

**ASCP Model Psychopharmacology Curriculum**

# **The Psychopharmacology of Violence**

***with emphasis on schizophrenia***

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Revision 100109a

# Major Teaching Points

- 1. Recognize the short-term psychopharmacologic options available to manage acute agitation and aggression**
- 2. Recognize the psychopharmacologic options available to decrease the frequency and intensity of these episodes over the longer-term**

# PRE-TEST QUESTIONS

1. Akathisia is a common side effect of which of the following medications?
  - A. Lorazepam
  - B. Haloperidol
  - C. Olanzapine
  - D. Ziprasidone
  - E. B & D
  - F. B, C, & D

# PRE-TEST QUESTIONS

**2. Acute agitation secondary to withdrawal from alcohol in a patient with schizophrenia is best treated with?**

- A. Lorazepam**
- B. Haloperidol**
- C. Olanzapine**
- D. Ziprasidone**

# PRE-TEST QUESTIONS

**3. Atypical antipsychotics are superior to the older neuroleptics because**

- A. They are more sedating**
- B. They cause less weight gain**
- C. They cause less extrapyramidal side effects**
- D. They have no effect on the QTc interval**
- E. A & C**

# PRE-TEST QUESTIONS

4. Which of the following has the most evidence supporting its use among patients with schizophrenia and aggressive behavior
- A. Adjunctive valproate
  - B. Adjunctive beta-blockers
  - C. Clozapine
  - D. Olanzapine
  - E. Lorazepam

# PRE-TEST QUESTIONS

5. Which of the following are approved by the FDA for persistent aggressive behavior?

- A. Lorazepam
- B. Ziprasidone
- C. Olanzapine
- D. Clozapine
- E. B & C
- F. A, B, & C
- G. D
- H. None of the above

# OUTLINE

- 1. Definitions**
- 2. Epidemiology**
- 3. Etiology and Assessment**
- 4. Management of Acute Agitation**
- 5. Management of Persistent Aggressive Behavior**



# OUTLINE

1. **Definitions**
2. **Epidemiology**
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# DEFINITIONS

- **Agitation**: excessive motor or verbal activity
- **Aggression**: used in the literature for both animals and humans
  - For humans can be verbal, physical against objects, or physical against people
- **Violence**: physical aggression by people against other people
- **Hostility**: loosely defined - aggression, irritability, suspicion, uncooperativeness, jealousy, etc.

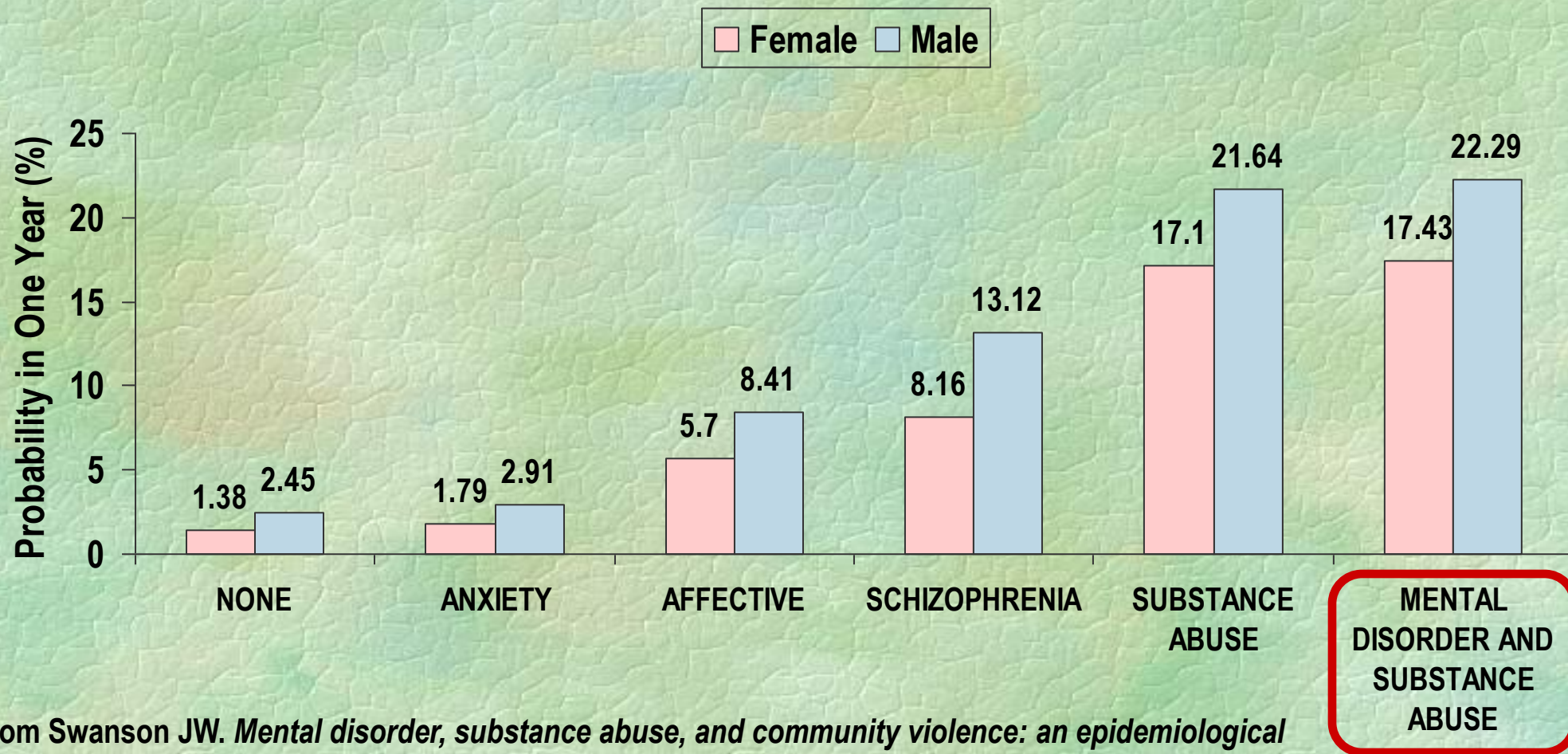
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# EPIDEMIOLOGY: COMMUNITY

- **Epidemiological Catchment Area (ECA) project**
  - **Structured diagnostic interviews of over 20,000 people in five areas of the United States**
  - **Data on violence collected in 50% (10,000 people)**
  - **Probability of violent behavior in patients with schizophrenia is 5 - 6 x higher than in persons without any diagnosed mental disorder (Swanson, 1994)**
- **Epidemiological studies done across the world show similar results**

# PROBABILITY OF VIOLENT BEHAVIOR AND CURRENT-YEAR PSYCHIATRIC DIAGNOSIS



From Swanson JW. *Mental disorder, substance abuse, and community violence: an epidemiological approach*, in *Violence and Mental Disorder: Developments in Risk Assessment*, Edited by Monahan J, Steadman HJ. Chicago, The University of Chicago Press, 1994, pp.101-136.

# EPIDEMIOLOGY: HOSPITAL

- In the first 24 hours after admission 33 (13%) of 253 patients physically attacked another person (McNiel and Binder, 1989)
- In the first 8 days after admission, 25 (9%) of 289 patients with schizophrenia/schizoaffective disorder assaulted someone at least once (Tanke and Yesavage, 1985)
- Recidivistic and transient assaultiveness
  - 5% cause over half of all incidents (Convit et al, 1990)
  - 12% accounted for 69% of 752 violent incidents (Owens et al, 1998)

# EPIDEMIOLOGY: CAVEAT

- Not all patients with psychotic disorders are aggressive, violent, or hostile
- Not all aggressivity, violence, or hostility is attributable to patients with psychotic disorders
- Most of the aggressive, violent, or hostile acts we witness in our daily lives, on the news, and elsewhere, are perpetrated by people without a DSM-IV Axis I major mental disorder
- Nonetheless, a small minority of patients with psychotic disorders are prone to aggressivity; this aggressivity may be persistent

# EPIDEMIOLOGY

## VIOLENT CRIME ATTRIBUTABLE TO MENTAL ILLNESS

**Objective:** This study aimed to determine the population impact of patients with severe mental illness on violent crime.

**Method:** Sweden possesses high-quality national registers of hospital admissions and criminal convictions. All individuals discharged from the hospital with ICD diagnoses of schizophrenia and other psychoses (N=1,122) were linked to the crime register to estimate the population-attributable risk of patients with severe mental illness to violent crime. The attributable risk was calculated by gender, three age bands (15–24, 25–39, and 40 years and over), and offense type.

**Results:** Over a 13-year period, there were 45 violent crimes committed per 1,000 inhabitants. Of these, 2.4 were at-

tributable to patients with severe mental illness. This corresponds to a population-attributable risk fraction of 5.2%. This attributable risk fraction was higher in women than men across all age bands. In women aged 25–39, it was 14.0%, and in women over 40, it was 19.0%. The attributable risk fractions were highest in those ages 15–24 (5.8% for male patients and 2.9% for female patients).

**Conclusions:** The population impact of patients with severe mental illness on violent crime, estimated by calculating the population-attributable risk, varies by gender and age. Overall, the population-attributable risk fraction of patients was 5.2%, suggesting that patients with severe mental illness commit one in 20 violent crimes.

5.2%  
(in Sweden)



# OUTLINE

1. **Definitions**
2. **Epidemiology**
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5. **Management of Persistent Aggressive Behavior**

# **ETIOLOGY OF VIOLENT BEHAVIOR: MULTI-FACTORIAL**

- **Co-occurring substance abuse, dependence, and intoxication**
- **Disease process: hallucinations and delusions**
- **Neuropsychiatric deficits and poor impulse control**
- **Underlying character pathology**
- **Chaotic environment**

# PATIENT ASSESSMENT

- Rule out somatic conditions
- Co-morbidity
  - Substance use disorders
  - Antisocial personality disorder/traits
- Adverse drug effects
  - Akathisia
- Risk assessment: past history of violence, access to weapons, criminal justice records, content of delusions

# HETEROGENEITY OF VIOLENT BEHAVIOR

**Table 1** Heterogeneity of violence: possible factors and treatment implications

	<b>Psychosis</b>	<b>Impulsivity</b>	<b>Psychopathy</b>
Features	Hallucinations, delusions, psychotic misinterpretation	Lack of planning, remorse	Planning, lack of remorse, predatory gain
Treatments	Antipsychotics	Adjunctive anticonvulsants	Non-pharmacological treatments

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# OVERVIEW OF TREATMENT

- **Environmental interventions**
  - **Clearing the room, show of force/concern, allow patient to talk**
- **Restraint, seclusion, calming blanket**
- **Non-specific sedating agents – offer early**
  - **Lorazepam vs. antipsychotics**

# ACUTE INTERVENTION: GOALS

- **Calm the patient**
- **Decrease likelihood of harm to self or others**
- **Allow diagnostic tests or procedures**
- **Attenuate psychosis**
- **Decrease need for seclusion/restraint**
  - **Decrease risk of staff and patient injury**
- **Sleep – not desirable when evaluating**

# LORAZEPAM

- **Non-specific sedation**
- **Reliably absorbed intramuscularly**
- **Short half-life (10 - 20 hours)**
- **No active metabolites**
- **0.5 mg to 2.0 mg q1-6h PO, SL, IM, IV**
- **Cautions: respiratory depression, ?disinhibition or paradoxical reactions**
- **Bonus: treats underlying alcohol or sedative withdrawal**
- **Drawback: not for prolonged use because of tolerance, withdrawal, and no/little effect on core symptoms of psychosis**



# Remembrances of Things Past...

- Acute Dystonia
- Oversedation
- Akathisia
- Parkinsonism
- Hypotension
- Tardive Dyskinesia

When the patient lashes out against "them"—

# THORAZINE®

brand of chlorpromazine

quickly puts an end to his violent outburst

'Thorazine' is especially effective when the psychotic episode is triggered by delusions or hallucinations.

At the outset of treatment, Thorazine's combination of antipsychotic and sedative effects provides both emotional and physical calming. Assaultive or destructive behavior is rapidly controlled.

As therapy continues, the initial sedative effect gradually disappears. But the antipsychotic effect continues, helping to dispel or modify delusions, hallucinations and confusion, while keeping the patient calm and approachable.

**SK & F** SMITH KLINE & FRENCH LABORATORIES  
leaders in psychopharmaceutical research



A reminder advertisement— For prescribing information, please see [PDR](#) or available literature.

