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Switching and Selecting Atypical Antipsychotic Drugs: Paliperidone

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Switching and selecting atypical antipsychotic drugs: Paliperidone

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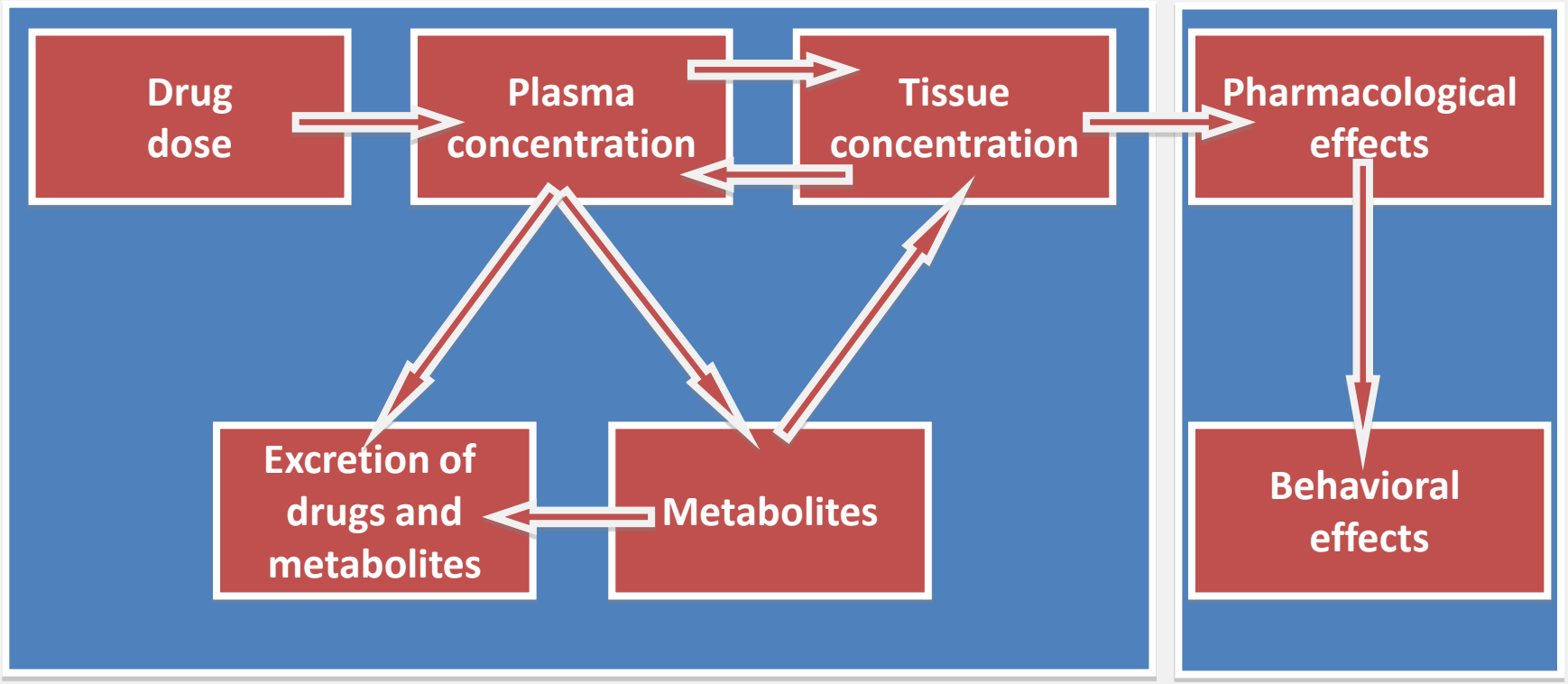
Disclosure

- Research, education & travel grant. Speakers group & advisory panels:
- Janssen Cilag
- Janssen Ortho
- Astra zeneca.Canada & UK
- Pfizer
- Roche pharmaceuticals
- Nicolus Pharmaceuticals
- SUN Pharma
- Prempharma
- Elli Lily

Learning objectives

- Needs and problems of switch
- Evidence about efficacy of switch
- Paliperidone
- Clinical practice of switching antipsychotics

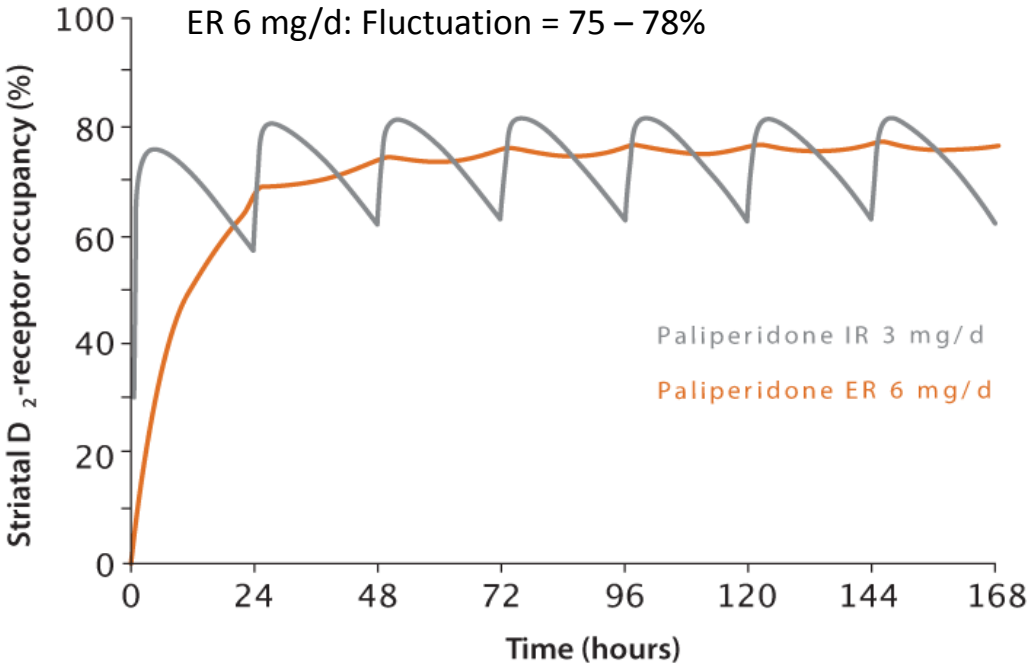
Pharmacokinetics vs. Pharmacodynamics



Variability is the major determinant of the dose-effect relationship in patients

D_2-Receptor Occupancy Fluctuation with Simulated Repeated Dosing

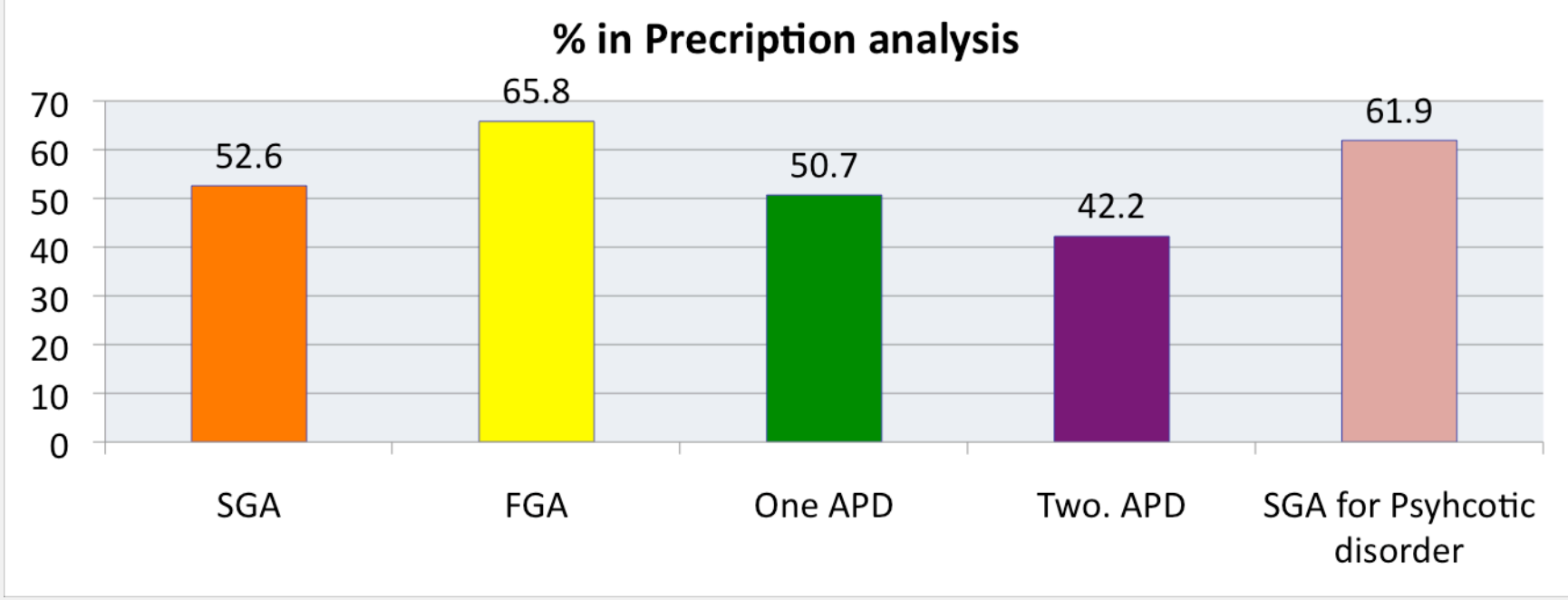
IR 3 mg/d: Fluctuation = 64 – 83%
ER 6 mg/d: Fluctuation = 75 – 78%



Karlsson P et al., Poster

What is the prescribing pattern

SGAs have become the first-line treatment for psychiatric disorders.



Bret P, Bret MC, Queuille E. Prescribing patterns of antipsychotics in 13 French psychiatric hospitals.Encephale. 2009 Apr;35(2):129-38.

