Atypical Antipsychotics to Achieve Remission With Adult Major Depressive Disorder: A Clinical and Economic Assessment

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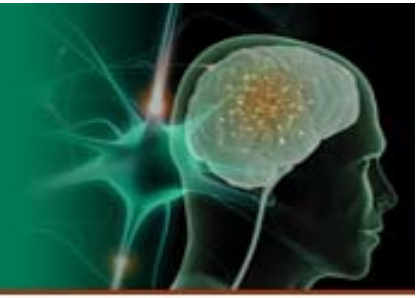
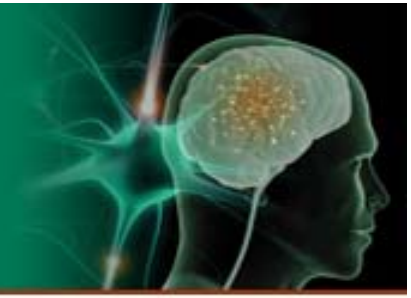
Faculty Disclosure



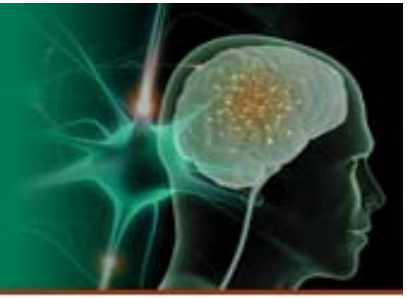
- **The *faculty* reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:**
  - Charles L. Raison, MD
    - Consulting fees: Biolex Therapeutics and PAMLAB LLC

Talking Points



- Assess the clinical and economic value of atypical antipsychotics for the treatment of adult patients with major depressive disorder (MDD) who do not achieve full remission
- Explain how the 2010 American Psychiatric Association (APA) Practice Guideline can integrate with a managed care algorithm for optimal value of therapeutic options

Treatment Resistant Depression (TRD)

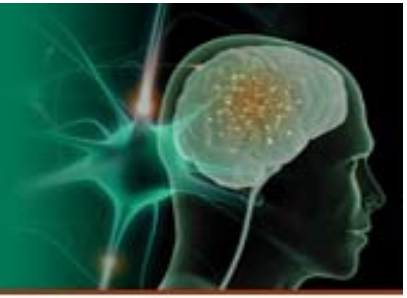


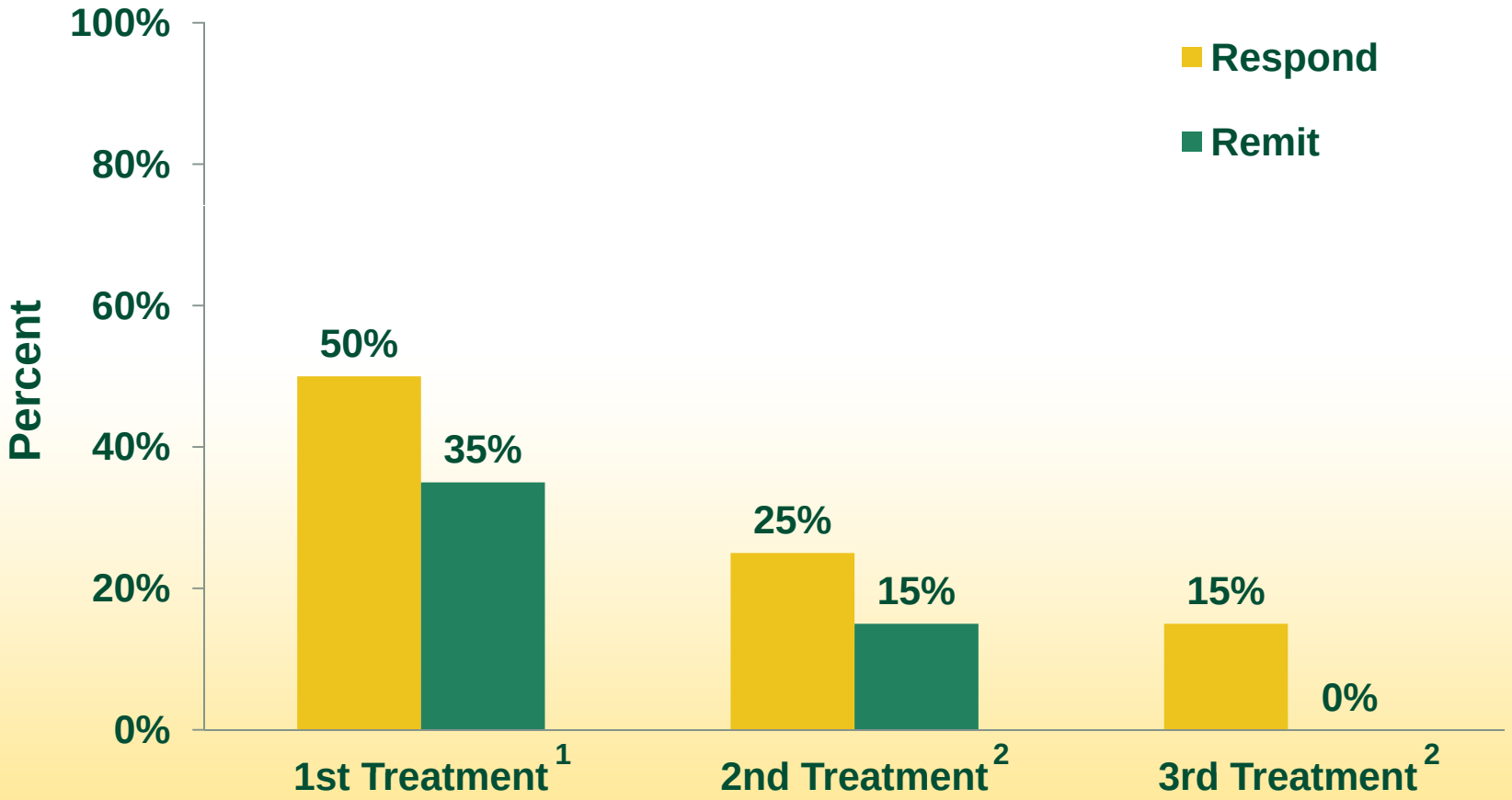
- TRD occurs when a patient fails to respond to adequate antidepressant therapy[1]
- At least 67% of patients in the STAR*D trial failed to achieve remission in first stage treatment[2]
- Each unsuccessful course of antidepressant therapy is associated with a lower likelihood of remission and higher relapse rates[2]

1. Gibson TB, et al. *Am J Manag Care*. 2010;16:370-377.
2. Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.

STAR*D=Sequenced Treatment Alternatives to Relieve Depression.

Over 20% of Patients With Major Depressive Disorder Have TRD

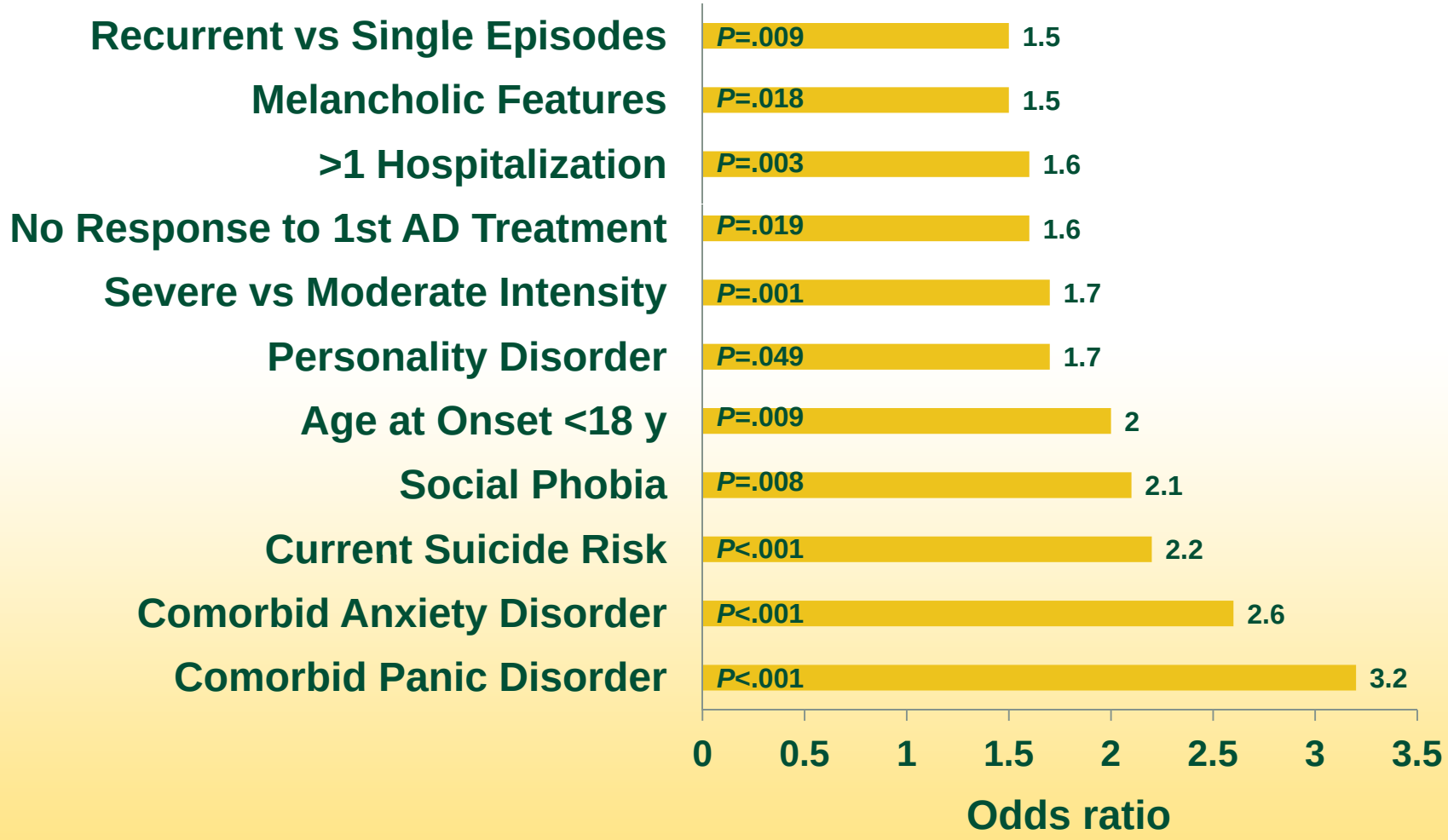




1. Robinson WD, et al. *J Am Board Fam Pract*. 2005;18:79-86.
2. Fava M, et al. for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494.

TRD=treatment resistant depression.

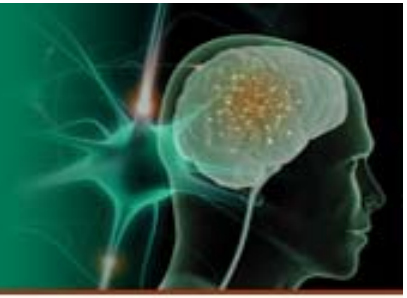
Factors Associated With Treatment Resistance in Patients With Major Depressive Disorder



Souery D, et. al. *J Clin Psychiatry*. 2007:68;1062-1070.