# FIRST-GENERATION ANTIPSYCHOTICS

- Universally cause sedation given high enough dose
- Intramuscular preparations available
- Low potency/high sedating agents vs. high potency/low sedating agents: hypotension, anticholinergic effects, seizure threshold
- ?Droperidol: medical back-up required; QTc prolongation - withdrawn from UK market
- Cautions: acute dystonia, akathisia, seizure threshold, tardive dyskinesia
- Bonus: (maybe) treats underlying psychosis

# HALOPERIDOL AND LORAZEPAM

- **HAL 5 mg IM + lorazepam 2 mg IM**
- **Faster acting than either agent alone**
- **Fewer injections required**
- **Decreased incidence of EPS vs. HAL alone**
- **Can be given in same syringe**
- **Caveats: Continuation of HAL as an antipsychotic treatment not be optimal: EPS, TD, efficacy limited to positive symptoms**

# SECOND-GENERATION ANTIPSYCHOTICS: NEW FORMULATIONS

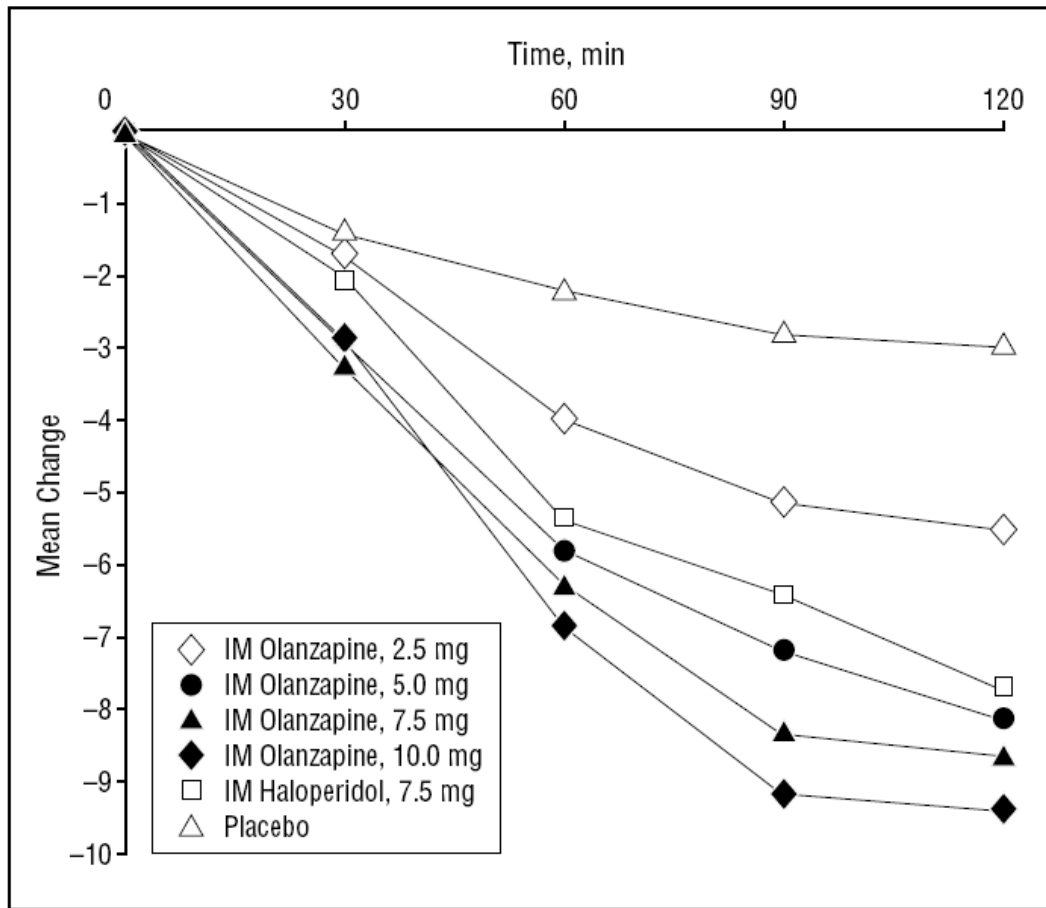
- **Liquid concentrate**
  - Liquid risperidone
  - Liquid aripiprazole
- **Orally disintegrating tablets**
  - Zydis olanzapine
  - M-tab risperidone
  - Discmelt aripiprazole
- **IM Formulations**
  - Olanzapine IM (short-acting)
  - Ziprasidone IM (short-acting)
  - Aripiprazole IM (short-acting)
  - Risperidone IM (long-acting depot)
  - Olanzapine IM (long-acting depot) – in development
- **Bonus: No EPS/akathisia, transition to oral dosing, treatment of underlying psychosis, including negative symptoms**

# OLANZAPINE IM

- **IM form evaluated in 4 randomized double blind placebo and active comparator studies**
  - Schizophrenia (2)
  - Bipolar mania (1)
  - Dementia (1) – not currently FDA-approved for this indication
- **Superior onset of efficacy to haloperidol IM and lorazepam IM**
  - No adverse event significantly more frequent for IM olanzapine vs IM haloperidol or IM lorazepam
- **Dosage 10 mg (2.5 to 5.0 mg for vulnerable patients, e.g. elderly)**
- **Favorable EPS profile**
- **Cautions: weight gain in long-term use**

# DOSING OF OLZ IM

## Efficacy during 2hrs After first Injection (LOCF)



Mean change in Positive and Negative Syndrome Scale Excited Component score from baseline to each time point within 2 hours after the first intramuscular (IM) injection. For IM olanzapine at 2.5 mg vs IM placebo,  $P=.65$  at 30 minutes,  $P=.05$  at 60 minutes,  $P=.02$  at 90 minutes, and  $P=.01$  at 120 minutes. For IM olanzapine at 5.0 mg vs IM placebo,  $P=.03$  at 30 minutes and  $P<.001$  at 60, 90, and 120 minutes. For IM olanzapine at 7.5 mg vs IM placebo,  $P=.007$  at 30 minutes and  $P<.001$  at 60, 90, and 120 minutes. For IM olanzapine at 10.0 mg vs IM placebo,  $P=.05$  at 30 minutes and  $P<.001$  at 60, 90, and 120 minutes. For IM haloperidol at 7.5 mg vs IM placebo,  $P=.34$  at 30 minutes and  $P<.001$  at 60, 90, and 120 minutes.

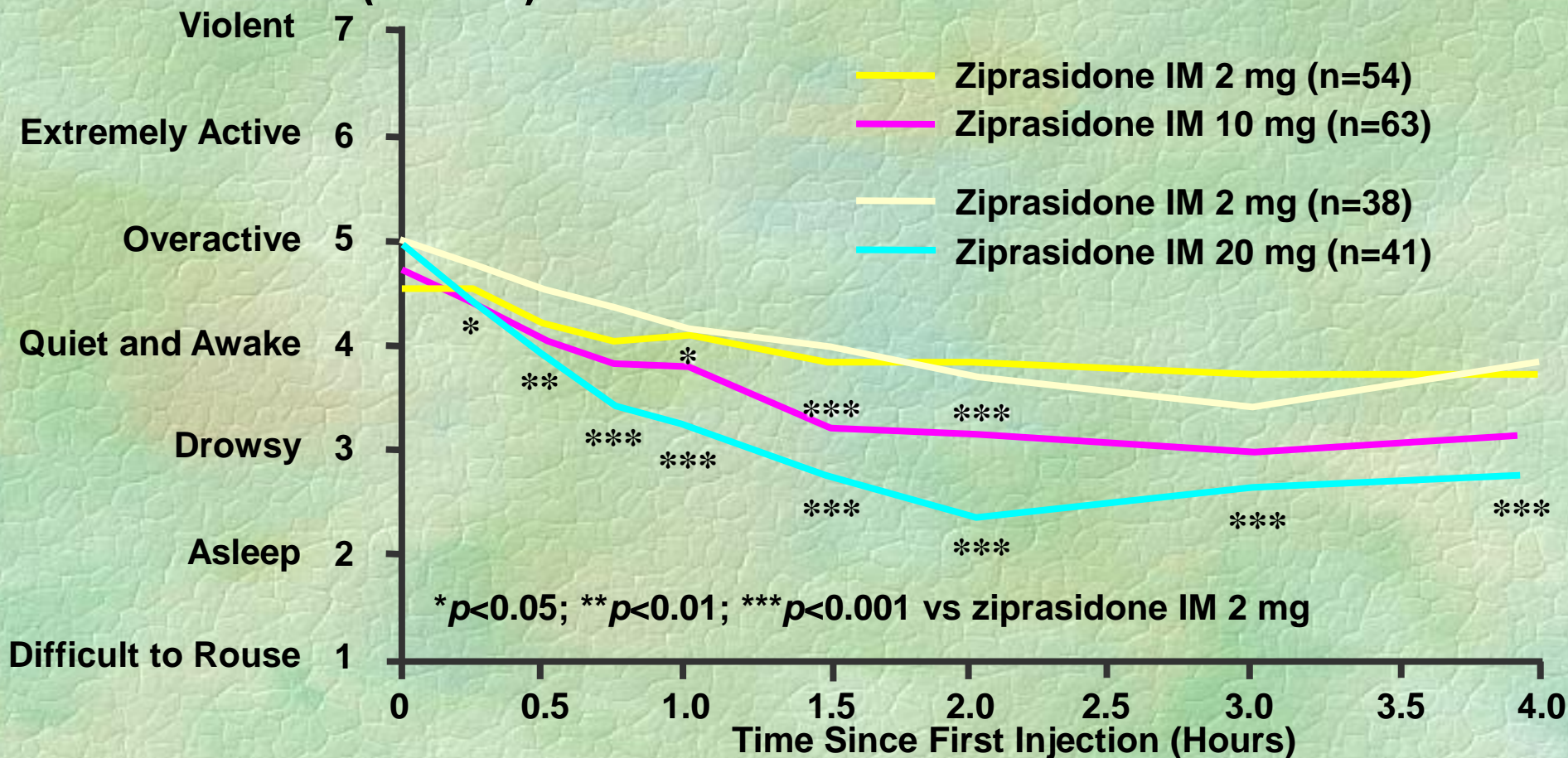
**\* $p < 0.05$  all active doses vs. placebo  
except OLZ 2.5 and HAL at 30 minutes**

# ZIPRASIDONE IM

- **Several studies using 2 mg, 10 mg, 20 mg of ziprasidone and comparisons with HAL IM**
- **Dose response 20 mg IM > 10 mg IM**
  - Superior to haloperidol IM
- **Favorable EPS profile**
- **Caution: Although the product label warns of prolongation of QTc interval, it is the same as seen with oral ziprasidone, and is *not* clinically relevant**

# ZIP IM

## IMPROVEMENT IN MEAN BEHAVIORAL ACTIVITY RATING SCALE (BARS) SCORES AFTER FIRST INJECTION



Lesem MD, Zajecka JM, Swift RH, et al. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *Journal Clinical Psychiatry* 62(1):12-18, 2001.

Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology (Berl)* 155: 128-134, 2001.



# ARIPIIPRAZOLE IM

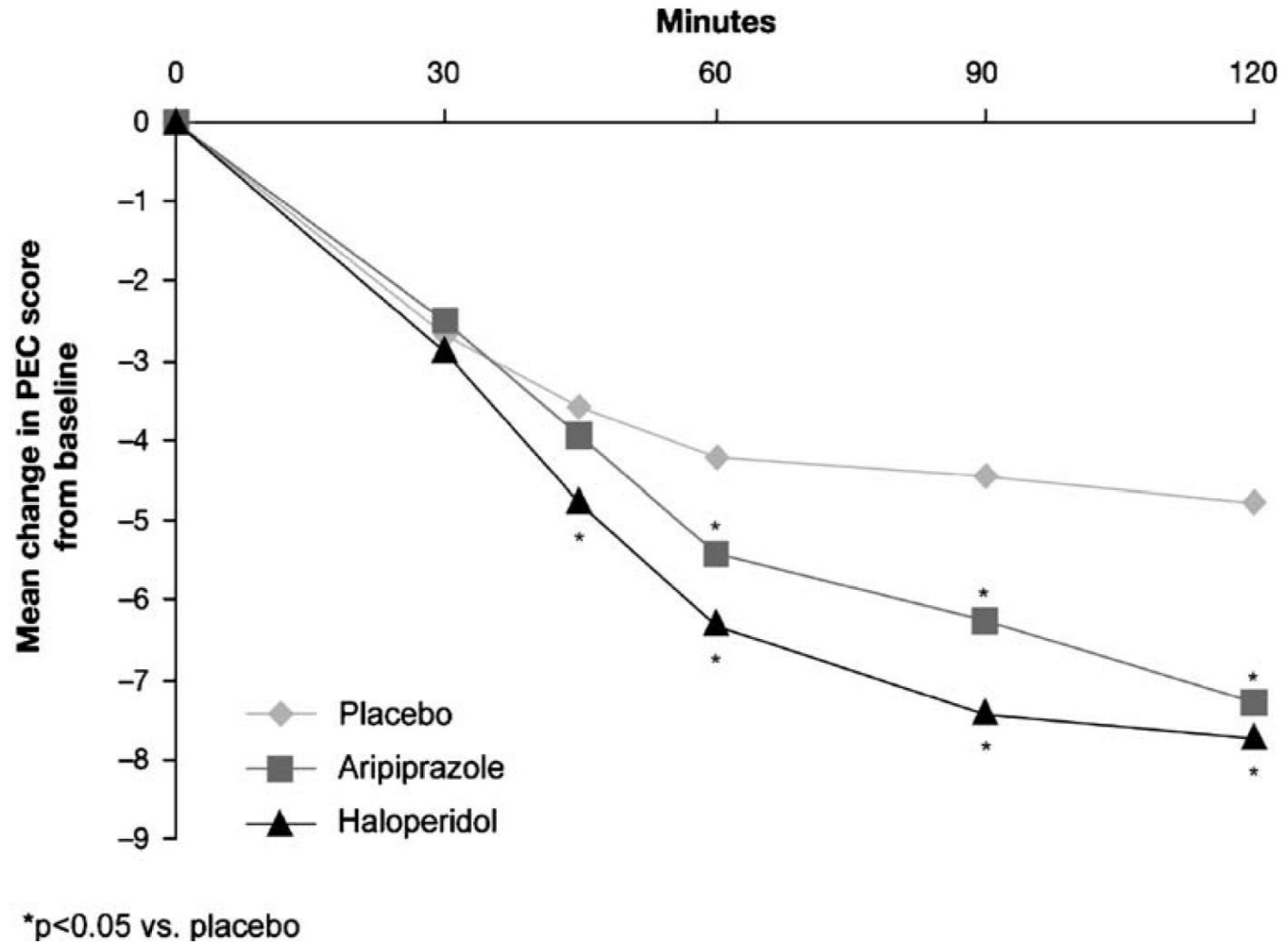
- **IM form evaluated in 3 randomized double blind placebo and active comparator studies**
  - Schizophrenia (2)
  - Bipolar mania (1)
- **Dosage 9.75 mg (5.25 mg for vulnerable patients, e.g. elderly)**
- **Favorable EPS profile**
- **Cautions: If parenteral benzodiazepine therapy is deemed necessary in addition to aripiprazole injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension**

# ARI IM: IMPROVEMENT IN PANSS-EC

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Psychopharmacology (2006) 188:281–292

**Fig. 1** Mean change in PEC score from baseline over the first 2 h after injection (LOCF). PEC = Positive and Negative Syndrome Scale Excited Component



Andrezina R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology (Berl)*. 2006;188(3):281-92.

