



# Psychiatric Emergencies

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# DISCLOSURE

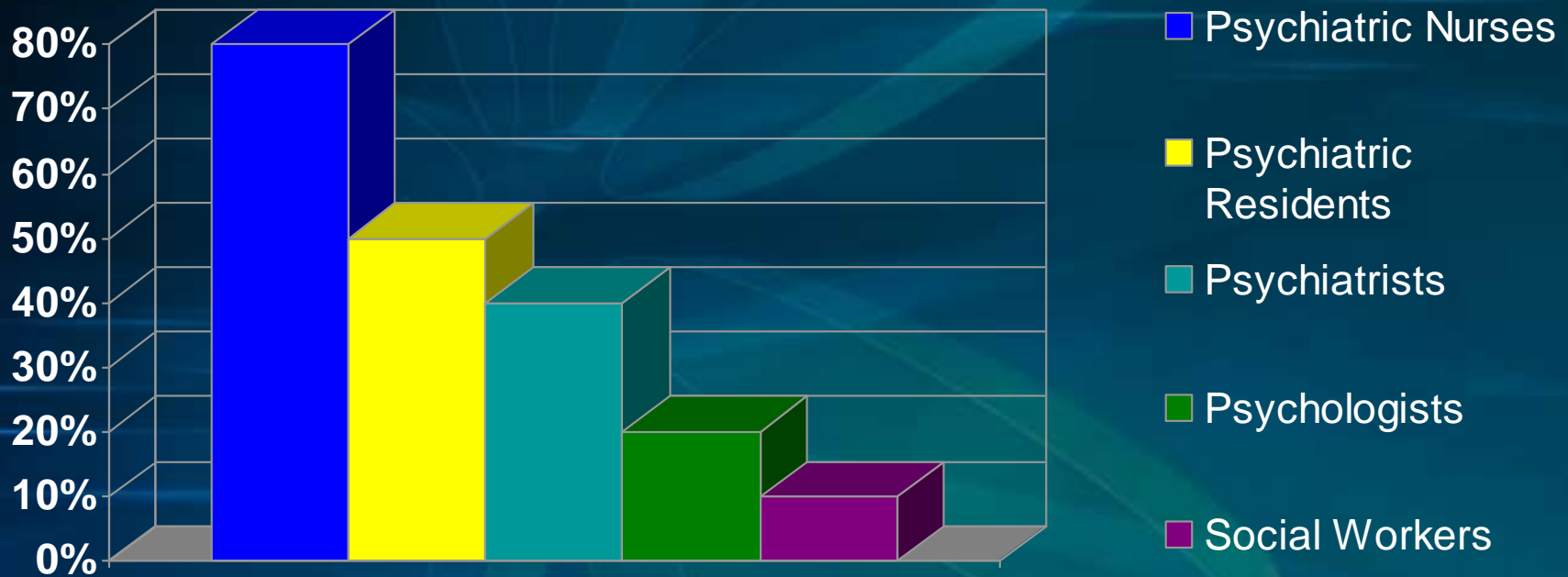
- Astra Zeneca (Advisory Committee, Speakers' Bureau)
- Bristol Myers Squibb (Advisory Committee, Speakers' Bureau)
- Eli Lilly (Advisory Committee, Speakers' Bureau, Research Support)
- Janssen (Advisory Committee, Speakers' Bureau)
- Lundbeck (Advisory Committee, Speakers' Bureau)
- Merck-Frosst (Research Support )
- Otsuka (Advisory Committee, Speakers' Bureau)
- Pfizer (Advisory Committee, Speakers' Bureau , Research Support)
- Purdue (Advisory Committee, Speakers' Bureau)
- Sunovion (Advisory Committee, Speakers' Bureau)

# Objectives

**At the end of the presentation the participant will be able to:**

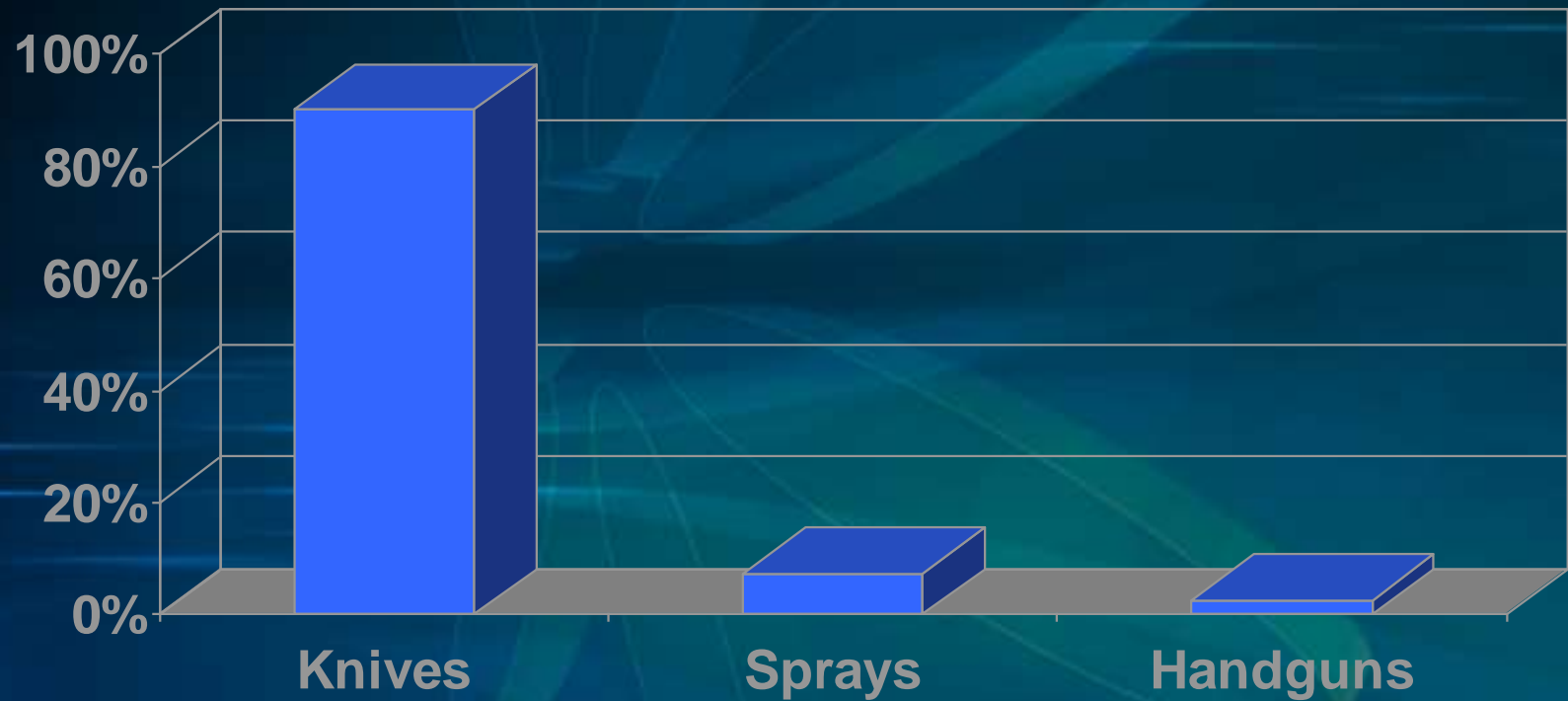
- Understand the causes of agitation in an Emergency setting.
- Master the current treatment options for patients with an acute psychotic episode and identify the unmet needs in this area.
- Explore the different new approaches in the management of the psychotic, demented agitated patient.

# NUMBERS ASSAULTED AT SOME POINT IN THEIR CAREER:



- 33% OF ATTACKS ARE IN PRIVATE OFFICES

# WEAPONS



# DSM-5 DIAGNOSES ASSOCIATED WITH

## AGGRESSIVE / VIOLENT BEHAVIOR

- **A: Aggressive behavior as an essential feature**
  - Intermittent Explosive Disorder
  - Conduct Disorder
  - Antisocial Personality Disorder
  - Borderline Personality Disorder
  - Sexual Sadism
  - Culture - Bound Syndromes

# DSM-5 DIAGNOSES ASSOCIATED WITH AGGRESSIVE / VIOLENT BEHAVIOR

- **B: 1- Aggressive behavior as an associated feature**
  - Substance-Related Disorders
  - Mental Retardation
  - Delirium, Dementia, Cognitive Disorders
  - Attention-deficit Disorder
  - Brief Psychotic Disorder
  - Delusional Disorder
  - Schizophrenia
  - Bipolar Disorders

## DSM-5 DIAGNOSES ASSOCIATED WITH AGGRESSIVE / VIOLENT BEHAVIOR

### ○ **B: 2- Systemic disorders associated with aggression**

- Hypoxia
- Electrolyte imbalance
- Hepatic disease
- Renal disease
- Systemic infection
- Hyper- or Hypothyroidism
- Heavy metals, insecticides, and poisons
- Vitamin deficiencies (thiamine, folate...)
- Hypoglycemia