AD=antidepressant.

Clinical Challenges Associated With TRD

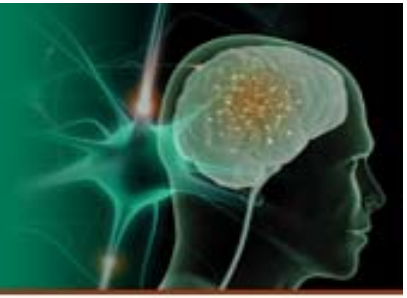


- Poorly defined; often misdiagnosed
- Inadequate treatment, under-treatment, delayed treatment
  - Failure to achieve remission with prior therapy
  - “Pseudo-resistance” observed in patients who have not received guideline-defined treatment
- Failure to address comorbid disorders
  - Substance abuse
  - Concurrent Axis I or II disorders
  - Other medical conditions
- Non-adherence to prescribed treatment regimen
  - Premature discontinuation of treatment associated with higher rates of relapse

Gaynes B. *J Clin Psychiatry*. 2009;70(Suppl 6):10-15.
Fava M. *Biol Psychiatry*. 2003;53:649-659.

TRD=treatment resistant depression.

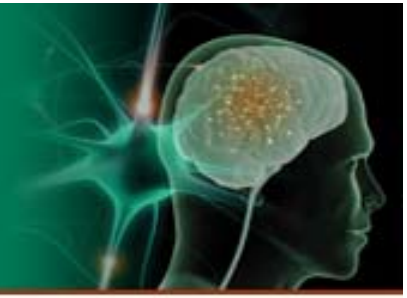
Levels of Treatment Resistance



Stage	Treatment Response
0	No single adequate trial of medication
1	Failure to respond to an adequate trial of 1 medication
2	Failure to respond to 2 different monotherapy trials of medications with different pharmacological profiles
3	Stage 2 + failure to respond to augmentation of 1 of the monotherapies
4	Stage 3 + failure of a second augmentation strategy
5	Stage 4 + failure to respond to electroconvulsive therapy (ECT)

Thase ME, Rush AJ. *J Clin Psychiatry*. 1997;58:23-29.
Souery D, et al. *J Clin Psychiatry*. 2006;67(Suppl 6):16-22.

Conventional Antipsychotic Use in Depression

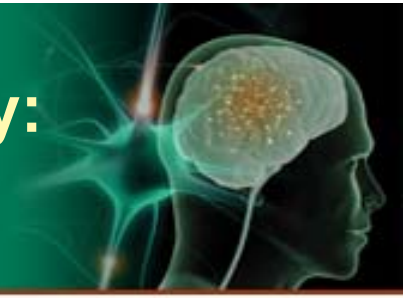


- Long history of use in depression (since 1959)
- Substantial literature (over 30 controlled studies)
- Effective for some patients and some symptoms
- Popular antipsychotic + tricyclic antidepressants combinations
- Risk of tardive dyskinesia led to decline in use of the conventional agents

Nelson JC. The use of antipsychotic drugs in the treatment of depression. In: Zohar J, Belmaker RH, eds. *Treating Resistant Depression*. New York, NY: PMA Publishing; 1987:131-146.

AP=antipsychotic.
TCA=tricyclic antidepressant.
TD=tardive dyskinesia.

Atypical Antipsychotics Neuropharmacology: These Agents Differ



Receptor	ARI	CLZ	HAL	OLZ	QUE	RIS	ZIP
D_1	265*	85	210	31	455	430	525
D_2	0.34*	125	0.7	11	160	4	5
D_3	0.8*	473	2	49	340	10	7
D_4	44*	9-21	3	27	1600	9	32
5-HT_{1A}	1.7*	770	1100	>1000	2450	210	3
5-HT_{2A}	3.4*	12	45	4	220	0.5	0.4
5-HT_{2C}	15*	8	>10,000	11	615	25	1
a_1	57	7	6	19	7	0.7	11
H_1	61*	6	440	7	11	20	50
M_1	>1000	1.9	>1500	2	120	>10,000	>1000

Data represented as K_i (nM).

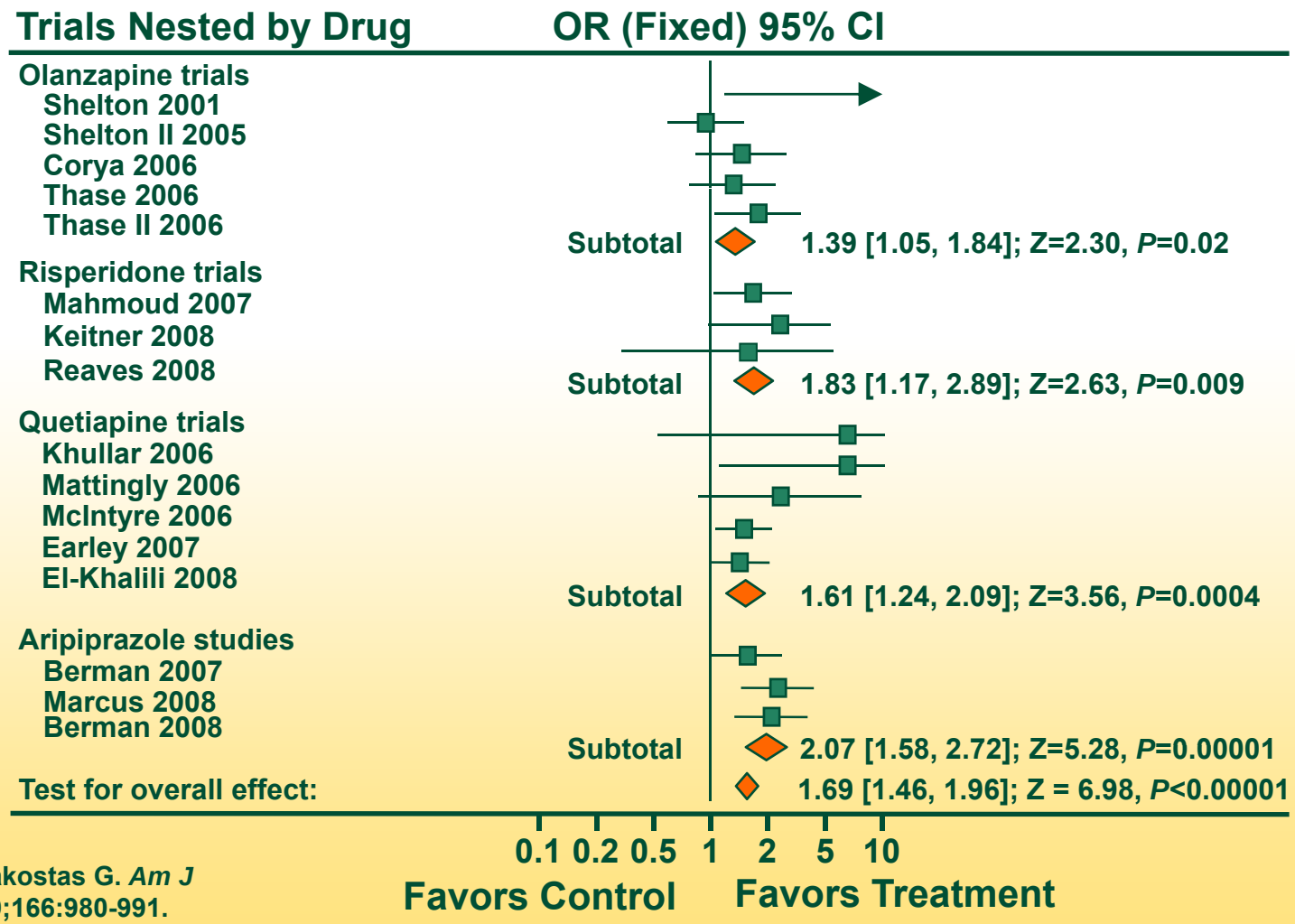
*Data with cloned human receptors.

Bymaster FP, et al. *Neuropsychopharmacology*. 1996;14:87-96.
Daniel DG, et al. *Neuropsychopharmacology*. 1999;20:491-505.
Farah A. Prim Care Companion *J Clin Psychiatry*. 2005;7:268-274.
ABILIFY (aripiprazole) Package Insert. Otsuka Pharmaceutical Co, Ltd. February 2011.
Shayegan DK, Stahl SM. *CNS Spectr*. 2004;9(10 Suppl 11):6-14.

ARI=aripiprazole.
CLZ=clozapine.
HAL=haloperidol.
OLZ=olanzapine.
QUE=quetiapine fumarate.
RIS=risperidone.
ZIP=ziprasidone.

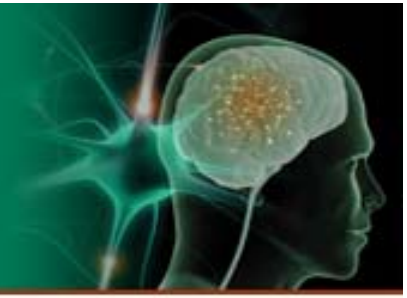
Meta-analysis of Response Rates in Double-blind Placebo-controlled Atypical Augmentation Trials

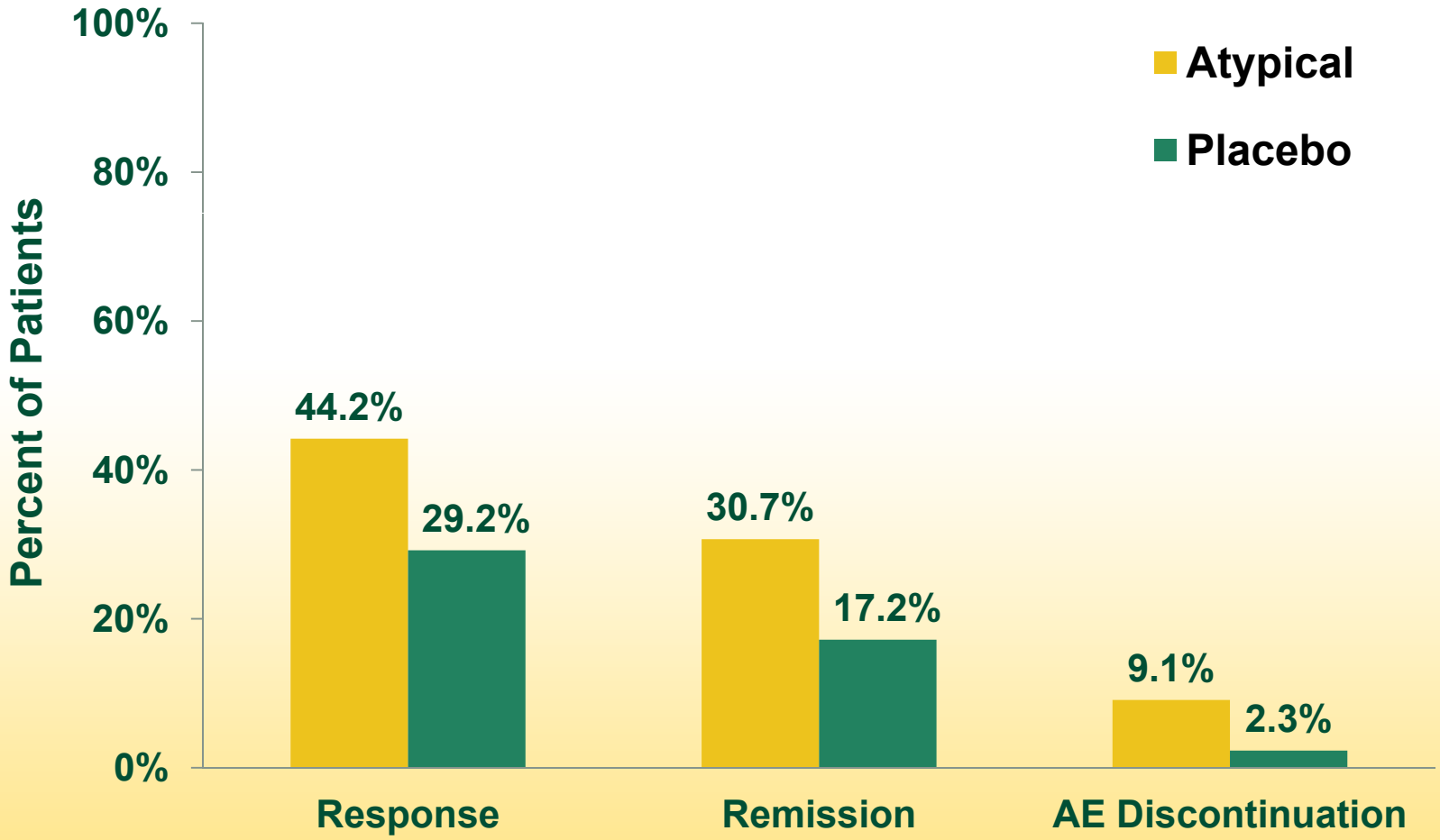
Odds Ratios of Response Rates With Atypical and Placebo