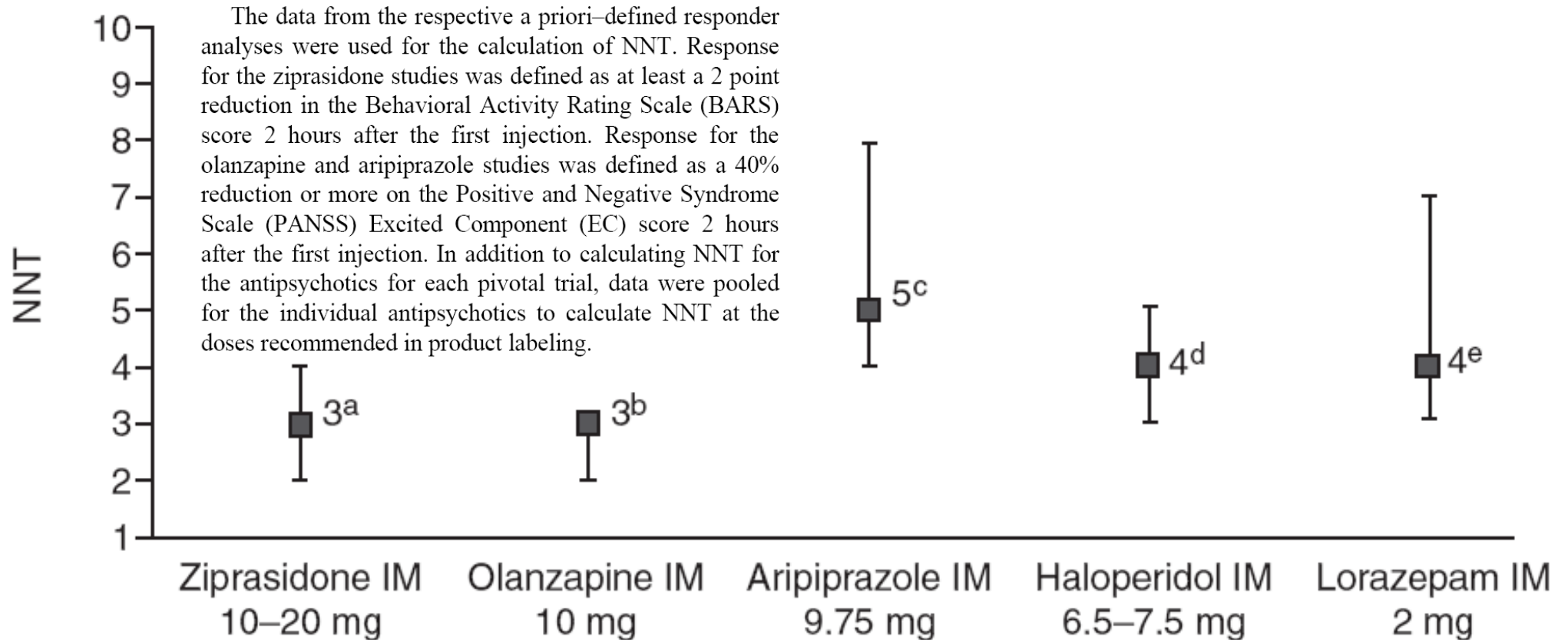
# NUMBER NEEDED TO TREAT

- How many patients would you need to treat with Drug A instead of Drug B before you would see one extra responder, or one adverse outcome?

**The smaller the NNT, the larger the differences between the two drugs, i.e. larger numbers mean more patients needed to treat to see the difference in effect**

# HOW DO TREATMENTS FOR ACUTE AGITATION COMPARE AGAINST PLACEBO?

Responders at 2 hours as defined *a priori* by each manufacturer



Citrome L. Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety. *J Clin Psychiatry* 2007;68(12):1876-85.

# COST<sup>1</sup>

<b>Lorazepam 2 mg IM</b>	<b>Haloperidol 5 mg IM</b>	<b>Ziprasidone 20 mg IM</b>	<b>Olanzapine 10 mg IM</b>	<b>Aripiprazole 9.75 mg</b>
<b>\$0.86</b>	<b>\$2.85</b>	<b>\$9.59<sup>2</sup></b>	<b>\$18.26</b>	<b>\$10.68</b>
<b>Avoidance of acute dystonia and akathisia</b>		<b>Priceless</b>		

1. Cost to Rockland Psychiatric Center pharmacy December 18, 2006

2. Cost prior to 2006 was \$37.43

# AGITATION: SUMMARY

- **Violent or threatening behavior is a frequent reason for admission, and may continue after admission**
- **New formulations (IM, PO) of second-generation antipsychotics provide several advantages over typical antipsychotics to patients who require acute intervention or who refuse oral antipsychotic treatment**

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# LONG-TERM APPROACHES

- **Sedation alone is inadequate**
- **Problem: when the primary treatment (e.g. antipsychotic medication) is inadequate in treating the primary underlying problem**
- **A common theme: the serotonergic neurotransmitter system – modulates impulsivity**



# PHARMACOTHERAPY: PERSISTENT AGGRESSION

- **Second-generation antipsychotics**
- **Mood stabilizers**
- **Beta blockers**
- **SSRIs**
- **Benzodiazepines (negative evidence)**

# SECOND-GENERATION ANTIPSYCHOTICS

## What is the evidence?

**Volavka J, Citrome L. Atypical Antipsychotics in the Treatment of the Persistently Aggressive Psychotic Patient: Methodological Concerns. Schizophrenia Research 35:S23-S33, 1999.**

**Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia. Part II: Long-Term Pharmacotherapeutic Strategies. Essential Psychopharmacology 5(1):17-30, 2002.**

**Citrome L, Nolan KA, Volavka J. Science-Based Treatment of Aggression and Agitation. In Fishbein D (Ed), The Science, Treatment, and Prevention of Antisocial Behaviors, Volume 2, Kingston, New Jersey: Civic Research Institute, Inc., 2004.**

# SECOND-GENERATION ANTIPSYCHOTICS

Rx	Studies	Outcome
CLO	>10 Open retrospective record reviews (N=~1000); NIMH-funded RCT (vs. OLZ, RIS, HAL) (N=157); NIMH-funded RCT (vs. OLZ, HAL) (N=110)	Decrease in seclusion/restraint, improvement in security level/discharge, clinical improvement in medical record, decrease in aggressive incidents, improvement in BPRS, improvement in NOSIE, <u>specific</u> decrease in PANSS Hostility Item (superior to HAL and RIS), decrease in Modified Overt Aggression Scale Total score (superior to OLZ and HAL)
RIS	Post-hoc subanalysis of Phase III RCT (vs. HAL or Placebo) (N=513); 3 open label comparisons (N=~100 )	<u>Specific</u> improvement in PANSS Hostility Item and BPRS Factor 4 (uncontrolled hostility/excitement) (superior to HAL and Placebo); decrease in seclusion/restraint; 2 negative reports

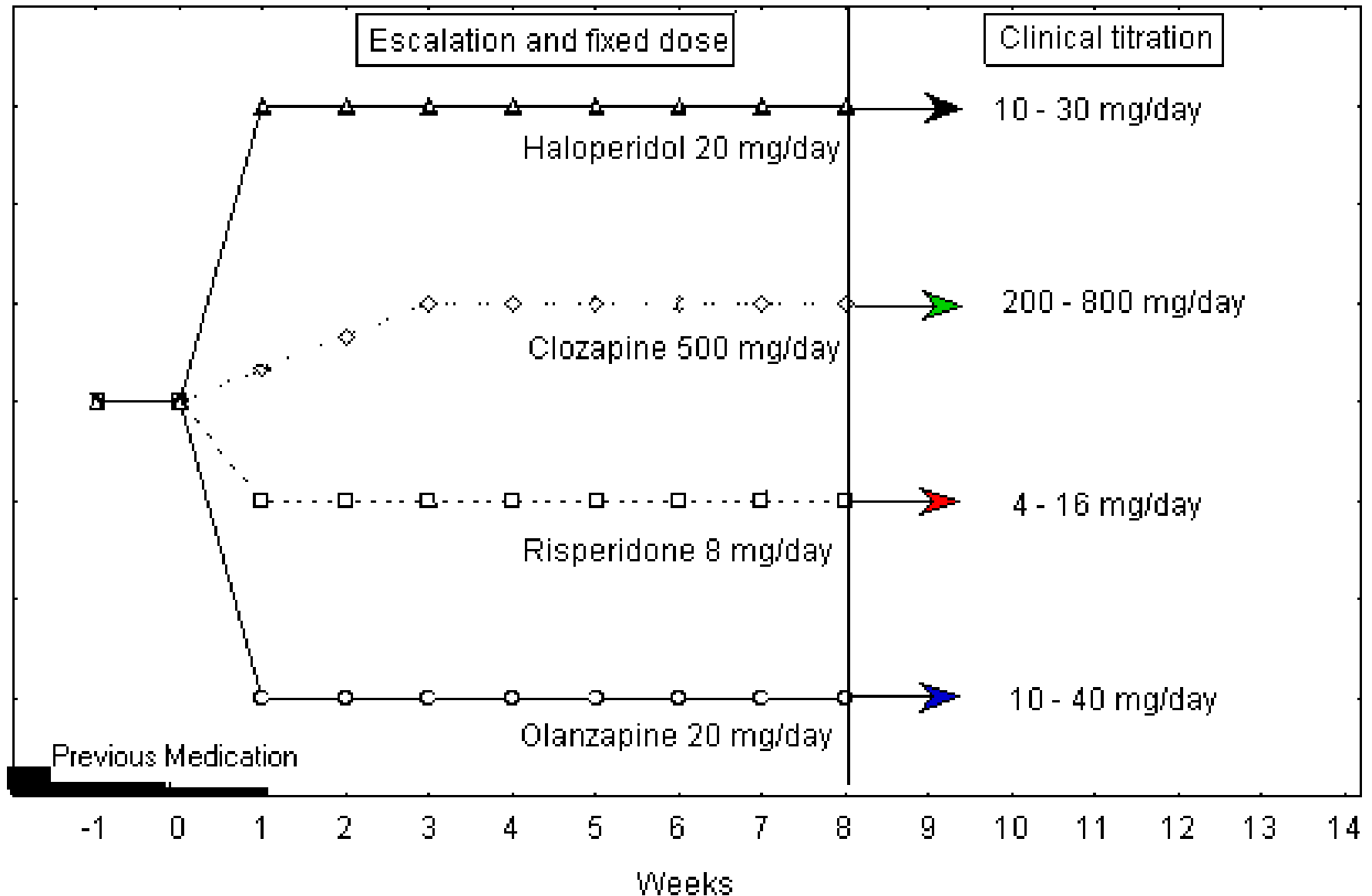
# SECOND-GENERATION ANTIPSYCHOTICS (Cont'd)

Rx	Studies	Outcome
OLZ	NIMH-funded RCT (vs. CLO, HAL) (N=110); Post-hoc subanalysis of Phase III RCT (vs. HAL) (N=388)	Decrease in Modified Overt Aggression Scale Total score (superior to HAL, inferior to CLO); Improvement in agitation
QUE	Post-hoc subanalysis of Phase III RCT (vs. HAL) (N=257); Post-hoc subanalysis of 3 Phase III RCTs (N=389); case reports (N=2)	Improvement in BPRS Hostility item; improvement in PANSS; anti-hostility specificity (vs. general antipsychotic effect) in one but not the other
ZIP	Post-hoc subanalysis of randomized, rater-blinded, 6-week open-label study comparing sequential intramuscular and oral ziprasidone with haloperidol (N=572)	ZIP demonstrated <u>specific</u> anti-hostility effects over time throughout the 6-week study period, and statistically significant superiority to haloperidol on this measure in the first week of treatment.
ARI	Post-Hoc subanalysis and meta-analysis of 5 Phase III RCTs (vs. HAL or vs. Placebo) (N=1,476)	<u>Specific</u> improvement in PANSS Hostility item vs. Placebo (but comparable to HAL)

# **CLO STUDY #1: EFFECTS OF CLO, OLZ, RIS, and HAL ON HOSTILITY (Funded by NIMH)**

- ▣ **Treatment-resistant inpatients (N=157)**
- ▣ **Schizophrenia or schizoaffective disorder**
- ▣ **Random assignment to clozapine (CLO), olanzapine (OLZ), risperidone (RIS), or haloperidol (HAL)**
- ▣ **Double-blind**
- ▣ **Followed prospectively for 14 weeks**
  - ▣ **Period 1: 8 weeks escalation and fixed dose**
  - ▣ **Period 2: 6 weeks variable dose**

## Schematic of experimental design: dosing in double-blind study



# CLO, OLZ, RIS, and HAL: VARIABLES

- **Primary measure of efficacy: PANSS hostility item**
  - **Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse and assaultiveness**
  - **Ratings range from 1 (hostility absent) to 7 (extreme hostility that includes marked anger resulting in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others)**
- **Two Covariates**
  - **Sum of PANSS measures of positive psychotic symptoms (delusions, suspiciousness/persecution, grandiosity, unusual thought content, conceptual disorganization, and hallucinatory behavior)**
  - **NOSIE measure of sedation (“is slow moving and sluggish”)**

