"Trattamento farmacologico degli esordi"

Marco Venuta

Le linee guida sulla schizofrenia sono assai poco consultate o rispettate in nome:

1. dell’autonomia di scelta
2. dell’unicità del proprio paziente
3. delle differenze tra i pazienti dei trial e del “mondo reale”
4. del consumo di tempo per la consultazione
5. del consumo di “lavoro cartaceo”
6. dell’aumento della spesa
7. della considerazione che ciò che si sta già facendo funziona
8. della considerazione che nessuno dei colleghi lo fa

AHRQ Agency for Healthcare Research and Quality

Advancing Excellence in Health Care

National Guideline Clearinghouse

2.608 linee guida al 1° settembre 2011

Tutte affermano di essere evidence-based, ma non mancano elementi palesemente contraddittori. Qualcuno si sta perdendo qualche evidenza? Qualcuno ha conflitti di interessi? Mancano revisioni esterne

Aree di contenuti delle linee guida sulla schizofrenia

	Expert 1999	APA 2008	PORT 2009	IPAP 2006	TMAP 2006	NICE 2009
Selezione dei farmaci	■	■	■	■	■	■
Interventi psicosociali	■	■	■			■
Documentazione sanitaria		■			■	■
Politica sanitaria	■					■
Settings del trattamento	■	■				■

Expert consensus guidelines, American Psychiatric Association, Patient Outcomes Research Team, International Psychopharmacology Algorithm Project, Texas Medication Algorithm Project, National Institute for health and Clinical Excellence

Contenuti delle linee guida sulla schizofrenia

	Expert 1999	APA 2008	PORT 2009	IPAP 2006	TMAP 2006	NICE 2009
Dosi per il mantenimento	■	■	■		■	■
Evitare terapie intermittenti	■	■	■	■	■	■
Farmaci contro gli EC		■			■	■
Indicazioni sullo switch	■					
Indicazioni sui costi	■					■

Expert consensus guidelines, American Psychiatric Association, Patient Outcomes Research Team, International Psychopharmacology Algorithm Project, Texas Medication Algorithm Project, National Institute for health and Clinical Excellence

Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study **CUtLASS 1** Arch Gen Psychiatry. 2006;63:1079–1087

Lieberman JA, Stroup TS, McEvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness **CATIE** Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209–1223.

Kahn RS, Fleischhacker WW, Boter H, et al. **EUFEST** study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371:1085–1097.

TMAP 2006

PORT 2009

NICE 2009

Raccomandazioni farmacologiche delle linee guida

	Expert 1999	APA 2008	PORT 2009	IPAP 2006	TMAP 2006	NICE 2009
Primo episodio / prima scelta	**SGA**	**SGA**	**SGA,FGA**	**SGA**	**SGA**	**SGA,FGA**
Seconda scelta	**SGA**	**SGA/FGA Clozapine**	**SGA,FGA**	**SGA**	**SGA,FGA**	**SGA,FGA**
Terza scelta	**Clozapine**	**Clozapine**	**Clozapine**	**Clozapine**	**Clozapine**	**Clozapine**
Quarta scelta	**Clozapine augment.**	**Clozapine augment.**	**-**	**Clozapine augment., SGA**	**Clozapine augment.**	**Clozapine augment.**
Quinta scelta	**-**	**-**	**-**	**-**	**SGA,FGA**	**-**
Sesta scelta	**-**	**-**	**-**	**-**	**Combinations**	**-**

