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Switching and Selecting Atypical Antipsychotic Drugs: Quetiapine

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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

Atypical antipsychotics: Clinical experience:

1. Factors warranting switch
2. My experience with XR
3. Are there differences amongst atypical
4. How to maximize clinical advantage

Despite lack of clarity in selection, 90% times each clinician gets it right.

Quetiapine Optimization: Case report

- Mrs B, 48 Years , Married
- Chronic schizophrenia with Chronic unremitted alcoholism, and chronic suicidality ,
- H/O 4 major attempt,
- F/U regular, > 20 Admissions,
- on Quetiapine 525 IR + Olanzapine 20 mg.
- Readmitted, APE,
- Day I – QUT.IR, 100 mg QHS, syncope attack, two episodes,
- Ref. General hospital, Cause-Unknown,
- Re-evaluated: opinion ‘she has this problem since the age of 20,
- no diagnosis was made,
- Reassessed for diagnosis and care plan

Schizophrenia with alcoholism & Suicidality Case Report..Conti.

- Target: psychosis, suicide, alcoholism, Involuntary admission
- Discontinued passes, Family Meeting.
- Discontinued olanzapine,
- Plan: Increase quetiapine to 800 mg/day gradually & monitor
- Once escalation was complete, we switch to XR 800 mg Q Super
- Increased 5 mg a day, i.e. 25 mg every 5th day,
- Vitals monitored, psychosocial therapy continued.
- 800 mg in 10 weeks, No further syncope
- Mental state: Remarkable change, 'Never felt like this', No suicidality.
- Discharged under care of her outpatient psychiatrist

Why do we need to switch?

- Lack of efficacy
- Acute relapse
- Side effects
  - Intolerability
  - Burden
- Failed
- optimization
- adjunct treatment
- ‘Patients-Choice’

Fundamental Process in switching APD

1. Establish a causal attribution
2. Understand course of side effect
3. Understand potential risk of individual patient
4. Be aware of the SE profile of other possible antipsychotics
5. Calculate SE risk of switch
6. Calculate efficacy risk of switching

Symptoms warranting a switch

Persistent EPS

Galactorrhea & Amenorrhea

Gynaecomastia & Impotence in men

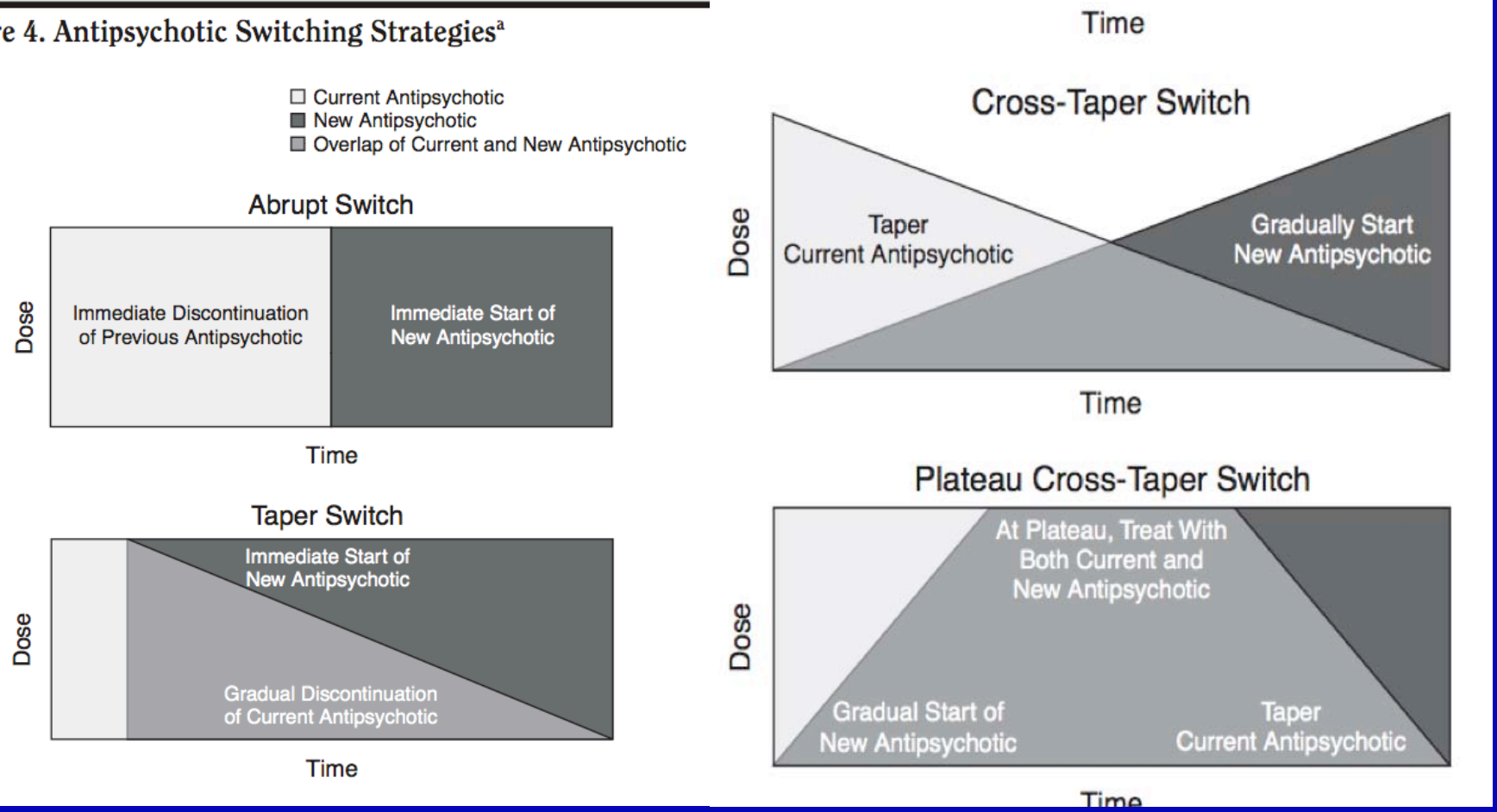
- Persistent Positive symptoms
- Persistent Negative symptoms
- Persistent Cognitive symptoms
- Persistent affective symptoms

Persistent poor Social Functioning

Weiden PJ,2006, Psychopharm

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

Clinical Consequences of switching

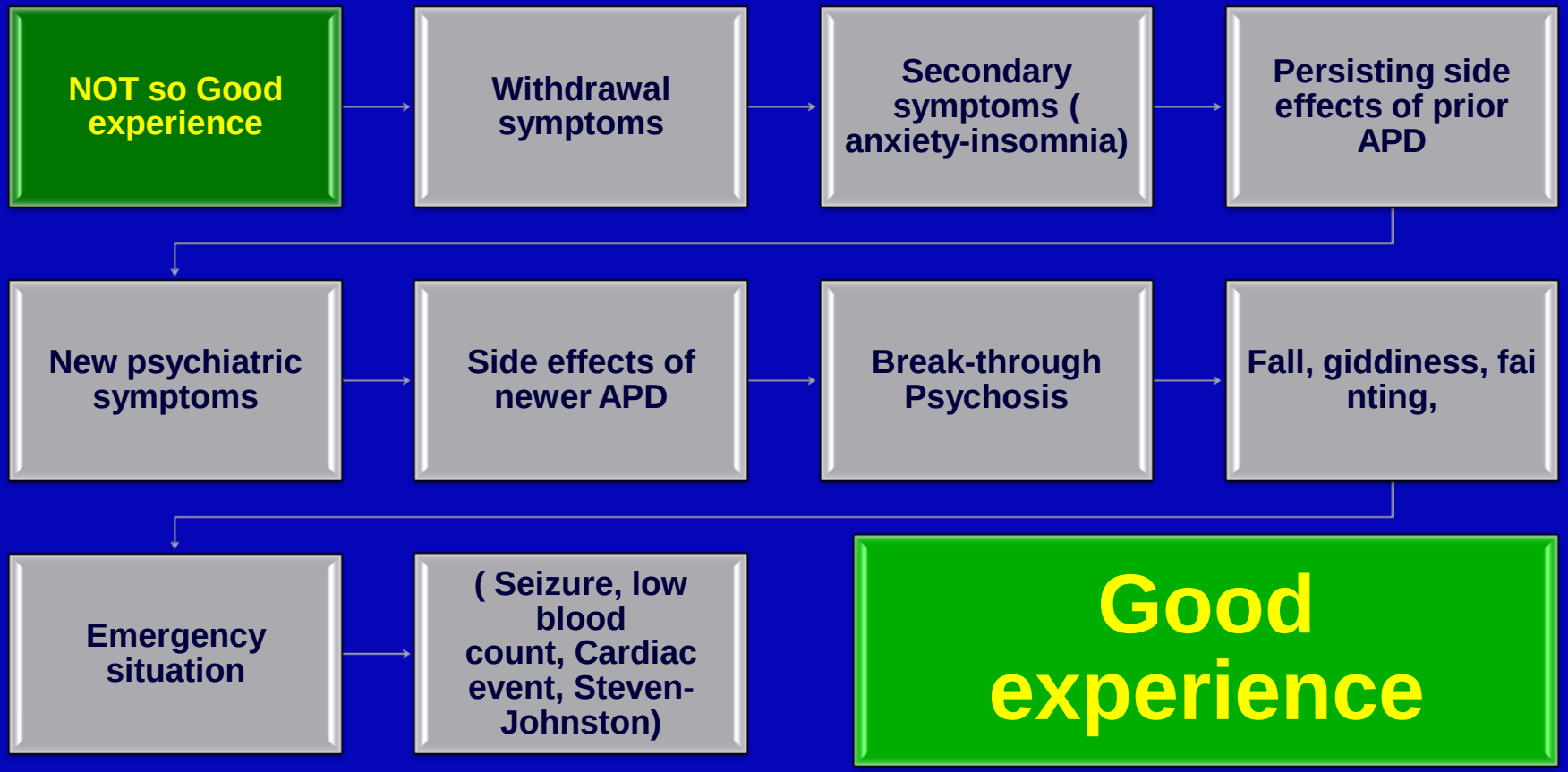
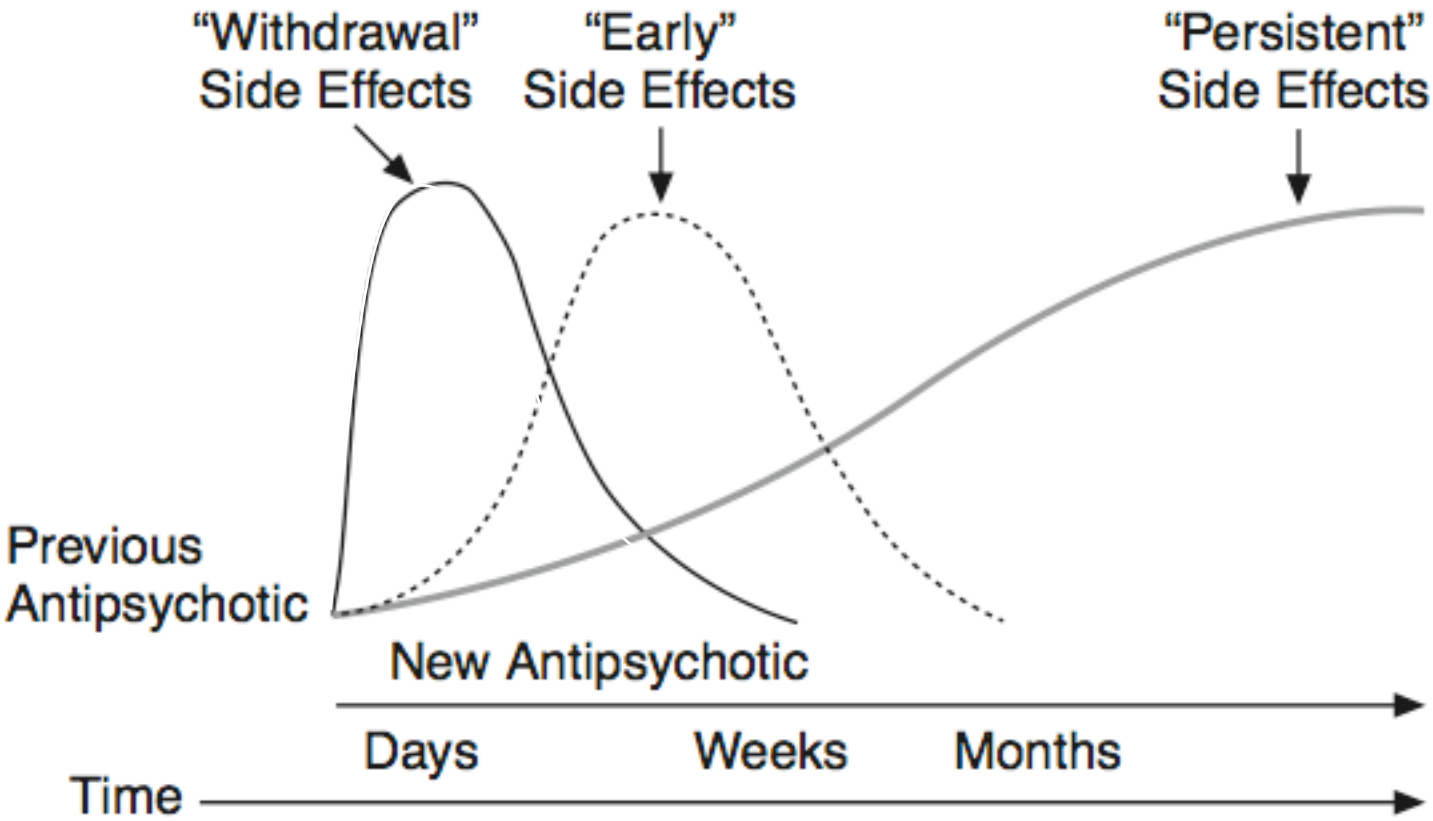
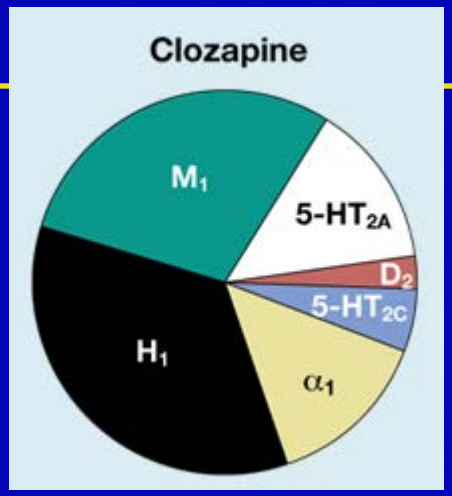
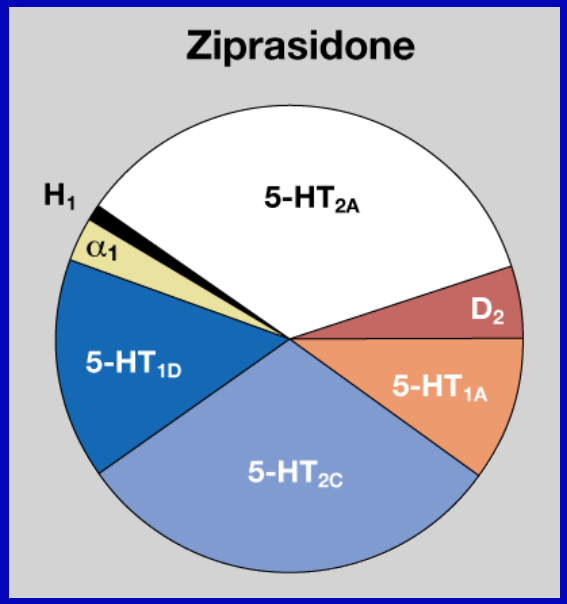