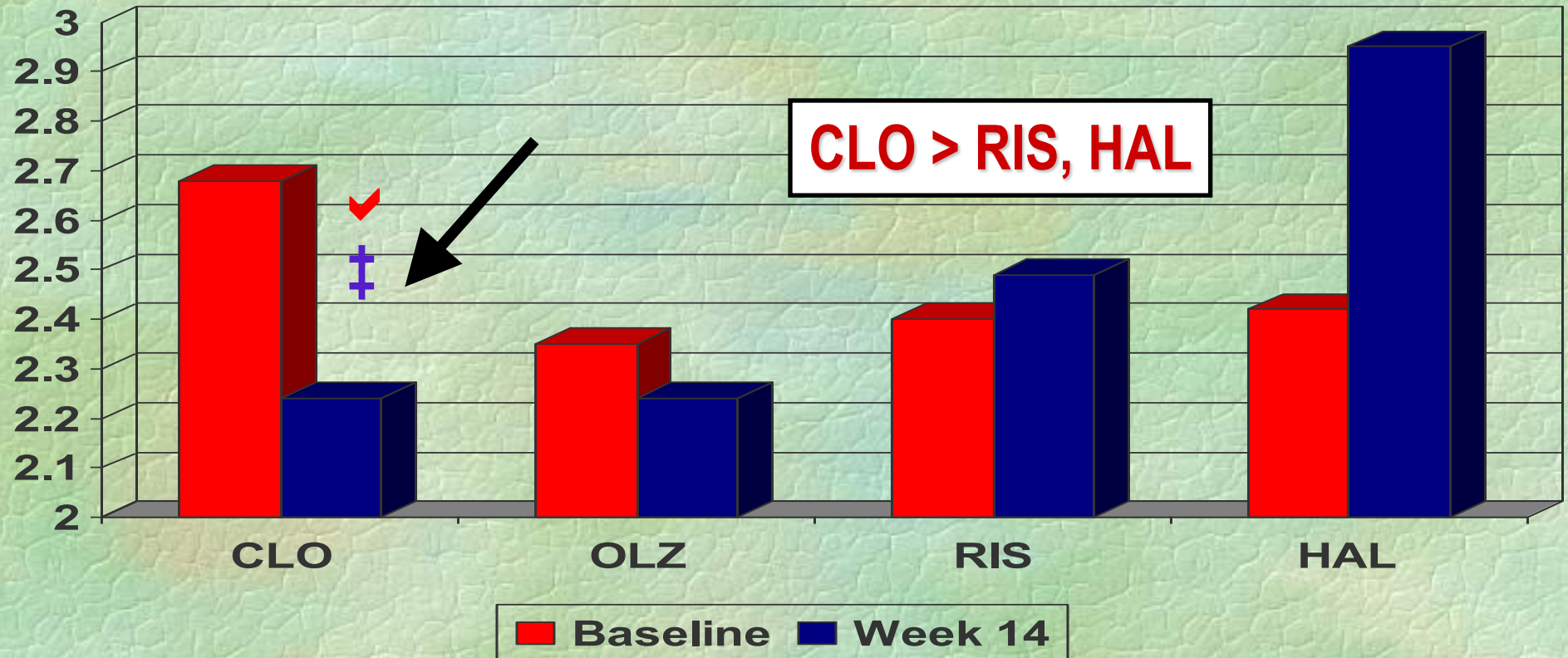
# SAMPLE: AGE, DURATION OF ILLNESS, NUMBER OF HOSPITALIZATIONS

Characteristic	CLO(N=40)		OLZ (N=39)		RIS (N=41)		HAL(N=37)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	42.0	7.9	41.1	7.3	42.3	9.8	37.6	10.9
Duration of illness (years)	21.5	7.6	18.7	8.0	20.4	10.0	17.3	7.5
Number of hospitalizations	9.8	6.1	9.8	6.2	12.7	12.9	9.4	6.1

Citrome L, Volavka J, Czobor P, et al. Effects of Clozapine, Olanzapine, Risperidone, and Haloperidol on Hostility Among Patients with Schizophrenia. *Psychiatric Services* 52(11): 1510-1514, 2001.



# PANSS HOSTILITY ITEM (LOCF)



- ✓ Significant change from baseline ( $p=0.019$ )
- ‡ Significant superiority in improvement compared to HAL ( $p=0.021$ ) or RIS ( $p=0.012$ )

Medication	Baseline	14 Weeks	Effect Size
CLO (N=40)	2.68 ± 1.58	2.24 ± 1.34	0.25
OLZ (N=39)	2.35 ± 1.47	2.24 ± 1.73	0.06
RIS (N=41)	2.40 ± 1.19	2.49 ± 1.61	0.05 (-)
HAL (N=37)	2.42 ± 1.26	2.95 ± 1.51	0.30 (-)

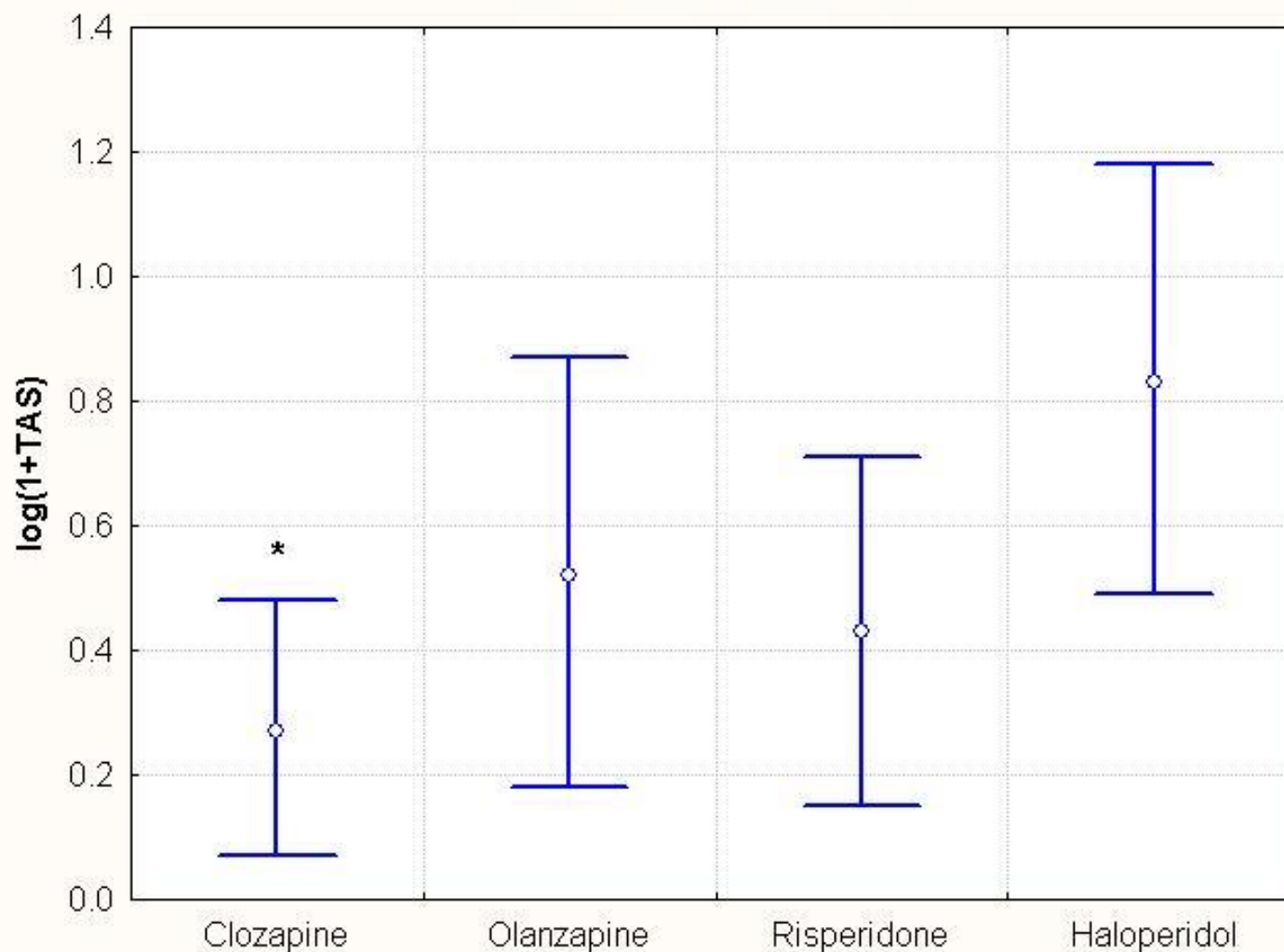
# **OVERT AGGRESSION SCALE**

## ***Weighted Scores***

- **Verbal aggression (1-4)**
- **Physical aggression against objects (2-5)**
- **Physical aggression against self (3-6)**
- **Physical aggression against others (3-6)**
- **Interventions by staff (1-5)**

Target Dose of CLO 500 mg/day to be reached on **Day 24** (achieved  $401.6 \pm 160.4$ )

**TOTAL AGGRESSION SEVERITY SCORE (TAS), FIRST 24 DAYS OF TREATMENT OMITTED**



\*: Clozapine vs. Haloperidol: Chi-square=8.24, df=1, p=0.004

# CLO, OLZ, RIS, and HAL: RESULTS

- Reduction of hostility over time reached statistical significance for CLO at 14 weeks (and at 8 weeks)
- Post-hoc analysis indicates CLO has significantly greater specific anti-aggressive effect than HAL or RIS, but *not* OLZ
- Neither RIS nor OLZ showed a superiority over HAL
- Effect on hostility appears independent of antipsychotic effect on other PANSS items that reflect delusional thinking, disorganized behavior or hallucinations, and independent of antipsychotic effect on sedation as measured by the NOSIE
- The findings were unchanged when assessing the possible confounds of the PANSS Anxiety/Depression Factor, the PANSS Excitement Item, akathisia (ESRS), ethnicity, and medication dose change over time

# **CLO STUDY #2: EFFECTS OF CLO, OLZ, and HAL ON HOSTILITY (Funded by NIMH)**

- ▣ **Physically-assaultive inpatients (N=110)**
- ▣ **Schizophrenia or schizoaffective disorder**
- ▣ **Random assignment to clozapine (CLO), olanzapine (OLZ), or haloperidol (HAL)**
- ▣ **Double-blind**
- ▣ **Followed prospectively for 12 weeks**
  - ▣ **Period 1: 6 weeks escalation and fixed dose**
  - ▣ **Period 2: 6 weeks variable dose**

# EFFECTS OF CLO, OLZ, and HAL ON HOSTILITY

**Table 1. Baseline Characteristics of Patients Assigned to Receive Clozapine, Olanzapine, and Haloperidol**

Characteristics	Clozapine (n = 37)	Olanzapine (n = 37)	Haloperidol (n = 36)	Test Statistic (P Value)*
Male, No. (%)	31 (83.8)	29 (78.4)	30 (83.3)	0.5 (.80)*
Race/ethnicity, No. (%)				
White	7 (18.9)	5 (13.5)	7 (19.4)	7.6 (.47)*
Black	20 (54.1)	28 (75.7)	21 (58.3)	
Hispanic	8 (21.6)	4 (10.8)	8 (22.2)	
Other	2 (5.4)	0	0	
Diagnosis, No. (%)				
Schizophrenia	27 (73.0)	23 (62.2)	21 (58.3)	1.9 (.40)*
Schizoaffective disorder	10 (27.0)	14 (37.8)	15 (41.7)	
Age at randomization, mean ± SD, y	35.1 ± 12.3	35.6 ± 9.4	32.7 ± 10.6	0.8 (.48)
Duration of illness, mean ± SD, y	15.7 ± 9.5	16.8 ± 11.2	13.9 ± 11.2	0.6 (.56)
Prior psychiatric hospitalizations, mean ± SD, No.	12.3 ± 9.8	11.4 ± 9.6	8.9 ± 4.7	1.8 (.18)
Positive and Negative Syndrome Scale scores, mean ± SD				
Positive subscale	22.9 ± 5.4	22.9 ± 5.7	23.0 ± 6.4	0.0 (.99)
Negative subscale	20.3 ± 4.5	18.9 ± 3.4	19.8 ± 4.7	1.1 (.34)
General subscale	43.2 ± 7.2	41.9 ± 7.4	42.6 ± 6.6	0.3 (.73)
Total	86.4 ± 14.4	83.7 ± 14.1	85.5 ± 13.2	0.4 (.70)

\* $\chi^2$  Was computed for the categorical variables and analysis of variance for the continuous variables.

**Krakowski M, Czobor P, Citrome L, et al. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 63(6):622-629, 2006.**

# EFFECTS OF CLO, OLZ, and HAL ON HOSTILITY

**Table 2. Differences in the Various Forms of Overt Aggression Among Patients Treated With Clozapine, Olanzapine, and Haloperidol\***

MOAS	Comparison	OR (95% CI) for Less Severe Violence†	$\chi^2$ (P Value)
Total score	Clozapine vs haloperidol	1.69 (1.6-1.8)	154.7 (<.001)‡
	Clozapine vs olanzapine	1.30 (1.2-1.4)	36.2 (<.001)†
	Olanzapine vs haloperidol	1.30 (1.2-1.4)	44.9 (<.001)‡
Physical aggression	Clozapine vs haloperidol	2.04 (1.8-2.3)	134.0 (<.001)‡
	Clozapine vs olanzapine	1.33 (1.2-1.5)	21.3 (<.001)‡
	Olanzapine vs haloperidol	1.54 (1.4-1.7)	54.0 (<.001)‡
Aggression against property	Clozapine vs haloperidol	1.85 (1.4-2.4)	18.6 (<.001)‡
	Clozapine vs olanzapine	1.10 (0.8-1.5)	0.1 (.78)

**CLO > OLZ > HAL for aggression**

**This is a selective antiaggressive effect: No difference in PANSS**

Abbreviations: CI, confidence interval; MOAS, Modified Overt Aggression Scale; OR, odds ratio.

