



Atypical Antipsychotics for the Treatment of Mood and Anxiety Disorders: New Evidence for Improving Response and Remission Rates



This program meets the accreditation criteria of The College of Family Physicians of Canada and has been accredited for one (1) Mainpro-1 credit per hour.

Disclosure

Advisory board or similar committee	
Clinical trials or studies	
Honoraria or other fees	Pfizer, AstraZeneca,
Research grants	

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Learning Objectives

- At the end of this session, physicians should have a better understanding of:
 - The burden of illness of major depressive disorder (MDD)
 - Common symptoms shared across various psychiatric diagnoses including MDD
 - The mechanism of antidepressant activity of atypical antipsychotics
 - The efficacy, safety, and tolerability profiles of atypical antipsychotics in mood and anxiety disorders

MDD: Prevalence and Impact

- Canada (2002 CCHS)¹
 - 12 month: 4.8%
 - Lifetime: 12.2%
- U.S. (2005 NES-ARC)²
 - 12 month: 5.3%
 - Lifetime: 13.2%

- MDD is associated with:^{1,2}
 - Impairment
 - Comorbidity
 - Poor physical health
 - Poor quality of life
 - Mortality

Why Study AAPs in Depression and Anxiety?

- Unmet medical need
 - High rates of failure (non or partial response) to current treatment
 - Many patients discontinue treatment prematurely due to tolerability issues
- Anecdotal reports
 - Physician experiences
- Observed Efficacy in Bipolar Depression studies
 - quetiapine, quetiapine extended release, olanzapine

Unmet medical need:

Cumulative Remission in STAR*D

Level	Interventions	Remission Rate*	Cumulative Remission
Step 1 N=3,671	<ul style="list-style-type: none">• CITALOPRAM	36.8%	36.8%
Step 2 N=1,439	<ul style="list-style-type: none">• Switch: VEN / BUP / SER• Combine: BUP / BUS• Switch / Combine: CT	30.6%	56.1%
Step 3 N=390	<ul style="list-style-type: none">• Switch: NOR / MIR• Augment: LI / T3	13.7%	62.1%
Step 4 N=123	<ul style="list-style-type: none">• Switch: TCP / MIR+VEN	13.0%	67.0%

* QIDS-SR₁₆ ≤ 5



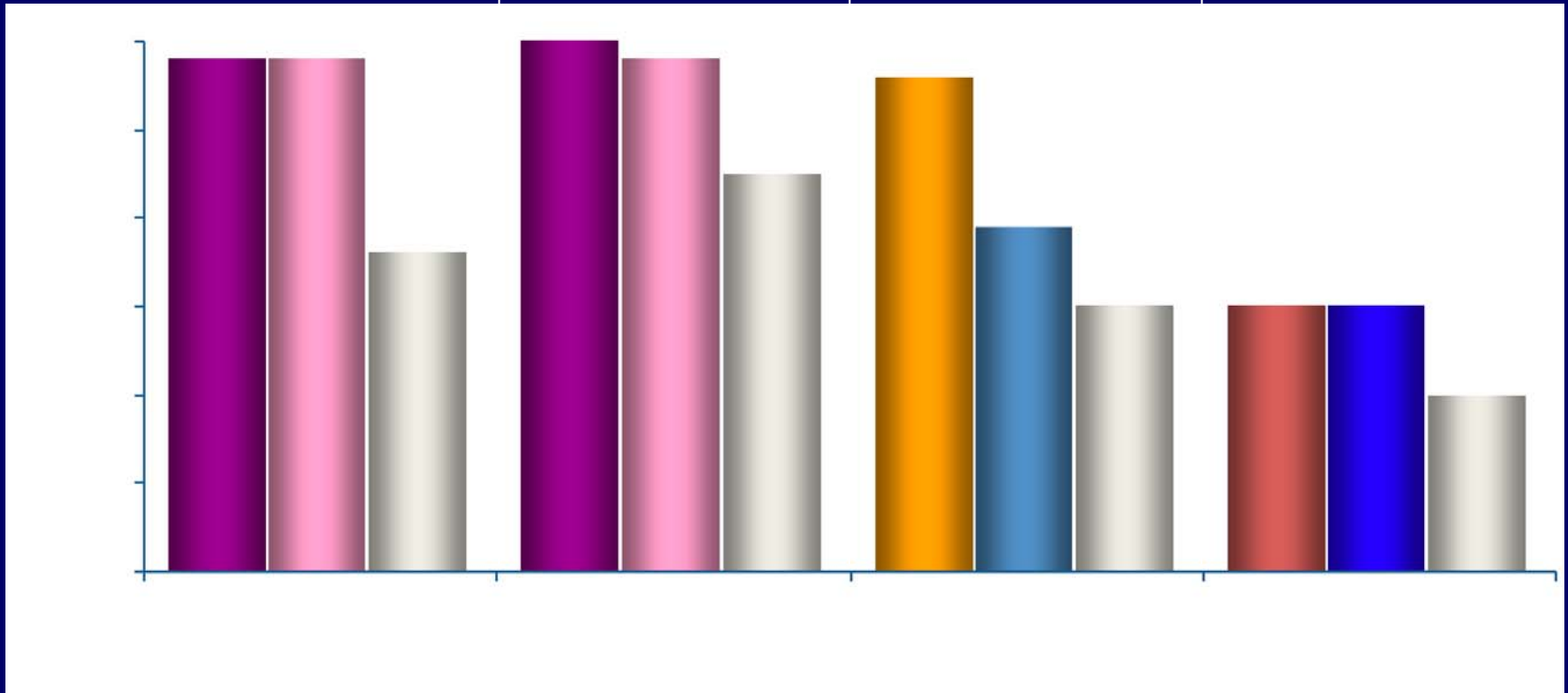
My perspective on the unmet needs in the treatment of depression