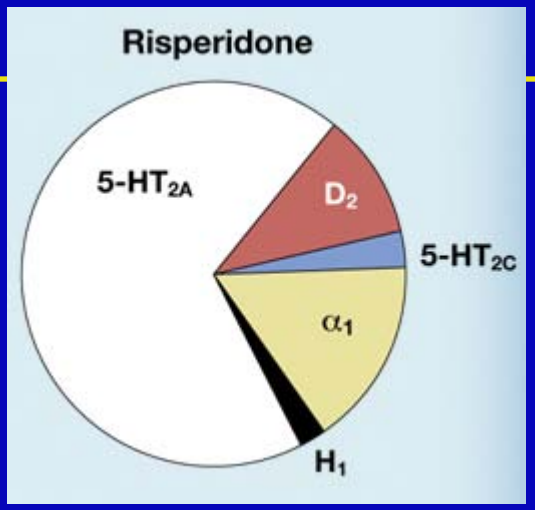
Figure 1. Time Course of Side Effects: Withdrawal, Early, and Persistent

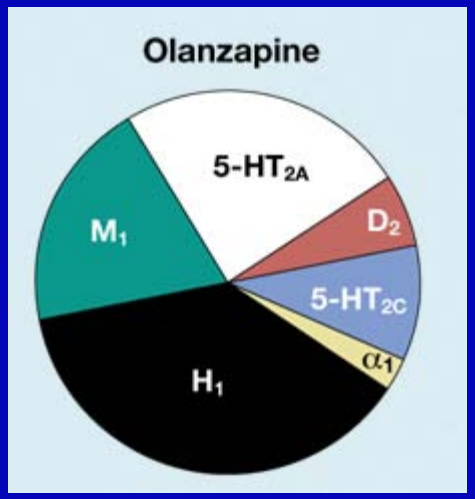


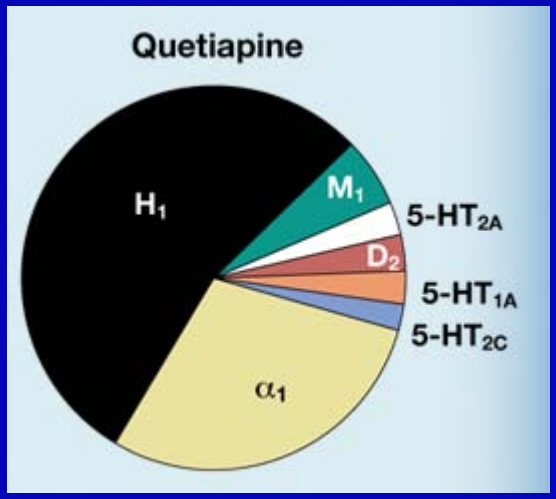
Pharmacology of Atypical Antipsychotics







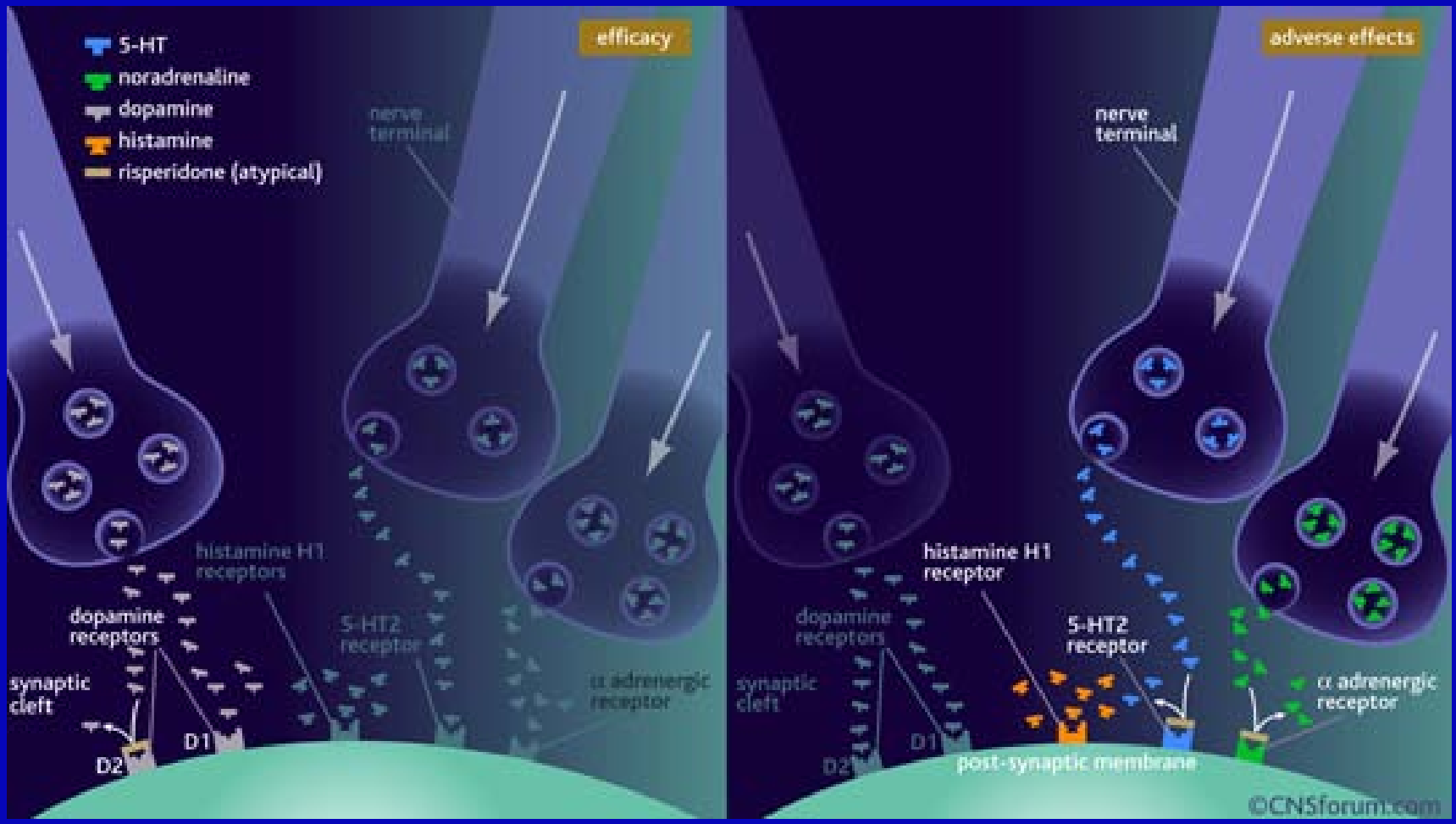




In vitro **findings may not correlate with clinical results.**

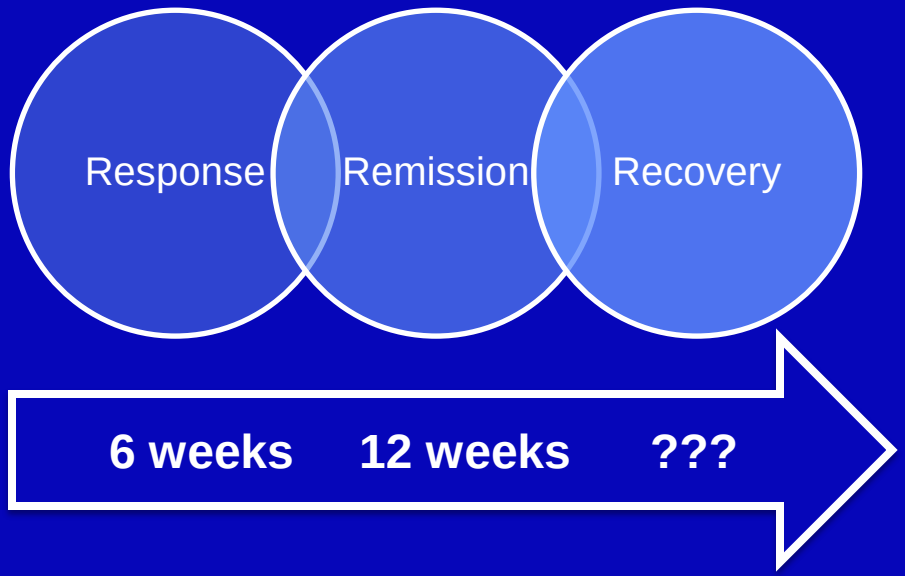
Zorn SH *et al*. In: *Interactive Monoaminergic Brain Disorders* (Palomo T, ed.), 1999, p.377-393.
Schmidt AW *et al*. *Eur J Pharmacol* 2001;425:197-201.