SGA = second generation antipsychotics, FGA = first generation antipsychotics

Cosa dice Cochrane: FGA vs SGA

AMISULPRIDE	Amisulpride may offer a **good general profile**, at least compared to high-potency 'typical' antipsychotics. It may also yield **better results** in some specific outcomes related to efficacy, such **as impro-vement of global state and general negative symptoms**. It might be **more acceptable and more tolerable** than high-potency conventional antipsychotics, **especially regarding extrapyramidal side-effects.**
ARIPIPRAZOLO	Aripiprazole presents **significant advantages in terms of tolerability**
CLOZAPINA	Clozapine **may be more effective** in reducing symptoms of schizophrenia, producing clinically meaningful improvements and postponing relapse, than typical antipsychotic drugs - **but data are weak and prone to bias**. **Participants were more satisfied** with clozapine
OLANZAPINA	The **large proportion of participants leaving studies early** in these trials makes it difficult to draw firm conclusions on olanzapine's clinical effects. For people with schizophrenia it may offer antipsychotic efficacy with **fewer extrapyramidal** adverse effects than typical drugs, but **more weight gain**.

Cosa dice Cochrane: FGA vs SGA

QUETIAPINA	Not much different with respect to treatment withdrawal and efficacy. In comparison to FGA quetiapine has a **lower risk of movement disorders but higher risks of dizziness, dry mouth and sleepiness.**
RISPERIDONE	May be **more acceptable** than FGA and have marginal benefits in terms of limited clinical improvement. Its **adverse effect profile may be better than haloperidol**. Any marginal benefits this drug may have to be balanced against its **greater cost and increased tendency to cause side effects such as weight gain**. Recent important longer term data favouring risperidone's effect on relapse needs to be replicated by researchers independently of the manufacturers.
ZIPRASIDONE	Currently data are limited. It may be an effective antipsychotic with **less extrapyramidal effects than haloperidol**. It also, however, **causes more nausea and vomiting than the typical drugs**
SGAs PER IL PRIMO EPISODIO	The results of this review are **inconclusive**. Whether the use of new generation antipsychotics really makes the treatment less off putting and enhances long-term compliance is unclear.

Cosa dice Cochrane: Clozapina

Clozapine versus other atypical antipsychotics for schizophrenia	Clozapine may be a **little more efficacious than zotepine and risperidone but further trials are required to confirm this finding**. (nothing more amisulpride, aripiprazole, olanzapine, quetiapine, sertindole, ziprasidone)
Newer atypical antipsychotic medication versus clozapine for schizophrenia	The equal effectiveness and tolerability of new atypical drugs in comparison with clozapine is not yet demonstrated. **Lack of statistical power to determine the comparative efficacy and effectiveness of newer atypical drugs makes it difficult to judge whether newer drugs are more effective, less effective or equivalent.** Trials of sufficient power, with longer duration, measuring clinically important outcomes, are needed to assess the true comparative clinical effectiveness, tolerability and cost effectiveness of newer drugs in relation to clozapine.
Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia	**Although clinical guidelines recommend a second antipsychotic in addition to clozapine in partially responsive patients with schizophrenia, the present systematic review was not able to show if any particular combination strategy was superior to the others.**

Raccomandazioni farmacologiche delle linee guida

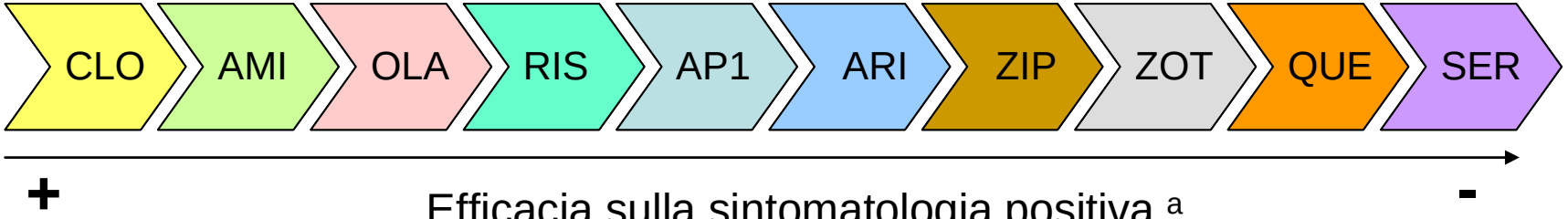
Le decisioni, più che dall'efficacia, sono orientate da:

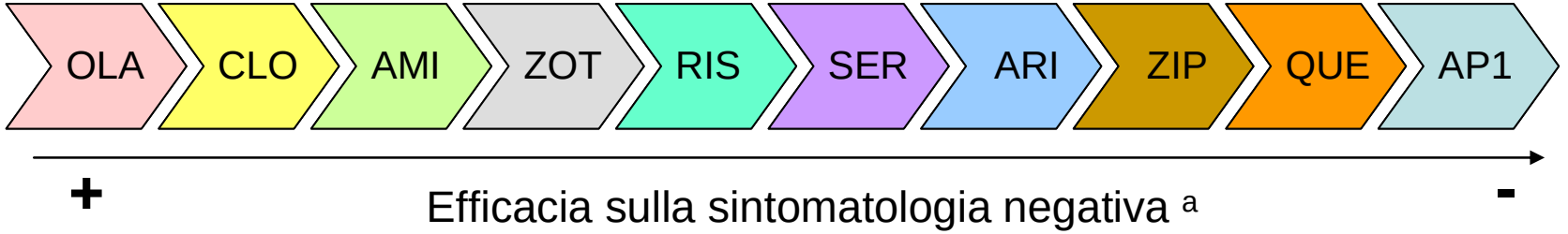
Effetti collaterali
Tollerabilità
Esiti nel lungo termine

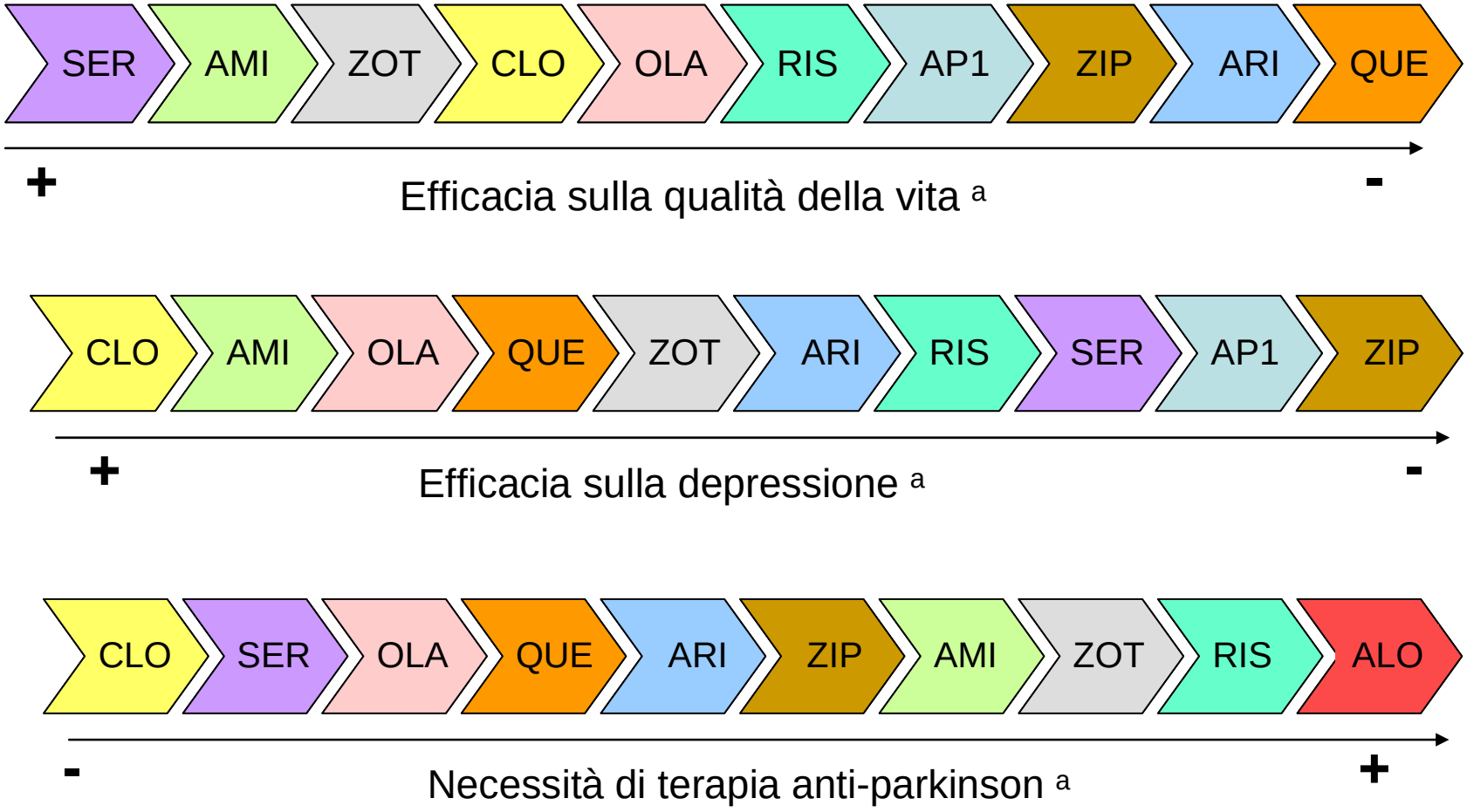
L’efficacia degli antipsicotici nella schizofrenia è ancora decisamente insoddisfacente.

