ASCP Model Psychopharmacology Curriculum

The Psychopharmacology of Violence

with emphasis on schizophrenia

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8th Edition

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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

Citrome L. The psychopharmacology of violence with emphasis on schizophrenia, Part 1: Acute treatment. Journal of Clinical Psychiatry 68(1):163-164, 2007.
Citrome L. The psychopharmacology of violence with emphasis on schizophrenia, Part 2: Long-term treatment. Journal of Clinical Psychiatry 68(2):331-332, 2007.

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

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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.

Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia.
Part I: Definitions, Epidemiology, Assessment, and Acute Treatment. Essential Psychopharmacology 5(1):1-16, 2002.

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EPIDEMIOLOGY: COMMUNITY

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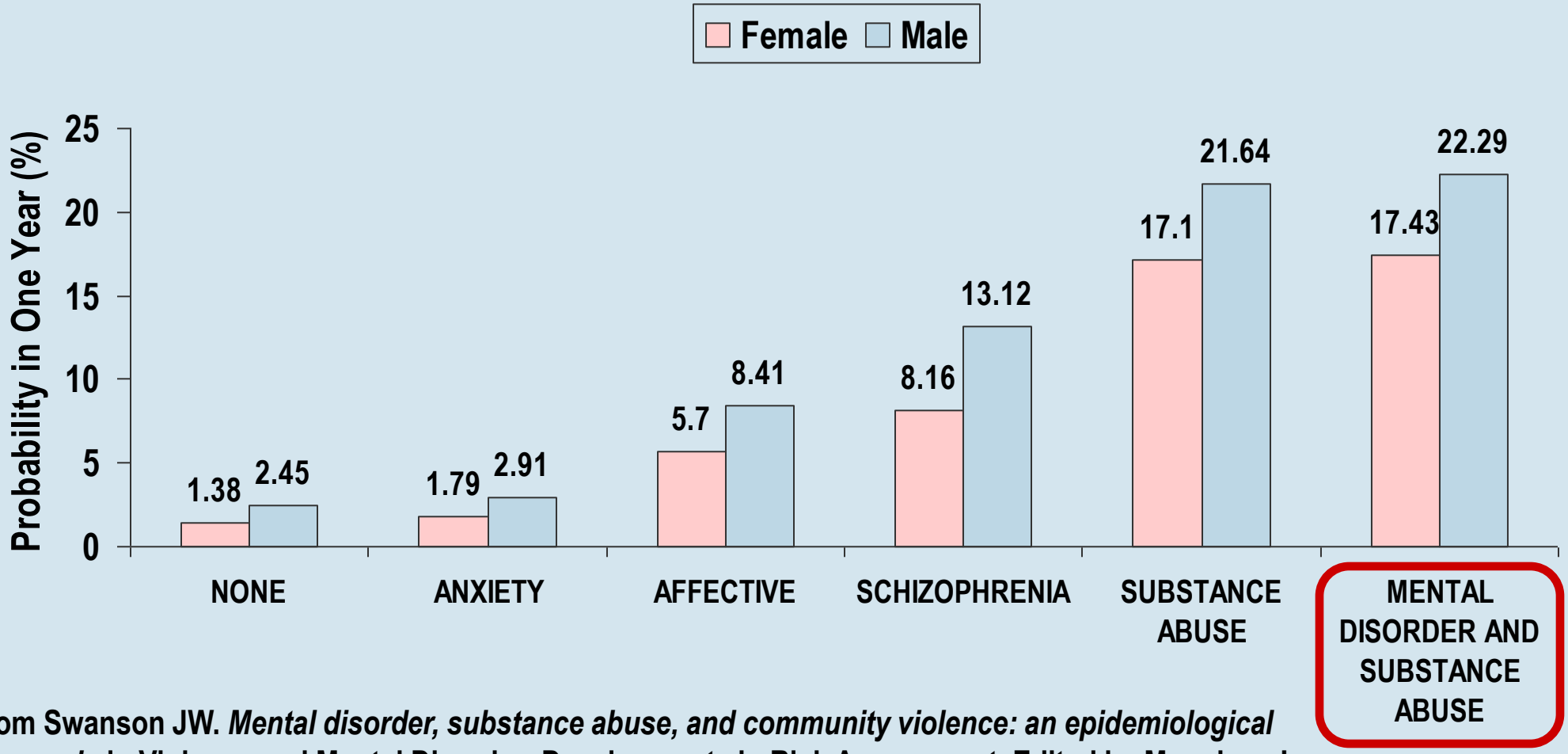
- Epidemiological Catchment Area (ECA) project
  - Structured diagnostic interviews of over 20,000 people in five areas of the United States
  - Data on violence collected in 50% (10,000 people)
  - Probability of violent behavior in patients with schizophrenia is 5 - 6 x higher than in persons without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

Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia.
Part I: Definitions, Epidemiology, Assessment, and Acute Treatment. Essential Psychopharmacology 5(1):1-16, 2002.

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)

Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia.
Part I: Definitions, Epidemiology, Assessment, and Acute Treatment. Essential Psychopharmacology 5(1):1-16, 2002.

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-5 major mental disorder
- Nonetheless, a small minority of patients with psychotic disorders are prone to aggressivity; this aggressivity may be persistent

Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia. Part I: Definitions, Epidemiology, Assessment, and Acute Treatment. Essential Psychopharmacology 5(1):1-16, 2002.

EPIDEMIOLOGY

VIOLENT CRIME ATTRIBUTABLE TO MENTAL ILLNESS

Objective: This study aimed to determine the population impact of patients with severe me[illegible]n violent crime.

Method: Swed[illegible]ossesses high-quality national regist[illegible]spital admissions and crim[illegible]onvic[illegible] All individuals discharged from the[illegible]pital with ICD diagnoses of schizophr[illegible]and other psychoses (N=[illegible]2) we[illegible]ked to the crime register t[illegible] 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 attributable to patients with severe mental illness. This corresponds to a population-att[illegible]e risk fract[illegible] of 5.2%. This at-t[illegible]tab[illegible]isk fra[illegible]on was higher in w[illegible]en t[illegible] men[illegible]oss all age bands. In w[illegible]en [illegible] 25–[illegible] it was 14.0%, and in wo[illegible]er 40[illegible] was 19.0%. The attributable risk fra[illegible]ons w[illegible]est in those ages 15–24 [illegible]% f[illegible]ale [illegible]tients and 2.9% for fe[illegible]e pat[illegible]s).

Conclusions: The p[illegible]la[illegible] 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%, suggesting that patients with severe mental illness commit one in 20 violent crimes.

5%

(in Sweden)

Fazel S, Grann M. The population impact of severe mental illness on violent crime.American Journal of Psychiatry 163(8):1397-1403, 2006.

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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

Volavka J, Citrome L. Heterogeneity of violence in schizophrenia and implications for long-term treatment. Int J Clin Pract 2008;62(8):1237-45.

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

Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia. Part I: Definitions, Epidemiology, Assessment, and Acute Treatment. Essential Psychopharmacology 5(1):1-16, 2002.

HETEROGENEITY OF VIOLENT BEHAVIOR

Table 1 Heterogeneity of violence: possible factors and treatment implications

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

Volavka J, Citrome L. Heterogeneity of violence in schizophrenia and implications for long-term treatment. Int J Clin Pract 2008;62(8):1237-45.

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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 – <u>offer early</u>
  - Lorazepam vs. antipsychotics

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

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

Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia.
Part I: Definitions, Epidemiology, Assessment, and Acute Treatment. Essential Psychopharmacology 5(1):1-16, 2002.

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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

Citrome L, Volavka J. Clinical Management of Persistent Aggressive Behavior in Schizophrenia. Part I: Definitions, Epidemiology, Assessment, and Acute Treatment. Essential Psychopharmacology 5(1):1-16, 2002.

Remembrances of Things Past…

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

Citrome L. Atypical Antipsychotics for Acute Agitation:
New Intramuscular Options Offer Advantages. Postgraduate Medicine 112(6):85-96, 2002.

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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

Citrome L. Atypical Antipsychotics for Acute Agitation: New Intramuscular Options Offer Advantages. Postgraduate Medicine 112(6):85-96, 2002.

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

Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation?
A multicenter, prospective, double-blind, emergency department study. Am J Emerg Med 15(4): 335-40, 1997.

SECOND-GENERATION ANTIPSYCHOTICS: NEW FORMULATIONS *

- Liquid concentrate
  - Liquid risperidone
  - Liquid aripiprazole
- Orally disintegrating tablets
  - Zydis olanzapine
  - M-tab risperidone
  - Discmelt aripiprazole
  - Sublingual asenapine
- Inhaled powders
  - Inhaled loxapine (a first-generation antipsychotic with some atypical characteristics)
- IM Formulations
  - Olanzapine IM (short-acting)
  - Ziprasidone IM (short-acting)
  - Aripiprazole IM (short-acting)
- Bonus: No EPS/akathisia, transition to oral dosing, treatment of underlying psychosis, including negative symptoms

Citrome L, Volavka J. The psychopharmacology of violence: making sensible decisions. CNS Spectr. 2014 Feb 26:1-8. [Epub ahead of print]

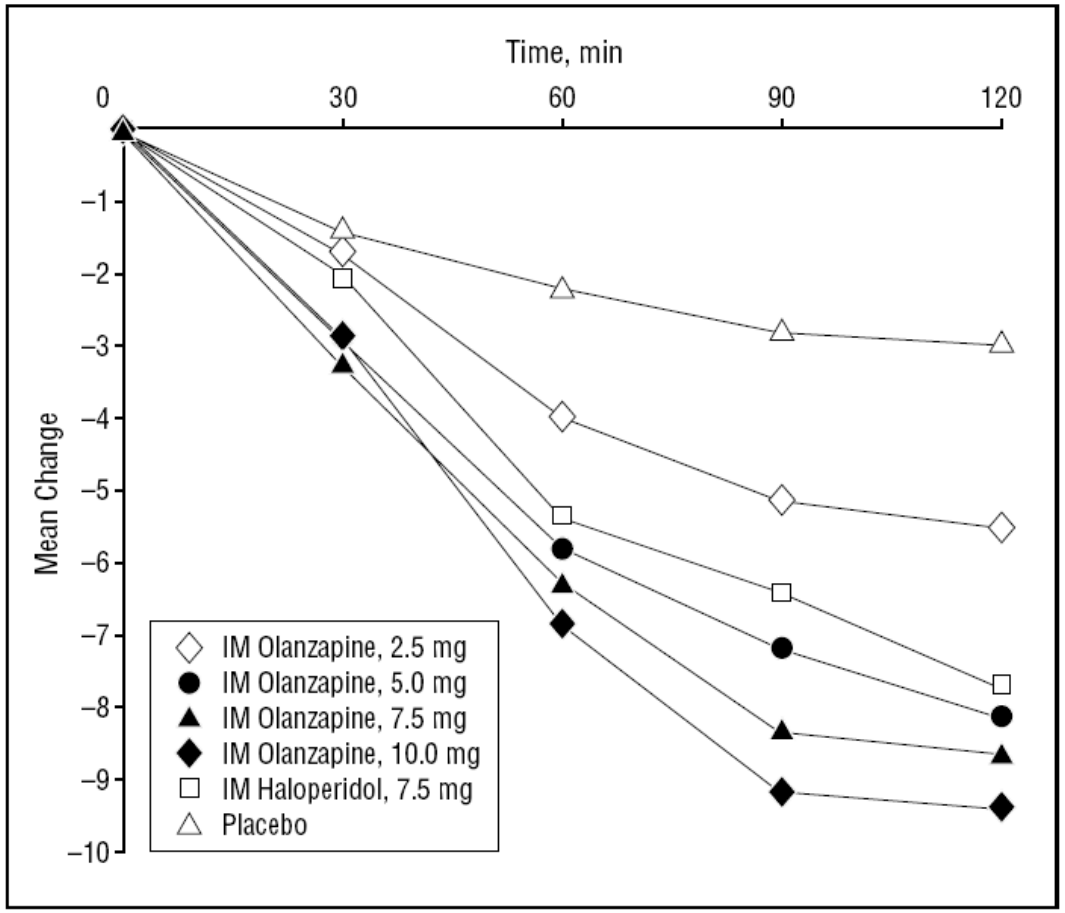
OLANZAPINE IM *

- IM form evaluated in randomized double blind placebo and active comparator studies
  - Schizophrenia
  - Bipolar mania
- 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

Citrome L. Atypical Antipsychotics for Acute Agitation: New Intramuscular Options Offer Advantages. Postgraduate Medicine 112(6):85-96, 2002.

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**

Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Archives of General Psychiatry 59(5):441-448, 2002.