The mechanism of action of second-generation neuroleptics (risperidone)



How long to wait for response

- An average of 3 weeks
- Sometimes as long as 3 months (clozapine)
- Variability in medical decisions.
- Early responders
- Late responders
- >50% reduction in PANSS over 12 weeks
- Drug trials 2 , 4, 12 weeks
- Sustained response Vs lost response in long-term



- **Considerable divergence of expert opinion**
- **One survey of experts indicated that a period of 2.6 to 5.5 weeks was required.**
- **Lack of minimal response after 1 or 2 weeks is a powerful Predictor of subsequent poor response**

1. Huber CG, Naber D, Lambert M. Incomplete remission and treatment resistance in first-episode psychosis: definition, prevalence and predictors. Expert Opin Pharmacother. 2008 Aug;9(12):2027-38.

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-

Criteria's for Response

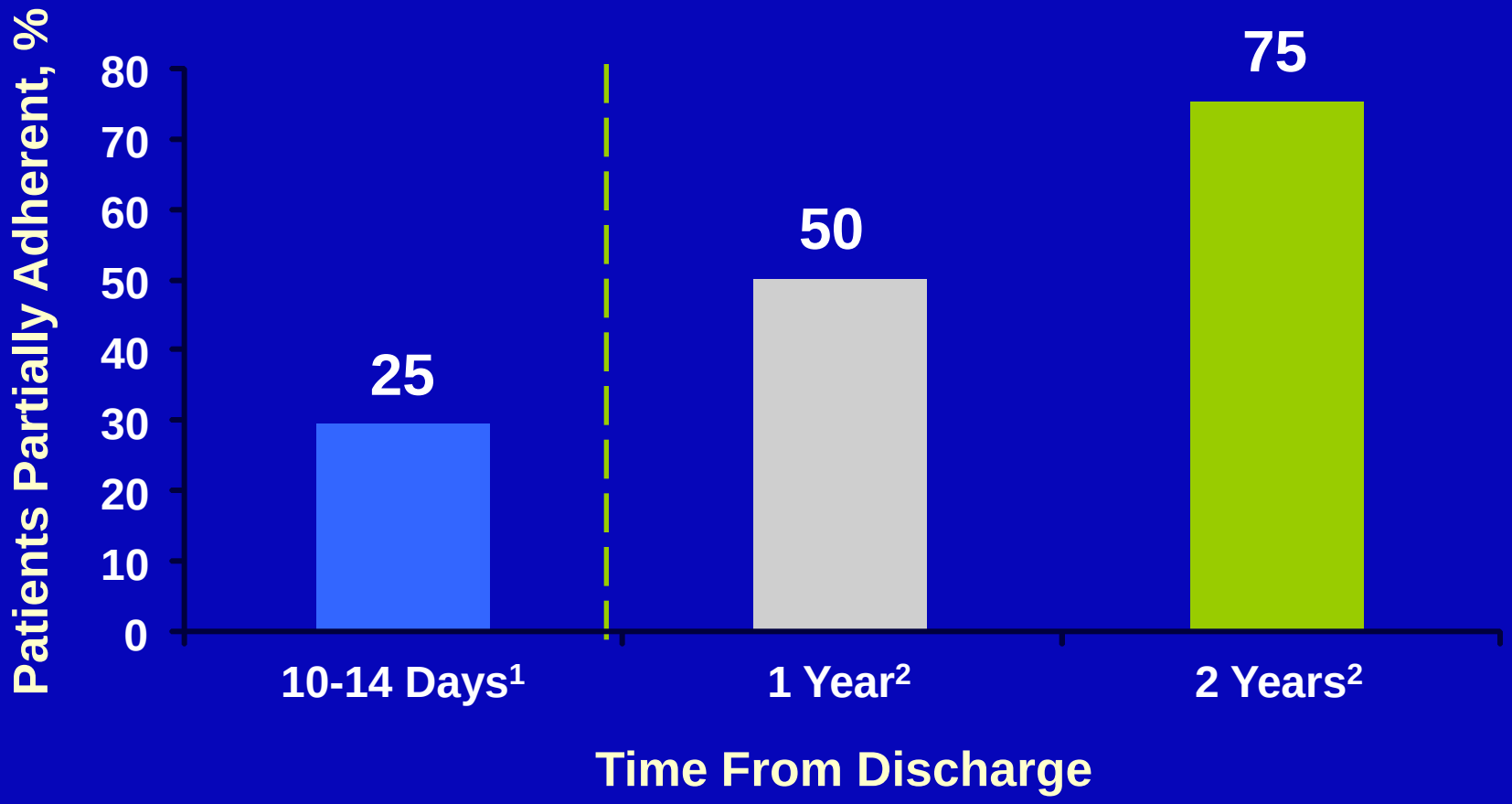
Poor Social functioning also a criteria for non-response [1]

Predicting response: early response

(2 wks) correlates to long-term efficacy .

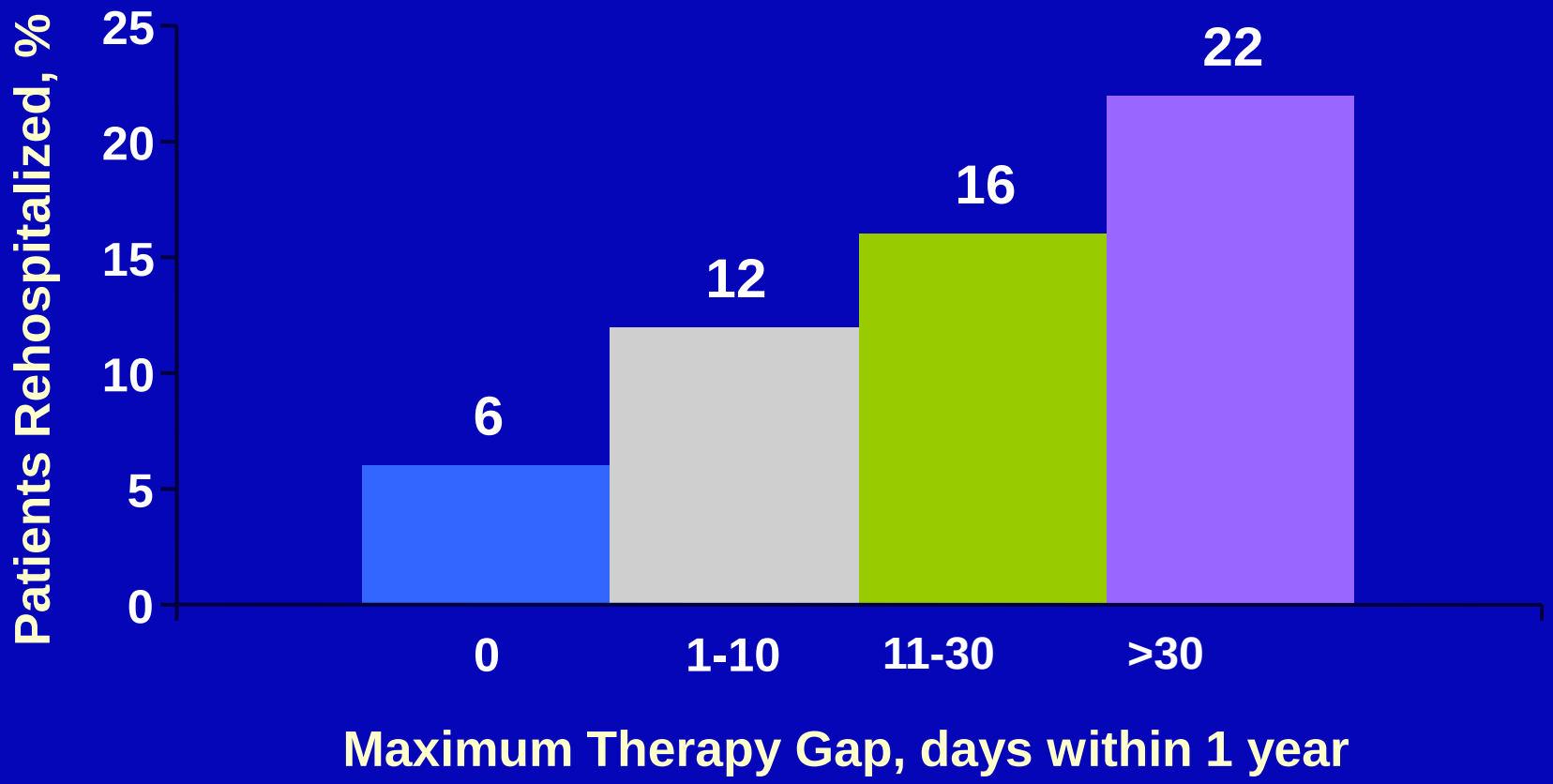
Leucht S, Busch R, Kissling W, Kane JM. Early prediction of antipsychotic nonresponse among patients with schizophrenia. J Clin Psychiatry. 2007 Mar;68(3):352-60

Partial Adherence in Schizophrenia Begins Early and Prevalence Increases Over Time



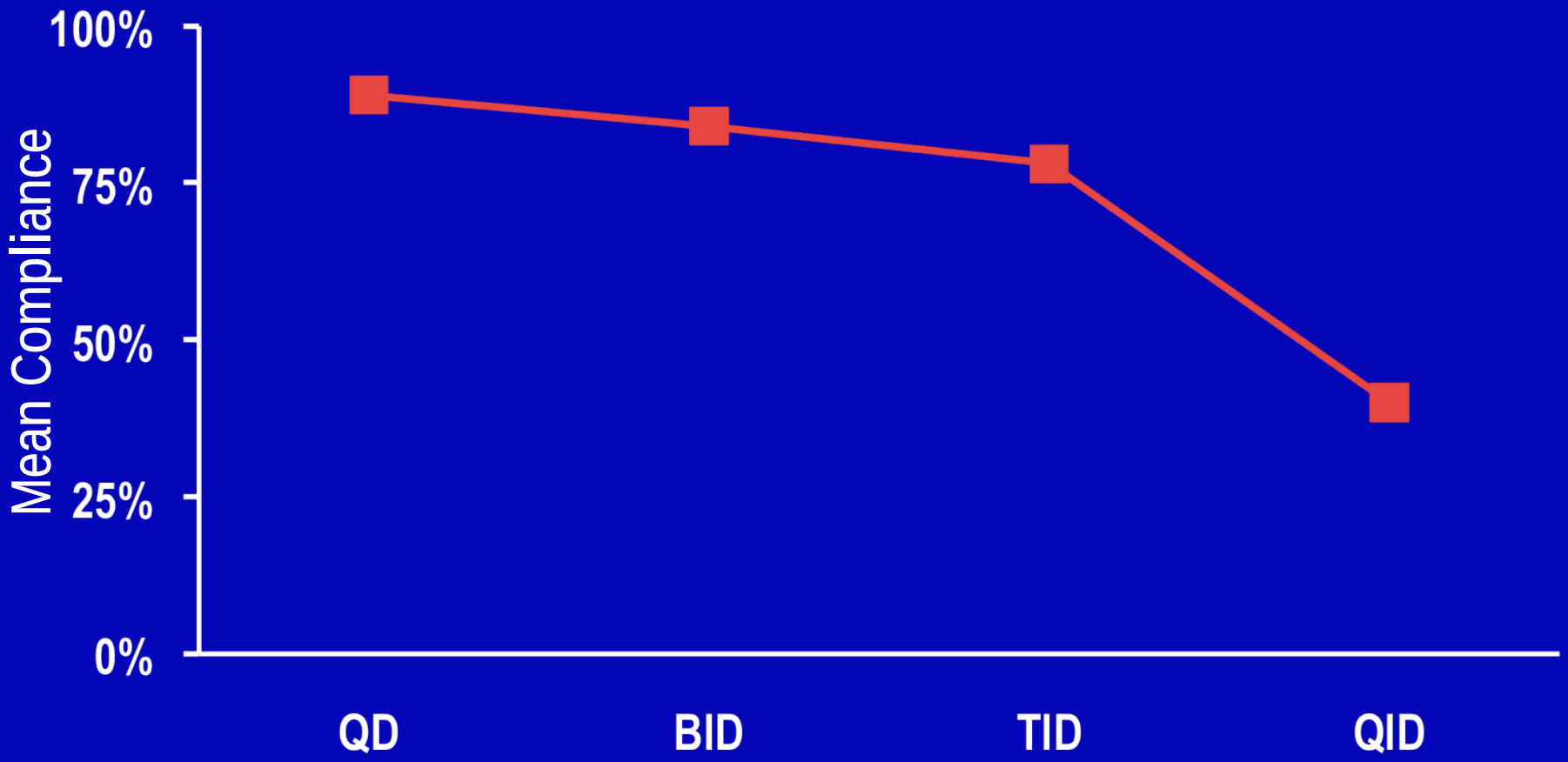
1. Velligan DI, et al. *Psychiatric Services*. 2003;54:665-667.
2. Weiden PJ, Zygmunt A. *J Prac Psych Behav Health*. 1997;March:106-110.