Psychotropic medications target symptoms... *not diagnoses*

Symptom domains	Symptom domains shared across diagnoses
<ul style="list-style-type: none">■ Depression■ Anxiety■ Agitation■ Psychosis	<ul style="list-style-type: none">■ Schizophrenia■ Bipolar disorder■ MDD■ GAD■ Other anxiety disorders (PTSD, OCD)■ Personality disorders

Response Rates with AAPs for Bipolar Depression

Response rates ($\geq 50\%$ decrease in depression rating scale)[†]



* $p < 0.05$ vs. PBO within studies.

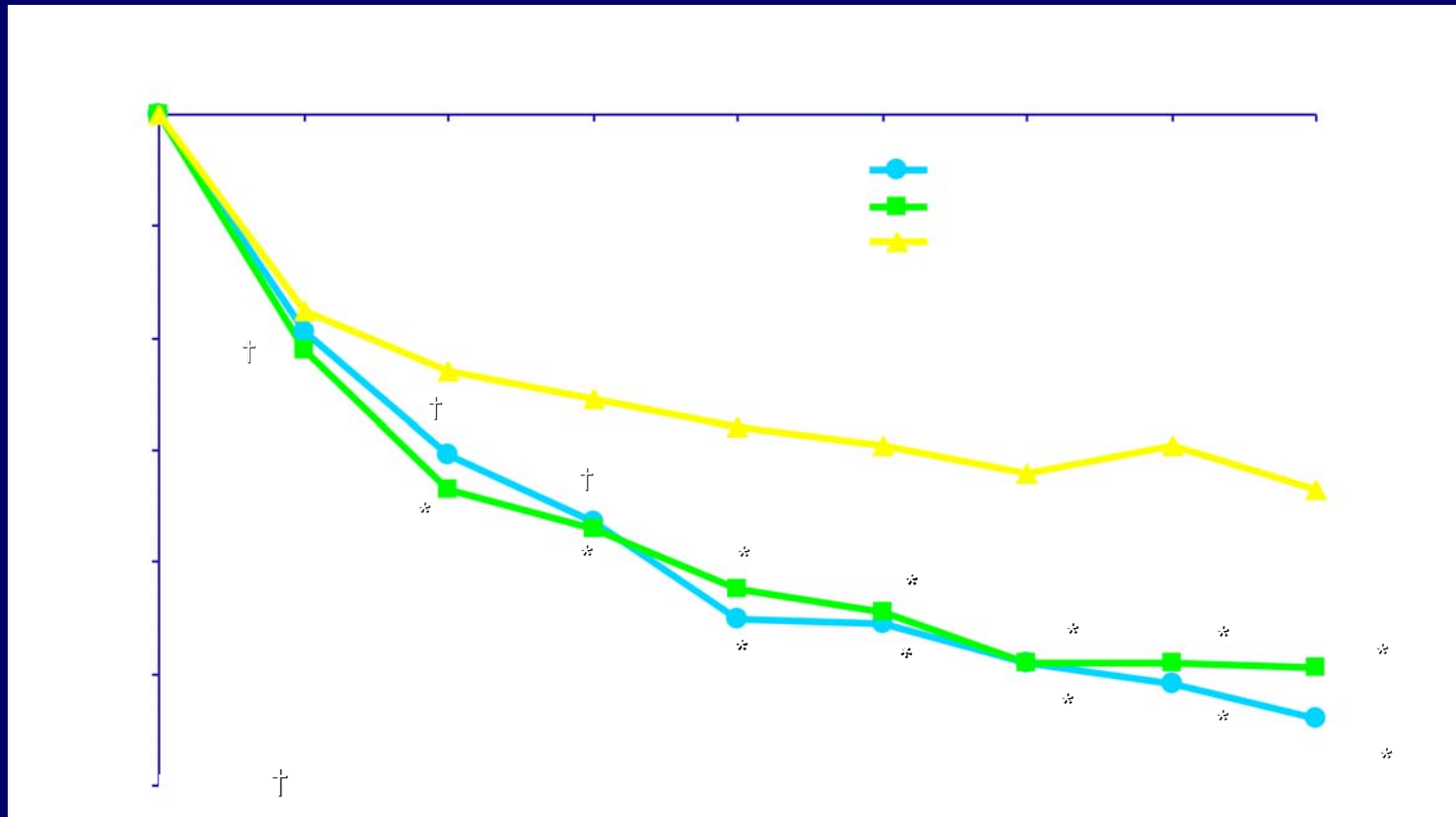
[†]Direct comparison cannot be made as data derived from different clinical trials