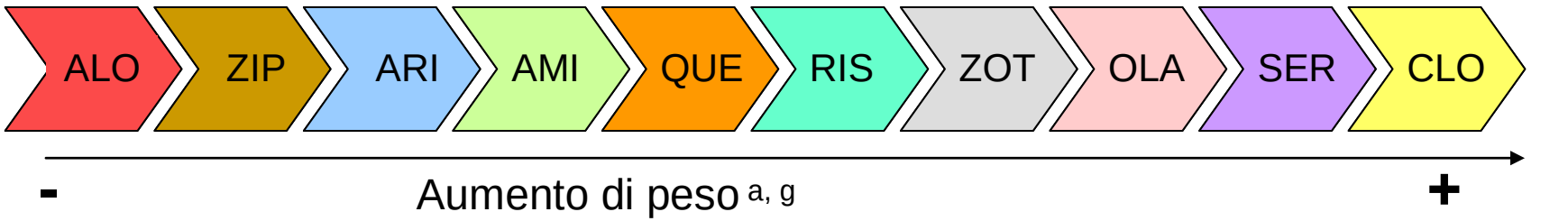
La quota di soggetti che completavano il trattamento iniziale valutata dopo 18 mesi nello studio CATIE era del 26%

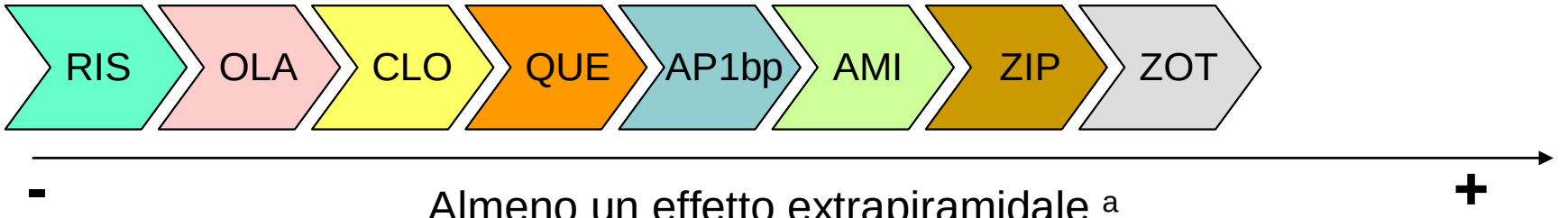

CLO
AMI
OLA
RIS
ZOT
ARI
AP1
SER
ZIP
QUE
+
-
Efficacia sulla sintomatologia totale a