Nelson JC, Papakostas G. *Am J Psychiatry*. 2009;166:980-991.

Overall Response and Remission Rates: 4 Atypicals, 16 Trials, 3840 Patients

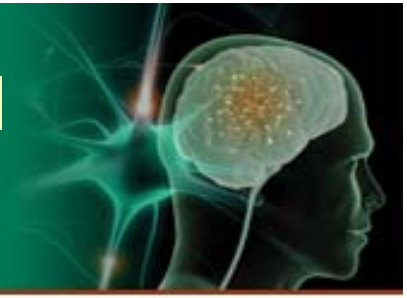


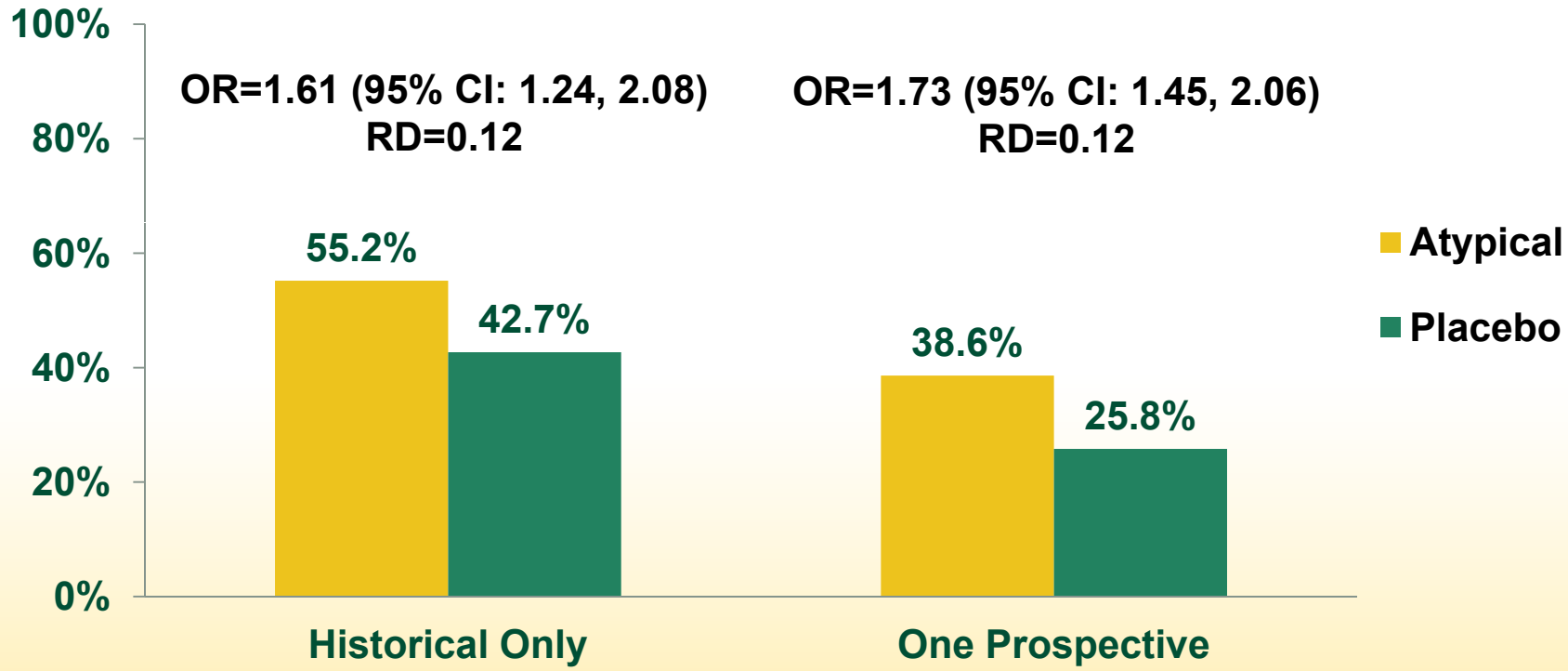


Nelson JC, Papakostas G. *Am J Psychiatry*. 2009;166:980-991.

AE=adverse event.

Sensitivity Analysis: Effect of Historical or Prospective Determination of TRD





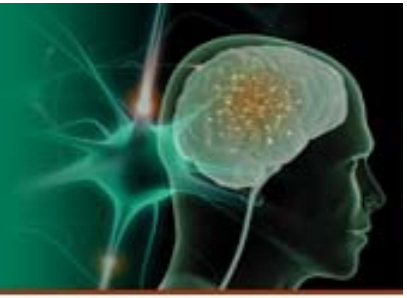
TRD was established with either history of drug failure or at least one prospective trial. Use of a prospective trial did not reduce drug effect but did reduce overall response suggesting the sample was more resistant.

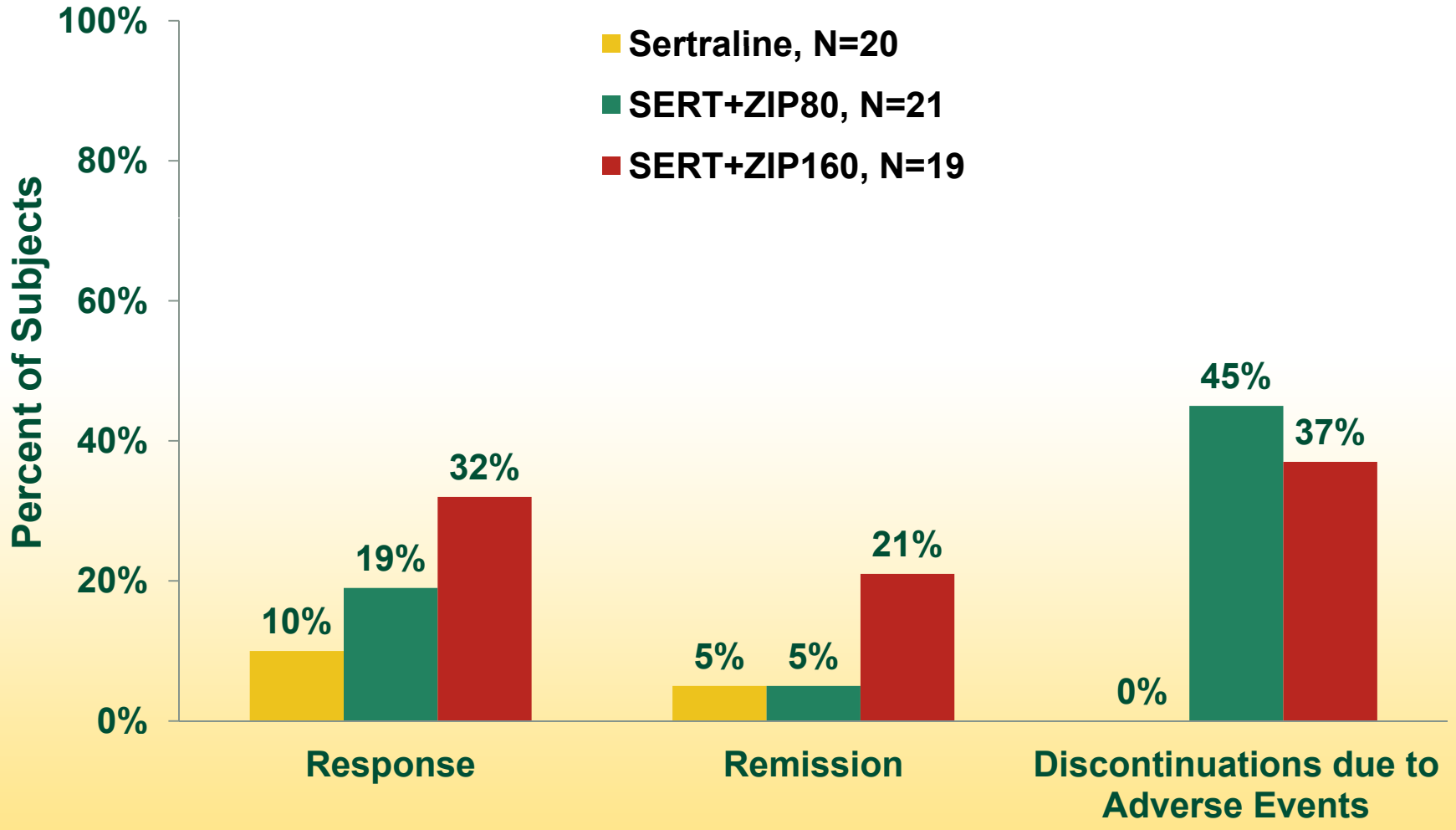
CI=confidence interval.
OR=odds ratio.
RD=risk difference.
TRD=treatment resistant depression.

Nelson JC, Papakostas G. *Am J Psychiatry*. 2009;166:980-991.