Case
Q2 To which APD

Switch to Paliperidone

Switch to Paliperidone

COMBINATION ATYPICALS: 1.Suzuki.T, Human psychopharmacology 2008; 23:455-463
2.Chan J, Journal of Psychopharmacology21(6) (2007) 657-664

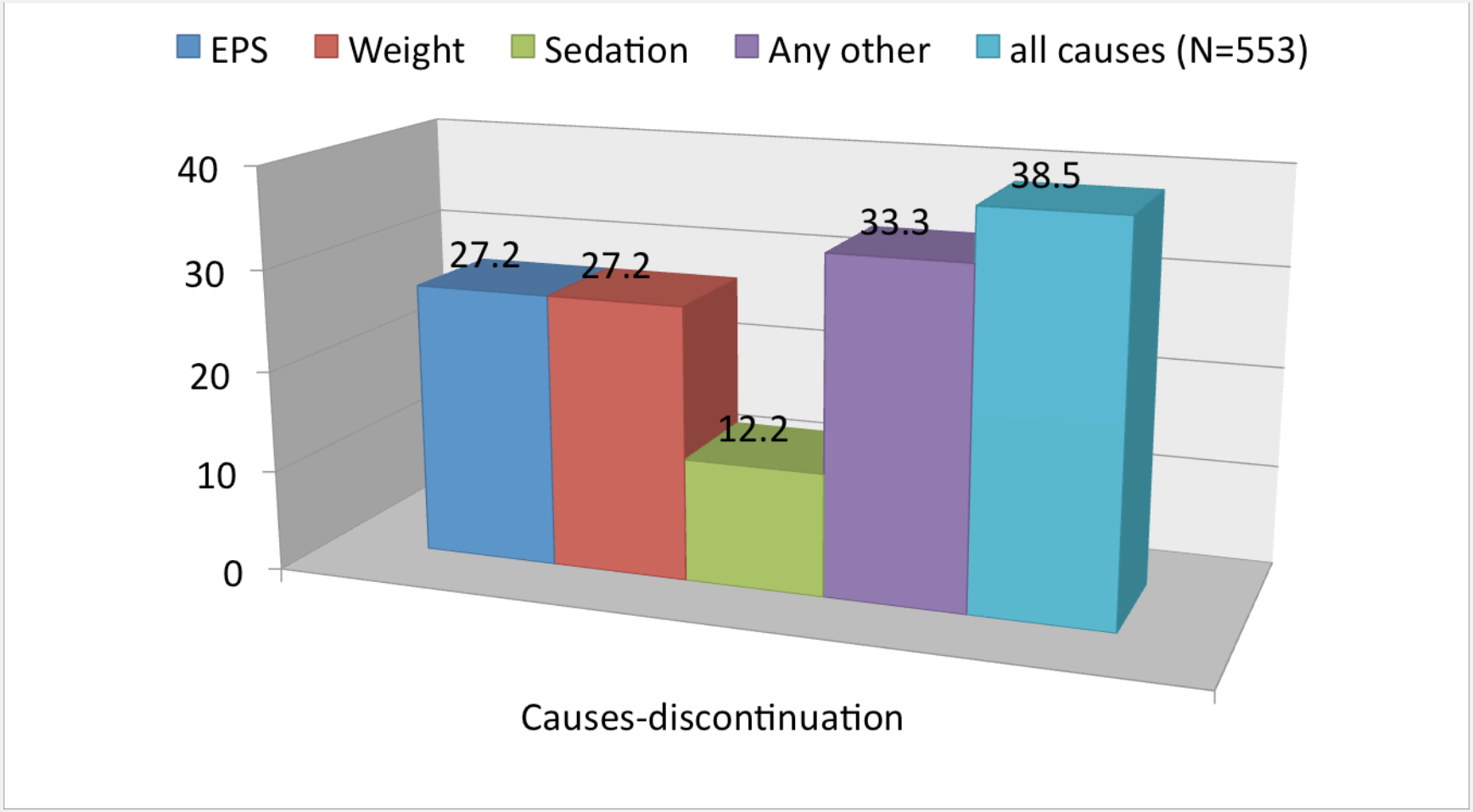
Switch:
when do we change APD?
How to select new APD

Selecting Antipsychotics

Acute Episode

Relapse

Why do patients discontinue medication? CATIE 1



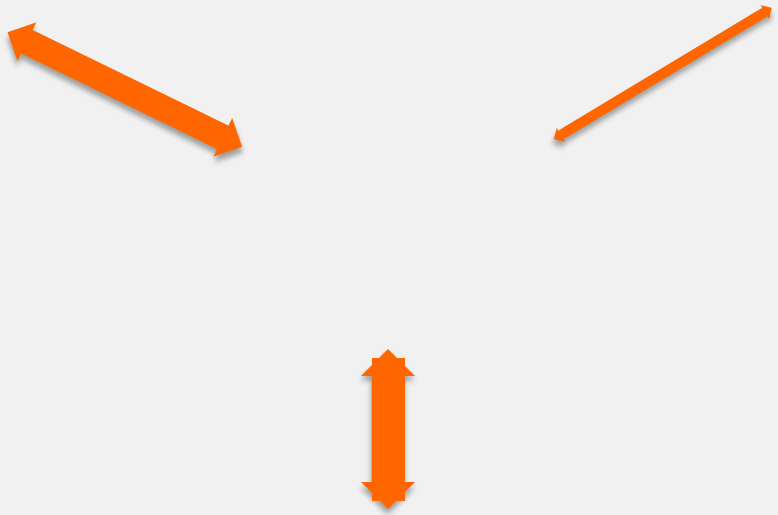
Weiden PJ.J.Clin Psychiatry 2007;68 [suppl 1]:12-19

CATIE – Phase 3, Symptom response

Drugs	ARIP	CLOZ	COMB	FLU-D	OLAN	PERP	QUET	RISP	ZIPR	P-value
PANSS – 3 months	0.506	0.002 ✓	0.002	0.005 ✓	0.002 ✓	0.084	0.013	0.044	0.045	0.832 ✖
PANSS-6	✔✔	0.006	<0.001 ✔	0.43	0.003 ✔	0.018	0.100	0.009	0.371	0.515 ✖

- Outcome of switch is dependent upon
  - Medication switched to
  - Medication switched from.

Model of factors that influence decision



Weiden PJ, J.Clin.Psychiatry, 2007;68(suppl 1)

Criteria's for Response

Reviews and Overviews

Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus

Nancy C. Andreasen, M.D., Ph.D.

New advances in the understanding of schizophrenia etiology, course, and treat-

group reviewed available definitions and assessment instruments to provide a con-

TABLE 2. Proposed Items for Remission Criteria With Cross-Scale Correspondence and Relationship to Historical Constructs of Psychopathology Dimensions and DSM-IV Criteria for Schizophrenia[a]

		Proposed Remission Criteria Items					
		Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS) Items		Positive and Negative Syndrome Scale Items		Brief Psychiatric Rating Scale (BPRS) Items	
Dimension of Psychopathology	DSM-IV Criterion	Criterion	Global Rating Item Number	Criterion	Item Number	Criterion[b]	Item Number
Psychoticism (reality distortion)	Delusions	Delusions (SAPS)	20	Delusions	P1	Grandiosity	8
						Suspiciousness	11
				Unusual thought content	G9	Unusual thought content	15
	Hallucinations	Hallucinations (SAPS)	7	Hallucinatory behavior	P3	Hallucinatory behavior	12
Disorganization	Disorganized speech	Positive formal thought disorder (SAPS)	34	Conceptual disorganization	P2	Conceptual disorganization	4
	Grossly disorganized or catatonic behavior	Bizarre behavior (SAPS)	25	Mannerisms/ posturing	G5	Mannerisms/ posturing	7
Negative symptoms (psychomotor poverty)	Negative symptoms	Affective flattening (SANS)	7	Blunted affect	N1	Blunted affect	16
		Avolition-apathy (SANS)	17	Social withdrawal	N4	No clearly related symptom	
		Anhedonia-asociality (SANS)	22				
		Alogia (SANS)	13	Lack of spontaneity	N6	No clearly related symptom	

[a] For symptomatic remission, maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required. Rating scale items are listed by item number.

[b] Use of BPRS criteria may be complemented by use of the SANS criteria for evaluating overall remission.

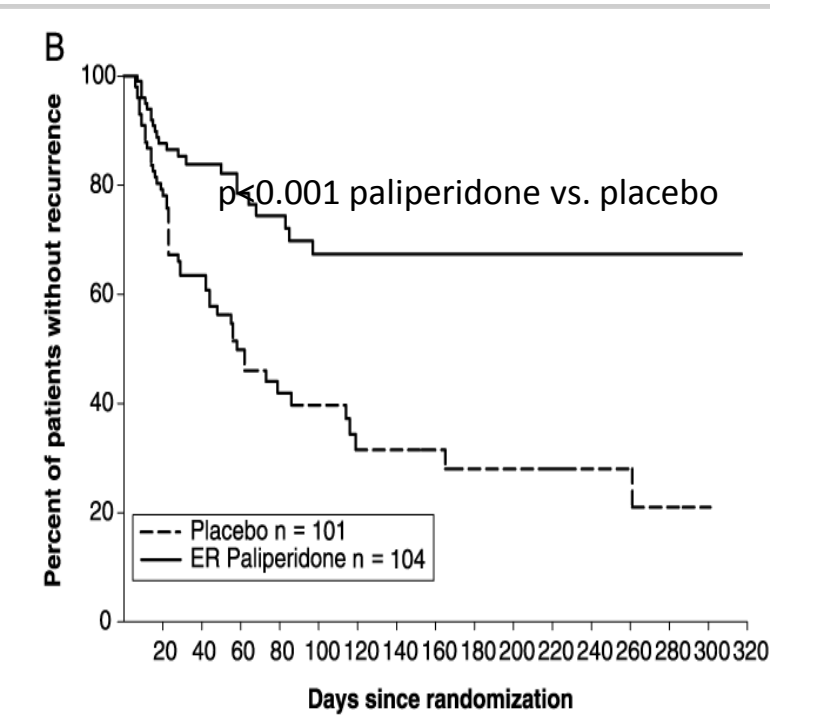
Efficacy and safety of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 52-week open-label studies.

Emsley R, Berwaerts J, Eerdekens M, Kramer M, Lane R, Lim P, Hough D, Palumbo J.
Int Clin Psychopharmacol. 2008

Paliperidone: Delayed Symptom Recurrence

- This analysis shows that paliperidone extended-release can maintain improvements in symptoms and functioning and is generally well tolerated for up to 52 weeks in schizophrenia patients.