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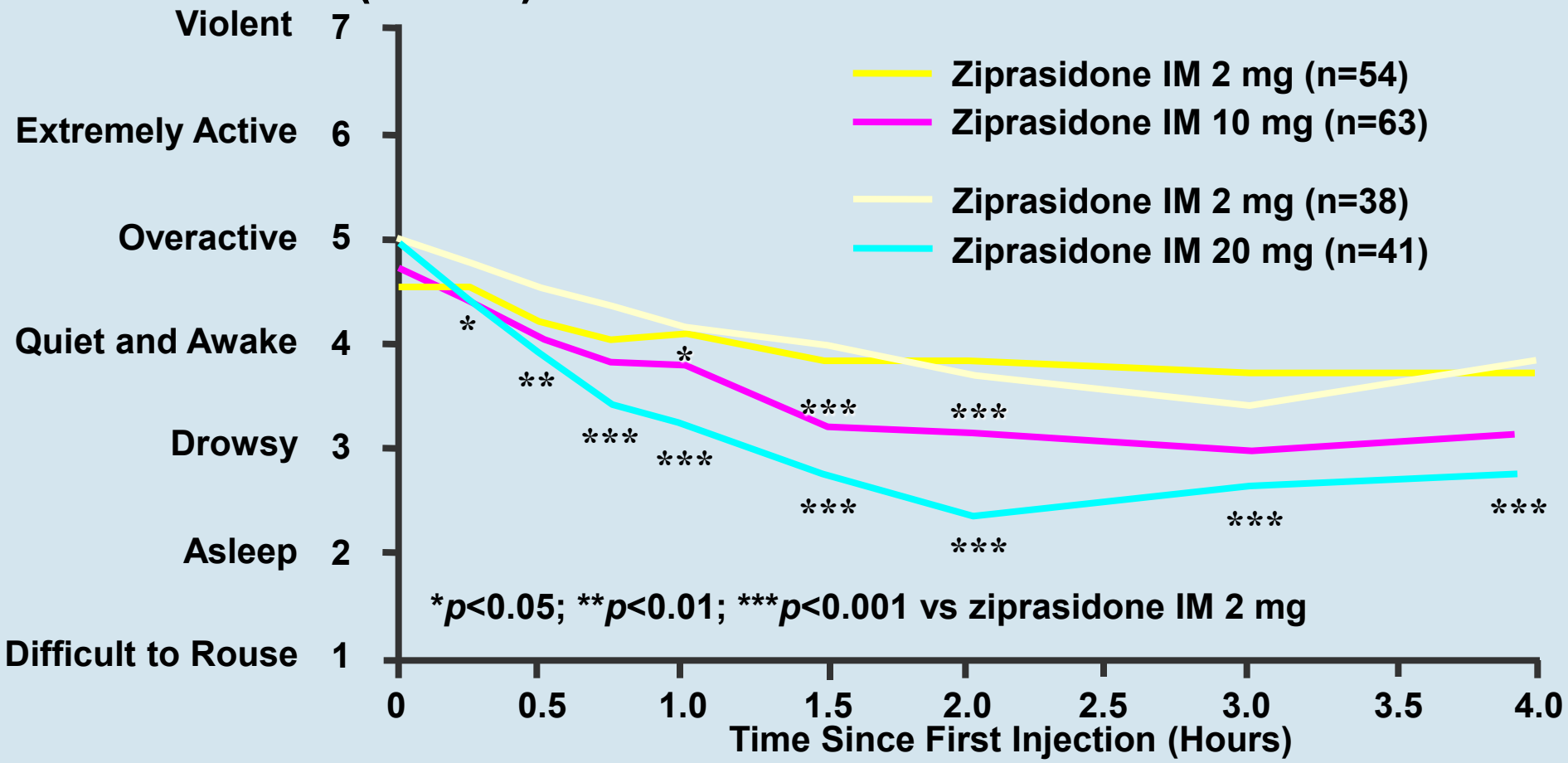
ZIPRASIDONE IM

- 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

Citrome L. Atypical Antipsychotics for Acute Agitation: New Intramuscular Options Offer Advantages. Postgraduate Medicine 112(6):85-96, 2002.

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.

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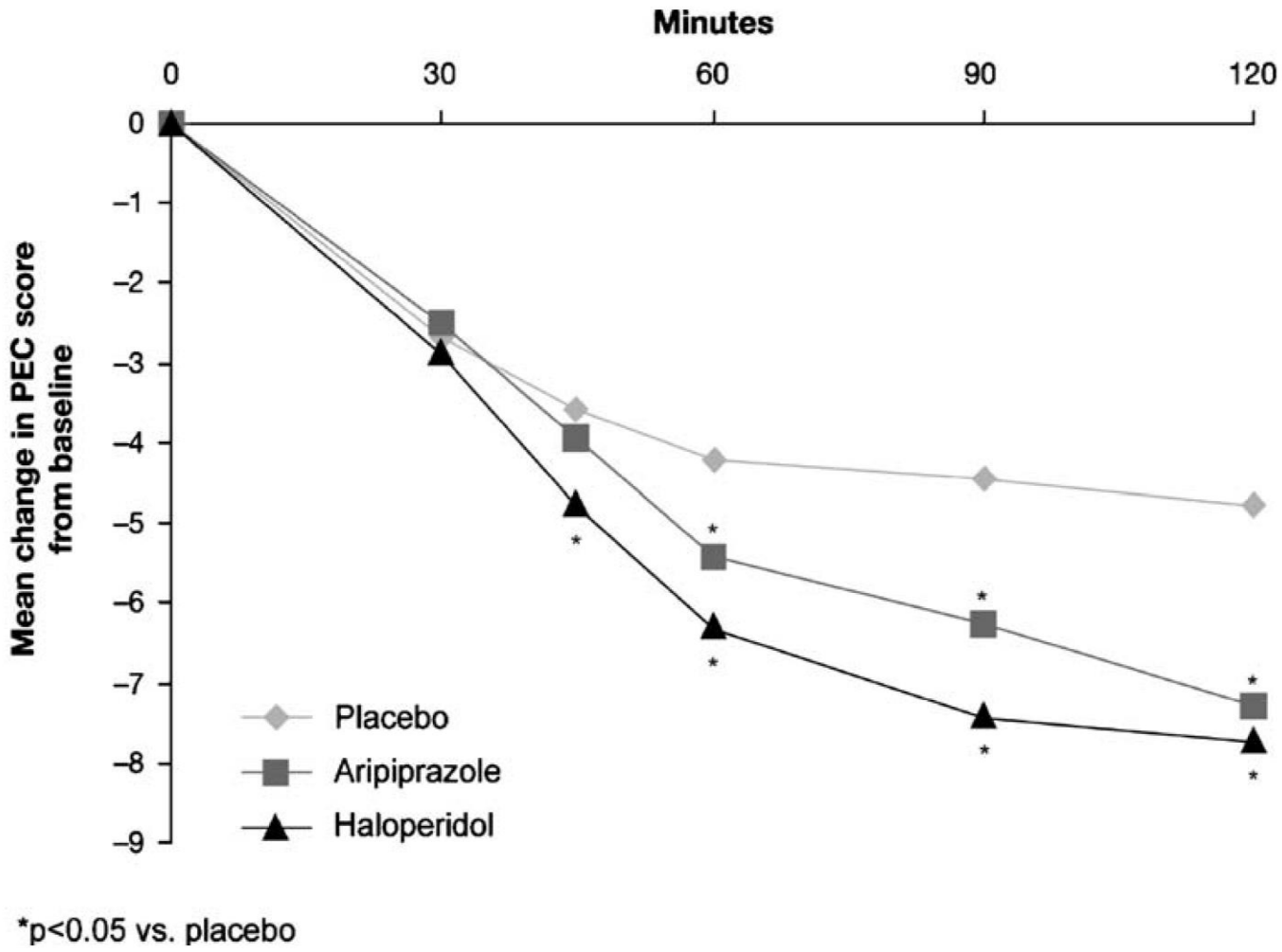
ARIPIPRAZOLE IM

- IM form evaluated in randomized double blind placebo and active comparator studies
  - Schizophrenia
  - Bipolar mania
- 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

Bristol-Myers Squibb. Abilify (aripiprazole) tablets, Abilify (aripiprazole) DiscMelt orally disintegrating tablets, Abilify (aripiprazole) oral solution, Abilify (aripiprazole) injection for intramuscular use only. Product information revised October 2006. Available at http://www.abilify.com. Accessed December 13, 2006.

ARI IM: IMPROVEMENT IN PANSS-EC

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

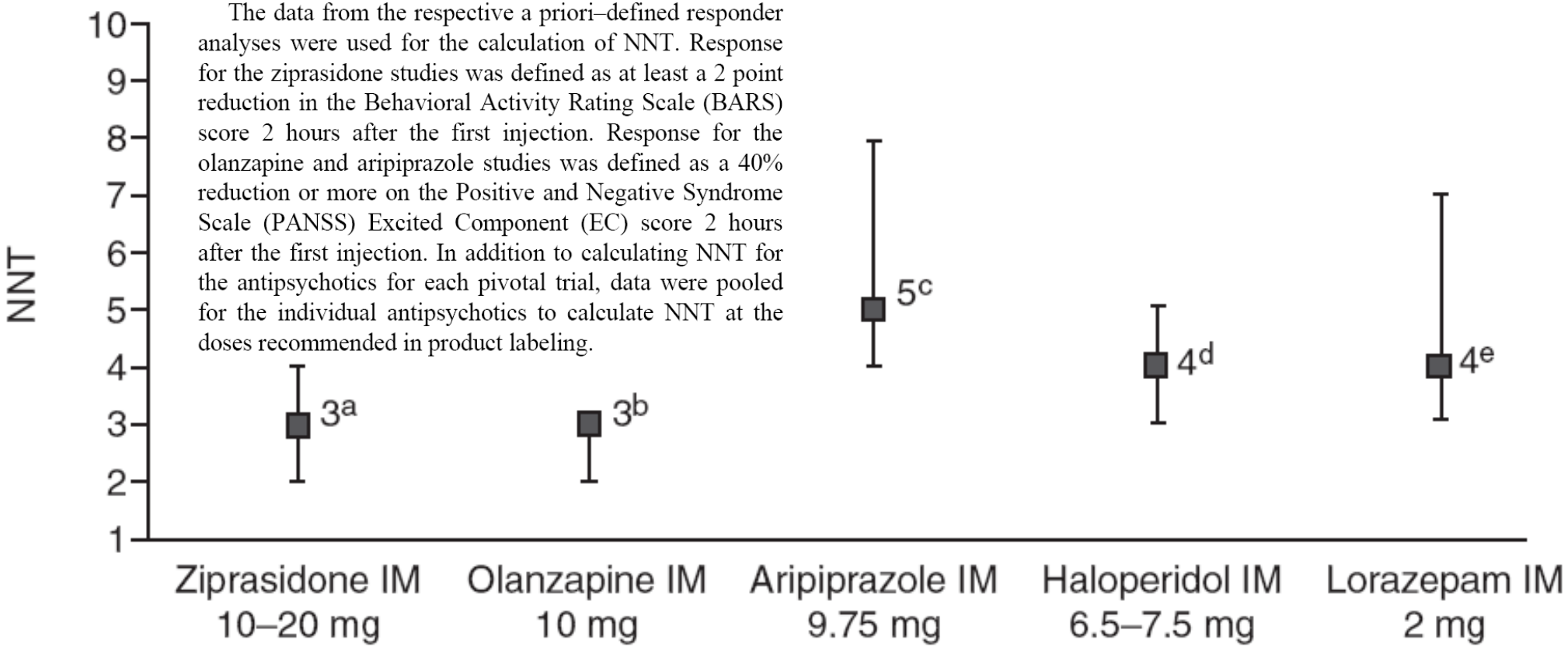
- How many patients would you need to treat with Drug A instead of Drug B before you would see one extra responder, or one adverse outcome?

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

Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. Acta Psychiatr Scand 2008;117(6):412-9.

HOW DO TREATMENTS FOR ACUTE AGITATION COMPARE AGAINST PLACEBO?

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



The data from the respective a priori–defined responder analyses were used for the calculation of NNT. Response for the ziprasidone studies was defined as at least a 2 point reduction in the Behavioral Activity Rating Scale (BARS) score 2 hours after the first injection. Response for the olanzapine and aripiprazole studies was defined as a 40% reduction or more on the Positive and Negative Syndrome Scale (PANSS) Excited Component (EC) score 2 hours after the first injection. In addition to calculating NNT for the antipsychotics for each pivotal trial, data were pooled for the individual antipsychotics to calculate NNT at the doses recommended in product labeling.

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[1]

Lorazepam 2 mg IM	Haloperidol 5 mg IM	Ziprasidone 20 mg IM	Olanzapine 10 mg IM	Aripiprazole 9.75 mg
$0.86	$2.85	$9.59[2]	$18.26	$10.68
Avoidance of acute dystonia and akathisia		Priceless		

1. Cost to Rockland Psychiatric Center pharmacy December 18, 2006
2. Cost prior to 2006 was $37.43

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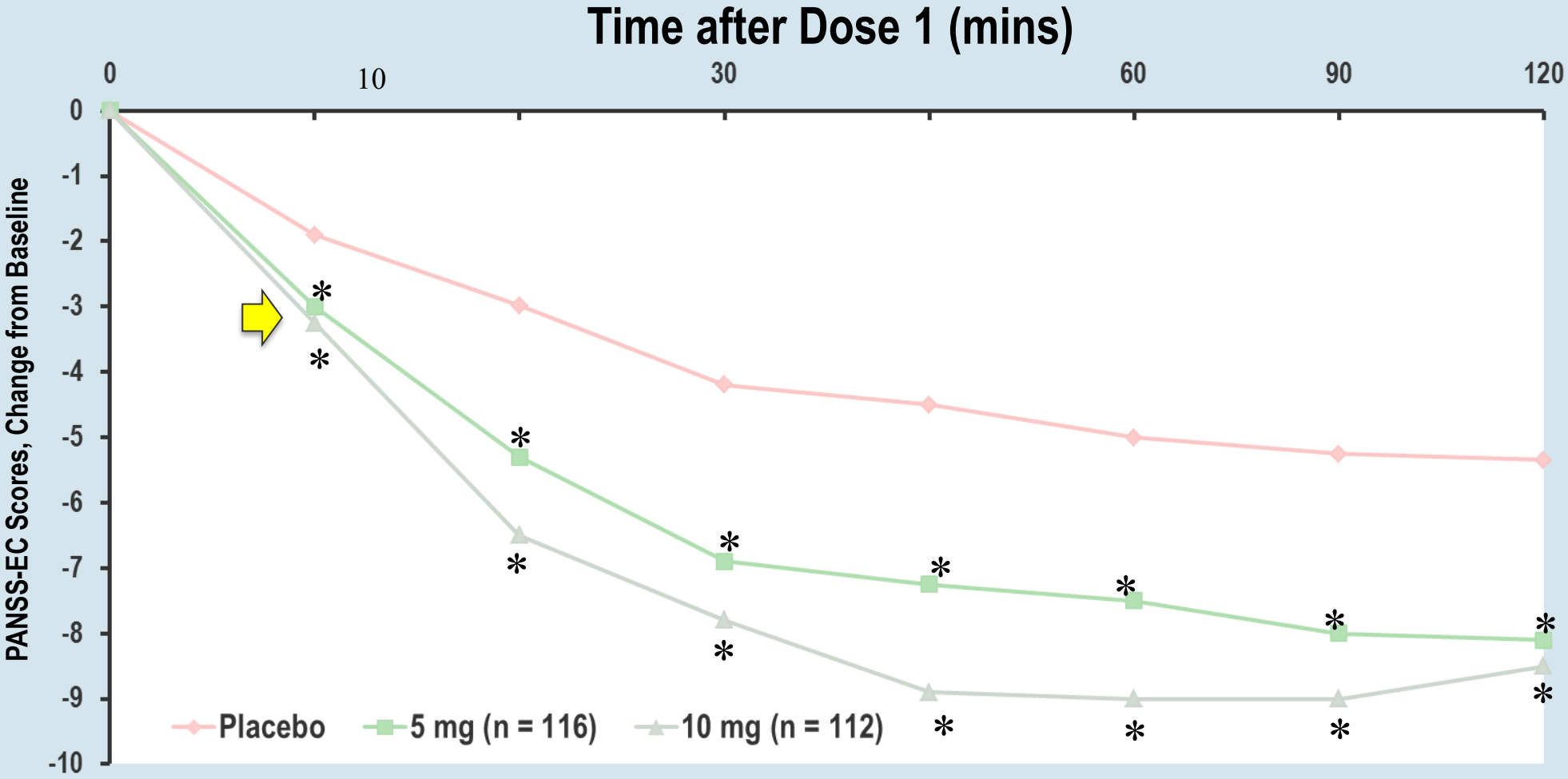
INHALED LOXAPINE

- Indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults, as established in randomized controlled trials
  - Schizophrenia (2; one was a Phase 3 pivotal study)
  - Bipolar mania (1)
- Rapid onset of efficacy
- Dosage 10 mg; only a single dose within a 24-hour period is recommended; administered only by a healthcare professional, in an enrolled healthcare facility
- Favorable EPS profile
- Cautions: Bronchospasm

Citrome L. *Current Psychiatry*. 2013;12(2):31-36.

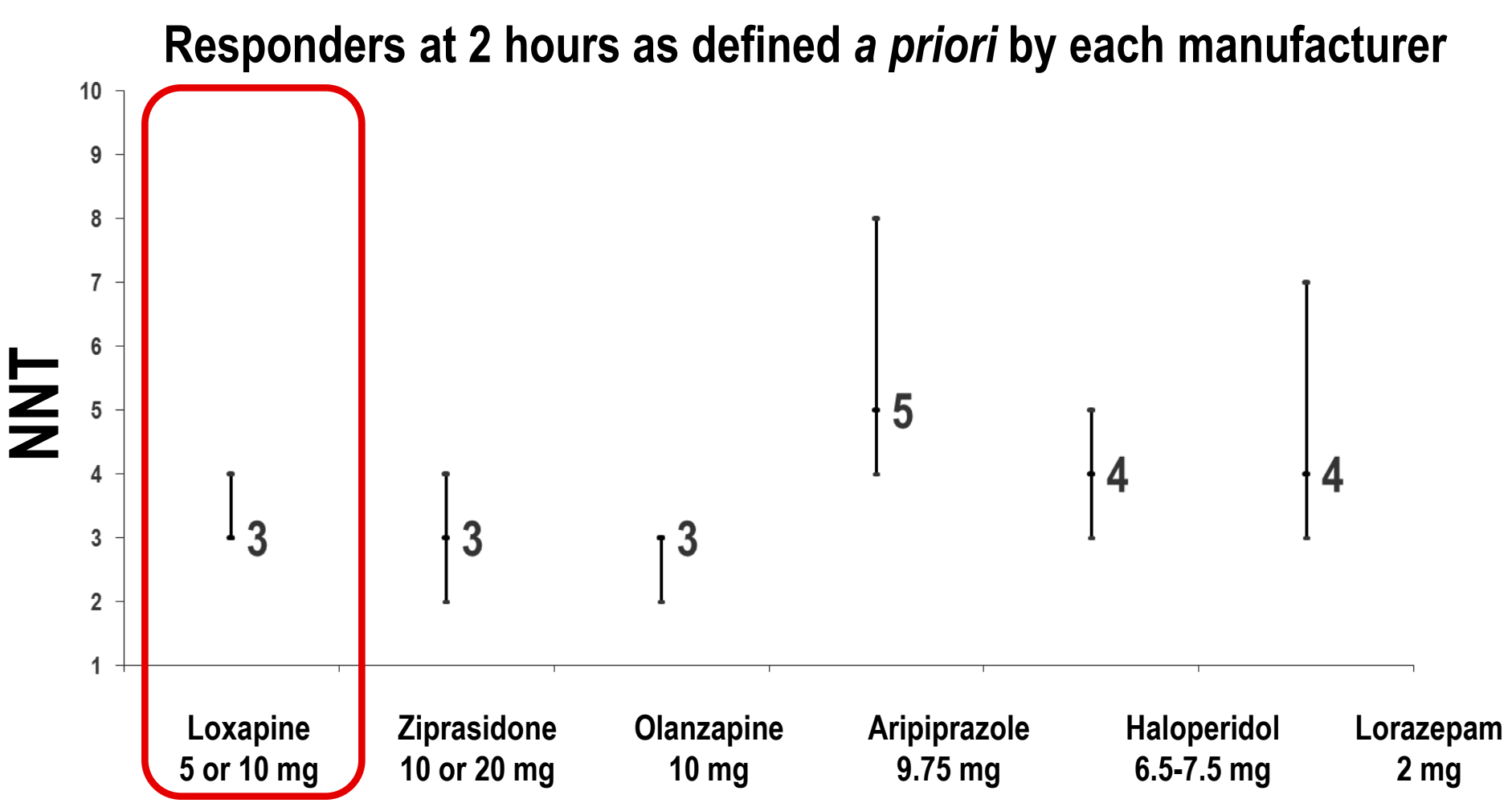
SCHIZOPHRENIA: INHALED LOXAPINE VS PLACEBO OVER TIME



*$P < .001$.

Lesem MD, et al. *Br J Psychiatry*. 2011;198(1):51-58.

NNT FOR RESPONSE AT 2 HOURS VS PLACEBO?



Citrome L. *Int J Clin Pract*. 2011;65(3):330-340.

INHALED LOXAPINE: REMS PROGRAM

- Bolded boxed warning regarding bronchospasm
- Prior to administering inhaled loxapine, patients must be screened for a history of pulmonary disease, and examined by chest auscultation for respiratory abnormalities such as wheezing
- After administration, patients are required to be monitored for signs and symptoms of bronchospasm at least every 15 minutes for at least 1 hour
- Inhaled loxapine is to be made available in the United States only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation)

REMS = Risk Evaluation and Mitigation Strategies.

Citrome L. *Current Psychiatry*. 2013;12(2):31-36.

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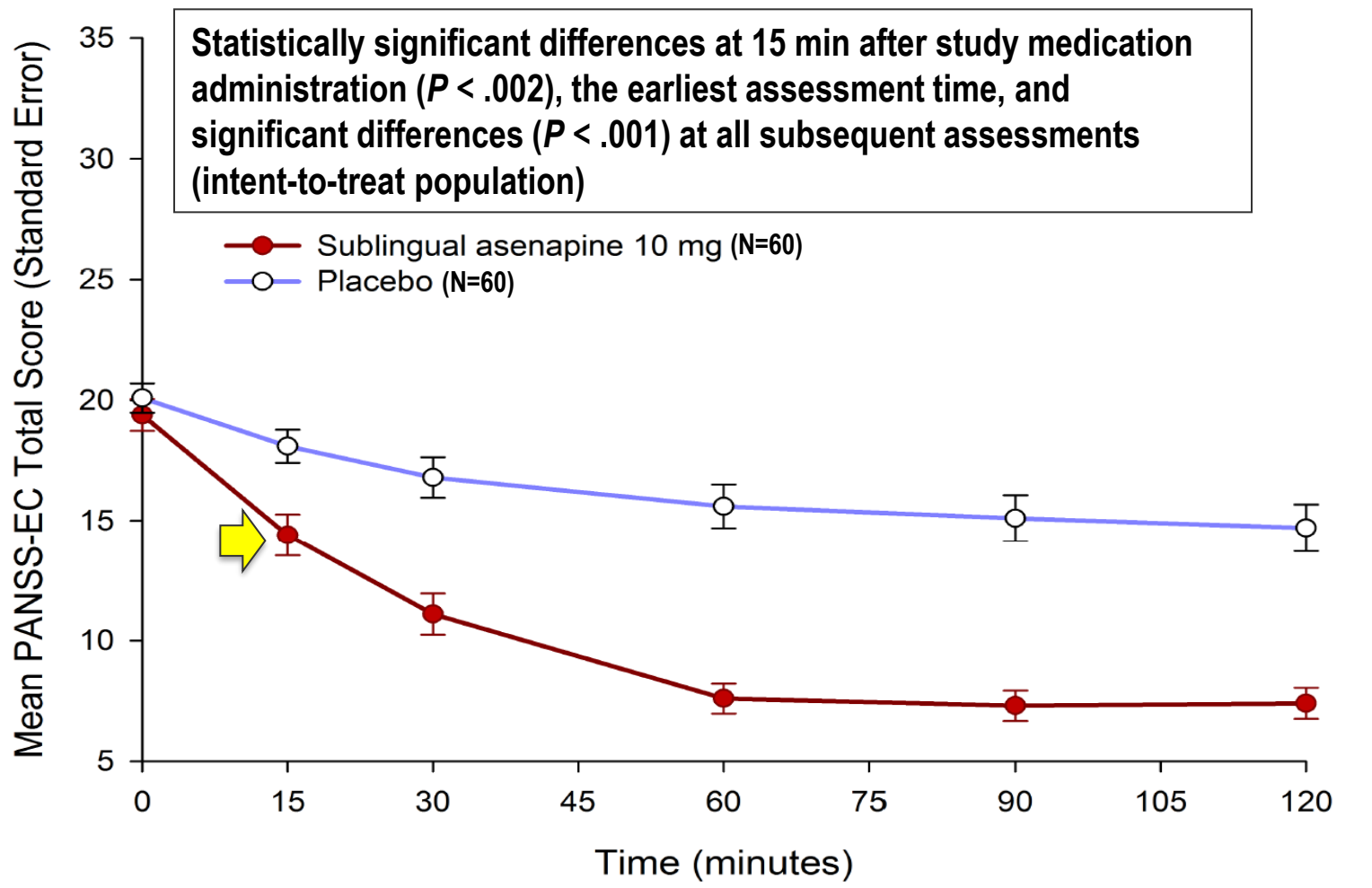
SUBLINGUAL ASENAPINE

- Approved in 2009 for treatment of
  - Acute schizophrenia
  - Acute mania or mixed episodes associated with bipolar I disorder
- Absorbed sublingually; T_{max} 30 to 90 minutes
- Was studied in agitated adults 18-65 years (*not FDA-approved for this indication*)
  - Presenting for treatment in an ED
  - Any diagnosis
  - PANSS-EC ≥14
  - Randomized to receive either a single dose of sublingual 10 mg tablet of asenapine or placebo
  - Only one single-site study – requires replication

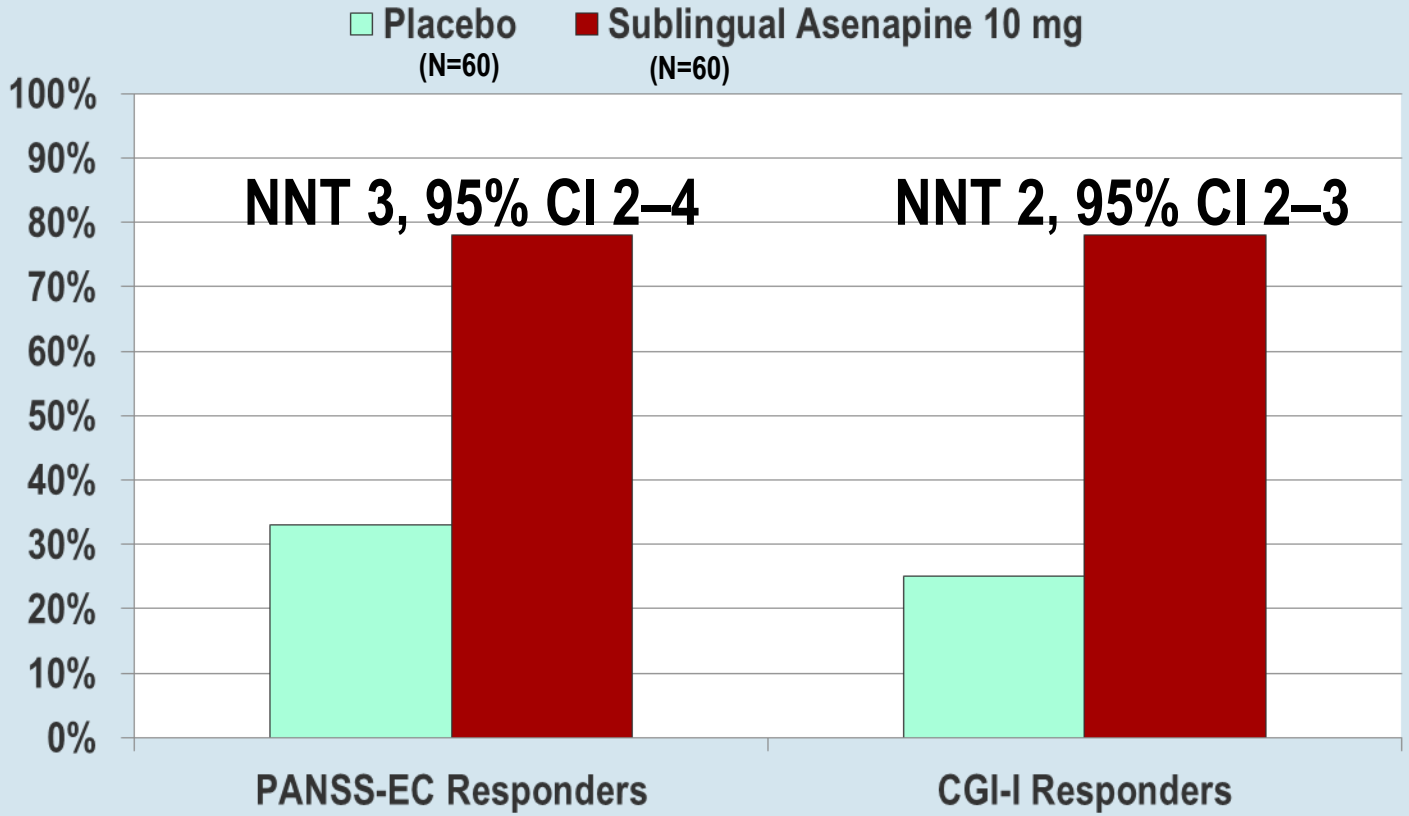
Merck Sharp & Dohme BV. Saphris (asenapine) prescribing information. 2014.
Pratts M, et al. *Acta Psychiatr Scand*. 2014 Jul;130(1):61-8.

