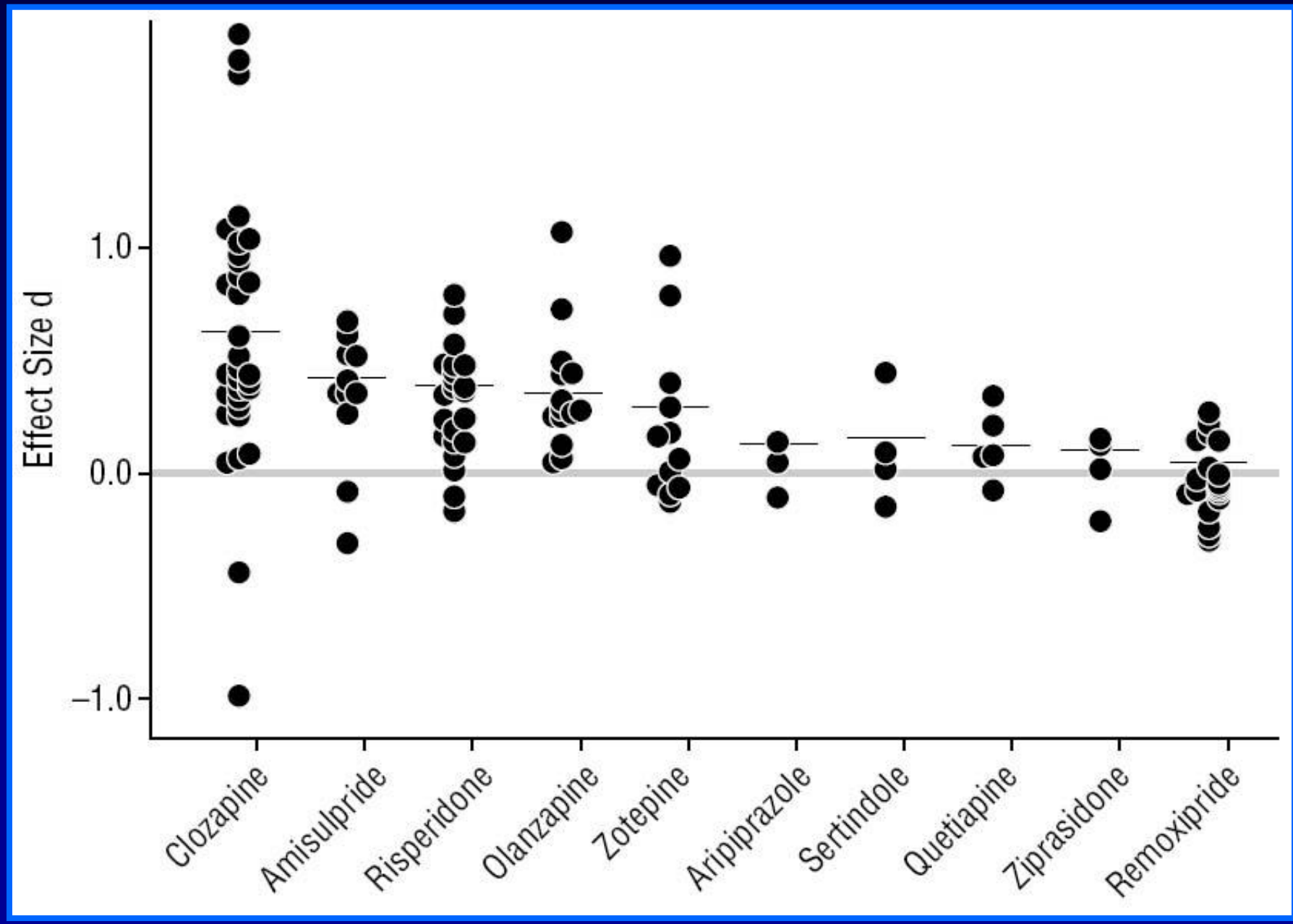
Ad eccezione delle benzodiazepine, le principali categorie di psicofarmaci non costituiscono delle classi omogenee, ma comprendono composti con proprietà farmacologiche, profilo di efficacia e tollerabilità in parte differenti

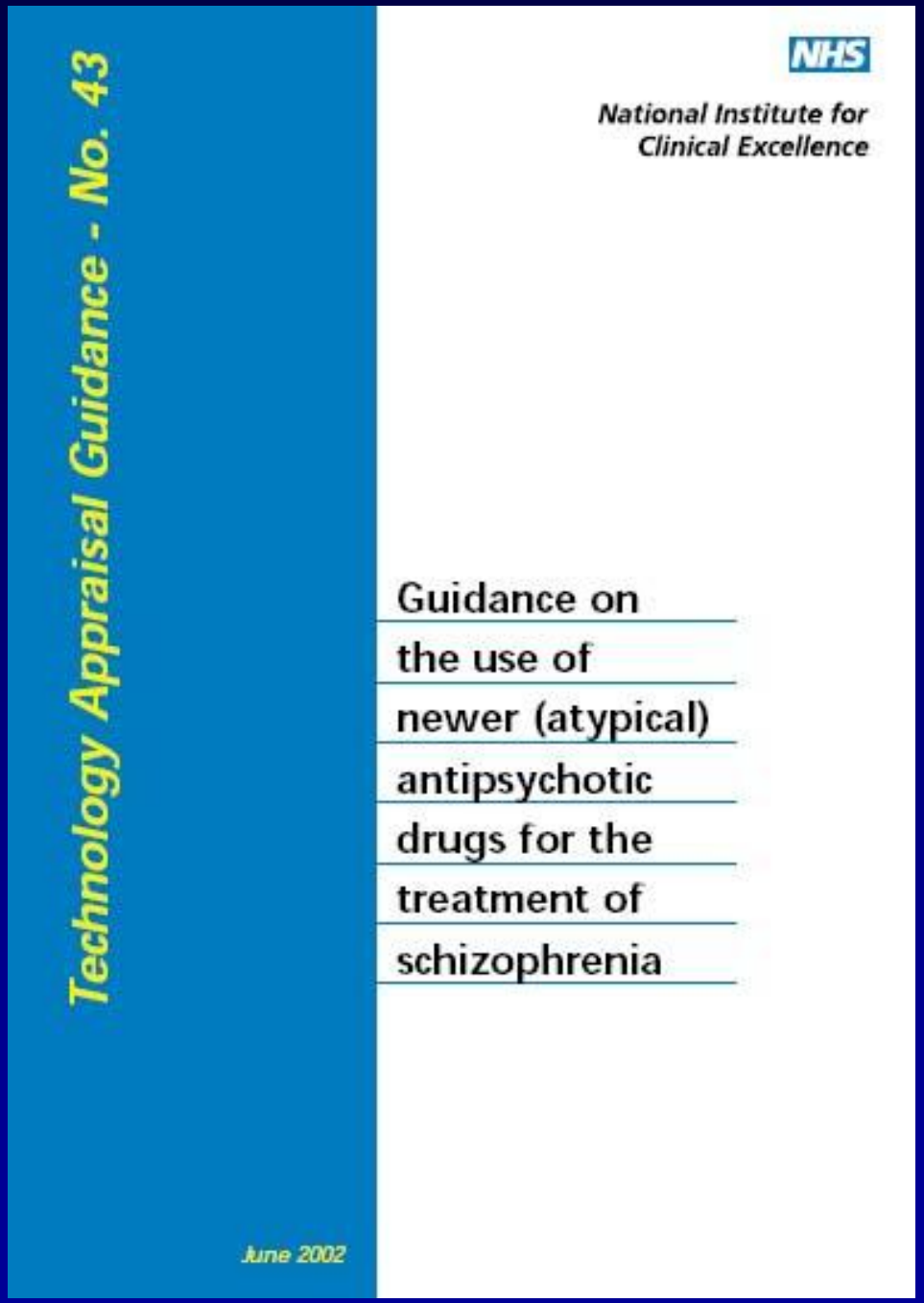
Antipsicotici atipici o di seconda generazione

- Clozapina
- Risperidone
- Olanzapina
- Quetiapina
- Amisulpride
- Aripiprazolo
- Paliperidone
- Ziprasidone
- Asenapina

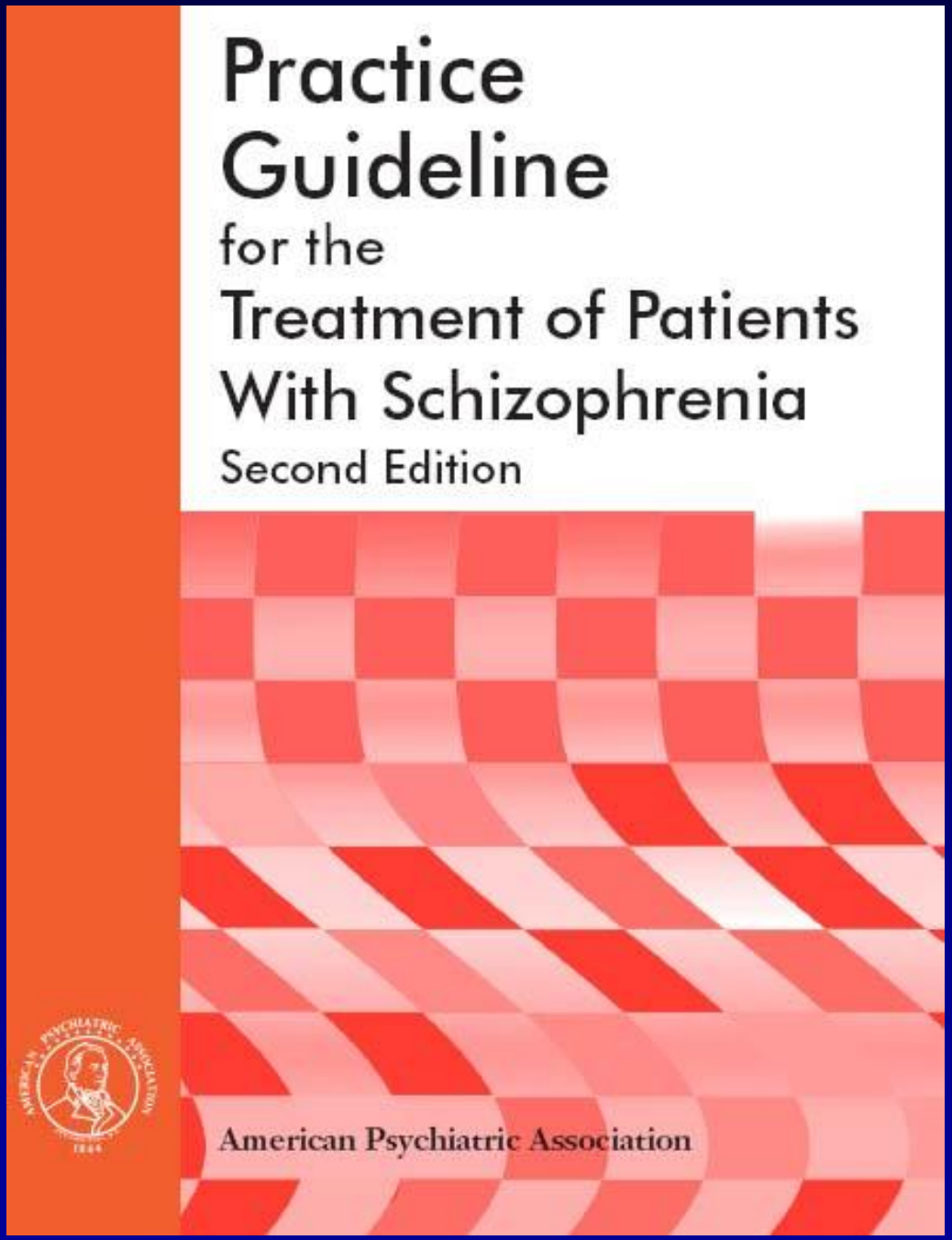
Potenziali vantaggi degli antipsicotici di seconda generazione

Tandon et al. Schizophr Res. 2008; 100: 20-38


Effect Size d
1.0
0.0
−1.0
Clozapine
Amisulpride
Risperidone
Olanzapine
Zotepine
Aripiprazole
Sertindole
Quetiapine
Ziprasidone
Remoxipride



"It is recommended that oral atypical antipsychotics are considered in the choice of first-line treatment for individuals with newly diagnosed schizophrenia"



"The second-generation antipsychotics should be considered as first line medications for patients in the acute phase, mainly because of the decreased risk of extrapyramidal side effects and tardive dyskinesia"

LEADING ARTICLE

CNS Drugs 2009; 23 (8): 649-659
1172-7047/09/0008-0649/$49.95/0

The CATIE and CUtLASS Studies in Schizophrenia

Results and Implications for Clinicians

Dieter Naber and *Martin Lambert*

Department of Psychiatry and Psychotherapy, Centre for Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