\*Generalized linear model analyses were used. An overall difference among the groups was found on each of the 4 measures of violence (see the "Aggressive Behaviors" subsection of the "Results" section). Pairwise differences are provided in the table.

†The odds ratio represents the odds of a lower MOAS score (one point) during the study period for the first as compared with the second medication in the pair for each type of aggressive behavior.

‡Results remain significant after correcting for multiple testing (Bonferroni correction).

# **SPECIFIC EFFECTS OF QUE ON HOSTILITY**

## **(Funded by Astra-Zeneca)**

- **Reanalysis of a previously reported 6-week RCT compared QUE vs HAL (N=257) on an agitation measure derived from the Brief Psychiatric Rating Scale (BPRS)**
- **QUE treatment reduced agitation scores significantly among patients with acute psychoses compared with placebo**
- **Compared with HAL, QUE treatment had a direct and significant effect on agitation that was independent of the improvement in psychotic symptoms**
  - **A second post hoc analysis of data from three RCTs (including above) showed that the improvements in hostility (vs. placebo) were highly correlated with improvements in positive symptoms and there was no consistent relationship between sedation and hostility**

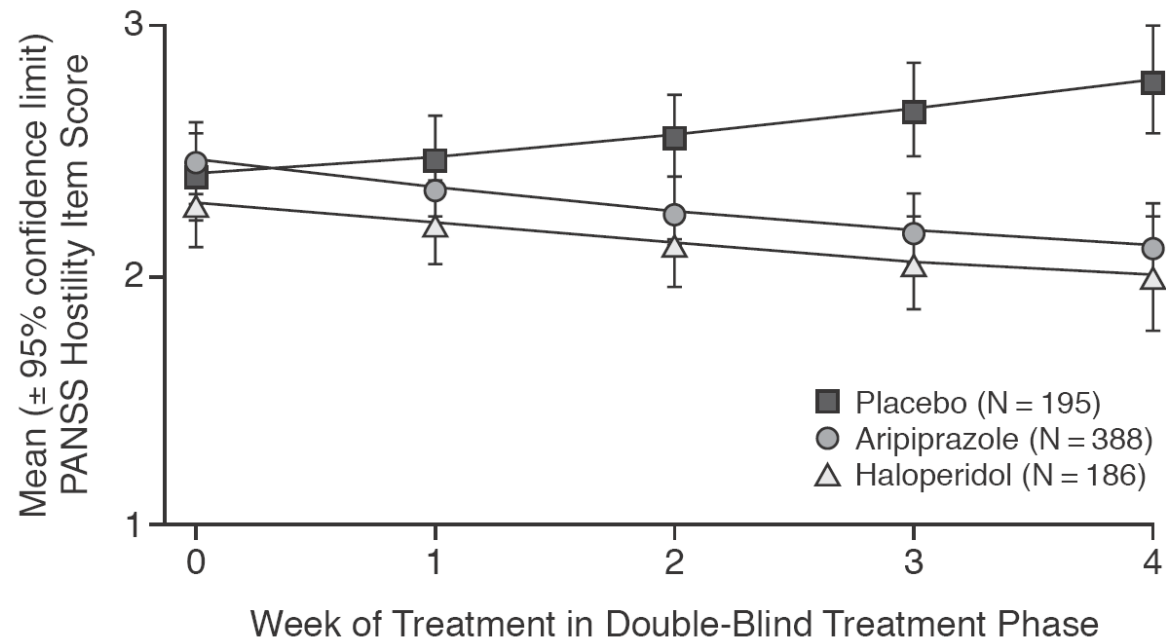


# **SPECIFIC EFFECTS OF ARI ON HOSTILITY**

## **(Funded by BMS/Otsuka)**

- **A total of 1476 patients diagnosed with DSM-IV schizophrenia or schizoaffective disorder were the subjects in 5 short-term, double-blind studies comparing ARI with placebo; 3 of these studies also included a comparison with HAL**
- **To determine the effect of ARI on hostility, post hoc analyses of the hostility item from the PANSS were conducted for the first 4 weeks of treatment; to test for specific anti-hostility effect, sedation and positive symptoms used as covariates**
- **ARI was superior to placebo and not significantly different from HAL in reducing hostility**

Figure 2. Change in Hostility During Treatment With Aripiprazole in 3 Short-Term, Placebo- and Active-Controlled Trials<sup>a</sup>



<sup>a</sup>The effects of aripiprazole and the active control, haloperidol, were not significantly different from each other, while both aripiprazole and haloperidol were superior to placebo. The difference between aripiprazole and placebo reached the level of statistical significance in weeks 2, 3, and 4. Haloperidol was significantly superior to placebo at all time points ( $p < .05$ ).

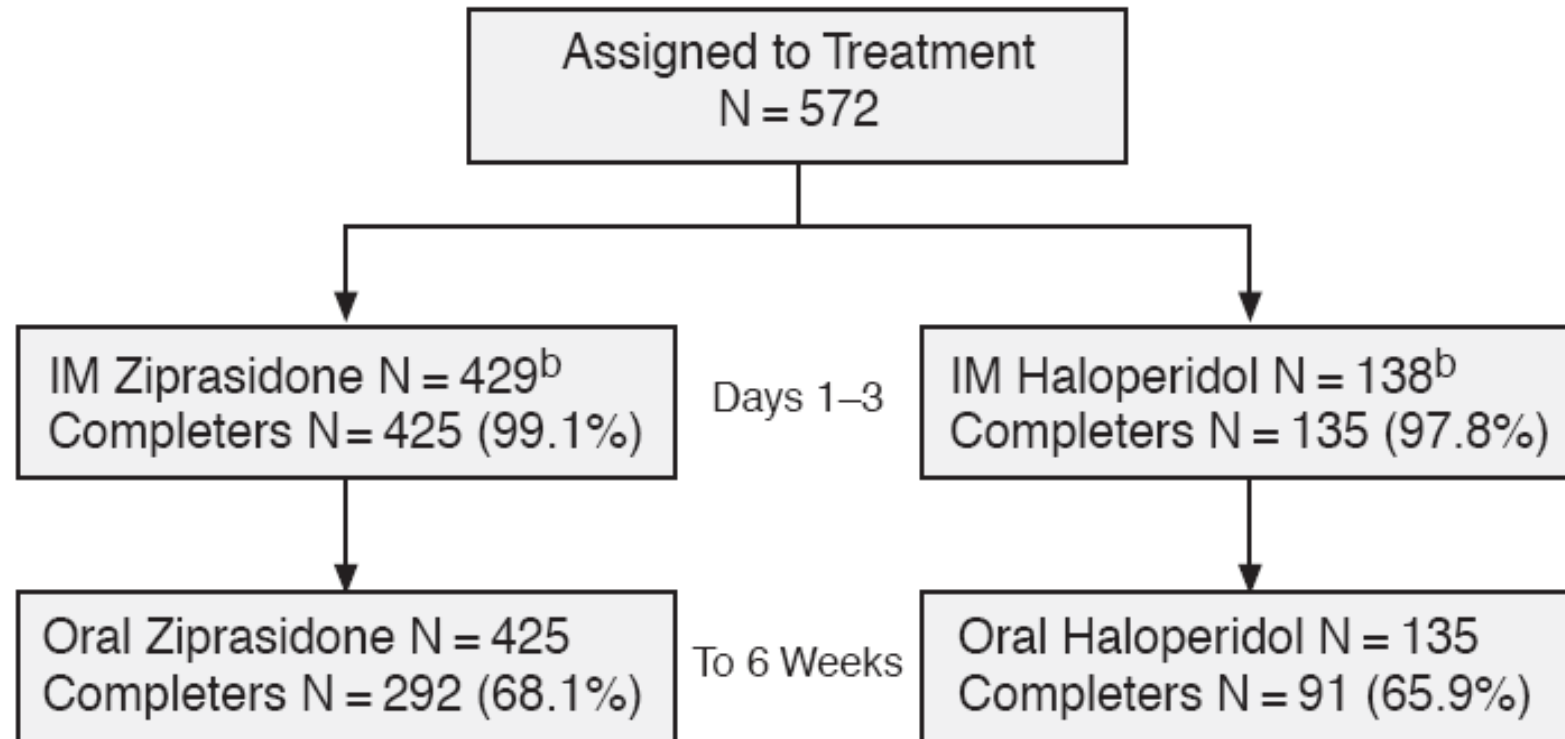
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

# **SPECIFIC EFFECTS OF ZIP ON HOSTILITY**

## **(Funded by Pfizer)**

- **A total of 572 patients diagnosed with schizophrenia or schizoaffective disorder were the subjects in a randomized, rater-blinded, 6-week open-label study comparing sequential intramuscular and oral ZIP with HAL**
- **To determine the effect of ZIP on hostility, post-hoc analyses of the “hostility” item from the BPRS were conducted; Introducing positive symptoms and akathisia as covariates tested specific anti-hostility effect**
- **ZIP demonstrated specific anti-hostility effects over time throughout the 42-day study period, and statistically significant superiority to haloperidol on this measure in the first week of treatment**

Figure 1. Disposition of Patients<sup>a</sup>



<sup>a</sup>Detailed flowchart available in Brook et al.<sup>20</sup>

<sup>b</sup>Received 1 or more doses.

Abbreviation: IM = intramuscular.

# ODDS RATIOS (AND 95% CONFIDENCE INTERVALS) FOR DECREASES IN HOSTILITY

Table 2. Decreases in Hostility With Ziprasidone and Haloperidol

Day	Odds Ratio (95% CI)			p Value (ziprasidone vs haloperidol)
	Ziprasidone Improvement Over Baseline <sup>a</sup>	Haloperidol Improvement Over Baseline <sup>a</sup>	Ziprasidone vs Haloperidol <sup>b</sup>	
1–3 (IM period)	2.89 (2.48 to 3.38)	1.85 (1.43 to 2.39)	1.56 (1.16 to 2.11)	.0032
7	3.84 (3.12 to 4.72)	2.43 (1.73 to 3.41)	1.58 (1.06 to 2.35)	.0232
14	5.64 (4.38 to 7.27)	3.15 (2.09 to 4.75)	1.79 (1.11 to 2.90)	.0177
28	9.97 (7.12 to 13.98)	4.38 (2.53 to 7.60)	2.27 (1.20 to 4.32)	.0119
42	20.27 (13.44 to 30.59)	9.37 (4.73 to 18.57)	2.16 (0.98 to 4.77)	.0557

<sup>a</sup>Time effect.

<sup>b</sup>Treatment and time interaction effect.

Abbreviation: IM = intramuscular.

Table 3. Decreases in Hostility With Ziprasidone and Haloperidol, After Adjustment for Covariates (specific antihostility effect)

Day	Odds Ratio (95% CI)			p Value (ziprasidone vs haloperidol)
	Ziprasidone Improvement Over Baseline <sup>a</sup>	Haloperidol Improvement Over Baseline <sup>a</sup>	Ziprasidone vs Haloperidol <sup>b</sup>	
1–3 (IM period)	1.64 (1.38 to 1.96)	1.09 (0.81 to 1.47)	1.50 (1.08 to 2.09)	.0149
7	1.56 (1.22 to 1.99)	0.98 (0.66 to 1.46)	1.59 (1.03 to 2.47)	.0358
14	1.64 (1.21 to 2.21)	1.01 (0.62 to 1.65)	1.62 (0.95 to 2.76)	.0765
28	1.57 (1.04 to 2.36)	0.82 (0.43 to 1.56)	1.91 (0.95 to 3.83)	.0683
42	1.93 (1.16 to 3.19)	1.06 (0.49 to 2.26)	1.83 (0.80 to 4.14)	.1496

<sup>a</sup>Time effect.

<sup>b</sup>Treatment and time interaction effect.

Abbreviation: IM = intramuscular.