# Mnemonic for The Medical Causes of Agitation

## **I GET SO MAD, MAN**

**Infection**

**Geriatric (Alzheimer 's disaease, Vascular dementia)**

**Epilepsy (seizures)**

**Trauma**

**Strokes / infarcts**

**Organic-Tumors**

**Medications**

**Acidosis (diabetic ketoacidosis, hypoxemia)**

**Delirium**

**Metabolic (electrolytes, renal)**

**Alcohol (drugs)**

**Neurologic(Huntington 's disease, multiple sclerosis)**

# Signs and symptoms of psychomotor agitation

Type	Signs and Symptoms
Changes in behaviour	<ul style="list-style-type: none"><li>• Combative attitude</li><li>• Inappropriate behaviour without clear purpose</li><li>• Hyperreactivity to stimuli</li><li>• Inability to remain quiet, seated or calm</li><li>• Exaggerated gesticulation</li><li>• Facial tension and angry expression</li><li>• Defiant and/or prolonged visual contact</li><li>• Raised tone of voice, silence or refusal to communicate</li><li>• Altered emotional state with appearance of anxiety, irritability or hostility</li><li>• Verbal and/or physical aggression against self or others or objects</li></ul>
Cognitive changes	<ul style="list-style-type: none"><li>• Fluctuations in the levels of consciousness</li><li>• Temporo-spatial disorientations</li><li>• Tendency to frustration</li><li>• Difficulty in anticipating consequences</li><li>• Delusional ideas and/or hallucinations</li></ul>
Change in physical parameters	<ul style="list-style-type: none"><li>• Fever</li><li>• Tachycardia</li><li>• Tachypnoea</li><li>• Sweating</li><li>• Tremor</li><li>• Neurological signs such as difficulty walking</li></ul>

# DSM-5 DIAGNOSES ASSOCIATED

## WITH AGGRESSIVE / VIOLENT BEHAVIOR

### **C: Aggressive behavior as an infrequent feature**

- Depressive Disorders
- Anxiety Disorders
- Dissociative Fugue
- Histrionic Personality Disorder
- Paranoid Personality Disorder

# Psychiatric Factors - Personality Traits

*Take history and observe for the following:*

- *Low frustration tolerance*
- *Inability to tolerate criticism "stress interview"*
- *Repetitive anti-social acts*
- *Reckless driving*
- *Egocentricity and entitlement*
- *Superficial relationships*
- *Paroxysmal violence*
- *Projection evident with lack of introspection*
- *Suspiciousness*

# Psychiatric Factors - Substance Abuse

- Alcohol:
  - Intoxication associated with most violent crimes including assaults, murders, rape
  - 62% of arrests for violence involve alcohol
- Amphetamines/cocaine/PCP:
  - disinhibition
  - grandiosity
  - paranoia
- THC: Decreases irritability; increase paranoia in schiz.
- Heroin: In one study found to be most common drug in violent males

# Findings requiring further evaluation

## • SYMPTOMS

- Memory loss, disorientation, confusion
- Severe Headache
- Muscle stiffness, weakness
- Heat intolerance, chills
- Weight loss, unintentional
- Psychosis new in onset
- Shortness of breath/chest pain
- Abdominal symptoms (including vomiting and diarrhea)

## • SIGNS

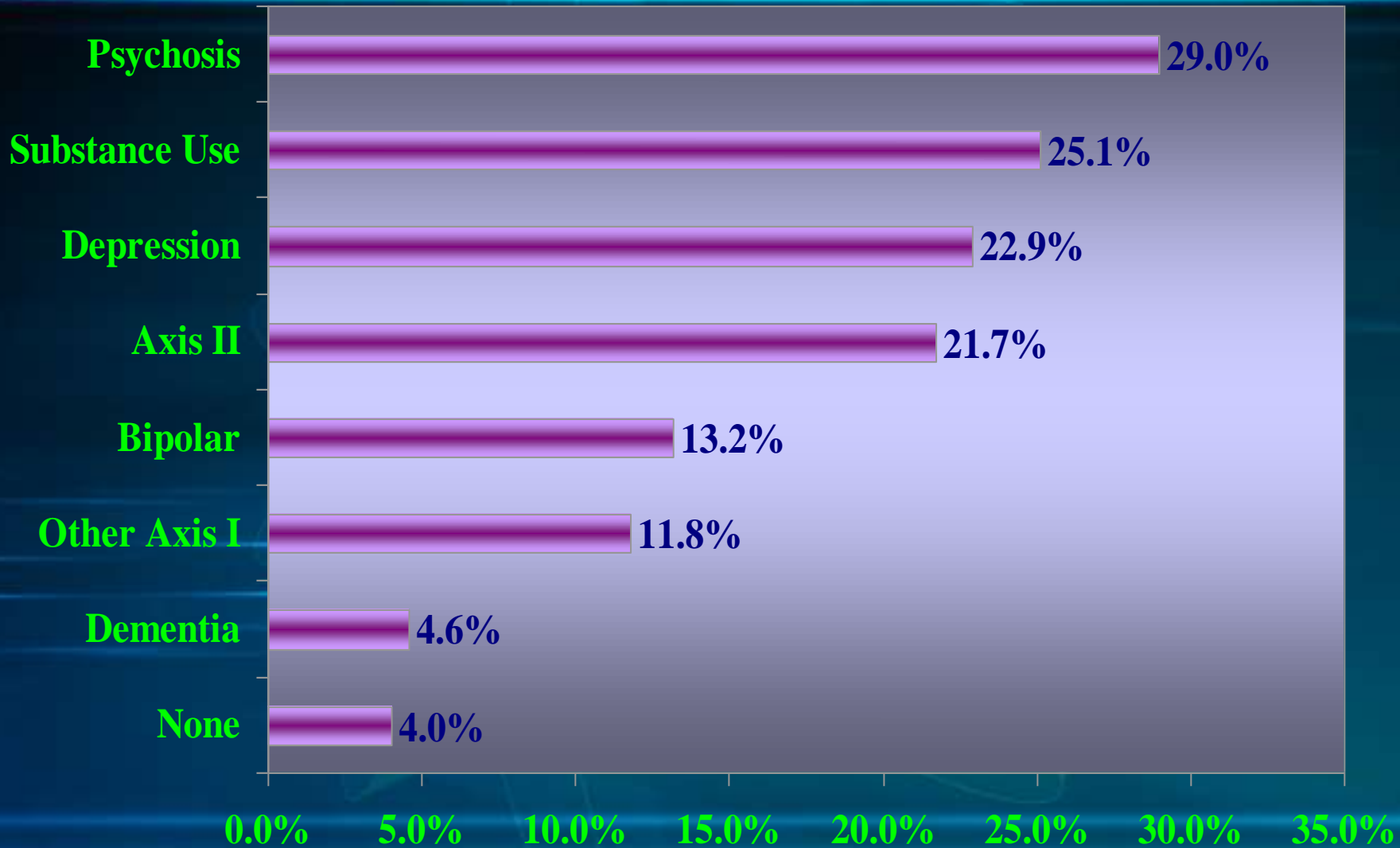
- Abnormal vital signs
- Evidence of trauma
- Abnormal neurologic examination (asymmetric pupils, focal weakness, seizure, slurred speech, incoordination)
- Cardiopulmonary abnormality
- Evidence of toxidrome (sympathomimetics, anticholinergics, serotonin syndrome, and more)
- Evidence of withdrawal state (alcohol, Benzodiazepines)
- Age > 45 yeras

# Diagnostic Considerations in the Violent Emergency Department Patient

- CT scan of the head
- Complete blood count
- Toxicology screen
- Ethanol level
- Point-of-care glucose
- Chemistry panel
- Liver function panel
- Urinalysis
- CK
- Lumbar puncture\*

\* Based on historical and physical findings suggestive of meningitis, encephalitis, or hemorrhage

# ER Presentations



Currier GC, Allen MH, Survey I, Inst on Psych.Services, New Orleans, 1999



# What is new now in the Psych. E.R. ?

## Increase

- Substance Abuse / Dependence
- Personality Disorders
- Major Depressive Disorder
- Disorders related to Stress
- PTSD
- Eating Disorders
- Atypical Psychosis

## Stable

- Bipolar Disorders
- Anxiety Disorders

## NO Change

- Schizophrenic Disorders

Definitely there is an increase in the number of visits, in comparison to the increase in the number of admissions and the decrease in the number of beds !