Medication Gaps Increase Risk of Hospitalization in “Adherent” Cohorts



Adapted with permission from Weiden PJ, et al. *Psychiatric Serv.* 2004;55:886-891.

Dosing Frequency & Compliance



Adapted from Kastrissios & Blaschke. *Ann Review Pharmacology & Toxicology*, 1997

Switch & persistent symptoms

- Positive symptoms
- Negative symptoms
- Cognitive
- Suicide
- Violence
- Substance abuse
- Poor social functioning

HALD, QUET, OLANZ

- RISP, QUET, CLOZ, ARIP, PALP
- RISP, ZPS, CLOZ, ARIP
- Clozapine
- Clozapine
- Clozapine
- Clozapine

Switch to Quetiapine

From Olanzapine

- **Reduced**
  - **Akathesia**
  - **Dyslipidemea**
  - **EPS**
  - **Prolactin**
  - **Weight**

From Ziprasidone

- **Reduced**
  - **Akathesia**
  - **EPS**
  - **insomnia**

Experience with Quetiapine XR
Clinical details

- N = 40
- Minimum Duration: 6 Weeks
- Maximum duration: 12 months
- Continued Treatment: 30
- Currently under follow up:25
- Discontinuation:10
  - Side effect: 3
  - Loss of effect:3
  - Intolerability:4

- Efficacy : excellent
- Good outcome: 18/25 (72%)
- Inadequate response: 2/25 (12%)
- Good Tolerability: 32/40(82%)
- Significant side effects: 5/40 (12.5%)
  - Increased sedation
  - Dryness of mouth
  - Rebound Insomnia
  - Somnolence

Dosing (N=33)

- 50 mg: 04
- 200 mg: 02
- 300 mg: 07
- 500 mg: 05
- 600 mg: 03
- 800 mg: 06
- 1000 mg: 01
- 1200 mg: 03

Diagnostic category

- Acute psychosis
- Schizophrenia (paranoid, Undifferentiated)
- Bipolar Affective Disorder (Manic episode)
- Bipolar depression
- Bipolar spectrum disorder
- Schizoaffective disorder
- Anxiety-insomnia

Symptom-syndrome response

Good : Behavior, Mood & affect, Sleep, Positive symptoms, Disorganization, Negative symptoms, Affective symptom, Depressed mood, Manic and hypo manic, Irritability, Insomnia, Suicidality, Concentration

- **Limited efficacy: Thought disorders , Delusions, First rank symptoms, Cognitive function , Residual feature, motivation**

Merits

- **Rapid titration**
- **Once a day dosing**
- **Easy administration**
- **Increased compliance**
- **Day time alertness**
- **Rapid response for behavior and mood symptoms**
- **Effect of suicidality**

Why XR?

- Historically:
- From Rapid Neuroleptization-to- Rapid Tranquilization in a range of indications
- Chlorpromazine IM/PO
- High dose fast escalation of Haloperidol IM/IV
- Rapid escalation of Lithium PO
- Rapid and fast valproic acid IM/PO
- Rapid Benzodiazepine IM/IV/PO
- Bolus Opiates IM

- No clinical benefit
- High risk of side effect
- CNS depression
- Acute cardiac event
- Delirium
- Movement disorder
- NMS

Comprehensive therapy

XR Quetiapine

1.Only oral

2. Less life-threatening side effects

3. No seizure or cardiac event

4. 800 mg day 2

Is switch clinically effective?

Switch studies

1. **Switch to XR: 68% achieved clinical benefit**
2. **Rosenheck RA et al, 2009, switch from Olanzapine to quetiapine: Vs. Continued on Olanzapine: No added benefit but High weight gain in Olanzapine**
3. ***Debert W, et al 2008, Olanzapine Vs Switch to Quetiapine: No difference in Relapse Rate at 200 days***
4. ***CATIE Switcher's Vs Stayer's : No difference in outcome at 18 Months within 5 groups, High weight gain for Olanzapine, 2009***
5. ***Switch to Quetiapine Vs Paliperidone: No difference in Long-term, extension phase, 2009***

Are there differences amongst atypical

1. No differences amongst SGA except Clozapine
2. Non-significant differences on axis & domains of schizophrenia
3. Choice within SGA remains mainly guided by side effect profile

The new ‘statistics’
Meta analysis

Are there differences

which are not seen?

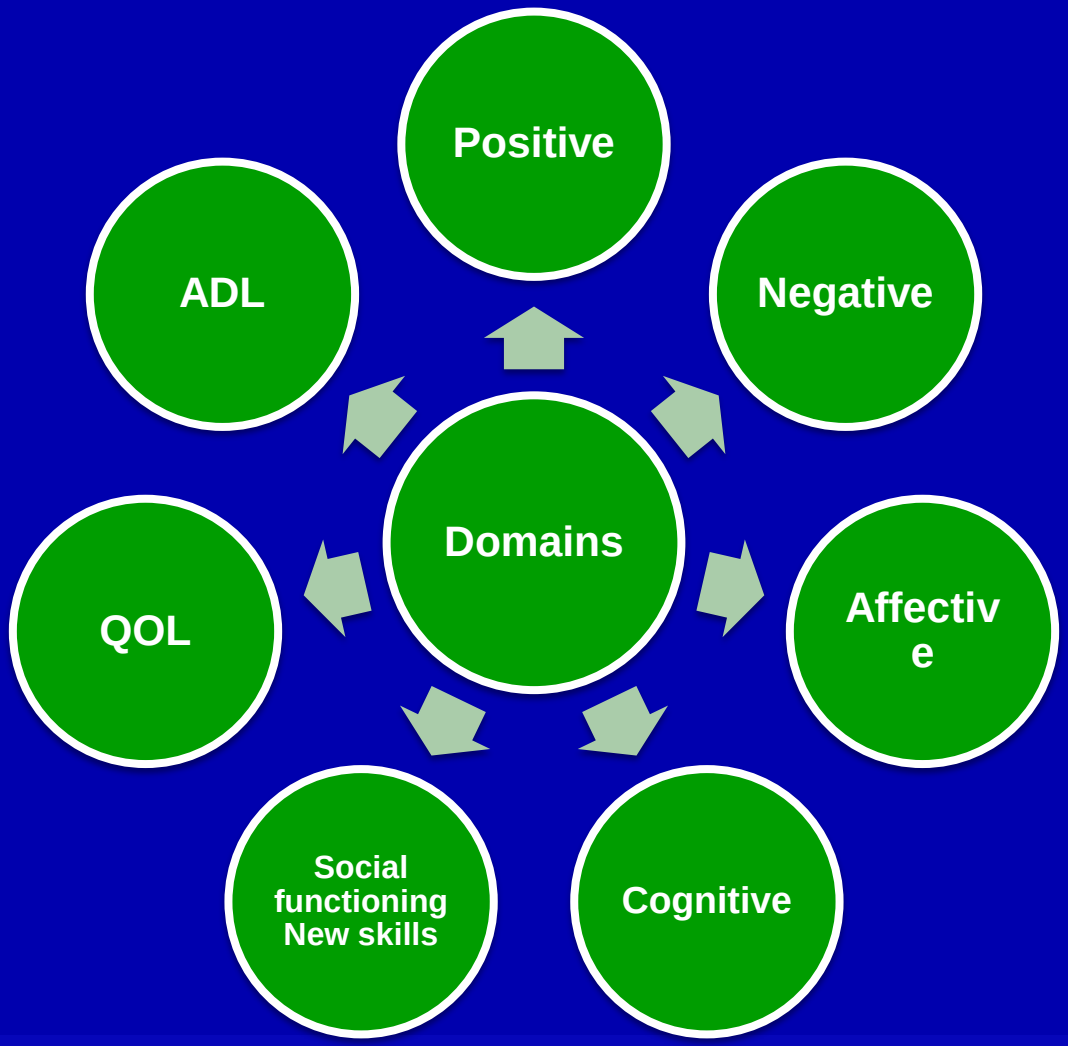
OR

Are the differences not there,

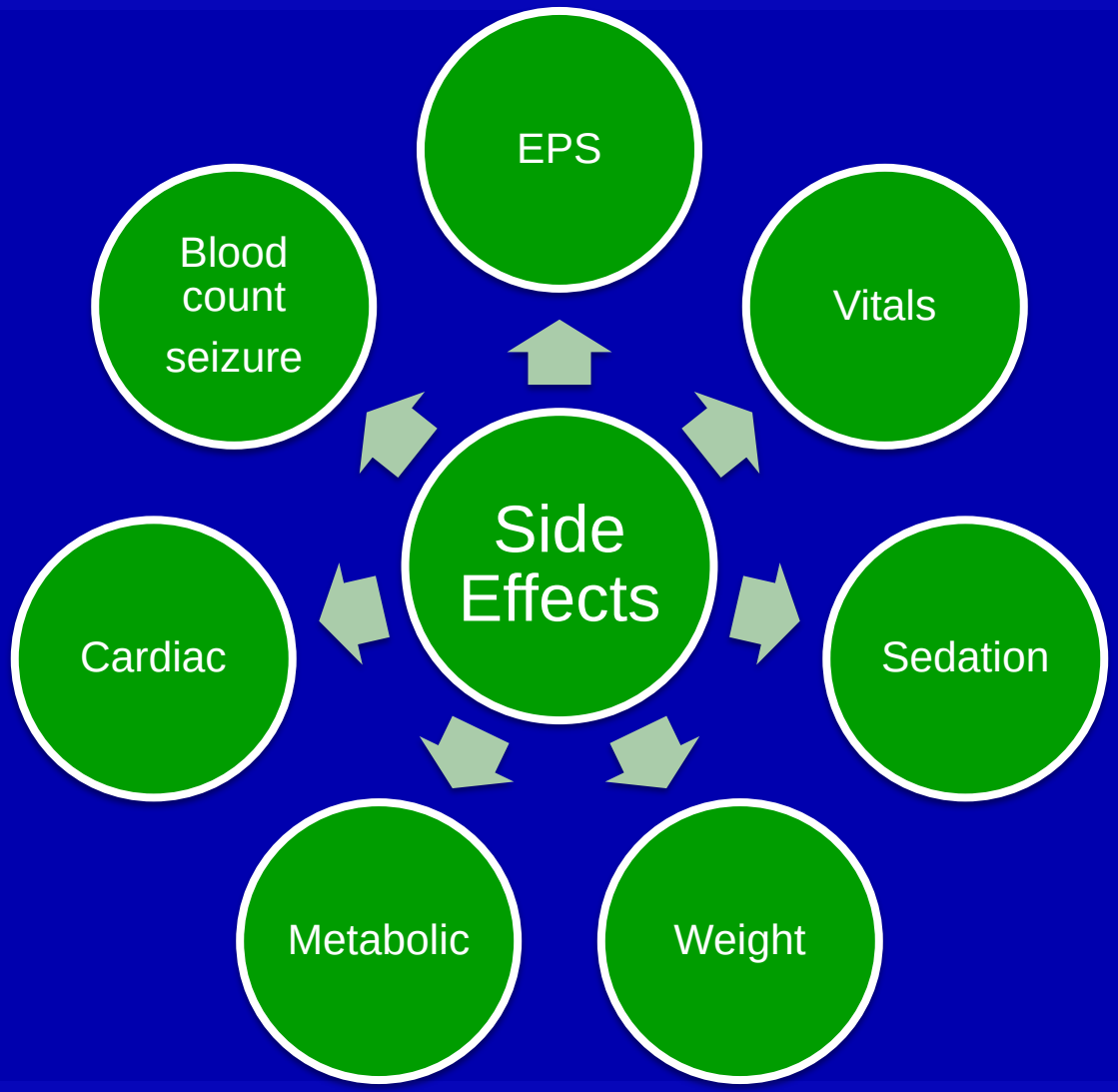
& we are trying to ‘fish’?