OLZ: olanzapine; PRX: paroxetine;
PBO: placebo; RIS: risperidone;
QUE: quetiapine; FLX: fluoxetine

1. Calabrese et al. *Am J Psychiatry* 2005;162:1351-60;
2. Thase et al. *J Clin Psychopharmacol* 2006;26:600-9;
3. Tohen et al. *Arch Gen Psychiatry* 2003;60:1079-88
4. Shelton, Stahl. *J Clin Psychiatry* 2004;65:1715-9

AAP Efficacy for Anxiety in Bipolar Depression

8 week, RCT in patients with bipolar depression (n=539)



2006: Emerging Indications for AAPs

Atypical antipsychotic drugs

- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone
- Paliperidone*
- Aripiprazole

Currently Approved for:

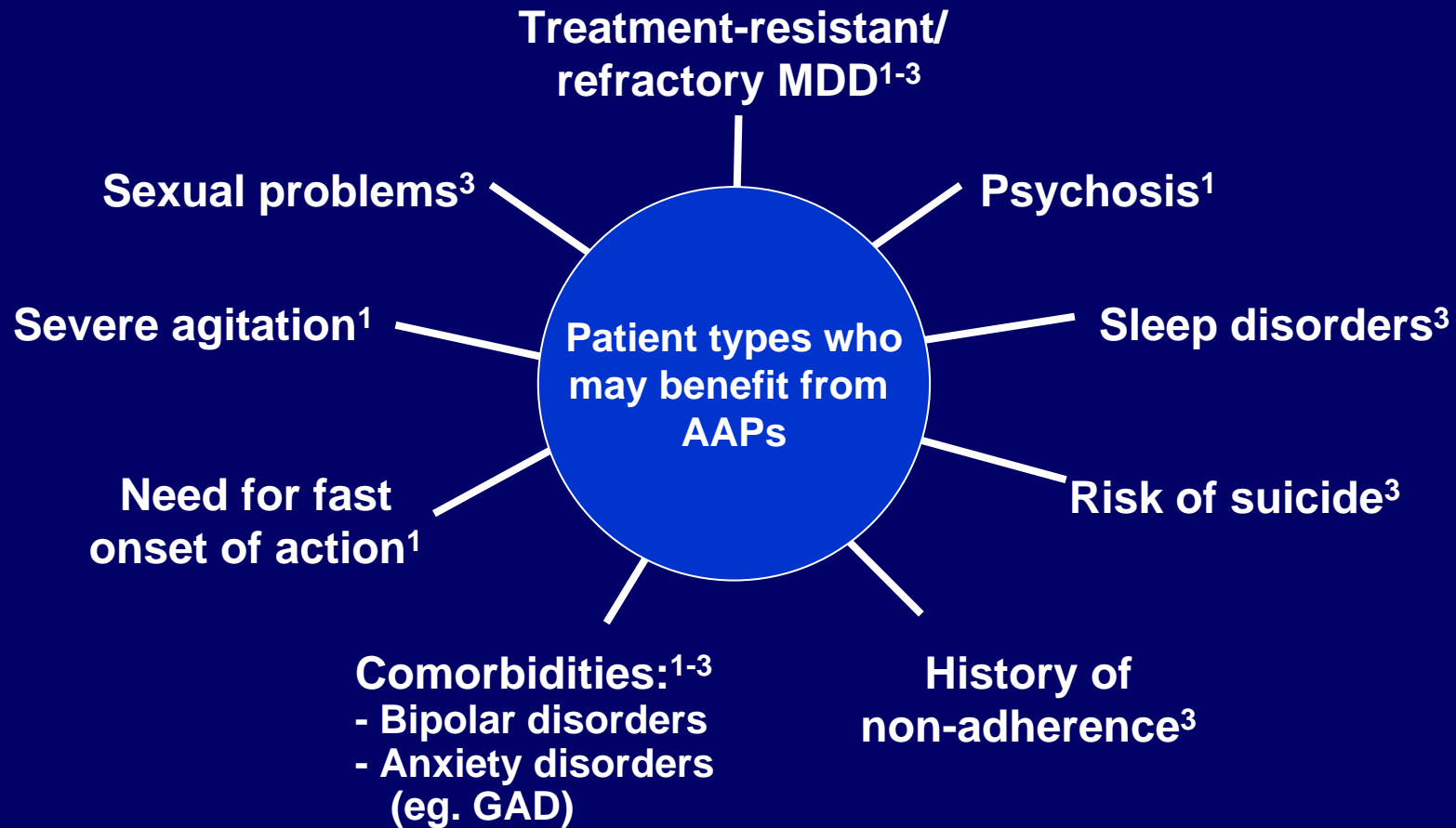
- Schizophrenia
 - Positive & negative symptoms
- Bipolar disorder

Emerging Indications:

- Major depressive disorder
 - Add-on and monotherapy
- Treatment resistant depression
- Generalized anxiety disorder
- Borderline personality disorder

* Not approved for bipolar disorder

Patients with MDD who may Benefit from AAP Therapy



1. Culpepper. *Primary Care Companion J Clin Psychiatry* 2003;5:27-32;

2. Nemeroff. *J Clin Psychiatry* 2005;66:13-21; 3. Ishak et al. *Curr Psychiatry Rep* 2004;6:422-4