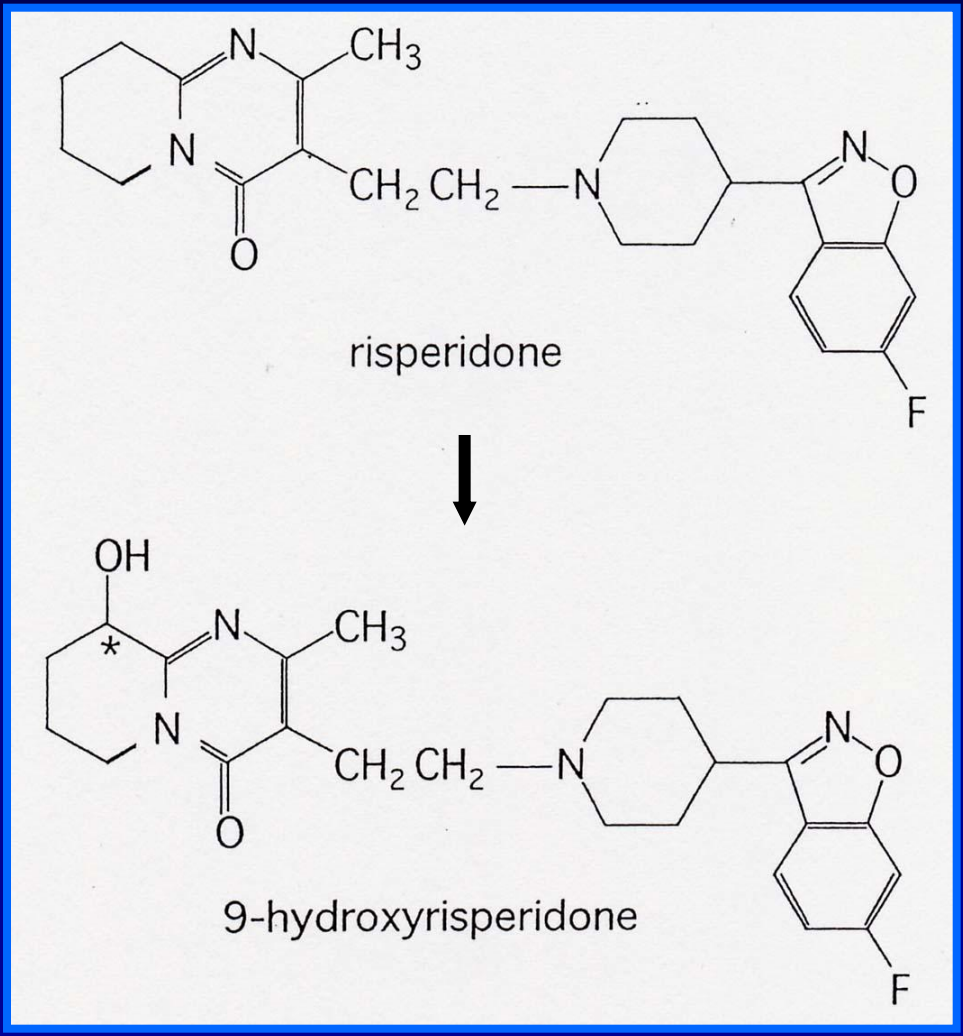
Antipsicotici di seconda generazione

Farmacocinetica

Parametri farmacocinetici dei nuovi antipsicotici

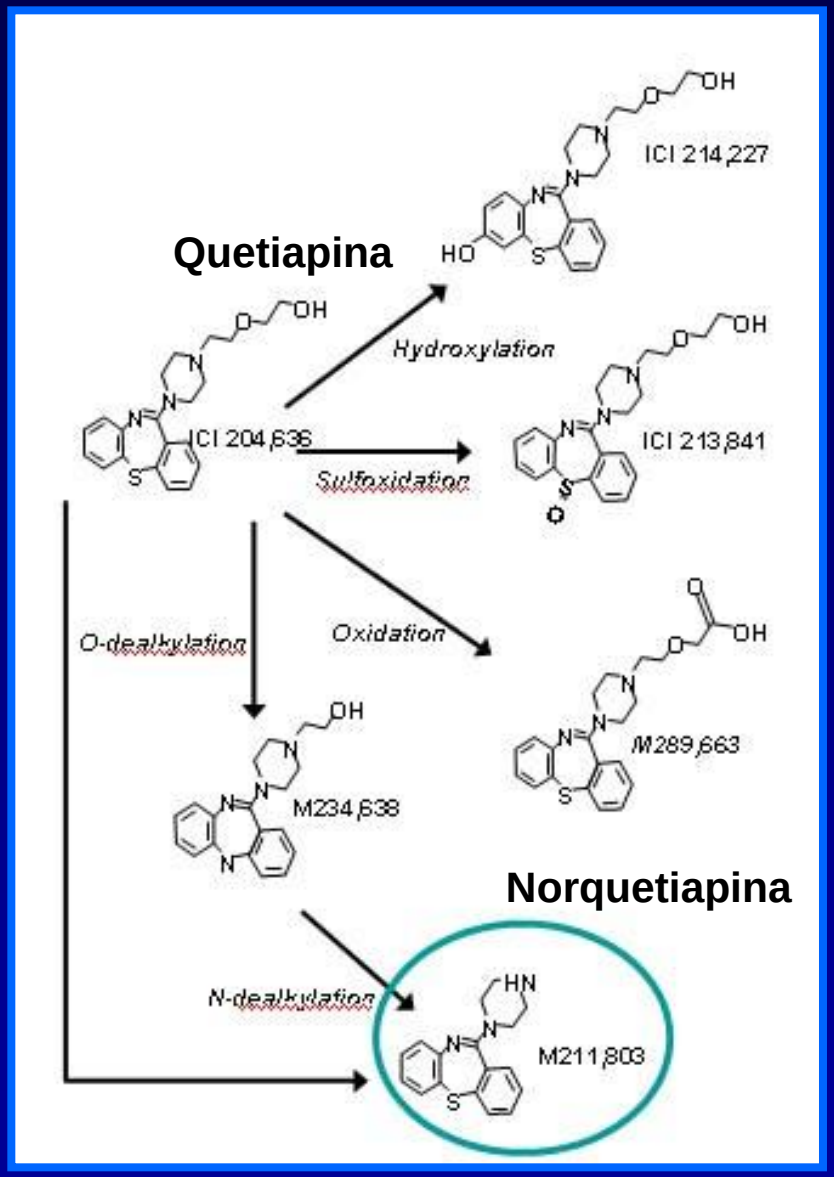
	Biodisponibilità (%)	Legame proteico (%)	Emivita (ore)	Enzimi metabolizzanti	Metaboliti attivi
Amisulpride	43-48	17	12	-	-
Aripiprazolo	87	99	48-68	CYP2D6, CYP3A4	Deidro-aripiprazolo
Asenapina	35	95	24	UGT1A4, CYP1A2	-
Clozapina	12-81	95	6-33	CYP1A2, CYP3A4	Norclozapina
Olanzapina	60-80	93	20-70	CYP1A2, UGT	-
Paliperidone	28	30	24	CYP2D6	-
Quetiapina	9	83	6-7	CYP3A4	Norquetiapina
Risperidone	68	90	3-24	CYP2D6	9-idrossirisperidone
Ziprasidone	60	99	4-10	Aldeide ossidasi	-

Metabolismo del risperidone



Metabolita attivo commercializzato come formulazione a rilascio prolungato (ER) su base osmotica

Metabolismo della quetiapina



Potente inibitore del trasportatore della noradrenalina e responsabile dell'effetto antidepressivo

Antipsicotici di seconda generazione

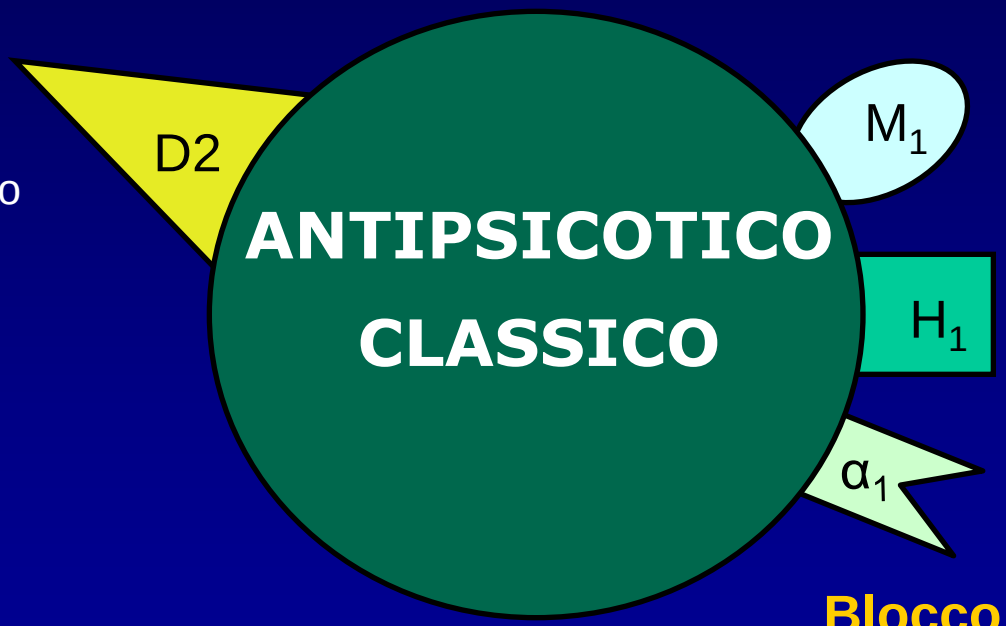
Farmacodinamica

Antipsicotici di prima generazione

Caratteristiche farmacodinamiche

Blocco recettori D_2

- effetto antipsicotico
- effetti extrapiramidali
- peggioramento sintomi negativi e deficit cognitivo
- iperprolattinemia