All Atypicals are SDA

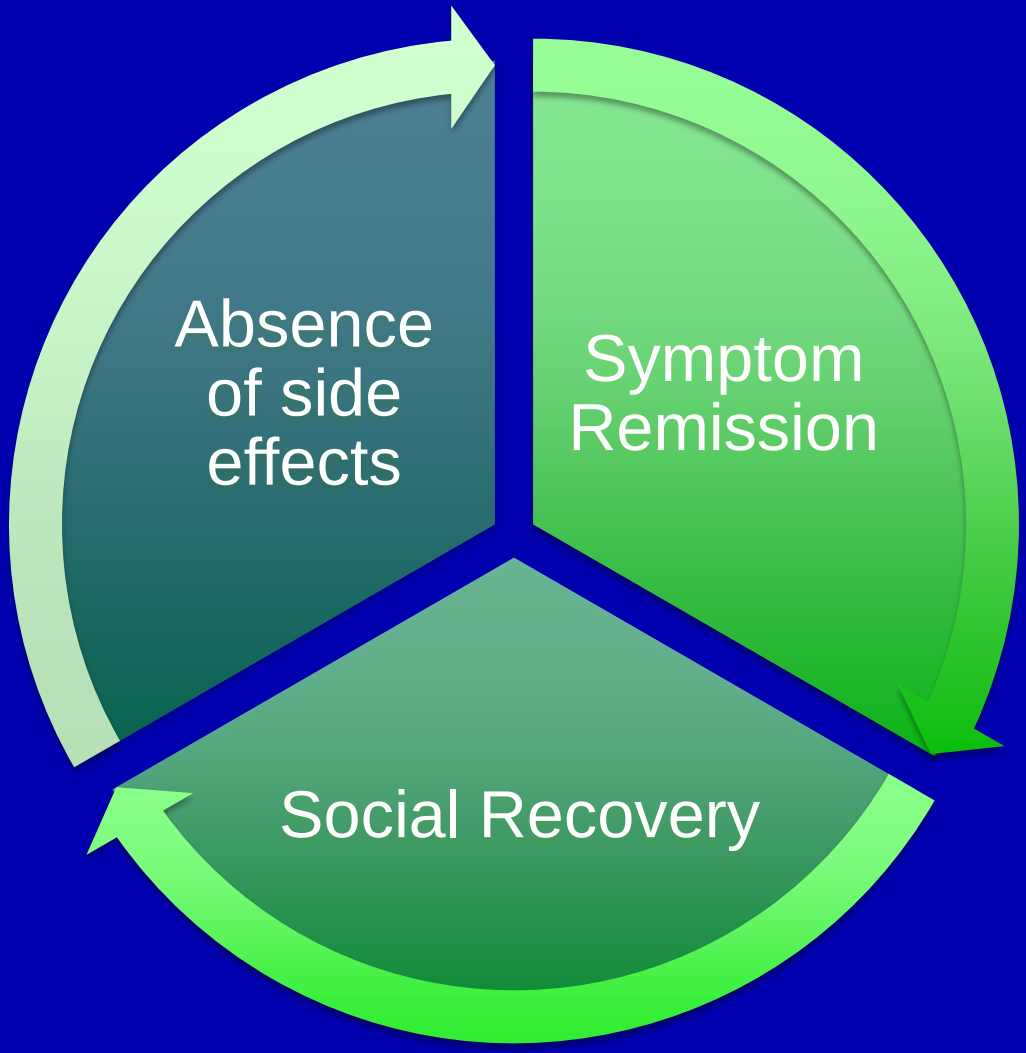
Differences are expected on efficacy & side effect



Differences are expected on efficacy & side effect



Parameters of monitoring



CATIE – Phase 3, Symptom response
No difference across all groups, However individual variations

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	<0.001 ✔✔	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.**

Stroup T et al, Schizophrenia Research 107 (2009) 1-12

Cognition, atypical antipsyhotics & Schizophrenia

- Commonest manifestation
- Deficit leads to functional & social decline
- Improvement mediates social recovery
- Number of Studies attempted, CATIE, CAFÉ, biases ?
- General impression – SGA – beneficial
- Benefit is small in effect size
- Better than FGA
- No difference across different molecules

Cognition & Atypicals: General Conclusions

“our hope from atypical antipsyhcotics for cognitive enhancement is lost… we may have to look somewhere else for this effect..”

M.Green, Editorial in AJP, 2007

Opinion : Academics

There is a moderate procognitive effect for early psychosis, poorly correlated with symptoms & all SGA have similar results, at 2, 6, 18 months

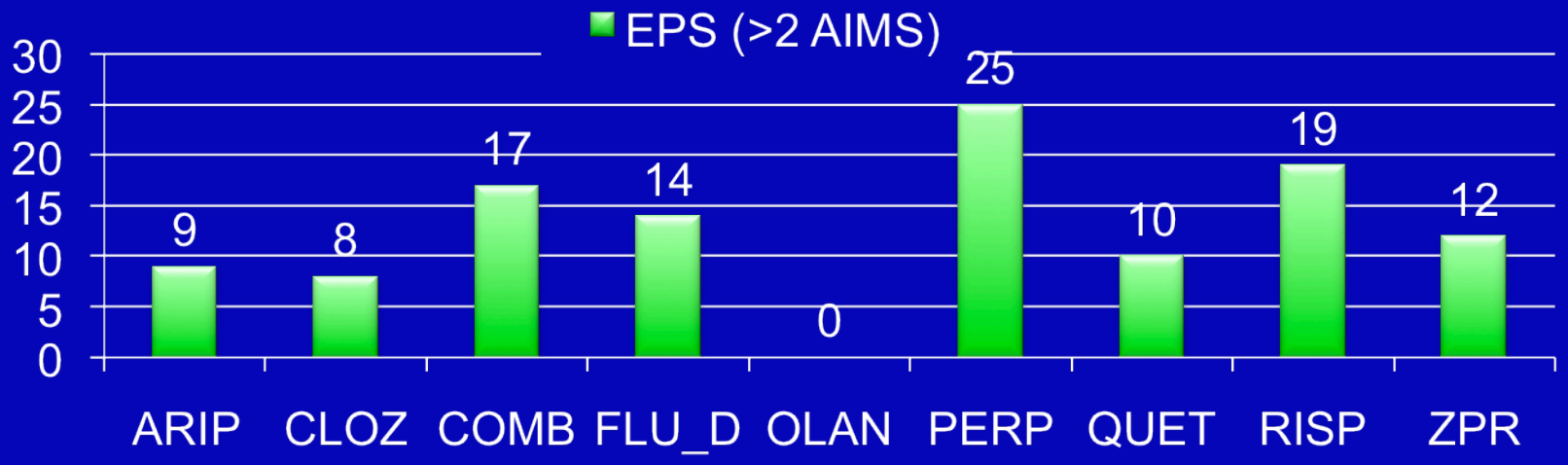
– **June 2009, AJP**

FGA & SGA: Broad spectrum
Case report. AB 52 years, Clozapine

- **Blood count improved in 2 weeks. Antipsychotics- free state for 3 weeks**
- ***Re-challenging clozapine??***
- **Started Pimozide 4 mg, increased to 12 mg per day,**
- **Discharged after 4 weeks, Regular follow up for 18 months,**
- **Good remission, ADL, good QOL, No major concerns,**

Are there differences in side effect profile

EPS across AAPD at 6 month outcome



Stroup T et al, Schizophrenia Research 107 (2009) 1-12

TD: High in Geriatric Population with SGA

Akathesia

- High dose
- High potency SGA
- Combination of SGA
- SGA with other psychotropics
- Bipolar depression
- Palliative care setting
- Comorbid SUD

EPSE, Akathesia Prevalence SGA	
Clozapine	35% (45%)
Risperidone	25-27%
Olanzapine	3%-6%
Quetiapine V Placebo	12.9 V 13.1% (21.4% with Lithium, DVS)
Aripiprazole	21% with ADD, RR 0.39

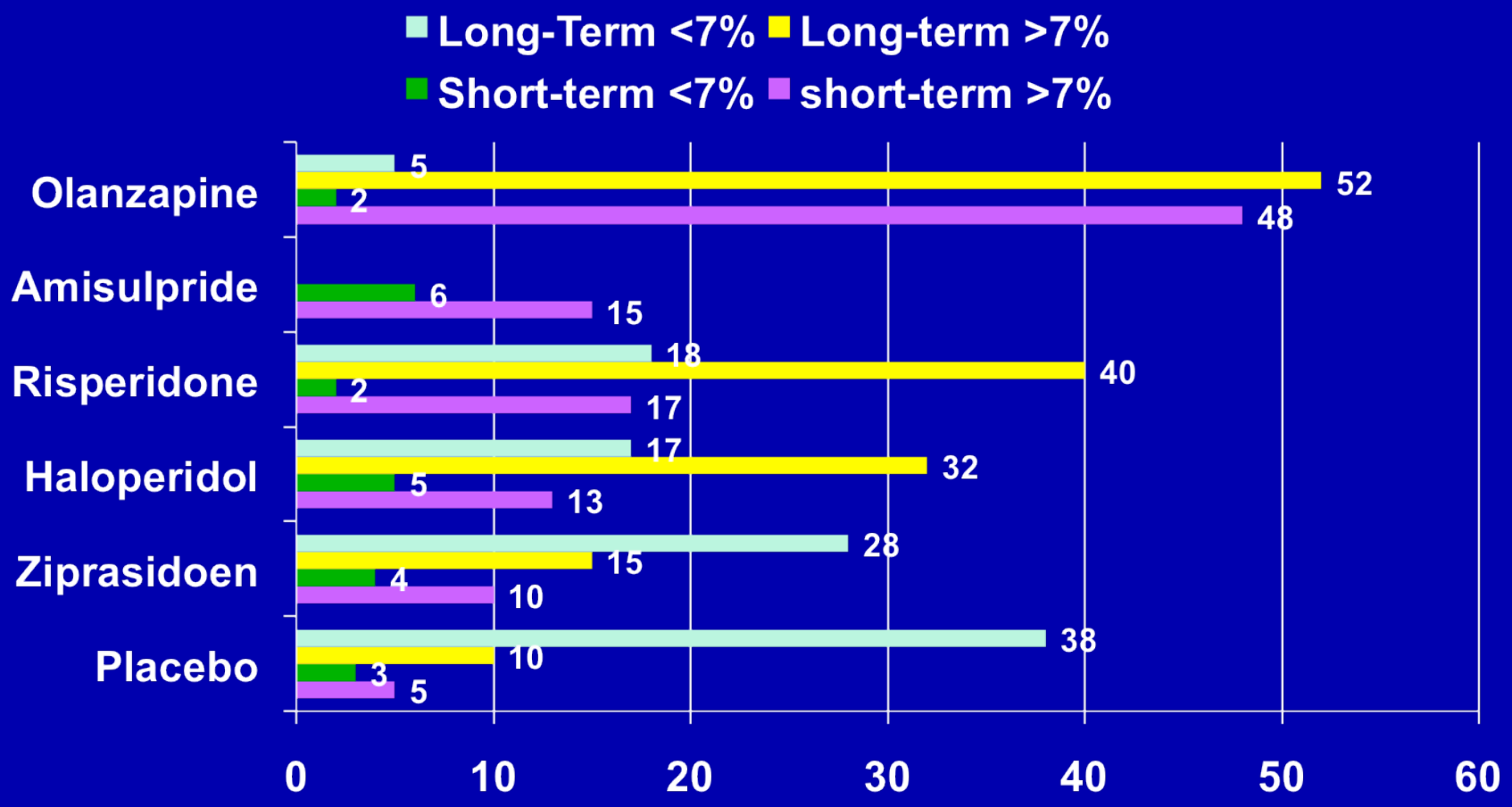
Antipsychotic Drugs and Obesity and Diabetes [1]