Adjunctive Ziprasidone, an Open-label Study

After Failure of One Historical Trial and One 6-week Prospective Sertraline Trial

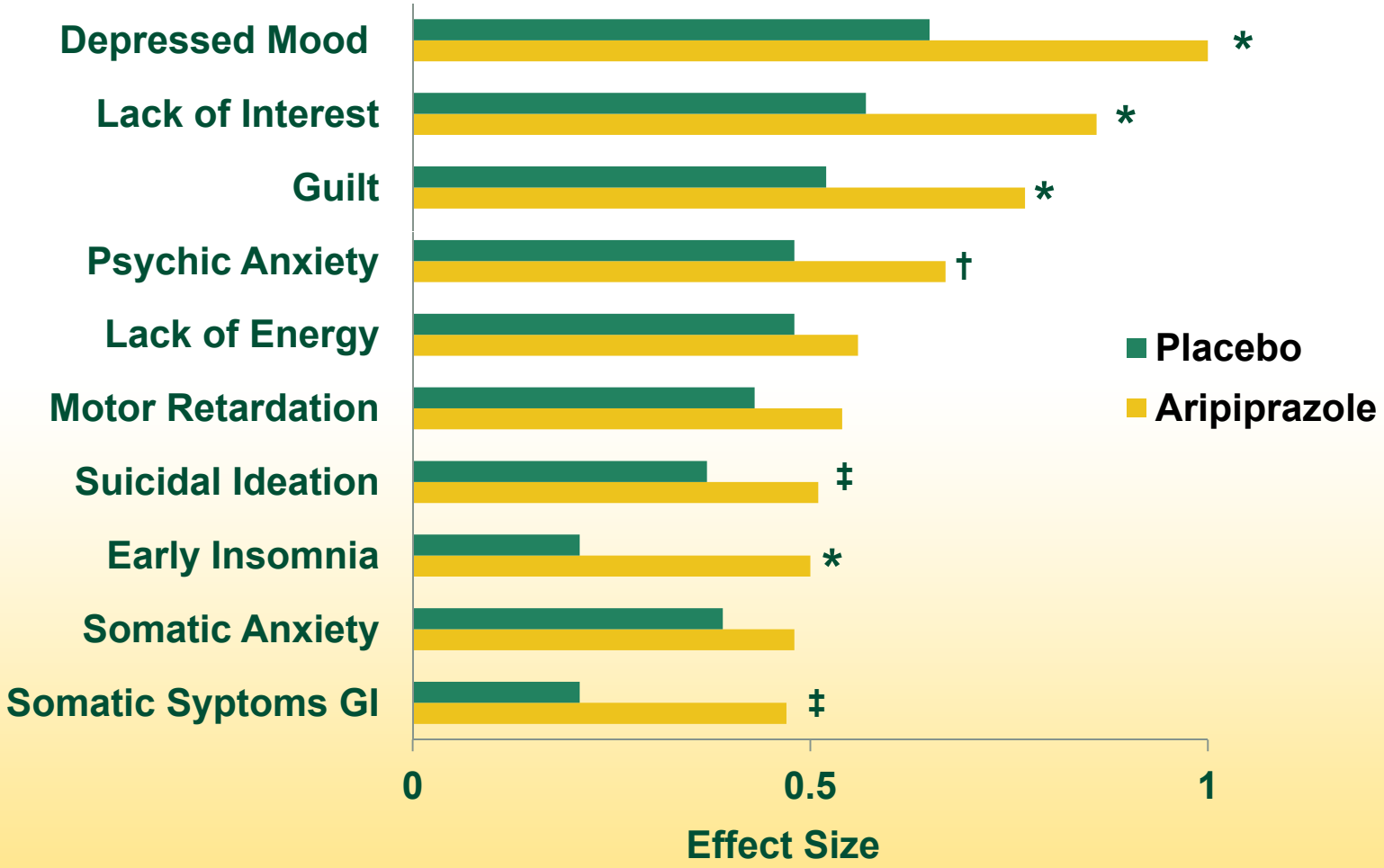




Dunner DL, et al. *J Clin Psychiatry*. 2007;68:1071-1077.

Which Symptoms Respond?

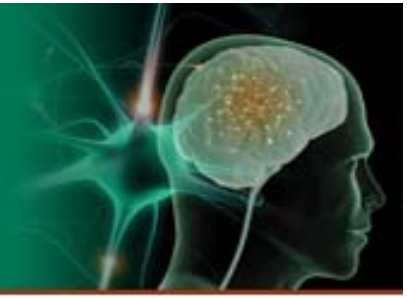
HAM-D Symptom Change With Aripiprazole and Placebo



* *P*<0.001
†*P*<0.01
‡*P*<0.05

Nelson JC, et al. *J Affect Disord*. 2010;120:133-140.

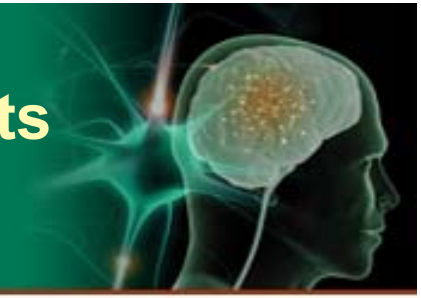
HAM-D=Hamilton Depression Rating Scale.

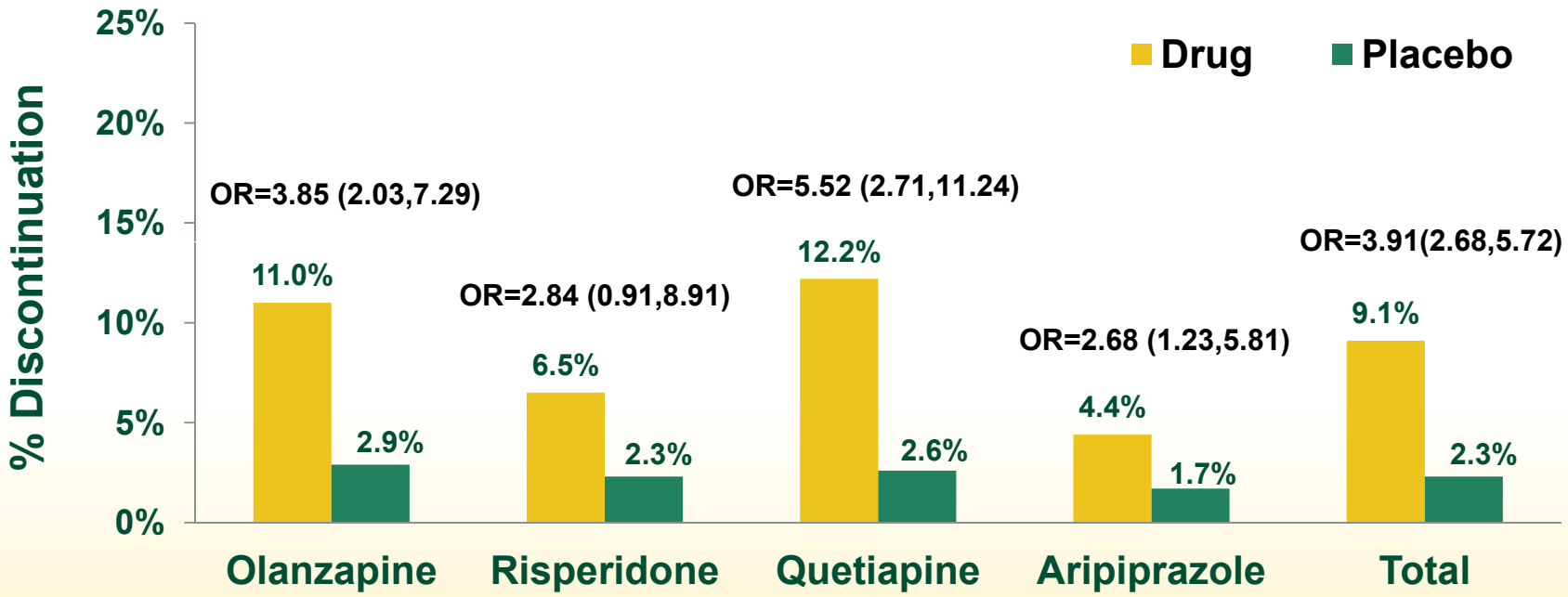


Atypical Antipsychotics: Side Effects

Discontinuations Secondary to Adverse Events

Pooled Discontinuation Rates From Meta-analysis



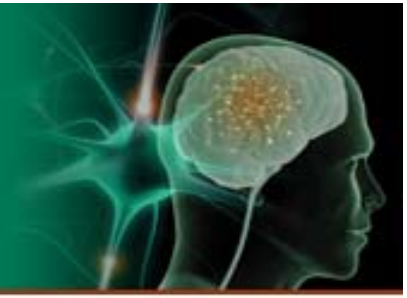


- In the meta-analysis, the odds ratios for the 4 agents did not differ significantly (χ^2=0.66, df=3, *P*=0.88)
  - However, the statistical power of these data is limited

Nelson JC, Papakostas G. *Am J Psychiatry*. 2009;166:980-991.

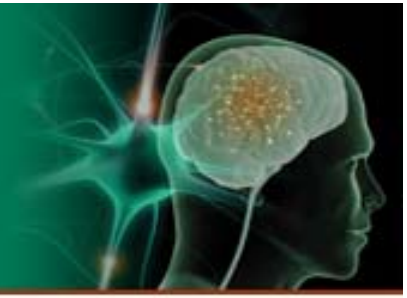
OR=odds ratio.

Extrapyramidal



- Dose-related with risperidone (common), ziprasidone and olanzapine (uncommon)
- Low with aripiprazole, but akathisia
- Very low with quetiapine

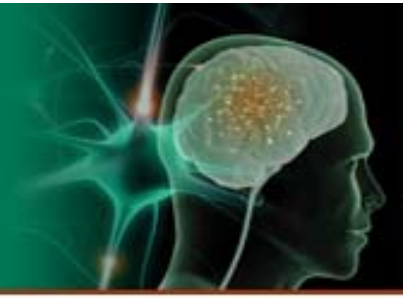
Akathisia With Aripiprazole



- In pooled database, risk of akathisia on aripiprazole was 24.5% and 4.4% on placebo
- 0.8% of patients (3/371) discontinued because of akathisia
- Severity: usually mild (49.5%) or moderate (43%)
- Akathisia resolved in 47/91 (52%) cases
- Most common interventions
  - Dose reduction
  - No intervention

Nelson JC, et al. Prim Care Companion *J Clin Psychiatry*. 2009;11:344-352.