SUBLINGUAL ASENAPINE 10 MG VS PLACEBO OVER TIME



Pratts M, et al. *Acta Psychiatr Scand*. 2014 Jul;130(1):61-8.

PANSS-EC RESPONDERS AND CGI-I RESPONDERS



PANSS-EC responders defined as ≥40% decrease from baseline;
CGI-I responders defined as a CGI-I of "1" (Very Much Improved) or "2" (Much Improved)

CGI-I = Clinical Global Impression-Improvement Scale.

Pratts M, et al. *Acta Psychiatr Scand*. 2014 Jul;130(1):61-8.

PROJECT BETA

- For psychosis-driven agitation in a patient with a known psychiatric disorder (eg, schizophrenia, schizoaffective disorder, bipolar disorder), antipsychotics are recommended over benzodiazepines because they address the underlying psychosis
- Second-generation antipsychotics with supportive data for their use in acute agitation are preferred over haloperidol either alone or with an adjunctive medication
- If the patient cannot cooperate with oral medications, IM ziprasidone or IM olanzapine is preferred for acute control of agitation

BETA = Best practices in Evaluation and Treatment of Agitation.

Wilson MP, et al. *West J Emerg Med*. 2012;13(1):26-34.

AGITATION: SUMMARY

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- Violent or threatening behavior is a frequent reason for admission, and may continue after admission
- New formulations (IM, PO) of second-generation antipsychotics (SGAs) provide several advantages over haloperidol in patients who require acute intervention or who refuse oral antipsychotic treatment; the IM SGAs are FDA-approved for agitation
- Inhaled loxapine offers another FDA-approved option that obviates the need for an injection

Citrome L, Volavka J. The psychopharmacology of violence: making sensible decisions. CNS Spectr. 2014 Feb 26:1-8. [Epub ahead of print]

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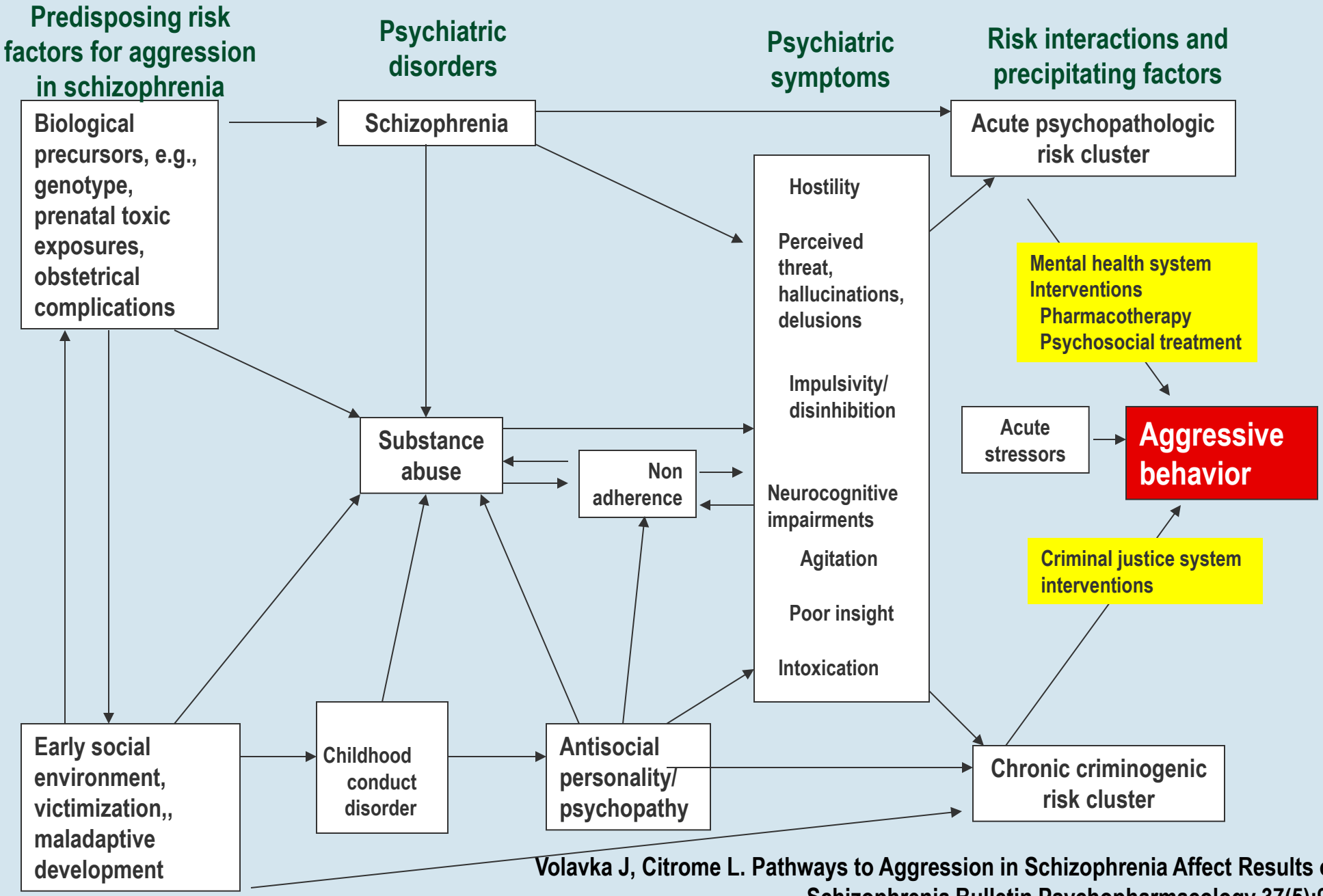
PROBABLE CAUSAL PATHWAYS TO AGGRESSION IN SCHIZOPHRENIA



Volavka J, Citrome L. Pathways to Aggression in Schizophrenia Affect Results of Treatment. Schizophrenia Bulletin Psychopharmacology 37(5):921-929, 2011

AFTER SHORT-ACTING IM ANTIPSYCHOTICS

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- **Oral antipsychotics**
  - Same antipsychotic used for acute control is a logical choice for continued treatment
  - Useful to have multiple formulations, such as regular tablets as well as orally-disintegrating tablets, for covertly noncompliant patients

- **Long-acting injectable (depot) antipsychotics**
  - If available, same antipsychotic used for acute control is a logical choice for continued treatment
  - Useful with overt and covert noncompliance (including medication administration over objection)
  - Supported by recently conducted prospective study of paliperidone palmitate vs oral antipsychotics in patients with schizophrenia, recent incarceration, and substance use
    - Paliperidone palmitate significantly delayed time to first treatment failure (including arrest/incarceration) vs daily oral antipsychotics

Citrome L, et al. *CNS Drugs*. 2011;25(12):1009-1021. Starr HL, et al. Presented at: American Psychiatric Association's 167th Annual Meeting; May 3-7, 2014; New York, NY. Poster NR8-150.

RECEIVING MEDICATIONS LOWERS VIOLENCE RISK

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- Swedish national registers N = 82,647 patients prescribed antipsychotics or mood stabilizers
- Compared with periods when participants were not on medication, violent crime fell by 45% in patients receiving antipsychotics (HR 0.55, 95% CI 0.47–0.64) and by 24% in patients prescribed mood stabilizers (0.76, 0.62–0.93)
- Mood stabilizers were associated with a reduced rate of violent crime only in patients with bipolar disorder

Fazel S, et al. *Lancet*. 2014;[Epub ahead of print].

PERSISTENT AGGRESSIVE BEHAVIOR:* TREATMENTS IN SCHIZOPHRENIA

- Second-generation antipsychotics (best evidence)
- Beta-blockers (second-best evidence)
- Mood stabilizers (weak evidence)
- Antidepressants (weak evidence)
- Benzodiazepines (negative evidence)

Citrome L, et al. *CNS Drugs*. 2011;25(12):1009-1021. Volavka J, et al. *Schizophr Bull*. 2011;37(5):921-929. Volavka J, et al. *Int J Clin Pract*. 2008;62(8):1237-1245.

SECOND-GENERATION ANTIPSYCHOTICS AND HOSTILITY

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

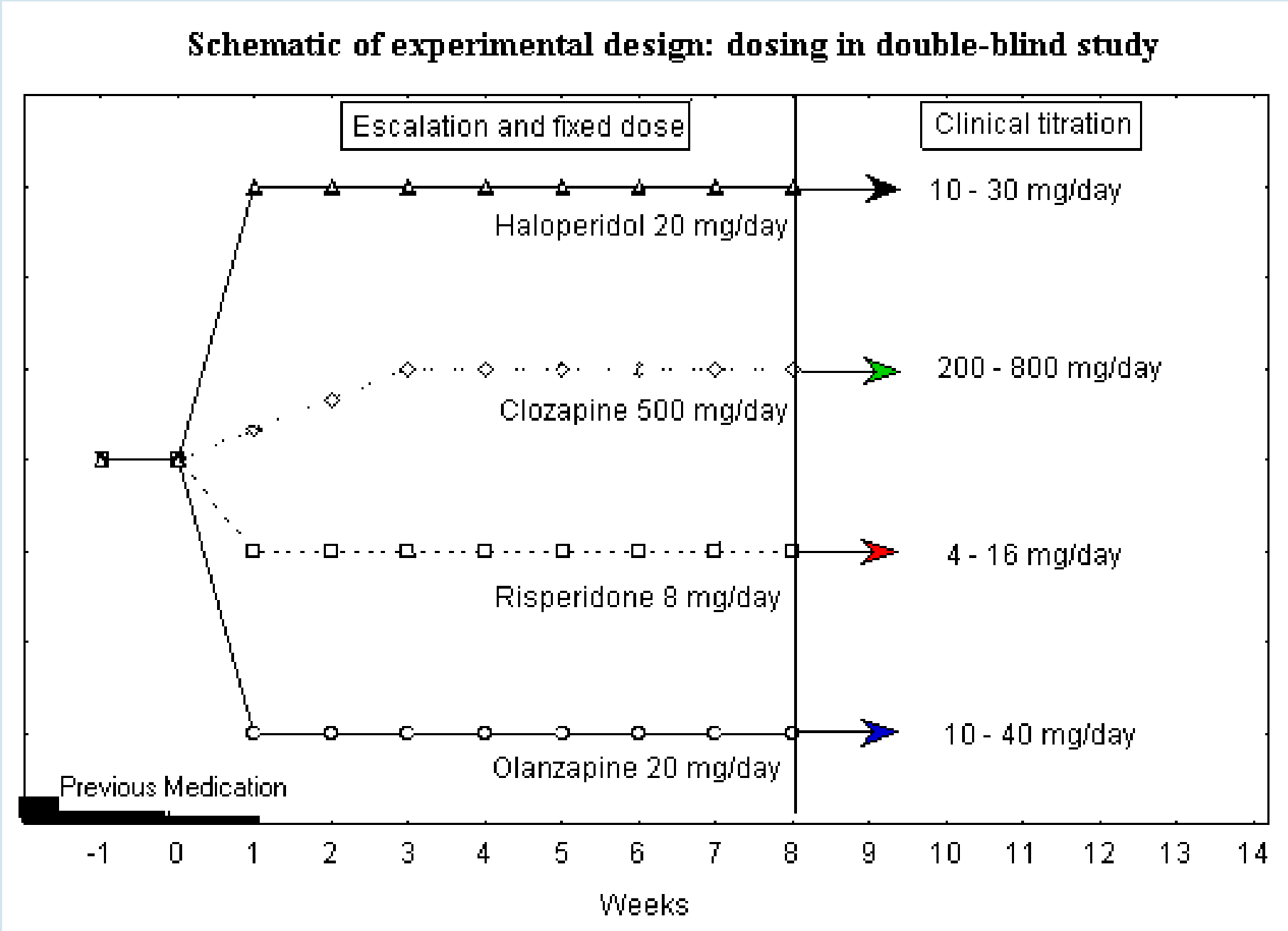
- **Operational difficulties: relative rarity of aggressive events, need for large sample size, need for lengthy baseline and trial periods, problems with selection/consent bias**
- **Very, very, few exist**

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

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

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.