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine (Clozaril)	+++	++	++
Olanzapine (Zyprexa)	+++	++	++
Risperidone (Risperdal)	++	+/-	+/-
Paliperidone (Invega)			
Quetiapine (Seroquel)	++	+/-	+
Aripiprazole* (Abilify)	+/-	-	-
Ziprasidone* (Geodon)	+/-	-	-

+ = increase effect; - = no effect; D = discrepant, results. *Newer drugs with limited long-term data, 1. ADA/APA Consensus Conference

Early Weight gain persists

Short (N=1717, 4-12 wks) & Long-term (N=1649, 52 wks),



Bruce,P et al, Weight effects associated with antipsychotics: A comparative database analysis, Schizophrenia research 110 (2009) 103-110

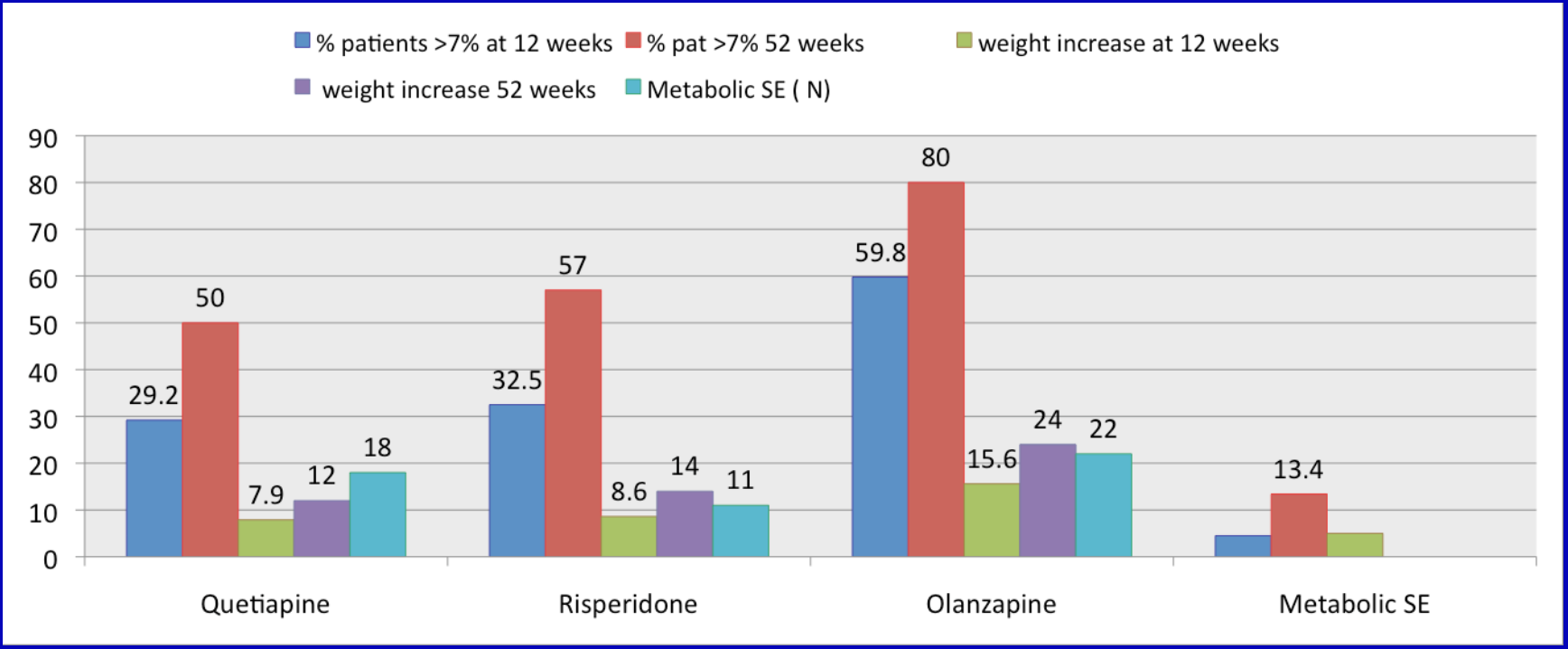
Diabetes and Antipsychotics

- Schizophrenia & Diabetes Mellitus:
  - Many studies shown ↑ risk in schizophrenia:
    - IGT, Insulin resistance
    - Type 2 Diabetes mellitus
      - 10% Schizophrenia > 6–8% general population
  - Studies over several decades, predating both typical & atypical neuroleptics
- RCT Data – Summary:
  - Results:
    - 9% of all patients Rx with antipsyhotics developed new DM
    - clozapine, olanzapine, haloperidol ↑ FBS
    - clozapine, olanzapine ↑ Fasting Cholesterol
    - No correlation between weight gain and FBS in this study

Do Atypical antipsychotics cause DM?

- **Basic Science**
  - **Normal insulin secretion, ↓ insulin sensitivity with ↑ weight**
- **1 flawed RCT, Cohort Studies, Case Reports/Studies**
  - **9% of patients Rx with any antipsyhotic developed new DM**
  - **clozapine, olanzapine, haloperidol ↑ FBS**
  - **clozapine, olanzapine ↑ Fasting Cholesterol**
  - **Less DM risk with Risperidone?**
- **Can DM be predicted or prevented?**
  - **Risk factors for T2DM**
    - **Obese, older, ethnic groups, FHx DM, etc.**
  - **Risk factors for DKA**
    - **Thin, younger, female?**

Metabolic profiles of SGA in early psychosis: Findings from the CAFE 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

Cardio-metabolic Disease Risk Factor

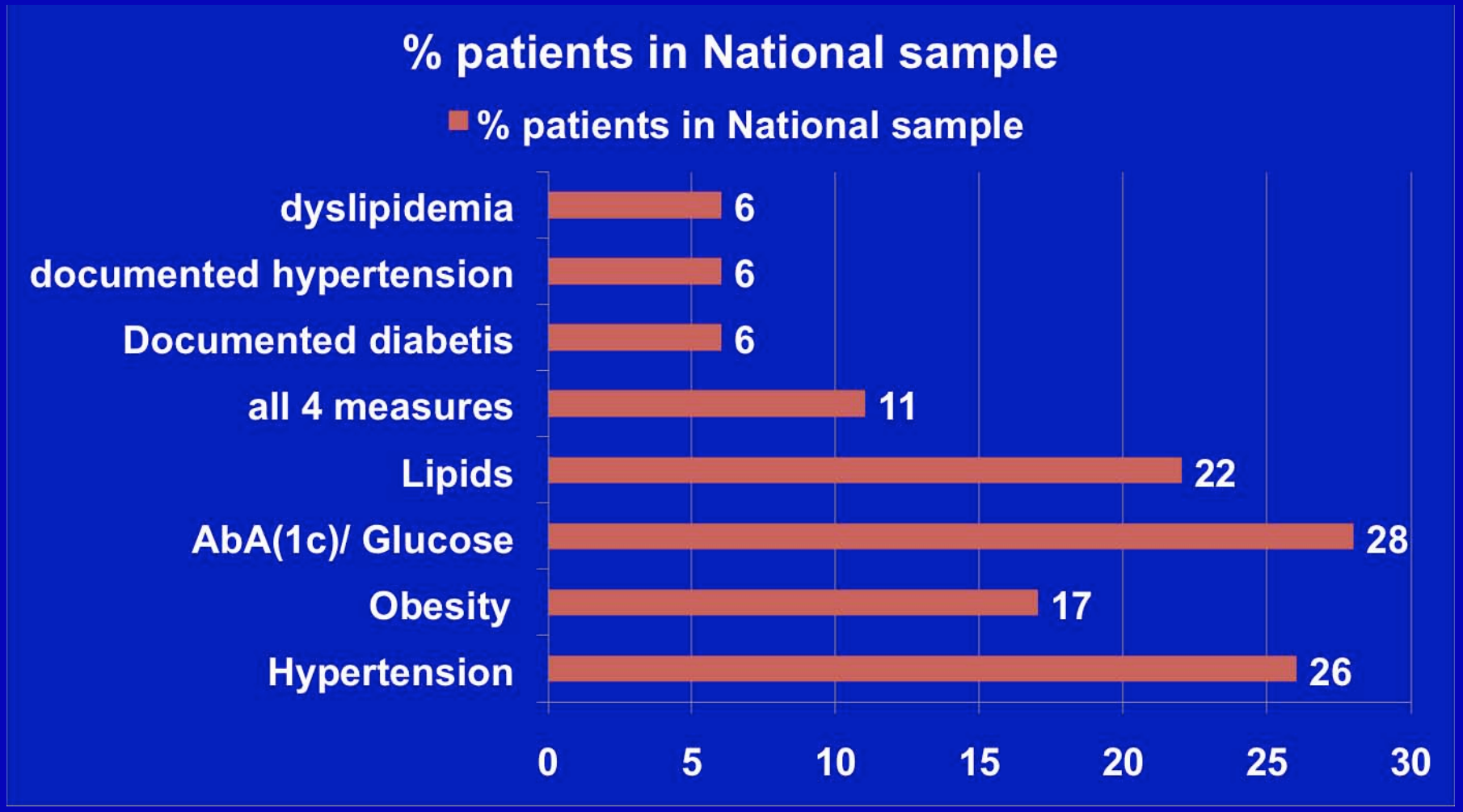
	Schizophrenia		Bipolar Disorder
Modifiable risk factor	Estimated Prevalence of risk factor (%)	Relative Risk	Estimated Prevalence of risk factor (%)
Obesity	45-55	1.5-2 x	26
Smoking	50-80	2-3 x	55
Diabetes	10-14	2 x	10
Hypertension	>18		15
Dyslipidemia		Up to 5 x	

