

ASCP Model Psychopharmacology Curriculum

The Psychopharmacology of Violence

with emphasis on schizophrenia

Leslie Citrome, MD, MPH

Nathan S Kline Institute for Psychiatric Research

Revision 022006

OBJECTIVES

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**
3. **Etiology and Assessment**
4. **Management of Acute Agitation**
5. **Management of Persistent Aggressive Behavior**

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.

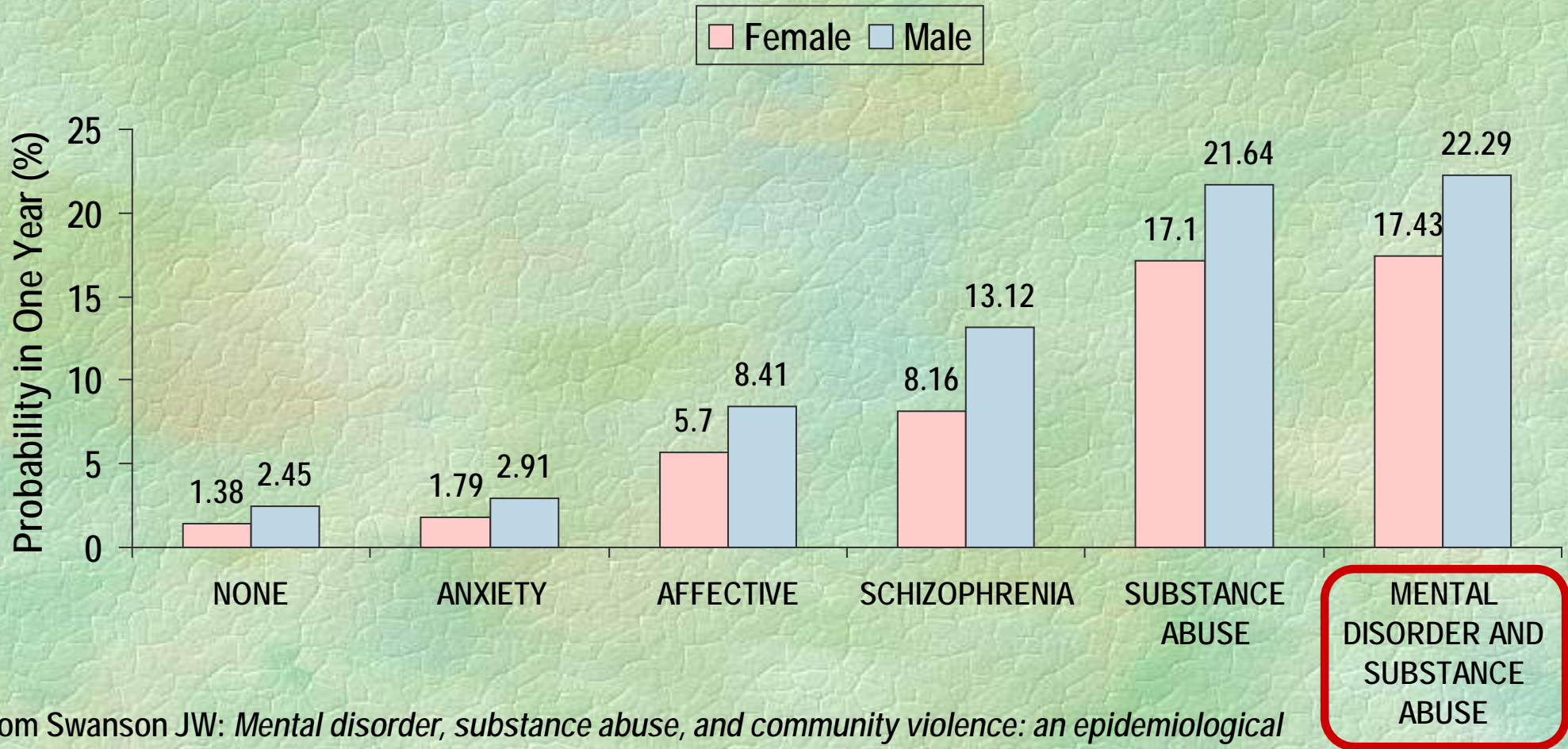
OUTLINE

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

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

OUTLINE

1. Definitions
2. Epidemiology
3. **Etiology and Assessment**
4. Management of Acute Agitation
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