Volavka J, Czobor P, Sheitman B, et al. Clozapine, Olanzapine, Risperidone, and Haloperidol in Patients with Chronic Schizophrenia and Schizoaffective Disorder. American Journal of Psychiatry 159(2):255-262, 2002.

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”)**

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.

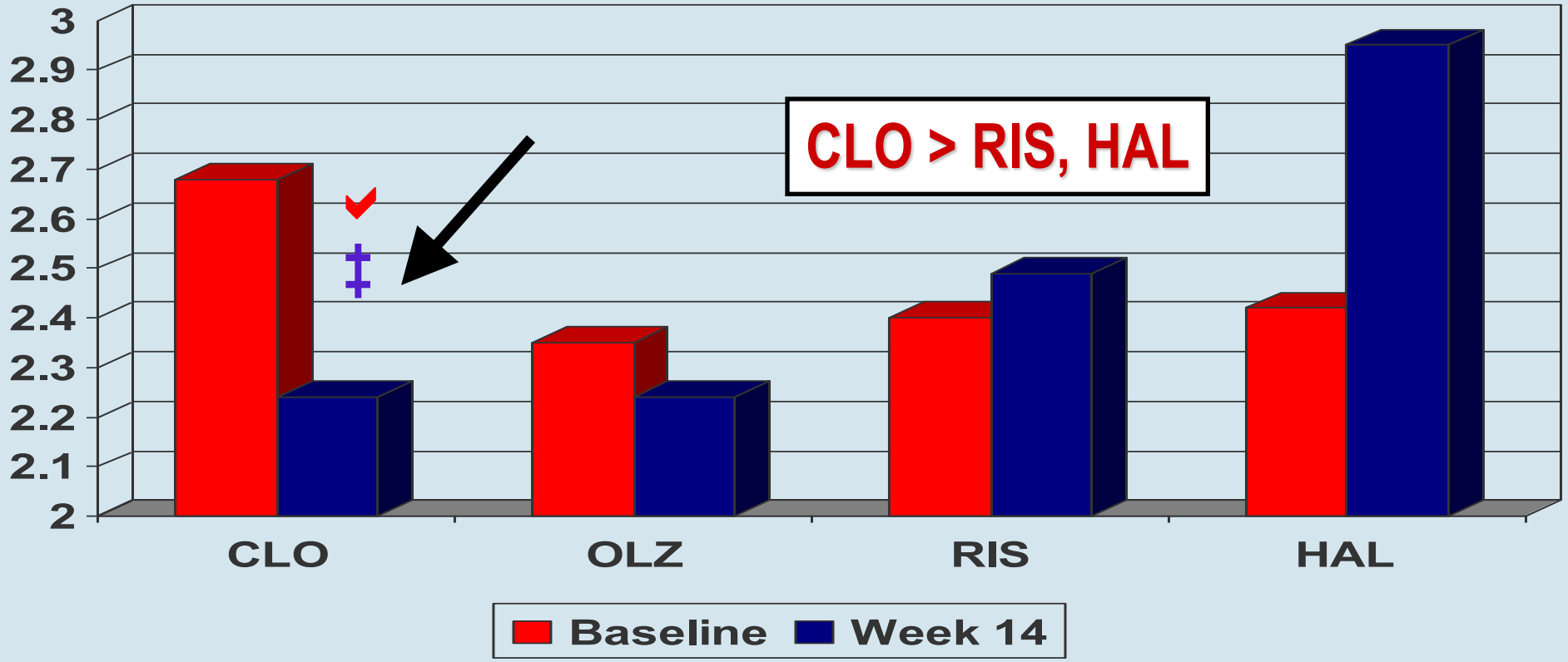
SAMPLE: AGE, DURATION OF ILLNESS, NUMBER OF HOSPITALIZATIONS

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 (-)

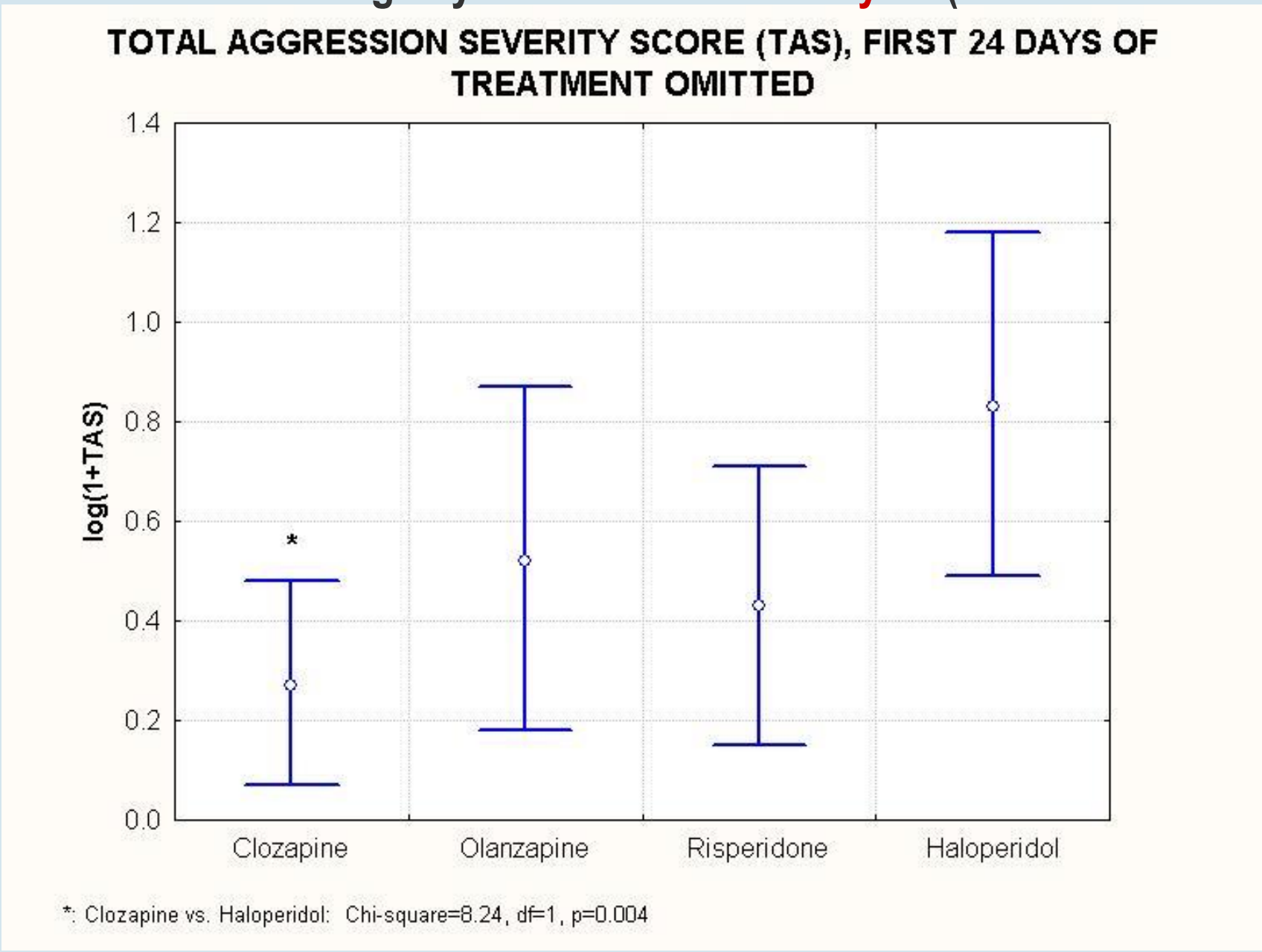
Citrome L, Volavka J, Czobor P, et al. Effects of Clozapine, Olanzapine, Risperidone, and Haloperidol on Hostility Among Patients with Schizophrenia. Psychiatric Services 52(11): 1510-1514, 2001.

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)

Silver JM, Yudofsky SC, Slater JA, et al. Propranolol treatment of chronically hospitalized aggressive patients. Journal of Neuropsychiatry and Clinical Neurosciences 11(3):328-335,1999.

Target Dose of CLO 500 mg/day to be reached on Day 24 (achieved 401.6 ± 160.4)



Volavka J, Czobor P, Nolan KA, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychopharmacology 24(2):225-228, 2004.

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

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.

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

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

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)

*χ^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†	χ^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)
Verb			

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).

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.

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

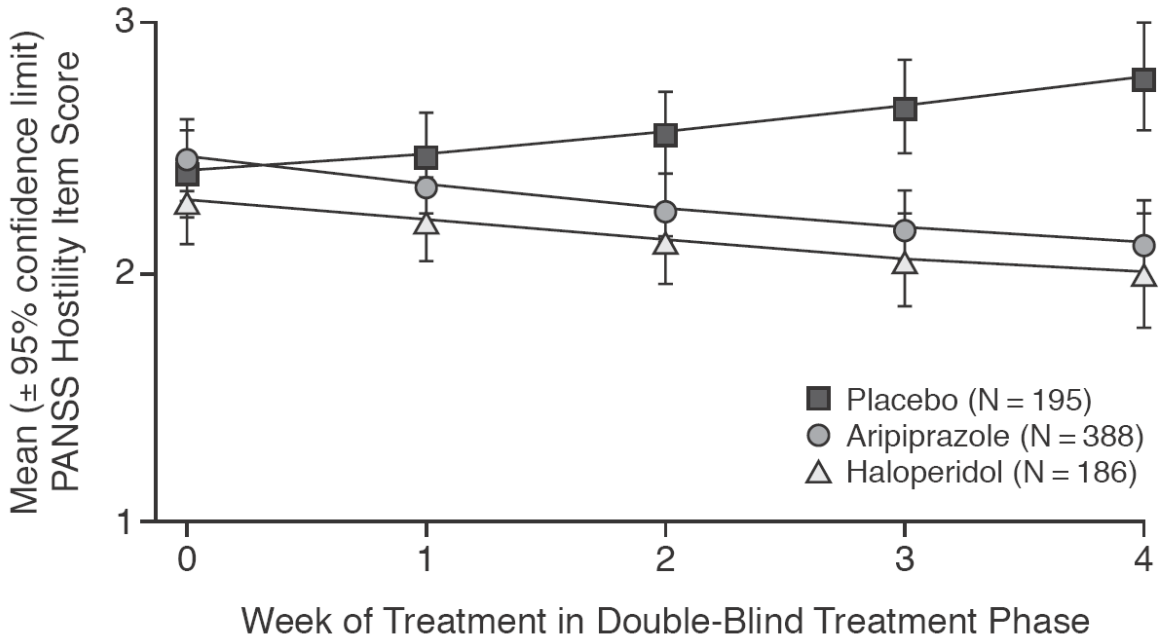
Chengappa KN, Goldstein JM, Greenwood M, et al. A post hoc analysis of the impact on hostility and agitation of quetiapine and haloperidol among patients with schizophrenia. Clinical Therapeutics 25:530-541, 2003; Arango C, Bernardo M. The effect of quetiapine on aggression and hostility in patients with schizophrenia. Human Psychopharmacology 20:237-241, 2005.

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

Volavka J, Czobor P, Citrome L, et al. Efficacy of Aripiprazole Against Hostility in Schizophrenia and Schizoaffective Disorder: Data From 5 Double-Blind Studies. Journal Clinical Psychiatry 66(11):1362-1366, 2005.

Figure 2. Change in Hostility During Treatment With Aripiprazole in 3 Short-Term, Placebo- and Active-Controlled Trials[a]



[a]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.

Volavka J, Czobor P, Citrome L, et al. Efficacy of Aripiprazole Against Hostility in Schizophrenia and Schizoaffective Disorder: Data From 5 Double-Blind Studies. Journal Clinical Psychiatry 66(11):1362-1366, 2005.

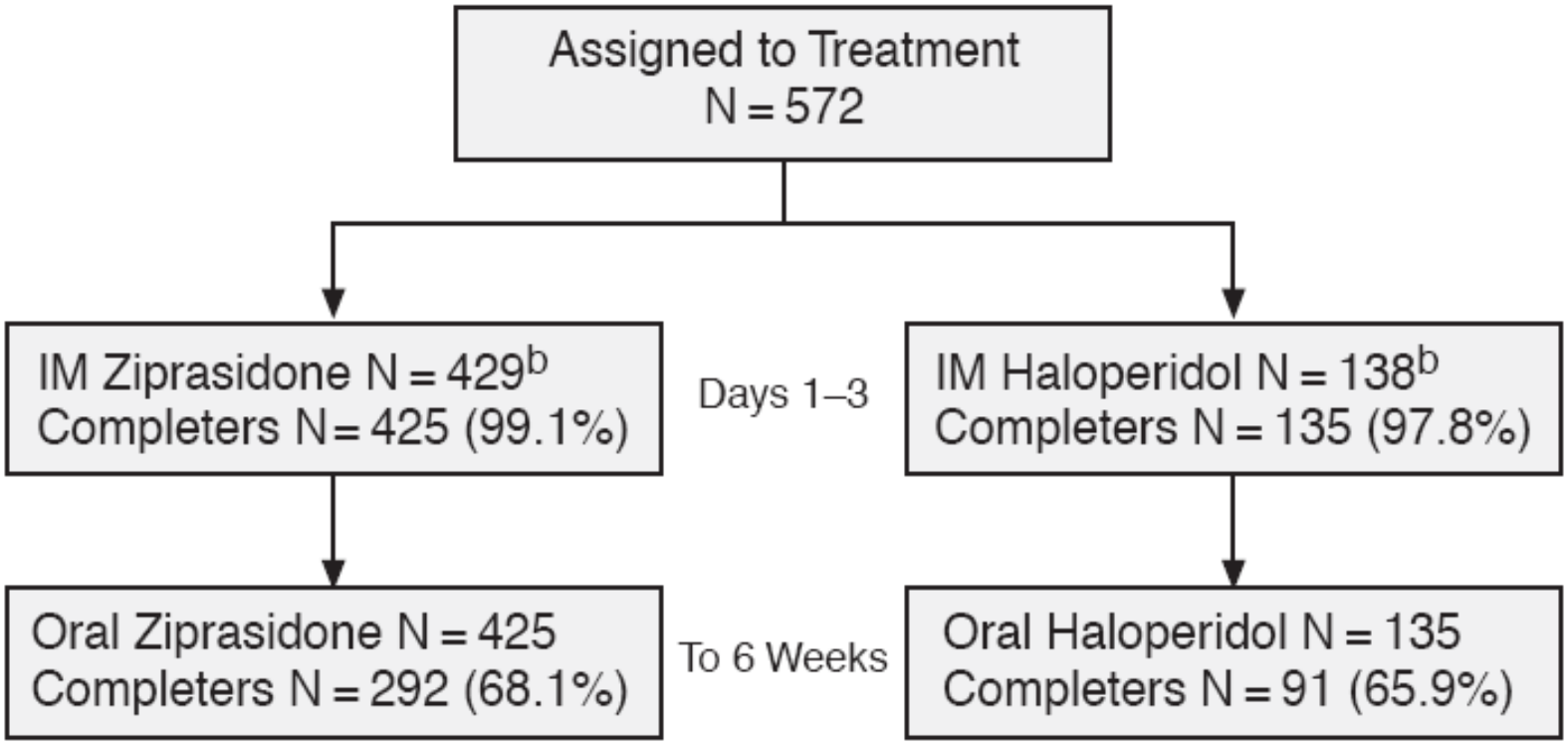
SPECIFIC EFFECTS OF ZIP ON HOSTILITY

(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

Citrome L, Volavka J, Czobor P, et al. Efficacy of ziprasidone against hostility in schizophrenia: post hoc analysis of randomized open-label study data, Journal of Clinical Psychiatry 67(4):638-642, 2006.

