Psychopharmacologic Treatment of Aggressive/Self Injurious Intellectually Disabled Adults

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MAJOR TEACHING POINTS FOR THIS LECTURE

1. Psychopharmacologic treatment of maladaptive behaviors (i.e. aggression, self- injurious behavior, disruption / destruction) in intellectually disabled individuals requires greater rigor than treatment of the general psychiatric population. Specific treatment guidelines have been developed when psychotropic drugs are used in this population, especially targeting determination of minimal effective doses and evaluation of the continuing need for drug treatment.

2. Relatively little controlled psychopharmacologic research has been performed in aggressive, intellectually disabled individuals. Antipsychotic agents are the most rigorously studied psychotropic agents used to treat such aggression. There is some evidence that mood stabilizers, lithium, SSRI's, and beta-adrenergic blocking drugs are effective. To date, most studies have been performed in children and adolescents, rather than in adults, and most trials in adults have been uncontrolled and utilized small numbers of subjects. .

Pre-Exam Question 1

The incidence of aggressive and self injurious behavior changes in the following ways as I.Q. decreases:

A. It decreases
B. It increases
C. It changes as related to the psychiatric diagnosis
D. None of the above

Pre-Exam Question 2

The consensus of medical experts is that the top two most effective treatments for aggression in intellectually disabled individuals are:

A. Conventional and atypical antipsychotic agents
B. Atypical antipsychotic agents and mood stabilizers
C. SSRI's and atypical antipsychotic agents
D. Beta Blockers and Naltrexone

Pre-Exam Question 3

The following antipsychotic medications have been shown to be useful in double blind placebo controlled studies for the treatment of aggression in the intellectually disabled:

A. Risperidone
B. Olanzapine
C. Quetiapine
D. None of the above
E. All of the above

Pre-Exam Question 4

If a previously aggressive individual has been successfully treated with antipsychotic agents, and relapses when withdrawn from these agents, the chance of relapse occurring during a future withdrawal attempt is:

A. Very high
B. Not related to previous attempts
C. Related to the psychiatric diagnosis
D. Low

Pre-Exam Question 5

The chances that an intellectually disabled individual in whom aggressive symptoms have been significantly controlled while receiving an antipsychotic agent having a successful medication withdrawal on a first attempt are approximately:

A. 95%
B. 60%
C. 20%

OUTLINE

1. INTRODUCTION, PRE-EXAM QUESTIONS AND OUTLINE (Slides 1-9)
2. LOW RESEARCH VOLUME FOR PSYCHOPHARMACOLOGY OF ID (Slide 10)
3. ID DEFINITIONS AND BEHAVIORAL PHENOTYPES (Slides 10-12)
4. ID BEHAVIORAL PROBLEMS, IMPLICATIONS, AND INCIDENCES (Slides 14-19)
5. PRINCIPALS OF ASSESSMENT AND TREATMENT (Slides 20-22)
6. TYPES OF MEDICATIONS USED FOR ID PATIENTS (Slide 23)
7. SUMMARY OF WHAT DRUGS EXPERTS RECOMMEND (Slides 24-39)
8. METHODS OF QUANTIFYING MALADAPTIVE BEHAVIORS (Slides 40-43)
9. OLANZAPINE TREATMENT OF ID AGGRESSION (Slides 44-46)
10. RISPERIDONE TREATMENT OF ID AGGRESSION (Slides 47-48)

Outline (cont.)

11. QUETIAPINE TREATMENT OF ID AGGRESSION (Slide 49)
12. OTHER STUDIES OF ID AGGRESSION IN CHILDREN AND ADULTS (Slides 50-56)
13. EFFECTS OF SEROTONERGIC ANTIDEPRESSANTS ON ID AGGRESSION (Slides 57-59)
14. EFFECTS OF TOPIRAMATE ON ID AGGRESSION (Slides 60-62)
15 EFFECTS OF ANTIPSYCHOTIC WITHDRAWAL ON ID AGGRESSION (63-64)
16. MINIMUM AND RELAPSE-INDUCING DOSES OF TYPICAL AND ATYPICAL ANTIPSYCHOTIC DRUGS (Slides 65-66)
17. REPEATED RELAPSES AFTER DRUG WITHDRAWAL FOLLOWING AN INITIAL DRUG WITHDRAWAL-INDUCED RELAPSE (Slide 67)
18. CONCERNS ABOUT USING ANTIPSYCHOTIC AND OTHER PSYCHOTROPIC MEDICATIONS IN ID POPULATIONS (Slides 68-71)
19. POST-EXAM QUESTIONS AND ANSWERS (Slides 72-77)

NUMBER OF PUBMED HITS FOR AUTISM/MENTAL RETARDATION AND OTHER PSYCHIATRIC DIAGNOSES ACROSS PSYCHOPHARMACOLOGY RELEVANT TERMS

	Psychotropic Drugs	Antidepressant Drugs	Antipsychotic Drugs	Risperidone	Olanzapine	Haloperidol
Autism	206	48	208	56	10	62
Mental Retardation	627	147	523	48	12	82
Schizophrenia	10837	1159	13875	1288	949	2654
Depression	12941	11309	3904	178	150	697
Geriatric	10591	5484	6543	352	238	933

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DEFINITIONS OF VARIOUS DEGREES OF MENTAL RETARDATION

1)

LEVEL OF MENTAL RETARDATION	IQ	PERCENTAGE
MILD	50-55 to 70	85%
MODERATE	35-40 to 50-55	10%
SEVERE	20-25 to 35-40	4%
PROFOUND	Below 20 or 25	1%

2) LIMITATION IN 2 OR MORE ADAPTIVE SKILLS*

3) ESTIMATED PREVALENCE OF MENTAL RETARDATION = 1 TO 3% IN THE GENERAL POPULATION

*Adaptive skills include communication, home living, community use, health and safety self care, social skills, self direction, functional academics, work.

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MR/DD Behavioral Phenotypes

Syndrome	Behavioral Features
Cornelia de Lange	Stereotypy, SIB
Fetal Alcohol Syndrome	ADHD, conduct problems
Pre/perinatal encephalopathy	ADHD
Heavy metal poisoning	Irritability, seizures, choreoathetosis
PKU	Seizures, hyperactivity
Lesch-Nyhan Syndrome	Severe self-biting, chorea

MR/DD Behavioral Phenotypes

Syndrome	Behavioral Features
Downs Syndrome	Dementia, oppositional defiant behavior
Prader Willi	Hyperphagia, OCD, skin picking
Tuberous Sclerosis	Autism, seizures, impulsivity, aggresion
Williams	ADHD, outgoing, talkative, language problems
Fragile X	ADHD, autism, SIB, stereotypy, hyperactivity
Angelman	Paroxysmal laughter, hand Flapping/clapping

BEHAVIORAL PROBLEMS ASSOCIATED WITH MENTAL RETARDATION**

*Physical aggression (hitting, biting, pushing)

*Verbal Aggression (yelling, screaming, cursing)

*Property Destruction (throwing objects, breaking furniture)

*Self-Injury (hitting, biting, scratching self)

Pica (ingesting inedible objects)

Rumination (regurgitation and swallowing gastric contents)

Self-induced vomiting

Polydipsia (inappropriate water drinking)

Wandering/AWOL

Inappropriate sexual behaviors

Over-activity/hyperactivity

* Major behaviors for which psychotropic agents are utilized. These are thought to occur in 5%-17% of the mentally retarded.

** Behaviors increase in intensity and frequency with decreasing IQ, and are most prevalent in those with the lowest 15% of IQs.

NARRATIVE EXCERPTS FROM NBR REPORTS INDICATING THE NEED FOR INCREASES IN THE DOSES OF CONVENTIONAL ANTIPSYCHOTIC DRUGS

"Has continued to do poorly since last review... Continues to have difficulties with SIB, aggression, destructive behavior and copraphagia. ... difficulties have worsened since last neuroleptic withdrawal."

"SIB, aggression and tantruming are essentially the same, but SIB has worsened."

"She tried to bite her mother and kicked out the windows on the unit."

"Her behavior is out of control... A marked escalation of aggression and disruption occurred."

"Has been louder and is more disruptive...Broke a glass... Patient's behavior has been deteriorating..."

"He continues to have a variety of target maladaptive behaviors including being louder, hand biting, more physical, intense rocking and pushing away."

"SIB and property destruction have worsened... Time in restraints has accelerated.... Decreased ability to control herself."

"The worsening has not been transient... There was a dramatic worsening of re-enforcers earned..."

"Since the last review she has had substantial worsening of SIB and appearance alteration..."

"He started SIB and has been involved in aggression..."

"All these difficulties have been demonstrated to be worsening (aggression, SIB, tantruming)..."

MAJOR TARGET SYMPTOMS OF CASES AT MURDOCH CENTER PREVIOUSLY OR CURRENTLY ENGAGED IN THE NBR PROCESS

	ALL CASES (N = 255)
AGGRESSION	73%
SELF-INJURIOUS BEHAVIOR (SIB)	45%
AGGRESSION PLUS SELF-INJURIOUS BEHAVIOR (SIB)	37%
DESTRUCTION/DISRIBUTION	41%
AGITATION	8%
OTHER	9%
UNDEFINED	15%

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CLINICAL DIAGNOSES OF 170 PATIENTS CURRENTLY IN THE NEUROBEHAVIORAL REVIEW PROCESS AT MURDOCH CENTER

AUTISTIC DISORDER	21%
BIPOLAR DISORDER	18%
MOOD DISORDER (DEPRESSION)	9%
STEREOTYPIC MOVEMENT DISORDER (WITH OR WITHOUT SIB)	6%
INTERMITTANT EXPLOSIVE DISORDER	9%
PERSONALITY DISORDER	3%
CONDUCT DISORDER	8%
PSYCHOTIC DISORDER	5%
ANXIETY DISORDER	2%
OBSESSIVE-COMPULSIVE DISORDER	4%
OTHER	4%
NO DIAGNOSIS	12%

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Behavior problems that often require inpatient treatment (hospitalization, institutionalization)

- Self-injury
  - SIB that produces injury (head bang, eye gouge, skin picking, biting)
- Aggression
  - Aggression that produced injury to others, property damage
- Severe ritualistic behaviors
  - SIB &/or aggression when ritual interrupted, or in response to change
- Pica
  - Ingesting foreign objects that requires medical intervention (e.g. surgery)
- Polydipsia
  - Water drinking that produces hyponatremic seizures

What are the clinical realities for patients with severe & persistent behavior disorders?

- Long-term institutionalization / frequent re-hospitalization

- Use of psychotropic medication
  - High doses of medication
  - Polypharmacy
  - Use of PRN & STAT medication

- Use of restrictive behavior management
  - seclusion / restraint
  - Environmental restrictions / modifications
  - 1:1+ staffing patterns

- Risk management issues
  - Increased risk of injuries (e.g.fractures)
  - Increased risk of abuse

Comprehensive Assessment of the Behavioral Problem

- A thorough medical and medication history must be obtained
  - ❖ R/O medication side effects (i.e. EPS, NMS, Serotonin syndrome).
  - ❖ R/O medical illness (constipation, infection, metabolic condition)
  - ❖ Functional analysis to rule out environmental etiology
- Direct Interview-consumer input may be limited by verbal ability

Psych/Behavioral Decompensation: Methods of Detection

- Medication is only one component of multi-faceted, holistic tx plan
- Inappropriate/poorly advised med use may complicate clinical picture
- Psych d/o may present uniquely in MR
- Consider rapidity of onset of behavioral changes
- Consider age of onset of changes
- Maintain high index of suspicion

PSYCHOTROPIC MEDICATION GUIDELINES

Do's

Treat any substance prescribed to improve or stabilize mood, mental status, or behavior as a psychotropic medication.

Use psychotropic medications with a coordinated multidisciplinary care plan.

Use psychotropic medication based on a psychiatric diagnosis or a specific behavioral-pharmacologic hypothesis and only after conducting a complete diagnostic and functional assessment.

Obtain written informed consent from guardian.

Track treatment efficacy by defining objective index behaviors and quality of life outcomes and measure them using empirical methods.

Monitor for tardive dyskinesia using standardized assessment instruments if antipsychotic or other dopamine blocking medications are prescribed.

Monitor for side effects using standardized assessment instruments.

Conduct clinical and data review on a regular and systematic basis.

Strive to use the lowest optimal effective dose.

Evaluate drug and monitoring practices through a peer or team quality review.

Don'ts

Don't use psychotropic drugs excessively, for convenience, as a substitute for meaningful psychosocial services or in quantities that interfere with quality of life activity.

Avoid frequent drug and dose changes.

Avoid intraclass polypharmacy and minimize interclass polypharmacy to the degree possible to decrease non-compliance and side effects.

Minimize: Long-term PRN orders, use of long-acting sedative hypnotics, long-term use of short acting sedative hypnotics, long-term use of benzodiazepines, high antipsychotic medication doses, and long-term use of anticholinergic medications.

MEDICATIONS USED TO TREAT CHALLENGING BEHAVIORS INCLUDING AGGRESSION, SELF-INJURY AND DISRUPTION/ DESTRUCTION IN THE INTELLECTUALLY DISABLED

- Conventional Antipsychotic Agents (thioridazine, haloperidol, chlorpromazine, etc.); Atypical Antipsychotic Agents (risperidone, olanzapine, aripiprazole).
- SSRI ANTIDEPRESSANTS: Fluoxetine, Paroxetine, Citalopram, etc.
- MOOD STABILIZERS: Lithium, Valproic Acid, Carbamazepine, Topiramate.
- OPIATE BLOCKERS: Naltrexone
- BENZODIAZEPINES: Diazepam, Clonazepam, etc.
- BETA BLOCKERS: Propranolol

What Do The Experts Say?