Sedation

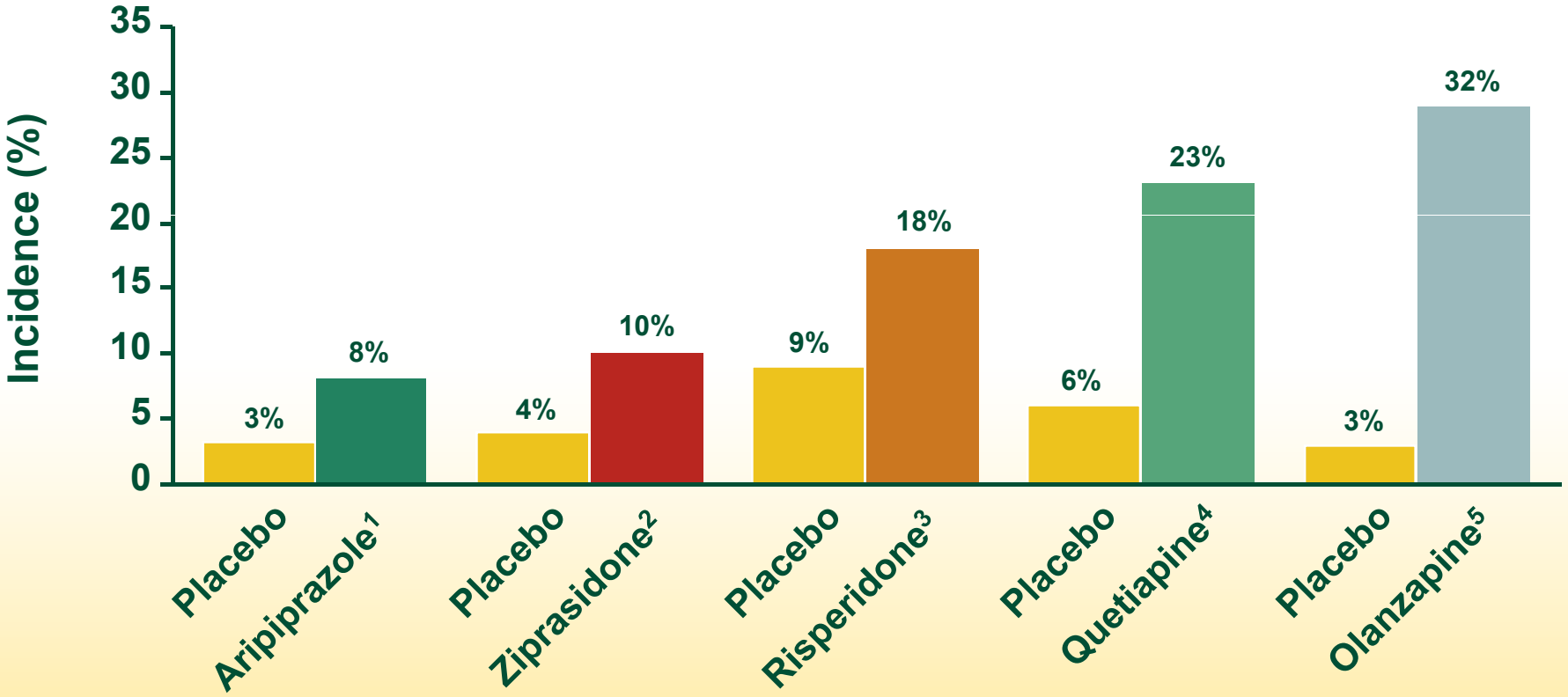


	Drug (%)	Placebo (%)
Olanzapine[1]	29	13
Quetiapine[2]	18	8
Risperidone[3]	14	4
Ziprasidone[4]	14	7
Aripiprazole[5]	7	4

Rates of sedation or somnolence (whichever is higher) in all adults or schizophrenia trials reported in the Prescribing Information.

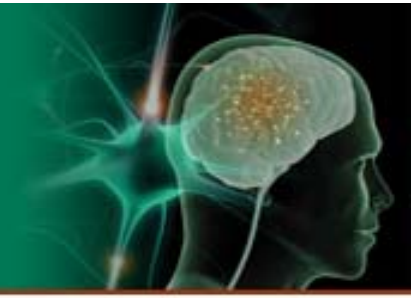
1. Zyprexa (olanzapine)Prescribing information. Lilly USA, LLC. June 2011.
2. Seroquel (quetiapine) Prescribing information. AstaZeneca, LP. July 2011.
3. Risperdal (risperidone) Prescribing information. Ortho-McNeil-Janssen Pharmaceuticals, Inc. April 2011.
4. Geodon (ziprasidone) Prescribing information. Pfizer, inc. December 2010.
5. Abilify (aripiprazole) Prescribing information. Bristol-Myers Squibb. February 2011.

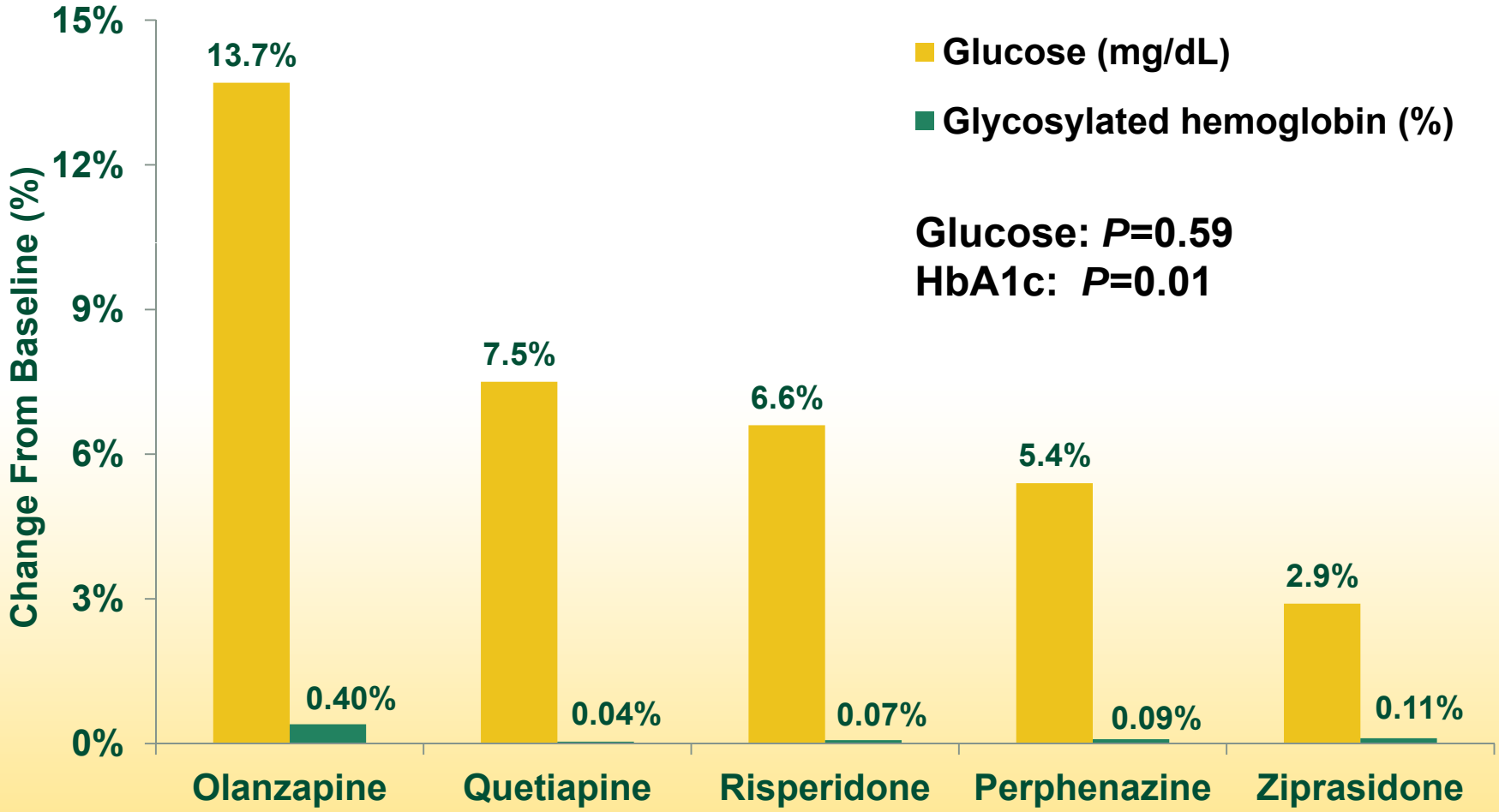
Clinically Significant (≥7%) Weight Gain During Antipsychotic Treatment



1. Abilify (aripiprazole) Prescribing information. Bristol-Myers Squibb. February 2011.
2. Geodon (ziprasidone) Prescribing information. Pfizer, inc. December 2010.
3. Risperdal (risperidone) Prescribing information. Ortho-McNeil-Janssen Pharmaceuticals, Inc. April 2011.
4. Seroquel (quetiapine) Prescribing information. AstaZeneca, LP. July 2011.
5. Zyprexa (olanzapine) Prescribing information. Lilly USA, LLC. June 2011.

CATIE Results: Metabolic Changes From Baseline

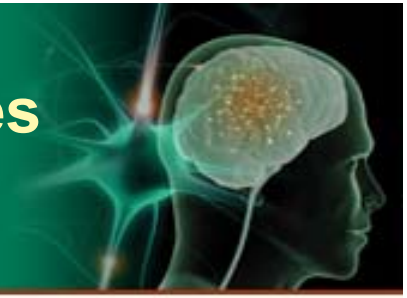




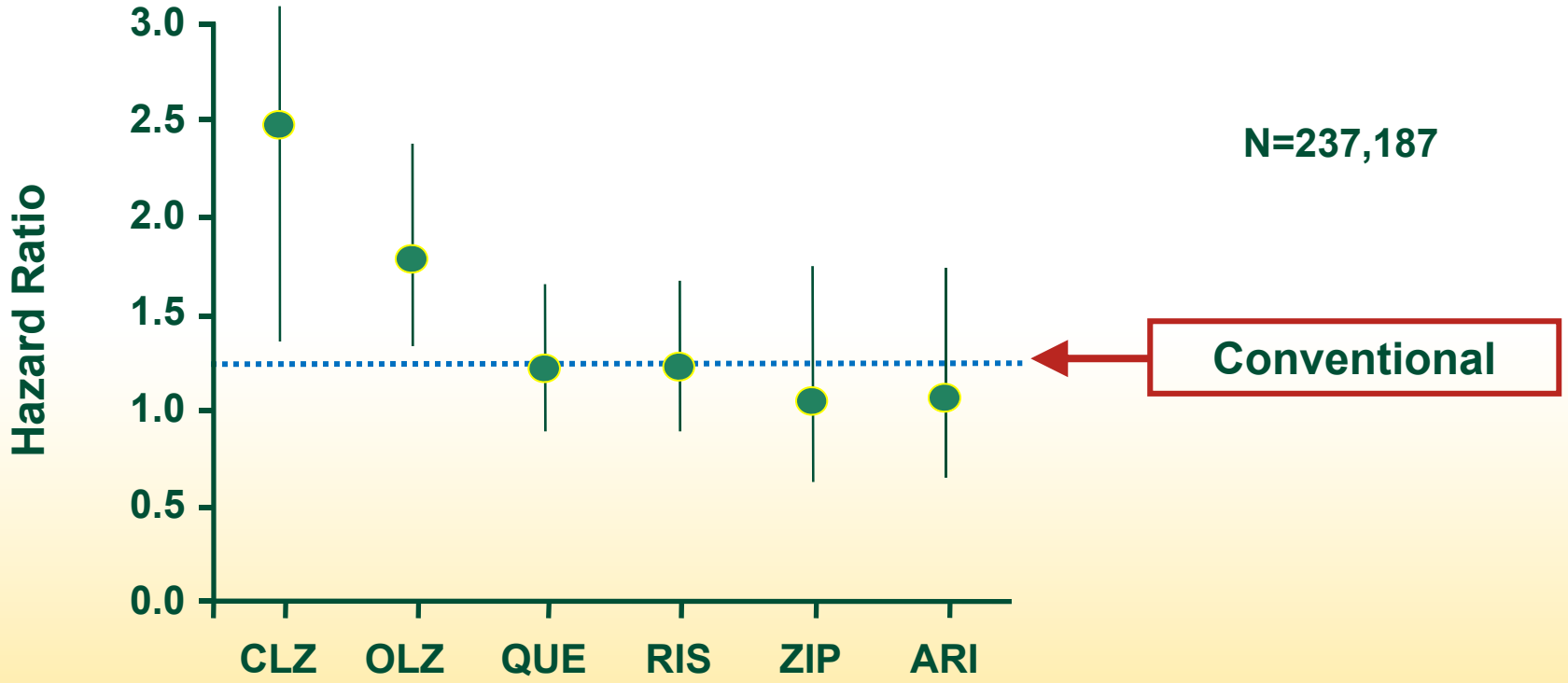
Lieberman JA, et al. *N Eng J Med*. 2005;353:1209-1223.