Figure 1. Disposition of Patients[a]



[a]Detailed flowchart available in Brook et al.[20]
[b]Received 1 or more doses.
Abbreviation: IM = intramuscular.

Citrome L, Volavka J, Czobor P, et al. Efficacy of ziprasidone against hostility in schizophrenia: post hoc analysis of randomized open-label study data, Journal of Clinical Psychiatry 67(4):638-642, 2006.

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[a]	Haloperidol Improvement Over Baseline[a]	Ziprasidone vs Haloperidol[b]	
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

[a]Time effect.
[b]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[a]	Haloperidol Improvement Over Baseline[a]	Ziprasidone vs Haloperidol[b]	
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

[a]Time effect.
[b]Treatment and time interaction effect.
Abbreviation: IM = intramuscular.

Citrome L, Volavka J, Czobor P, et al. Efficacy of ziprasidone against hostility in schizophrenia: post hoc analysis of randomized open-label study data, Journal of Clinical Psychiatry 67(4):638-642, 2006.

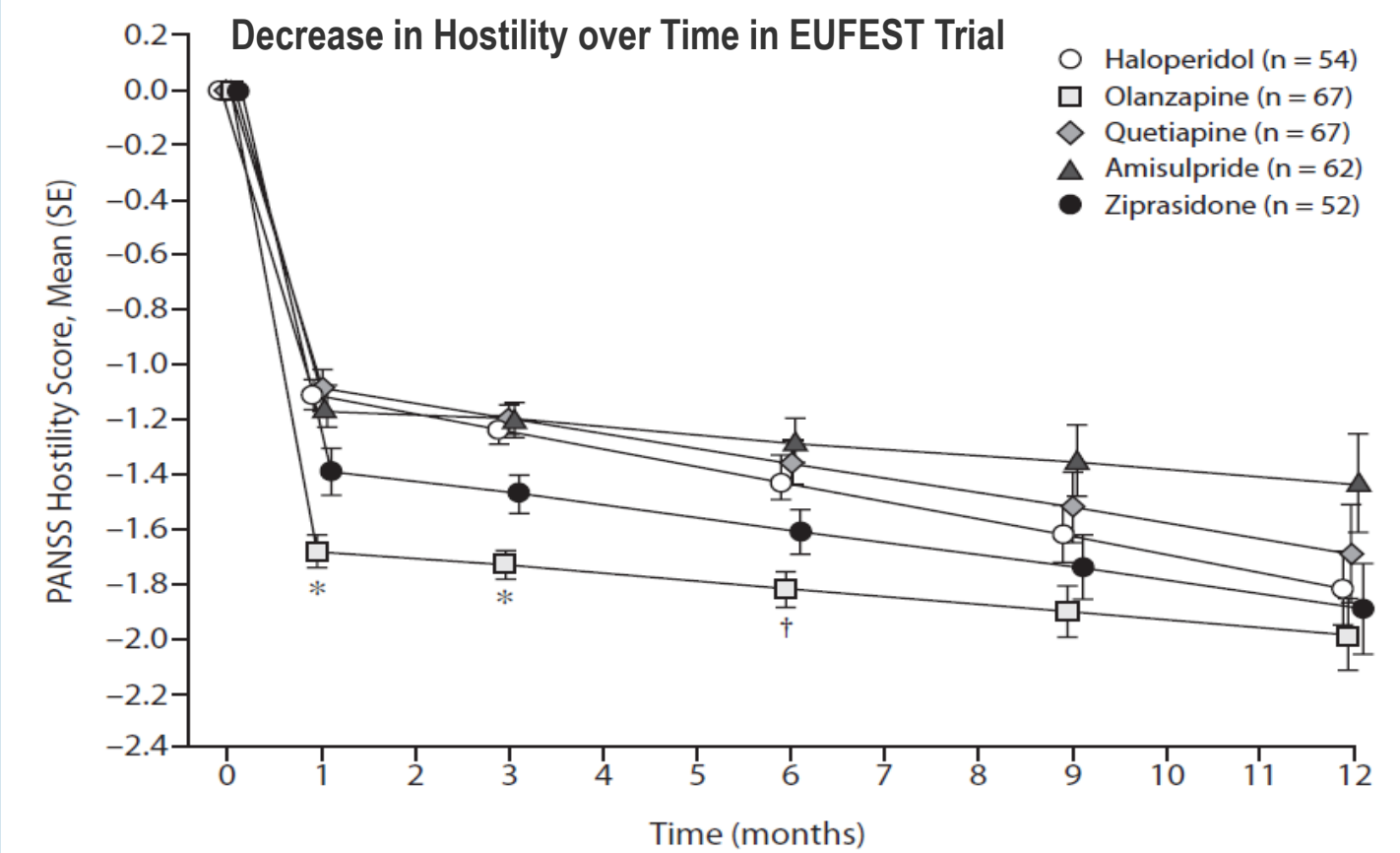
EUFEST: FIRST-EPISODE SCHIZOPHRENIA

- Compared were haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone on hostility
- Open-label, randomized trial conducted in 14 countries in 498 patients aged 18-40 years
- PANSS hostility item in a subset of 302 patients showing at least minimal hostility (a score >1) at baseline
- Treatment-group contrasts for hostility change showed that, at months 1 and 3, olanzapine was significantly superior ($P < .05$) to haloperidol, quetiapine, and amisulpride in reducing hostility
- Secondary analyses demonstrated that these results were at least partly specific to hostility
- Olanzapine appears to be a superior treatment for hostility in early phases of therapy for first-episode schizophrenia
  - This efficacy advantage of olanzapine must be weighed against its adverse metabolic effects and propensity to cause weight gain

EUFEST = European First-Episode Schizophrenia Trial.

Volavka J, et al. *J Clin Psychiatry*. 2011;72(7):955-961.

EUFEST: FIRST-EPISODE SCHIZOPHRENIA (CONTINUED)



*$P < .05$ versus haloperidol, amisulpride, and quetiapine.
†$P = .08$ versus amisulpride.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Volavka J, **et** al. *J Clin Psychiatry*. 2011;72(7):955-961.

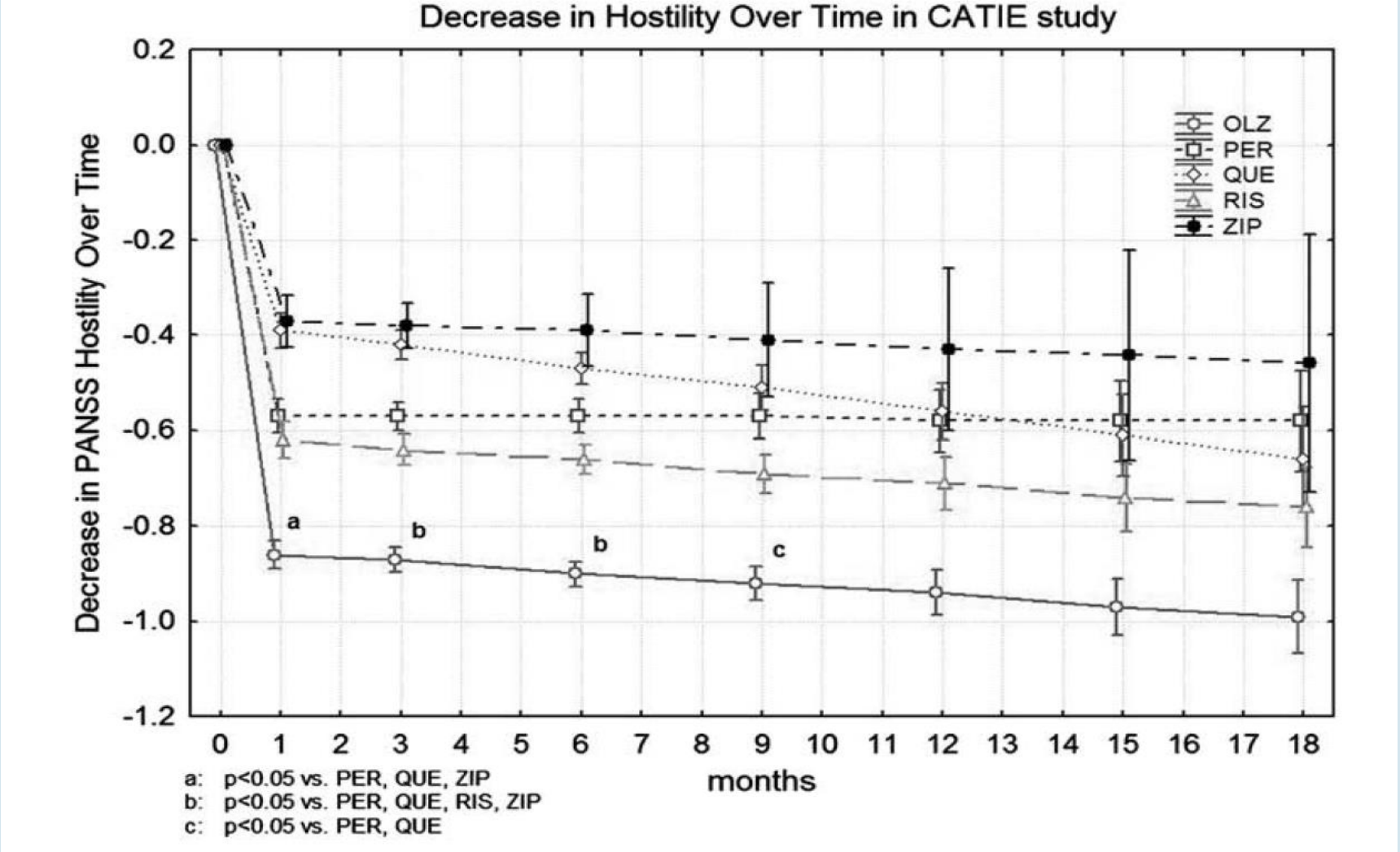
CATIE: CHRONIC SCHIZOPHRENIA

- Compared were olanzapine, perphenazine, risperidone, quetiapine, and ziprasidone
- Double-blind, randomized trial; data were acquired in the 18-month Phase 1 of the CATIE study
- PANSS hostility item in a subset of 614 patients who showed at least minimal hostility (a score >1) at baseline
- Olanzapine was significantly superior to perphenazine and quetiapine at months 1, 3, 6, and 9
  - It was also significantly superior to ziprasidone at months 1, 3, and 6, and to risperidone at months 3 and 6
- Results are consistent with those of a similar post-hoc analysis of hostility in first-episode subjects with schizophrenia enrolled in the EUFEST trial, where olanzapine demonstrated advantages compared with haloperidol, quetiapine, and amisulpride

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Volavka J, et al. *CNS Spectr*. 2013;[Epub ahead of print].

CATIE: CHRONIC SCHIZOPHRENIA (CONTINUED)



Volavka J, et al. *CNS Spectr*. 2013;[Epub ahead of **print**].