OUTLINE

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

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

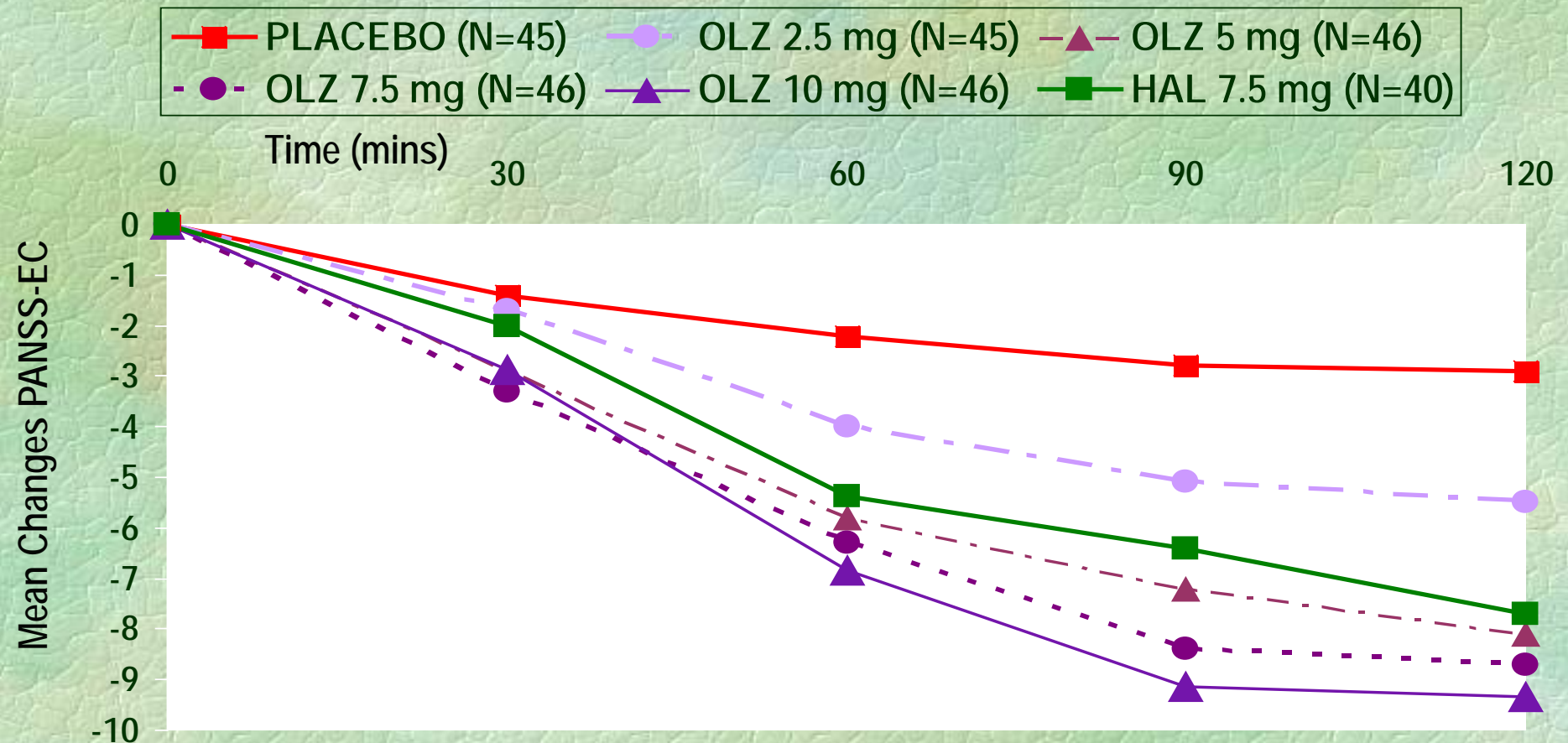
- Liquid concentrate
 - Liquid risperidone
 - Liquid aripiprazole
- Orally disintegrating tablets
 - Zydis olanzapine
 - M-tab risperidone
- IM Formulations
 - Olanzapine IM (short-acting)
 - Ziprasidone IM (short-acting)
 - Aripiprazole IM (short-acting) – in development
 - Risperidone IM (long-acting 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)



Breier A et al., Arch Gen Psychiatry, 2002;59:441-448.

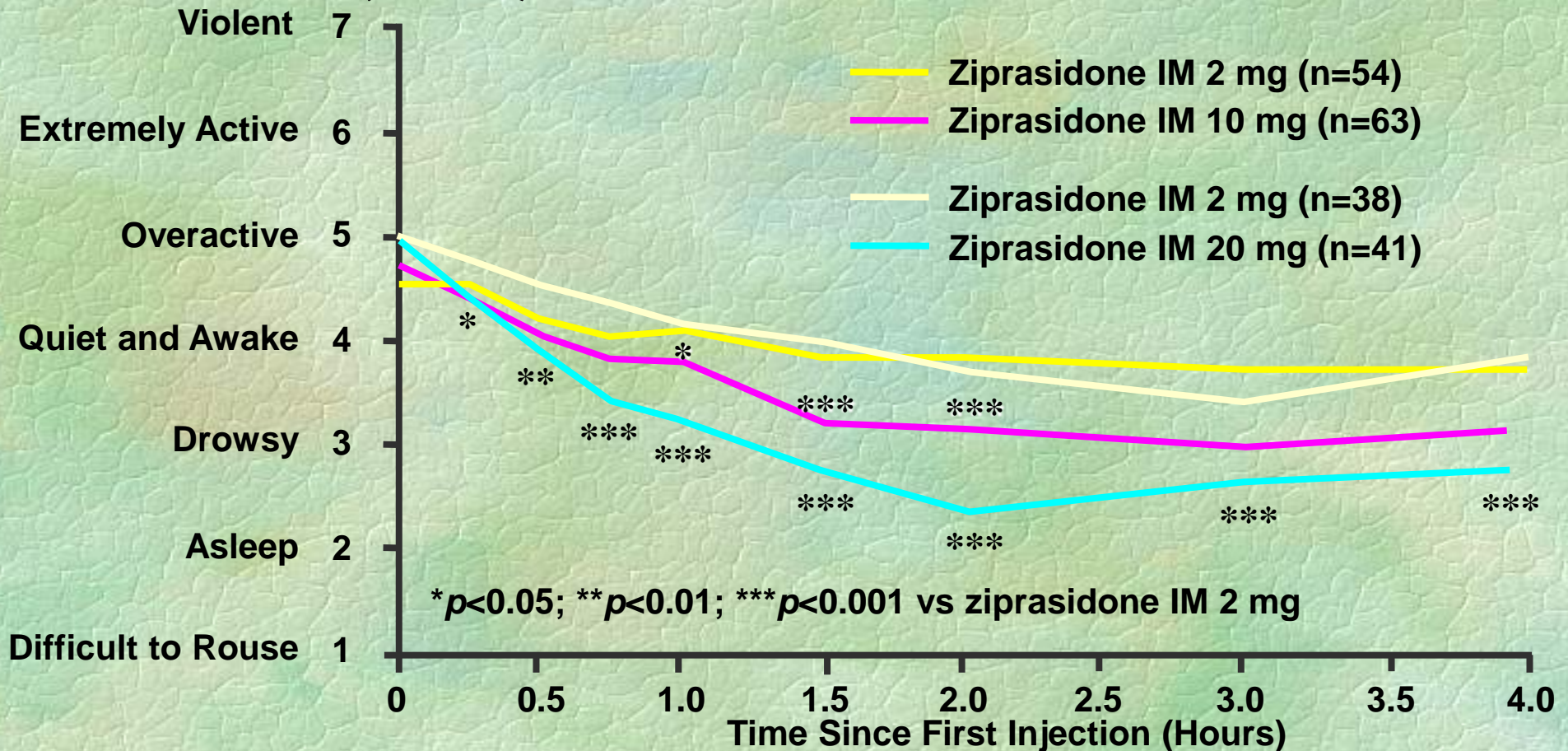
* $p < 0.05$ all active doses vs. placebo
except OLZ 2.5 and HAL at 30 minutes