- **SECURITY ?**

# IN EMERGENCY

- **PSYCHOLOGICAL APPROACH**
- **PHYSICAL APPROACH**

**PHARMACOLOGICAL APPROACH**

# FIRST CONTACT WITH

## ACUTELY

### VIOLENT PATIENTS

- Safety first
- To talk or not to talk and where ?
- Talking with the violent patient
- Interviewing and the physical environment
- Physical manoeuvres by the clinician
- Firearms and hostage situations

# Principles of treatment

- 1. **Define the etiology** (e.g., delirium, intoxication, primary psychiatric disturbance)
- 2. **Careful history**
  - substance abuse (→ drug screen)
  - medications?
  - psychiatric interview
  - infection? (esp. in elderly)
  - careful neurological exam

# TO TALK OR NOT TO TALK ?

- DELIRIUM, DEMENTIA  
TALK first  
MEDICATION
- AMNESTIC & OTHER  
COGNITIVE DISORDERS  
TALK first  
MEDICATION
- FUNCTIONAL PSYCHOSIS  
±TALK  
MEDICATION
- PERSONALITY, ANXIETY  
DISORDERS , ETC...  
TALK  
± MEDICATION

# Traditional ED treatment of the agitated patient



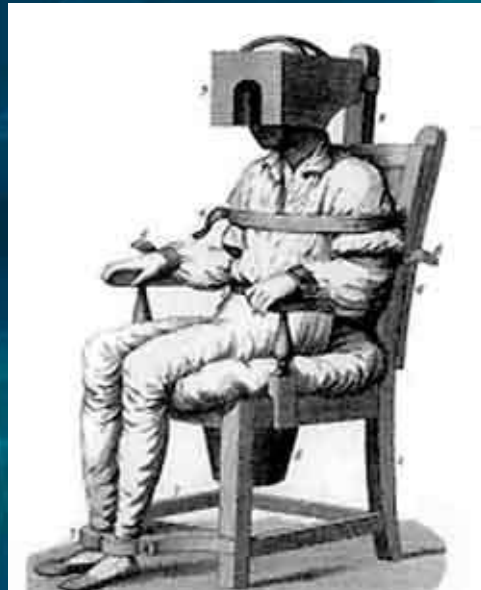
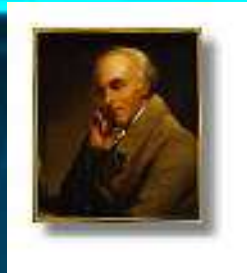
Restraints



Seclusion



Sedation



Rush's 'Tranquilliser'. Circa 1811 The aim was to inhibit sensation, therefore irritation and so reduce maniacs to a condition of calm? WIL





# APPLICATION OF PHYSICAL RESTRAINT TECHNIQUE



Application of alternative measures 

Effective?

NO

YES

**RESTRAINT**

**NO RESTRAINT**

Preparation of environment and patient  

Continue algorithm for the management of agitation

Introduction of measures    

Specific restraint form record

Maintenance of restraint   

Assessment of need for restraint  

Restraint need

NO need for restraint

Removal of restraint 

GRADUAL REMOVAL

Assessment of restraint procedure

## Level I :Non-violent Interventions:

Separate patient from other people if possible.

Remove any type of weapons or objects which could serve as weapons.

Make sure that you have a way out of the room if the situation escalates.

Present a calm, supportive appearance.

Speak clearly.

Show respect, remain non-judgemental.

Avoid staring and give some distance.

Ask why they are upset and what could be done about it.

(How can we help you?)

## Level II

### **If Violence Appears Imminent:**

If verbal interventions fail then you need to move to a higher level of intervention called the **Show of Force**.

A "Take Down" Team is composed of 5 people as a minimum, one person to control the head and one person for each extremity.

Designate one person as the leader and four followers.

To begin, gather around the leader with an image of confidence.

The leader states "come calmly or you will go in restraints".


The leader states the reason why restraints are needed.

Give the patient a few seconds to back down.

# Goals of Therapy in Agitation

- Acutely control agitation
- Prevent injury to self or others
- Improve patient comfort
- Facilitate assessment of underlying causes
- Promote active engagement in treatment
- Begin the process of restoring sense of well being
- Establish a framework for long-term therapy of underlying psychiatric illness

# PHARMACOLOGICAL APPROACH

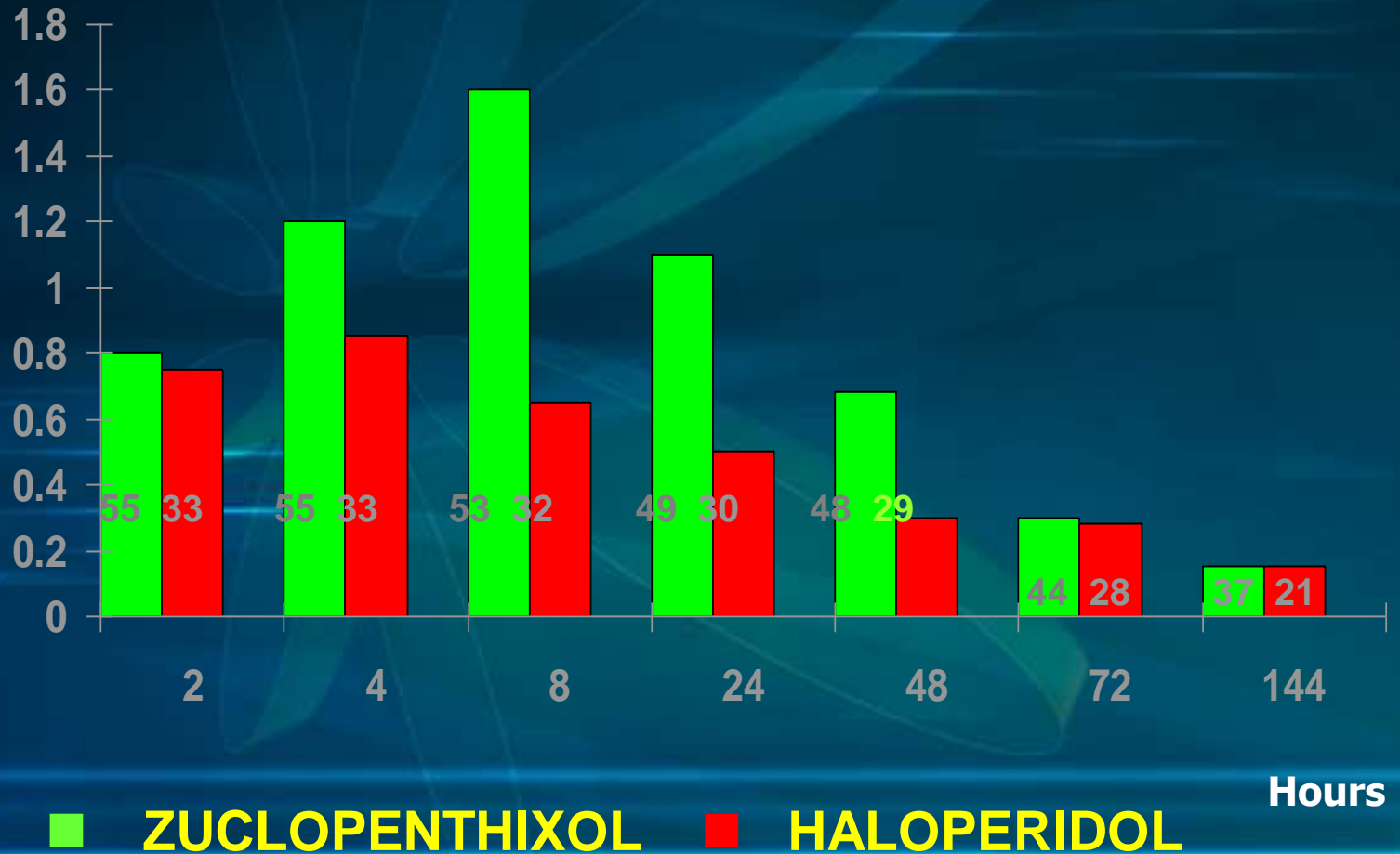
- LOXAPINE : PO / LIQ / SC / Nasal / IM
- CLOPIXOL "ACUPHASE" : IM q 3 days
- DROPERIDOL : IM / IV 
- HALOPERIDOL: PO / IM / IV
- THIOTHIXENE : PO / IM
- LORAZEPAM : PO / IM / IV
- MIDAZOLAM : IM / IV
- KETAMINE : IM / IV
- AMOBARBITAL SODIUM: IM