Mechanistic Comparison: Understanding AAP Efficacy in MDD

Agent(s)	Serotonin	Norepinephrine	Dopamine
SSRIs¹	<ul style="list-style-type: none"> Block 5-HT reuptake Down-regulate presynaptic / activate postsynaptic 5-HT_{1A} receptors 	<ul style="list-style-type: none"> Some SSRIs inhibit norepinephrine reuptake 	<ul style="list-style-type: none"> Some SSRIs inhibit dopamine reuptake Increase dopamine D₃ receptors
SNRI^{1,2}	<ul style="list-style-type: none"> Block 5-HT reuptake 	<ul style="list-style-type: none"> Inhibits norepinephrine reuptake at high doses 	<ul style="list-style-type: none"> Some inhibition of dopamine reuptake
Olanzapine¹	<ul style="list-style-type: none"> 5-HT_{2A} receptor antagonist 5-HT_{1A} receptor partial agonist 5HT_{2C} antagonism 	<ul style="list-style-type: none"> α₁-adrenergic receptor antagonist 	<ul style="list-style-type: none"> Dopamine D₂ receptor antagonist
Quetiapine¹	<ul style="list-style-type: none"> 5-HT_{2A} antagonist 5-HT_{1A} receptor partial agonist 5HT_{2C} antagonism 	<ul style="list-style-type: none"> α_{2b} receptor antagonist 	<ul style="list-style-type: none"> Dopamine D₂ receptor antagonist