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: 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.

COST¹

Lorazepam 2 mg IM	Haloperidol 5 mg IM	Ziprasidone 20 mg IM	Olanzapine 10 mg IM
\$1.02	\$1.72	\$9.58 ²	\$17.16
Number of injections required (clinical trial data)		1 (42%) or 2 (37%) ³	1 (76%) ⁴
Avoidance of acute dystonia and akathisia		Priceless	

1. Cost to Rockland Psychiatric Center pharmacy January 12, 2006
2. Cost prior to 2006 was \$37.43
3. Daniel DG et al, Psychopharmacology (Berl) 155:128-134, 2001
4. Breier A et al, Arch Gen Psychiatry 59:441-448, 2002

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

OUTLINE

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

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

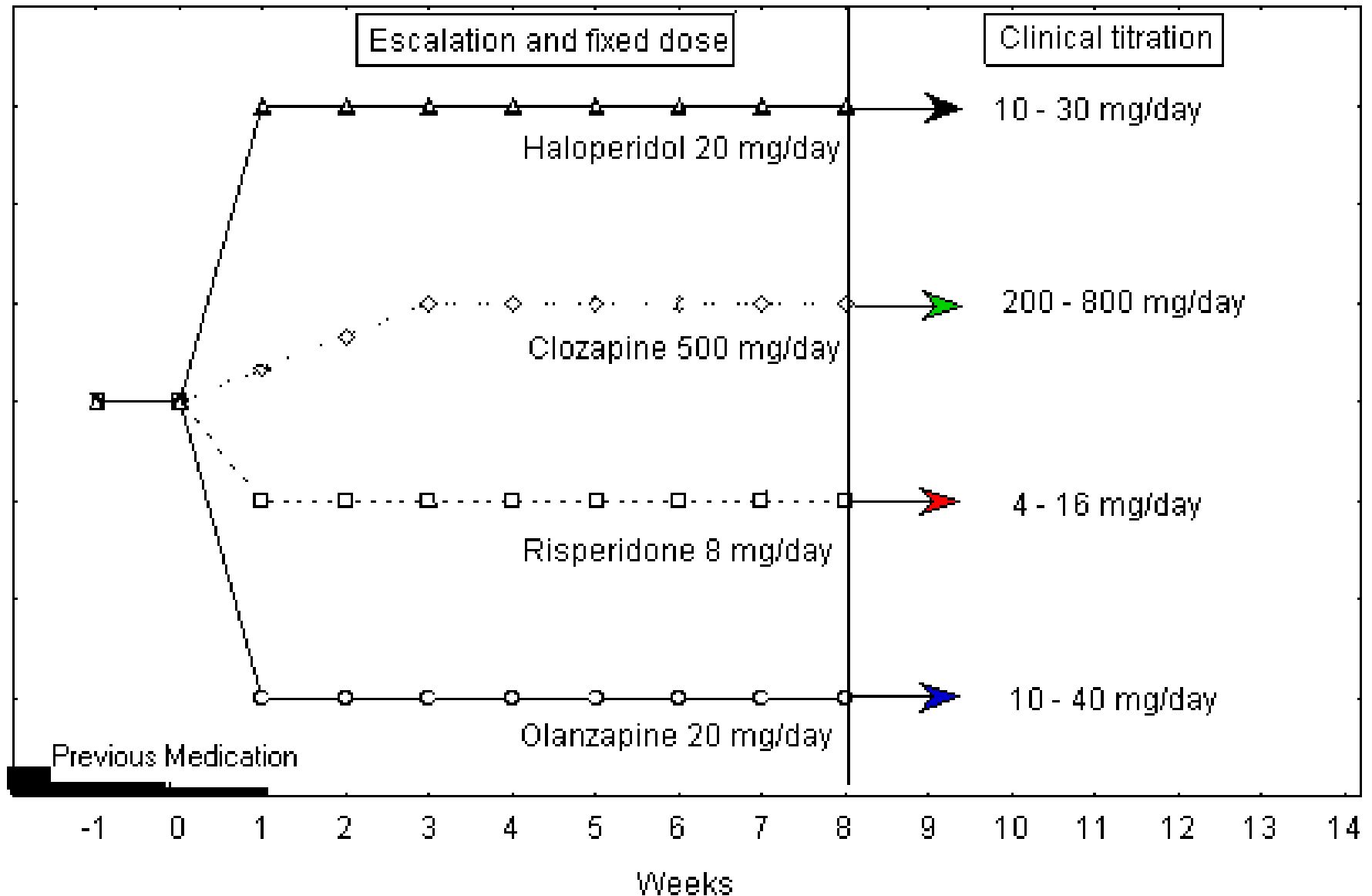
SECOND-GENERATION ANTIPSYCHOTICS (Cont'd)