# Agitation and Disturbed Behaviours

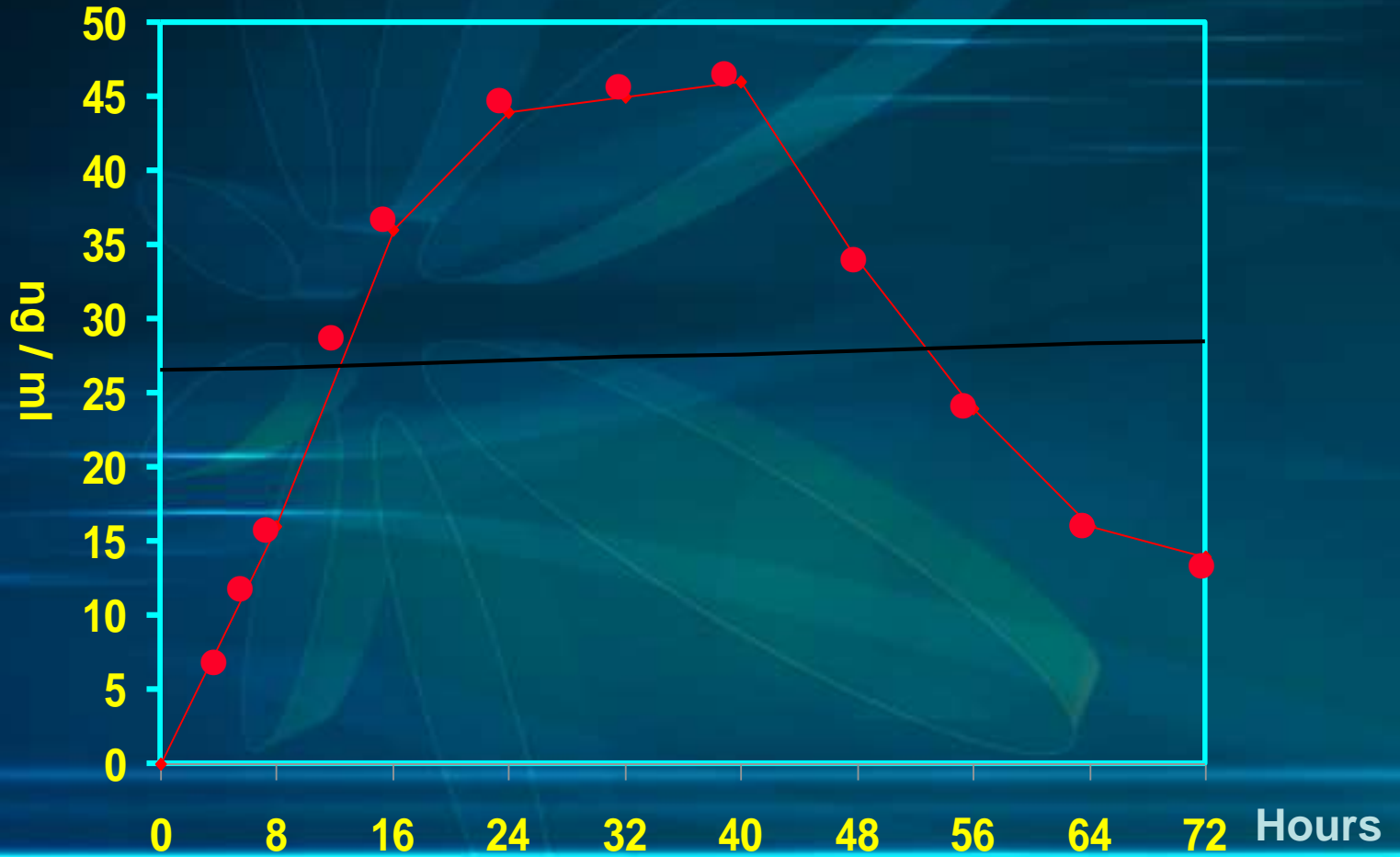
## The ideal parenteral medication for agitation and disturbed behaviours in acute schizophrenia

- relatively rapid onset of action
- efficacy in high proportion of treated patients
- sustained efficacy and simple transition to oral treatment
- low risk of acute dystonia and other EPS
- low risk of excessive sedation and respiratory depression
- low risk of QTc prolongation

# SEDATION



# PHARMACOKINETICS



**CLOPIXOL Acuphase**  
**100 mg I.M.**



## **Im lorazepam v. haloperidol + promethazine**

- Randomised 200 patients to receive lorazepam 4mg or haloperidol 10 mg + promethazine 25-50 mg mix.
- Randomization was according to a computer-generated random numbers list in varying sized blocks of less than 10
- Patient was followed-up at 15, 30, 60, 120, 240 minutes and at 2 weeks.
- Rating for the 1st 2 h was not blind. The evaluation at 4 h was blind.
- Lor. 4 mg(100%) – Hal+Prom. (96% on 50mg and 4% on 25 mg)

## Im lorazepam v. haloperidol + promethazine

- No serious adverse effects (EPS) were reported for either treatment except respiratory difficulties in some patients treated with lorazepam
- About 15% of patients were physically restrained and less than 10% were given additional medication over the 4 h.
- The two treatment regimens evaluated in this study are inexpensive, effective and available worldwide

# Im lorazepam v. haloperidol + promethazine : Clinical implications

- Intramuscular lorazepam (4mg) is as effective as haloperidol(10mg) plus promethazine (25-50mg) in controlling violence or agitation.
- If rapid sedation is required, the haloperidol-promethazine combination is superior to lorazepam.
- Pragmatic randomized trials of interventions relevant to low-income countries, with limited funding, clinically meaningful outcomes and low attrition rates, are possible within the field of mental health.

# Im lorazepam v. haloperidol + promethazine : Limitations

- Assessments over the first 2 hours were not blind and were carried out by multiple raters.
- The effects of both interventions could be dose-related.
- Haloperidol alone or in combination with a benzodiazepine was not evaluated

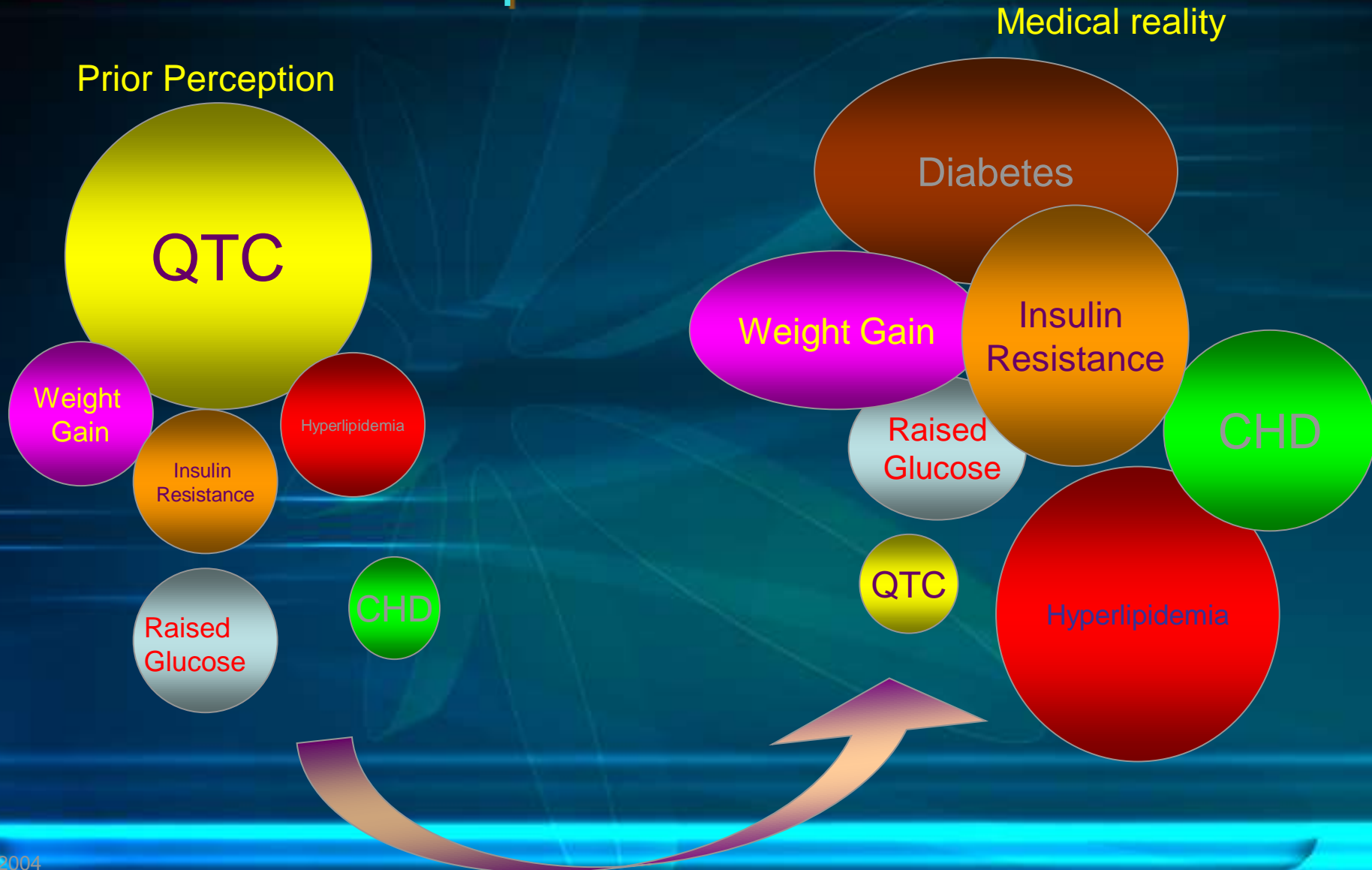
# SEDATION OF THE AGITATED PATIENT IN EMERGENCY : NEUROLEPTICS (NLP) OR BENZODIAZEPINES (BZD)

- Brazilian multicenter trial (3 Psychiatric ER services), 301 patients, published in the BMJ in 2003
- **Midazolam** MZD 15mg IM versus **Haloperidol** 5mg/**Promethazine** 50mg IM HP(single blind, different doses)
- **Results**
  - Rapid Sedation with MDZ vs HP (superior effect of MDZ in the first 2 hours)
  - 1 adverse effect in each arm (1 convulsive crisis with HP et 1 respiratory dépression with MDZ)
  - 5% more restraints in the MDZ group
  - 6% more of relapse into agitation in the MDZ group (note that 25% of total patients had a second episode of agitation within 24h)

# SEDATION OF THE AGITATED PATIENT IN EMERGENCY : NEUROLEPTICS (NLP) OR BENZODIAZEPINES (BZD)

- **Most of the patients in the two arms received a dose of neuroleptic !**
- «All the patients received a complementary treatment in the first 24 hours, the majority of them received high doses of NLP » G. Huf, personal communication
- **Author's Conclusion :**
  - **If rapid action is required, with available observation go for MDZ**
  - **If not go for: HP**