Does the remission sustain??



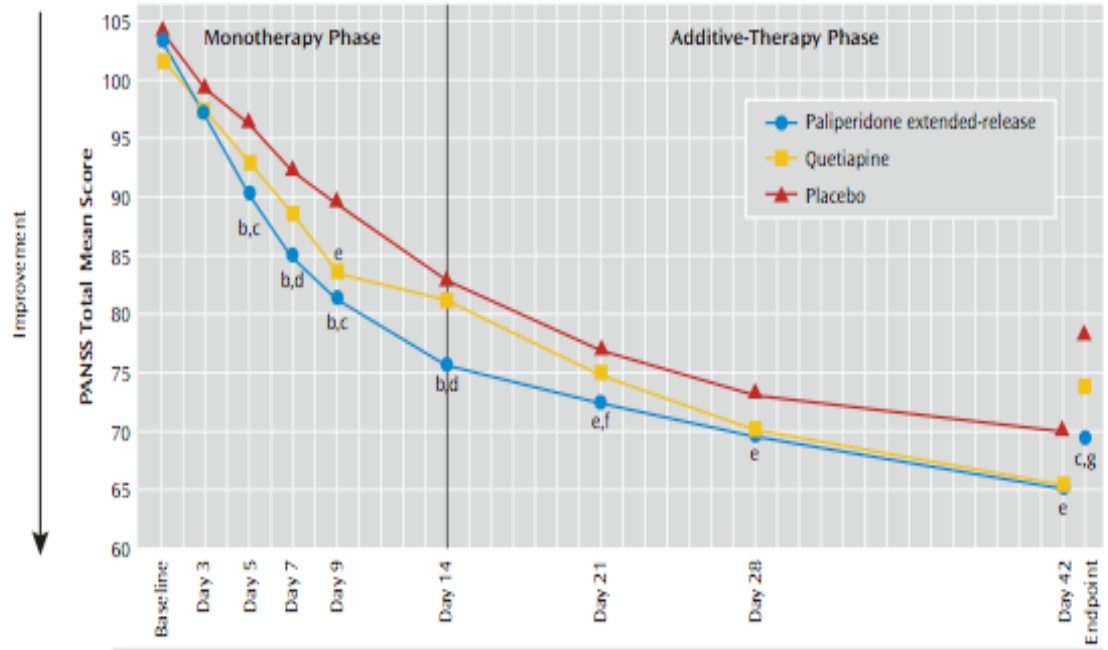
Kramer et al. *J Clin Psychopharmacol*, 2007

Randomized, Double-Blind, Placebo-Controlled Study of Paliperidone Extended-Release and Quetiapine in Inpatients With Recently Exacerbated Schizophrenia

Is paliperidone better than other AAPD?

Canuso CM, Dirks B, Randomized, Double-Blind, Placebo-Controlled Study of Paliperidone Extended-Release and Quetiapine in Inpatients With Recently Exacerbated Schizophrenia. Am J Psychiatry. 2009 May 1

FIGURE 2. Mean Positive and Negative Syndrome Scale (PANSS) Total Score by Visit in Patients With Recently Exacerbated Schizophrenia Treated With Paliperidone Extended-Release, Quetiapine, or Placebo (Intent-to-Treat Population)[a]



Paliperidone extended-release	N[h] = 157	147	136	148	146	141	138	132	122 157
Quetiapine	N[h] = 157	152	145	150	148	134	121	113	105 157
Placebo	N[h] = 80	74	74	79	75	68	59	56	51 80

[a] Observed cases, baseline through day 42; last observation carried forward at day 42 endpoint.
[b] p<0.001 compared with placebo.
[c] p<0.05 compared with quetiapine.
[d] p<0.001 compared with quetiapine.
[e] p<0.05 compared with placebo.
[f] p<0.01 compared with quetiapine.
[g] p<0.01 compared with placebo.
[h] A visit window was used for PANSS assessments at each time point.

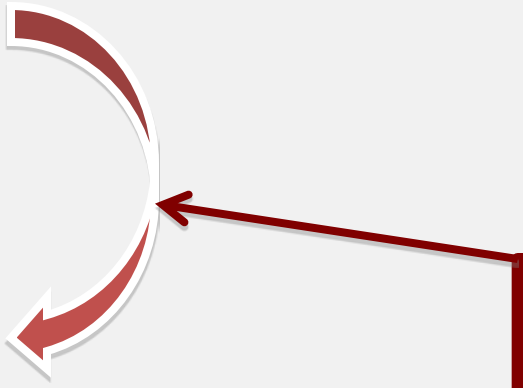
Expected clinical benefits of
paliperidone extended-release formulation
when compared with risperidone immediate-release.
Pani L, Marchese G.Expert Opin Drug Deliv. 2009

Is it same or better than Risperidone

KW, 20 years, FES admitted 3 weeks, discharged in ‘good remission’ Olan 10 mg BID, April 2008

Texas Algorithm, 2006

What are evidence-based recommendations for selecting Antipsychotic medication?



Partial or
No Response

Consider earlier trail of clozapine in atients with a H/O recurrent suicidality, violence, or comorbid substance abuse. Persistence of positive symptoms > 2years warrants & >5 years requires a clozapine trial, independent of number of antipsychotic trials.

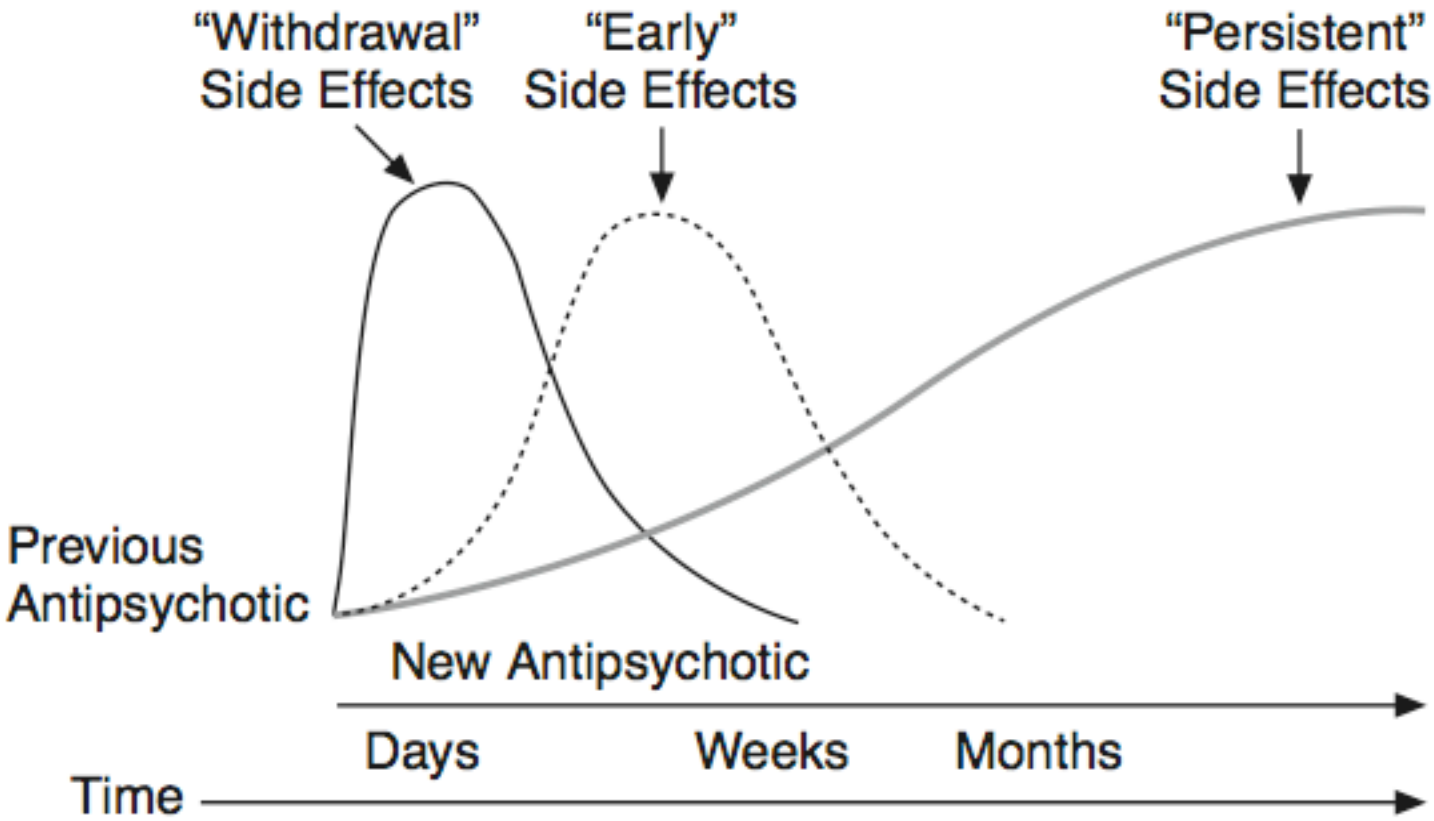
Benefits of switching

Figure 2. Potential Side Effect Benefits When Switching Between Antipsychotic Medications[a,b]