The Expert Consensus Survey,

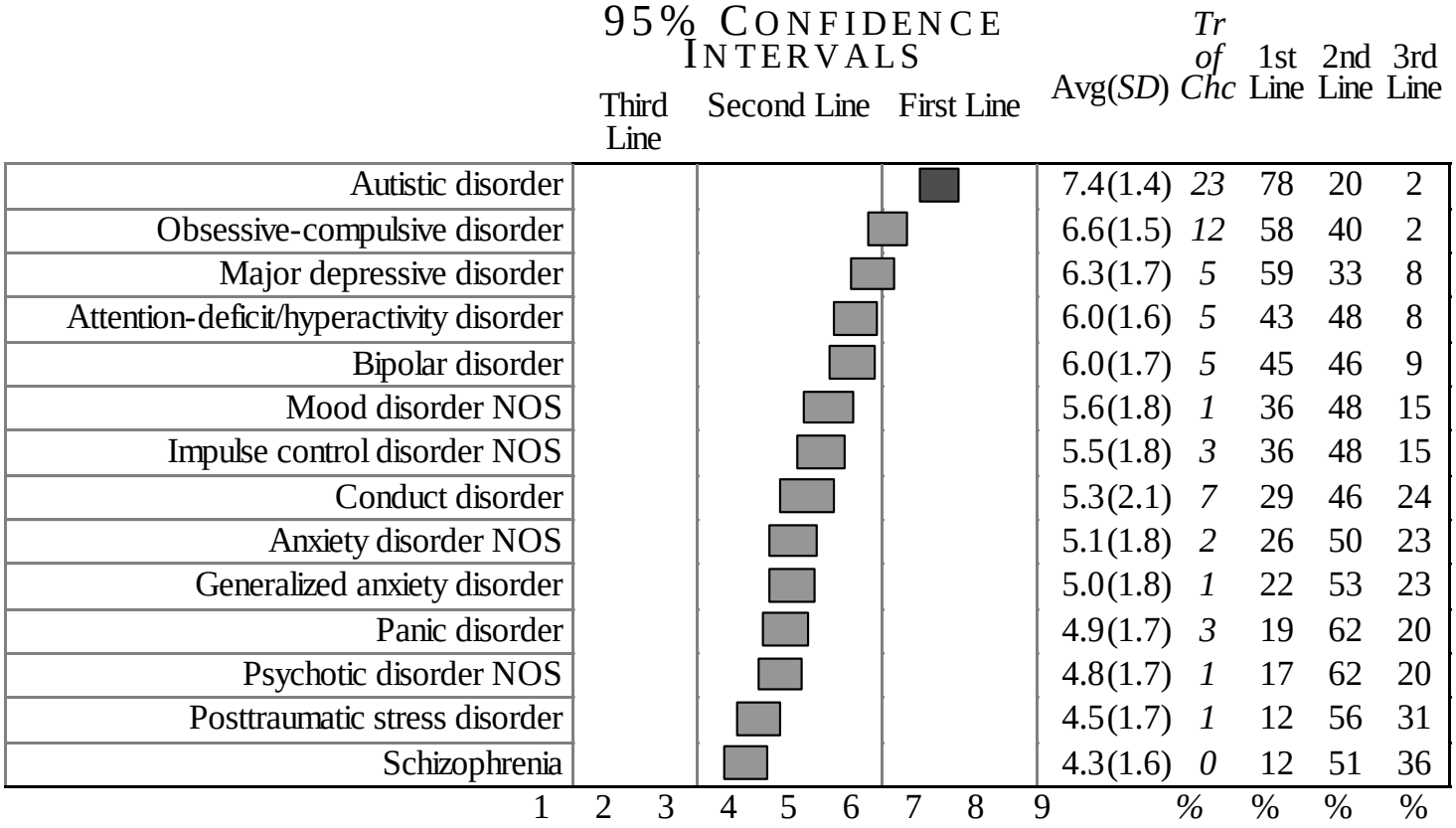
J. Rush & A. Frances (2000). A*merican Journal on Mental Retardation, 105,* 159-228.

How To Read Results

- 1-9 point scale
- 1= extremely inappropriate
- 9= extremely appropriate
- “first-line” treatment= scores $\geq$6.5
- “second-line” treatment= scores between 3.5 and 6.49
- [*]= rated 9 by $\geq$ half of experts

Survey Questions Answered by All the Experts

1. There is some controversy in the field about how possible it is to diagnose specific DSM-IV disorders reliably in clients/patients with ***more severe MR***. Use a rating of 7–9 if you can usually to always diagnose the disorder reliably in someone with more severe MR, 4–6 if you sometimes can, and 1–3 if you rarely to never can.


95% CONFIDENCE INTERVALS
Third Line
Second Line
First Line
Avg(SD)
Tr of Chc
1st Line
2nd Line
3rd Line
Autistic disorder 7.4(1.4) 23 78 20 2
Obsessive-compulsive disorder 6.6(1.5) 12 58 40 2
Major depressive disorder 6.3(1.7) 5 59 33 8
Attention-deficit/hyperactivity disorder 6.0(1.6) 5 43 48 8
Bipolar disorder 6.0(1.7) 5 45 46 9
Mood disorder NOS 5.6(1.8) 1 36 48 15
Impulse control disorder NOS 5.5(1.8) 3 36 48 15
Conduct disorder 5.3(2.1) 7 29 46 24
Anxiety disorder NOS 5.1(1.8) 2 26 50 23
Generalized anxiety disorder 5.0(1.8) 1 22 53 23
Panic disorder 4.9(1.7) 3 19 62 20
Psychotic disorder NOS 4.8(1.7) 1 17 62 20
Posttraumatic stress disorder 4.5(1.7) 1 12 56 31
Schizophrenia 4.3(1.6) 0 12 51 36
1 2 3 4 5 6 7 8 9
% % % %

Survey Questions Answered by All the Experts (Cont.)

4. How necessary is it to prescribe a medication as part of the ***initial treatment plan*** for a patient who clearly meets full DSM-IV criteria for the following disorders? Assume that appropriate behavioral interventions are being provided.

	Medication experts			Psychosocial experts		
	Avg	Rank	*Tr of Chc*	Avg	Rank	*Tr of Chc*
Schizophrenia	8.9	Chc	*91*	7.8	1st	*41*
Bipolar disorder, manic	8.7	Chc	*80*	7.8	1st	*34*
Bipolar disorder, depressed	8.6	Chc	*71*	7.5	1st	*25*
Major depressive disorder	8.1	Chc	*50*	7.4	1st	*25*
Psychotic disorder NOS	7.8	1st	*49*	6.8	2nd	*18*
Obsessive-compulsive disorder	7.0	1st	*18*	5.6	2nd	*5*
Panic disorder	6.9	2nd	*20*	5.2	2nd	*5*
Attention-deficit/hyperactivity disorder	6.7	2nd	*14*	5.5	2nd	*5*
Stereotypic movement disorder	6.4	2nd	*9*	4.0	3rd	*2*
Generalized anxiety disorder	5.8	2nd	*4*	5.1	2nd	*5*
Posttraumatic stress disorder	5.7	2nd	*2*	4.4	2nd	*2*
SMD without self-injurious behavior	4.6	2nd	*2*	2.5	3rd	*0*
Conduct disorder	4.1	2nd	*2*	2.7	3rd	*0*
Substance abuse disorder	3.6	3rd	*0*	3.4	3rd	*0*
Pica	3.4	3rd	*0*	2.1	3rd	*0*
Adjustment disorder	2.9	3rd	*0*	2.3	3rd	*0*
			%			*%*

Survey Questions Answered by All the Experts (Cont.)

5. Now rate the appropriateness of including a medication in the ***initial treatment plan*** for a client/patient with one of the following **target symptoms**. Assume that the symptom is present at a level that is severe, persistent, and markedly impairing, but that a clear-cut and specific DSM-IV diagnosis cannot be made.

	Medication experts			Psychosocial experts		
	Avg	Rank	*Tr of Chc*	Avg	Rank	*Tr of Chc*
Self-injurious behavior with risk of lasting harm	**8.1**	**Chc**	***53***	6.3	2nd	*19*
History of behavioral deterioration when off medication	**7.9**	**1st**	***40***	**7.4**	**1st**	***15***
Aggression to others that poses a risk	**7.9**	**1st**	***44***	5.9	2nd	*9*
Symptoms are very severe	**7.8**	**1st**	***44***	6.5	2nd	*6*
Previous good response to medication	**7.7**	**1st**	***36***	6.7	2nd	*9*
Lack of response to psychosocial interventions	**7.4**	**1st**	***27***	6.8	2nd	*9*
Symptoms interfere with individual's participation in rehabilitation	**6.9**	**1st**	***11***	5.4	2nd	*0*
Family history of good response	6.4	2nd	*9*	5.0	2nd	*0*
Symptoms have persisted > a few weeks	6.2	2nd	*11*	5.1	2nd	*2*
Symptoms very disruptive to family or staff	6.0	2nd	*7*	4.2	2nd	*0*
Family history of psychiatric disorder	5.6	2nd	*0*	4.7	2nd	*4*
Client/patient requests medication	5.3	2nd	*0*	3.8	3rd	*0*
Family/staff requests that patient receive medication	4.4	2nd	*0*	3.5	3rd	*0*
The mental retardation is severe or profound	4.0	3rd	*2*	3.2	3rd	*0*
			%			*%*

Survey Questions Answered by All the Experts (Cont.)

6. What factors would make you more likely to use medications in the initial treatment of a target symptom regardless of whether it is possible to make a specific DSM-IV diagnosis?

	Medication experts			Psychosocial experts		
	Avg	Rank	*Tr of Chc*	Avg	Rank	*Tr of Chc*
Self-injurious behavior with risk of lasting harm	**8.1**	**Chc**	***53***	6.3	2nd	*19*
History of behavioral deterioration when off medication	**7.9**	**1st**	***40***	**7.4**	**1st**	***15***
Aggression to others that poses a risk	**7.9**	**1st**	***44***	5.9	2nd	*9*
Symptoms are very severe	**7.8**	**1st**	***44***	6.5	2nd	*6*
Previous good response to medication	**7.7**	**1st**	***36***	6.7	2nd	*9*
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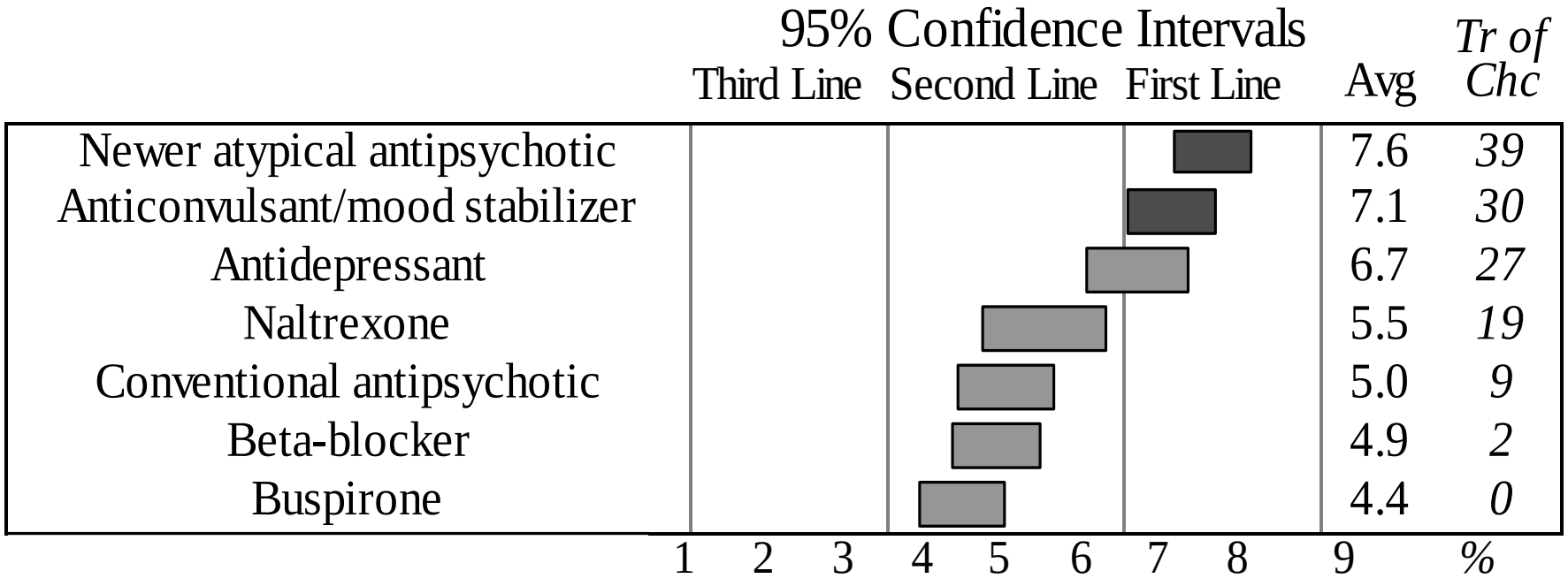
Symptoms interfere with individual's participation in rehabilitation	**6.9**	**1st**	***11***	5.4	2nd	*0*
Family history of good response	6.4	2nd	*9*	5.0	2nd	*0*
Symptoms have persisted > a few weeks	6.2	2nd	*11*	5.1	2nd	*2*
Symptoms very disruptive to family or staff	6.0	2nd	*7*	4.2	2nd	*0*
Family history of psychiatric disorder	5.6	2nd	*0*	4.7	2nd	*4*
Client/patient requests medication	5.3	2nd	*0*	3.8	3rd	*0*
Family/staff requests that patient receive medication	4.4	2nd	*0*	3.5	3rd	*0*
The mental retardation is severe or profound	4.0	3rd	*2*	3.2	3rd	*0*
			%			*%*

Survey Questions Answered Only by Medication Experts (Cont.)