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

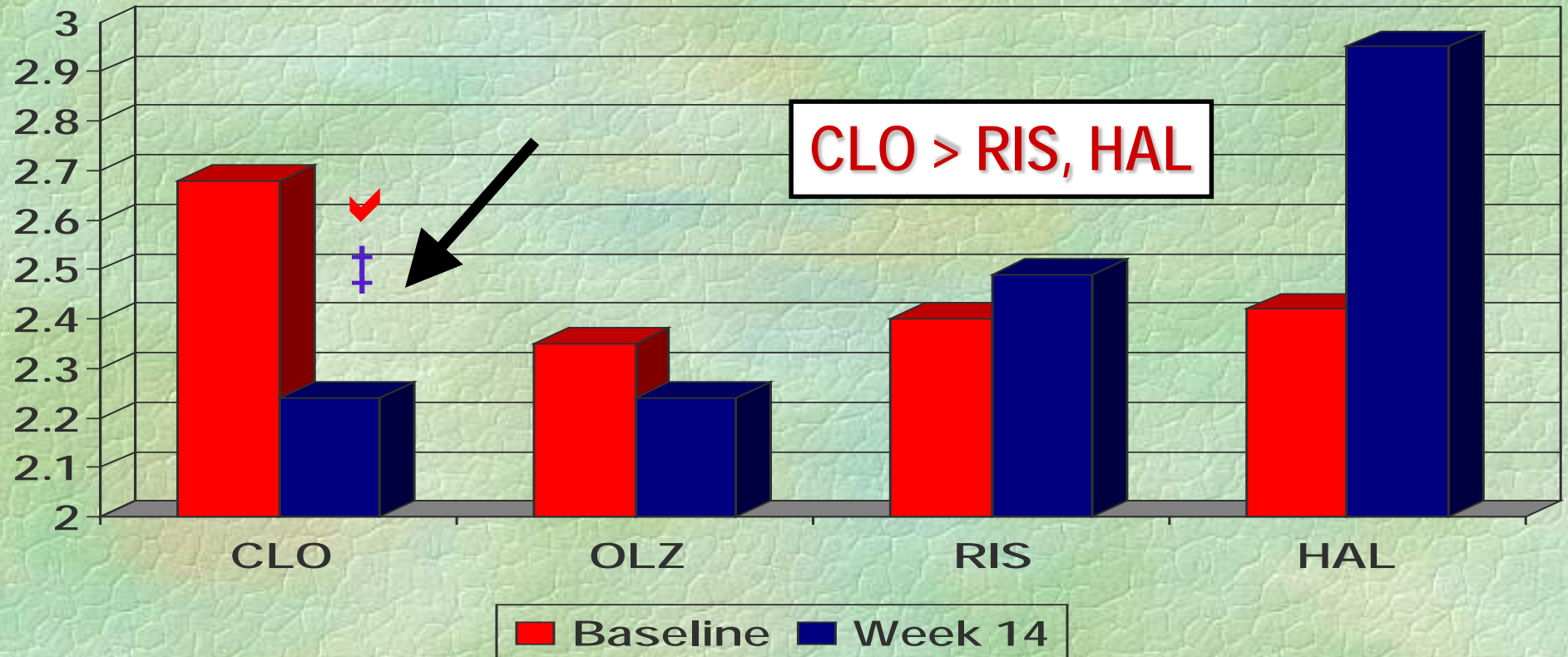
- Primary measure of efficacy: PANSS hostility item
 - Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse and assaultiveness
 - Ratings range from 1 (hostility absent) to 7 (extreme hostility that includes marked anger resulting in extreme 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, Sheitman B, Lindenmayer JP, McEvoy J, Cooper TB, Chakos M, Lieberman J: 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 (-)