Public Health measures for metabolic side effects

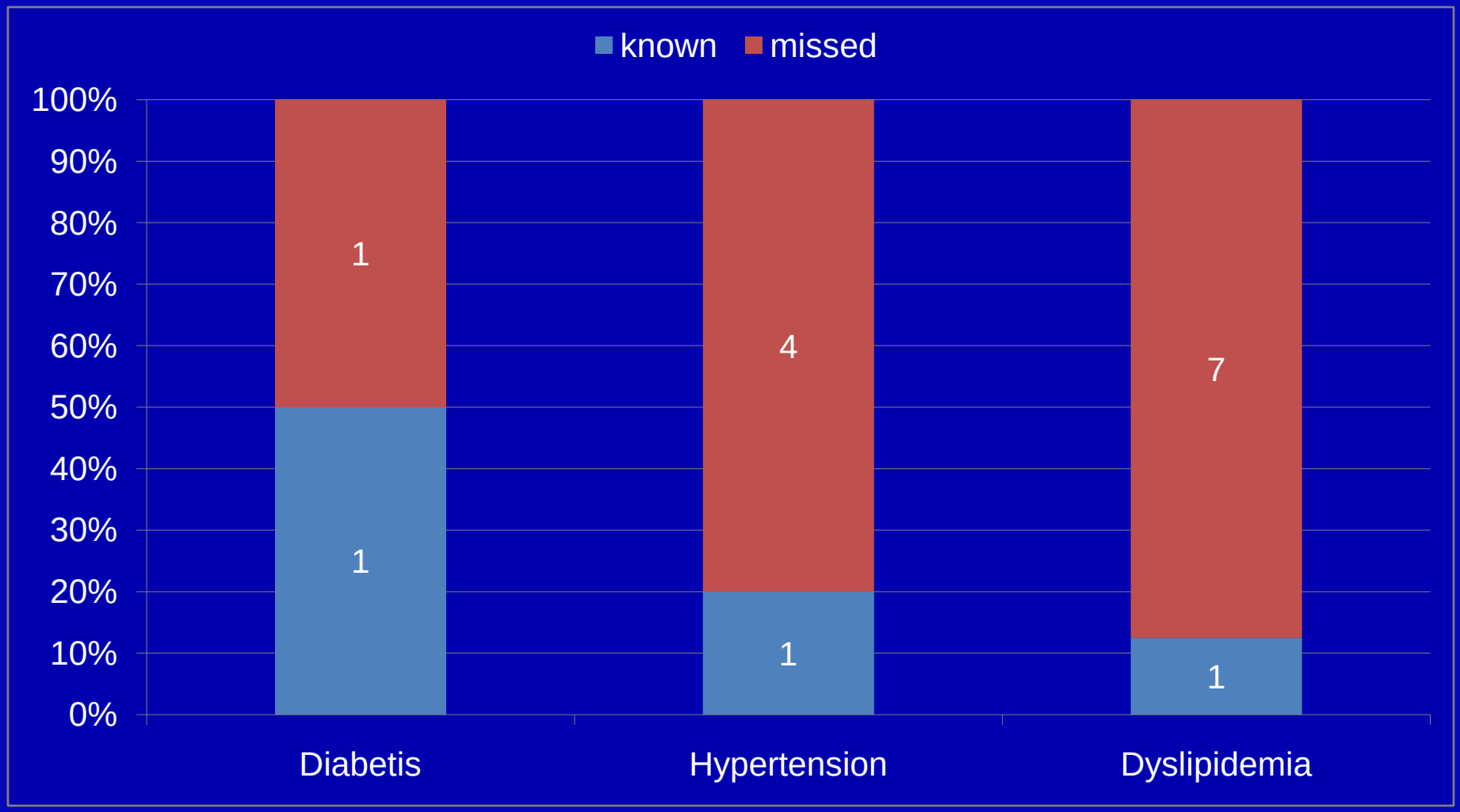
- Meta analysis (N=35K, 152 mortality study): 2 fold risk of premature death.
- CVD leading cause of death in SMI: US public sector data.
- 8.3X (5x Female) increase in death 1991-1995, CVD mortality in ‘first hospitalization’.
- Varying effect on FGA & SGA
- Adiposity dependent effect
- Insulin resistance.
- Risk of dyslipidemia, obesity, weight gain, raised blood sugar

Newcomer J.W, J. Clinical psychiatry, 2007;68 [suppl.4] : 8-13

Atypical antipsychotics & Comorbidity
A UK audit of screening for the metabolic side effects of antipsychotics in community patients

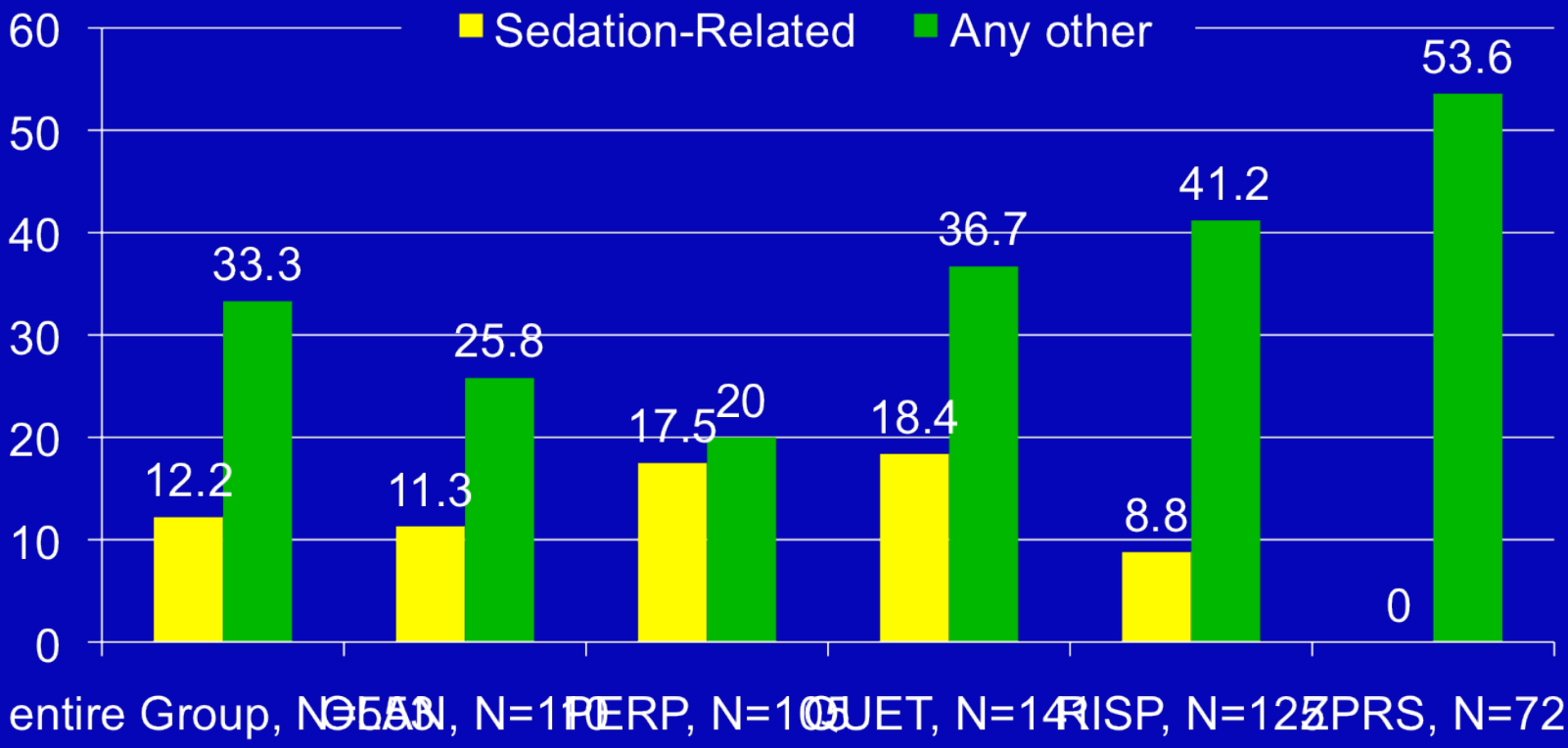


Under detected metabolic Side effects: UK sample



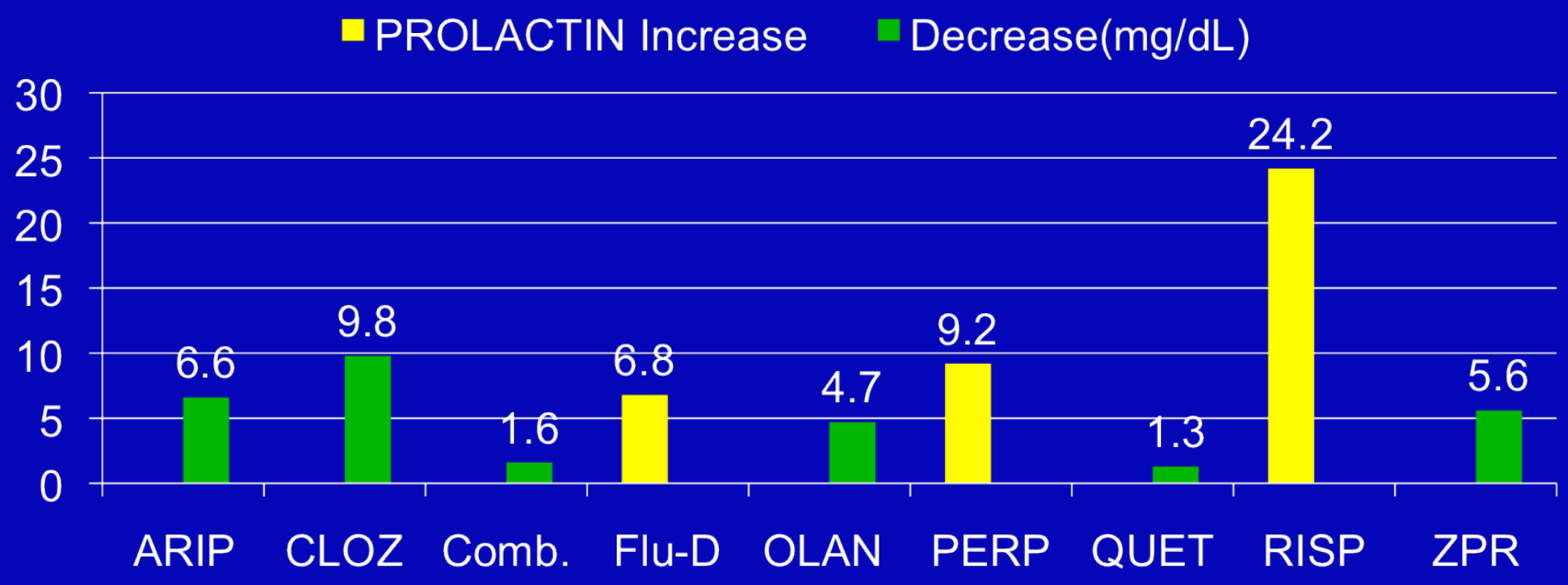
Sedation – related Discontinuation

- **It is every day -affair**



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

Prolactin and antipsychotics



Stroup T et al, Schizophrenia Research 107 (2009) 1-12

Factors compromising outcome and efficacy in treatment of schizophrenia

- Axis I – Psychiatric co morbidity (>20%),

  SUD (>50%)
- Axis II – Learning disability, (5%)

  Personality Disorder (10-15%)
- Axis III – Physical comorbidity (30-40%),

  Treatment emergent symptoms (>50%)
- Axis IV – Rarely absent
- Axis V - Functioning – consider as outcome criteria

Sketch model of barriers in Care in Schizophrenia

Patient & their Personalities

Mental illness & illness-related disability-stress

Treatment – related factors

Family related factors

Organizational & mental health system barriers

Need for Change in Strategy

Maximizing Outcome: Strategies

- Care plan
- Continuity
- Rapport
- Multi-factorial
- Goals
- Achievable objectives
- Assessment
- Follow up

1. Treatment of side effects
2. Use of
    1. ADJUNCT
    2. COMBINATION APD
    3. Potentiation of APD
    4. For added efficacy
3. Treatment of psychiatric comorbidities
    1. Anxiety –phobia, dysthymia, OCD