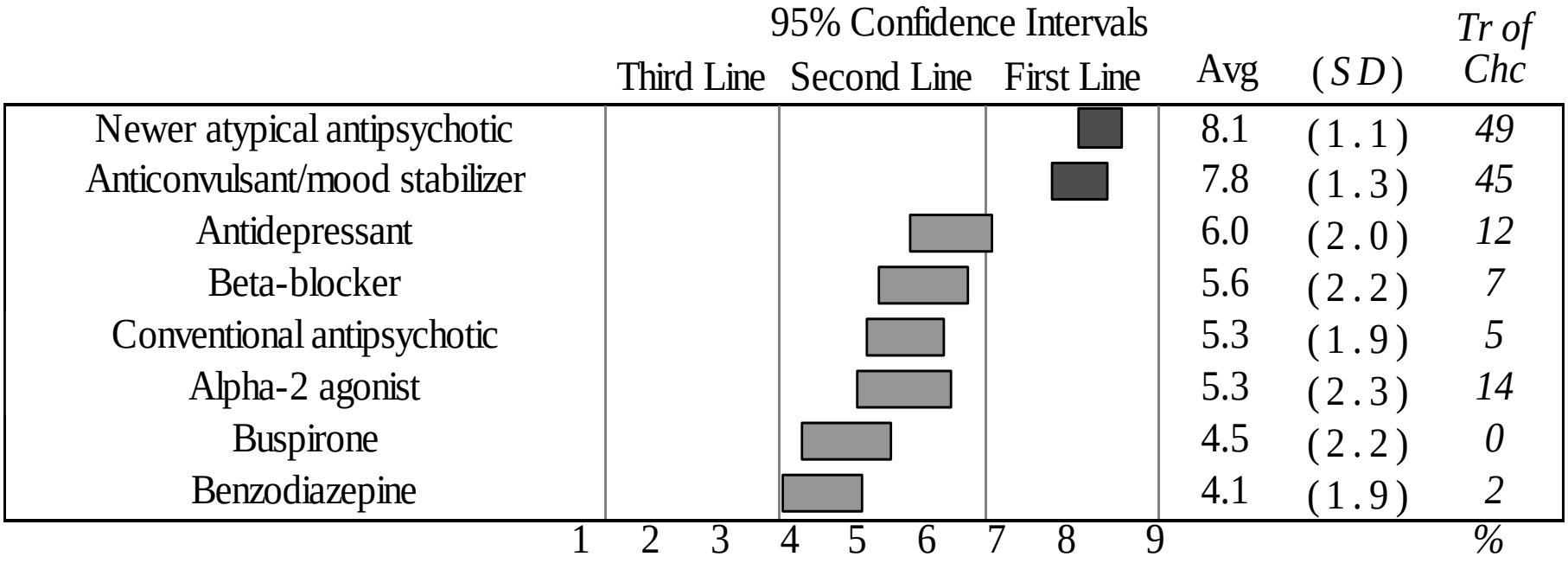
19a. Rate the following classes of medications for treating a patient with MR with severe ***self-injurious behavior***.



Benzodiazepines and sedating antihistamines were rated 3rd line.

Survey Questions Answered Only by Medication Experts (Cont.)

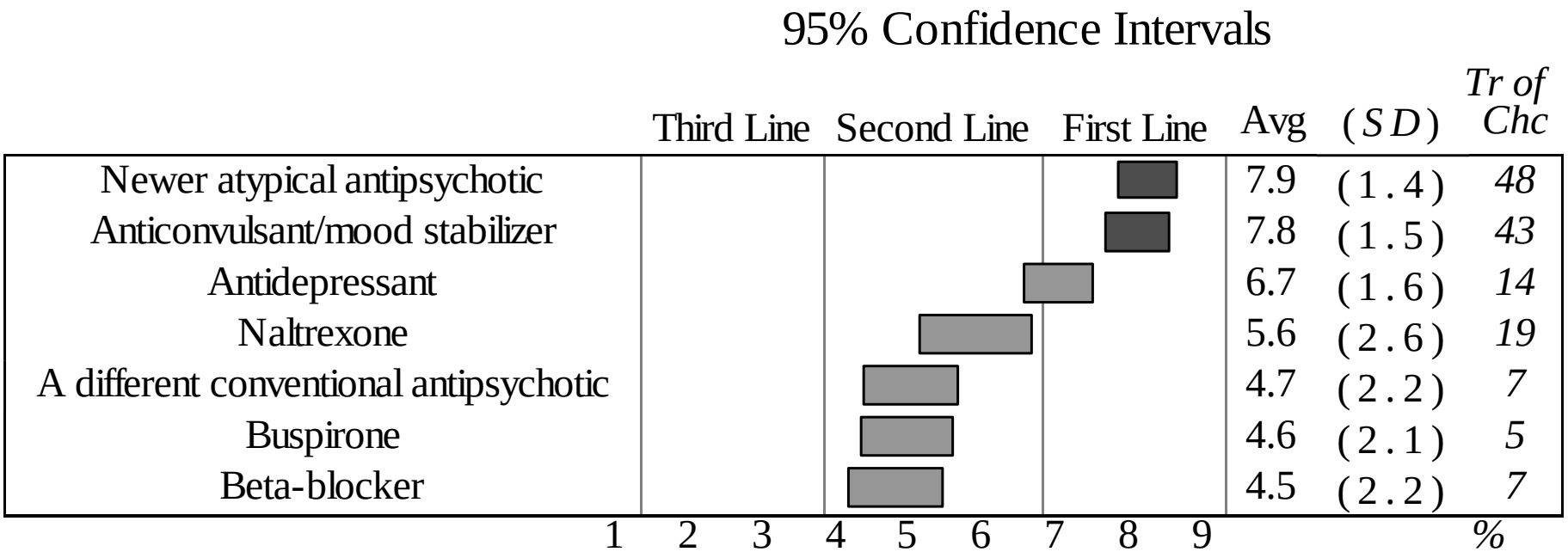
19b. Rate the following classes of medications for treating a patient with severe and persistent ***physical aggression to people or property***.



Psychostimulants and sedating antihistamines were rated 3rd line.

Survey Questions Answered Only by Medication Experts (Cont.)

41a. Now assume ***no response*** to an adequate initial trial of a ***conventional antipsychotic*** for **SIB**. Rate the appropriateness of switching to the following.


95% Confidence Intervals
Third Line
Second Line
First Line
Avg
(SD)
Tr of Chc
Newer atypical antipsychotic
7.9
(1.4)
48
Anticonvulsant/mood stabilizer
7.8
(1.5)
43
Antidepressant
6.7
(1.6)
14
Naltrexone
5.6
(2.6)
19
A different conventional antipsychotic
4.7
(2.2)
7
Buspirone
4.6
(2.1)
5
Beta-blocker
4.5
(2.2)
7
1 2 3 4 5 6 7 8 9
%

QUARTERLY WRITTEN SUMMARIES REVIEWING STATUS OF INDIVIDUALS AND CHANGES SINCE LAST NBR

1. SUBJECT DIAGNOSIS
2. PSYCHOTROPIC AND OTHER MEDICATIONS GIVEN AND MEDICATION CHANGES SINCE LAST REVIEW
3. SIGNIFICANT ADVERSE OR SIDE EFFECTS
4. WEIGHT CHANGES
5. TARGET SYMPTOMS
6. CHANGES IN BEHAVIORAL INTERVENTION PLANS
7. MONITORING METHODS
8. PROGRESS TOWARD GOALS
9. TARGET SYMPTOMS AND OTHER BEHAVIORAL CHANGES
10. LONGITUDINAL QUANTITATIVE GRAPHING OF TARGET BEHAVIORS

Define the “problem”

- Quantify behavioral frequency, intensity
- 10 point behavioral frequency and severity rating continuum
- Anchored, well-defined scales
- Facilitates communication

Mikkelson EJ. Psychiatric Annals 29. 1999, May

Mikkelson's 10 Point Rating Continuum-Frequency/Severity

1. One event q 6 mo
2. One event q 3-6 mo
3. One event q 1-3 mo
4. One event q 1-4 wk
5. One event q wk
6. 2-3 events q wk
7. 6-7 events q wk
8. 1-2 events daily

1. Mild/infrequent annoyance to self/others
2. Severe disruption to QOL of self/others
3. Significant verbal aggression, periodic mild property dest.
4. Frequent destruction of property
5. Frequent SIB or aggression barely leading to tissue damage
6. Frequent SIB or aggression leading to tissue damage
7. Disfiguring SIB or aggression inflicted on others