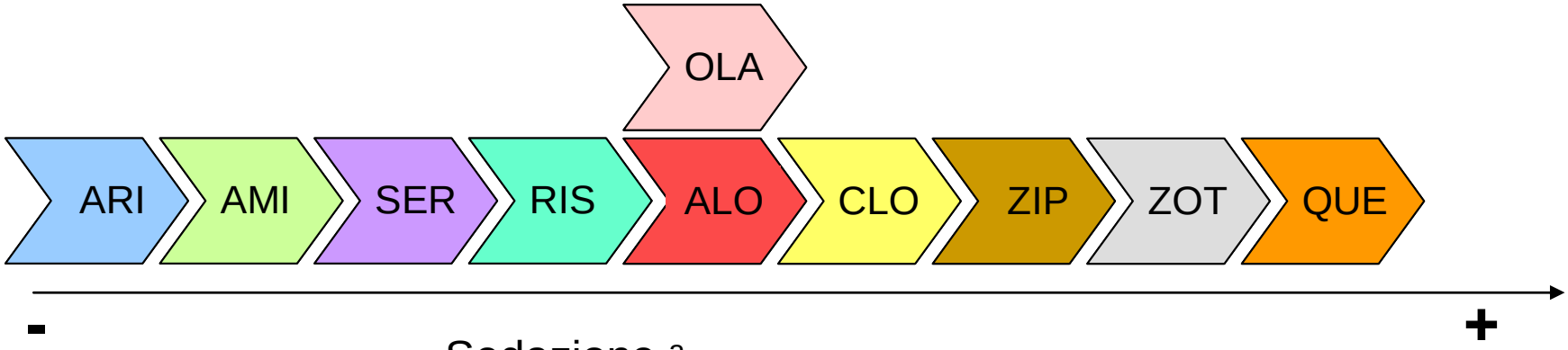

CLO
AMI
OLA
RIS
AP1
ARI
ZIP
ZOT
QUE
SER
+
-
Efficacia sulla sintomatologia positiva a