1. Yatham, et al. *J Clin Psych* 2005;66:40-8;

2. Harvey et al. *Arch Gen Psychiatry* 2000;57:503-9

Bymaster, F., *Neuropsychopharmacology*, 14:87-96, 1996

Proposed Models for Antidepressant Efficacy

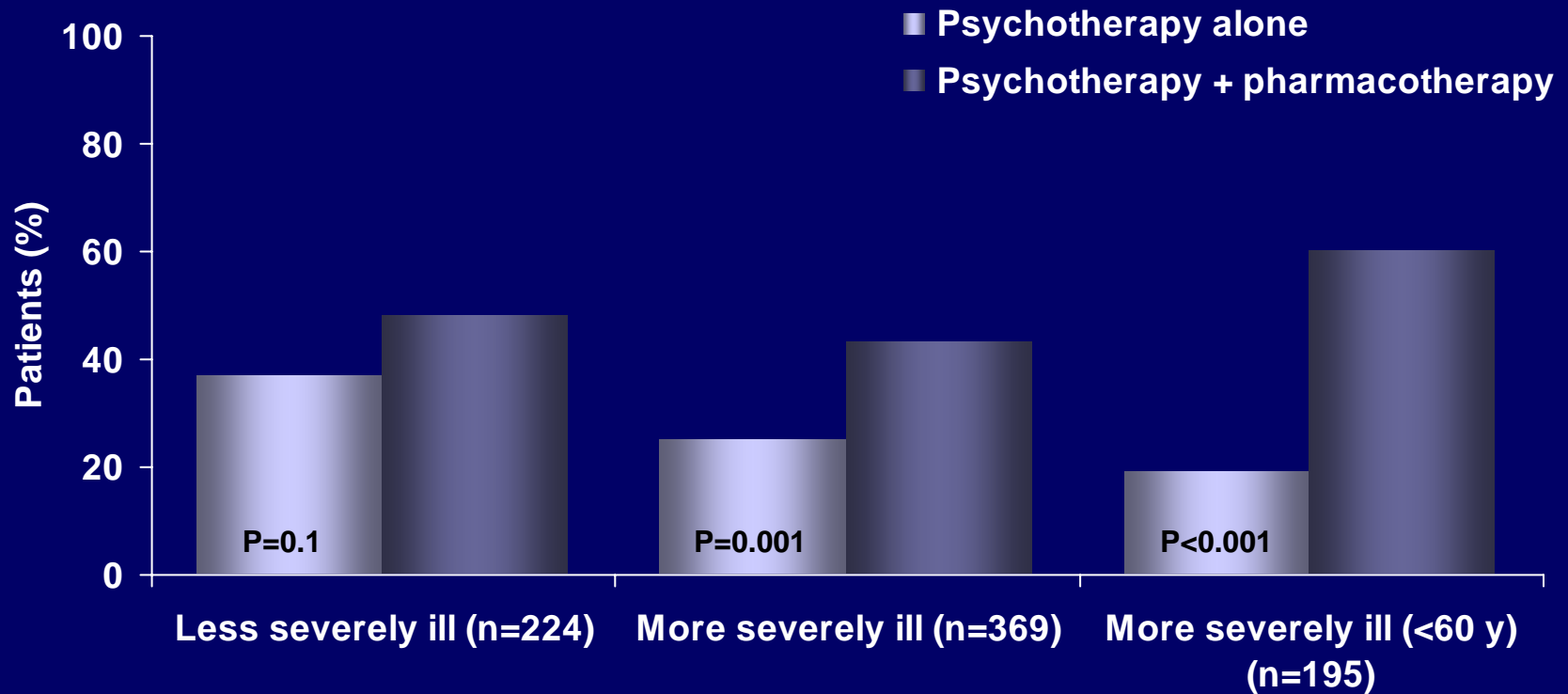
- Target of antidepressant development shifting from neurotransmitter effects to novel mechanisms:
 - Brain Derived Neurotrophic Factor (BDNF)
 - Second Messenger Systems (e.g., G-proteins, cyclic AMP)

Brain Derived Neurotrophic Factor (BDNF)

- BDNF stimulates neuronal repair and remodeling
- Depression correlates with reduced hippocampal volume and reduced BDNF levels
- Antidepressants and Antipsychotics shown to increase BDNF expression in hippocampus

Combined Psychosocial and Pharmacological Treatment

16 week mega-analysis of 6 trials, recovery* rates (n=595)



*HAM-D score ≤ 7 for at least 4 wks that was maintained until wk 16
Psychotherapy was IPT (interpersonal therapy) or CBT (cognitive behavioural therapy)