Blocco recettori M_1

- secchezza delle fauci
- visione offuscata
- stipsi
- ritenzione urinaria

Blocco recettori H_1

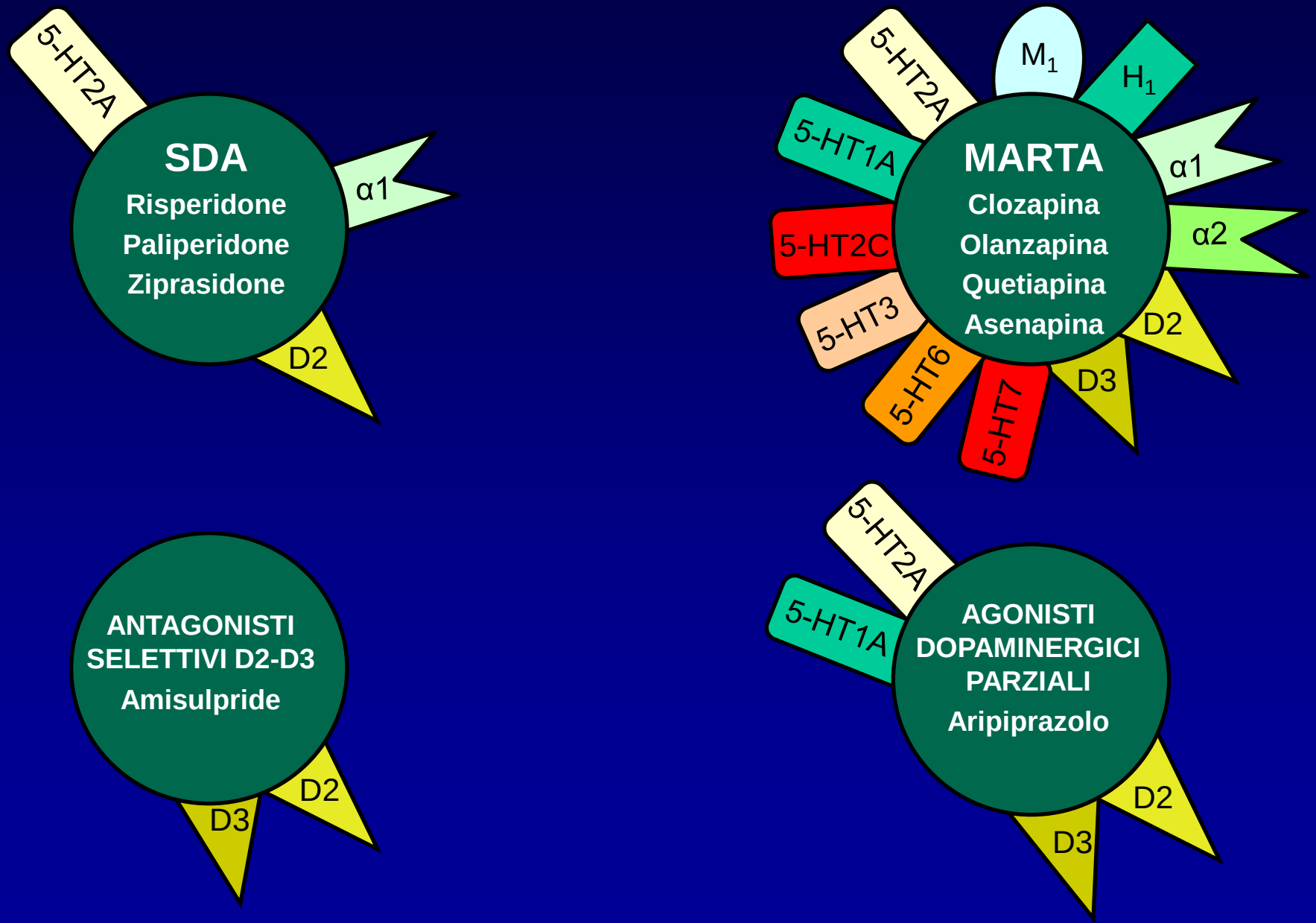
- aumento di peso
- sonnolenza

Blocco recettori α_1

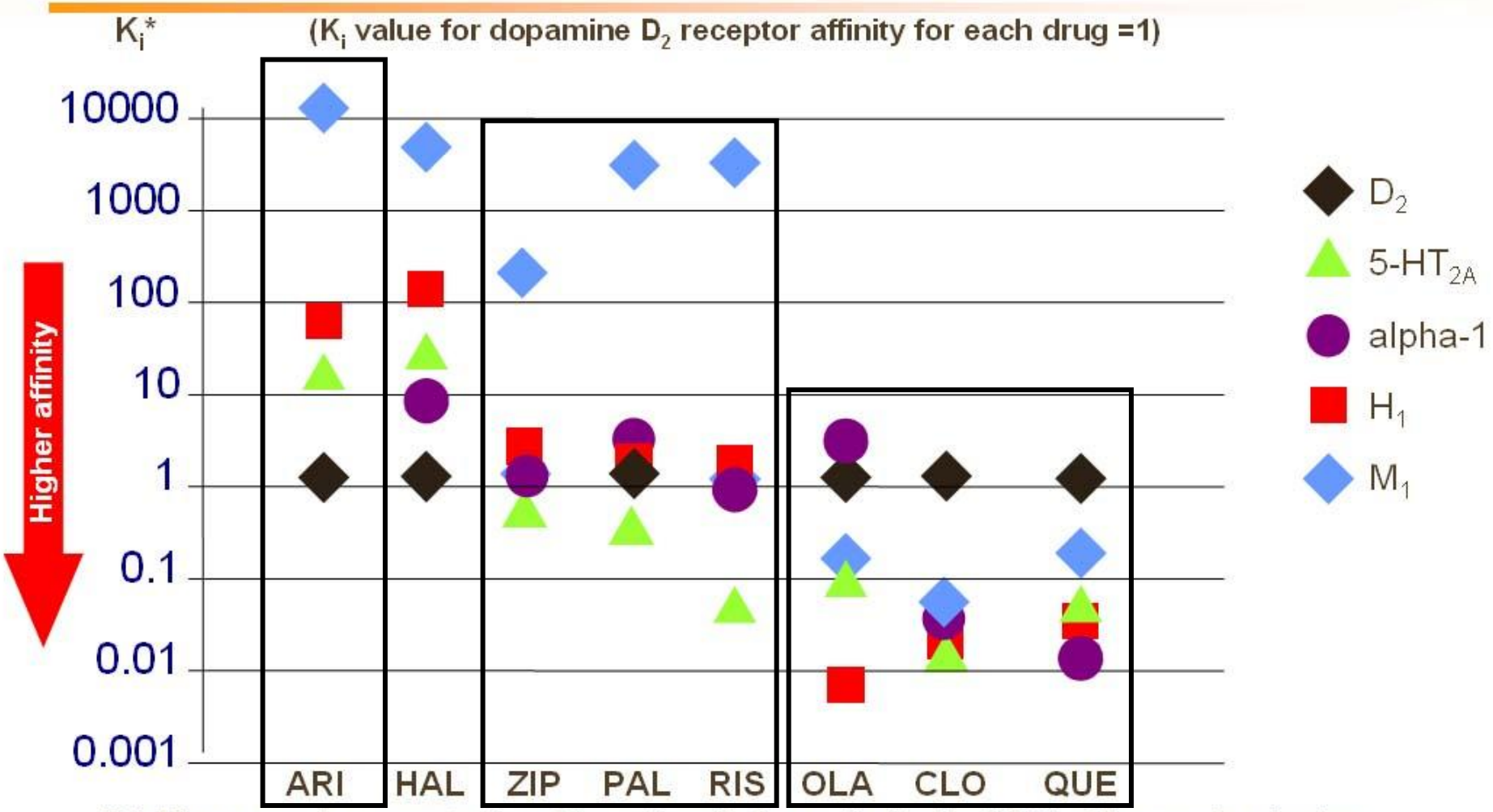
- ipotensione
- vertigini
- sonnolenza

Antipsicotici di seconda generazione

Caratteristiche farmacodinamiche



Approximate *relative* K_i values for receptor binding profiles of selected antipsychotics



K_i (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro
(i.e. lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors.
ARI: aripiprazole; HAL: haloperidol: ZIP: ziprasidone; PAL: paliperidone; RIS: risperidone; OLA: olanzapine; CLO: clozapine; QUE: quetiapine

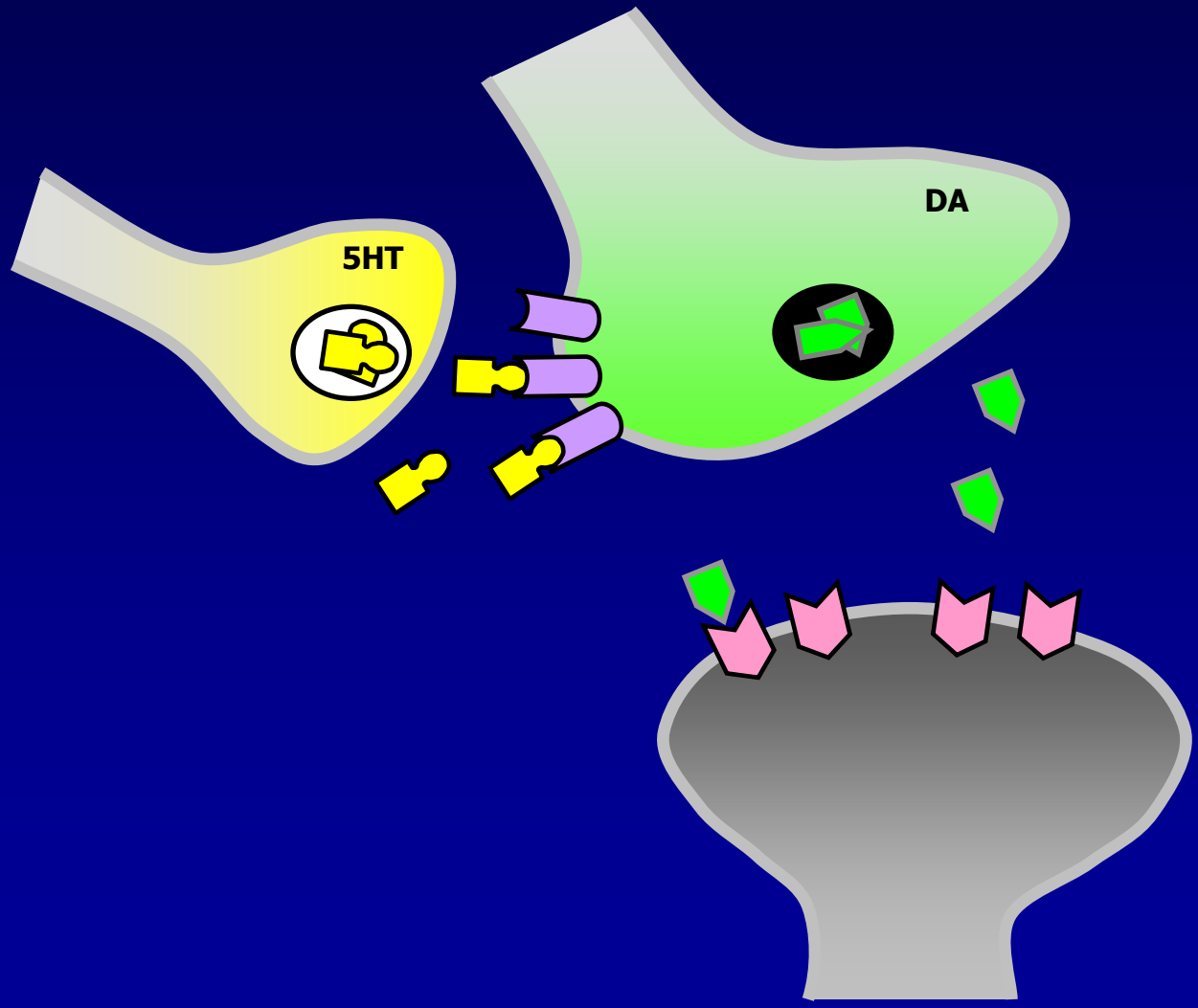
Adapted from: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36

Meccanismo d'azione dei nuovi antipsicotici

- Antagonismo recettoriale 5-HT_{2A}/D_2 (maggiore affinità per i recettori 5-HT_{2A} che per i recettori D_2)
- Rapida dissociazione dal recettore dopaminergico D_2
- Maggiore affinità per i recettori D_2 mesolimbici e mesocorticali rispetto a quelli nigrostriatali
- Agonismo parziale dei recettori D_2
- Azione su altri recettori (5-HT_{1A}, 5-HT_{1D}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7, adrenergico, colinergico muscarinico, NMDA, GABA) con azione modulatoria sul rilascio di altri neurotrasmettitori
- Azione neurotrofica e neuroprotettiva

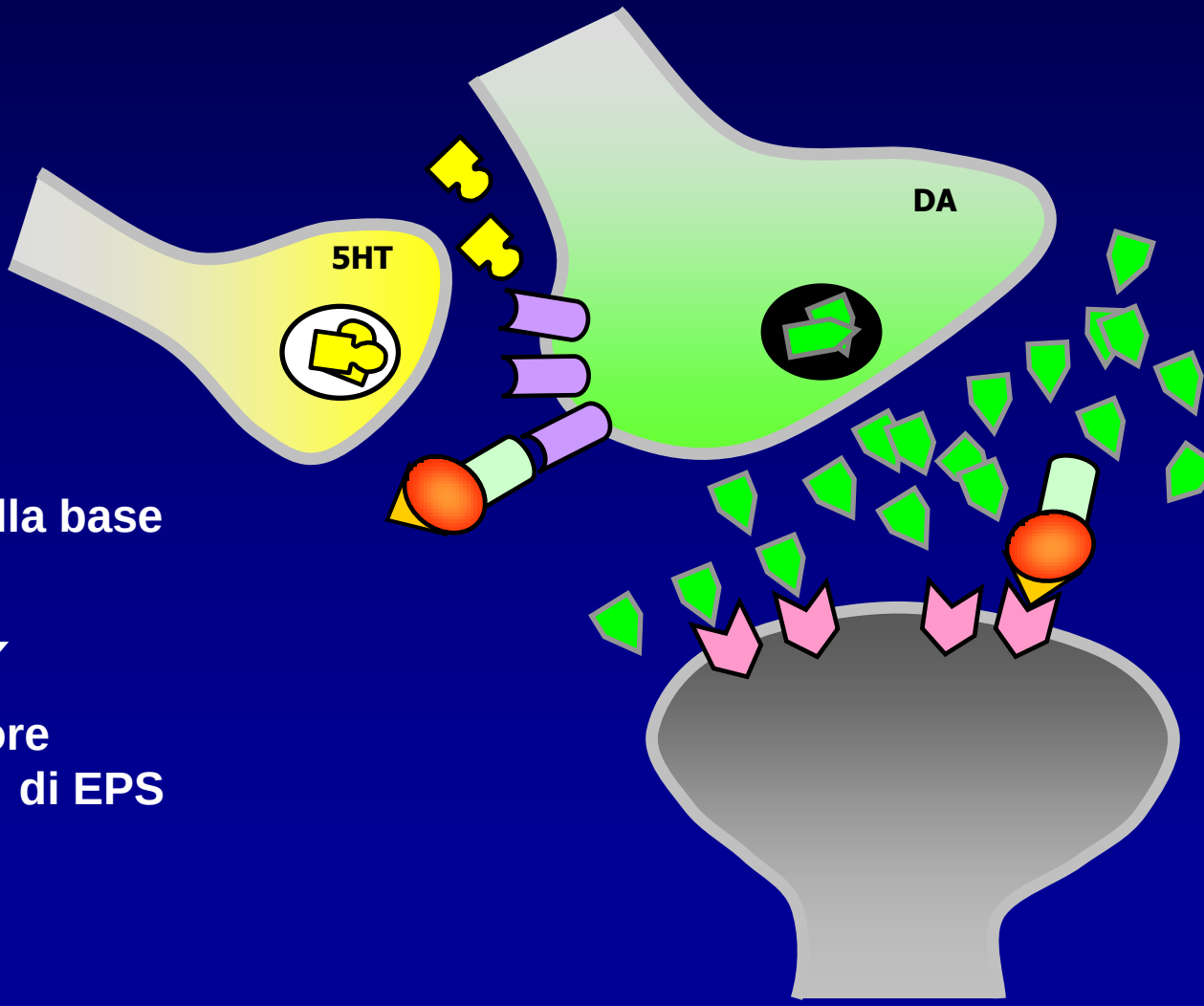
Ruolo dei recettori $5HT_{2A}$ nel meccanismo d'azione degli antipsicotici