CATIE=Clinical Antipsychotic Trials of Intervention Effectiveness.

Adjusted* Hazard Ratio for New Onset Diabetes in Schizophrenia and Bipolar Patients



Patients Enrolled in 3 Managed Care Groups

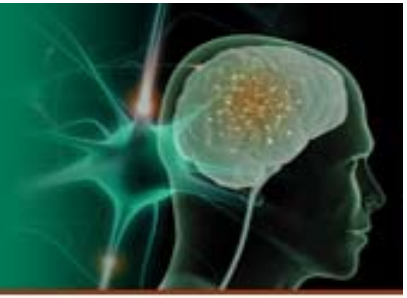


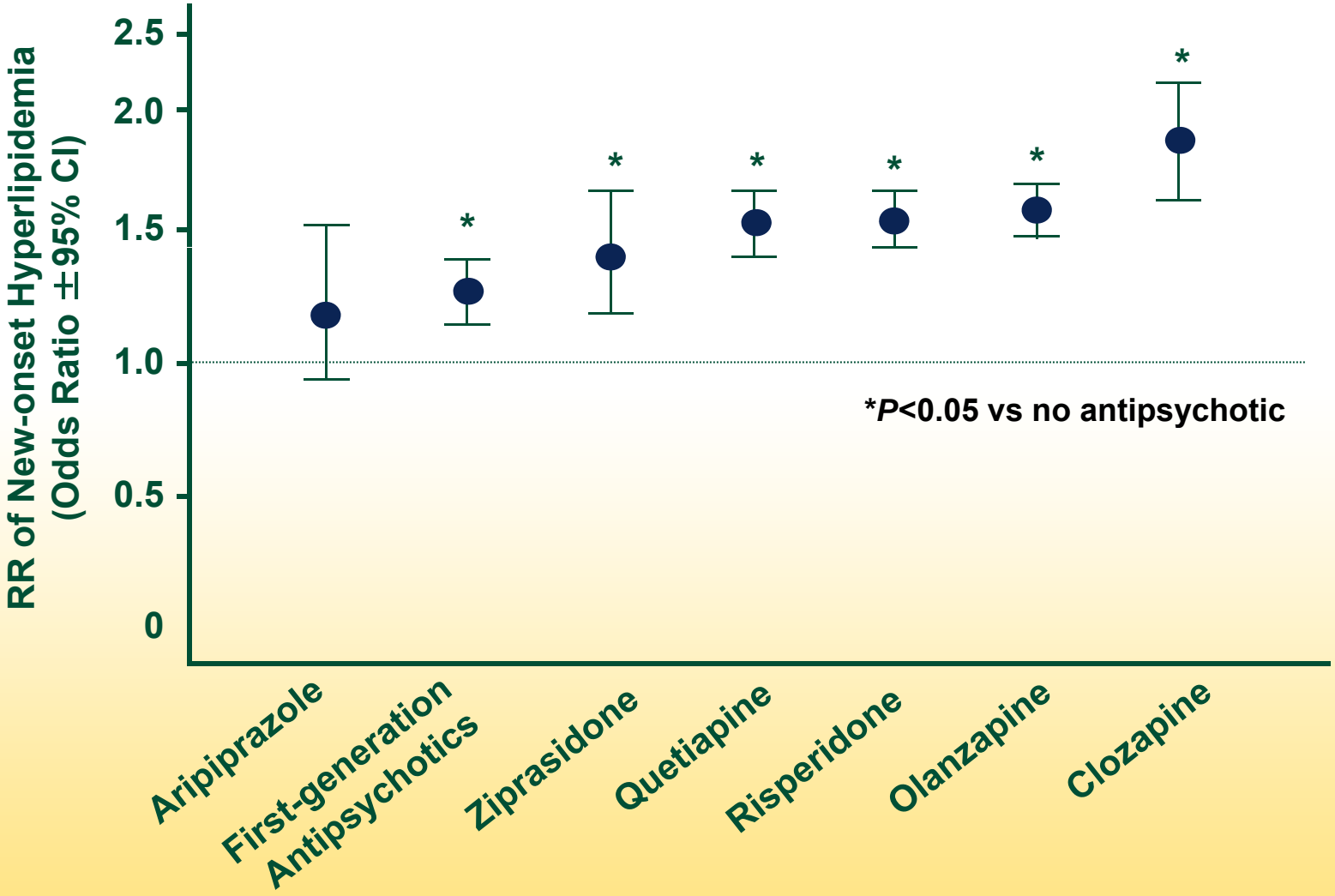
*Controlled for age, gender, history of antipsychotic use, confounding medications, excess weight (simple cohort).

Ulcickas-Yood M, et al. Presented at the 23rd Annual Meeting of the International Society of Pharmacoepidemiology. August 19-22, 2007; Quebec City, Canada.

CLZ=clozapine.
OLZ=olanzapine.
QUE=quetiapine fumarate.
RIS=risperidone.
ZIP=ziprasidone.
ARI=aripiprazole.

Antipsychotics and Hyperlipidemia

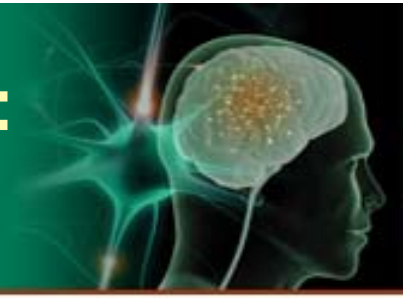




Olfson M, et al. *Am J Psychiatry*. 2006;163:1821-1825.

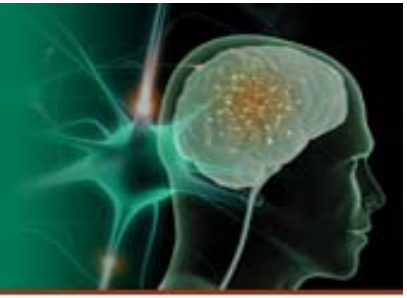
RR=relative risk.

Use of Atypical Antipsychotics for TRD: Summary



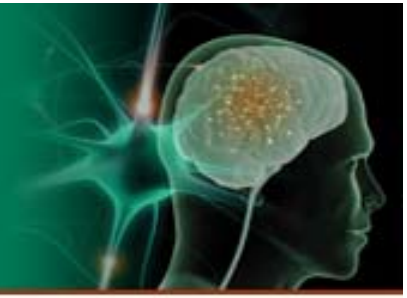
- Augmentation treatments are commonly employed
- For most augmentation strategies
  - Evidence from controlled trials limited
  - Small numbers
  - Are patients really treatment resistant?
- Atypical antipsychotic augmentation
  - Largest database
  - Patients treatment resistant
  - Significant efficacy
  - Adjunctive aripiprazole and the olanzapine/fluoxetine combination are the only agents approved for treatment of TRD in the United States
  - Safety and tolerability issues need to be considered

TRD=treatment resistant depression.