Mikkelson's Algorithm for Intervention

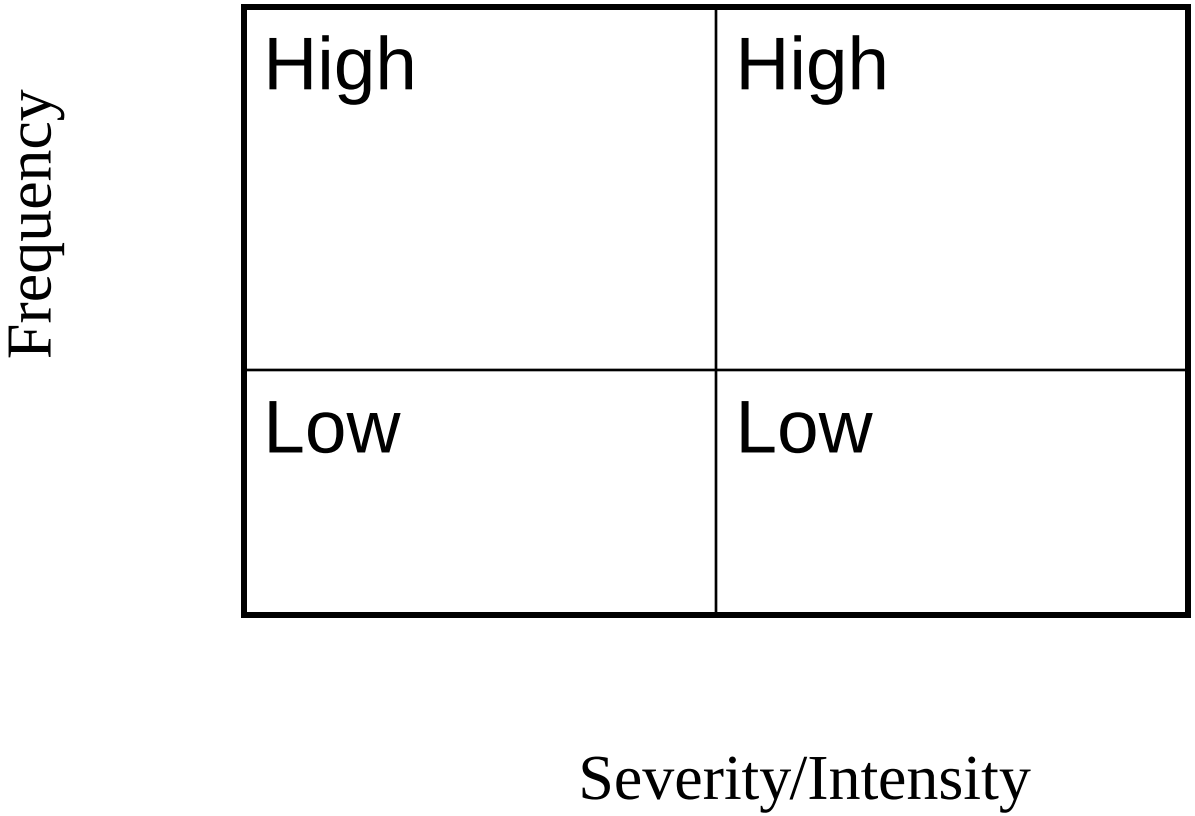


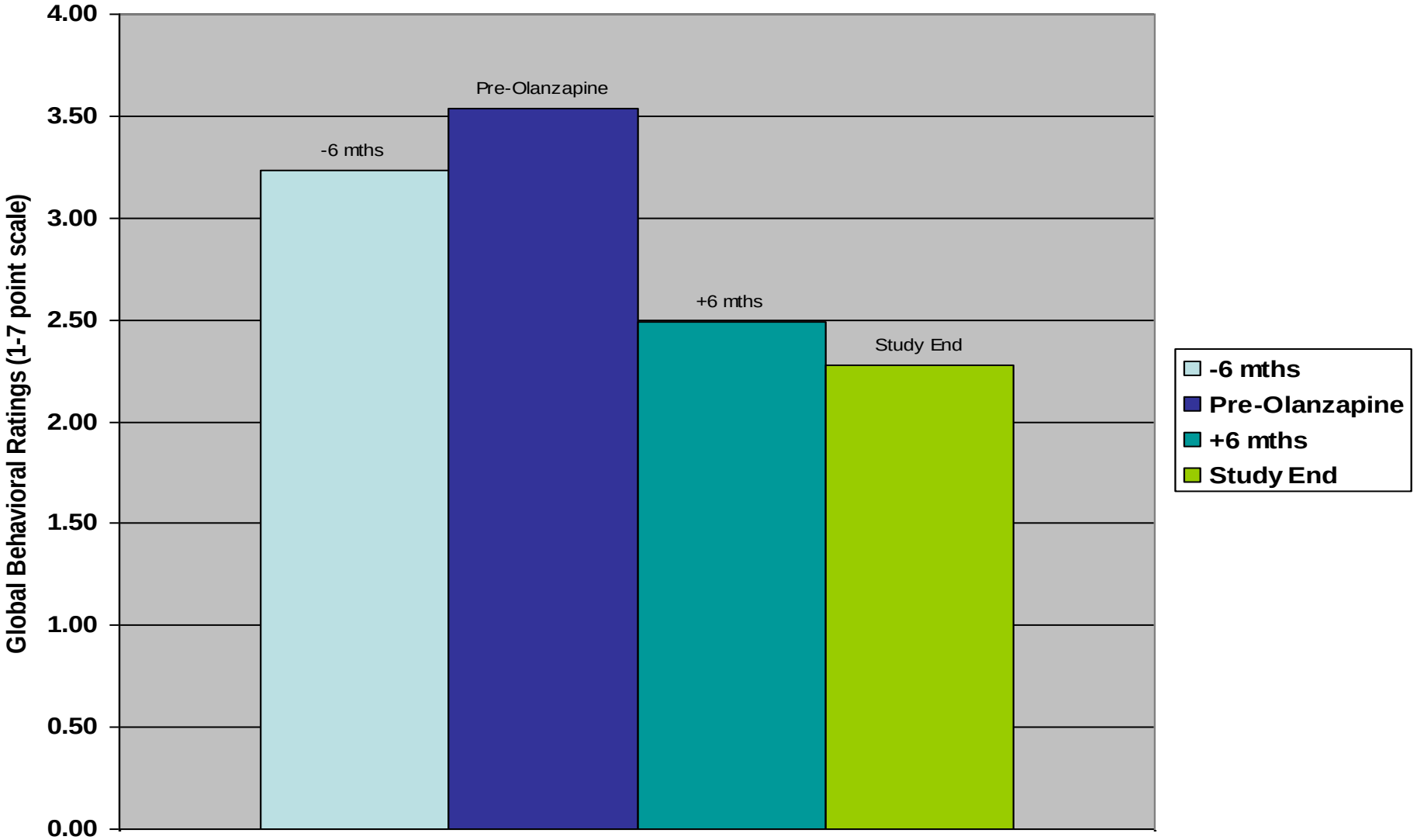
Table 1

DESCRIPTIVE INFORMATION ON 20 INSTITUTIONALIZED INTELLECTUALLY DISABLED ADULTS RECEIVING OLANZAPINE FOR CHALLENGING BEHAVIORS

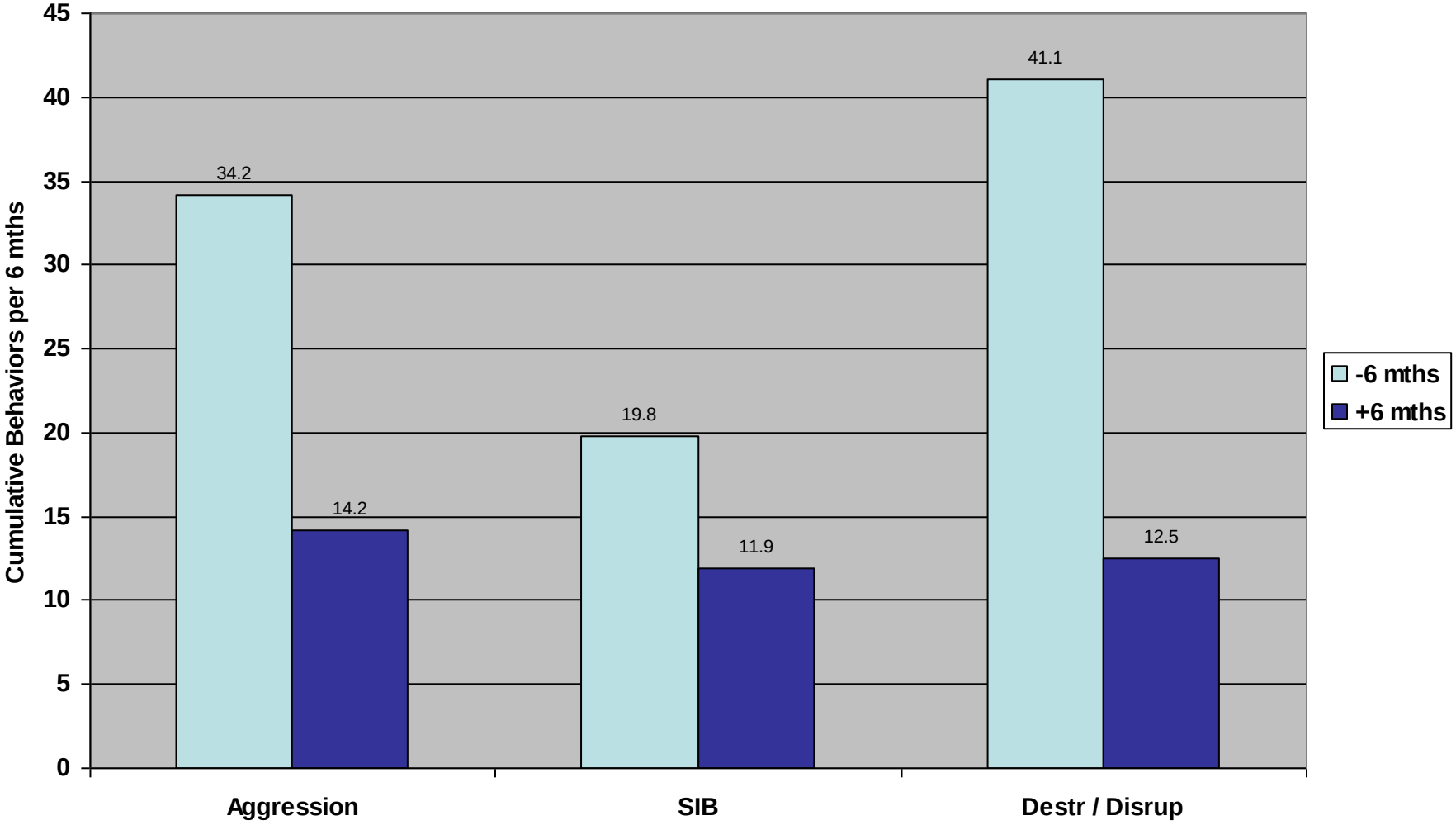
CASE	GENDER/AGE/ETHNICITY	PSYCHIATRIC DIAGNOSIS	LEVEL OF RETARDATION	
			COGNITIVE	ADAPTIVE
A.	M/45/AA	BEHAV. DIS., EXPLOSIVE PERSONALITY DIS.	SEVERE	SEVERE
B.	M/52/W	BEHAV. DISORDER NOS	PROFOUND	PROFOUND
C.	M/53/W	MOOD DIS. NOS, CHRONIC SCHIZ.	SEVERE	SEVERE
D.	M/18/W	AUTISM	SEVERE	PROFOUND
E.	F/40/AA	BPAD	SEVERE	PROFOUND
F.	F/33/W	BPAD, INTERMITTENT EXPLOSIVE DIS.	SEVERE	SEVERE
G.	M/52/W	NO DIAGNOSIS	PROFOUND	PROFOUND
H.	F/54/W	PSYCHOSIS NOS	MODERATE	PROFOUND
I.	M/54/W	PARANOID SCHIZ, OCD	MILD	PROFOUND
J.	M/30/W	AUTISM, BPAD	PROFOUND	PROFOUND
K.	M/24/W	BEHAV. DIS. NOS, INTERMITTENT EXPLOSIVE DIS.	PROFOUND	PROFOUND
L.	F/41/W	BPAD, BEHAV. DIS, NOS	MODERATE	PROFOUND
M.	F/55/AA	SCHIZOPHRENIA VS BPAD	PROFOUND	PROFOUND
N.	F/38/AA	MAJOR DEPRESSIVE DIS. WITH PSYCHOSIS	SEVERE	PROFOUND
O.	F/49/AA	INTERMITTENT EXPLOSIVE DISORDER	MILD	SEVERE
P.	F/50/AA	BPAD	SEVERE	PROFOUND
Q.	F/40/W	BPAD	PROFOUND	PROFOUND
R.	F/43/W	BEHAV. DISORDER NOS, BPAD	PROFOUND	PROFOUND
S.	F/46/W	AUTISM, SCHIZOPHRENIA, OCD	PROFOUND	MODERATE
T.	M/36/W	BPAD	MODERATE	PROFOUND

Abbreviations: M = Male, F = Female, W = White, AA = African American
BPAD = Bipolar Affective Disorder, OCD = Obsessive-Compulsive Disorder

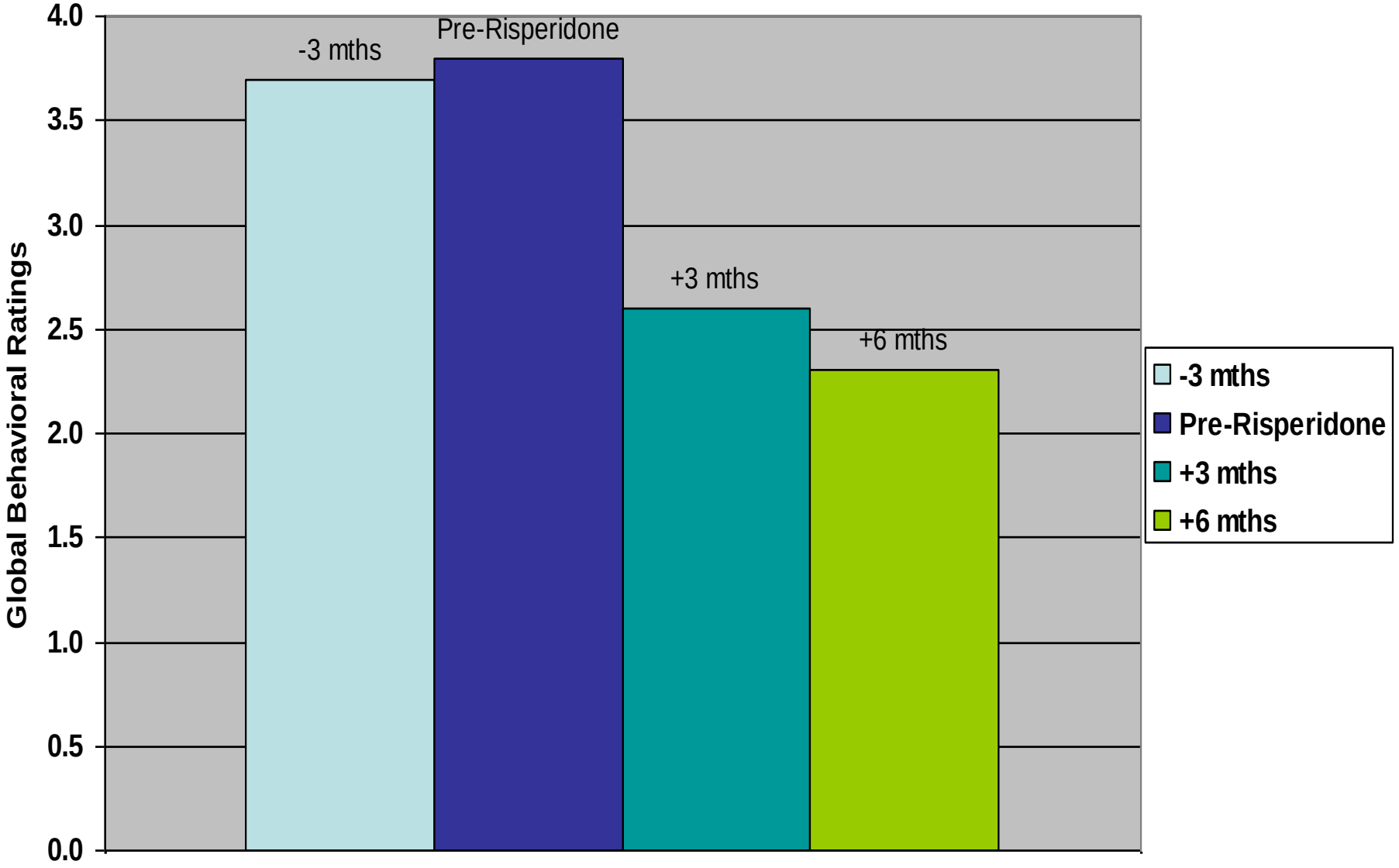
Global Behavioral Ratings of 20 Adults with Mental Retardation Before and After beginning Treatment with Olanzapine.