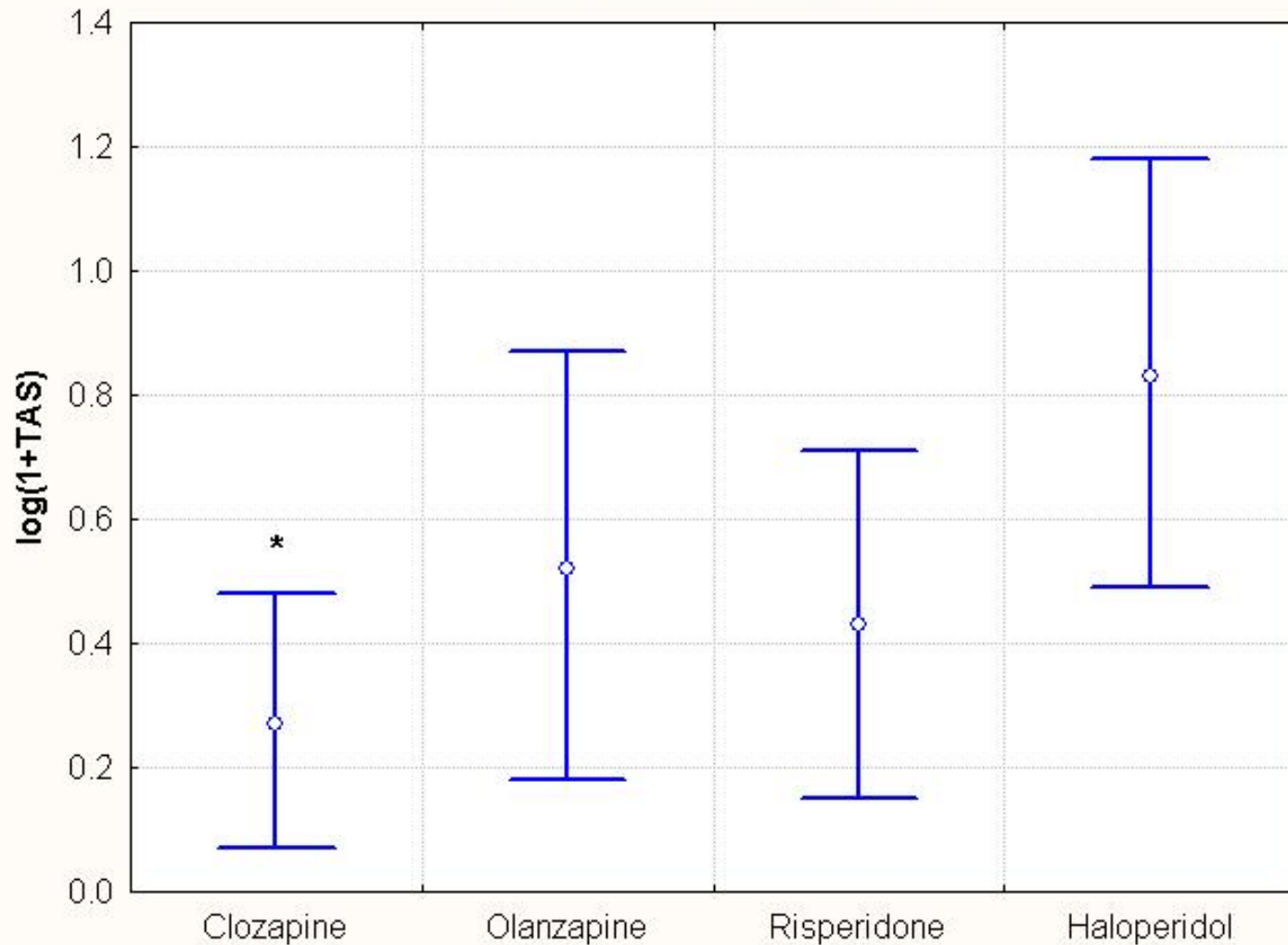
OVERT AGGRESSION SCALE

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 ± 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

Table 1. Baseline Characteristics of Patients Assigned to Receive Clozapine, Olanzapine and Haloperidol¹.

Characteristics	Clozapine (N=37)		Olanzapine (N=37)		Haloperidol (N=36)		χ^2	p
	Demographic							
Male, No. (%)	31	(83.8)	29	(78.4)	30	(83.3)	0.5	0.80
Race/ethnicity, No. (%)								
White	7	(18.9)	5	(13.5)	7	(19.4)		
African American	20	(54.1)	28	(75.7)	21	(58.3)	7.6	0.47
Hispanic	8	(21.6)	4	(10.8)	8	(22.2)		
Other	2	(5.4)	0	(0.0)	0	(0.0)		
Diagnosis, No (%)								
Schizophrenia	27	(73.0)	23	(62.2)	21	(58.3)	1.9	0.40
Schizoaffective Disorder	10	(27.0)	14	(37.8)	15	(41.7)		
							F	p
Mean age at randomization, y	35.1	(12.3)	35.6	(9.4)	32.7	(10.6)	0.8	0.48
Mean duration of illness, y	15.7	(9.5)	16.8	(11.2)	13.9	(11.2)	0.6	0.56
Mean number of prior psychiatric hospitalizations	12.3	(9.8)	8.9	(4.7)	11.4	(9.6)	1.8	0.18
Positive and Negative Syndrome Scale Scores								
Positive subscale	23.0	(5.4)	23.0	(5.7)	23.0	(6.4)	0.0	0.99
Negative subscale	20.3	(4.5)	19.0	(3.4)	19.8	(4.7)	1.1	0.34
General subscale	43.2	(7.2)	41.9	(7.4)	42.6	(6.6)	0.3	0.73
Total	86.4	(14.4)	83.7	(14.1)	85.5	(13.2)	0.4	0.70

Table 2. Differences in the Various Forms of Overt Aggression Among Patients Treated with Clozapine, Olanzapine and Haloperidol¹.

MOAS	Comparison	Analysis			
		OR (95% CI) for <u>less</u> severe violence ²	χ^2	p	
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	NS	
	Olanzapine vs. haloperidol	1.67 (1.3-2.2)	16.4	<.001*	
Verbal Aggression	Clozapine vs. haloperidol	1.35 (1.2-1.5)	21.7	<.001*	
	Clozapine vs. olanzapine	1.32 (1.1-1.5)	17.6	<.001*	
	Olanzapine vs. haloperidol	1.03 (0.9-1.2)	0.3	NS	

Table 3. Change in the Positive and Negative Syndrome Scale (PANSS) Total Score and in the Three PANSS Subscale Scores (With Baseline Values as Covariates)¹.