La stimolazione dei recettori 5-HT_{2A} inibisce il rilascio di dopamina



Ruolo dei recettori $5HT_{2A}$ nel meccanismo d'azione degli antipsicotici

Gli antipsicotici atipici aumentano il rilascio di dopamina bloccando i recettori 5-HT_{2A}



Corteccia prefrontale

↓

Miglioramento dei sintomi negativi, cognitivi e depressivi

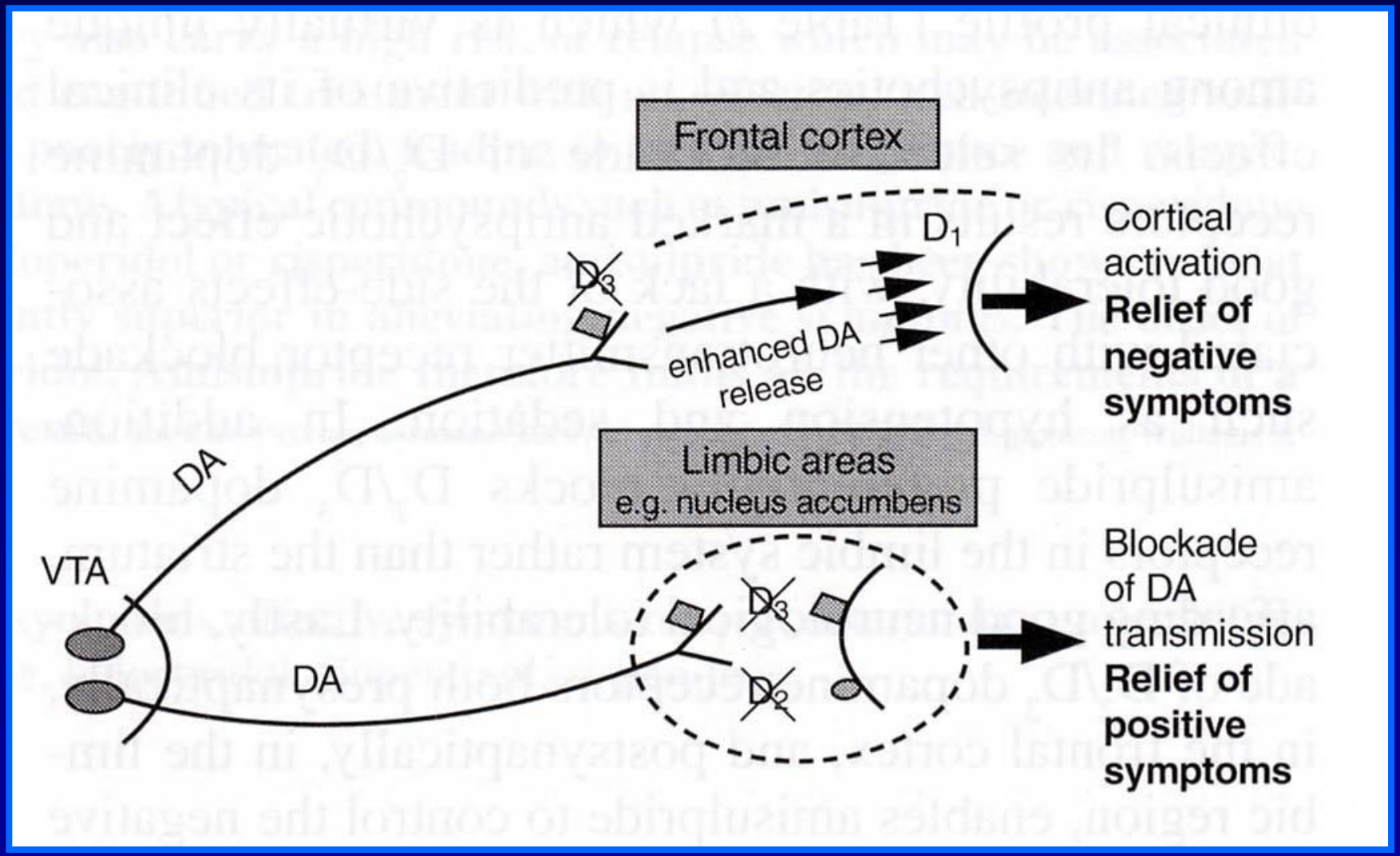
Gangli della base

↓

Minore incidenza di EPS

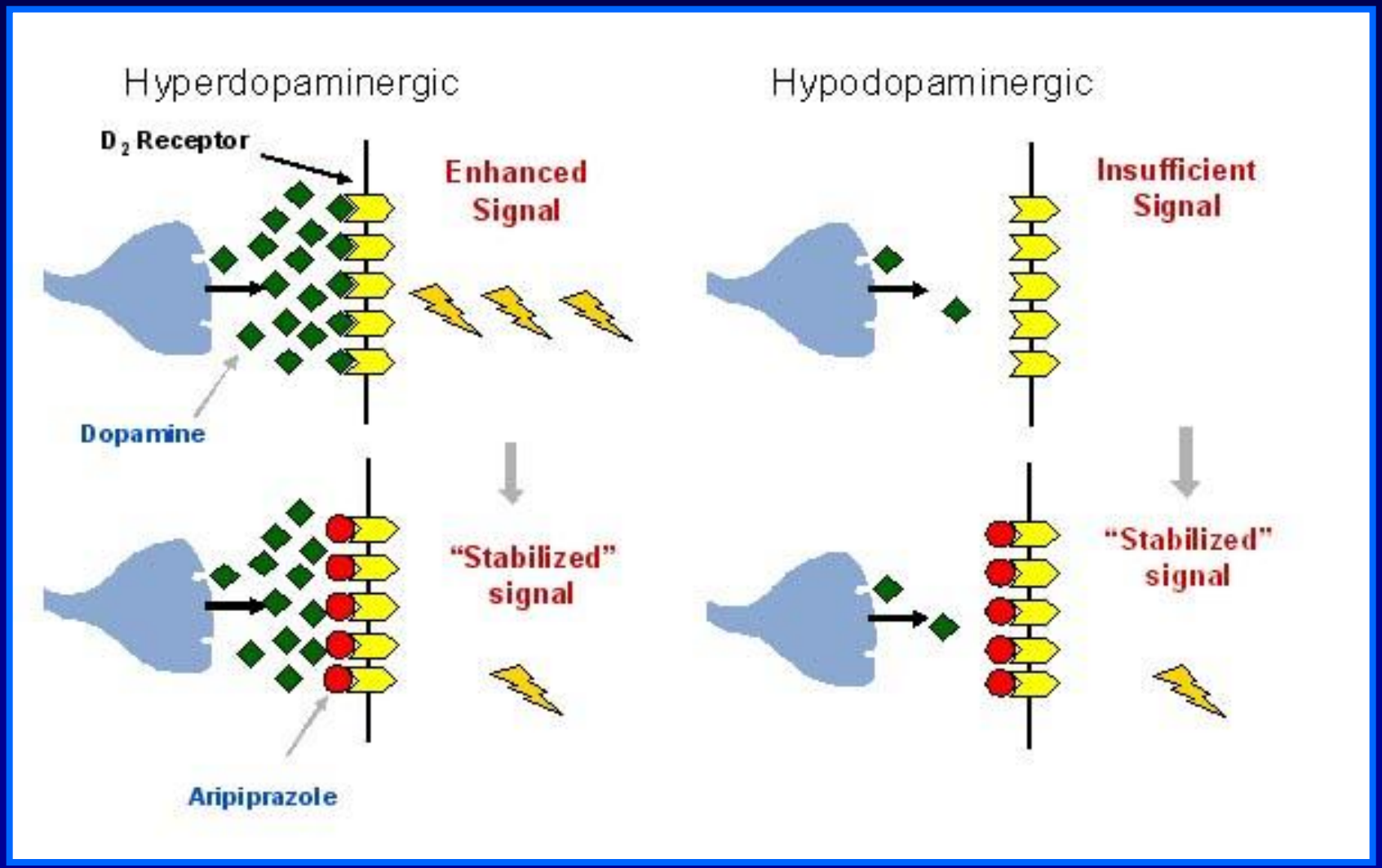
Antagonisti selettivi D_2/D_3

Amisulpride



Agonisti dopaminergici parziali

Aripiprazolo



Antipsicotici di seconda generazione

Meccanismi di potenziamento della trasmissione monoaminergica

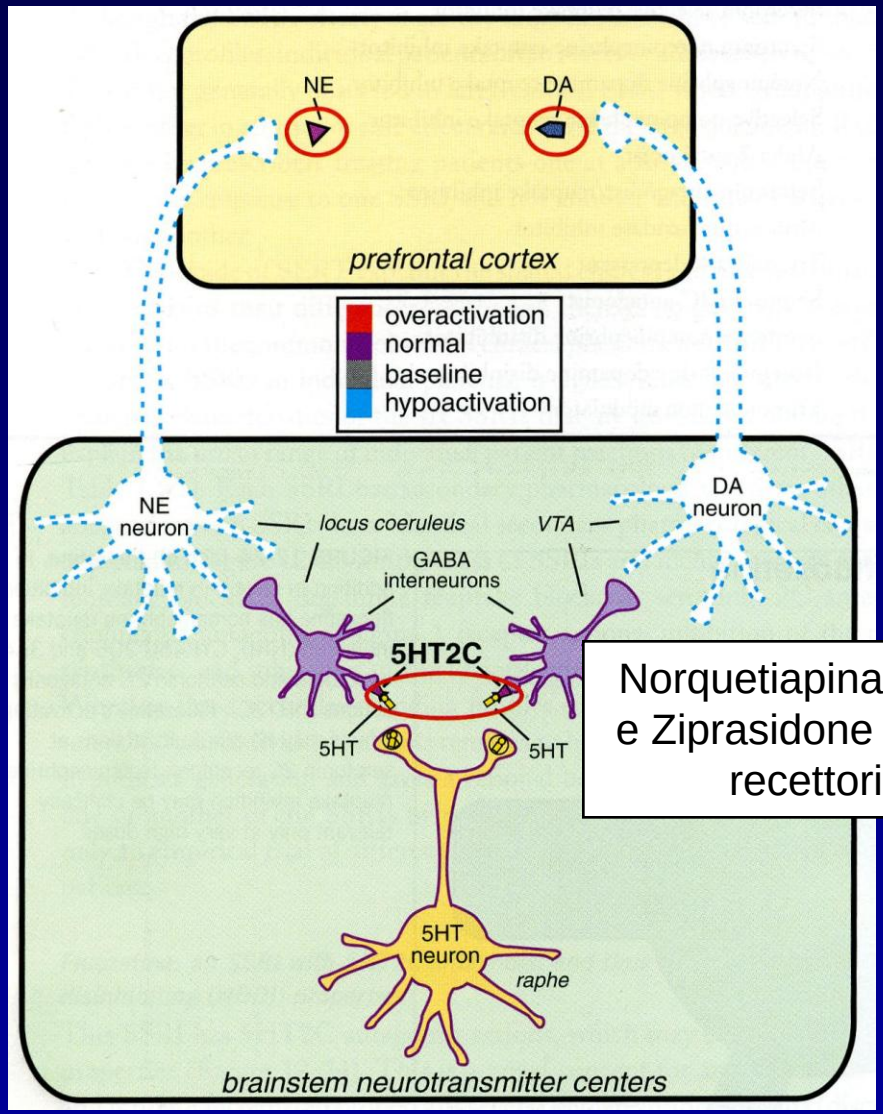
Meccanismi neurotrasmettitoriali

- **Agonismo parziale recettori $5HT_{1A}$**
- **Antagonismo recettori $5HT_{2A}$**
- **Antagonismo recettori $5HT_{2C}$**
- **Antagonismo recettori α_2-adrenergici**
- **Blocco trasportatore noradrenalina e serotonina**