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; somewhat better than others in EUFEST and CATIE as well
- 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

Citrome L, Volavka J. The psychopharmacology of violence: making sensible decisions. CNS Spectr. 2014 Feb 26:1-8. [Epub ahead of print]

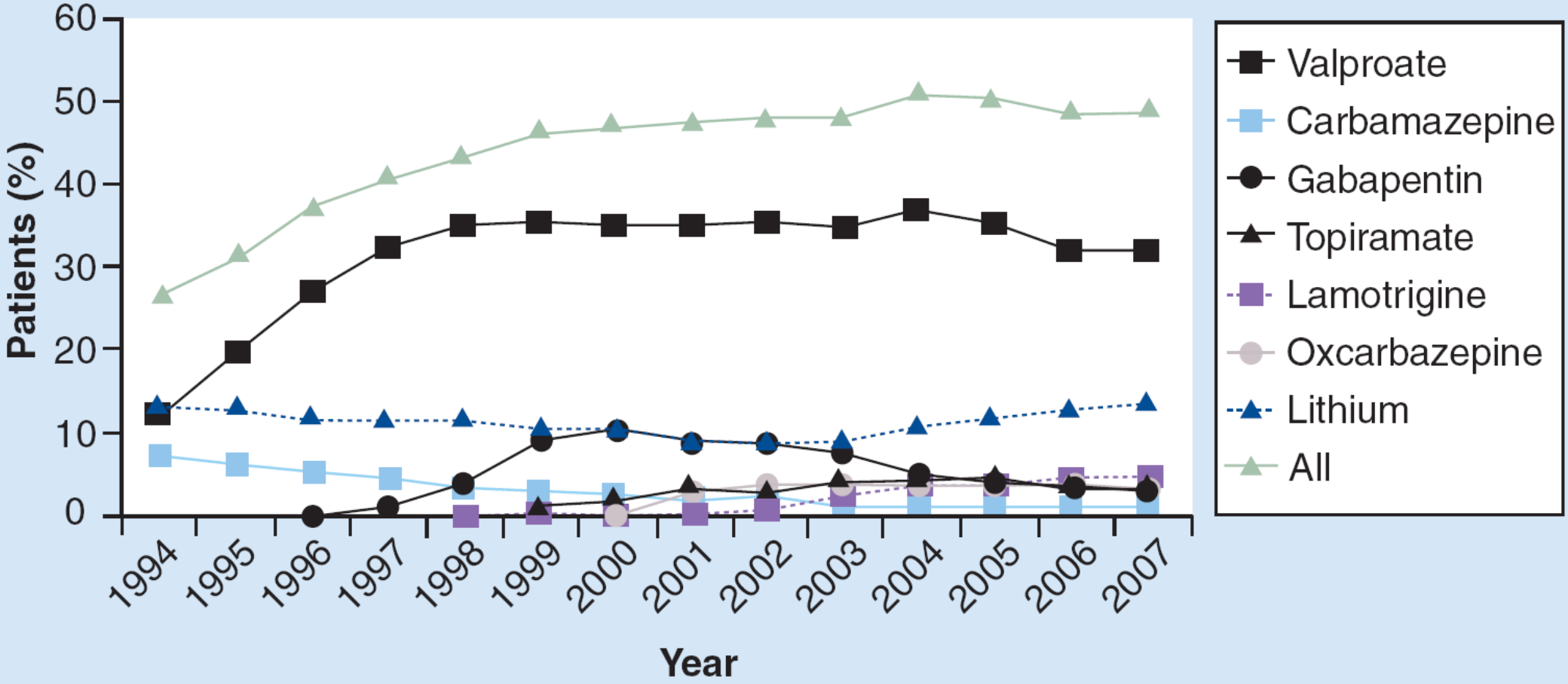
MOOD STABILIZERS

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).



Citrome L. *Expert Rev Neurother*. 2009;9:55-71.

*

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

Adapted from Citrome L. *Expert Rev Neurother*. 2009;9:55-71.

ADJUNCTIVE CARBAMAZEPINE IN SCHIZOPHRENIA

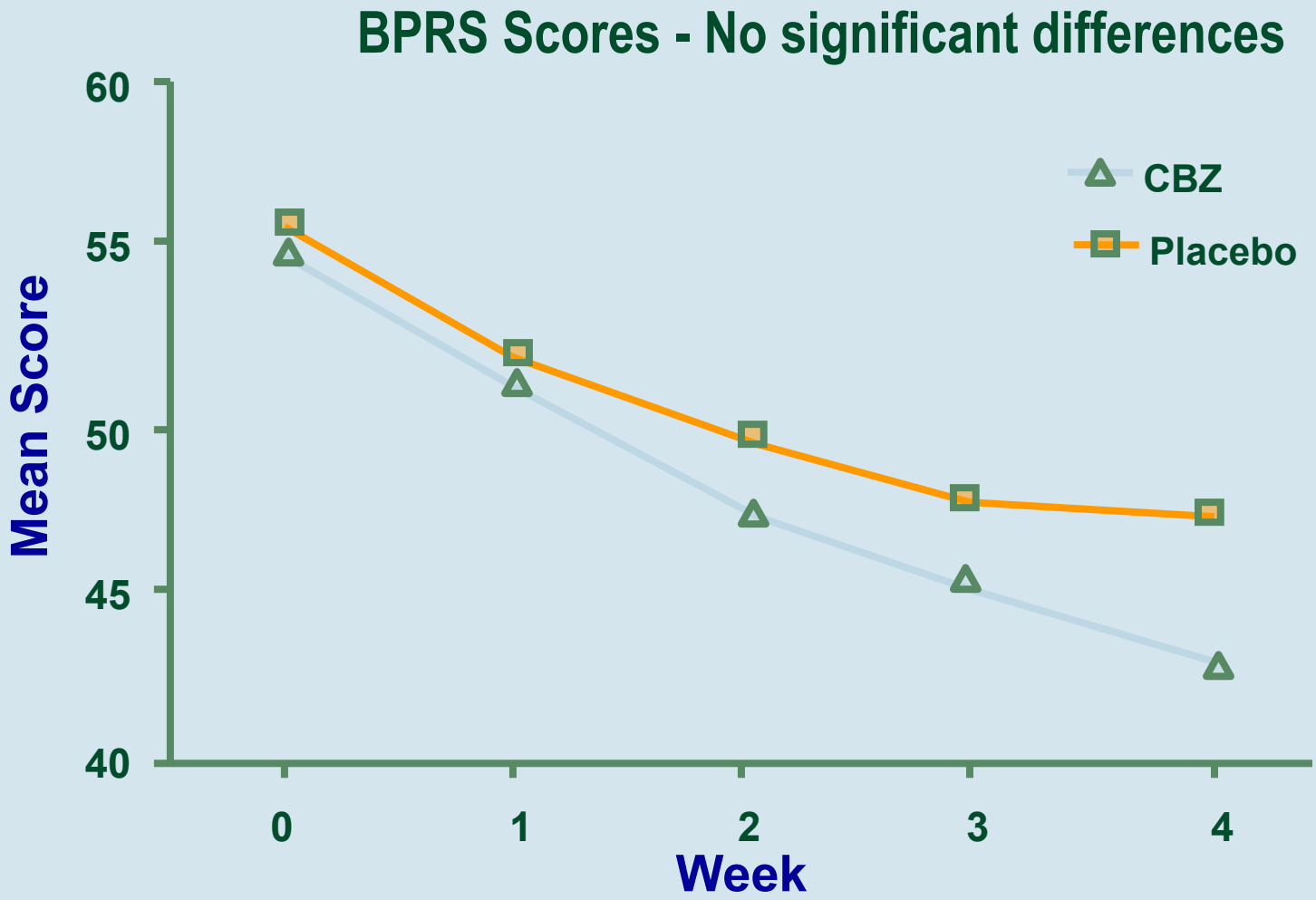
RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis	
Okuma *et al.* (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'	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)
Neppe (1983)	CBZ 600 mg/day vs placebo added to AP (crossover)	11	42	Inpatients, eight with schizophrenia (and EEG abnormalities)	Improvement in "Overall Clinical Rating" with CBZ
Ohlmeier *et al.* (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	OLZ monotherapy was superior to perazine plus CBZ on positive symptoms on PANSS and BPRS
Dose *et al.* (1987)	CBZ 600–1200 mg/day vs placebo added to HAL	22	28	Inpatients with schizophrenia or schizoaffective disorder	No difference on BPRS; Same proportion discontinued the study early on CBZ than on placebo
Nachshoni *et al.* (1994)	CBZ 600 mg/ day vs placebo added to AP	28	49	Inpatients with 'residual schizophrenia with negative symptoms'	No difference on BPRS or SANS; Same proportion discontinued the study early on CBZ than on placebo
Simhandl *et al.* (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	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
Hesslinger *et al.* (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	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)

Citrome L. *Expert Rev Neurother*. 2009;9:55-71.

CARBAMAZEPINE IN SCHIZOPHRENIA

Efficacy:Time Course of Outcomes



Okuma T, et al. *Acta Psychiatr Scand*. 1989;80:250-259.

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
Suspiciousness							
Carbamazepine	3.7	2.9	< 0.05				
Placebo	3.6	3.1					
Uncooperativeness							
Carbamazepine	3.9	3.0					
Placebo	4.1	3.3				< 0.05	
Excitement							
Carbamazepine	4.4	2.7					
Placebo	4.2	2.9				< 0.05	< 0.05

Okuma T, et al. *Acta Psychiatr Scand*. 1989;80:250-259.

ADJUNCTIVE LAMOTRIGINE AND SCHIZOPHRENIA

RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Tiihonen *et al.* (2003)	LAM 200 mg/day vs placebo added to CLO (crossover)	34	84	Male inpatients with CLO-resistant chronic schizophrenia (not exacerbation)
Kremer *et al.* (2004)	LAM 400 mg/day vs placebo added to AP	38	70	Inpatients with treatment-resistant schizophrenia
Akhondzadeh *et al.* (2005)	LAM 150 mg/day vs placebo added to RIS	36	56	Inpatients with schizophrenia
Zoccali *et al.* (2007)	LAM 200 mg/day vs placebo added to CLO	60	168	Outpatients with treatment-resistant schizophrenia
Goff *et al.* (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 *et al.* (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 ≥ 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

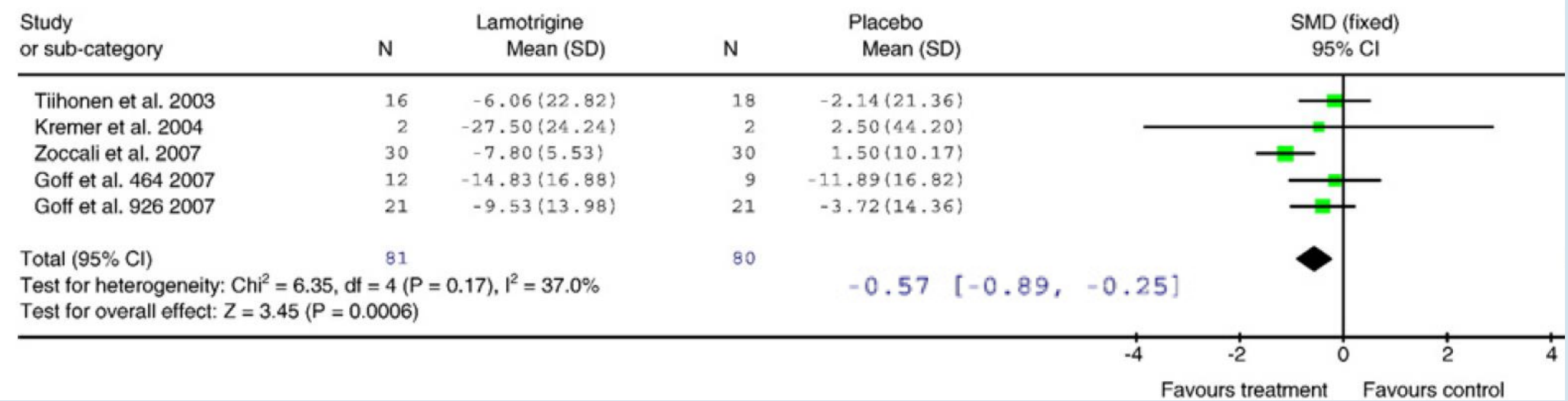
Improvement on negative, positive and general psychopathological symptomatology; Higher proportion discontinued the study early on placebo than on LAM (NNT 30, not statistically significant)

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)

Citrome L. *Expert Rev Neurother*. 2009;9:55-71.

WHAT ABOUT LAMOTRIGINE IN CLOZAPINE-RESISTANT SCHIZOPHRENIA?



Tiihonen J, et al. Schizophr Res 2009;109:10-14.

ADJUNCTIVE TOPIRAMATE AND SCHIZOPHRENIA

RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis	
Kim *et al.* (2006)	TOP 100 mg/day vs nothing added to OLZ (although randomized, the study was not double-blind)	60	84	Outpatients with schizophrenia	**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)**
Ko *et al.* (2005)	TOP 100 mg/day vs TOP 200 mg/day vs placebo added to AP	66	84	Inpatients with schizophrenia and overweight	**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**
Tiihonen *et al.* (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)	**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)**
Afshar *et al.* (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 ≥100 mg/day for the previous 2 months; inpatient or outpatient status not described	**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)**

Citrome L. ***Expert Rev Neurother***. 2009;9:55-71.

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

McEvoy JP, Scheifler PL, Frances A. The Expert Consensus Guideline Series, Treatment of Schizophrenia 1999. Journal of Clinical Psychiatry 60(Suppl 11):43, 1999.

ADJUNCTIVE VALPROATE AND SCHIZOPHRENIA

RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Hesslinger *et al.* (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 *et al.* (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 *et al.* (1998)	VAL 900–1200 mg/day vs placebo added to HAL	42	28	Inpatients with acute, non-manic schizophrenic or schizoaffective psychosis
Wassef *et al.* (2000)	VAL (plasma level 75–100 µg/ml) vs placebo added to HAL	12	21	Inpatients with acute exacerbation of chronic schizophrenia
Casey *et al.* (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 *et al.* (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

Citrome L. *Expert Rev Neurother*. 2009;9:55-71.