# Side Effects of Atypical Antipsychotics: Shift in Risk Perception



# ANTIPSYCHOTICS

## ATYPICAL

Dibenzodiazepines (Clozaril)

Thienobenzodiazepine (Olanzapine)

Dibenzo-oxepino pyrroles (Asenapine)

Phenylpiperazines (Abilify)

Benzisoxasole (Risperidone)

Benzisoxasole (Paliperidone)







Benzisothiazol (Ziprasidone)

Dibenzothiazepines (Quetiapine)

Azapirone (Lurasidone)



# Pharmacodynamics of Antipsychotics

Receptor	Aripiprazole	Asenapine	Clozapine	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
	<b>Therapeutic effect:</b> Receptor antagonism treats psychosis <b>Side effects:</b> EPS, secondary negative symptoms, endocrine effects								
	<b>Therapeutic effect:</b> Receptor agonism has antidepressant and anxiolytic action								
	<b>Therapeutic effect:</b> Receptor antagonism reduces EPS, improves negative symptoms and cognition								
	<b>Side effects:</b> Orthostatic hypotension, sedation, dizziness, reflex tachycardia								
	<b>Side effects:</b> Sedation, increased appetite, weight change, hypotension								
	<b>Side effects:</b> Blurred vision, dry mouth, constipation, urinary retention, impaired memory								

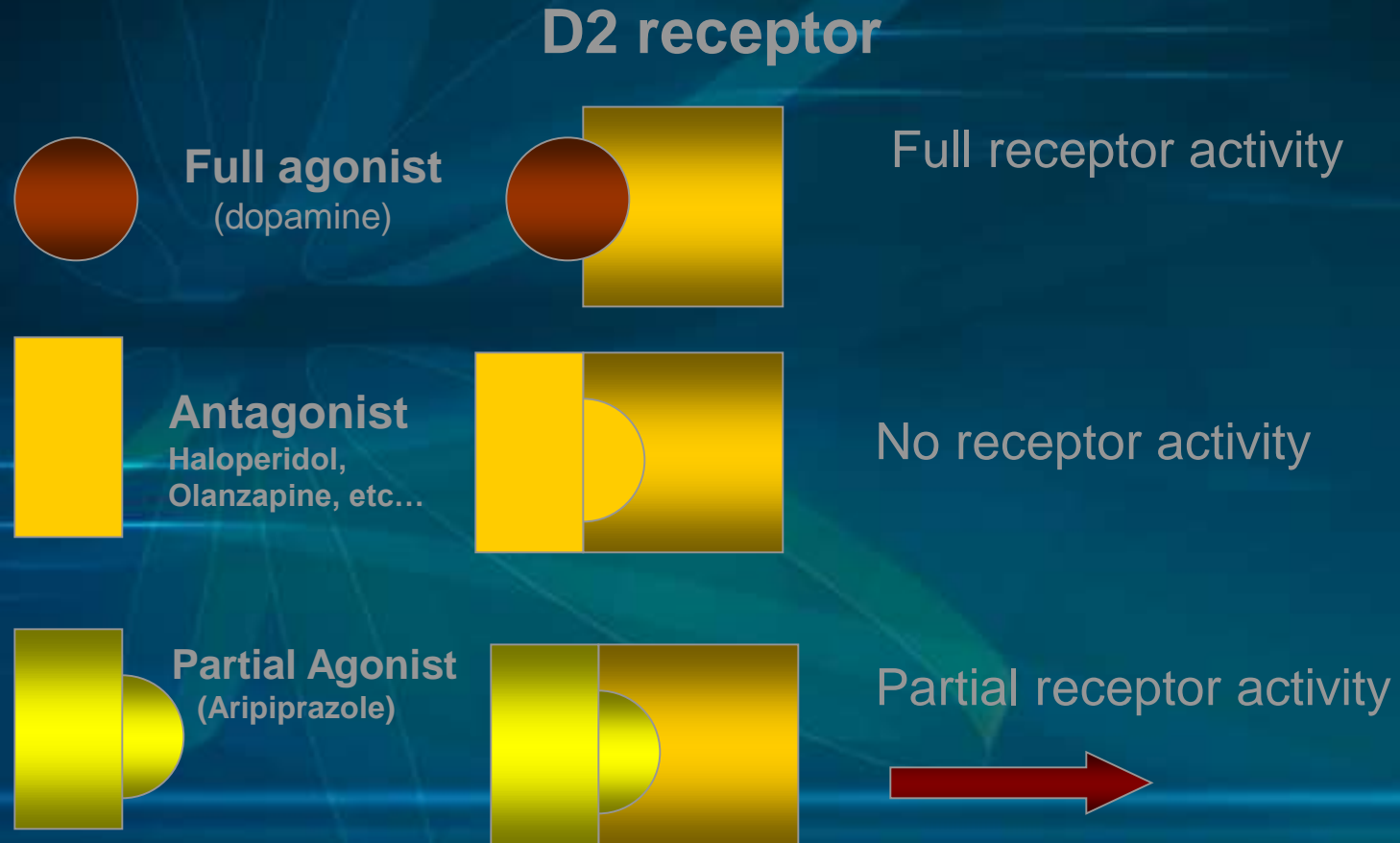
 Partial agonist

Ki (nM):	
10,000	= -      10-100 = +++
1000-10,000	= +      1-10 = ++++
100-1000	= ++      0.1-1.0 = +++++

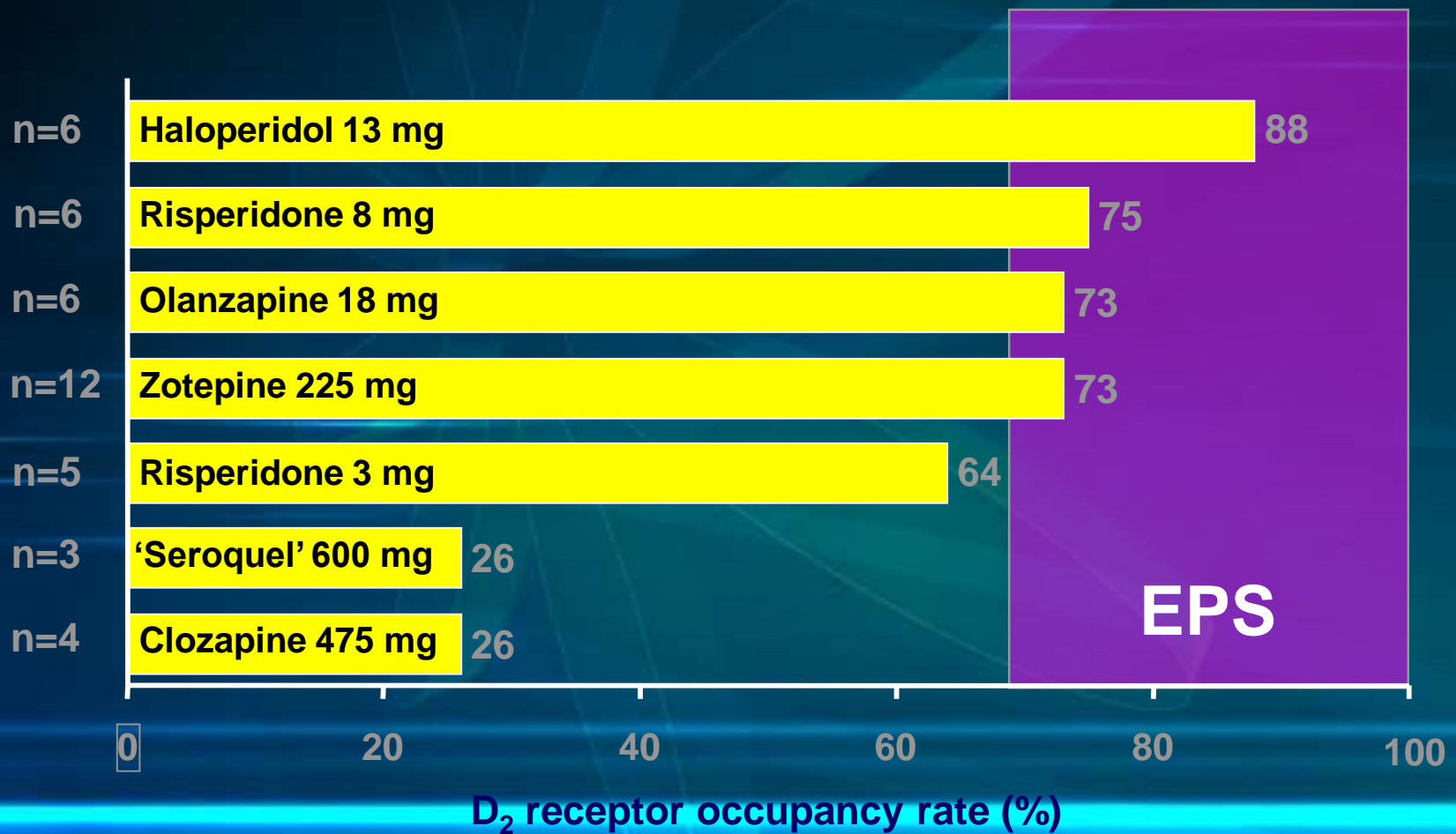
RM Procyshyn ©

*Note: The greater the number of “+”, the greater the affinity of the drug for the receptor subtype*