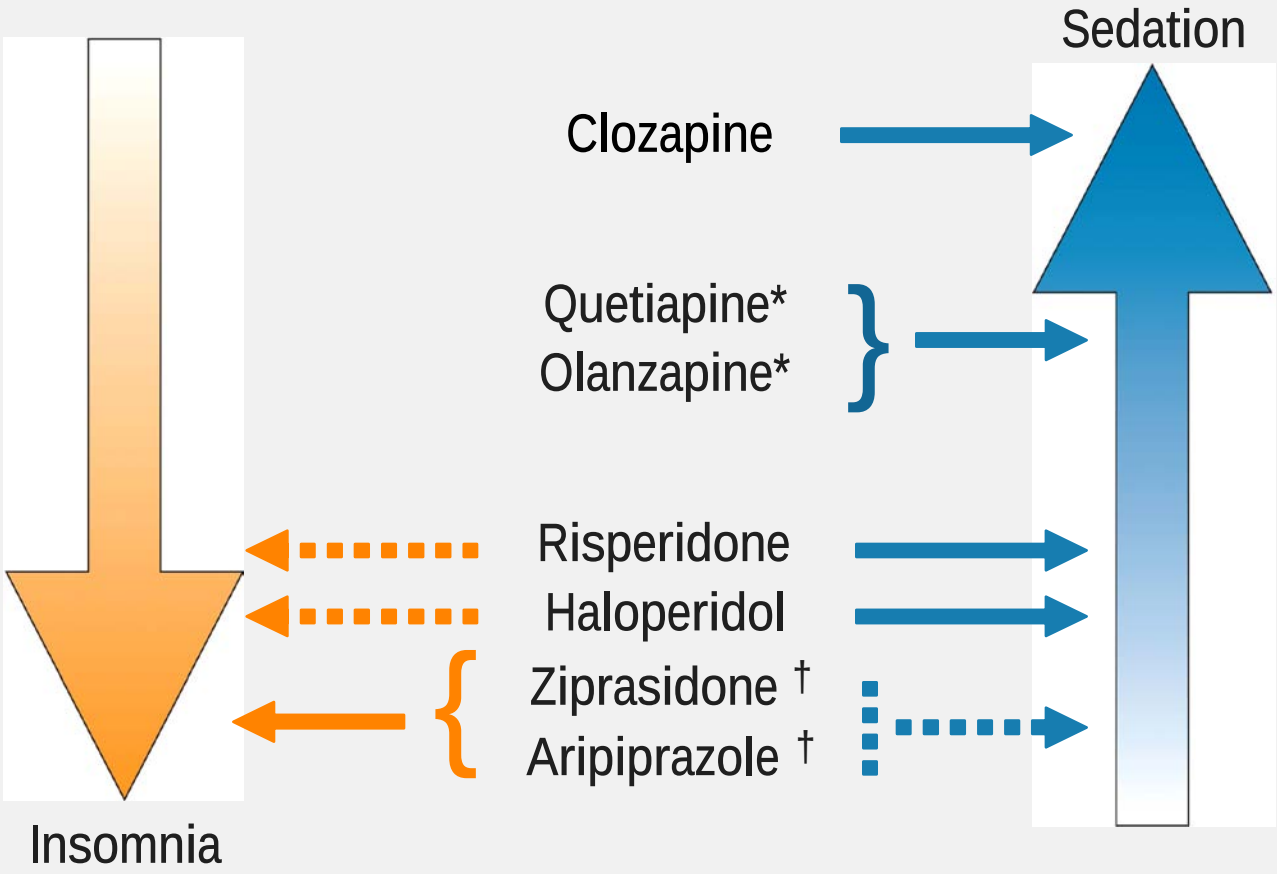
Preswitch Antipsychotic	Postswitch Antipsychotic: Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Haloperidol	↓↓ EPS ↓↓ Prolactin ↓ Akathisia ↓ Sedation	↓↓ Akathisia ↓↓ EPS ↓↓ Prolactin	↓↓↓ Akathisia ↓↓↓ EPS ↓↓ Prolactin	↓ Akathisia ↓ EPS	↓↓ EPS ↓↓ Prolactin ↓ Akathisia ↓ Sedation
Aripiprazole		↓ Akathisia ↓ Insomnia	↓↓ Akathisia ↓ EPS ↓ Insomnia	↓ Insomnia	↓ Akathisia ↓ Insomnia
Olanzapine	↓↓↓ Dyslipidemia ↓↓↓ Weight ↓↓ Sedation ↓ Prolactin		↓ Akathisia ↓ Dyslipidemia ↓ EPS ↓ Prolactin ↓ Weight	↓ Dyslipidemia ↓ Sedation ↓ Weight	↓↓↓ Dyslipidemia ↓↓↓ Weight ↓↓ Sedation
Quetiapine	↓↓ Sedation ↓ Dyslipidemia ↓ Orthostatic Hypotension ↓ Weight	↓ Orthostatic Hypotension		↓ Sedation	↓↓ Sedation ↓ Dyslipidemia ↓ Orthostatic Hypotension ↓ Weight
Risperidone	↓↓↓ Prolactin ↓ Dyslipidemia ↓ EPS ↓ Orthostatic Hypotension ↓ Sedation ↓ Weight	↓↓ Akathisia ↓↓ EPS ↓↓ Prolactin ↓ Orthostatic Hypotension	↓↓↓ Akathisia ↓↓↓ EPS ↓↓↓ Prolactin		↓↓ EPS ↓↓ Prolactin ↓↓ Weight ↓ Dyslipidemia ↓ Orthostatic Hypotension ↓ Sedation
Ziprasidone	↓ Prolactin ↓ Sedation	↓ Akathisia ↓ Insomnia	↓ Akathisia ↓ EPS ↓ Insomnia	↓ Insomnia	

[a]Reprinted with permission from Weiden.[6]

Figure 1. Time Course of Side Effects: Withdrawal, Early, and Persistent



Antihistaminic Effects of Antipsychotics



* Sedation is dose-related and usually abates after several weeks.

† Sedation also possible; insomnia usually abates after several weeks.

Adapted from Weiden, P. J., 2007

Incidence of Cardiac Adverse Events Occurring in ≥ 5% of Patients, n (%)

Paliperidone ER Groups

AE	Placebo N=355	3 mg N=127	6mg N=235	9mg N=246	12mg N=242	15mg N=113
Tachycardia	10 (3)	3 (2)	17 (7)	18 (7)	18 (7)	2 (2)
Sinus Tachycardia	15 (4)	11 (9)	9 (4)	10 (4)	17 (7)	8 (7)
QTc Prolongation	9 (3)	4 (3)	9 (4)	7 (3)	12 (5)	4 (4)

No clinically relevant difference between proportions of QTc in pali vs. placebo groups (1.6% vs. 1.4%)

Meltzer et al. ICOSR 2007

EPS-Related Adverse Events

Paliperidone ER Groups

	Placebo	3mg	6mg	9mg	12mg	15mg
Percent	11	13	10	25	26	24

Bipolar Disorder | Depot Injections

P-01-246

PLASMA LEVELS OF PALIPERIDONE IN A NATURALISTIC SETTING

INSTITUTIONS

1. EVK Gelsenkirchen, Dept. of Psychiatry, Psychotherapy and Psychosomatics, Gelsenkirchen, Germany
2. Hygiene-Institut des Ruhrgebiets, Gelsenkirchen, Germany

AUTHORS

1. Heiko Ullrich[1], Dr., MD, ullrich@evk-ge.de
2. Matthias Weber[2], Dr., MD
3. Ralf Kudling[1], Dr., MD
4. Eckhard Klieser[1], Prof. Dr., MD

Aims: Paliperidone is a new compound with a special extended release formulation, which was introduced in Germany in 2007. Aim of our examination was to search for a correlation between plasma-levels of the compound and efficacy and tolerability in a naturalistic setting.

Methods: Of all inpatients at the evangelical clinics in Gelsenkirchen with the diagnosis of a paranoid schizophrenia according to ICD-10, who received a pharmacological treatment with paliperidone in 2007, 21 patients (14 female/7 male, mean age 42 +/-14.7years) underwent blood testing for paliperidone-plasma-concentration. Paliperidone / 9-hydroxyrisperidone was detected by a validated method using liquid chromatography/tandem mass spectrometry (LC/ESI-MS/MS) after protein precipitation and dilution. In the linear range of 2 - 200 µg/l (r = 0.9996) the LLOQ was 2 ng/ml and the inter-day-precision at 20 µg/l was 6.6%.

Results: Severity of illness before treatment was overall 4.4 with a range of 1.2 on the CGI. Treatment outcome was 2.3 with a range of 0.9 on the cgi. Side-effects were not observed. The mean paliperidone-dose was 7.7 (+/- 2.7) mg/day, 6 patients received 12 mg daily. Plasma-concentrations of paliperidone were 36.25 +/-20.13µg/l for all patients, 54.73 +/- 12.84µg/l for the 12-mg-group and 28.86 +/- 17.76 µg/l for the 6-mg-group. The correlation between dose and plasma-concentration was 0.59, there were no correlations observed for severity of illness, outcome or side-effects.

Conclusions: In our sample, treatment with paliperidone was safe and effective. We could establish a dose-plasma-level-correlation in a naturalistic setting with a mean plasma concentration for 9-hydroxyrisperidone of 36.25 µg/l.