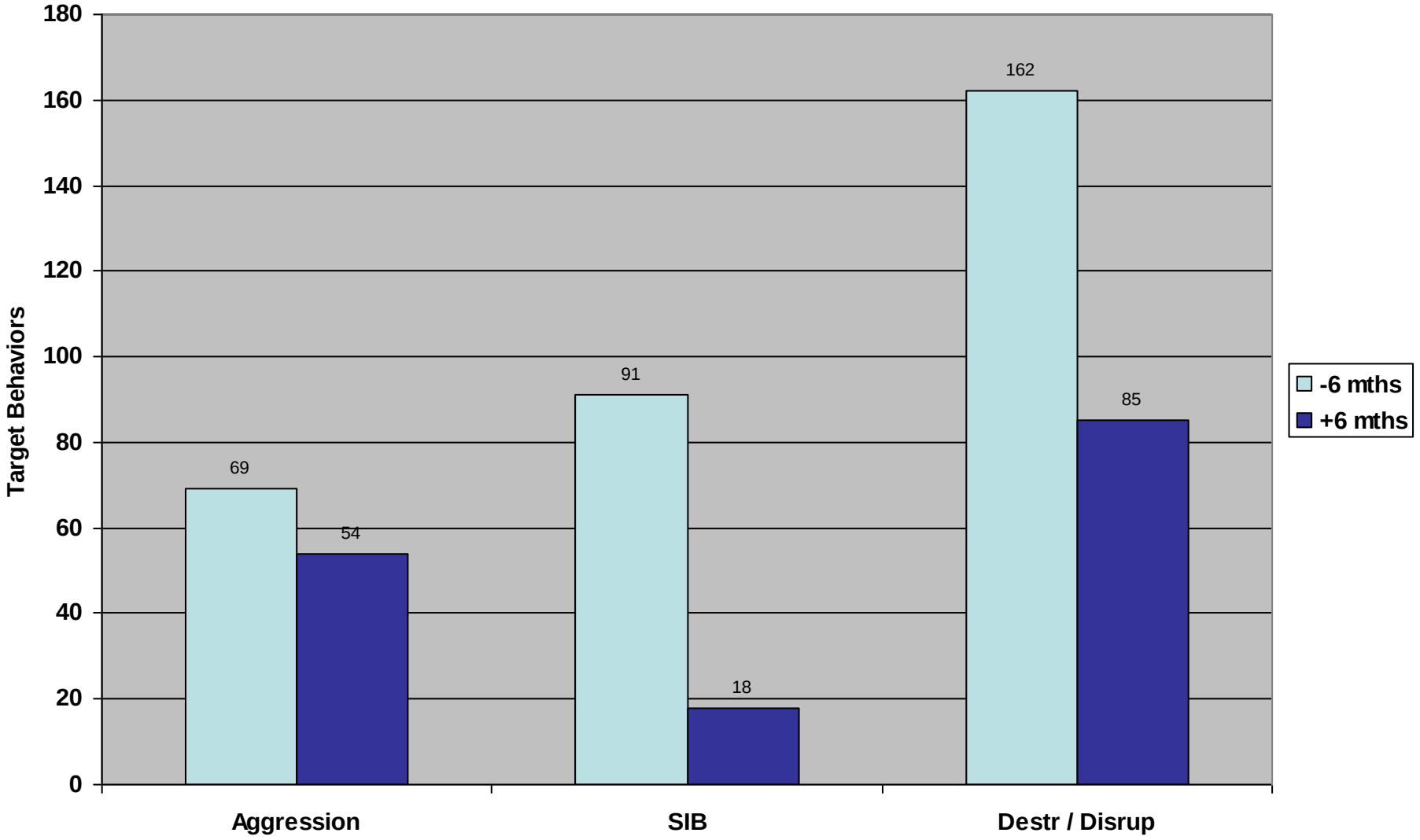
Target Behaviors Measured over 6 mths before and after starting Olanzapine Treatment in 20 Mentally Retarded Adults.



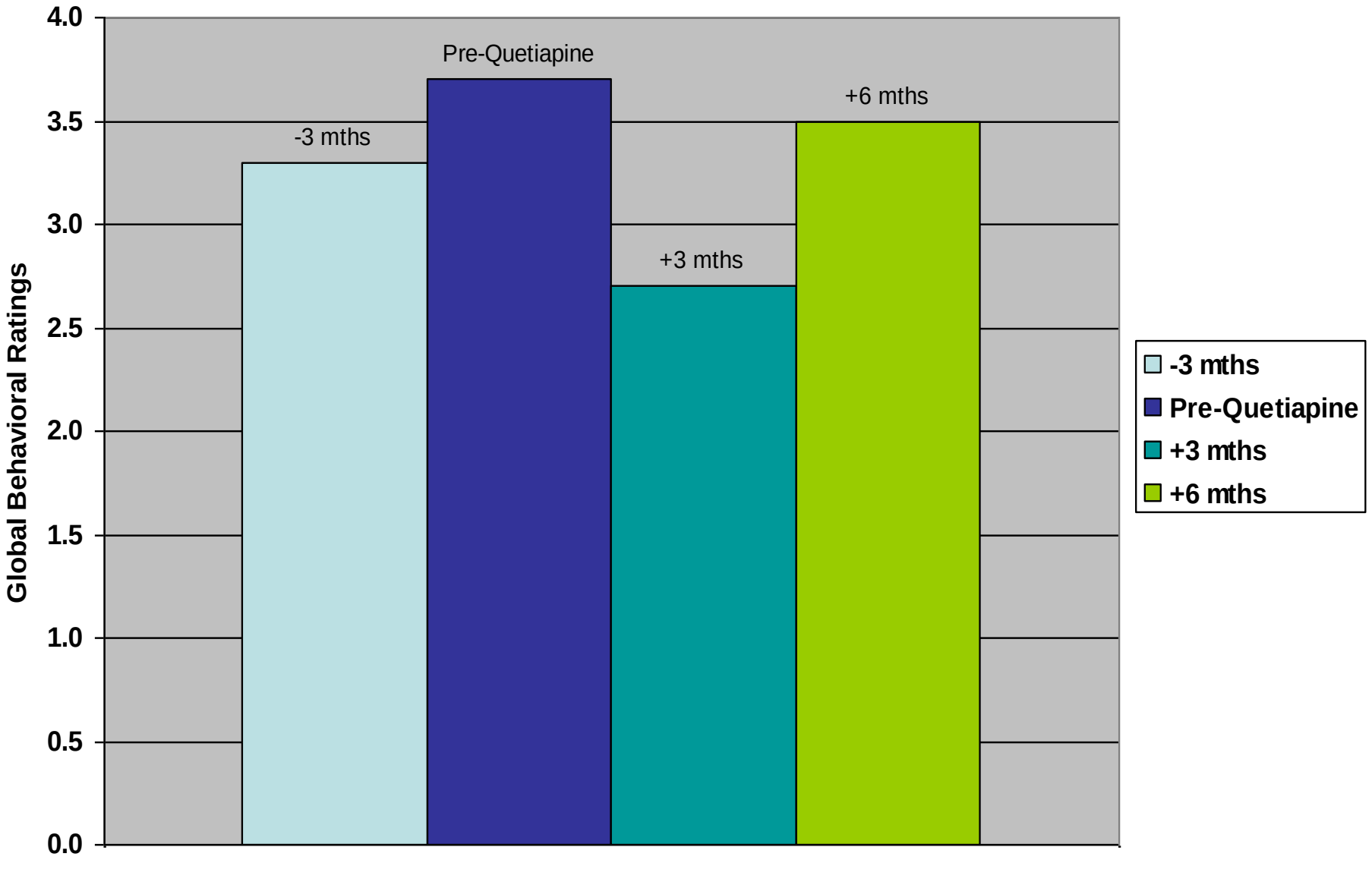
Mean of Global Behavioral Ratings of 11 Adults with Mental Retardation Before and After Treatment with Risperidone (Risperdal)



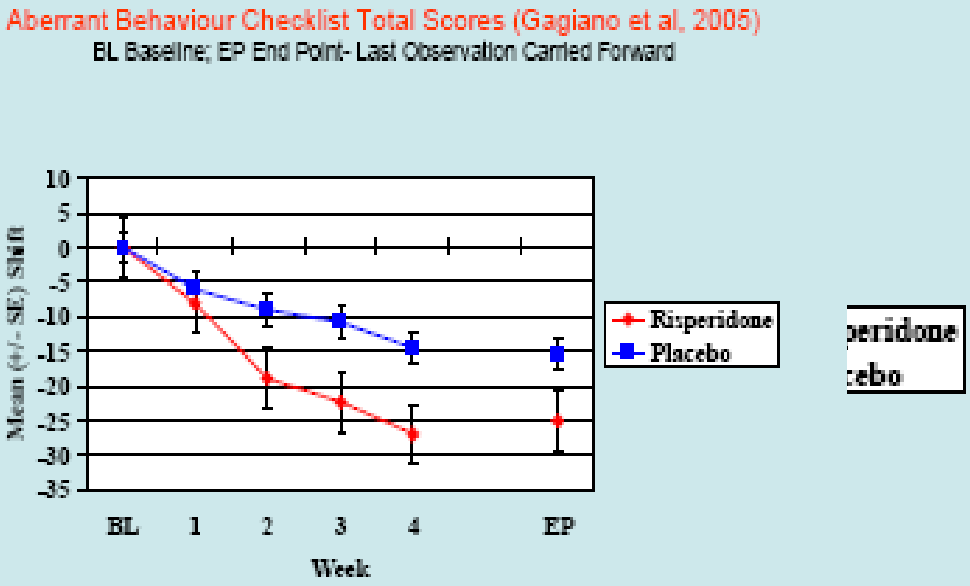
Mean of Cumulative Measured Target Behaviors Before and After Risperidone (Risperdal) Treatment in 11 Mentally Retarded Adults.



Mean of Global Behavioral ratings of 9 Adults with Mental Retardation Before and After Treatment with Quetiapine (Seroquel).



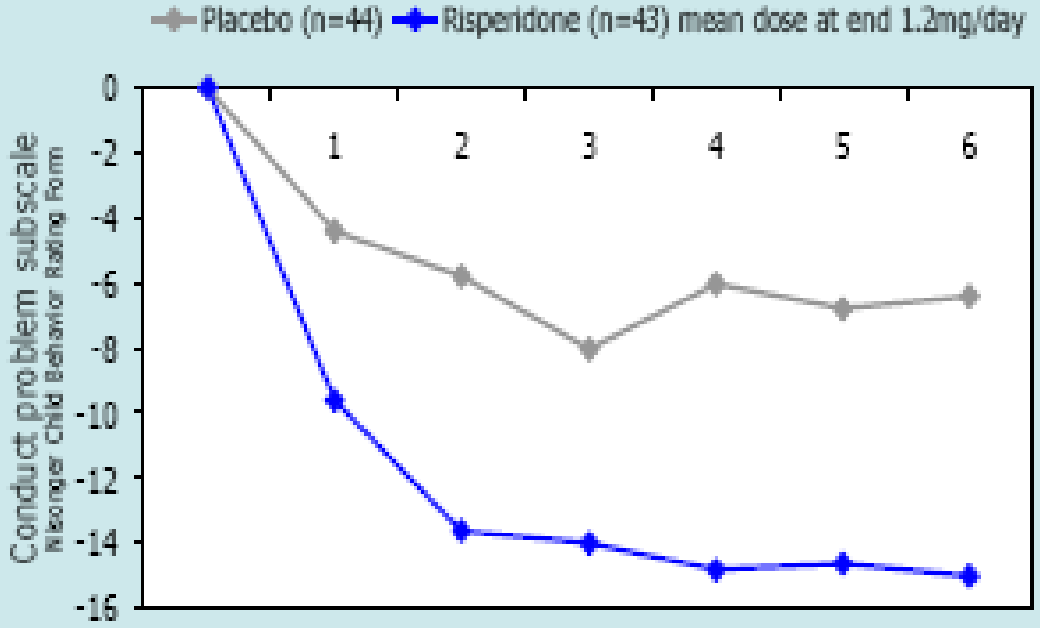
Aberrant Behaviour Checklist Total Scores (Gagiano et al. 2005)



Gagiano et al, Psychopharmacology, 2005

- **Participants:** 77 adults (18-57 years); ID + no psychiatric disorders.
- **Intervention:** Risperidone (n=39); Placebo (n=38). RCT. Open label with Risperidone (n=58) 1-4 mgs/ day (mean dose 1.8 mgs/ day) add-on.
- **Methods:** RCT + Open label.
- **Follow up:** RCT 4 weeks; open label 48 weeks.
- **Outcomes:** Primary outcome = ABC total score; BPI + CGI-S + VAS (target behaviours); Cognitive outcome: CPT + MV-CVLT; Extrapyramidal symptoms: ESRS.
- **Results:** ANCOVA (ITT): Least square means. RIs = 52% Improved; Placebo = 31% Improved (NNT = 5). ABC: p=0.036; CGI: p<0.05. Somnolence = 23-41%; Wt. Gain = 3.8+/-0.6. QTc = OK; ESRS = OK.
- **Comments:** Good quality study and supports the use of risperidone among adults, reasonable number in cohort; good design; good outcome measure; good stats. Short period of follow up in the RCT part (4 weeks), under powered, not one target behaviour.