# SUMMARY:

## SECOND-GENERATION ANTIPSYCHOTICS AND HOSTILITY

- **CLO: Strongest evidence from two NIMH-funded RCTs**
  - Reductions of hostility and aggression appear to be selective, i.e. independent of the general antipsychotic effects of CLO, and independent of sedation
- **RIS: Conflicting evidence**
  - May also have a selective effect on hostility (Czobor et al, 1995), reduce seclusion use (Chengappa et al 2000), but negative reports also exist (Buckley et al, 1997; Beck et al, 1997)
- **OLZ: Better than HAL, but not as good as CLO, as evidenced in an NIMH-funded RCT**
- **QUE: Selective effect on hostility in one post-hoc analysis (and better than HAL), but selectivity of effect (vs. general antipsychotic effect) in question in another post-hoc analysis (vs. placebo)**
- **ARI: In one post-hoc analysis, ARI had a specific anti-hostility effect and superior to placebo, but not to HAL**
- **ZIP: In one post-hoc analysis, ZIP had a specific anti-hostility effect and superior to HAL at start of treatment**

# **SECOND-GENERATION ANTIPSYCHOTICS AND HOSTILITY**

**Double-blind studies with subjects specifically selected because of aggressive behavior are needed**

- **Operational difficulties: relative rarity of aggressive events, need for large sample size, need for lengthy baseline and trial periods, problems with selection/consent bias**
- **Very, very, few exist**

# MOOD STABILIZERS



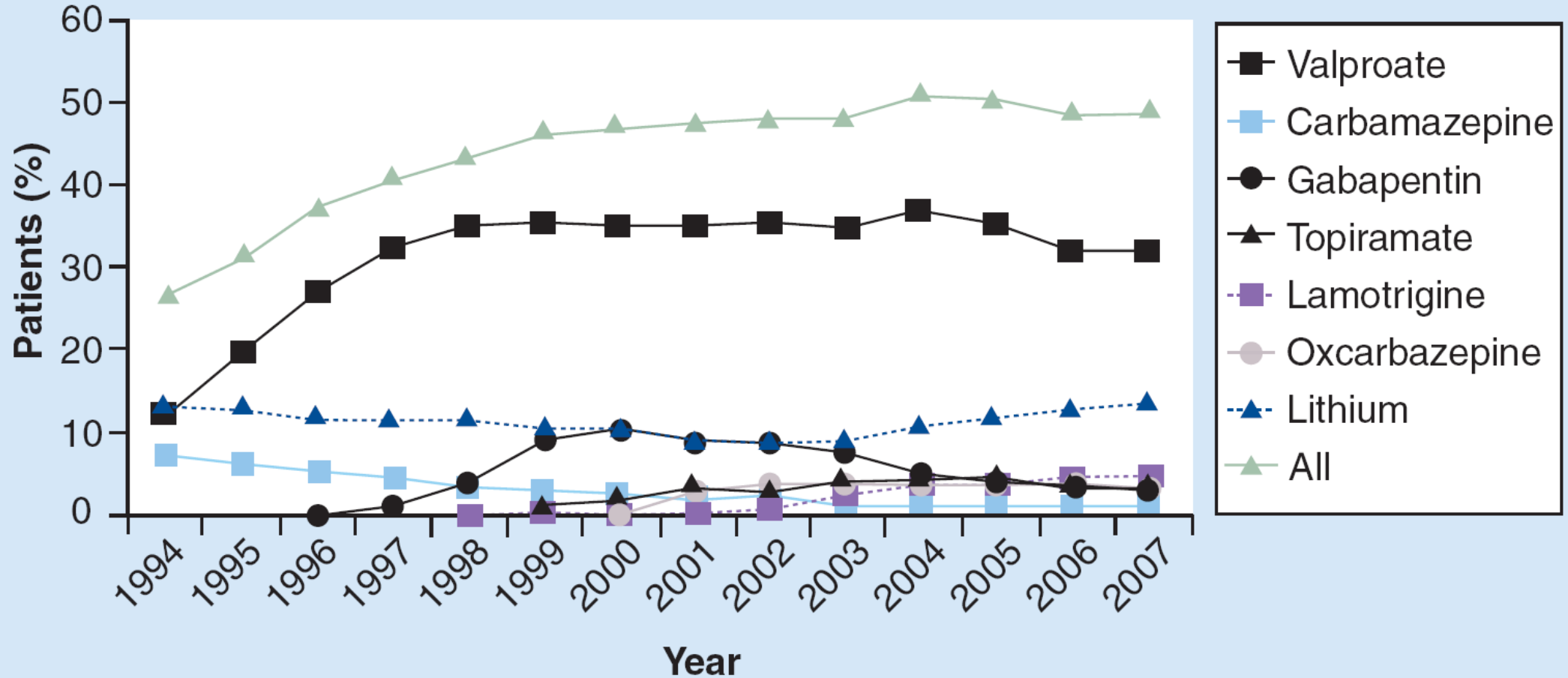
## What is the evidence?

Citrome L. Adjunctive lithium and anticonvulsants for the treatment of schizophrenia: what is the evidence? *Expert Rev Neurother* 2009; 9(1):55-71.

Citrome L. Adding lithium or anticonvulsants to antipsychotics for the treatment of schizophrenia: useful strategy or exercise in futility? *J Clin Psychiatry* 2009;70(6):932-3.



Figure 1. Percentage of inpatients with schizophrenia receiving adjunctive mood stabilizers within the New York State Office of Mental Health from 1994 (n = 8405) to 2007 (n = 3038).



# ADJUNCTIVE MOOD STABILIZER USE IN PATIENTS WITH SCHIZOPHRENIA – SIGNALS/EVIDENCE FOR EFFICACY

AGENT	CASE REPORTS AND OPEN STUDIES	RANDOMIZED CONTROLLED TRIALS	UTILITY (Benefit?)
Lithium	✓ (many)	✓	Probably not
Carbamazepine	✓ (many)	✓ (7)	?
Valproate	✓ (many)	✓ (8)	?
Gabapentin	✓ (5, +/-)	0	Probably not
Lamotrigine	✓ (few, +/-)	✓ (6)	?
Topiramate	✓ (few, +/-)	✓ (4)	Probably not
Oxcarbazepine	✓ (3, +/-)	0	Probably not
Lithium	✓ (many)	✓ (10)	Probably not

# ADJUNCTIVE CARBAMAZEPINE IN SCHIZOPHRENIA

## RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Okuma <i>et al.</i> (1989)	CBZ 200–1200 mg/day vs placebo added to AP (double-blind but not randomized)	162	28	Inpatients or outpatients with schizophrenia or schizoaffective disorder and who 'showed excited psychotic states that responded unsatisfactorily to previous neuroleptic treatment'
Neppe (1983)	CBZ 600 mg/day vs placebo added to AP (crossover)	11	42	Inpatients, eight with schizophrenia (and EEG abnormalities)
Ohlmeier <i>et al.</i> (2007)	CBZ (mean 404 mg/day) added to perazine vs OLZ alone (although randomized, the study was not double-blind)	23	21	Inpatients with schizophrenia
Dose <i>et al.</i> (1987)	CBZ 600–1200 mg/day vs placebo added to HAL	22	28	Inpatients with schizophrenia or schizoaffective disorder
Nachshoni <i>et al.</i> (1994)	CBZ 600 mg/day vs placebo added to AP	28	49	Inpatients with 'residual schizophrenia with negative symptoms'
Simhandl <i>et al.</i> (1996)	CBZ (plasma level 15–42 µmol/l) vs Li (0.6–1.2 mmol/l) vs placebo added to AP	42	42	Schizophrenia (treatment-nonresponsive), inpatient or outpatient status not described
Hesslinger <i>et al.</i> (1999)	CBZ (mean 567 mg/day) vs VAL (mean 757 mg/day) vs nothing added to HAL (although randomized, the study was not double-blind)	27	28	Inpatients with schizophrenia or schizoaffective disorder

**No difference on BPRS; Possible improvement on suspiciousness, uncooperativeness and excitement with CBZ; Higher proportion discontinued the study early on CBZ than on placebo (NNT 17, not statistically significant)**

**Improvement in "Overall Clinical Rating" with CBZ**

**OLZ monotherapy was superior to perazine plus CBZ on positive symptoms on PANSS and BPRS**

**No difference on BPRS; Same proportion discontinued the study early on CBZ than on placebo**

**No difference on BPRS or SANS; Same proportion discontinued the study early on CBZ than on placebo**

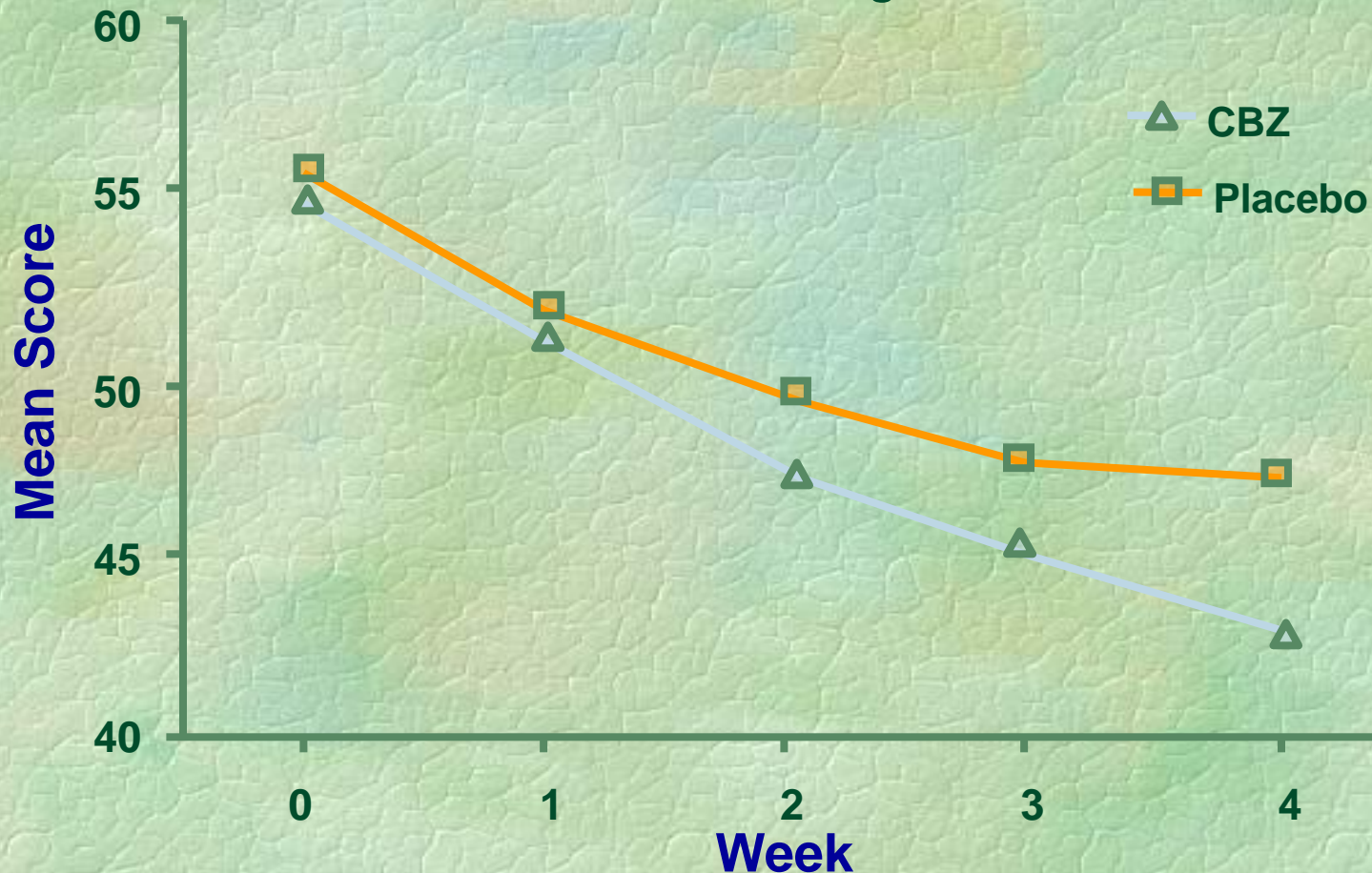
**No difference on BPRS; within groups CBZ and Li improved on CGI from baseline; Li superior to CBZ and placebo on CGI; Both BPRS total score as well as CGI showed a deterioration (not statistically significant) between weeks 6 and 8, when all patients were on placebo**

**CBZ was associated with significantly lower HAL plasma levels and with a worse clinical outcome compared with antipsychotic monotherapy; Higher proportion discontinued the study early on CBZ than on placebo (NNT 5, not statistically significant)**

# CARBAMAZEPINE IN SCHIZOPHRENIA

## *Efficacy: Time Course of Outcomes*

BPRS Scores - No significant differences



# CARBAMAZEPINE IN SCHIZOPHRENIA

## *Efficacy: BPRS Individual Item Scores*

### IMPROVEMENT

BPRS Item	Mean Score		P-value (Per weeks of therapy)				
	Week 0	Week 4	0	1	2	3	4
	<b>Suspiciousness</b>						
Carbamazepine	3.7	2.9	< 0.05				
Placebo	3.6	3.1					
<b>Uncooperativeness</b>							
Carbamazepine	3.9	3.0				< 0.05	
Placebo	4.1	3.3					
<b>Excitement</b>							
Carbamazepine	4.4	2.7				< 0.05	< 0.05
Placebo	4.2	2.9					

# ADJUNCTIVE LAMOTRIGINE AND SCHIZOPHRENIA

## RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Tiihonen <i>et al.</i> (2003)	LAM 200 mg/day vs placebo added to CLO (crossover)	34	84	Male inpatients with CLO-resistant chronic schizophrenia (not exacerbation)
Kremer <i>et al.</i> (2004)	LAM 400 mg/day vs placebo added to AP	38	70	Inpatients with treatment-resistant schizophrenia
Akhondzadeh <i>et al.</i> (2005)	LAM 150 mg/day vs placebo added to RIS	36	56	Inpatients with schizophrenia
Zoccali <i>et al.</i> (2007)	LAM 200 mg/day vs placebo added to CLO	60	168	Outpatients with treatment-resistant schizophrenia
Goff <i>et al.</i> (2007; Study 1)	LAM 100–400 mg/day vs placebo added to AP	209	84	Inpatients or outpatients with schizophrenia and with stable, residual psychotic symptoms
Goff <i>et al.</i> (2007; Study 2)	LAM 100–400 mg/day vs placebo added to AP	210	84	Inpatients or outpatients with schizophrenia and with stable, residual psychotic symptoms

Improvement in BPRS, PANSS positive and PANSS general psychopathology; Most robust effect seen in the most ill patients (N=10) (BPRS  $\geq$  45); No improvement in negative symptoms; Higher proportion discontinued the study early on VAL than on placebo (NNT 174, not statistically significant)

Improvement in PANSS positive, general psychopathology and total symptoms scores in completers; No difference in negative symptoms or total BPRS; No difference with intent-to-treat analyses; Higher proportion discontinued the study early on placebo than on LAM (NNT 15, not statistically significant)