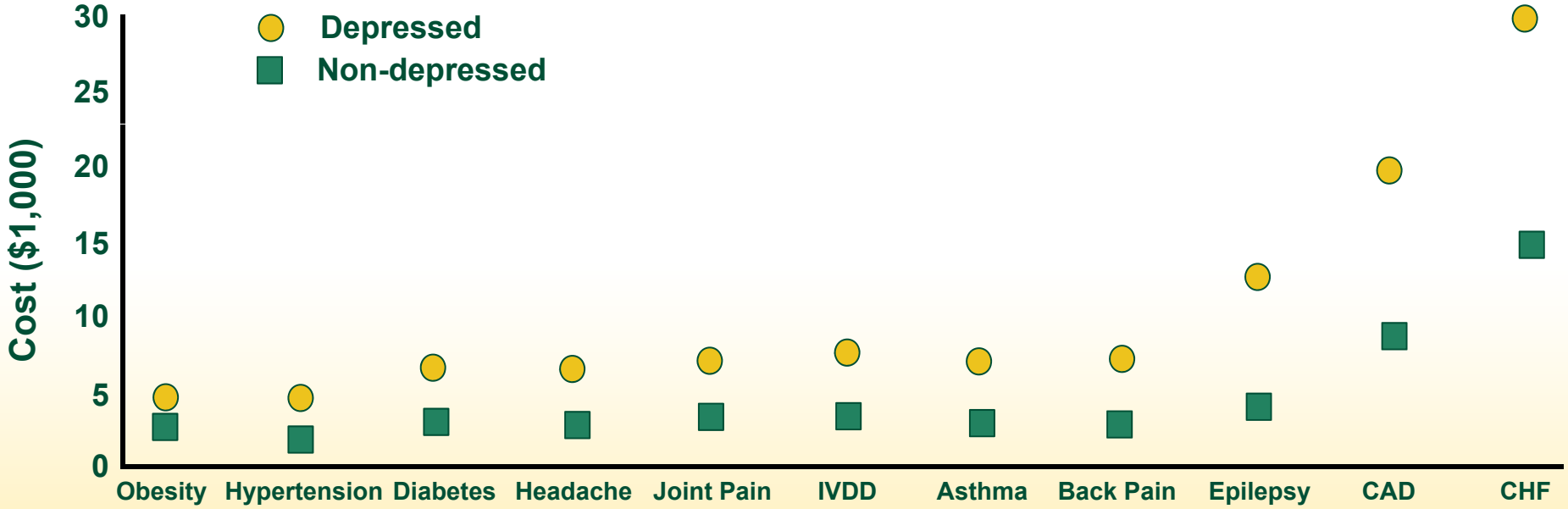


Treatment Resistant Depression: Managed Care Considerations

Annual per-Patient Cost Is Higher in Patients With Depression



Median Annual Cost per Patient

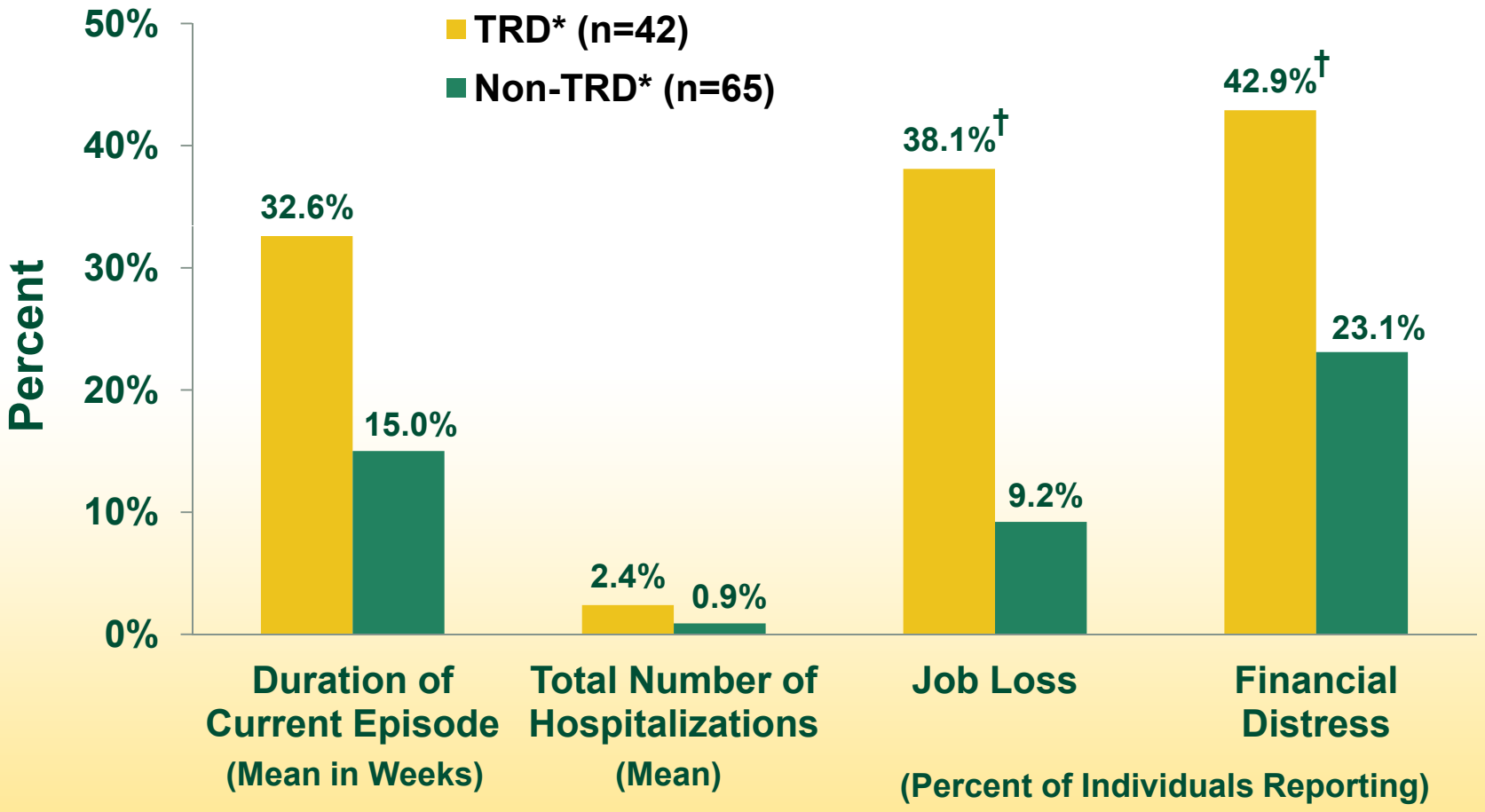


Insurance claims for 618,780 patients examined for total annual non-mental health cost of care in 11 chronic diseases. In each disease cohort, median annual non-mental health cost was calculated for individuals with and without depression.

CAD=coronary artery disease.
CHF=congestive heart failure.
IVDD=intervertebral disc disease.

Welch CA, et. al. *Psychosomatics*.2009:50;392-401.

Patients With TRD* Report Greater Clinical and Economic Burden

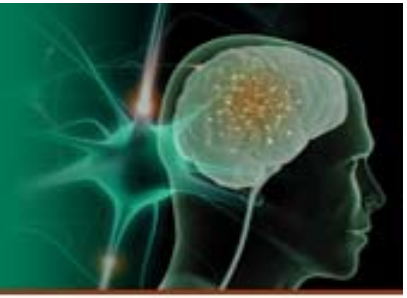


* TRD considered non-response to ≥2 treatments.
†*P*<0.05

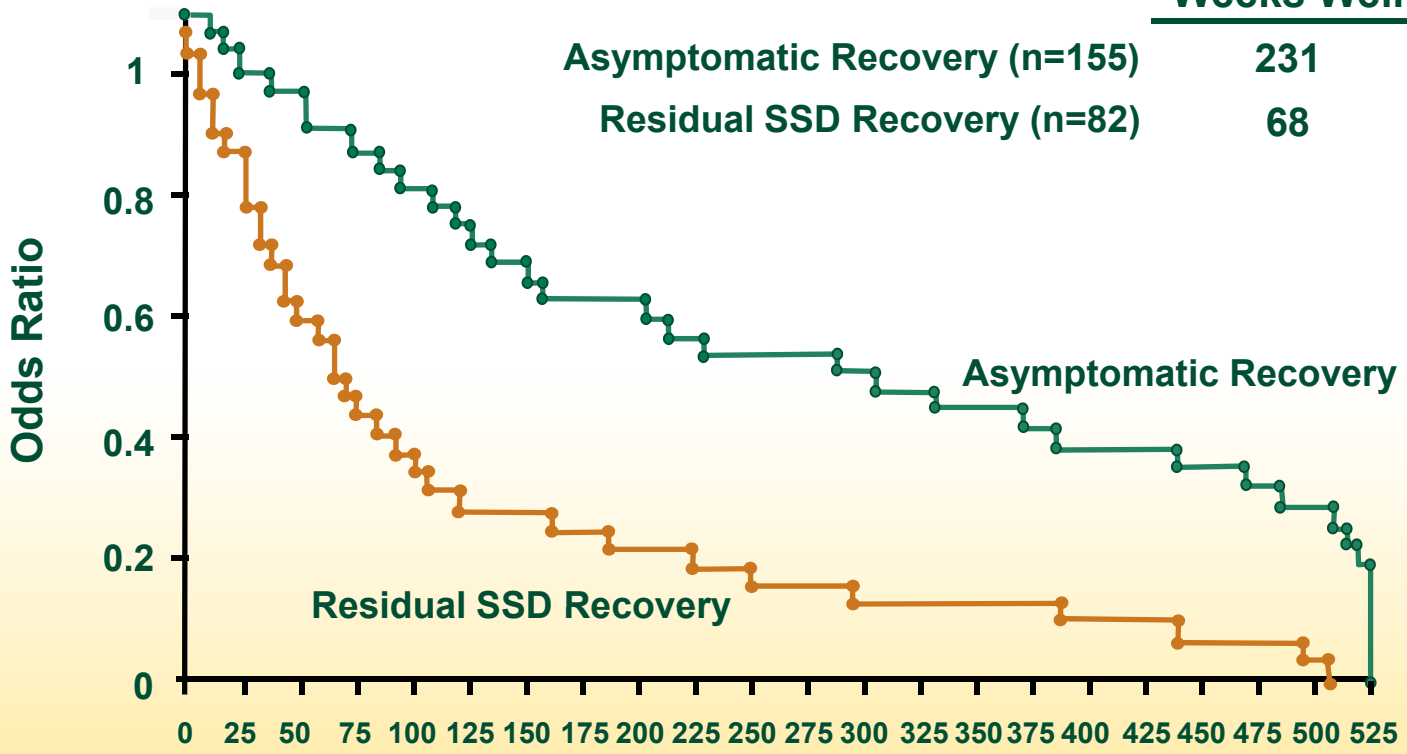
Amital D, et. al. *J of Affective Disorders*. 2008:110;260-264.

TRD=treatment resistant depression.

Failure to Achieve Initial Remission Produces Poor Long-term Outcomes



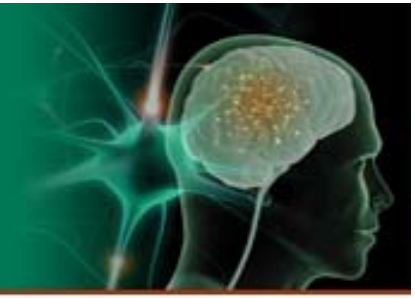
	Median Weeks Well	(95% Confidence Interval)
Asymptomatic Recovery (n=155)	231	(169-332)
Residual SSD Recovery (n=82)	68	(49-88)

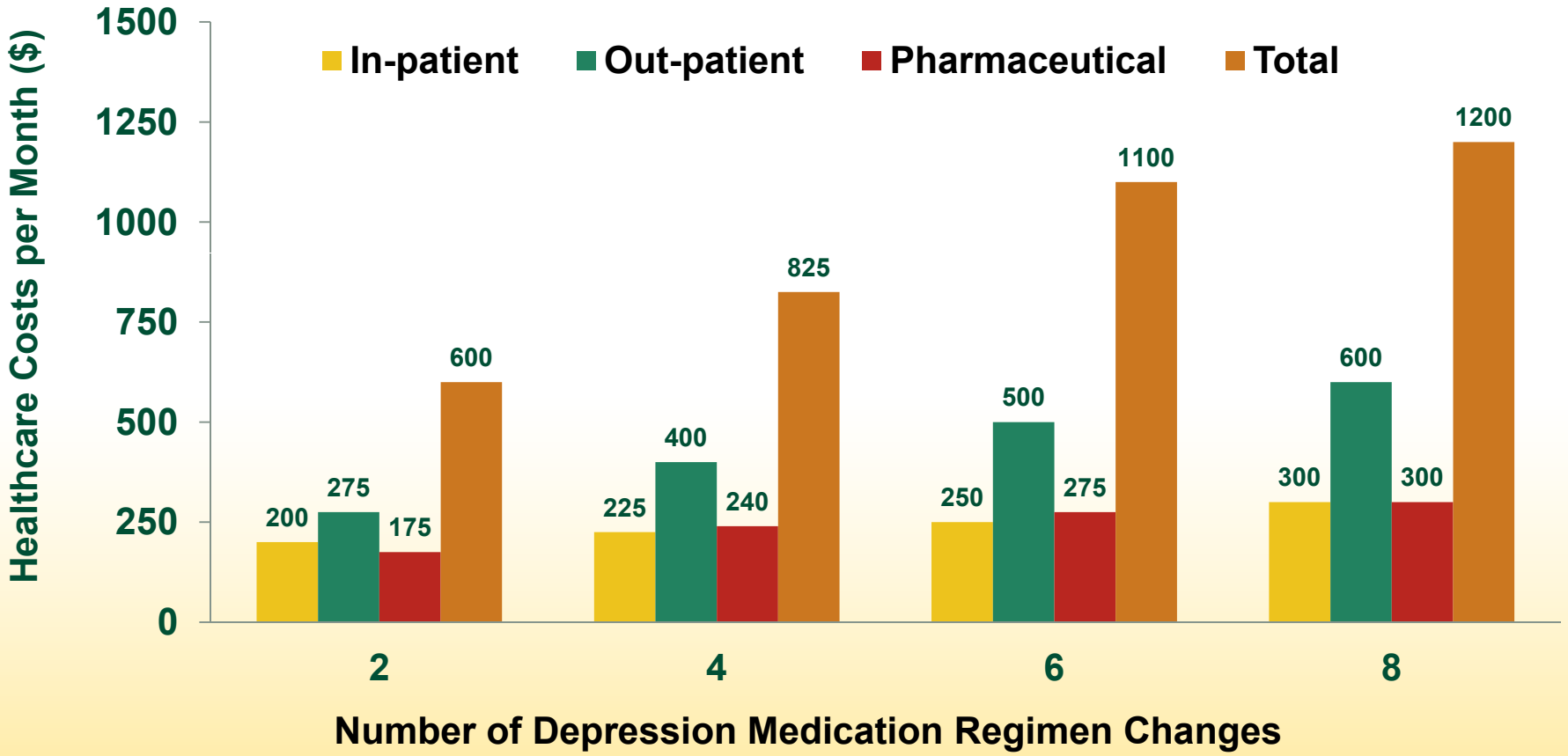


Judd LL, et. al. *J Affect Disord*. 1998:50;97-108.