# Intrinsic Activity Describes the Ability of a Compound to Stimulate Receptors



# Antipsychotics: striatal D<sub>2</sub> receptor occupancy rates

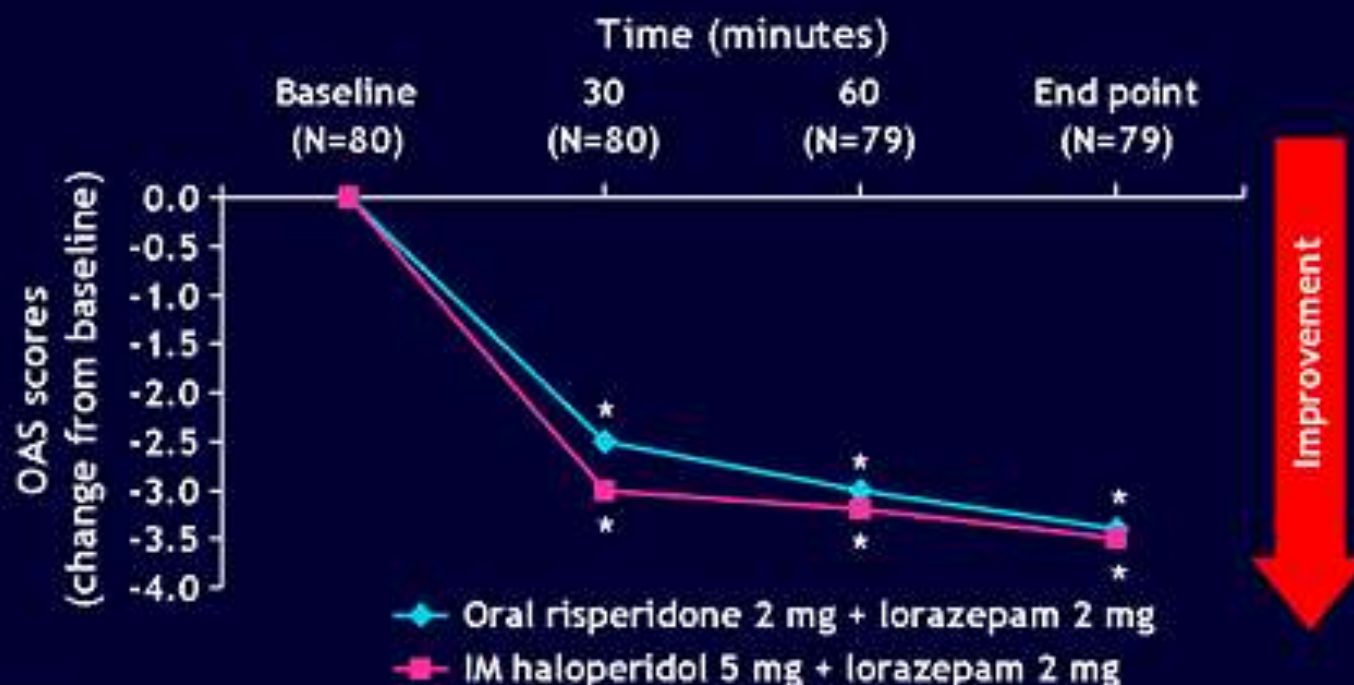


EPS

# ATYPICAL ANTIPSYCHOTICS

- **ARIPIIPRAZOLE 10-15 mg + Lorazepam**
- **ASENAPINE: 10mg- 20 mg P.O. (Sublingual)**
- **OLANZAPINE: 10mg – 20 mg P.O.(Zydis)**
- **RISPERIDONE: 2mg – 3mg P.O. Liquid**
- **RISPERIDONE: 2mg – 3mg M-Tab**
- **QUETIAPINE: 200 mg P.O. max 600 mg**

## Stabilization of Acute Agitation: Oral Risperidone vs IM Haloperidol

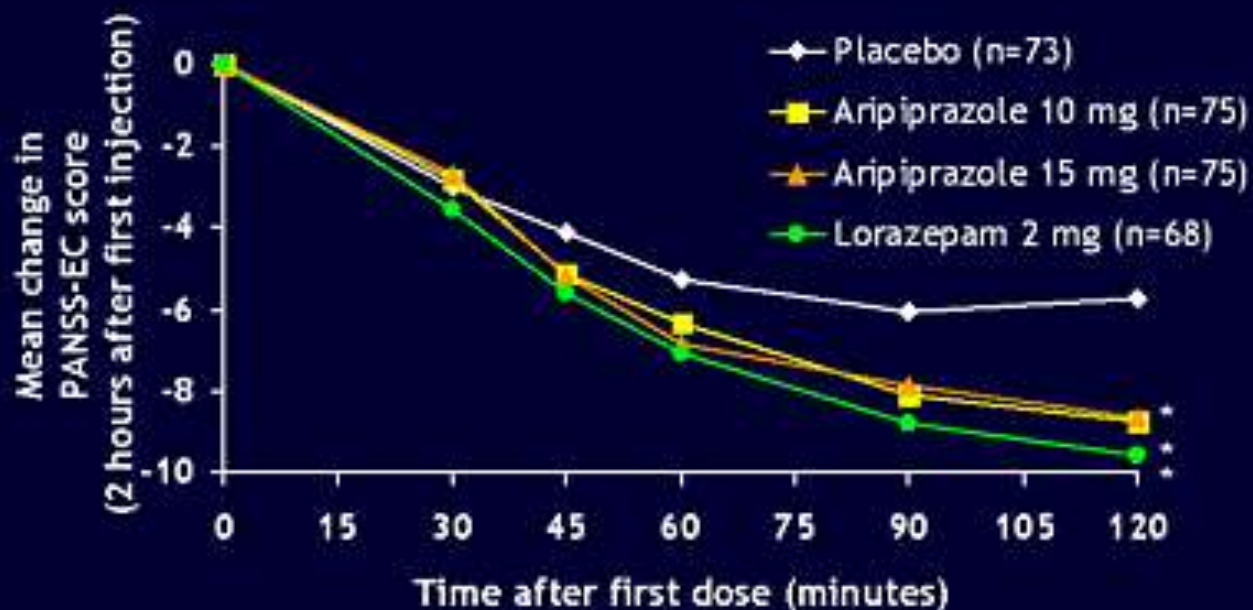


OAS=Overt Aggression Scale.

\* $P < .0001$  vs baseline.

Adapted from Currier GW et al. *J Clin Psychiatry*. 2004;65:386-394.

## Treatment for Acute Stabilization: Aripiprazole and Lorazepam



\*P < .001 vs placebo.

PANSS-EC=Positive and Negative Syndrome Scale-Excitement Component.

Oren D et al. Paper presented at 158th APA Annual Meeting, May 21-26, 2005, Atlanta, Ga. Abstract NR275.

# Zydis

- **Orally disintegrating formulation of Zyprexa**
  - begins to melt instantly on contact with saliva
  - does not require water
  - can be dissolved in beverages

## **Bioequivalent to Zyprexa tablets**

- same efficacy, safety and faster action
- transition from IM to PO

## **Enhanced ease of use may promote compliance**

- patients who tend to cheek and then spit medications
- patients who have difficulty swallowing oral medications
- Adolescents, geriatric patients in crisis
- ? Borderline Personality Disorder in crisis

# The Alcoholic Patient in The E.R.

- **Atypical Antipsychotics:**
  - Decrease cravings and substance use in dual-diagnosed patients.

So what about this ?

**Neurontin 200 mg + Olanzapine 10 mg**

**Neurontin 200 mg + Quetiapine 200 mg**



# Atypical Antipsychotics and Comorbid Substance Use Disorder

## • Authors Study design

- Conley et al 98 Open-label
- Noordsy et al 99 Naturalistic
- Littrell et al 01 Open-label
- Noordsy et al 01 Naturalistic
- Tsuang et al 02 pilot double-blind trial
- Sattar et al 03 Case report
- Huang 1996 Naturalistic
- E.Brown et al 02 Open-label