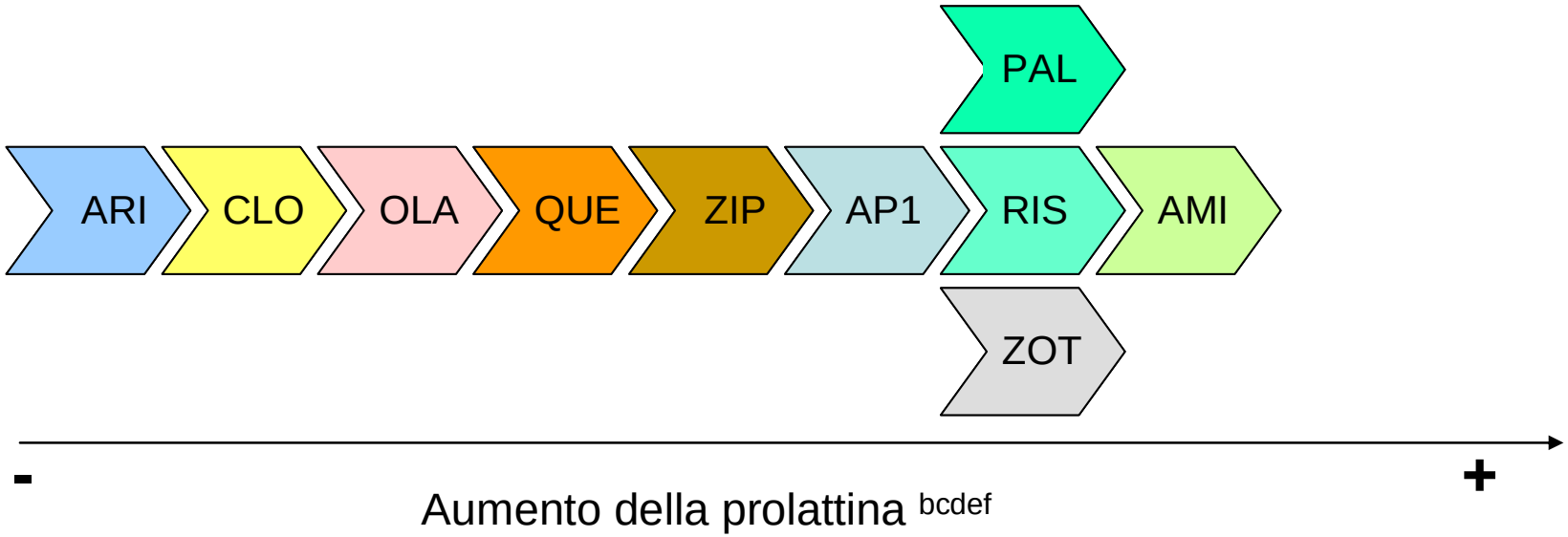

OLA
CLO
AMI
ZOT
RIS
SER
ARI
ZIP
QUE
AP1
+
-
Efficacia sulla sintomatologia negativa a


SER AMI ZOT CLO OLA RIS AP1 ZIP ARI QUE
+
-
Efficacia sulla qualità della vita a
CLO AMI OLA QUE ZOT ARI RIS SER AP1 ZIP
+
-
Efficacia sulla depressione a
CLO SER OLA QUE ARI ZIP AMI ZOT RIS ALO
-
+
Necessità di terapia anti-parkinson a


ALO
ZIP
ARI
AMI
QUE
RIS
ZOT
OLA
SER
CLO
-
Aumento di peso a, g
+


RIS
OLA
CLO
QUE
AP1bp
AMI
ZIP
ZOT
-
Almeno un effetto extrapiramidale a
+


OLA
ARI
AMI
SER
RIS
ALO
CLO
ZIP
ZOT
QUE
-
Sedazione a
+


PAL
ARI
CLO
OLA
QUE
ZIP
AP1
RIS
AMI
ZOT
-
+
Aumento della prolattina bcdef

Antipsicotici con segnalazioni di Torsades / Arresto cardiaco

(elenco non esaustivo)

Aloperidolo	Meyer-Massetti et al. 2010;Jolly et al. 2009; Poluzzi et al .2009; Sicouri et al. 2008
Amisulpride	Chung e Chua, 2010; Karlsson et al. 2009
Aripiprazolo	Karlsson et al. 2009
Cloropromazina	Sicouri et al. 2008
Clozapina	Karlsson et al. 2009;Sicouri et al. 2008
Droperidolo	Sicouri et al. 2008
Flufenazina	Stollberger et al. 2005
Levomepromazina	Kondou et al. 1993
Loxapina	Sicouri et al. 2008
Olanzapina	Jolly et al. 2009; Karlsson et al. 2009
Perfenazina	Sicouri et al. 2008
Pimozide	Sicouri et al. 2008, Krahenbuhl 1995
Quetiapina	Poluzzi et al .2009; Karlsson et al. 2009; Sicouri et al. 2008
Risperidone	Jolly et al. 2009; Poluzzi et al .2009; Karlsson et al. 2009; Sicouri et al. 2008; Hennessy et al. 2002
Sertindolo	Karlsson et al. 2009; Sicouri et al. 2008
Sulpiride	Karlsson et al. 2009; Huang et al. 2007
Sultopride	Sicouri et al. 2008
Tioridazina	Sinkiewicz et al 2006; Sicouri et al. 2008; Hennessy et al. 2002; Reilly et al. 2002
Trifluorperazina	Sicouri et al. 2008
Ziprasidone	Poluzzi et al .2009; Karlsson et al. 2009; Sicouri et al. 2008; Heinrich et al. 2006