SSD=sub-syndromal depression;
subthresohold depressive symptoms.

Healthcare Utilization Rises As Degree of Treatment Resistance Increases

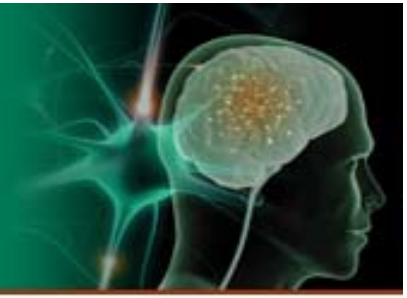




Data from the MEDSTAT MarketScan Private Pay Fee for Service (FFS) Database; analysis of 7737 patients with depression (ICD-9) with ≥2 unsuccessful trials of antidepressant medication at an adequate dose for at least 4 weeks.

Russell JM, et. al. *J Clin Psychiatry*. 2004:65;341-347.

Integrating Current TRD Practice Guidelines Into the Managed Care Treatment Algorithm

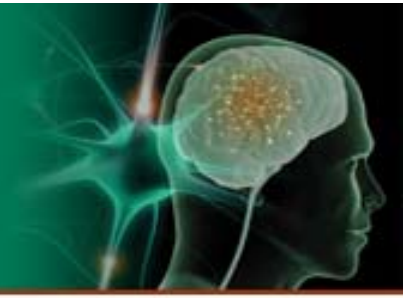


- Identify optimal, cost-effective treatment strategies[1]
  - Inadequate dose or duration of antidepressant therapy can prevent remission[2,3]
- Goal of treatment is remission[3]
  - 4-8 weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention
  - If at least a moderate improvement in symptoms is not observed within 4-8 weeks of treatment initiation, the treatment plan should be adjusted

1. Hoffman L, et al. *Am J Manag Care*. 2002;9:70-80.
2. Tierney JG. *J Manag Care Pharm*. 2007;13(suppl S-a):S2-S7.
3. American Psychiatric Association. *Am J Psychiatry*. 2010;167:1-152.

TRD=treatment resistant depression.

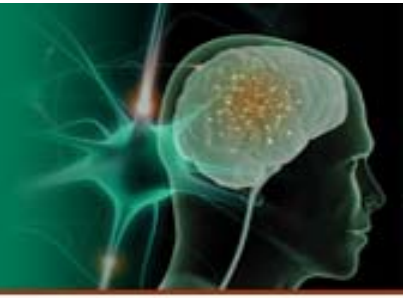
Guideline-recommended Strategies for Treatment of Refractory Depression



- Optimize the medication dose
- Switch to a different antidepressant
  - Within class or different class
- Augment the treatment regimen with a non-depressant agent
- Combine the initial antidepressant with a second anti-depressant agent or depression-focused psychotherapy

American Psychiatric Association. *Am J Psychiatry*. 2010;167:1-152.

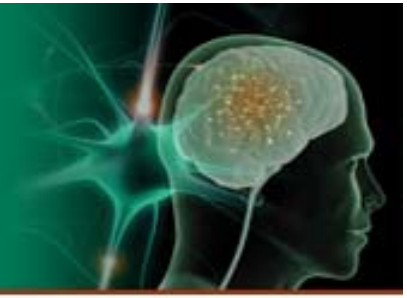
Importance of Adherence

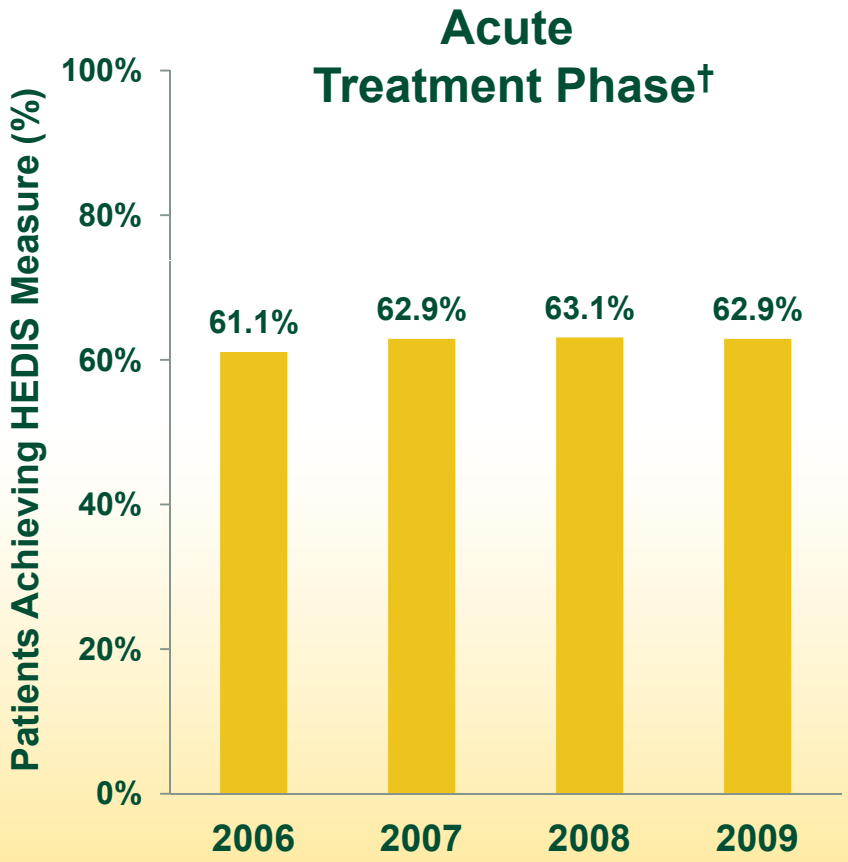


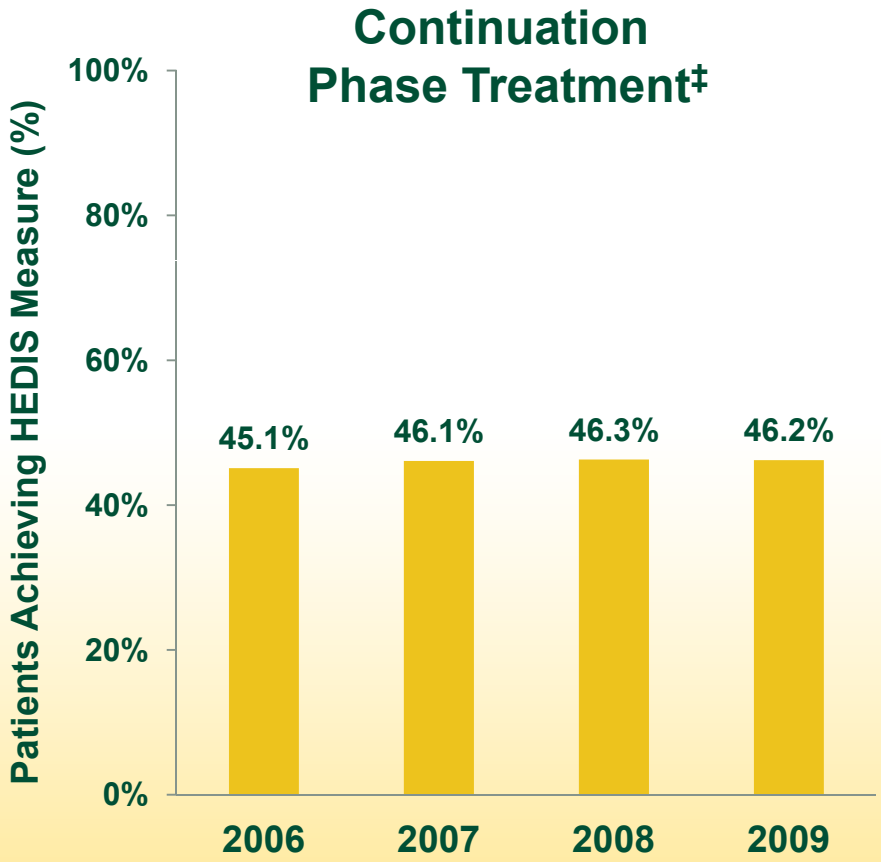
- ≥50% of patients fail to adhere to their medication as prescribed[1]
- Medical costs are $432/month higher in non-adherent vs adherent patients[3]
- Assess reasons given for poor adherence[3]
  - Side effects
  - Fears of addiction/dependence
  - Lack of understanding of the need for regular adherence

1. Sheehan DV, et al. *J Manag Care Pharm*. 2005;11:S354-361.
2. Cantrell CR, et al. *Med Care*. 2006;44:300-303.
3. American Psychiatric Association. *Am J Psychiatry*. 2010;167:1-152.

Implementation of MDD Sequenced Treatment Strategies Can Help Improve HEDIS Scores*







* HMO means.

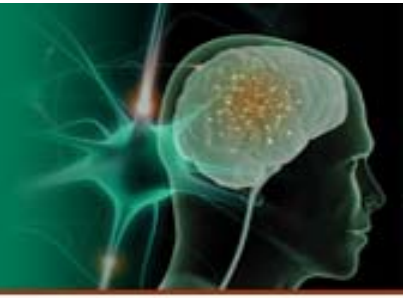
† Percentage of newly diagnosed and treated members who remained on an antidepressant medication for at least 84 days.

‡Percentage of newly diagnosed and treated members who remained on an antidepressant medication for at least 180 days.

National Committee for Quality Assurance. The State of Healthcare Quality. 2010.

MDD=major depressive disorder.
HEDIS=Healthcare Effectiveness Data and Information Set.

TRD and Managed Care: Summary



- Managed care must identify optimal, cost-effective strategies for depression treatment[1]
  - Initial and subsequent treatment efficacy, tolerability, and adherence influence clinical outcomes and pharmaco-economic aspects of care[2]
  - Depressed patients who complete the recommended course of therapy utilize fewer healthcare resources vs those who discontinue therapy[3]
  - Regular adherence is associated with reduced overall healthcare costs[4]
  - Effective implementation of guideline-recommended sequenced therapy may improve HEDIS scores[5]

1. Hoffman L, et al. *Am J Manag Care*. 2002;9:70-80.
2. Tierney JG. *J Manag Care Pharm*. 2007;13(suppl S-a):S2-7.
3. Eaddy MT, et al. *J Manag Care Pharm*. 2005;11:145-150.
4. Sheehan DV, et al. *J Manag Care Pharm*. 2005;11:S354-361.
5. National Committee for Quality Assurance. The State of Healthcare Quality. 2010.

TRD=treatment resistant depression.
HEDIS=Healthcare Effectiveness Data and Information Set.