Contents lists available at ScienceDirect

Schizophrenia Research

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

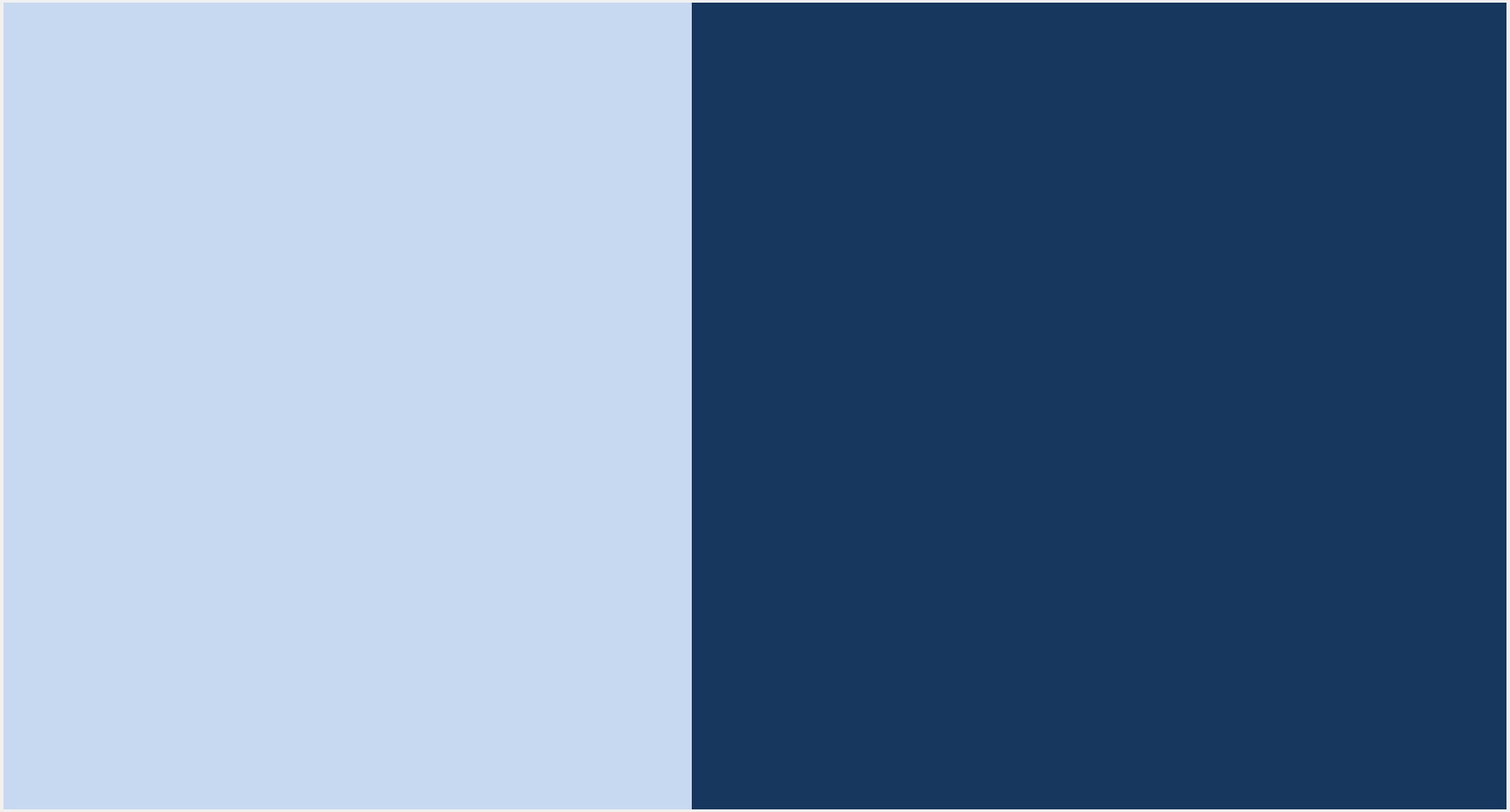
Does switching to a new antipsychotic improve outcomes? Data from the CATIE Trial

Robert A Rosenheck [a,*], Sonia Davis [b], Nancy Covell [c], Susan Essock [c], Marvin Swartz [d], Scott Stroup [b], Joseph McEvoy [d], Jeffrey Lieberman [c]

[a] Yale Medical School, New Haven, CT, United States
[b] University of North Carolina Medical School, Chapel Hill, NC, United States
[c] Columbia College of Physicians and Surgeons, New York, NY, United States
[d] Duke University Medical School, Durham, NC, United States

Switching to a new medication yielded no advantage over staying on the previous
medication. Staying on olanzapine was associated with greater weight gain.

Outcome switching: CATIE, 2009



Clinical benefit in switching antipsychotics

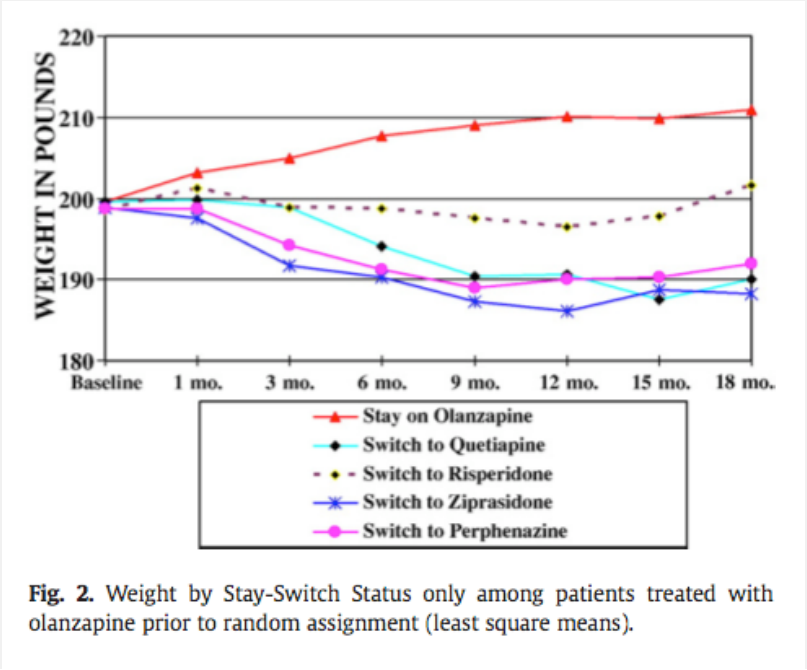


Fig. 2. Weight by Stay-Switch Status only among patients treated with olanzapine prior to random assignment (least square means).

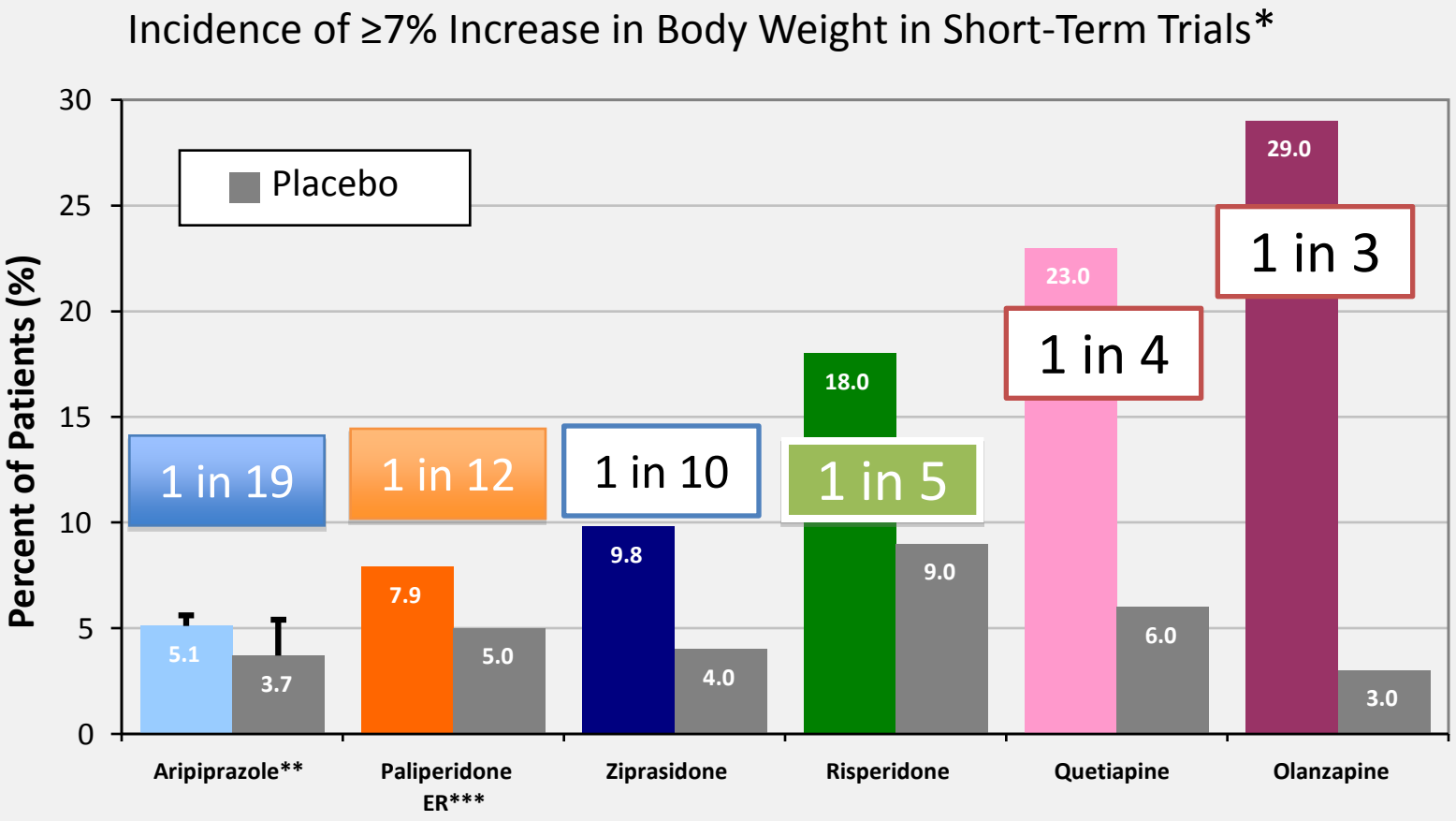
- Limitations
- Subjects were not 'unresponsive' dose, duration of previous APD was not known, so 'mirror-image' comparison was not possible

- Previous CATIE demonstrated equal efficacy in Head-head trial
- This study reiterates equal benefit in switching