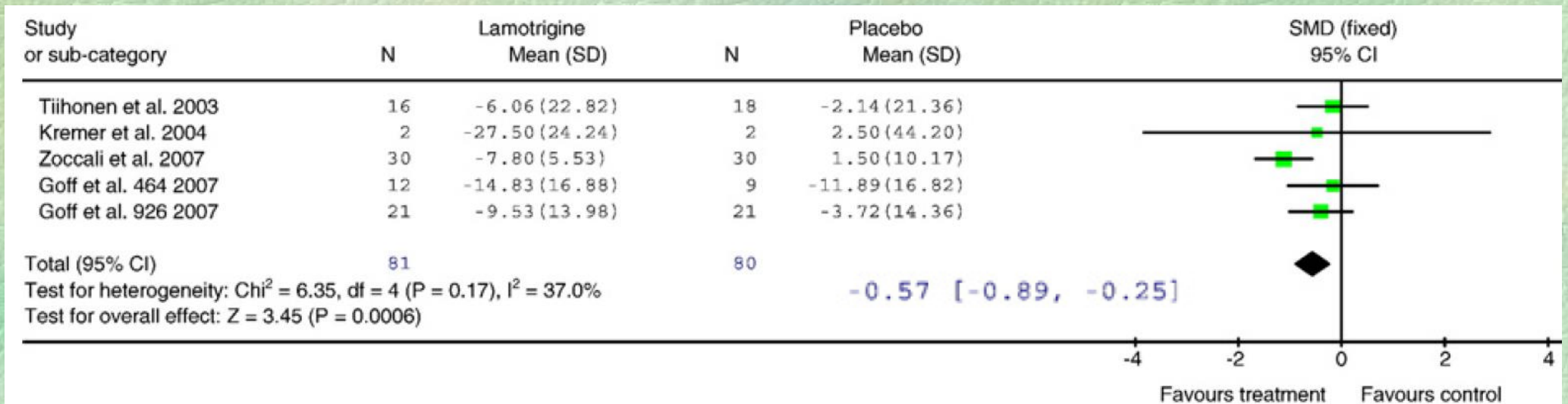
Superiority over RIS alone in the treatment of negative symptoms, general psychopathology and PANSS total scores; patients' attention improved on the Stroop color-naming subtest (time and error); Same proportion discontinued the study early on LAM than on placebo

Improvement on negative, positive and general psychopathological symptomatology; Higher proportion discontinued the study early on placebo than on LAM (NNT 30, not statistically significant)

SANS total score and CGI improved more with placebo than lamotrigine; Higher proportion discontinued the study early on LAM than on placebo (NNT 25, not statistically significant)

Cognitive composite score improved more with lamotrigine than with placebo; Higher proportion discontinued the study early on placebo than on LAM (NNT 18, not statistically significant)

# WHAT ABOUT LAMOTRIGINE IN CLOZAPINE-RESISTANT SCHIZOPHRENIA?



# ADJUNCTIVE TOPIRAMATE AND SCHIZOPHRENIA

## RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Kim <i>et al.</i> (2006)	TOP 100 mg/day vs nothing added to OLZ (although randomized, the study was not double-blind)	60	84	Outpatients with schizophrenia
Ko <i>et al.</i> (2005)	TOP 100 mg/day vs TOP 200 mg/day vs placebo added to AP	66	84	Inpatients with schizophrenia and overweight
Tiihonen <i>et al.</i> (2005)	TOP 300 mg/day vs placebo added to AP (crossover)	26	84	Male inpatients with treatment-resistant chronic schizophrenia (on CLO, OLZ or QUE)
Afshar <i>et al.</i> (2008)	TOP up to 300 mg/day vs placebo added to CLO	32	56	Patients with schizophrenia between 18 and 45 years of age who had poor clinical outcome in spite of long-term treatment with several types of AP medications and who were under treatment with clozapine at a maximum tolerable dose of $\geq 100$ mg/day for the previous 2 months; inpatient or outpatient status not described

**TOP was associated with less weight gain at weeks 4, 8 and endpoint; Improvement on the PANSS total were observed in both groups and not significantly different; Higher proportion discontinued the study early on placebo than on TOP (NNT 15, not statistically significant)**

**With TOP 200 mg, body weight, body mass index, waist measurement, and hip measurement decreased significantly compared with TOP 100 and placebo groups; Waist-to-hip ratio did not change in any group; BPRS decreased by 0.4%, 3.2%, and 2.9% in the placebo, TOP 100 mg, and TOP 200 mg groups, respectively**

**Improvement in PANSS general; No difference in total PANSS, PANSS positive, or PANSS negative; Higher proportion discontinued the study early on TOP than on placebo (NNT 127, not statistically significant)**

**TOP group had a greater reduction in psychopathology as measured by the PANSS than the placebo group; Similar significant decline patterns were found in the PANSS positive, negative, and general psychopathology subscales; Clinical response (more than 20% reduction in PANSS) was significantly higher in topiramate-treated subjects than controls (50% vs 12.5%, NNT 3, 95% CI: 2 to 13)**



# **VALPROATE AND THE EXPERT CONSENSUS GUIDELINE SERIES: Treatment of Schizophrenia 1999**

- **Adding valproate was ranked first for the problem of aggression/violence**
- **Adding valproate was ranked first for the problem of agitation/excitement and history of substance abuse**
- **Adding valproate was ranked second for agitation/excitement with no history of substance abuse (adding a benzodiazepine was first)**

*Not based on research evidence per se. Represent the clinical experience of 57 experts on the medication treatment of schizophrenia*

# ADJUNCTIVE VALPROATE AND SCHIZOPHRENIA

## RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Hesslinger <i>et al.</i> (1999)	CBZ (mean 567 mg/day) vs VAL (mean 757 mg/day) vs nothing added to HAL (although randomized, the study was not double-blind)	27	28	Inpatients with schizophrenia or schizoaffective disorder
Ko <i>et al.</i> (1985)	VAL 1600–2400 mg/day vs placebo added to AP (crossover)	6	28	Inpatients with neuroleptic-resistant chronic schizophrenia (not exacerbation)
Fisk and York (1987)	VAL 1200 or 1500 mg/day vs placebo added to AP	62	42	Inpatients with chronic psychosis and tardive dyskinesia
Dose <i>et al.</i> (1998)	VAL 900–1200 mg/day vs placebo added to HAL	42	28	Inpatients with acute, non-manic schizophrenic or schizoaffective psychosis
Wassef <i>et al.</i> (2000)	VAL (plasma level 75–100 µg/ml) vs placebo added to HAL	12	21	Inpatients with acute exacerbation of chronic schizophrenia
Casey <i>et al.</i> (2003)	VAL (mean 2300 mg/day) vs placebo added to OLZ or RIS	249	28	Inpatients with acute schizophrenia
Abbott Laboratories (2006)	VAL (extended-release, mean 2900 mg/day) vs placebo added to OLZ or RIS (data from web disclosure)	402	84	Inpatients with acute schizophrenia
Citrome <i>et al.</i> (2007)	VAL (plasma level 50–100 µg/ml) vs nothing added to RIS (although randomized, the study was not double-blind)	33	56	Inpatients with schizophrenia and hostile behavior

**VAL had no significant effect on either plasma levels of HAL or on psychopathology; Same proportion discontinued the study early on VAL than on placebo**

**No VAL effect noted**

**No differences in mental state and behavior; Higher proportion discontinued the study early on VAL than on placebo (NNT 22, not statistically significant)**

**No difference on BPRS; Possible effect on “hostile belligerence”; Higher proportion discontinued the study early on placebo than on VAL (NNT 55, not statistically significant)**

**Significant Improvement in CGI and SANS, but not BPRS**

**Improvement on PANSS; Higher proportion discontinued the study early on placebo than on VAL (NNT 10, not statistically significant)**

**No advantage for combination treatment with adjunctive VAL; Higher proportion discontinued the study early on placebo than on VAL (NNT 62, not statistically significant)**

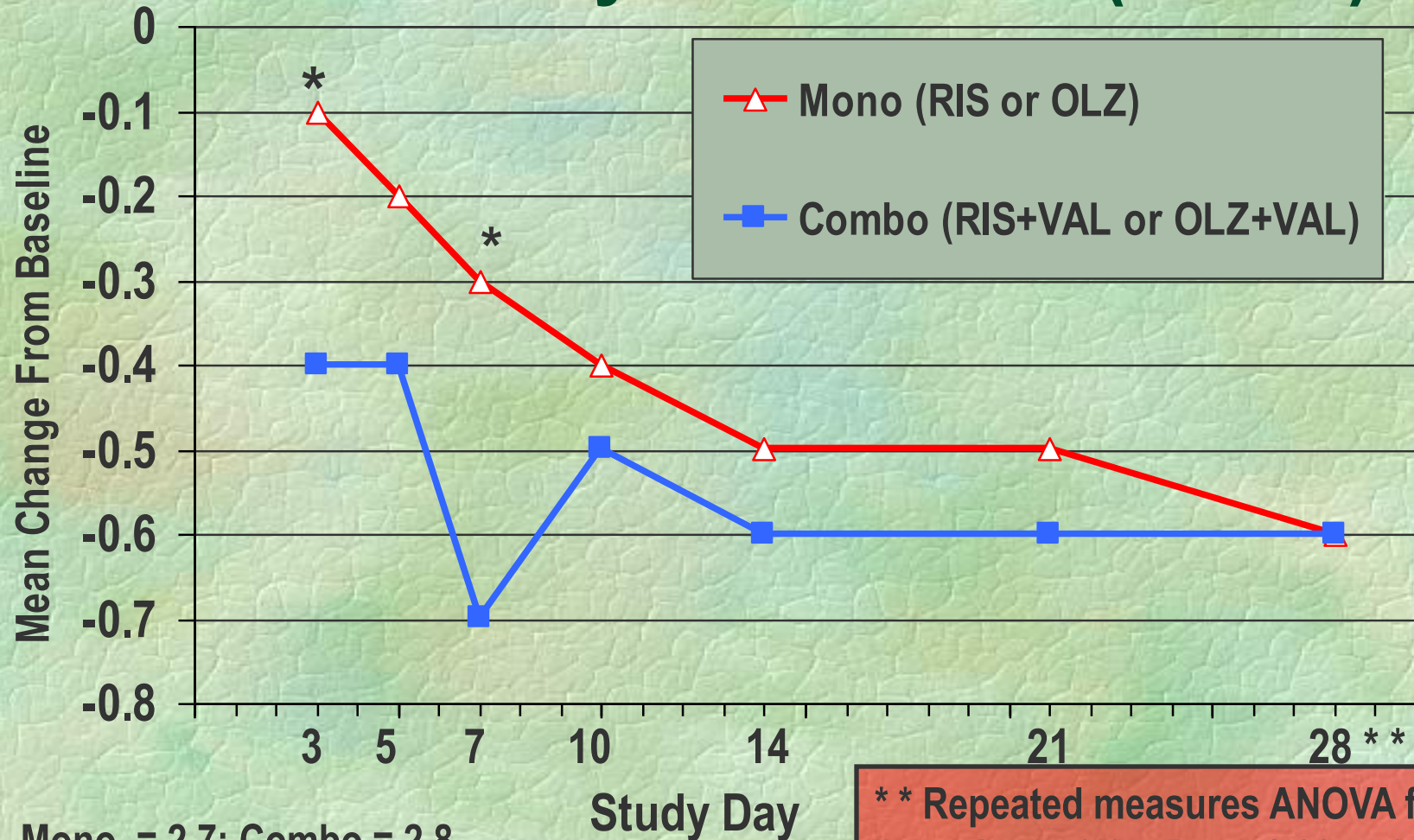
**Although significantly fewer patients randomized to monotherapy completed the study (NNT 4, 95% CI: 2 to 88), no significant differences between monotherapy or combination treatment were observed in change of the rating instruments used, including the PANSS**

# VALPROATE: AN ANTIAGGRESSIVE AGENT?

## Eighteen Reports - 184 Patients

- **Overall response rate of 77.1% (response defined as a 50% reduction of target behavior)**
  - Diagnoses: a broad spectrum of disorders
  - Only 16 with schizophrenia
  - Mostly case reports or retrospective chart reviews
- **2 double-blind studies (16 patients with borderline personality disorder; 20 children and adolescents with explosive temper and mood lability)**
- **Need to disentangle studies of valproate for aggression and those for schizophrenia**
  - Data remains limited, but promising