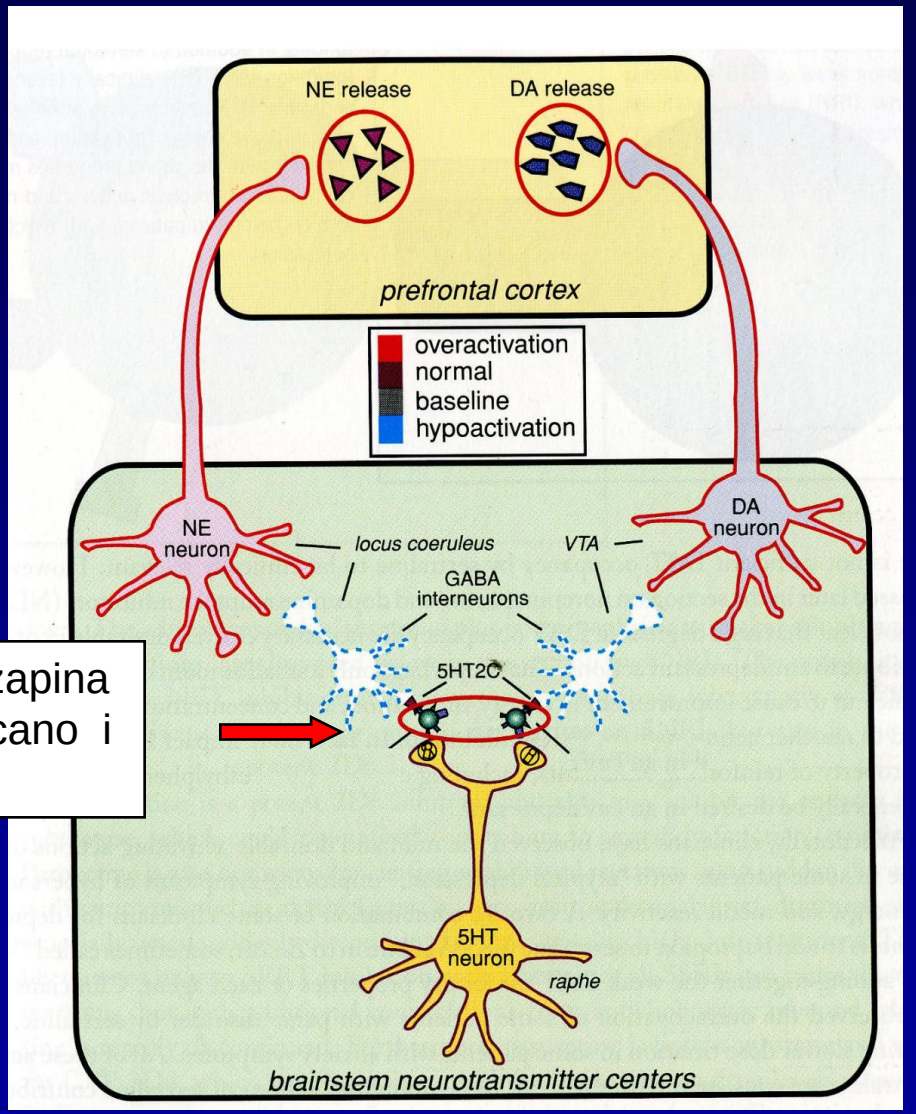
Potenziamento della trasmissione monoaminergica a livello corticale

Modified from Blier and Szabo, J Clin Psychiatry, 2005 and Stahl, Essential Psychopharmacology, 2008

Recettori $5HT_{2C}$: effetto inibitorio sul rilascio di dopamina e noradrenalina nella corteccia prefrontale



Norquetiapina, Olanzapina e Ziprasidone e bloccano i recettori $5HT_{2C}$

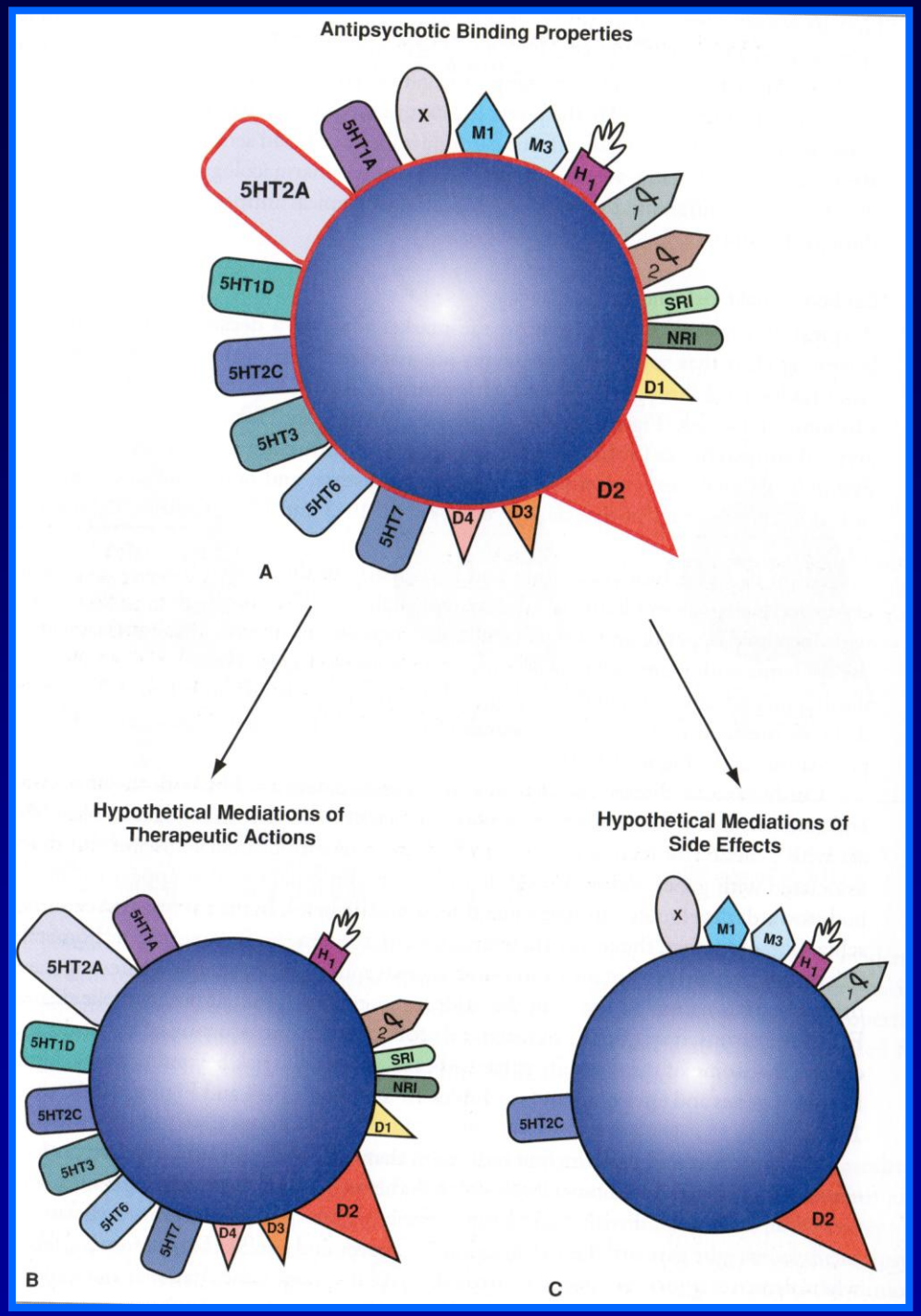


Stahl, Essential Psychopharmacology, 2008

Norquetiapina: potente inibitore del trasportatore della noradrenalina

Compound / drug	NET Ki (nM)
Quetiapine	>10000
Norquetiapine	35
Clozapine	3168
Olanzapine	>10000
Risperidone	>10000
Aripiprazole	2093
Haloperidol	2122
Nortriptyline	2
Duloxetine	8
Amitriptyline	13.3 – 35
Nomifensine	16 – 29
Paroxetine	40 – 85

Goldstein et al., 2007

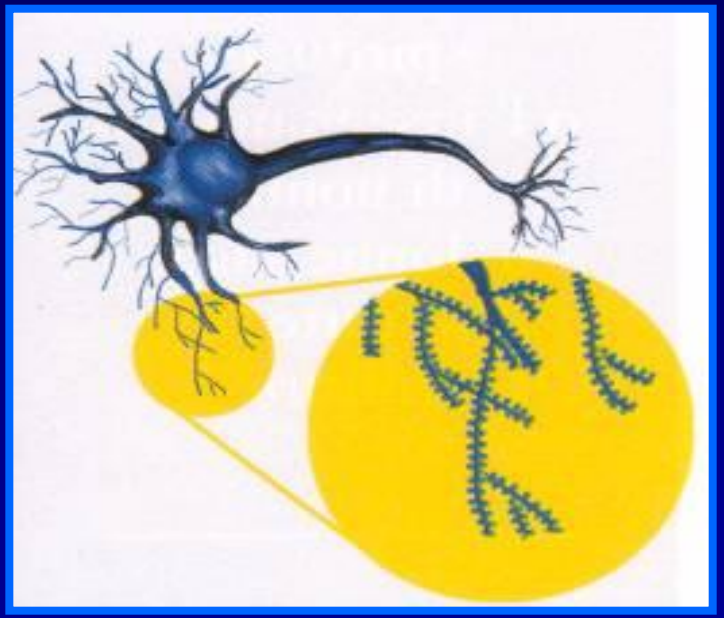


Stahl, Essential Psychopharmacology, 2008

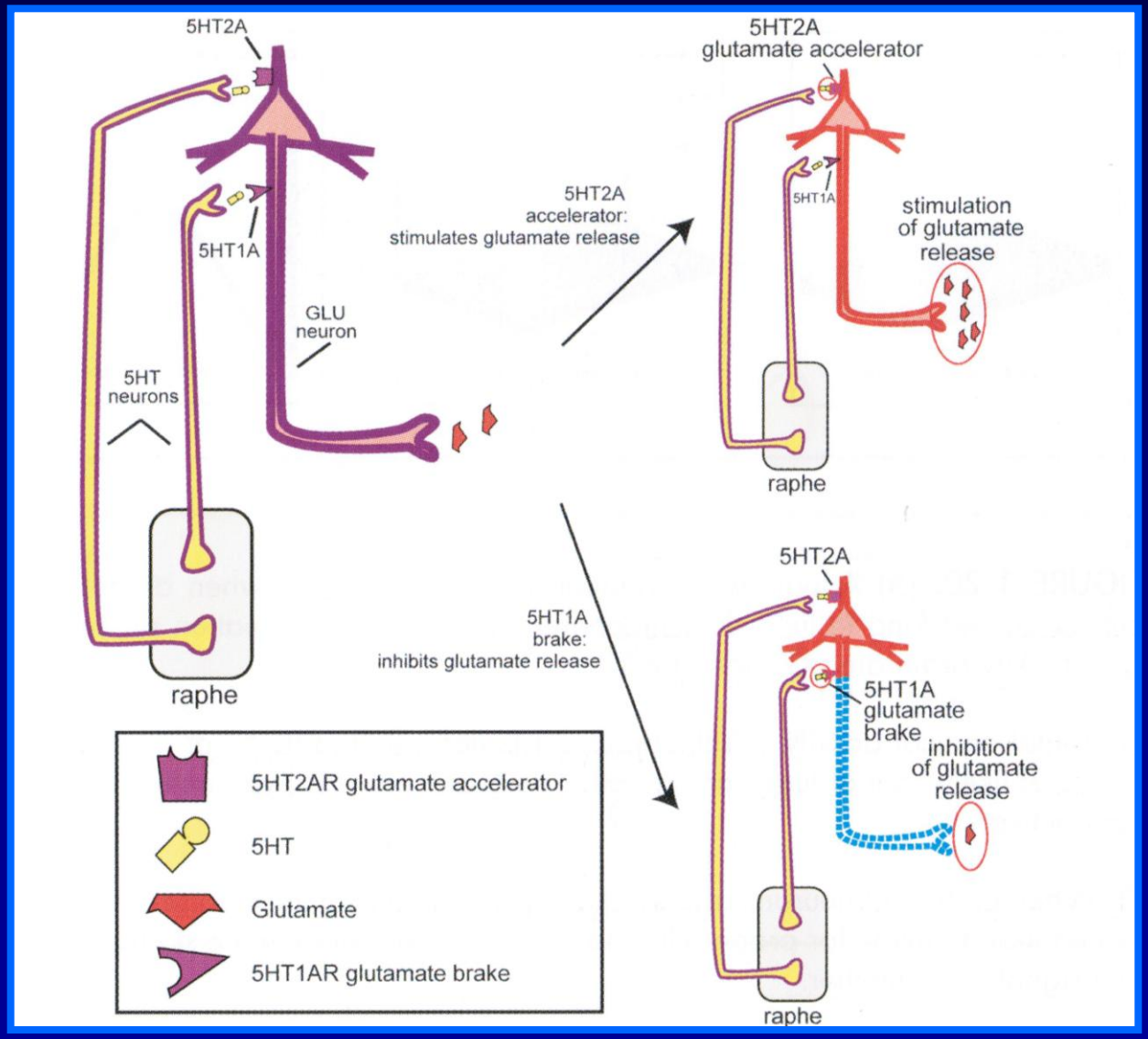
Azione neurotrofica e neuroprotettiva dei nuovi antipsicotici

Possibili meccanismi:

- inibizione della neurotossicità da glutammato
- aumento dell'espressione di fattori neurotrofici
- stimolazione della neurogenesi ippocampale