	Olanzapine monotherapy					Risperidone monotherapy					Quetiapine monotherapy				
	Stay	Switch				Stay	Switch				Stay	Switch			
	Mean	Mean	Stay vs Switch			Mean	Mean	Stay vs Switch			Mean	Mean	Stay vs Switch		
N=	*N*=73	*N*=224	*F*	*df*	*p*	*N*=56	*N*=196	*F*	*df*	*p*	*N*=16	*N*=71	*F*	*df*	*p*
Clinical status															
PANSS															
Total	68.2	70.2	2.95	1, 1086	0.08	69.6	67.7	2.36	1, 974	0.12	70.9	67.4	2.05	1, 276	0.12
Positive	15.7	16.3	3.16	1, 1088	0.08	16.2	15.9	0.88	1, 975	0.35	17.7	17.1	1.61	1, 276	0.22
Negative	18.7	19.2	1.71	1, 1087	0.19	19.4	18.6	3.89	1, 974	0.05	18.6	17.9	0.78	1, 276	0.38
General psych	33.7	34.6	2.09	1, 1087	0.15	34.0	33.1	1.94	1, 974	0.16	34.6	32.4	2.98	1, 276	0.09
Neurocognitive function	0.014	0.015	0.02	1, 1109	0.89	0.022	0.020	0.01	1, 1000	0.93	0.077	0.033	1.55	1, 287	0.21
Depression (Calgary Scale)	1.44	1.47	1.12	1, 1088	0.29	1.40	1.39	0.07	1, 976	0.79	1.51	1.44	1.30	1, 275	0.25
Alcohol use	1.41	1.39	0.25	1, 1088	0.62	1.40	1.40	0.00	1, 976	0.99	1.46	1.31	3.25	1, 276	0.07
Drug use	1.25	1.25	0.01	1, 1088	0.93	1.30	1.26	0.76	1, 976	0.38	1.38	1.31	0.68	1, 276	0.41
Quality of life															
Heinrichs Carpenter QOLI	4.54	4.58	0.30	1, 405		2.79	2.83	0.30	1, 358	0.58	2.74	2.78	0.07	1, 106	0.80
Lehman Quality of life scale	4.54	4.58	0.30	1, 405	0.58	4.43	4.55	1.58	1, 353	0.21	4.33	4.43	0.35	1, 106	0.55
SF 12															
Physical component score	47.63	48.97	4.78	1, 404	0.03	49.33	49.18	0.06	1, 361	0.81	47.07	47.93	0.46	1, 105	0.50
Mental component score	43.30	41.97	3.69	1, 405	0.06	42.76	44.14	3.34	1, 360	0.07	42.30	43.40	0.71	1, 106	0.40
Side effects															
AIMS (TD)	0.19	0.19	0.00	1, 1089	0.97	0.19	1.60	0.88	1, 978	0.35	0.37	0.33	0.69	1, 279	0.41
Akathisia (Barnes)	0.26	0.25	0.09	1, 1090	0.76	0.30	0.26	1.32	1, 979	0.25	0.34	0.34	0.19	1, 279	0.67
EPS (Simpson/Angus)	0.19	0.21	0.64	1, 1088	0.43	0.19	0.18	0.00	1, 978	0.97	0.20	0.21	0.03	1, 279	0.86
Weight	203.60	197.40	18.89	1, 1081	<0.0001	197.80	197.77	0.00	1, 959	0.98	201.5	200.0	0.29	1, 266	0.59
Costs															
Health costs (log transformation)(2)	4.70	4.71	0.01	1, 1109	0.94	4.74	4.67	0.07	1, 999	0.79	5.34	5.02	0.48	1, 286	0.49

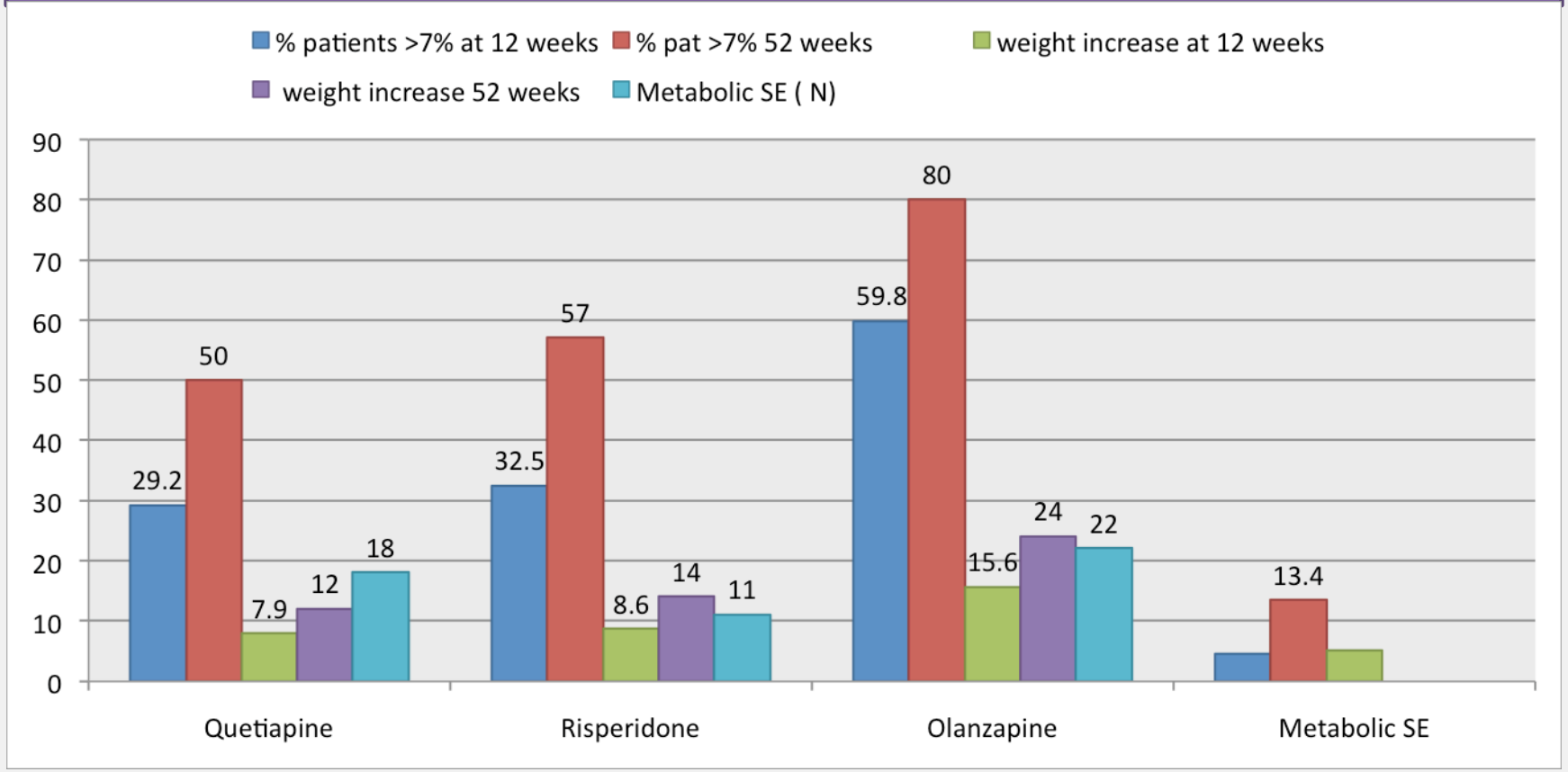
1) Mean value of all follow-up assessments controlling for treatment group, time, the baseline value of the dependent variable and the interaction of the baseline

Weight Gain Comparision of Atypical Antipsychotics



*Based on United States Product Inserts
**Error bars reflect reporting of weight gain in PI by baseline BMI
***confirmation of US PI

Metabolic profiles of second-generation antipsychotics in early psychosis: Findings from the CATIE study.2009



Patel JK, Buckley PF Metabolic profiles of second-generation antipsychotics in early psychosis: Findings from the CAFE study. Schizophr Res. 2009 Jun;111(1-3):9-16. Epub 2009

Monitoring Guidelines

Table 2. Screening and Monitoring for Patients With Schizophrenia[a,b]

Parameter	Baseline	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	Quarterly	Annually	Every 5 Years
Personal/family history	✓					✓	
Weight (body mass index)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

[a]Reprinted with permission from the American Diabetes Association.[7]
[b]More frequent assessments may be warranted based on clinical status.

WHO IS A CANDIDATE FOR SWITCHING?
Expert Consensus Guidelines recommend
the combination of psychosocial interventions
plus a trial switch to an antipsychotic with less weight gain liability.

(J Clin Psychiatry 2007;68[suppl 4]:34–39)