General Utility of Psychological Therapies in GAD

- Meta-analyses clearly demonstrate that CBT:
 - Reduces anxiety symptoms
 - More effective than no treatment and nonspecific psychological treatment methods
- Magnitude of benefits comparable to those with antidepressants in some studies
- CBT appears to be beneficial in both individual and group settings
- Benefits of CBT may be maintained for 6-24 months

Atypical Antipsychotics in Unipolar Depression (Major Depressive Disorder)

A Review of Current Evidence

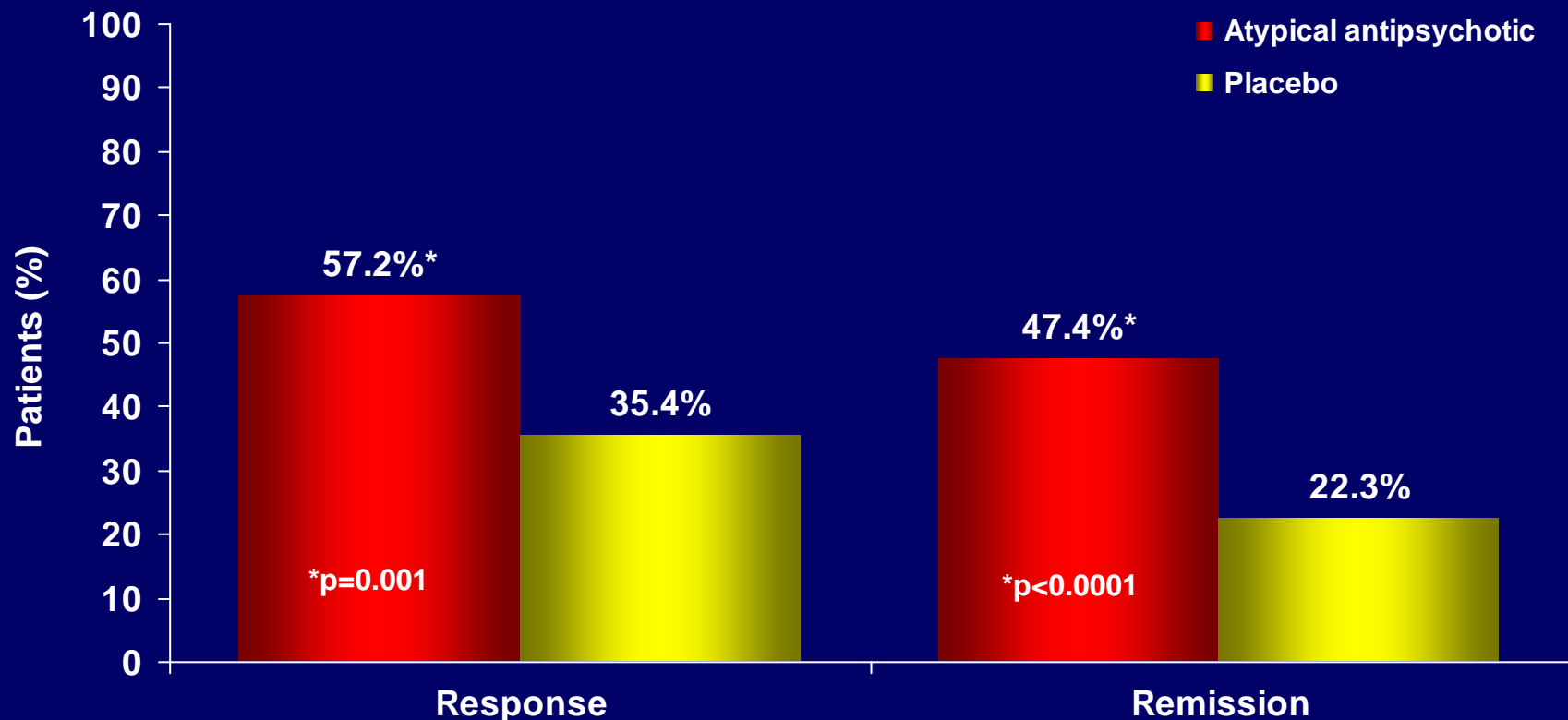
Augmentation Strategies for MDD: Published Evidence

Initial drug therapy	Augmentation drug prescribed (% of pts)	Studies	Placebo control
Antidepressant-antidepressant			
NDRI	SSRI (25.9)	5	0
SSRI	NaSSA (6.7)	3	1
NDRI	NaSSA (3)	0	0
SSRI	Tetracyclic (2.9)	3	2
SNRI	NDRI (2.8)	0	0
Antidepressant-antipsychotic			
SSRI	Atypical (52.3)	11	3
NDRI	Atypical (3.9)	0	0