## • Sample

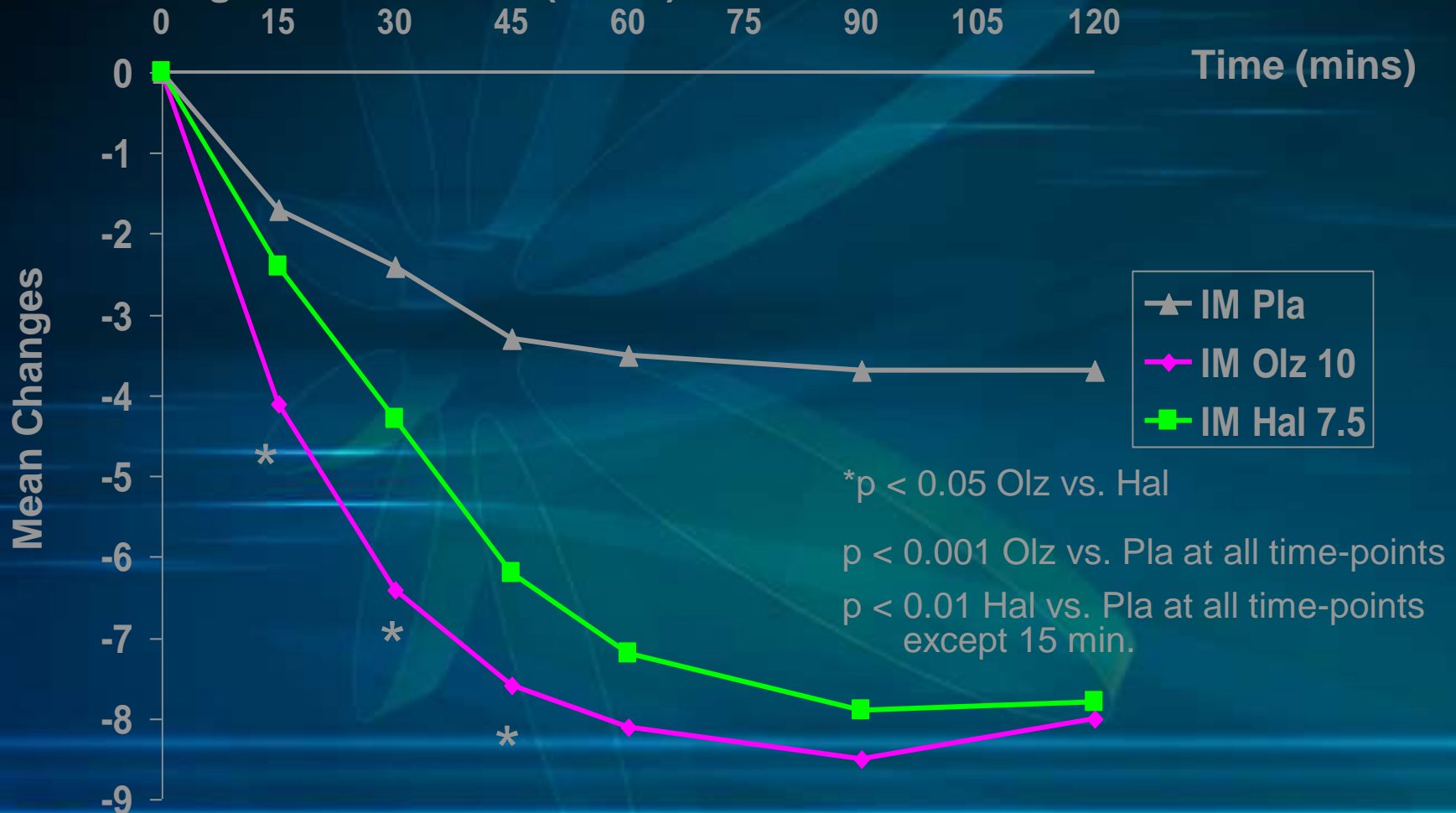
- 60, treatment resistant Schiz., 38% with Comorbid SUD
- 70, Schiz. With Comorbid SUD
- 30, Schiz. And Comorbid SUD
- 104, Schiz. With ETOH/ Drugs
- 4, Schiz. and Cocaine abuse
- 1, Schizoaffective and Cocaine
- 7, Schiz., Comorbid ETOH
- 17, Bipolar Cocaine Abuse

# INTRAMUSCULAR NEUROLEPTICS

- CHLORPROMAZINE** (Largactil)
- METHOTRIMEPRAZINE** (Nozinan)
- THIOTHIXENE** (Navane)
- ZUCLOPENTHIXOL** (Clopixol)
- HALOPERIDOL** (Haldol)
- LOXAPINE** (Loxapac)
- OLANZAPINE** (Zyprexa)
- ZIPRASIDONE** (Zeldox)
- ARIPIIPRAZOLE** (Abilify)

# HGHB - PANSS-EC During First 2 Hours

Visitwise Change from Baseline (LOCF)

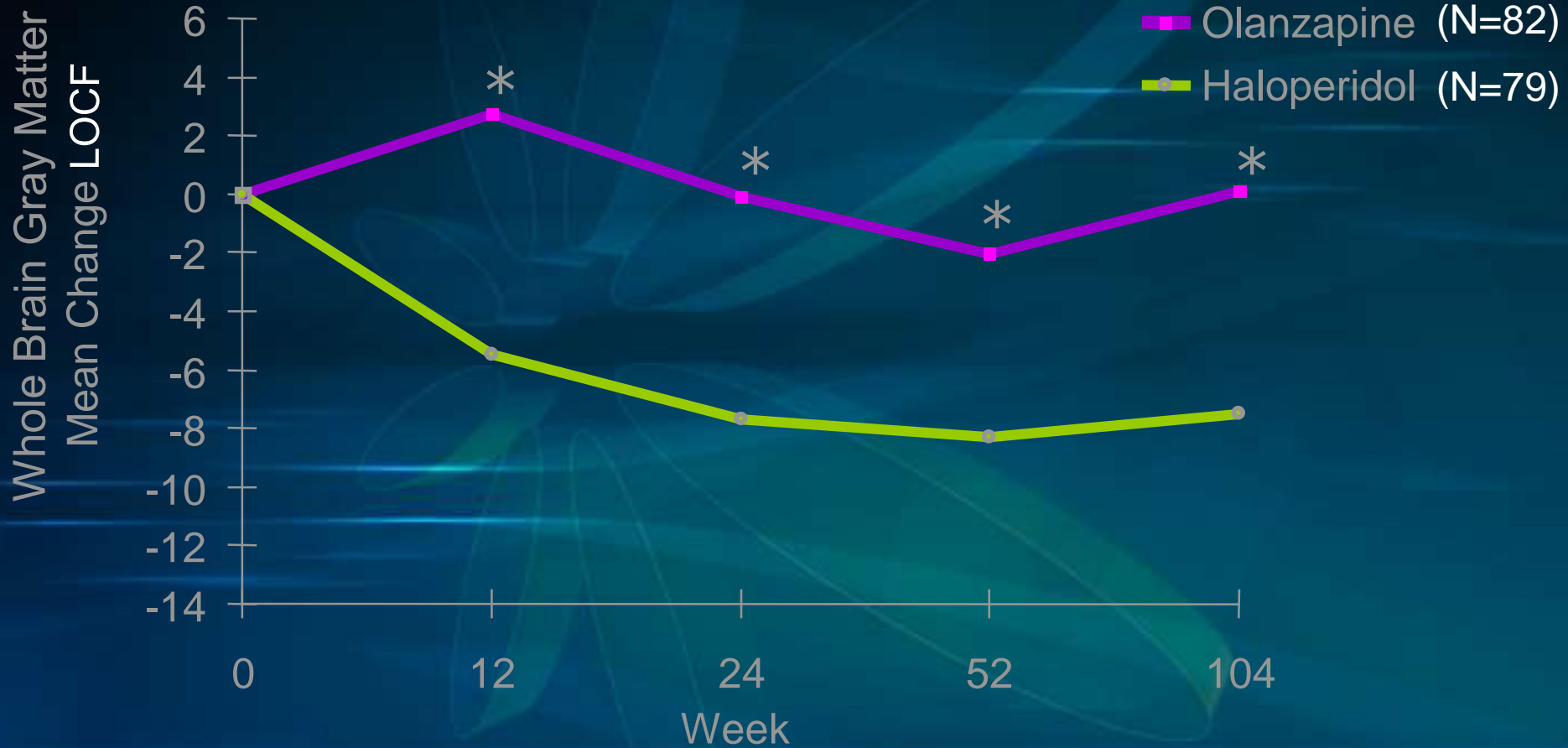


# Naturalistic multicenter study of IM Olanzapine in the treatment of acutely agitated manic or schizophrenic patients

- Scores at baseline: PANSS-EC ( $26.5 \pm 5.9$ )
- **Results:**
  - 2 hours: decrease of 9.6 in the PANSS-EC endpoint ( $16.9 \pm 9.3$ )
  - 24 hours: statistically and clinically significant reduction in the PANSS-EC scores ( $11.6 \pm 5.3$ )
  - Mean decrease of -14.9 and 5.3.