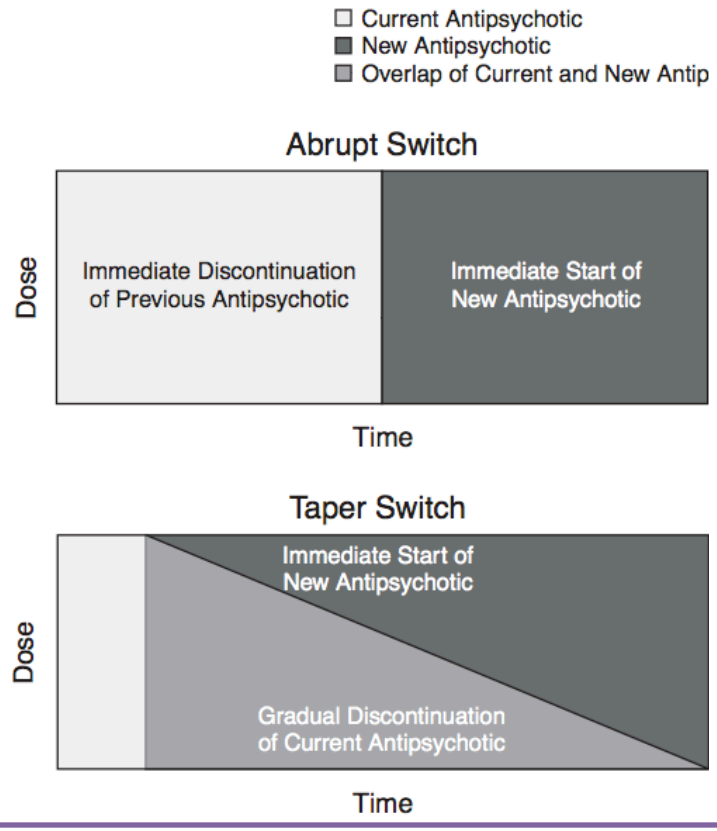
Side effects of Antipsychotics

Seizure, Arrhythmias, Blood count, Prolactin, Weight , & Metabolic

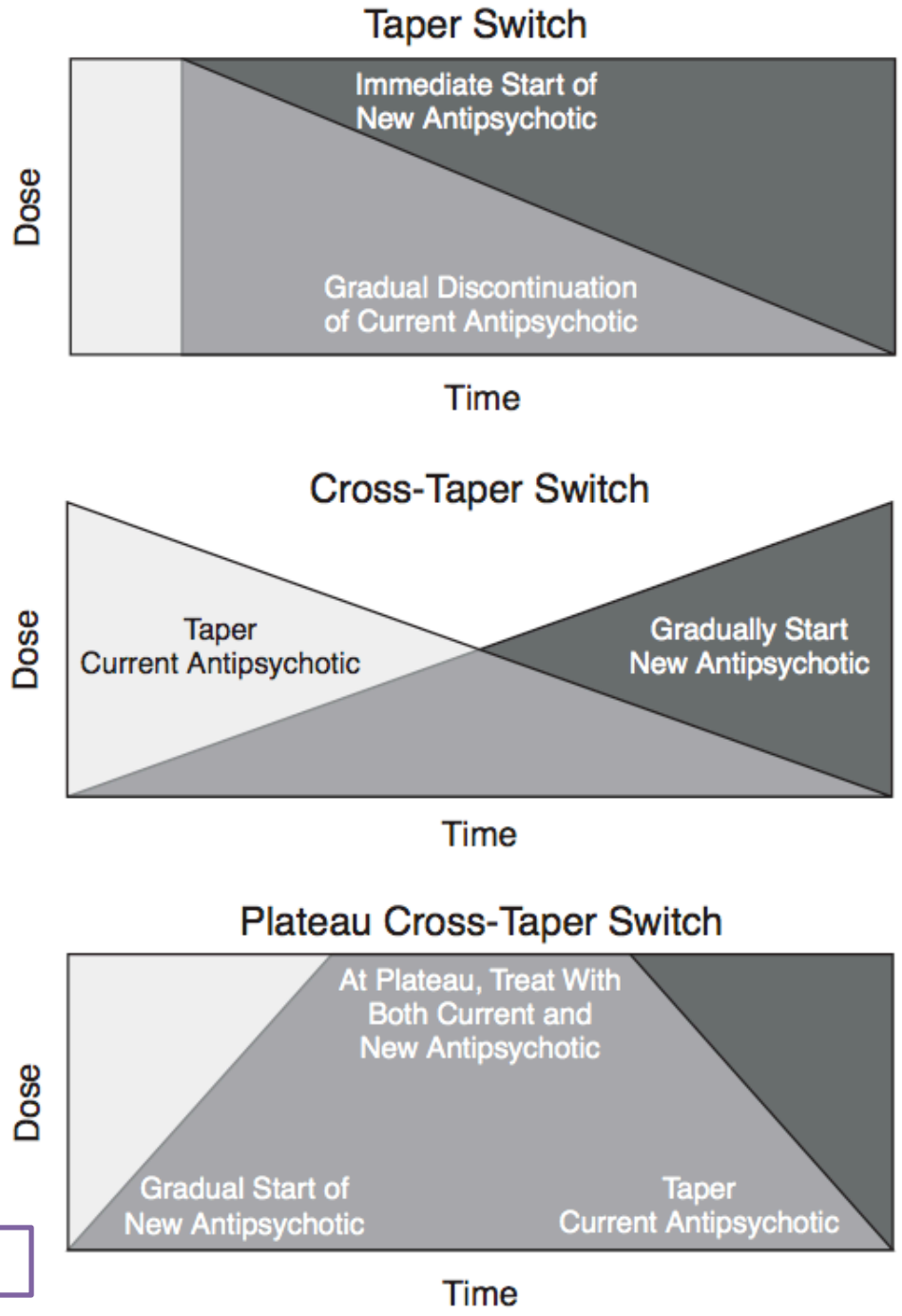
- Atypical antipsychotic drugs and the risk **of sudden cardiac Death** ,
  - LH . N Engl J Med. 2009 May 14;360(20):2137;[Potentially lethal cardiac side effects caused by psychiatric drugs] Sawicke L, Sturla S.Vertex. 2008 Nov-Dec;19(82):387-93
- **[Hematological adverse effects** caused by psychiatric drugs
  - Mazaira S.Vertex. 2008 Nov-Dec;19(82):378-86
- **Akathisia** and second-generation antipsychotic drugs
  - Kumar R, Sachdev PS. Curr Opin Psychiatry. 2009 May;22(3):293-99.
- Antipsychotic agents and **cardiometabolic morbidity** in youth.
  - Kruszewski SP, Paczynski RP.Arch Pediatr Adolesc Med. 2009 Apr;163(4):394-5; author reply 395
- **Weight gain, metabolic parameters,** and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol.
  - Krakowski M, Czobor P, Citrome L.Schizophr Res. 2009 May;110(1-3):95-102
- Association between antipsychotic drugs, antidepressant drugs, and venous **thromboembolism**.
  - Lacut K.Clin Adv Hematol Oncol. 2008 Dec;6(12):887-90.
- Antipsychotic-induced **hyperprolactinemia.**
  - Bostwick JR, Guthrie SK, Ellingrod VL.Pharmacotherapy. 2009 Jan;29(1):64-73.

SWITCHING STRATEGIES FOR ANTIPSYCHOTIC MEDICATION

Figure 4. Antipsychotic Switching Strategies[a]



Lambert TJ. Switching antipsychotic therapy: what to expect and clinical strategies for improving therapeutic outcomes. J Clin Psychiatry 2007;68(suppl 6):10–13



Switching only changes nature of Problem

- Do's (check list)
  - Measuring clinical condition
  - Physical health
  - Base line investigation (EKG, Blood work)
  - Explain
  - Review all medications
  - Attention to D-D-I (take help from Pharmacist)
  - Read new information
  - Monitor
  - Frequent appointment

- Quantification and measurement in psychosis
  - SAPS-SANS
  - PANSS
  - BPRS
  - HDRS
  - ADL
  - GAF
  - QOL

Clinical Consequences of switching

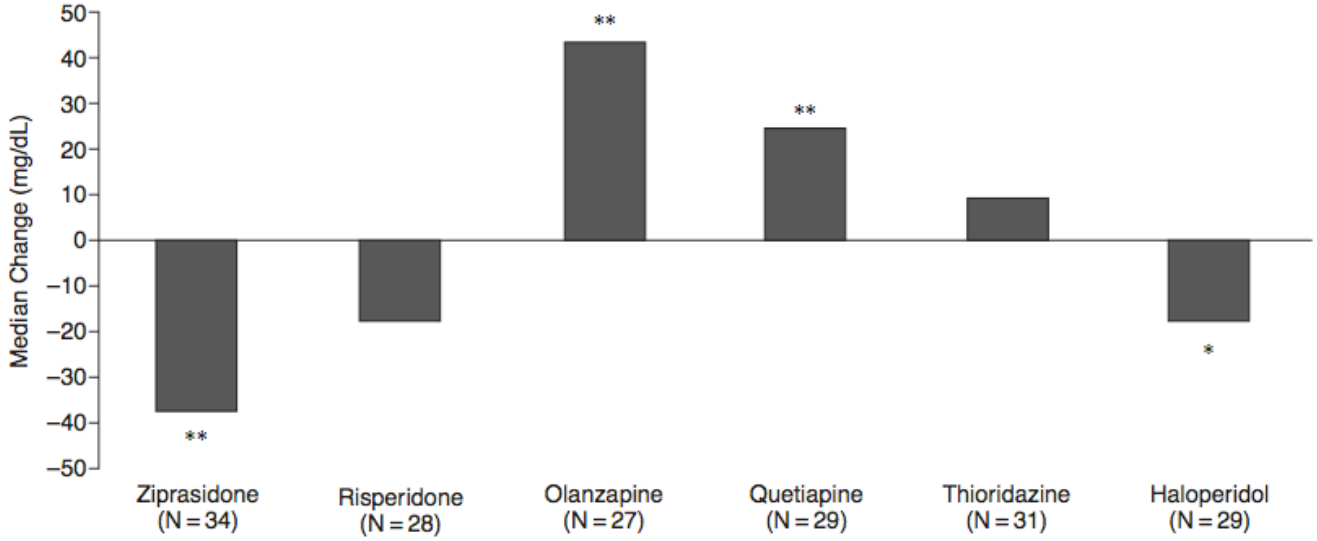
- Good experience for every one
  - Do not reduce the level of monitoring
  - Late consequences and Risk of non-compliance.

- Into bigger problem
  - Withdrawal symptoms of antipsychotic
  - Increase in secondary symptoms (anxiety-insomnia)
  - Persisting side effects of prior APD
  - Emergence of new psychiatric symptoms
  - Side effects of newer APD
  - Break-through Psychosis
  - Fall, giddiness, fainting,
  - Emergency situation (Seizure, low blood count, Cardiac event, Steven-Johnston)

Differences in effects on fasting triglyceride levels were also found between agents in a short, open-label, parallel- group SWITCHING STRATEGIES