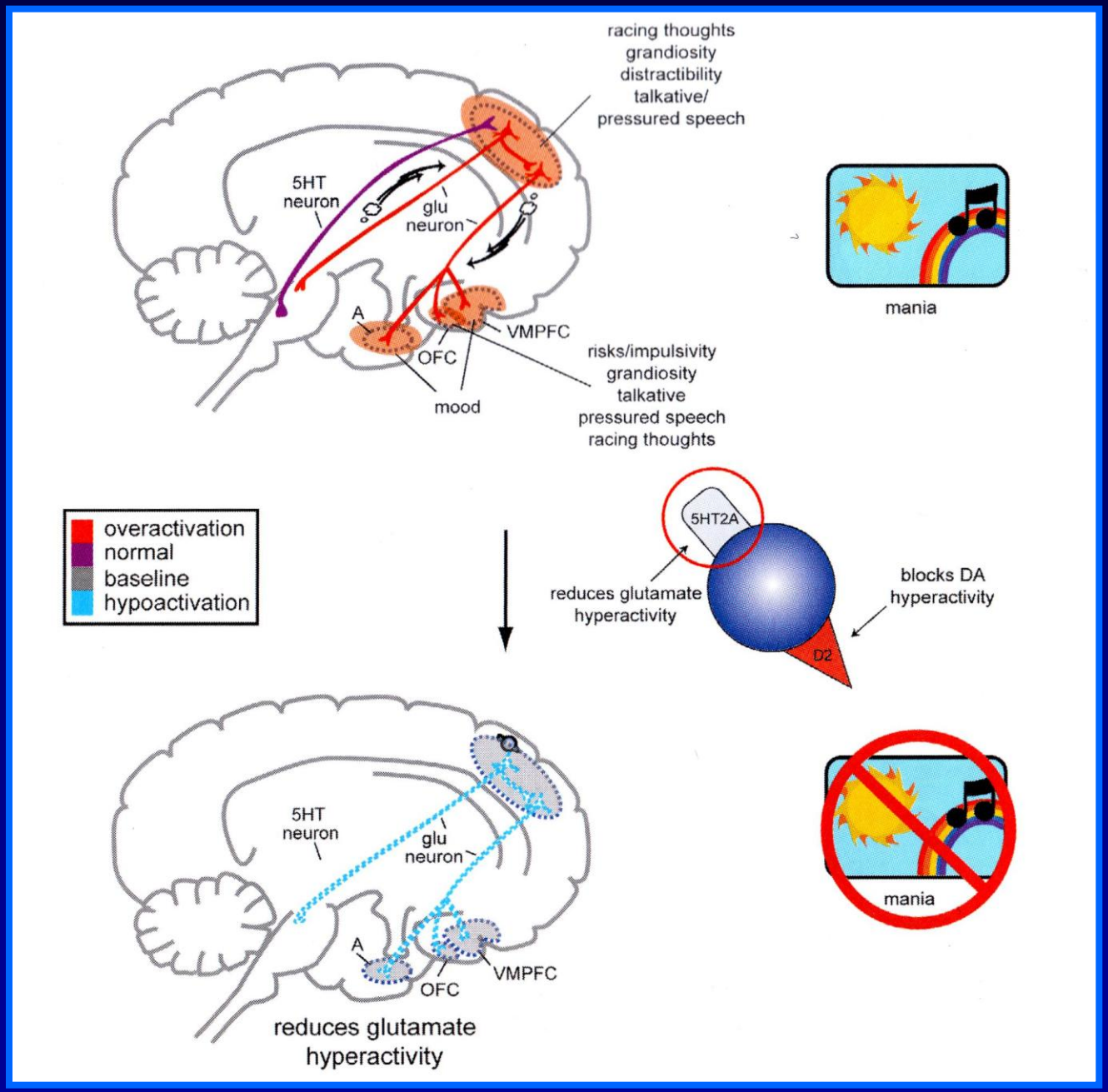


Antipsicotici atipici e glutammato



Ruolo della serotonina nel controllo del rilascio di glutammato nella corteccia

Stahl, Essential Psychopharmacology, 2008



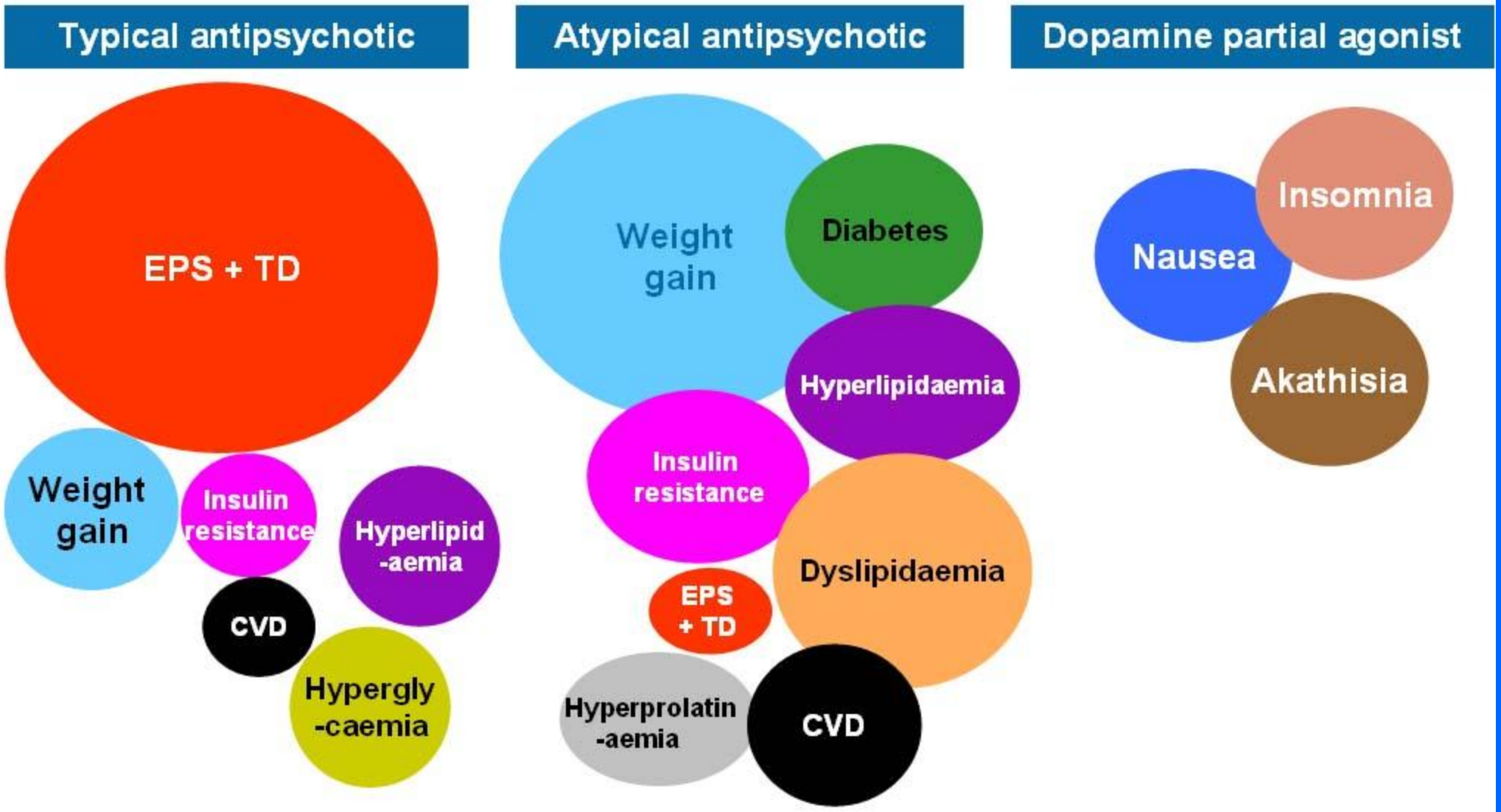
Mania

I nuovi antipsicotici riducono l'iperattivita glutammatergica

Stahl, Essential Psychopharmacology, 2008

Antipsicotici di seconda generazione

Tollerabilità



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

Typical Antipsychotics

Potent dopamine D_2 receptor antagonists

Inhibit D_2 receptors in the mesolimbic system (improving +ve symptoms), nigrostriatal pathway (may cause EPS) and tuberoinfundibular pathway (may cause hyperprolactinaemia)

Example: HAL, CHL

Atypical Antipsychotics

Potent 5-HT_{2A} and D_2 receptor antagonists

Inhibit 5-HT_{2A} receptors, thereby increasing the release of dopamine in cortex and hippocampus (improving cognition and –ve symptoms), and in nigrostriatal pathway (fewer EPS); inhibit D_2 receptors in the mesolimbic system (improving +ve symptoms)

Example: OLN, QUE, RIS, ZIP

Potent partial agonist at D_2 and 5-HT_{1A} receptors and moderate antagonist at 5-HT_{2A} receptors

Partial agonism at D_2 receptors reduces dopaminergic hyperactivity in the mesolimbic region (improving +ve symptoms); partial agonism at 5-HT_{1A} receptors compensates for dopamine hypoactivity in the mesocortical region and antagonism at 5-HT_{2A} receptors increases the release of dopamine in cortex and hippocampus (improving –ve symptoms and cognition); intrinsic activity moderates the inhibition of dopaminergic neurotransmission in the nigrostriatal pathway (fewer EPS) and tuberoinfundibular pathway (less hyperprolactinaemia)

Currently available: ARI

Common Adverse Events of Selected Agents

EPS: HAL > RIS > ZIP, ARI > OLN, QUE

Prolactin elevation: HAL, RIS > OLN, QUE, ZIP, ARI

Sedation: OLN, QUE > HAL, RIS, ZIP, ARI

Weight gain: OLN > RIS, QUE > HAL, ARI, ZIP

Risk of diabetes: OLN > QUE, RIS > ARI, HAL, ZIP

Worsening of lipid profile: OLN > QUE, RIS > ARI, HAL, ZIP

QT_c prolongation: ZIP > RIS > ARI, OLN, QUE

Typical and atypical antipsychotics also bind, with varying affinities, to other serotonergic and dopaminergic receptors, and α-adrenergic, histaminergic and muscarinic receptors, which may contribute to their tolerability profiles

Dhillon, Drugs 2012; 72: 133-162

Drug	Weight gain	Anticholinergic	Hypotension	Sedation	Prolactin elevation	EPS
Clozapine						
Olanzapine						
Risperidone						
Quetiapine						
Ziprasidone						
Aripiprazole						

Incidence/severity:

= high
= moderate
= low
= low/very low
= very low

EPS = Extrapyramidal Symptoms

Taylor, Paton & Kerwin. The Maudsley Prescribing Guidelines 9th Edition

Movement Disorders
Vol. 21, No. 5, 2006, pp. 589–598

Research Review

Epidemiology of Tardive Dyskinesia: Is Risk Declining With Modern Antipsychotics?

Daniel Tarsy, MD,[1,2*] and Ross J. Baldessarini, MD[3,4]

Schizophrenia Bulletin vol. 38 no. 1 pp. 167–177, 2012
doi:10.1093/schbul/sbq042
Advance Access publication on May 31, 2010

Second-Generation Antipsychotic Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons

Christine Rummel-Kluge[*,1], Katja Komossa[1], Sandra Schwarz[1], Heike Hunger[1], Franziska Schmid[1], Werner Kissling[1], John M. Davis[2], and Stefan Leucht[1]

Pena MS et al.