PANSS variable	Medication group	Analysis		
		Mean (SD)	F	p
Total Score	Clozapine	2.39 (14.2)	1.23	NS
	Olanzapine	4.83 (9.7)		
	Haloperidol.	0.58 (15.2)		
Positive symptoms.	Clozapine	1.54 (5.0)	2.30	NS
	Olanzapine	1.41 (3.6)		
	Haloperidol	-0.50 (5.3)		
Negative symptoms	Clozapine	-0.56 (4.9)	1.65	NS
	Olanzapine	0.72 (3.0)		
	Haloperidol	0.44 (4.6)		
General Psychopathology	Clozapine	1.43 (7.0)	1.21	NS
	Olanzapine	2.69 (5.5)		
	Haloperidol	0.64 (8.2)		

SPECIFIC EFFECTS OF QUE ON HOSTILITY (Funded by Astra-Zeneca)

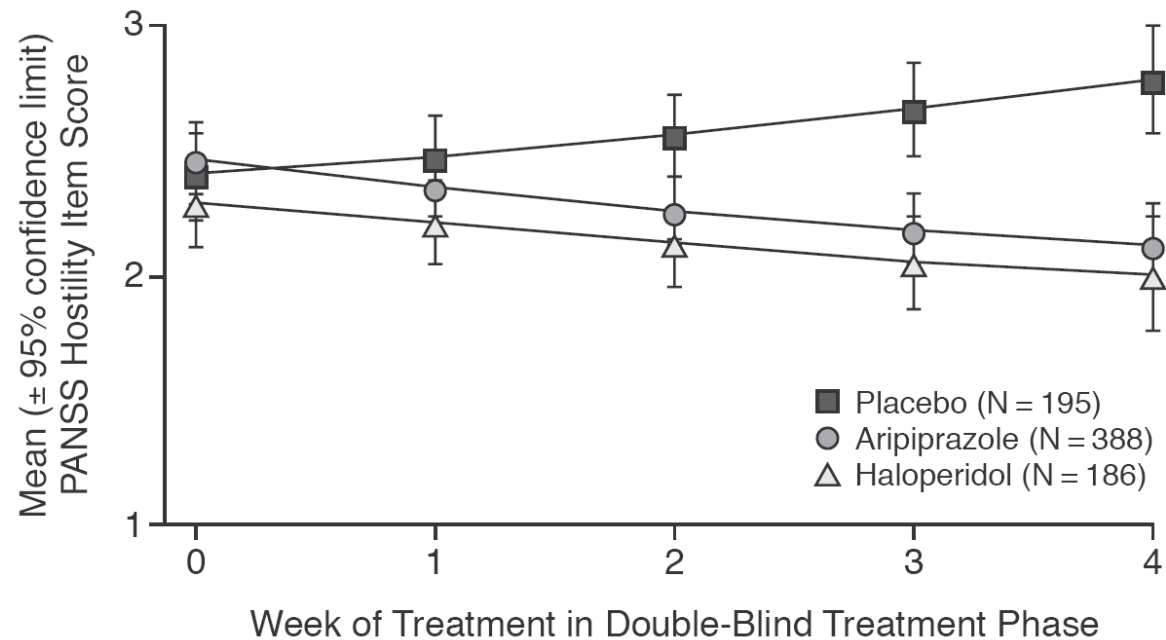
- Reanalysis of a previously reported 6-week RCT compared QUE vs HAL (N=257) on an agitation measure derived from the Brief Psychiatric Rating Scale (BPRS)
- QUE treatment reduced agitation scores significantly among patients with acute psychoses compared with placebo
- Compared with HAL, QUE treatment 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^a



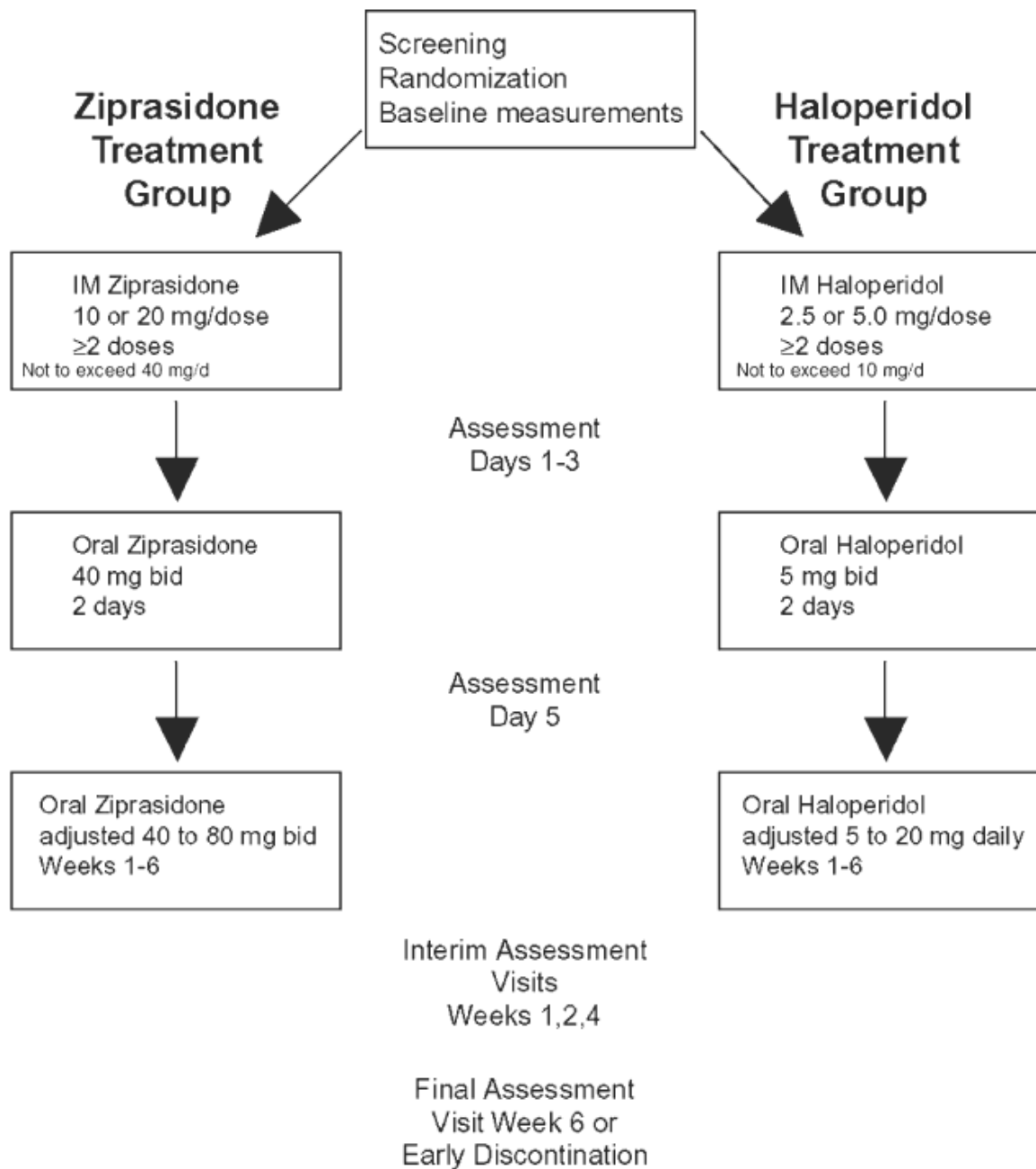
^aThe effects of aripiprazole and the active control, haloperidol, were not significantly different from each other, while both aripiprazole and haloperidol were superior to placebo. The difference between aripiprazole and placebo reached the level of statistical significance in weeks 2, 3, and 4. Haloperidol 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