Buckley and Correll

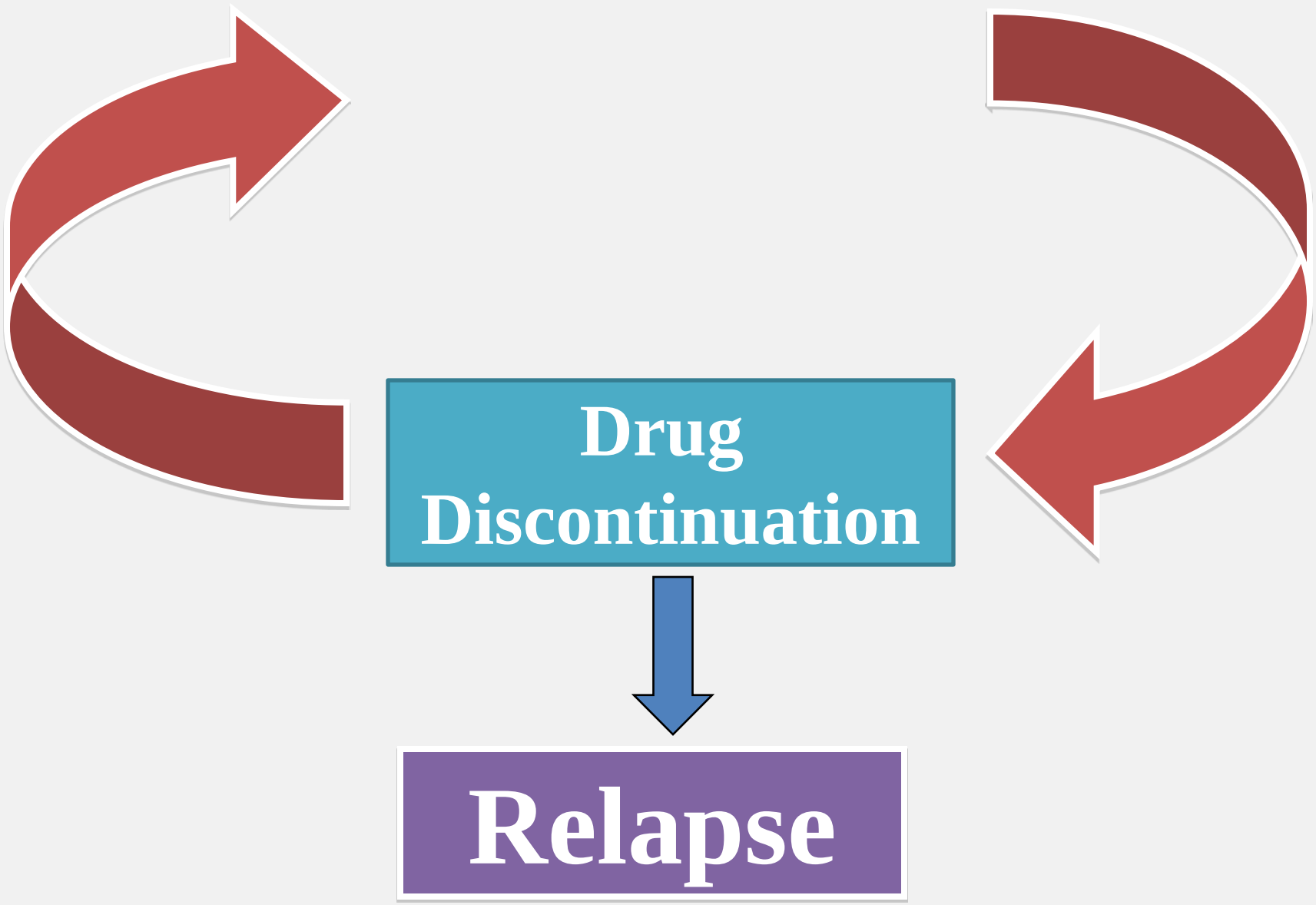
Figure 3. Changes in Fasting Triglyceride Levels After Switching Antipsychotic Medications[a]



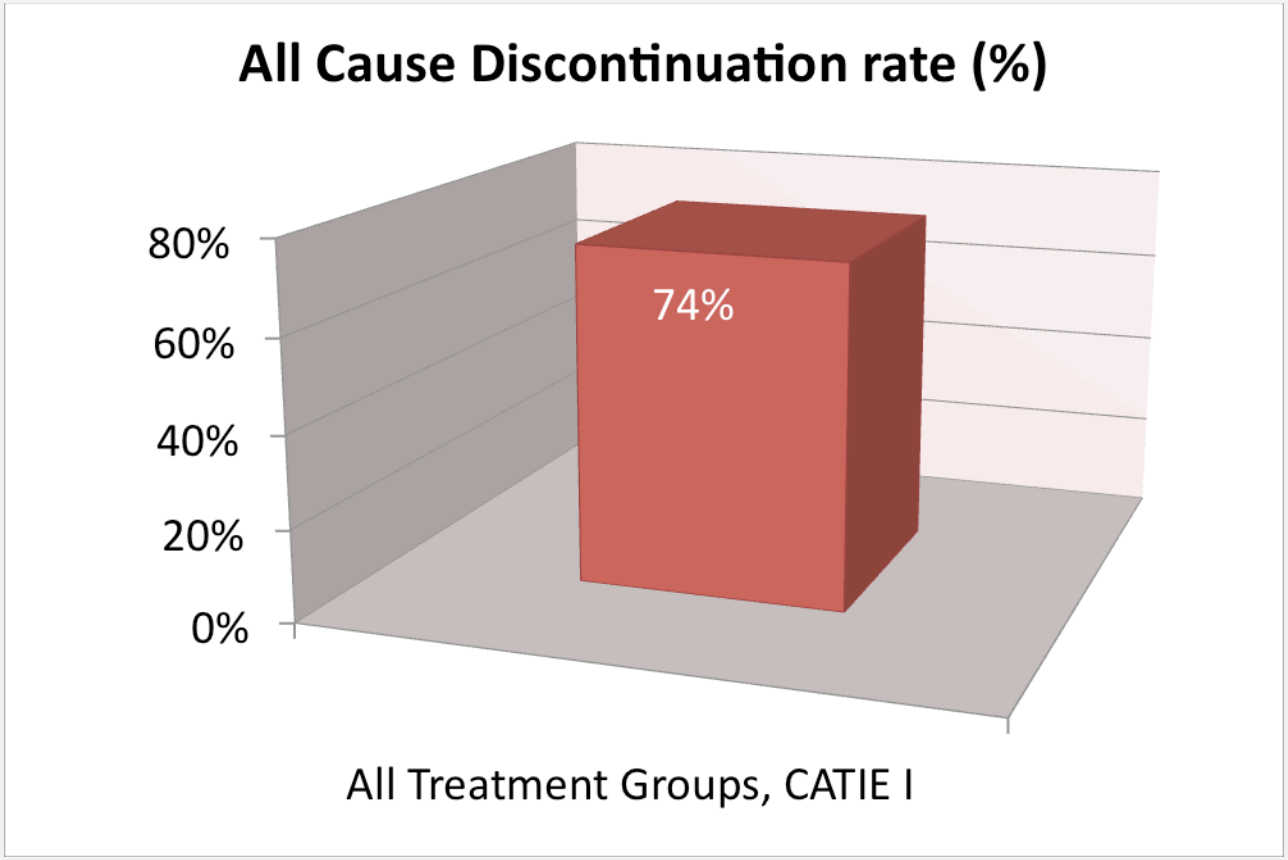
[a]Data from Pfizer FDA Briefing Document.[53] Change from baseline to peak exposure at end of study (15–25 days).
*p < .01.
**p < .001.

Pfizer Inc. Briefing Document for Zeldox Capsules (zipra- sidone HCl). Submitted to FDA Psychopharmacological Drugs Advisory Committee; July 19, 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/ 3619b1a.pdf. Accessed Dec 15, 2006

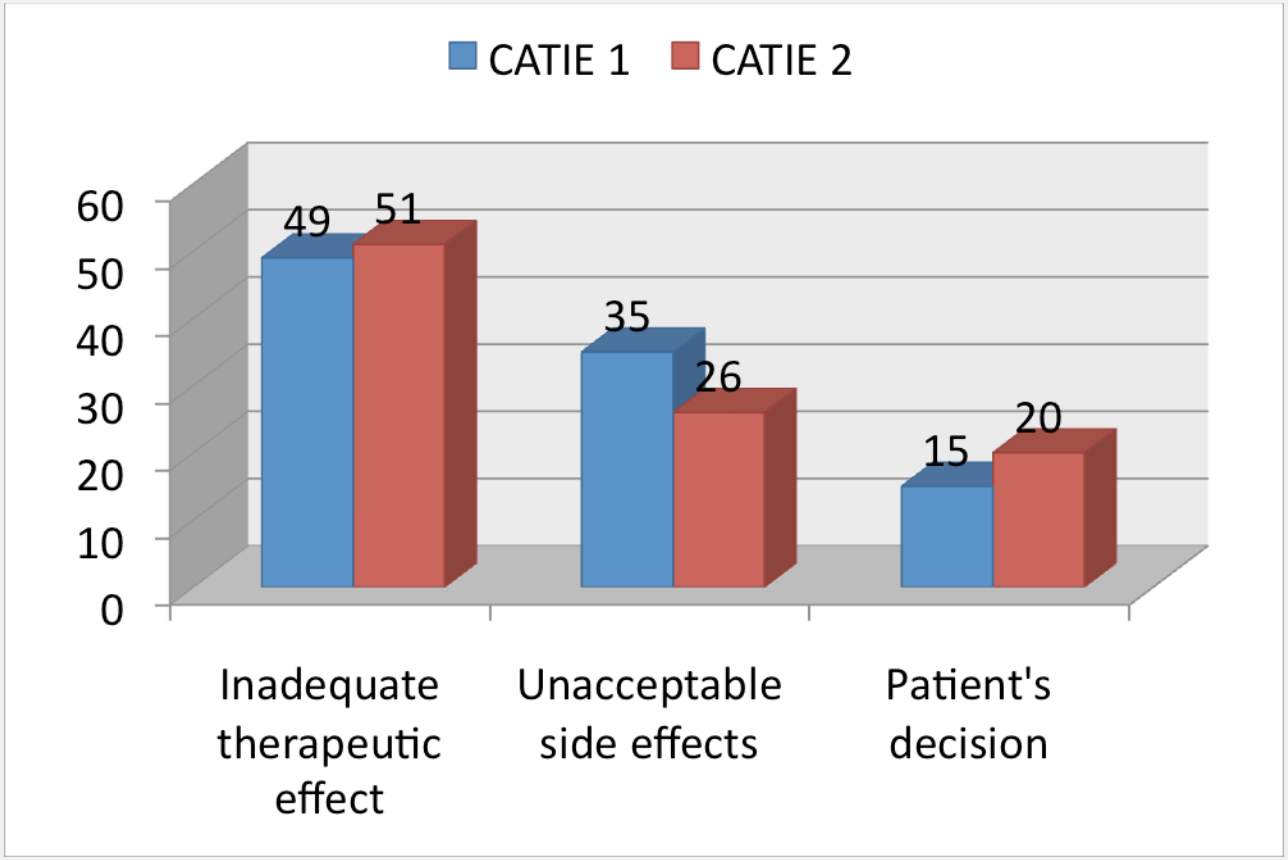
Determinants of outcome in schizophrenia


Drug
Discontinuation
Relapse

Non-adherence is a sign of Partial or Complete Non-response



Non-adherence or discontinuation is associated (marker) of poor efficacy



Final message

- Switching should be NOT be a priority situation.
- It does not give any superiority in terms of efficacy amongst SGA except clozapine
- Outcome of switch depends upon both the previous and the new molecule
- The first clinical option should be optimization of dose, schedule, education & non-drug therapies.
- It should be opted only if clinical conditions are compelling
- Whenever switch, due consideration should be given to all denominators of its outcome.
- Not to compromise efficacy
- Not to continue with side effects