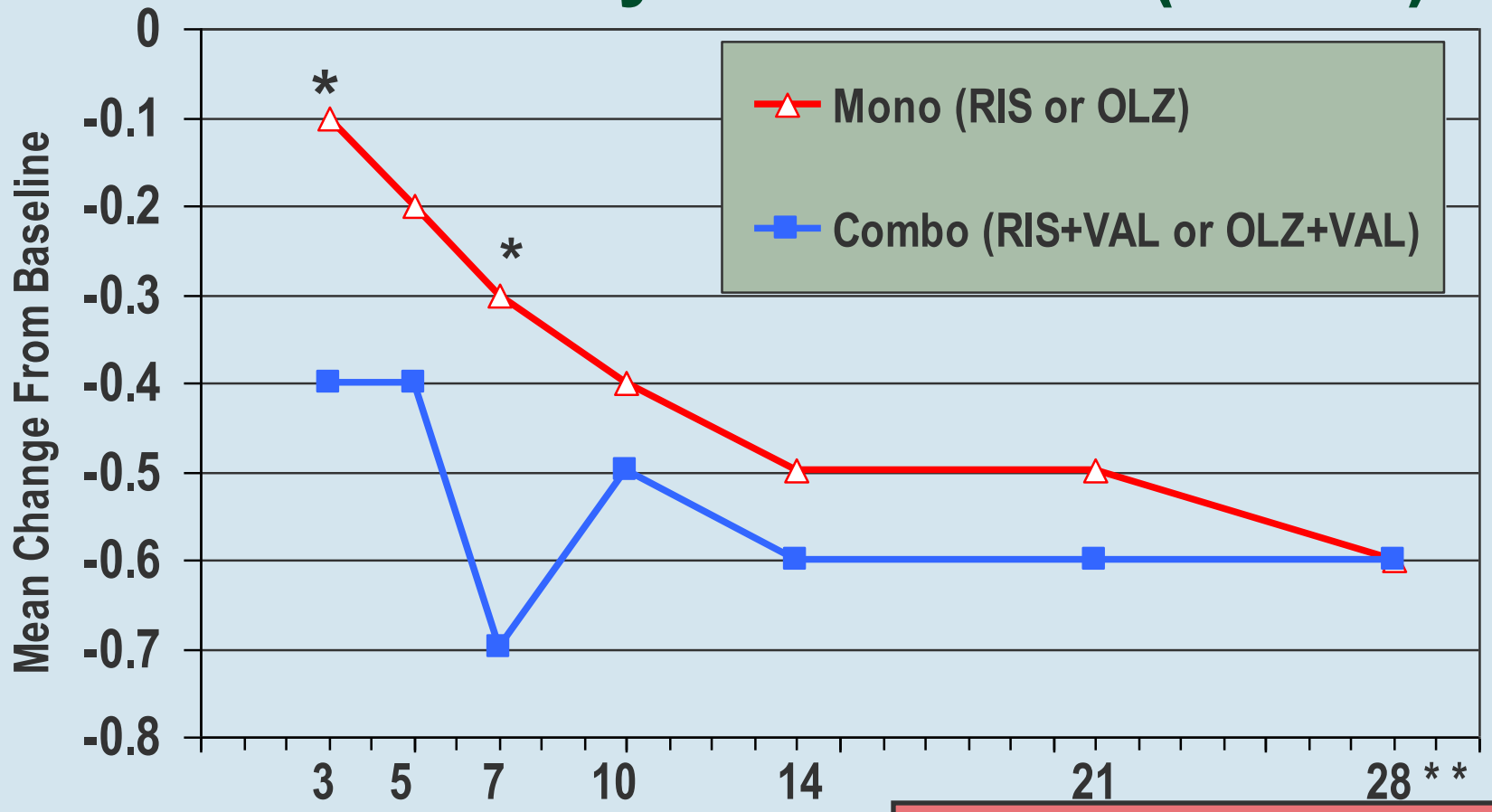
VALPROATE: AN ANTIAGGRESSIVE AGENT?

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

Lindenmayer JP, Kotsaftis A. Use of sodium valproate in violent and aggressive behaviors: a critical review. Journal of Clinical Psychiatry 61:123-128, 2000;
Citrome L. Schizophrenia and Valproate. Psychopharmacology Bulletin 37(Suppl 2):74-88, 2003.

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



*p<0.05

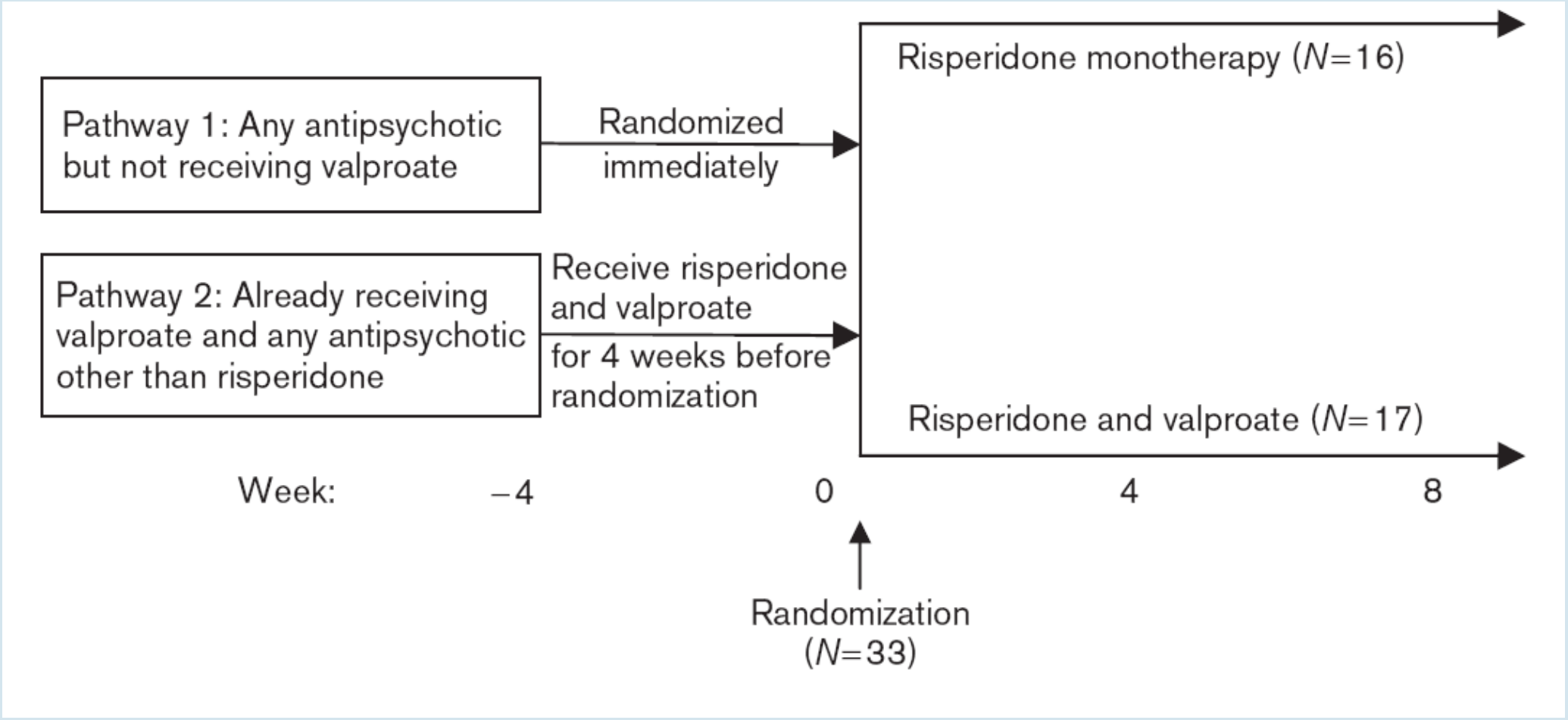
Baseline: Mono = 2.7; Combo = 2.8

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

Citrome L, Casey DE, Daniel DG, et al. Effects of Adjunctive Valproate on Hostility in Patients with Schizophrenia Receiving Olanzapine or Risperidone: A Double-Blind Multi-Center Study. Psychiatric Services 55(3):290-294, 2004.

RIS ALONE vs RIS + VAL

Randomized Clinical Trial: Open Label; Blinded Raters



Citrome L, Shope CB, Nolan KA, et al. Risperidone alone versus risperidone plus valproate in the treatment of patients with schizophrenia and hostility. International Clinical Psychopharmacology 2007;22(6):356-62.

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)

Citrome L, Shope CB, Nolan KA, et al. Risperidone alone versus risperidone plus valproate in the treatment of patients with schizophrenia and hostility. International Clinical Psychopharmacology 2007;22(6):356-62.

ADJUNCTIVE LITHIUM IN SCHIZOPHRENIA, I

RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis	
Gerlach *et al.* (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	Li appeared to have a suppressive effect on psychomotor agitation and aggression
Small *et al.* (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	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
Carman *et al.* (1981)	Li (target level 0.75–1.3 mEq/l) vs placebo added to AP (crossover)	18	4	Inpatients with schizophrenia or schizoaffective disorder	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
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	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)
Collins *et al.* (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 did not result in symptomatic improvement; Higher proportion discontinued the study early on Li than on placebo (NNT 3, 95% CI: 2 to 4)

Citrome L. *Expert Rev Neurother*. 2009;9:55-71.

ADJUNCTIVE LITHIUM IN SCHIZOPHRENIA, II

RCTs

Author (year)	Intervention (parallel double-blind randomized design unless noted)	n	Length (days)	Diagnosis
Schulz *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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

Citrome L. *Expert Rev Neurother*. 2009;9:55-71.

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

Volavka J. Neurobiology of Violence. 2nd Edition. Washington, DC: American Psychiatric Publishing, 2002.

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

Volavka J. Neurobiology of Violence. 2nd Edition. Washington, DC: American Psychiatric Publishing, 2002.

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

Volavka J. Neurobiology of Violence. 2nd Edition. Washington, DC: American Psychiatric Publishing, 2002.

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)

Citrome L, Volavka J. Treatment of Violent Behavior. In Tasman A, Lieberman J, Kay J (Eds): Psychiatry, 2nd Edition, John Wiley & Sons, Ltd, 2003.
Volavka J. Neurobiology of Violence. 2nd Edition. Washington, DC: American Psychiatric Publishing, 2002.

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

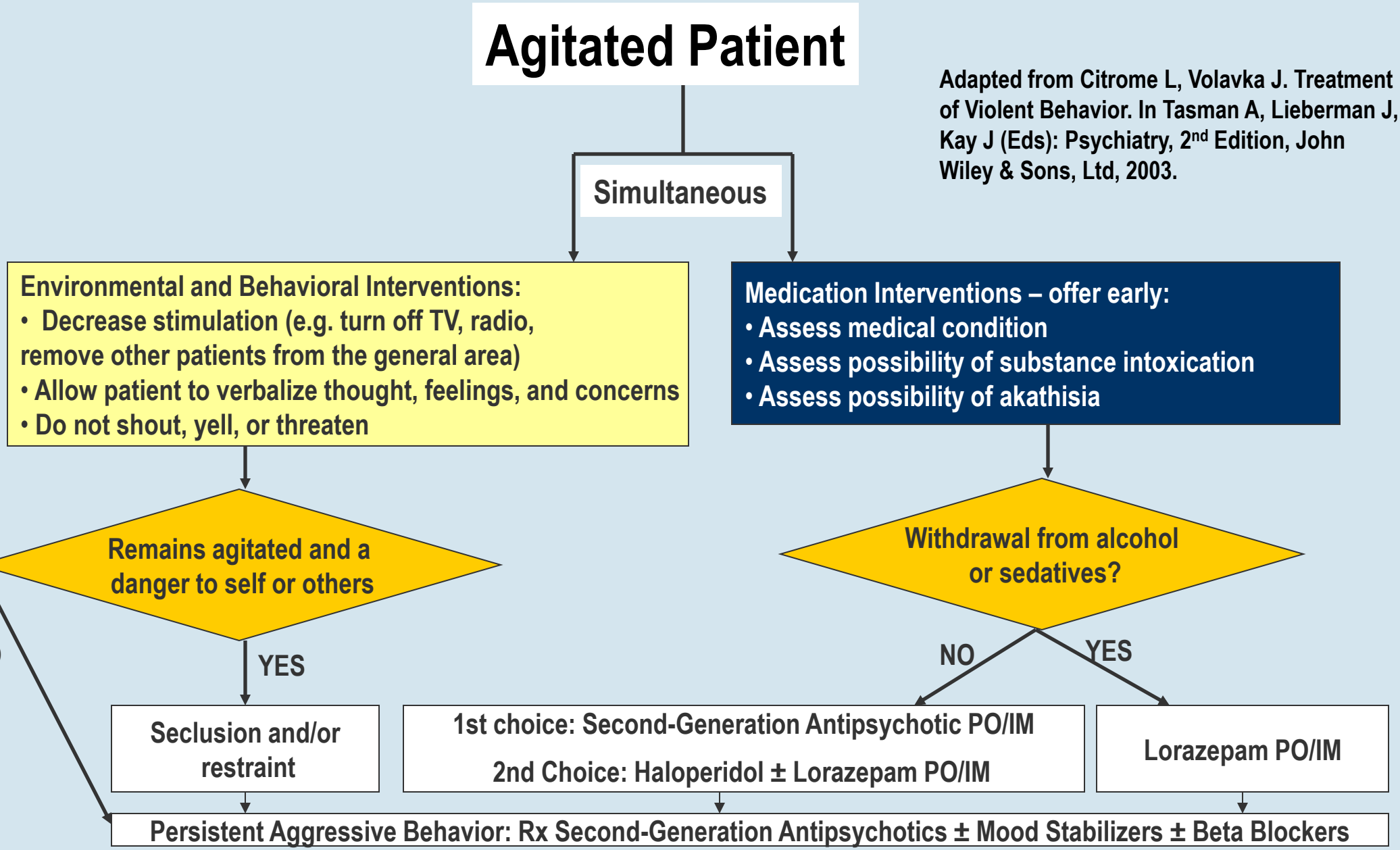
Citrome L, Volavka J. Treatment of Violent Behavior. In Tasman A, Lieberman J, Kay J (Eds): Psychiatry, 2nd Edition, John Wiley & Sons, Ltd, 2003.
Volavka J. Neurobiology of Violence. 2nd Edition. Washington, DC: American Psychiatric Publishing, 2002.

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

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

MANAGEMENT OF AGITATION: OVERVIEW *



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.

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