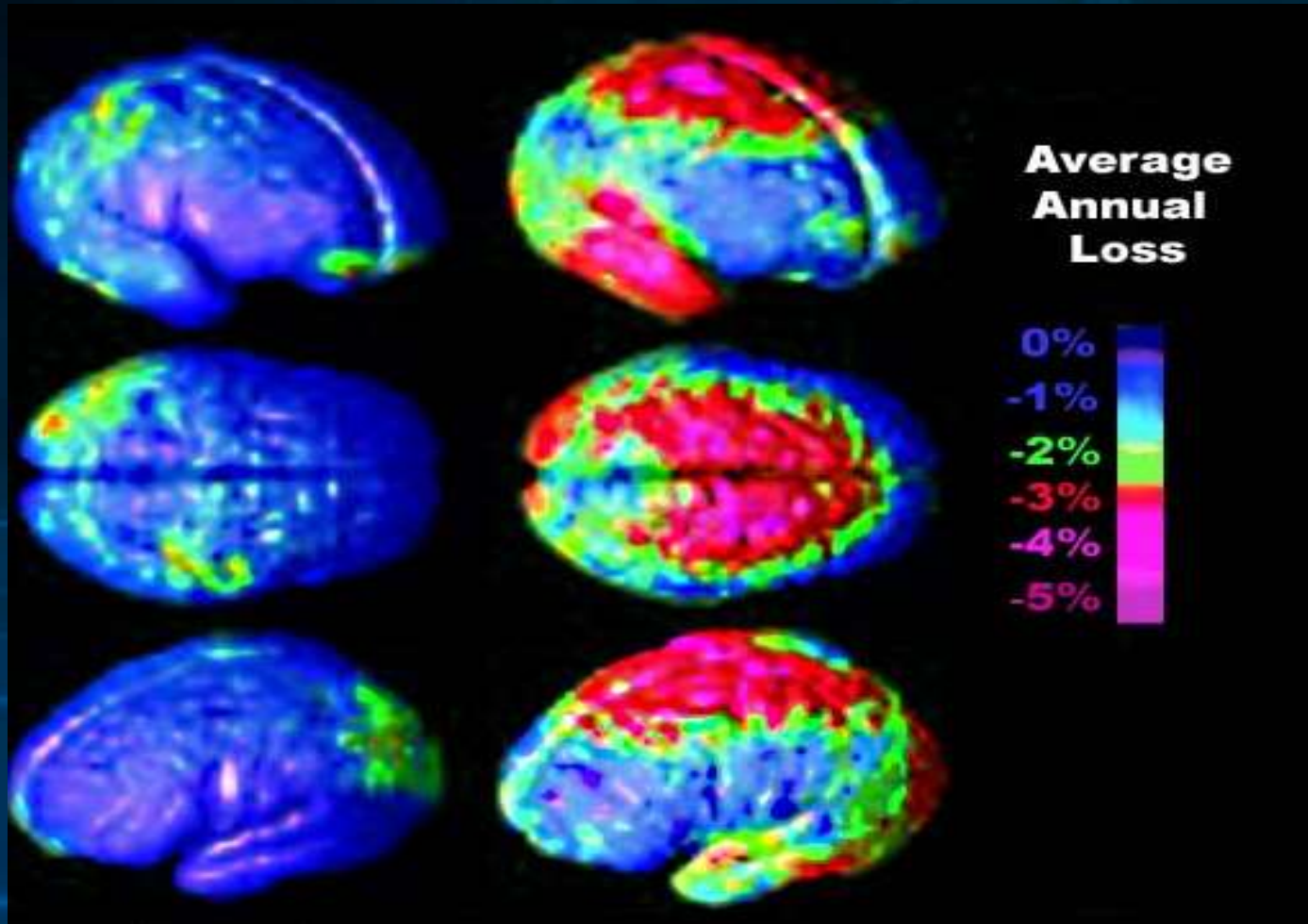
Naturalistic data on the effectiveness of IM Olanzapine in the treatment of acute agitation in patients with schizophrenia, bipolar and psychotic disorders, that is in line data obtained in RDB clinical trials.

# Olanzapine vs. Haloperidol: Effects on Gray Matter in First-episode Schizophrenia Patients



\* p-value < 0.05

# Accelerated Brain Gray Matter Loss in Very Early-Onset Schizophrenia

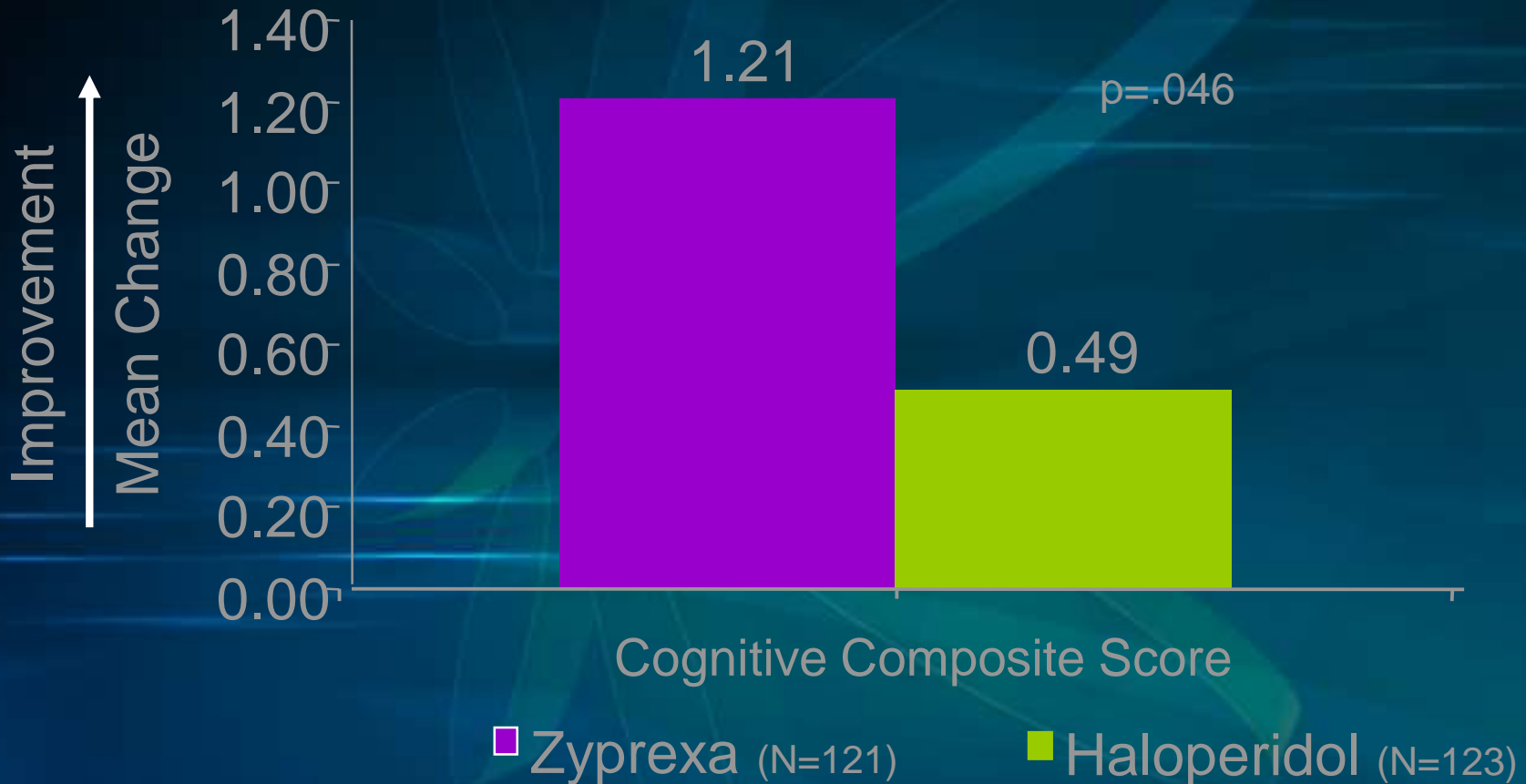


Normal  
Adolescents

Schizophrenia  
Subjects

Thompson et al, *PNAS*, 2001, 11650-11655

# Olanzapine Improves Cognition in First-episode Schizophrenic Patients



# Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia

## A Randomized Clinical Trial

Agitation is common among patients with Alzheimer disease; safe, effective treatments are lacking.

159 Patients (Average age 78) combination + 127 on placebo

Patients with probable Alzheimer disease, clinically significant agitation (Clinical Global Impressions–Severity agitation score  $\geq 4$ ), and a Mini-Mental State Examination score of 8 to 28 participated at 42 US study sites. Stable dosages of antidepressants, antipsychotics, hypnotics, and anti-dementia medications were allowed.



# Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia

## A Randomized Clinical Trial

- Quinidine inhibits dextromethorphan's metabolism
- Combination results in 20 fold increase in bioavailability of the active agent
- Involved in modulating glutamate, serotonin, norepinephrine, and potentially other neurotransmitters.
- Effect on Nicotinic Alpha-3 Beta-4 receptor antagonism
- Sigma-1 receptor agonist
  
- the exact mechanism of action responsible for the reduction of dementia-associated agitation is not known.
  
- Patients on active track began on 20 mg of D and 10 mg of Q PO QD
- Titrated to 30 mg D and 10 mg Q over 2 weeks
- After 10 weeks: 93 patients had reduction of 50% vs 25% in placebo (66 controls)

# Adverse Events

The most commonly occurring treatment-emergent adverse events (>3% and greater than placebo) were **falls** (8.6% vs 3.9%), **diarrhea** (5.9% vs 3.1%), urinary tract infection (5.3% vs 3.9%), and **dizziness** (4.6% vs 2.4%) for dextromethorphan-quinidine vs placebo, respectively

10-week phase 2 randomized clinical trial,  
combination dextromethorphan-quinidine  
demonstrated clinically relevant efficacy for agitation  
and was well tolerated.

Jeffrey L. Cummings,MD, Constantine G. Lyketsos, MD,et al JAMA September 22/29, 2015

# TARGET SYMPTOMS

**AGGRESSIVENESS**

**ANXIETY**

**PSYCHOMOTOR AGITATION**

**IMPULSIVITY**

**OPPOSITION**



“ Here’s your discharge, and a note of apology to the nurses for you to sign.”

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