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

Day	Odds Ratio ZIP improvement over baseline (time effect)	Odds Ratio HAL improvement over baseline (time effect)	Odds Ratio ZIP vs HAL (treatment and time interaction effect)	P value ZIP vs HAL
1-3 (IM Period)	2.89 (2.48-3.38)	1.85 (1.43-2.39)	1.56 (1.16-2.11)	0.0032
7	3.84 (3.12-4.72)	2.43 (1.73-3.41)	1.58 (1.06-2.35)	0.0232
14	5.64 (4.38-7.27)	3.15 (2.09-4.75)	1.79 (1.11-2.90)	0.0177
28	9.97 (7.12-13.98)	4.38 (2.53-7.60)	2.27 (1.20-4.32)	0.0119
42	20.27 (13.44- 30.59)	9.37 (4.73- 18.57)	2.16 (0.98-4.77)	0.0557

ODDS RATIOS (AND 95% CONFIDENCE INTERVALS) FOR DECREASES IN HOSTILITY AFTER ADJUSTMENT FOR COVARIATES (SPECIFIC ANTI-HOSTILITY EFFECT)

Day	Odds Ratio ZIP improvement over baseline (time effect)	Odds Ratio HAL improvement over baseline (time effect)	Odds Ratio ZIP vs HAL (treatment and time interaction effect)	P value ZIP vs HAL
1-3 (IM Period)	1.64 (1.38-1.96)	1.09 (0.81-1.47)	1.50 (1.08-2.09)	0.0149
7	1.56 (1.22-1.99)	0.98 (0.66-1.46)	1.59 (1.03-2.47)	0.0358
14	1.64 (1.21-2.21)	1.01 (0.62-1.65)	1.62 (0.95-2.76)	0.0765
28	1.57 (1.04-2.36)	0.82 (0.43-1.56)	1.91 (0.95-3.83)	0.0683
42	1.93 (1.16-3.19)	1.06 (0.49-2.26)	1.83 (0.80-4.14)	0.1496

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

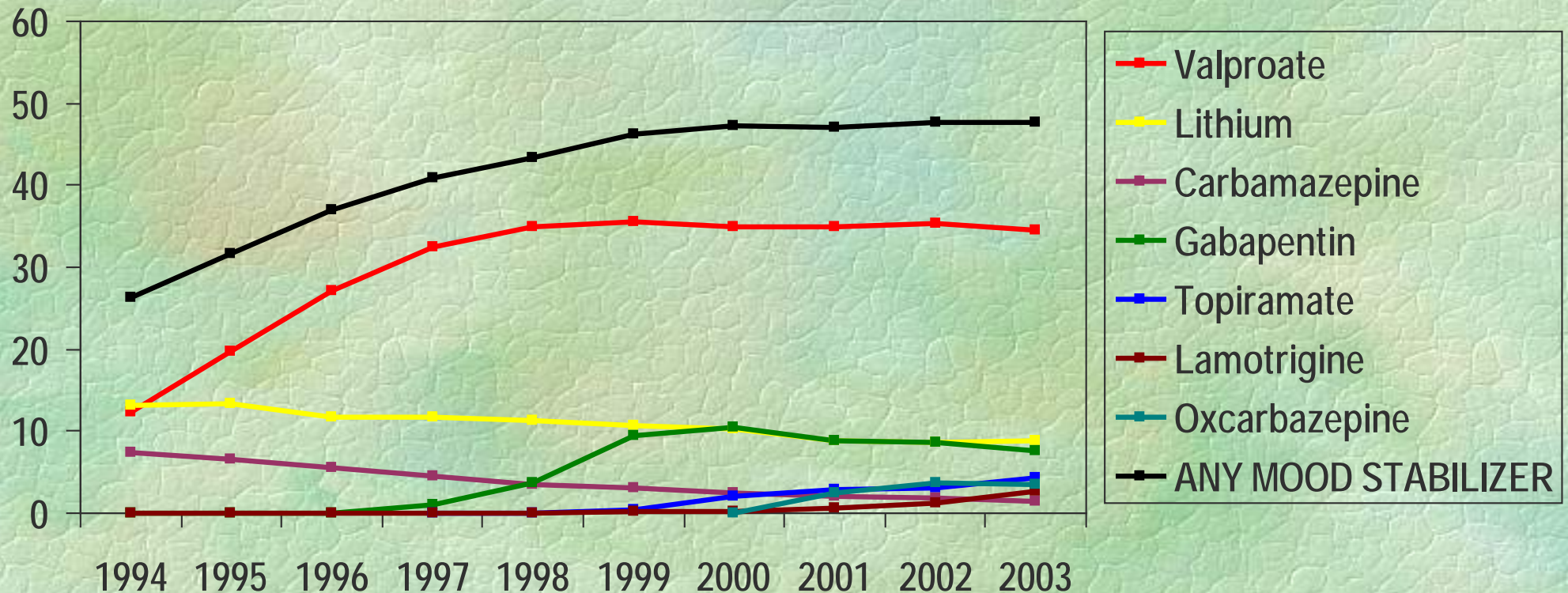
- Operational difficulties: relative rarity of aggressive events, need for large sample size, need for lengthy baseline and trial periods, problems with selection/consent bias
- Very, very, few exist

MOOD STABILIZERS

What is the evidence?