Tardive dyskinesia and other movement disorders secondary to aripiprazole

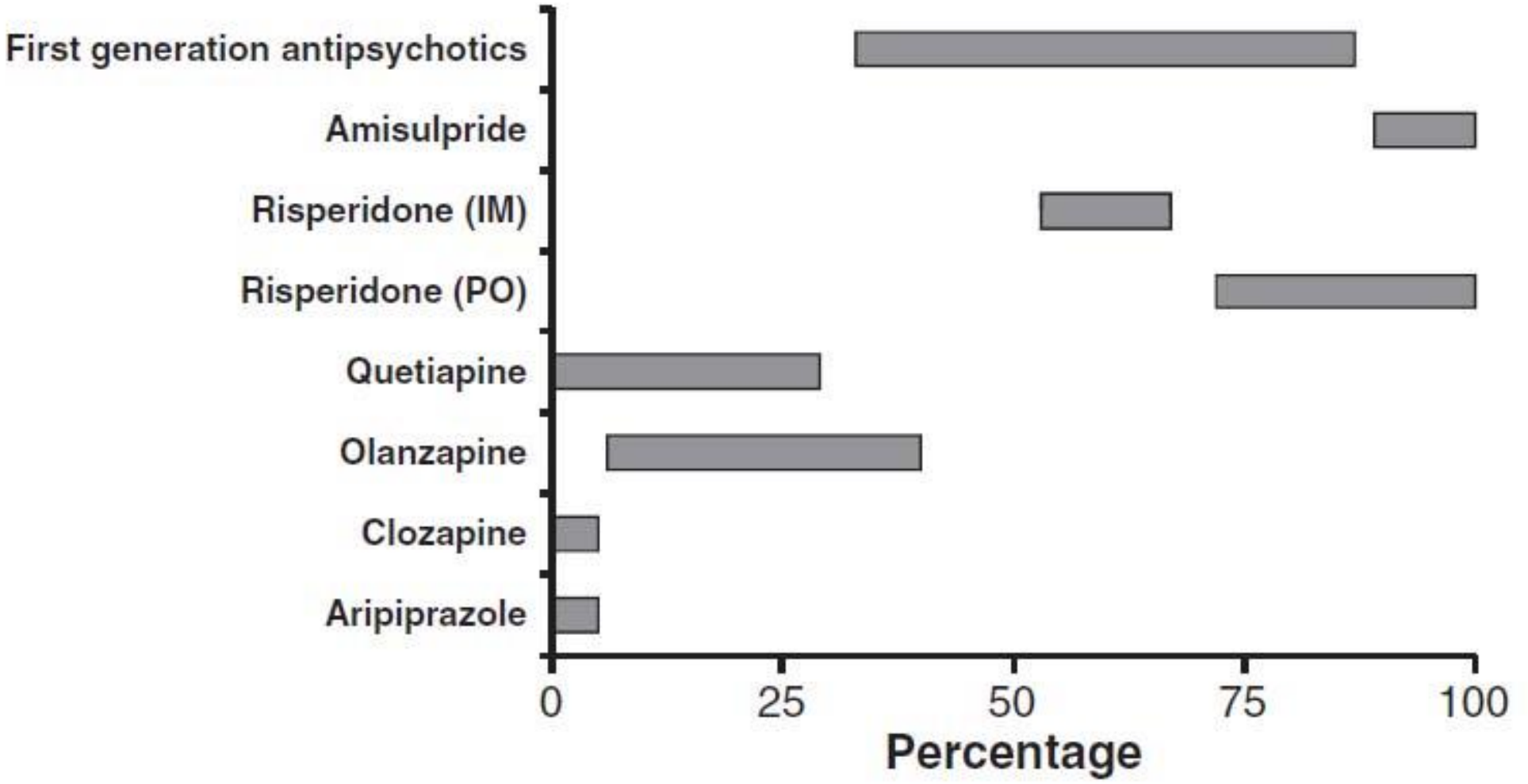
Mov Disord 2011; 26: 147-152

Alexander J, Bickerstaff S

Aripiprazole induced tardive dyskinesia-accruing evidence

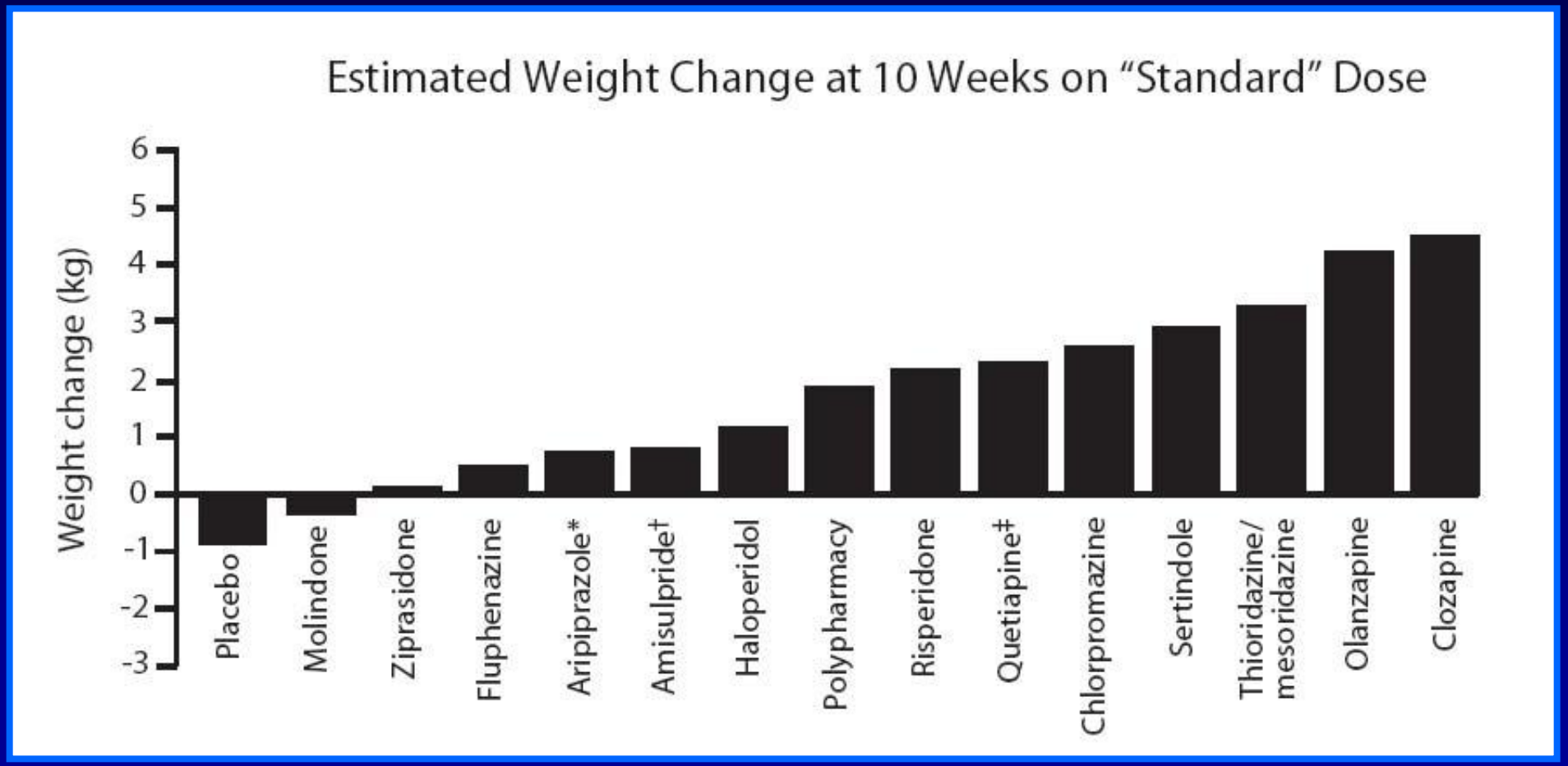
Aust N Z J Pychiatry 2012 Sep 18

Iperprolattinemia da antipsicotici: prevalenza



Holt and Peveler, Clin Endocrinol 2011; 74: 141-147

Antipsicotici ed aumento di peso



Newcomer, CNS Drugs 2005; 19(suppl 1): 1-93 (adapted from Allison et al., 1999)

Antipsicotici atipici ed effetti metabolici

	Aumento ponderale	Rischio diabetogeno	Modificazioni assetto lipidico
Clozapina	+++	+	+
Olanzapina	+++	+	+
Risperidone	++	D	D
Quetiapina	++	D	D
Aripiprazolo	+/-	-	-
Ziprasidone	+/-	-	-

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity

Diabetes Care, February 2004

Schizophrenia Research 123 (2010) 225–233

Contents lists available at ScienceDirect

Schizophrenia Research

Results: We included 48 studies with 105 relevant arms. Olanzapine produced more weight gain than all other second-generation antipsychotics except for clozapine where no difference was found. Clozapine produced more weight gain than risperidone, risperidone more than amisulpride, and sertindole more than risperidone. Olanzapine produced more cholesterol increase than aripiprazole, risperidone and ziprasidone. (No differences with amisulpride, clozapine and quetiapine were found). Quetiapine produced more cholesterol increase than risperidone and ziprasidone. Olanzapine produced more increase in glucose than amisulpride, aripiprazole, quetiapine, risperidone and ziprasidone; no difference was found with clozapine. *Conclusions:* Some SGAs lead to substantially more metabolic side effects than other SGAs. When choosing an SGA for an individual patient these side effects with their potential cause of secondary diseases must be weighed against efficacy and characteristics of the individual patient.

Original Paper

Effects on prolongation of Bazett's corrected QT interval of seven second-generation antipsychotics in the treatment of schizophrenia: a meta-analysis

Albert KK Chung and Siew-eng Chua

Psychopharm

Journal of Psychopharmacology
25(5) 646–666

DOI: 10.1177/0269881110376685
jop.sagepub.com
SAGE

REVIEW ARTICLE

CNS Drugs 2011; 25 (6): 473-490
1172-7047/11/0006-0473/$49.95/0

Assessing QT Interval Prolongation and its Associated Risks with Antipsychotics

Jimmi Nielsen,[1] *Claus Graff,*[2] *Jørgen K. Kanters,*[3,4] *Egon Toft,*[5] *David Taylor*[6,7] and *Jonathan M. Meyer*[8]

Antipsicotici e prolungamento del QTc

Drug	Mean QTc interval changes (ms)
Aripiprazole	0
Olanzapine	0-2
Risperidone	0-5
Quetiapine	6
Haloperidol	7
Pimozide	13
Ziprasidone	4.5-22
Sertindole	20
Thioridazine	25-30

Nielsen et al., CNS Drugs 2011; 25: 473-490

Nuove formulazioni degli antipsicotici di seconda generazione

Soluzione orale, gocce
- risperidone, aripiprazolo

Compresse orodispersibili
- olanzapina, aripiprazolo, risperidone

Compresse sublinguali
- asenapina

Compresse a rilascio prolungato
- paliperidone, quetiapina

Preparazioni per via intramuscolare ad azione rapida
- olanzapina, aripiprazolo, ziprasidone

Formulazioni iniettabili a lunga durata d’azione
- risperidone a rilascio prolungato, olanzapina pamoato, paliperidone palmitato

Indicazioni dei nuovi antipsicotici

	Schizofrenia	D. Bipolare Mania	D. Bipolare Depressione	D. Bipolare Profilassi	Depressione maggiore
Amisulpride	X				
Aripiprazolo	X	X		X	
Asenapina	X	X			
Clozapina	X				
Olanzapina	X	X		X	
Paliperidone	X				
Quetiapina IR	X	X	X	X	
Quetiapina ER	X	X	X	X	X
Risperidone	X	X			
Ziprasidone	X	X			

CLINICAL REVIEW

CLINICIAN'S CORNER

Efficacy and Comparative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults

A Systematic Review and Meta-analysis

Alicia Ruelaz Maher, MD
Margaret Maglione, MPP
Steven Bagley, MD
Marika Suttorp, MS
Jian-Hui Hu, MPP
Brett Ewing, MS
Zhen Wang, MS
Martha Timmer, MS
David Sultzer, MD
Paul G. Shekelle, MD, PhD

Context Atypical antipsychotic medications are commonly used for off-label conditions such as agitation in dementia, anxiety, and obsessive-compulsive disorder.

Objective To perform a systematic review on the efficacy and safety of atypical antipsychotic medications for use in conditions lacking approval for labeling and marketing by the US Food and Drug Administration.

Data Sources and Study Selection Relevant studies published in the English language were identified by searches of 6 databases (PubMed, EMBASE, CINAHL, PsycInfo, Cochrane DARE, and CENTRAL) from inception through May 2011. Controlled trials comparing an atypical antipsychotic medication (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine, iloperidone, or paliperidone) with placebo, another atypical antipsychotic medication, or other pharmacotherapy for adult off-label conditions were included. Observational studies with sample sizes of greater than 1000 patients were included to assess adverse events.

- Risperidone, olanzapina, aripiprazolo e, in misura minore, quetiapina sono efficaci nel trattamento dei disturbi comportamentali associati a demenza
- La quetiapina è efficace nel trattamento del disturbo da ansia generalizzata
- Il risperidone è efficace come trattamento del disturbo ossessivo-compulsivo resistente agli SSRI

Reviews and Overviews

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S.

Am J Psychiatry 2006; 163: 185-194

Gli Autori hanno condotto, in cieco, un'analisi di 34 confronti "testa-a-testa" tra antipsicotici di seconda generazione, trovando che il risultato dello studio, in oltre il 90% dei casi, favoriva il farmaco prodotto dallo sponsor

A Meta-Analysis of Head-to-Head Comparisons of Second-Generation Antipsychotics in the Treatment of Schizophrenia

Stefan Leucht, M.D.

Katja Komossa, M.D.

Christine Rummel-Kluge, M.D.

Caroline Corves, M.Sc.

Heike Hunger

Franziska Schmid

Claudia Asenjo Lobos, M.Sc.

Sandra Schwarz

John M. Davis, M.D.

Objective: Whether there are differences in efficacy among second-generation antipsychotics in the treatment of schizophrenia is a matter of heated debate. The authors conducted a systematic review and meta-analysis of blinded studies comparing second-generation antipsychotics head-to-head.