Double-blind Study of Risperidone in Children with Sub-Average Intelligence



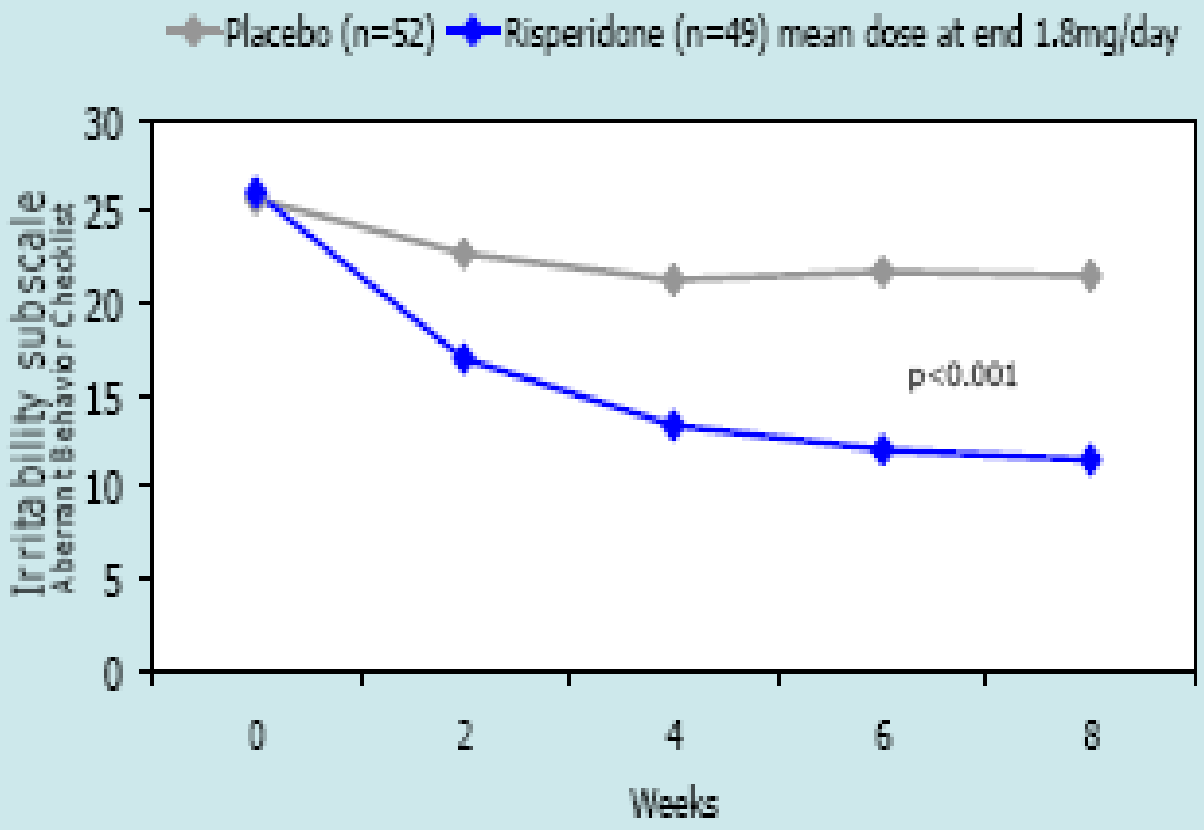
LOCF, Significant difference by week 1 (p=0.007)

(Aman et al 2002)

Aman et al, AJP, 2002

- **Participants:** 115 children (5-12 years); IQ 36-48.
- **Intervention:** Risperidone 0.02-0.06 mg/ kg/ day vs. placebo.
- **Methods:** Multi centre, RCT (parallel design).
- **Follow up:** 6 weeks.
- **Outcomes:** Nisonger Child Behaviour Rating form (conduct problem subscale) + ABC subscales, BPI, VAS, CGI.
- **Results:** Risperidone –15.2 vs. placebo –6.2; significant improvement according to all subscales + ABC-irritability/ hyperactivity subscales, BPI-aggressive/ destructive behaviour subscales, CGI and VAS. Adverse effects: headache and somnolence (not extrapyramidal symptoms). Weight gain Risperidone 2.2 kg vs. placebo 0.9 kg.
- **Comments:** Good quality study and supports the use of risperidone among children. Slightly low powered and the method of randomisation and concealment are not well (CONSORT) described, short period of follow up.

DOUBLE-BLIND STUDY OF RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIOURAL PROBLEMS



Research Units on Pediatric Psychopharmacology of Autism 2002

Research Units on Pediatric Psychopharmacology Autism Network; NEJM, 2002

- **Participants:** 101 children (5-17 years) autism; 74 ID + 12 Borderline IQ.
- **Intervention:** Risperidone 0.5-3.5 mg/ day (n=49) vs. placebo (n=52).
- **Methods:** Multi-centre, RCT (parallel design).
- **Follow up:** 8 weeks.
- **Outcomes:** ABC irritability subscale, CGI-I.
- **Results:** Risperidone 56.9% reduction in score vs. placebo 14.1% ($p<0.001$); CGI much or very much improved: Risperidone 69% vs. placebo 12% ($p<0.001$). Average weight gain Risperidone 2.7±2.9 kg vs. placebo 0.8±2.2 kg ($p<0.001$). Increased appetite, fatigue, drowsiness, dizziness, drooling more common in Risp. ($p<0.05$). 2/3rd with positive response in 8 weeks maintained at 6 months.
- **Comments:** Good quality study and supports use of risperidone among children. Slightly low powered and the method of randomisation and concealment are not well described, short period of follow up.

Research Units on Pediatric Psychopharmacology Autism Network; AJP, 2005 (Continuation study)

- **Participants:** Phase I: 63 children (5-17 years) autism; 53 ID + 7 Borderline IQ. Phase II: 38 children autism; 31 ID + 5 Borderline IQ.
- **Intervention:** Risperidone mean dose 1.96 mg/ day.
- **Methods:** Multi-centre, Follow up from the RCT.
- **Follow up:** Phase I: 4 months open label continuation with risperidone. Phase II: 8 weeks double blind placebo controlled withdrawal vs. continuation with risperidone.
- **Outcomes:** ABC irritability subscale.
- **Results:** Phase I: Change in ABC subscale small and non-significant. Average weight gain 5.1 kg ($p<0.001$). Phase II: Relapse in 63% gradual placebo substitution vs. 13% for continued risperidone.
- **Comments:** Risperidone showed persistent efficacy and good tolerability for intermediate length treatment of children with autism and ID. Somnolence disappeared after a few weeks but weight gain persisted. Did authors take into account the behavioural adverse effect of withdrawal?

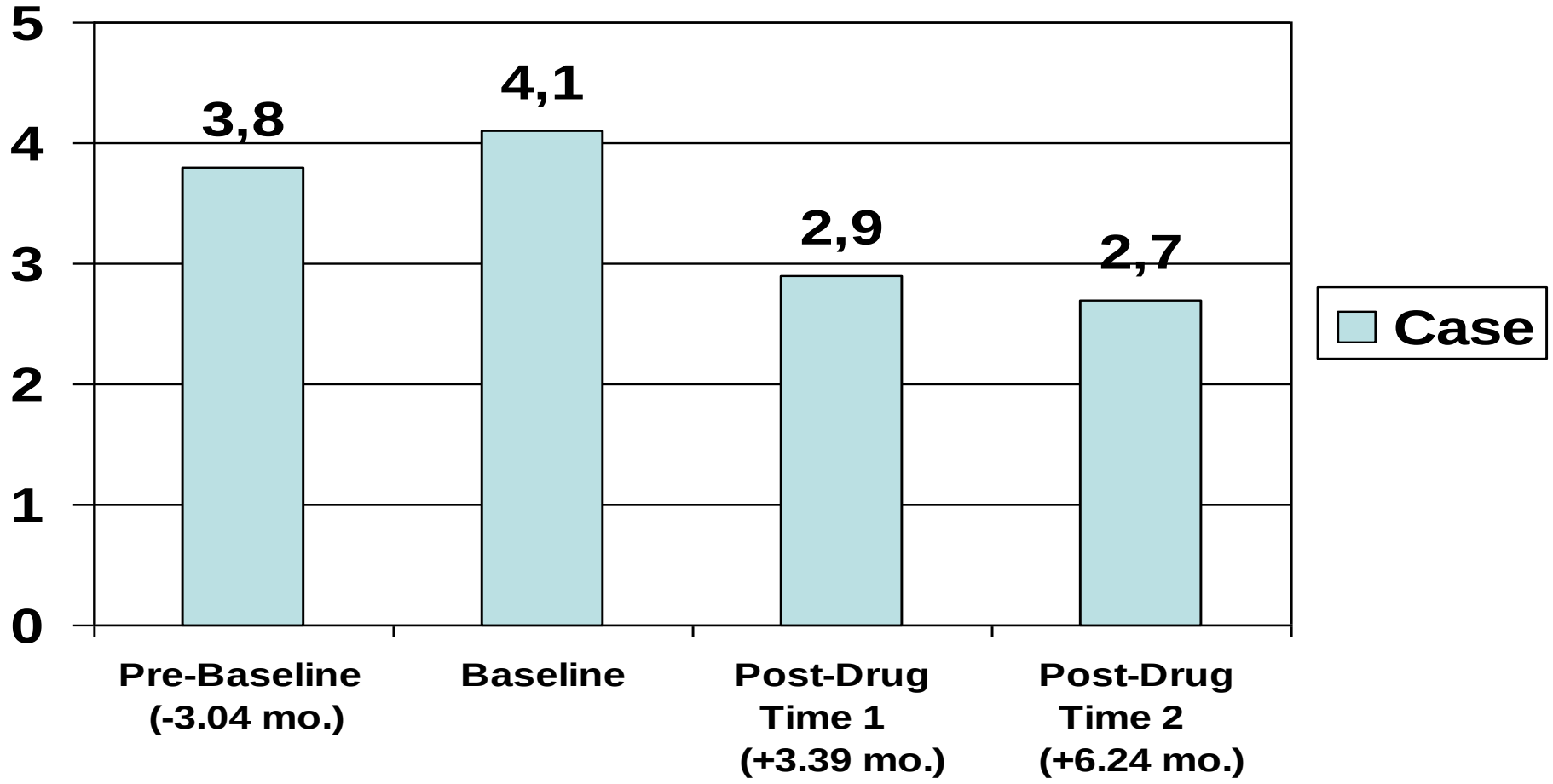
Table 1

DIAGNOSTIC AND DEMOGRAPHIC DATA ON 38 INTELLECTUALLY DISABLED INSTITUTIONALIZED ADULTS RECEIVING SEROTONERGIC ANTIDEPRESSANTS

CASE #	AGE, RACE, GENDER	DIAGNOSIS	CASE #	AGE, RACE, GENDER	DIAGNOSIS
1	30 AA MALE	BPAD.*, DEP.	21	42 W FEMALE	BPAD
2	68 AA FEMALE	BEHAV. DIS.	22	35 W MALE	BEHAV. DIS.
3	36 W MALE	AUTISM	23	72 AA MALE	BPAD, BEHAV. DIS.
4	30 W MALE	AUTISM	24	45 W FEMALE	OCD, SCHIZOPHRENIA
5	50 W MALE	AUTISM	25	79 W FEMALE	OCD, AUTISM
6	36 AA FEMALE	SCHIZOPHRENIA	26	57 W MALE	LANGUAGE DIS.
7	22 W MALE	BEHAV. DIS., AUTISM	27.	50 W MALE	OCD, SCHIZOPHRENIA
8	32 W FEMALE	NO DIAGNOSIS	28	56 W FEMALE	AFFECTIVE DIS.
9	54 W MALE	AUTISM	29	70 W FEMALE	BPAD
10	47 W MALE	BPAD	30	48 W MALE	MAJOR DEP.
11	33 AA FEMALE	DEP.	31	50 AA MALE	NO DIAGNOSIS
12	49 AA FEMALE	NO DIAGNOSIS	32	42 W FEMALE	DEP.
13	52 AA MALE	BEHAV. DIS., SCHIZ.	33	24 W MALE	BEHAV. DIS.
14	45 W FEMALE	BPAD	34	33 W FEMALE	OCD, AUTISM, BPAD
15	22 AA MALE	EXPLOSIVE DIS.	35	53 W FEMALE	BEHAV. DIS.
16	52 W FEMALE	BPAD	36	35 AA MALE	MOOD DIS., NOS
17	18 W MALE	AUTISM	37	52 W MALE	PERSONALITY DIS.
18	71W FEMALE	CONDUCT DIS.	38	43 W FEMALE	BPAD
19	74 W FEMALE	MOOD DIS.			
20	36 AA MALE	DEP., DISRUPT. DIS.			

*BPAD = BIPOLAR AFFECTIVE DISORDER, BEHAV. = BEHAVIORAL, DIS. = DISORDER, DEP. = DEPRESSION, DIS. = DISRUPTIVE, OCD = OBSESSIVE-COMPULSIVE DISORDER, AA = AFRICAN AMERICAN, W = WHITE.