Cosa dice Cochrane: Discinesia tardiva

Anticholinergic medication	**No confident statement** can be made about the effectiveness
Benzodiazepines	One small study reports some preliminary evidence that may have **some effect**. Routine clinical use is **not indicated** and these treatments remain experimental.
Calcium channel blockers	The effects are **unknown.**
Cholinergic medication	The clinical effects of older cholinergic drugs are **unclear**, as too few, too small studies leave many questions unanswered.
Vitamin E	Small trials of limited quality suggest that vitamin E may protect against deterioration of TD. There is **no evidence** that vitamin E improves symptoms.
Neuroleptic reduction and/or cessation and neuroleptics	Limited data from small studies using neuroleptic reduction or specific neuroleptic drugs as treatments for TD did **not provide any convincing evidence** of the value of these approaches.
Miscellaneous treatments	There is **no strong evidence** to support the everyday use of any of ceruletide, gamma-linolenic or eicosapentaenoic acid, oestrogen, phenylalanine, lithium, insuline, piracetam

Cosa dice Cochrane: Acatisia acuta

Anticholinergic medication	At present, there is **no reliable evidence** to support or refute the use of anticholinergics
Benzodiazepines	Over a short follow-up period, the use of benzodiazepines **may reduce the symptoms** of antipsychotic-induced acute akathisia.
Beta blockers	There are **insufficient data** to recommend beta-blocking drugs for akathisia. These drugs are experimental for this problem.

Cosa dice Cochrane: vari EC

Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems	Evidence from this review suggests that switching antipsychotic medication to one with lesser potential for causing weight gain or metabolic problems **could be an effective** way to manage these side effects, but the **data were weak** due to the limited number of trials in this area and small sample sizes.
Management of sexual dysfunction due to antipsychotic drug therapy	**Sildenafil may be a useful option** in the treatment of antipsychotic-induced sexual dysfunction in men with schizophrenia, **but this conclusion is based only on one small short trial**. No evidence for selegiline.
Pharmacological treatments for psychosis-related polydipsia	Neither the studies with oral demeclocycline, nor with the opiate antagonist naloxone, nor with placebo offer useful data to the clinician.
Pharmacological interventions for clozapine-induced hypersalivation	**Antimuscarinics** (astemizole, diphenhydramine, propantheline, doxepin) were the most commonly evaluated drugs.There are currently **insufficient data** to confidently inform clinical practice.

Le certezze sono poche, e per di più…

Esiste una enorme variabilità individuale nella gestione dei farmaci, nella risposta, nella suscettibilità e nella tolleranza ai diversi effetti collaterali per cui nessun approccio singolo funziona per tutti i pazienti (WPA).

Le linee guida sono comunque un'opzione per migliorare la qualità delle cure

E' fondamentale che le linee guida vengano condivise dai clinici, ricordandosi che rispondono a due diversi obiettivi:

1. **Un supporto alla migliore scelta clinica nel trattare un dato paziente**

2. **La conformazione e il monitoraggio dei comportamenti clinici da parte delle organizzazioni e delle amministrazioni**

Ma la pur necessaria condivisione di per sé non è sufficiente:

Seguire linee guida vuol dire tenere una osservazione precisa delle terapie, dei loro effetti terapeutici e collaterali e documentare tutto ciò con cura in cartella.

Lo studio di Cradock e coll. ci dice che questo avviene correttamente sui sintomi psicotici nel 55%, sugli effetti collaterali nell'85%, e dunque le decisioni spesso sono prese in modo poco comprensibile rispetto a ciò che è documentato

Raccomandazioni di monitoraggio minimo per la salute fisica dei pazienti in terapia antipsicotica. WPA, 2008

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually
History	X					X
Weight (BMI)	X	X	X	X	X	
Waist circumference	X			X		X
Blood pressure	X			X		X
Fasting Gluc & Hb A_{1c}	X			X		X
Fasting lipid profile	X			X		X
Sexual Function	X	X		X	X	
EPS and TD	X	X	X	X	X	
Ocular evaluation	X					X

The frequency of monitoring may need to be increased if the patient has additional vulnerability to that adverse effect or the agent utilized is more likely to cause it. Other monitoring based on agent and patient.

Agent-specific monitoring (eg., WBC monitoring with clozapine).