Method: Searches of the Cochrane Schizophrenia Group's register (May 2007) and MEDLINE (September 2007) were conducted for randomized, blinded studies comparing two or more of nine second-generation antipsychotics in the treatment of schizophrenia. All data were extracted by at least three reviewers independently. The primary outcome measure was change in total score on the Positive and Negative Syndrome Scale; secondary outcome measures were positive and negative symptom subscores and rate of dropout due to inefficacy. The results were combined in a meta-analysis. Various sensitivity analyses and metaregressions were used to examine bias.

Results: The analysis included 78 studies with 167 relevant arms and 13,558 participants. Olanzapine proved superior to aripiprazole, quetiapine, risperidone, and ziprasidone. Risperidone was more efficacious than quetiapine and ziprasidone. Clozapine proved superior to zotepine and, in doses >400 mg/day, to risperidone. These differences were due to improvement in positive symptoms rather than negative symptoms. The results were rather robust with regard to the effects of industry sponsorship, study quality, dosages, and trial duration.

Conclusions: The findings suggest that some second-generation antipsychotics may be somewhat more efficacious than others, but the limitations of meta-analysis must be considered. In tailoring drug treatment to the individual patient, small efficacy superiorities must be weighed against large differences in side effects and cost.

(Am J Psychiatry 2009; 166:152–163)

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis

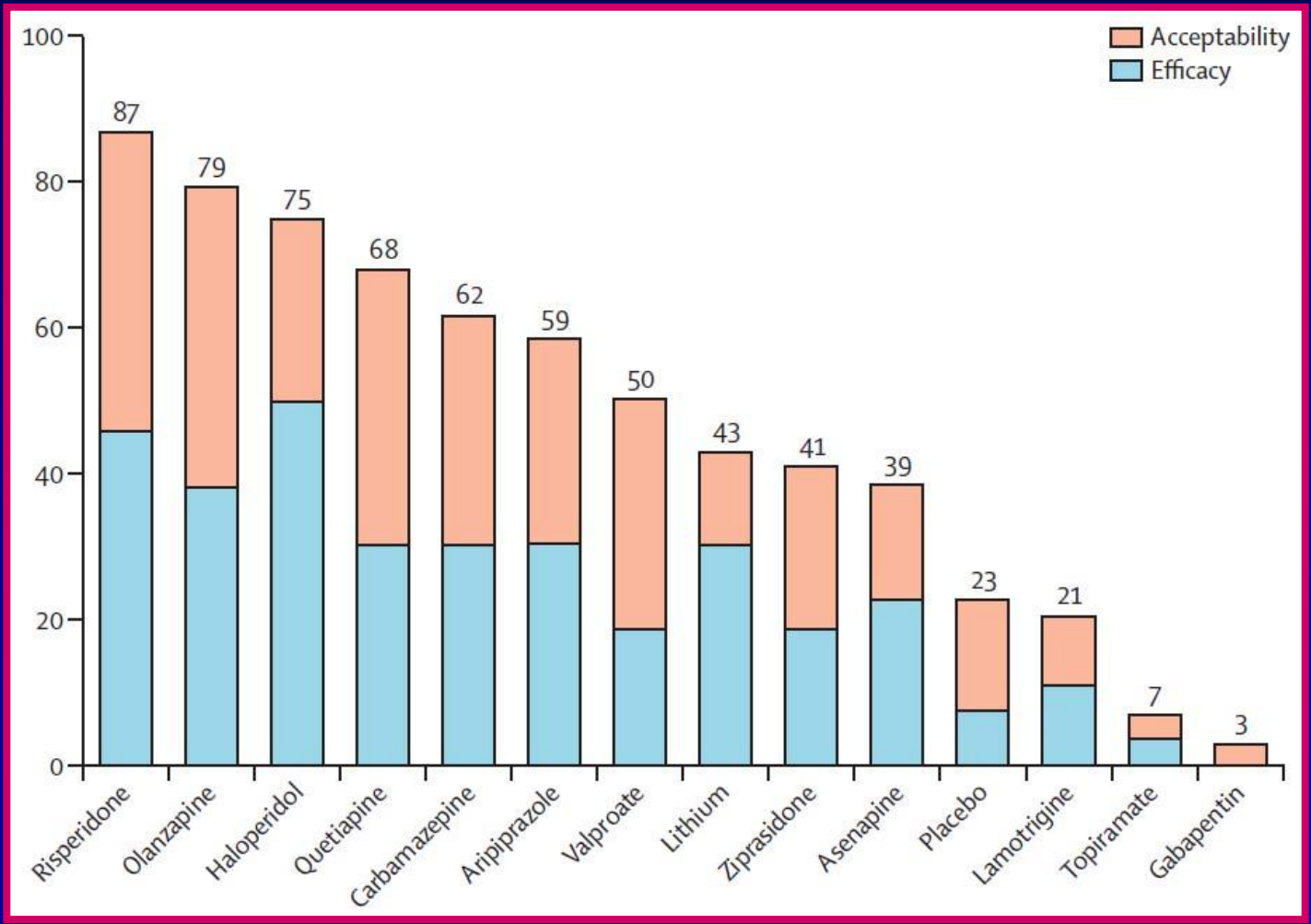
Lancet 2009; 373: 31–41

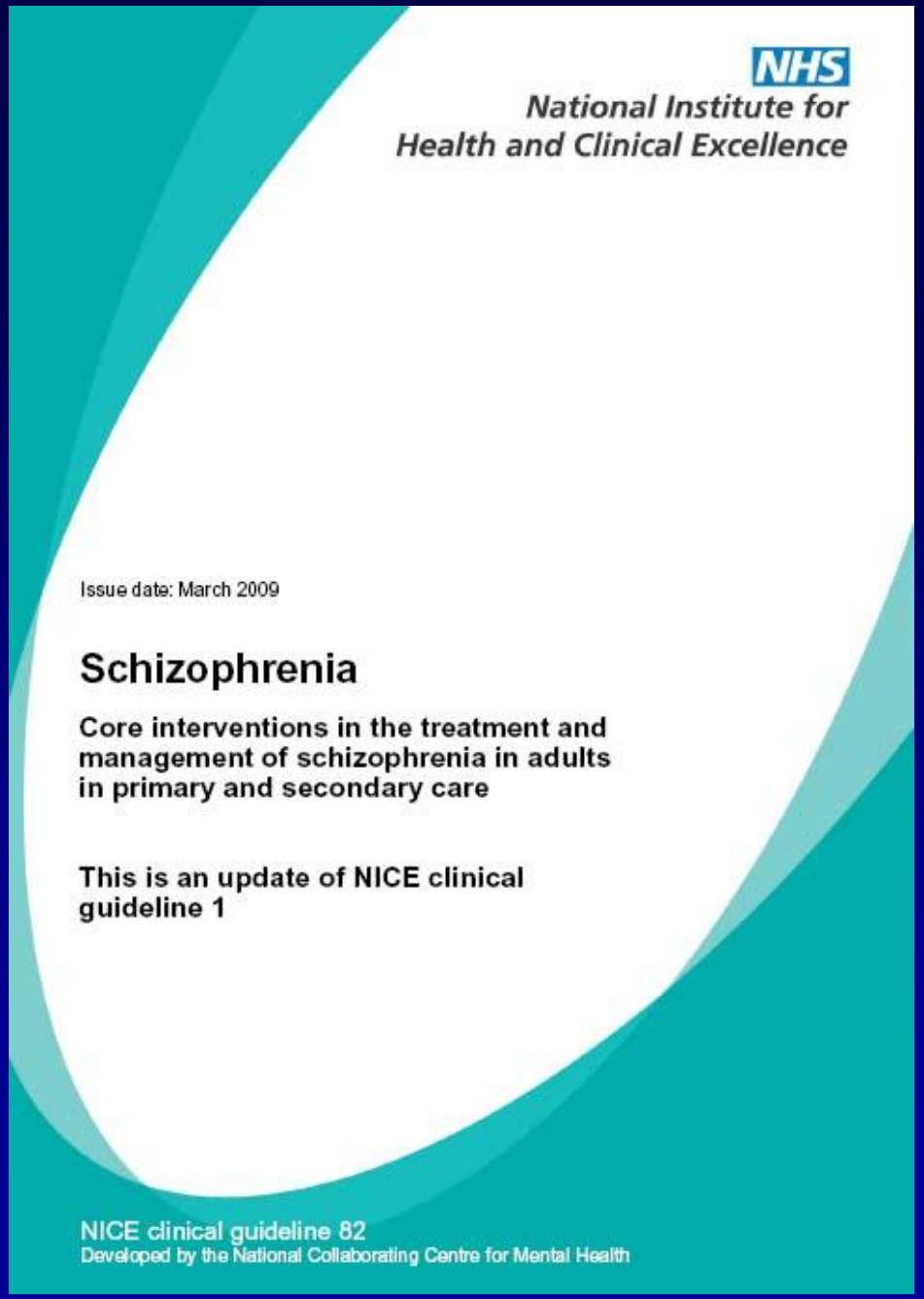
- Four SGA, namely clozapine, amisulpride, olanzapine and risperidone, were better than FGA for overall efficacy
- SGA induced fewer EPS
- With the exception of aripiprazole and ziprasidone, SGA induced more weight gain
- SGA differ in many properties and are not a homogeneous class

Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

Andrea Cipriani, Corrado Barbui, Georgia Salanti, Jennifer Rendell, Rachel Brown, Sarah Stockton, Marianna Purgato, Loukia M Spineli, Guy M Goodwin, John R Geddes

Lancet 2011; 378: 1306-1315





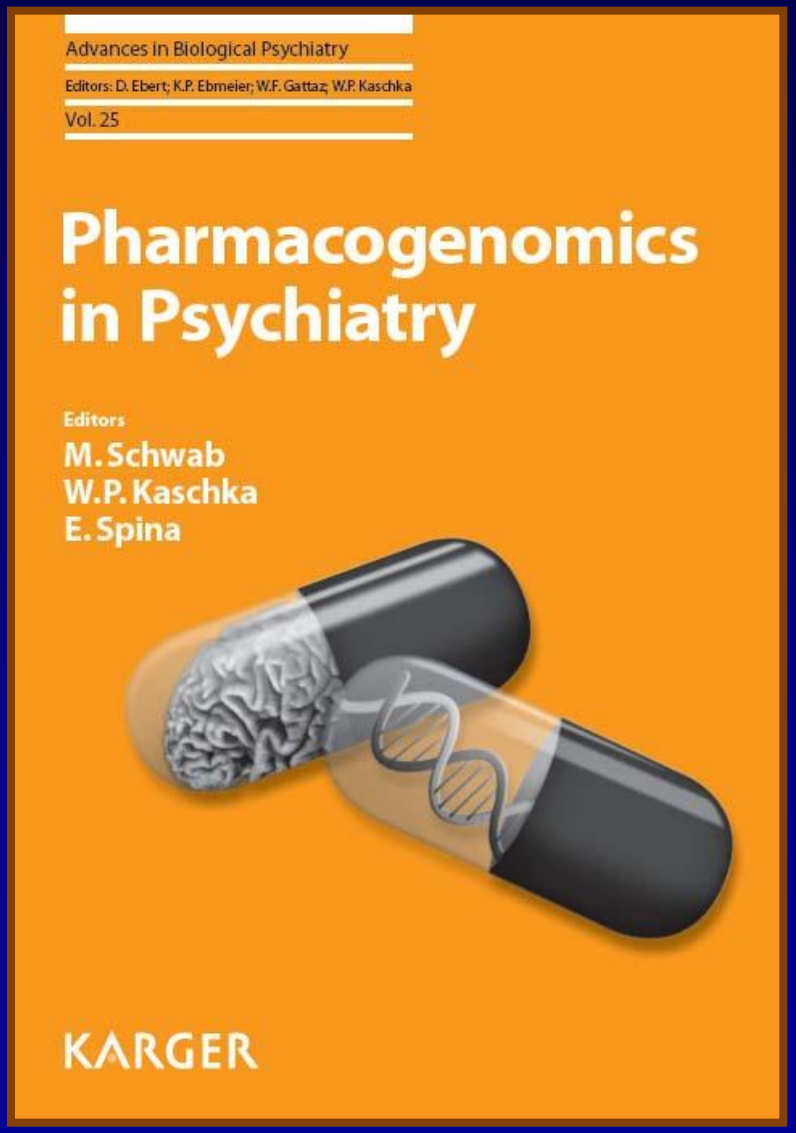
The selection of the antipsychotic drug should be based on benefit and side-effect profile (extrapyramidal symptoms vs metabolic side effects)

Classi terapeutiche omogenee: mito o realtà?

La scelta del farmaco da prescrivere in pazienti con patologie psichiatriche deve essere basata sul rapporto rischio-beneficio, sul costo di acquisizione e deve tener conto delle caratteristiche di ciascun paziente

Prescrizione razionale degli antipsicotici

Farmacogenetica e farmacogenomica



…The only FDA-required pharmacogenetic test in psychiatry is a test for one drug and for one racial group, and it only eliminates the risk of a relatively rare idiosyncratic adverse drug reaction (HLA-B*1502 genotyping in Asians for carbamazepine)…

Grazie per

l’attenzione!