GLOBAL RATINGS OF 38 INTELLECTUALLY DISABLED ADULTS BEFORE AND AFTER RECEIVING SEROTONERGIC ANTIDEPRESSANTS



RATINGS FOR SPECIFIC BEHAVIORS BEFORE AND AFTER RECEIVING SEROTONERGIC ANTIDEPRESSANTS IN 38 DEVELOPMENTALLY DISABLED ADULTS

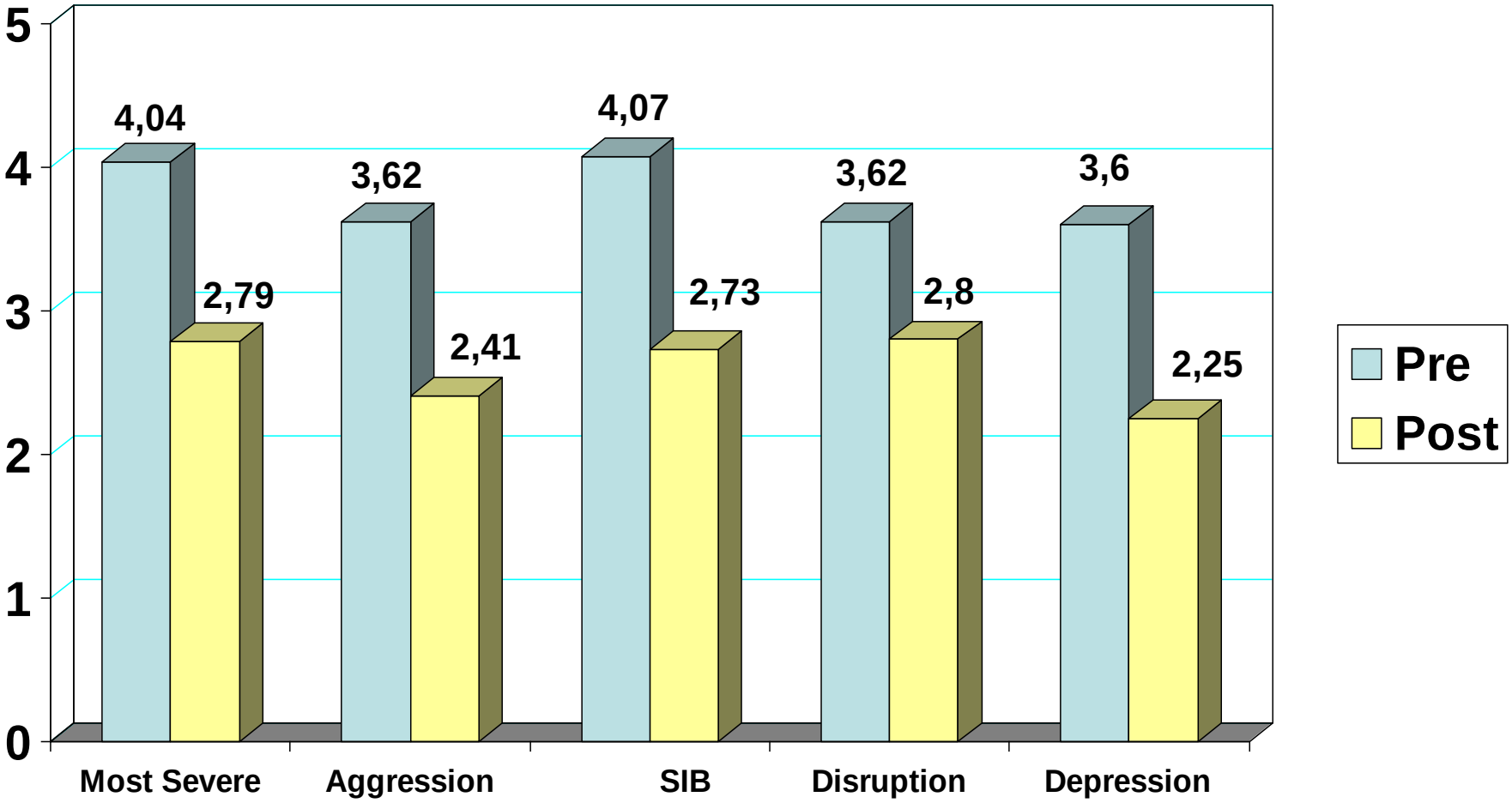


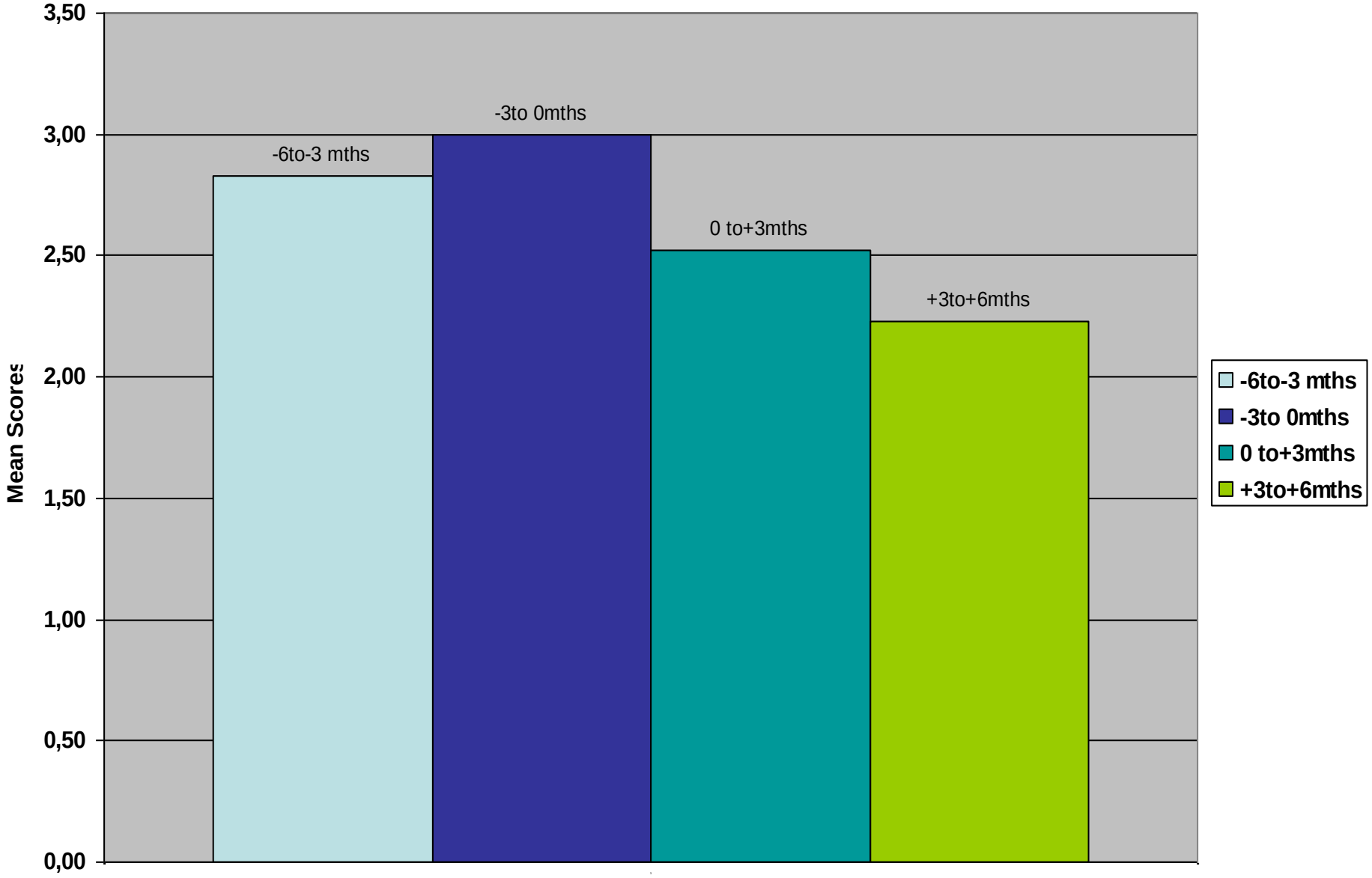
Table 1

DESCRIPTIVE INFORMATION 0N 22 INSTITUTIONALIZED INTELLECTUALLY DISABLED ADULTS RECEIVING TOPIRAMATE FOR CHALLENGING BEHAVIORS

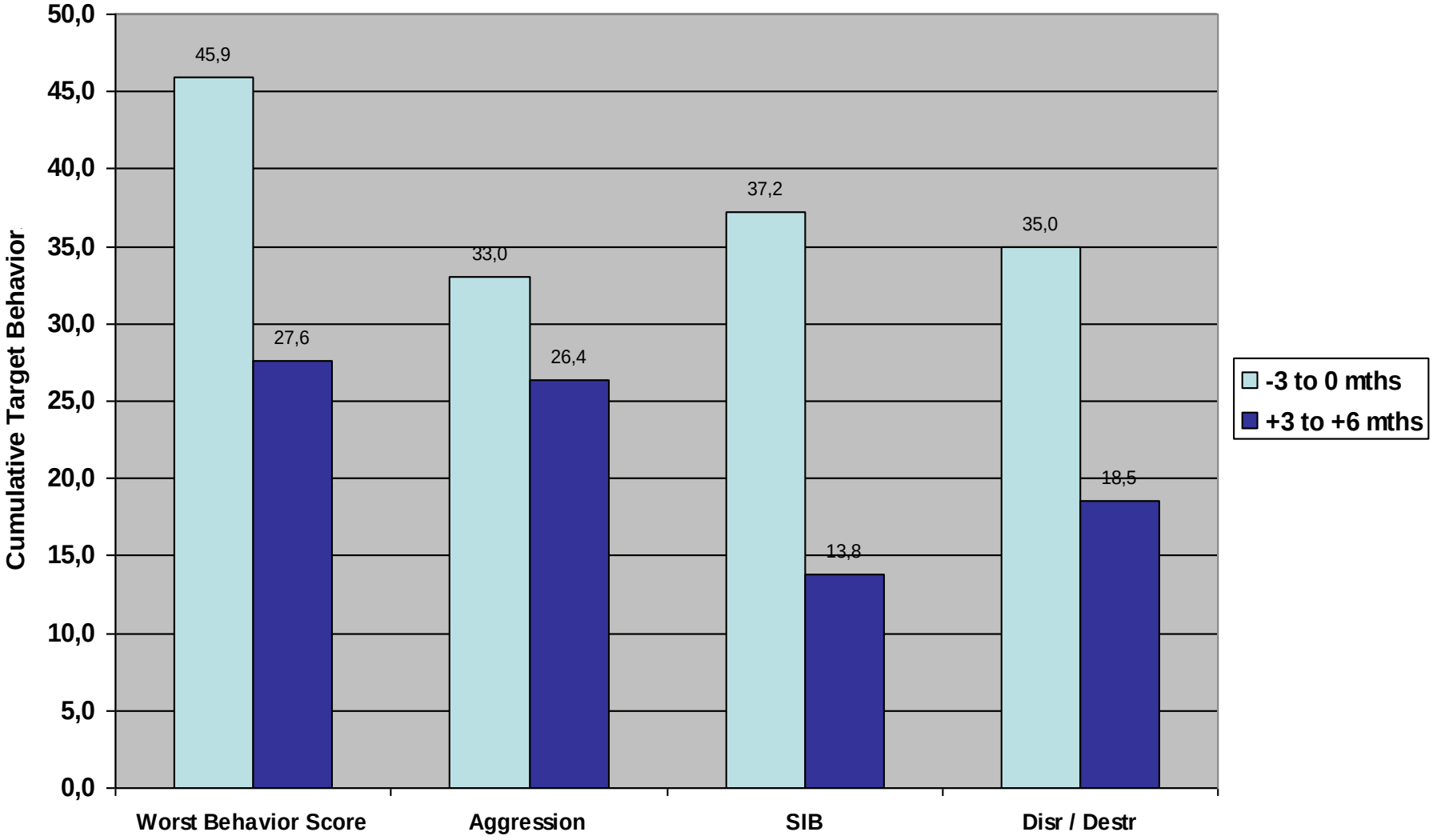
CASE	GENDER/AGE/ETHNICITY	DIAGNOSIS	SEIZURES	LEVEL OF RETARDATION	
				COGNITIVE	ADAPTIVE
1.	F/70/AA	BPAD, AUTISM, OCD	+	PROFOUND	PROFOUND
2.	M/51/W	BPAD	+	PROFOUND	PROFOUND
3.	M/53/W	BPAD	-	SEVERE	PROFOUND
4.	M/51/W	BPAD	-	PROFOUND	PROFOUND
5.	F/52/W	BPAD	-	PROFOUND	PROFOUND
6.	F/43/W	BPAD	+	PROFOUND	PROFOUND
7.	F/51/W	BPAD	-	PROFOUND	PROFOUND
8.	F/52/W	BPAD, ANXIETY, AUTISM	-	PROFOUND	PROFOUND
9.	F/25/W	BPAD	-	SEVERE	SEVERE
10.	F/42/W	BPAD	-	PROFOUND	PROFOUND
11.	M51/W	BPAD	-	SEVERE	PROFOUND
12.	F/50/AA	BPAD	+	SEVERE	PROFOUND
13.	M/69/AA	BPAD	-	PROFOUND	PROFOUND
14.	F/33/W	BPAD, AUTISM, OCD?	+	PROFOUND	PROFOUND
15.	F/40/AA	BPAD	-	SEVERE	PROFOUND
16.	M/50/W	AUTISM, OCD	+	PROFOUND	PROFOUND
17.	F/37/W	MAJOR DEPRESSION	+	PROFOUND	PROFOUND
18.	M/48/W	MAJOR DEPRESSION	+	MODERATE	SEVERE
19.	M/48/AA	? AFFECTIVE DISORDER	-	SEVERE	SEVERE
20.	F/38/AA	MOOD DISORDER NOS	-	SEVERE	SEVERE
21.	F/45/AA	NONE	+	PROFOUND	PROFOUND
22.	F/26/AA	DEPRESSIVE DISORDER, NOS	-	PROFOUND	PROFOUND

Abbreviations: M = Male, F = Female, W = White, AA = African American
BPAD = Bipolar Affective Disorder, OCD = Obsessive-Compulsive Disorder

Mean of the Global Behavioral Severity Ratings of 22 Intellectually Disabled Adults Before and After Beginning Topiramate Treatment.