PERCENT INPATIENTS WITH SCHIZOPHRENIA RECEIVING MOOD STABILIZERS

*New York State Office of Mental Health
1994 (N=8,405) through 2003 (N=3,721)*



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

AGENT	CASE REPORTS AND OPEN STUDIES	RANDOMIZED DOUBLE-BLIND CLINICAL TRIALS	UTILITY
Lithium	✓	✓	?+
Carbamazepine	✓	✓	+/±
Valproate	✓	✓	+/±
Gabapentin	✓	0	?-
Lamotrigine	✓	✓	+/±
Topiramate	✓	0	?-
Oxcarbazepine	✓	0	?-

Adapted from Citrome L: Schizophrenia and Valproate. Psychopharmacology Bulletin 37(Suppl 2):74-88, 2003 ;
 Citrome L: What Role for Mood Stabilizers? Current Psychiatry 3(12):23-40, 2004

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)

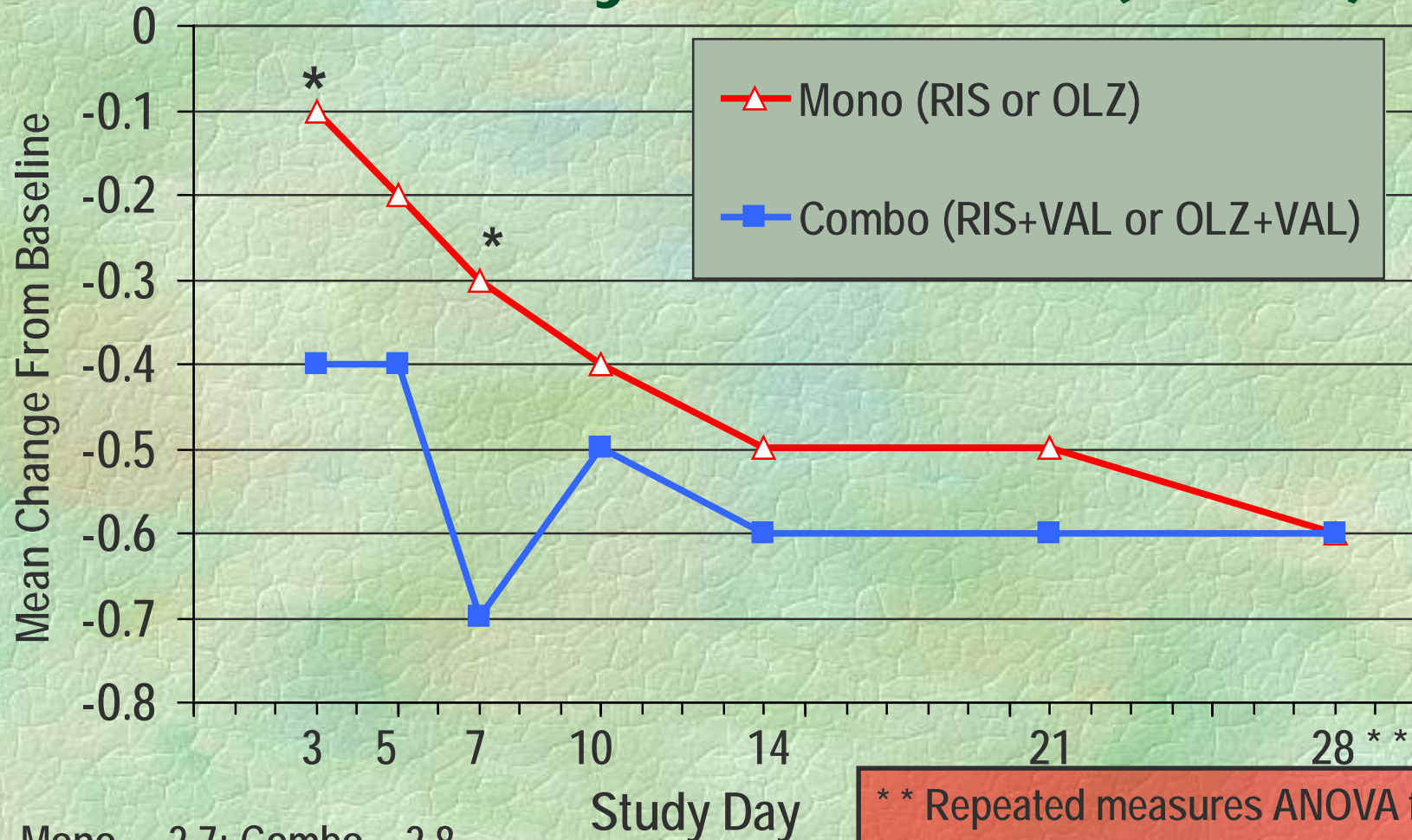
Not based on research evidence per se. Represent the clinical experience of 57 experts on the medication treatment of schizophrenia

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

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

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, 2nd 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