# SELECTIVE EFFECT ON HOSTILITY? PANSS Hostility Item Score (LOCF)



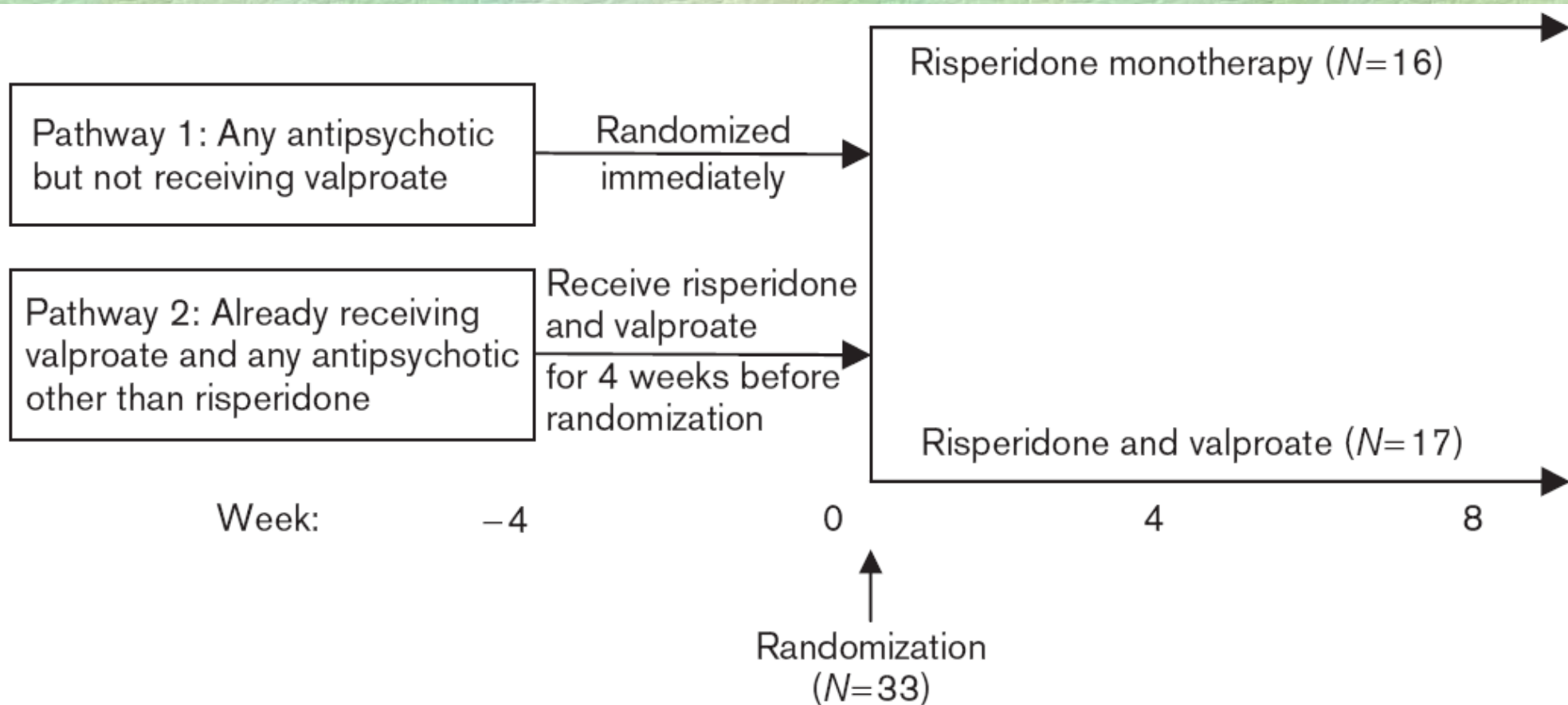
\*p<0.05

Baseline: Mono = 2.7; Combo = 2.8

\*\* Repeated measures ANOVA for Days 1-7 p<0.05; Days 1-28 p=0.078

# RIS ALONE vs RIS + VAL

## Randomized Clinical Trial: Open Label; Blinded Raters



# RIS ALONE vs RIS + VAL

- No between-group differences were observed in change of the Buss-Durkee Hostility Inventory, Barratt Impulsiveness Scale, PANSS total scores, or the hostility item of the PANSS
- For the Overt Aggression Scale, there were no significant effects of either time or study medication or time x study medication in the analysis of data from completers or in the analysis of data from all randomized subjects
- Significantly fewer subjects randomized to risperidone alone completed the study (chi-sq=8.62, df=1, p=.003)

# ADJUNCTIVE LITHIUM IN SCHIZOPHRENIA, I

## RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Gerlach <i>et al.</i> (1975)	Li (target level 0.8–1.2 mEq/l) vs placebo added to AP (at least two subjects were drug-free) (crossover)	20	21	Inpatients with neuroleptic-induced tardive dyskinesia (not all with schizophrenia), psychiatrically stable no changes in medication for at least 2 months
Small <i>et al.</i> (1975)	Li (target level 0.6–1.0 mEq/l) vs placebo added to AP (crossover)	22	4	Chronically ill inpatients with schizophrenia or schizoaffective disorder who had failed to respond satisfactorily to any previous treatment
Carman <i>et al.</i> (1981)	Li (target level 0.75–1.3 mEq/l) vs placebo added to AP (crossover)	18	4	Inpatients with schizophrenia or schizoaffective disorder
Wilson (1993)	Li (mean level 0.98 mEq/l) vs placebo added to HAL	21	56	Inpatients with schizophrenia who did not have concurrent affective disorders and who had not responded to previous trials of conventional AP medication
Collins <i>et al.</i> (1991)	Li (mean level 0.7 mmol/l) vs nothing added to AP (although randomized, the study was not double-blind)	44	28	Detained patients in an English special (maximum security) hospital with schizophrenia and persistence of psychotic symptoms despite adequate neuroleptic treatment

Li appeared to have a suppressive effect on psychomotor agitation and aggression

Both blind psychiatric and nursing data and nonblind clinical judgments or outcome showed that there was significant improvement with adjunctive Li, particularly in psychiatric global assessments of severity of illness and BPRS ratings of mannerisms and posturing, cooperation, and excitement

The Inpatient Behavioral Rating Scale was conducted by research nurses and with adjunctive Li, 10 patients exhibited less 'arousal,' while 2 showed increases in those symptoms; Psychosis score decreased in 5 patients and increased in 1; Depression score demonstrated improvement in 5 and worsened in 5

Improvement in symptoms correlated with the non-blind adjustment of antipsychotic dose but not with lithium or placebo treatment; Higher proportion discontinued the study early on Li than on placebo (NNT 6, not statistically significant)

Li did not result in symptomatic improvement; Higher proportion discontinued the study early on Li than on placebo (NNT 3, 95% CI: 2 to 4)

# ADJUNCTIVE LITHIUM IN SCHIZOPHRENIA, II

## RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Schulz <i>et al.</i> (1999)	Li (target level 0.8–1.0 mEq/l) vs placebo added to fluphenazine decanoate	41	56	Outpatients with schizophrenia or schizoaffective disorder who failed to be stabilized symptomatically after at least 6 months of treatment with fluphenazine decanoate
Johnstone <i>et al.</i> (1988)	Li (target level 0.5–1.2 mmol/l) vs pimozide vs Li and pimozide	120	28	Inpatients with a first psychotic episode and those with previous episodes were included, but the study was confined to those who had required admission because of psychotic symptoms not more than 2 weeks before assessment for the study
Terao <i>et al.</i> (1995)	Li (mean level at end of 8 weeks 0.52 mEq/l) vs placebo added to AP (crossover)	21	8	Male inpatients with schizophrenia and persistent mental symptoms despite long-term neuroleptic treatment
Hogarty <i>et al.</i> (1995)	Li (mean level 0.474 mmol/l in first 6 weeks, 0.586 mmol/l in the second 6 weeks) vs placebo added to low dose fluphenazine decanoate	29	84	Outpatients with schizophrenia or schizoaffective disorder and persistent anxiety for at least 3 months prior to the study; positive symptoms of schizophrenia either absent or, if present, did not interfere with adjustment
Huang and Bowden (1984)	Li (target level 0.6–1.2 mEq/l) vs placebo added to HAL or other AP	10	28	Inpatients with chronic schizophrenia

**Both groups showed significant improvement in psychopathology as measured by the BPRS, but there were no significant differences in response between Li vs placebo groups; Moreover patients originally treated with adjunctive placebo did not have significantly greater improvement when receiving open-label adjunctive Li; Higher proportion discontinued the study early on Li than on placebo (NNT 9, not statistically significant)**

**Li had no significant effect upon positive, negative or depressive symptoms, but had a significant effect in reducing elevation of mood; There was no evidence of an interaction between Li and pimozide, nor of any additional benefit by combining these drugs; In 30 patients who had achieved recovery and followed for relapse over a period of up to 6 years double-blind, pimozide was significantly more effective than placebo and no significant effect for Li was found**

**Adjunctive Li improved anxiety-depression but did not improve anergia, thought disturbance, activation, or hostile-suspiciousness as measured by BPRS or negative symptoms measured by SANS**

**Lithium positively affected multiple indexes of anxiety and anxious depression at 12 weeks but not at 6**

**No efficacy or effectiveness outcomes reported**



# **BETA-ADRENERGIC BLOCKERS**

**What is the evidence?**

**Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia.  
Part II: Long-Term Pharmacotherapeutic Strategies. Essential Psychopharmacology 5(1):17-30, 2002.**

# BETA BLOCKERS

## Typical Diagnoses of the Aggressive Patients Treated

- **Head injury**
- **Seizure disorder**
- **Mental retardation**
- **Dementia**
- **Conduct disorder**
- **Attention deficit disorder**
- **Schizophrenia**

# BETA BLOCKERS AND AGGRESSION

- **Propranolol treatment of aggression in patients with Organic Brain Disease – at least 14 reports for a total of 97 subjects, with 85 improved (88%), dose range 40 to 1600 mg/day**
- **Pindolol in “organic” patients (1 study) and nadolol in schizophrenia (2 studies) - all three studies done under double-blind, placebo-controlled, conditions; Nadolol used as adjunctive treatment**
- **Side effects – hypotension, bradycardia, respiratory difficulty, nightmares, ataxia, lethargy, ?depression**

# **BETA BLOCKERS AND AGGRESSION**

## **Summary**

- **The antiaggressive effects are suggested by many case reports and are confirmed by three controlled studies**
- **The effects are reported for a broad spectrum of psychiatric disorders**
- **The onset of the antiaggressive effect may be delayed (4 to 6 weeks)**
- **Dose-limiting adverse effects include hypotension and bradycardia**
- **The mechanism of the antiaggressive effect is not well understood**

# SSRIs



**What is the evidence?**

**Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia. Part II: Long-Term Pharmacotherapeutic Strategies. Essential Psychopharmacology 5(1):17-30, 2002.**

# ANTIDEPRESSANTS: SSRIs

- **Fluoxetine:** Open trials suggested antiaggressive effects in personality disorders (Coccaro et al, 1990) and in schizophrenia (Goldman and Janecek, 1990)
- **Citalopram:** A double-blind, crossover study demonstrated antiaggressive effects of adjunctive citalopram in chronic schizophrenia (Vartiainen et al, 1995)

# **BENZODIAZEPINES**

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**What is the evidence?**

**Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia.  
Part II: Long-Term Pharmacotherapeutic Strategies. Essential Psychopharmacology 5(1):17-30, 2002.**

# BENZODIAZEPINES: POOR CHOICE

- Clonazepam - Negative evidence!
  - Double-blind placebo-controlled trial in schizophrenic patients receiving antipsychotics (Karson et al. 1982)
  - No additional therapeutic benefit was observed
  - Violent behavior observed during the course of clonazepam treatment
- Although the consensus guidelines recommend continued use of lorazepam for patients with schizophrenia with agitation or excitement (but with no history of substance abuse) (McEvoy et al. 1999), such use can be problematic because of physiological tolerance
  - Missing scheduled doses of lorazepam may result in withdrawal symptoms that can lead to agitation or excitement, as well as irritability and a greater risk for aggressive behavior



# LONG-TERM MANAGEMENT: SUMMARY

- Treat underlying disorder
- Clozapine more effective than first-generation antipsychotics in reducing aggressivity in schizophrenia, and superior to risperidone and olanzapine
- Adjunctive valproate commonly utilized but more work is needed; some evidence exists for carbamazepine and lamotrigine; lithium in schizophrenia and aggression has not been adequately studied
  - In contrast, all four have been well studied in bipolar disorder
- Beta-blockers, well studied in brain injured patients, may be helpful as an adjunctive agent for aggression and schizophrenia

# MANAGEMENT OF AGITATION: OVERVIEW

## Agitated Patient

Adapted from Citrome L, Volavka J. Treatment of Violent Behavior. In Tasman A, Lieberman J, Kay J (Eds): Psychiatry, 2<sup>nd</sup> Edition, John Wiley & Sons, Ltd, 2003.

Simultaneous

### Environmental and Behavioral Interventions:

- Decrease stimulation (e.g. turn off TV, radio, remove other patients from the general area)
- Allow patient to verbalize thought, feelings, and concerns
- Do not shout, yell, or threaten

### Medication Interventions – offer early:

- Assess medical condition
- Assess possibility of substance intoxication
- Assess possibility of akathisia

Remains agitated and a danger to self or others

Withdrawal from alcohol or sedatives?

NO

YES

NO

YES

Seclusion and/or restraint

1st choice: Second-Generation Antipsychotic PO/IM  
2nd Choice: Haloperidol ± Lorazepam PO/IM

Lorazepam PO/IM

Persistent Aggressive Behavior: Rx Second-Generation Antipsychotics ± Mood Stabilizers ± Beta Blockers

# POST-TEST QUESTIONS

1. Akathisia is a common side effect of which of the following medications?
- A. Lorazepam
  - B. Haloperidol
  - C. Olanzapine
  - D. Ziprasidone
  - E. B & D
  - F. B, C, & D

**ANSWER: B**

# POST-TEST QUESTIONS

**2. Acute agitation secondary to withdrawal from alcohol in a patient with schizophrenia is best treated with?**

- A. Lorazepam**
- B. Haloperidol**
- C. Olanzapine**
- D. Ziprasidone**

**ANSWER: A**

# POST-TEST QUESTIONS

**3. Atypical antipsychotics are superior to the older neuroleptics because**

- A. They are more sedating**
- B. They cause less weight gain**
- C. They cause less extrapyramidal side effects**
- D. They have no effect on the QTc interval**
- E. A & C**

**ANSWER: C**

# POST-TEST QUESTIONS

4. Which of the following has the most evidence supporting its use among patients with schizophrenia and aggressive behavior
- A. Adjunctive valproate
  - B. Adjunctive beta-blockers
  - C. Clozapine
  - D. Olanzapine
  - E. Lorazepam

**ANSWER: C**

# POST-TEST QUESTIONS

5. Which of the following are approved by the FDA for persistent aggressive behavior?

- A. Lorazepam
- B. Ziprasidone
- C. Olanzapine
- D. Clozapine
- E. B & C
- F. A, B, & C
- G. D
- H. None of the above

**ANSWER: H**