Mean of Measured Cumulative Target Behaviors for 3 mths before and 3 to 6 mths after starting Topiramate Treatment in 19 Intellectually Disabled Adults.



NARRATIVE EXCERPTS FROM NBR REPORTS INDICATING THE NEED FOR INCREASES IN THE DOSES OF CONVENTIONAL ANTIPSYCHOTIC DRUGS

"Has continued to do poorly since last review... Continues to have difficulties with SIB, aggression, destructive behavior and copraphagia. ... difficulties have worsened since last neuroleptic withdrawal."

"SIB, aggression and tantruming are essentially the same, but SIB has worsened."

"She tried to bite her mother and kicked out the windows on the unit."

"Her behavior is out of control... A marked escalation of aggression and disruption occurred."

"Has been louder and is more disruptive...Broke a glass... Patient's behavior has been deteriorating..."

"He continues to have a variety of target maladaptive behaviors including being louder, hand biting, more physical, intense rocking and pushing away."

"SIB and property destruction have worsened... Time in restraints has accelerated.... Decreased ability to control herself."

"The worsening has not been transient... There was a dramatic worsening of re-enforcers earned..."

"Since the last review she has had substantial worsening of SIB and appearance alteration..."

"He started SIB and has been involved in aggression..."

"All these difficulties have been demonstrated to be worsening (aggression, SIB, tantruming)..."

Mean of Most Severe Behavior, Aggression, SIB and Destr/Disrup Behavioral Scores in the Month Before the Determination of Minimal Fully Effective Dose (A) and of Relapse Inducing (B) Doses in Intellecually Disabled Individuals.

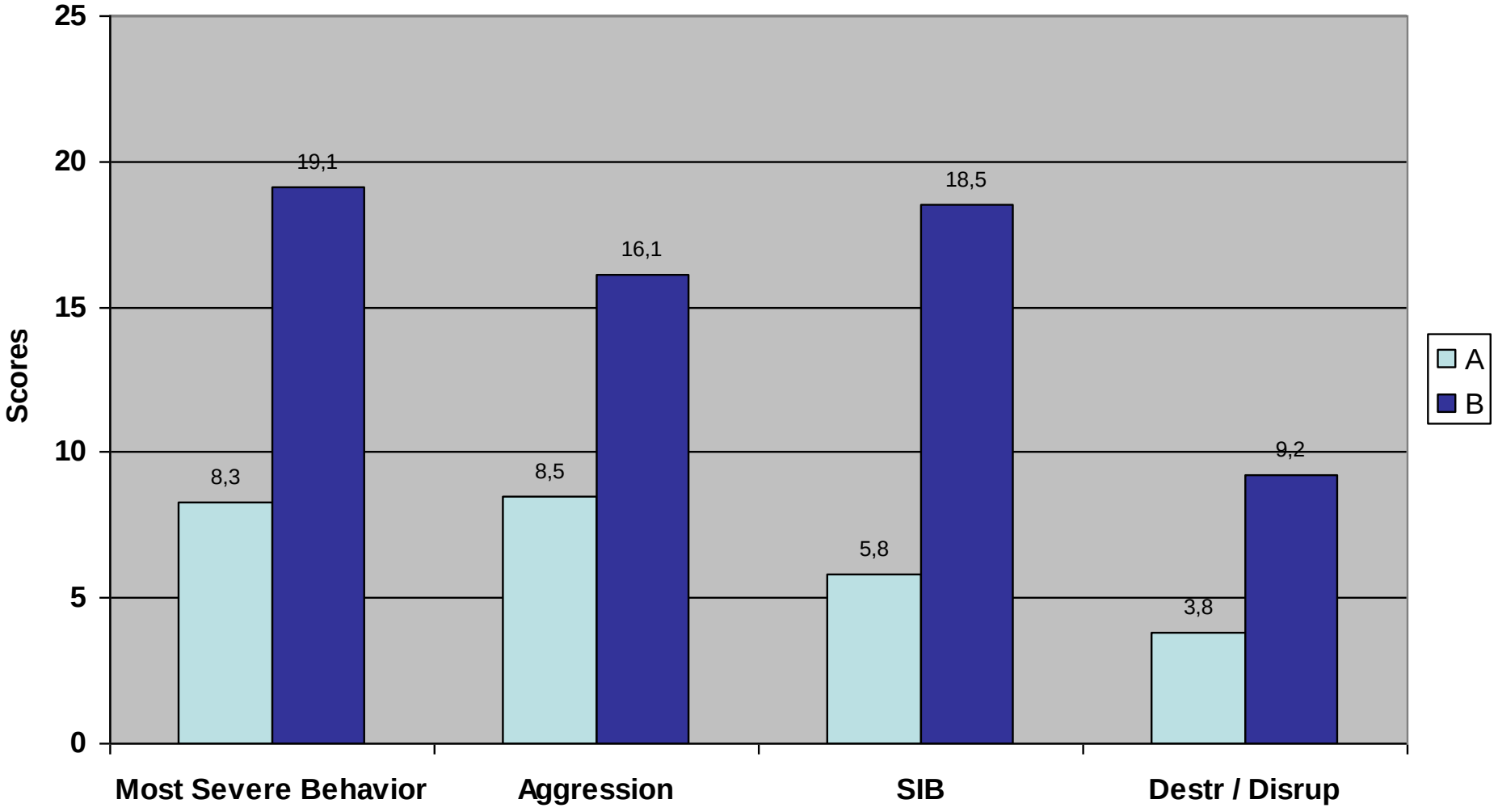


TABLE 2

HIGH AND LOW POTENCY CONVENTIONAL ANTIPSYCHOTIC DRUG DOSES MAINTAINING STABILITY AND CAUSING RELAPSE IN INTELLECTUALL DISABLED INDIVIDUALS

CASE #	DRUG	INITIAL STABILIZING DOSE (MG/DAY)	LOWEST EFFECTIVE DOSE (MG/DAY)	RELAPSE INDUCING DOSE (MG/DAY)	RE-INSTITUTION DOSE (MG/DAY)
1	haloperidol	30.0	3.0	2.0	3.0
2	haloperidol	20.0	18.0	15.0	25.0
3	haloperidol	19.0	15.0	12.0	15.0
4	haloperidol	15.0	5.0	4.0	20.0
5	haloperidol	3.0	2.0	1.0	2.0
6	haloperidol	6.0	2.0	1.0	3.0
7	haloperidol	15.0	13.0	9.0	13.0
8	haloperidol	30.0	1.5	0	5.0
9	haloperidol	17.0	17.0	15.0	17.0
10	haloperidol	3.0	3.0	0	5.0
11	haloperidol	15.0	10.0	0	30.0
12	haloperidol	10.0	2.0	0	5.0
13	haloperidol	8.0	6.5	6.0	8.0
14	haloperidol	1.0	0.5	0	2.0
15	haloperidol	1.5	1.5	0	2.0
16	haloperidol	10.0	3.0	1.5	3.0
17	loxapine	100 (10.0)	75.0 (7.5)	50.0 (5.0)	75.0 (7.5)
18	thiothixene	5.0 (1.7)	5.0 (1.7)	4.0 (1.3)	5.0 (1.7)
19	thiothixene	2.0 (0.7)	2.0 (0.7)	1.0 (0.3)	5.0 (1.7)
	MEAN ± SEM=	11.4 ±2.1*	5.9±1.3	3.8±1.2	8.8±2.0
20	chlorpromazine*	50	50	0	75
21	chlorpromazine	150	150	100	150
22	chlorpromazine	1000	400	375	500
23	chlorpromazine	400	200	75	200
24	thioridazine	175	175	100	125
25	thioridazine	100	50	25	100
26	thioridazine	230	15	130	200
27	thioridazine	175	125	75	150
28	thioridazine	200	200	100	200
29	thioridazine	200	150	50	200
30	thioridazine	150	75	50	100
31	thioridazine	300	150	100	200
32	thioridazine	800	40	0	200
33	thioridazine	150	75	25	75
34	thioridazine	400	250	200	250
	MEAN ±SEM=	298±68.5	149.3±24.1	93.6±24.2	181.6±26.6

*All doses expressed in chlorpromazine equivalents. 1 mg chlorpromazine = 1 mg thioridazine. Self-Injurious Behavior = SIB

** ( ) = Doses expressed as haloperidol equivalents.

Tab2antipsychotic/manu/nov03

Mean Least Effective and Relapse Associated Doses of Risperidone and Olanzapine in 43 Individuals with Intellectual Disability

	N	Least Effective Dose (mg/day)	Relapse Associated Dose (mg/day)
Risperidone	28	2.50 ± 1.40 (range 0.75-7.5)*	l.82 ± 1.26 (range 0-6.5)
Olanzapine	15	9.13 ± 5.66 (range 3.0-15.0)	5.48 ± 4.04 (range 0-15.0)

	N	Clinically Determined Dose
Risperidone	28	2.90 ± 2.01 mg/day (range 0.75-6.0 mg/day)
Olanzapine	16	11.41 ± 7.8 mg/day (range 5.0-30 mg/day)

* Mean ± Standard Deviation

DISTRIBUTION OF SUBSEQUENT RELAPSES IN 51 INDIVIDUALS WITH INTELLECTUAL DISABILITY WHO RELAPSED FOLLOWING AN ANTIPSYCHOTIC DRUG WITHDRAWAL ATTEMPT

Number of Additional Relapses Between 1990 and 2005	Number of Individuals Relapsing	Percentage of Individuals Relapsing
0	10*	17.5%
1	14	24.6%
2	19	33.3%
3	10	17.5%
4	4	7.0 %

* These individuals continued on antipsychotic medications after their initial relapse

CONCERNS ABOUT PSYCHOTROPIC DRUG USAGE IN THE INTELLECTUALLY DISABLED

- Use mostly based on extrapolation of knowledge re: effects in populations without ID

- Psychotropic medications (Children/ Adol.) interact with developing brain different from adults (Vitiello and Jensen 1995)

  ? ID affects brain development.

- Adverse effects of psychotropic drugs (Christian et al, 1999) and the adverse effects that occur in PWID (Hubert, 1992; Wilson et al. 1998, Baumeister et al 1998)

PSYCHOTROPIC DRUG USAGE CONCERNS-CONTINUED

- increased risk of developing side effects (Deb and Fraser 1994; Kalachnik, 1999)

- side effects may be less predictable and less well-recognised.

CONTROLLED NEGATIVE STUDY BY TYRER ET AL.

- Tyrer et al (Lancet, 2008), in a controlled, double blind study, reported that haloperidol, risperidone, and placebo exerted equal anti-aggressive effects in an intellectually disabled outpatient population.

ANTIPSYCHOTICS

- Equivocal evidence for the efficacy of risperidone among adults with ID with problem behaviours
- Adequate evidence based on studies on children with ID (with or without autism) that risperidone is effective in the management of problem behaviours
- Concern about adverse effects such as somnolence and weight gain (not much evidence available on other adverse effects such as metabolic and cardiac)
- Long term follow up studies among children are reassuring as for the adverse effects

Post Exam Question 1

The incidence of aggressive and self injurious behavior changes in the following ways as I.Q. decreases:

A. It decreases
B. It increases
C. It changes as related to the psychiatric diagnosis
D. None of the above

Post Exam Question 2

The consensus of medical experts is that the top two most effective treatments for aggression in intellectually disabled individuals are:

A. Conventional and atypical antipsychotic agents
B. Atypical antipsychotic agents and mood stabilizers
C. SSRI's and atypical antipsychotic agents
D. Beta Blockers and Naltrexone

Post Exam Question 3

The following antipsychotic medications have been shown to be useful in double blind placebo controlled studies for the treatment of aggression in the intellectually disabled:

A. Risperidone
B. Olanzapine
C. Quetiapine
D. None of the above
E. All of the above

Post Exam Question 4

If a previously aggressive individual has been successfully treated with antipsychotic agents, and relapses when withdrawn from these agents, the chance of relapse occurring during a future withdrawal attempt is:

A. Very high
B. Not related to previous attempts
C. Related to the psychiatric diagnosis
D. Low

Post Exam Question 5

The chances that an intellectually disabled individual in whom aggressive symptoms have been significantly controlled while receiving an antipsychotic agent having a successful medication withdrawal on a first attempt are approximately:

A. 95%
B. 60%
C. 20%

Answers to Pre and Post Exams

1. B
2. B
3. A
4. A
5. B