Clinical options: need for innovation

Varying level of evidence

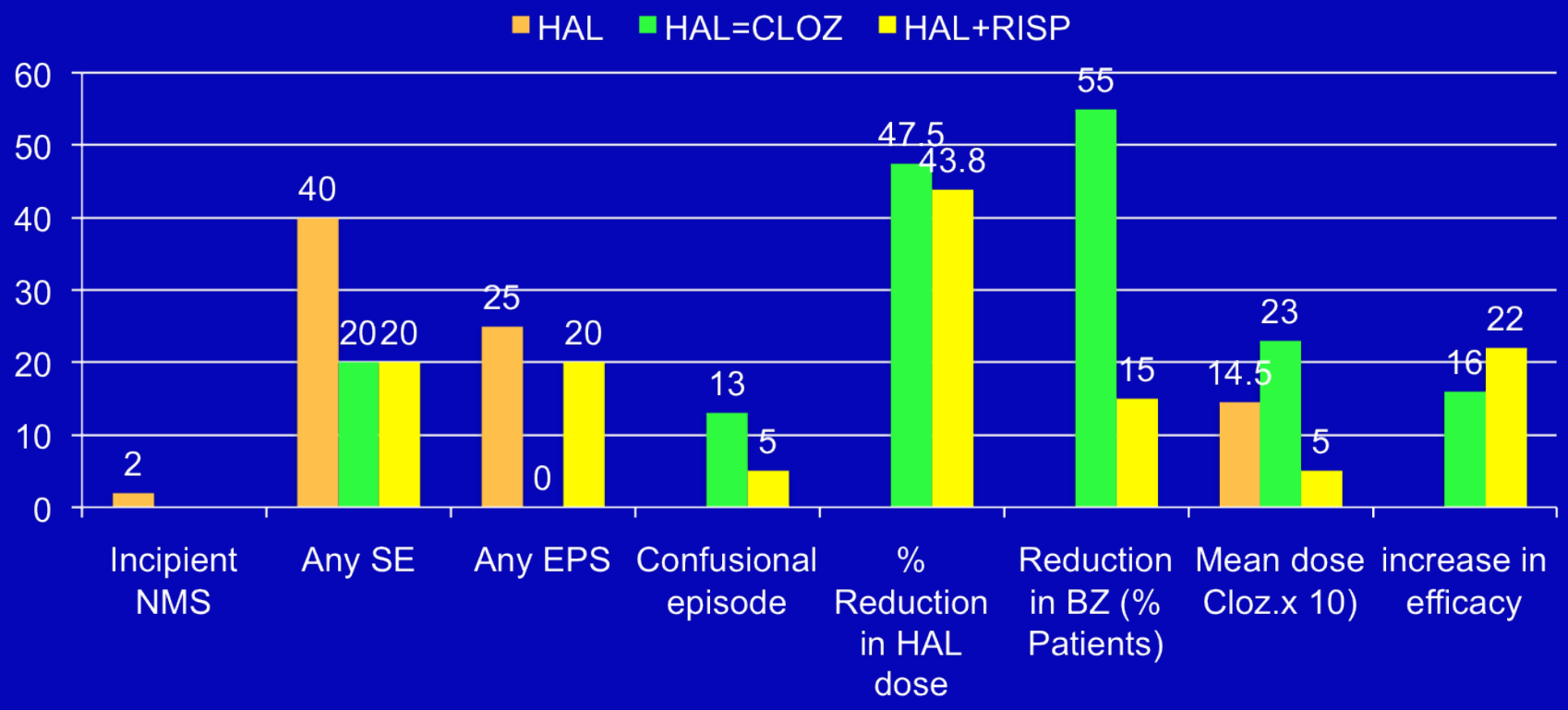
- Typical antipsychotics
- Atypical antipsychotics
- SGA + BZ &/ ADD + &/ Mood stabilizers
- Combination of FGA + SGA
- Combination of 2 SGA
- Clozapine
- Clozapine + SGA
- Clozapine + FGA+ SGA
- ECT
- Clozapine + ECT
- TMS

Psychosocial therapies are part of comprehensive management

- Various therapies — Psychosocial
- Family therapy
- CBT in Psychosis
- Cognitive remediation

Experiments

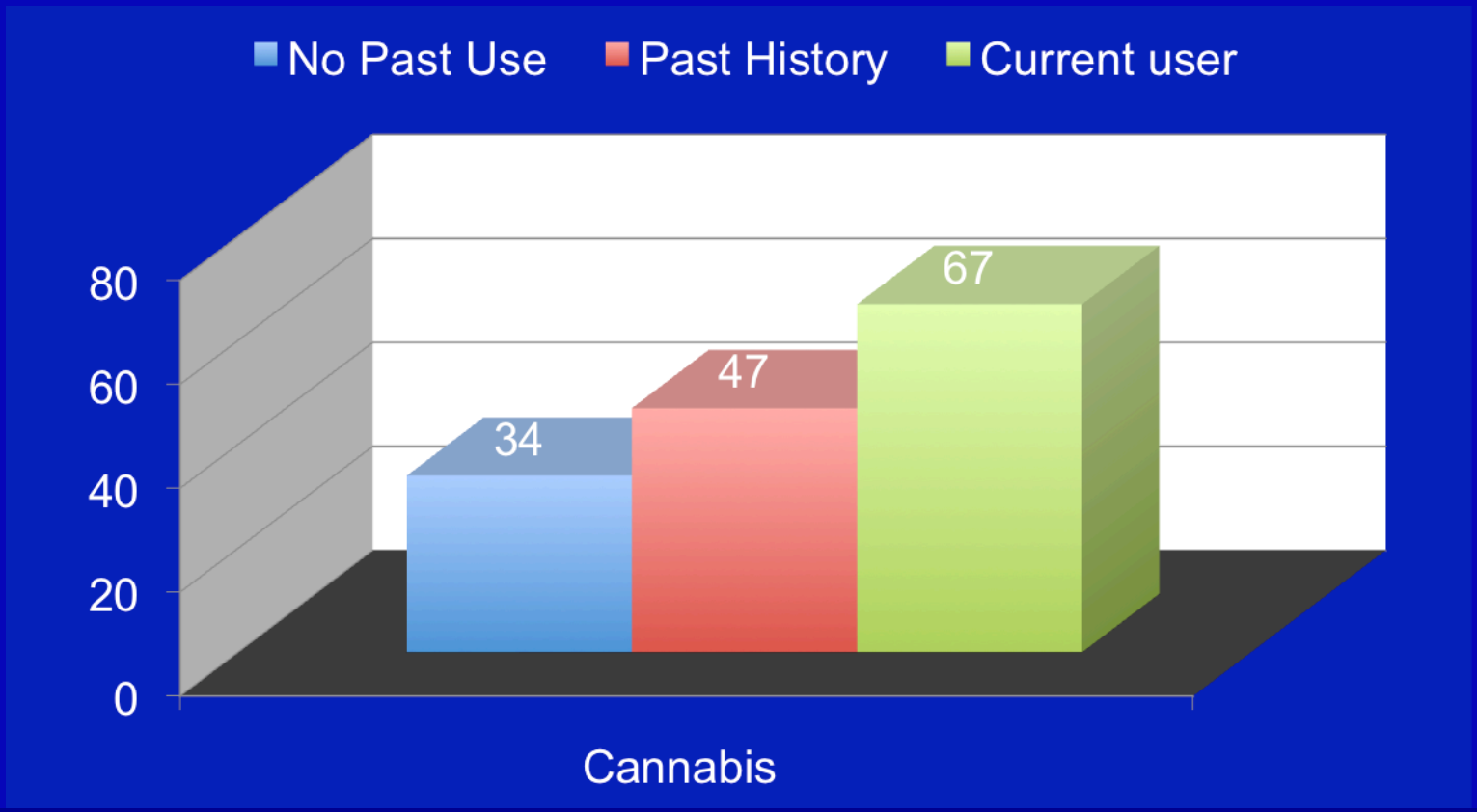
Add-on Risperidone & Clozapine to haloperidol non-responders. Randomized Open level. N=90)



Shrivastava,A et al. American psychiatric Association Annual Meeting,Abtracts 2000

Schizophrenia has substantially high risk of Comorbidity (Vs. population) : OR: 4.6

Nonadharence in schizophrenia and Comorbid Substance abuse. [1]
High rates of psychiatric and other medical conditions. More than 75% [2]



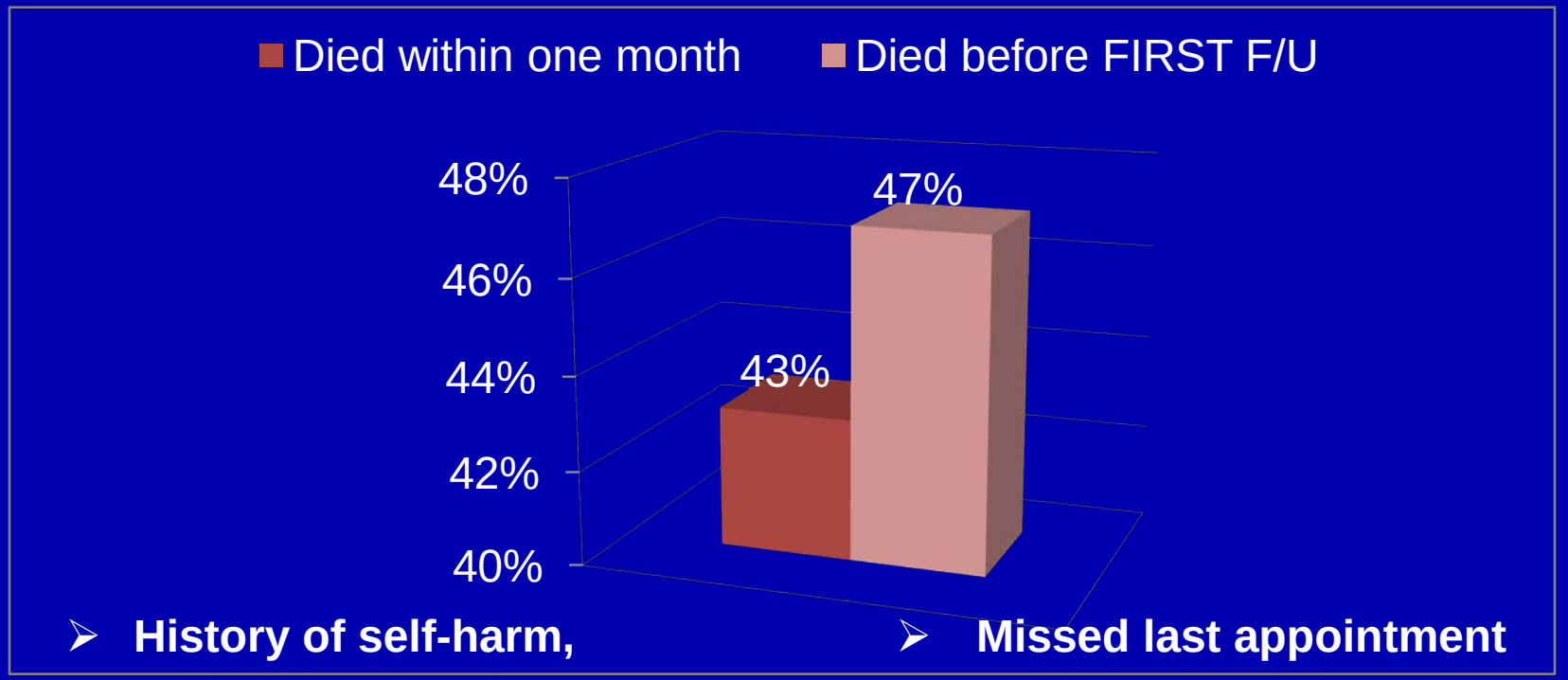
1.Hunt GE et al, Schizphr.Res, 2002; 64: 253-264, 2.Carney et al 2006 J.Gen.Intern.Med

Cannabis

Explanation for close relationship between Psychosis & cannabis is still unclear.

High suicide in recently discharged patients

N=238, Death by suicide within 3 month of discharge



- **History of self-harm,**
- **symptoms at last contact**
- **Initiated own discharge**
- **Missed last appointment**
- **Detained for compulsory treatment: low risk**

Final message

- 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 persist with side effects.