NDRI: norepinephrine-dopamine reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressant; SNRI: serotonin-norepinephrine reuptake inhibitor

AAPs as Adjunct to Antidepressants in TRD

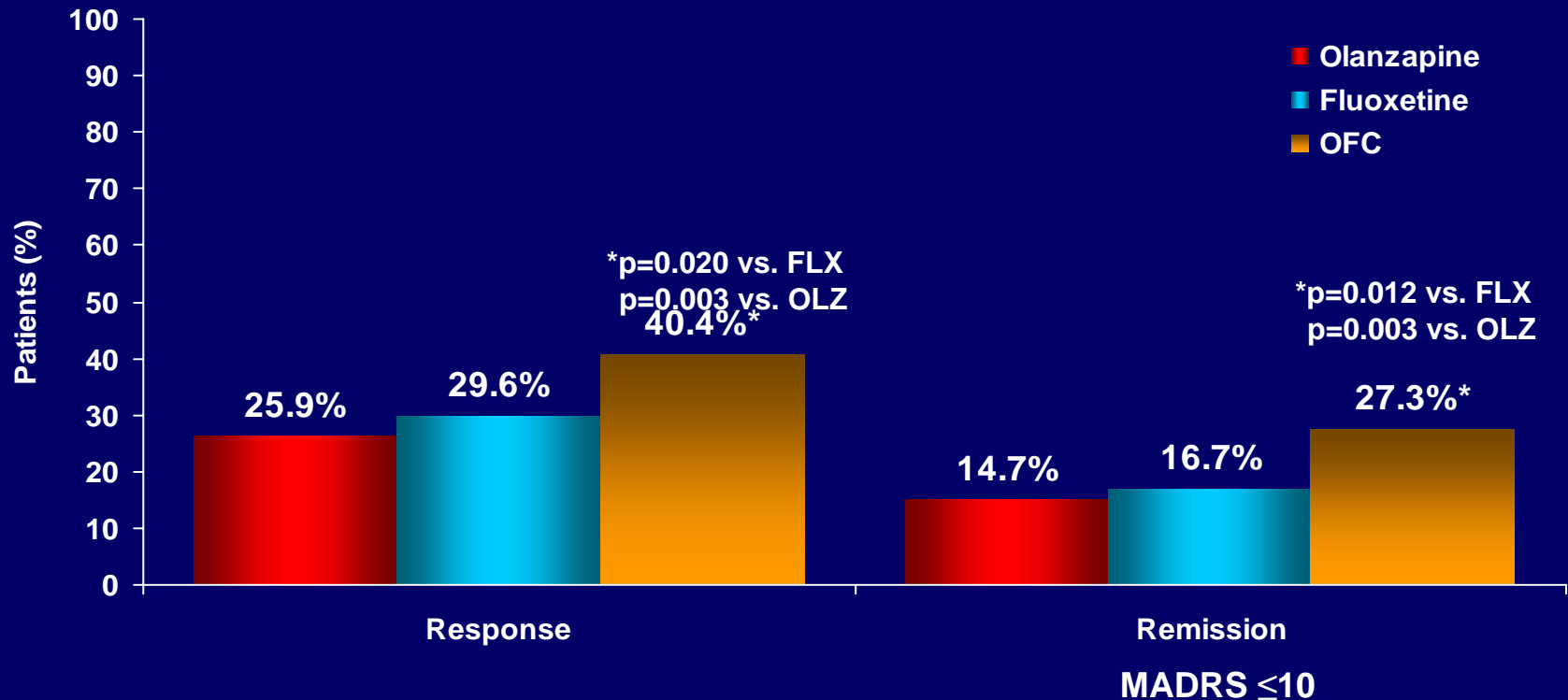
Meta-analysis of 10 RCTs, pooled response & remission rates (n=1500)



AAPs included: olanzapine, quetiapine, risperidone

Olanzapine-Fluoxetine Combination for Resistant Depression

Pooled results of 2 parallel, 8 week RCTs of olanzapine, fluoxetine, or combination, change in MADRS and remission rates (n=605)



Resistant: Incomplete response to one historical course of AD other than FLX and one 8-wk course of FLX during current MDE

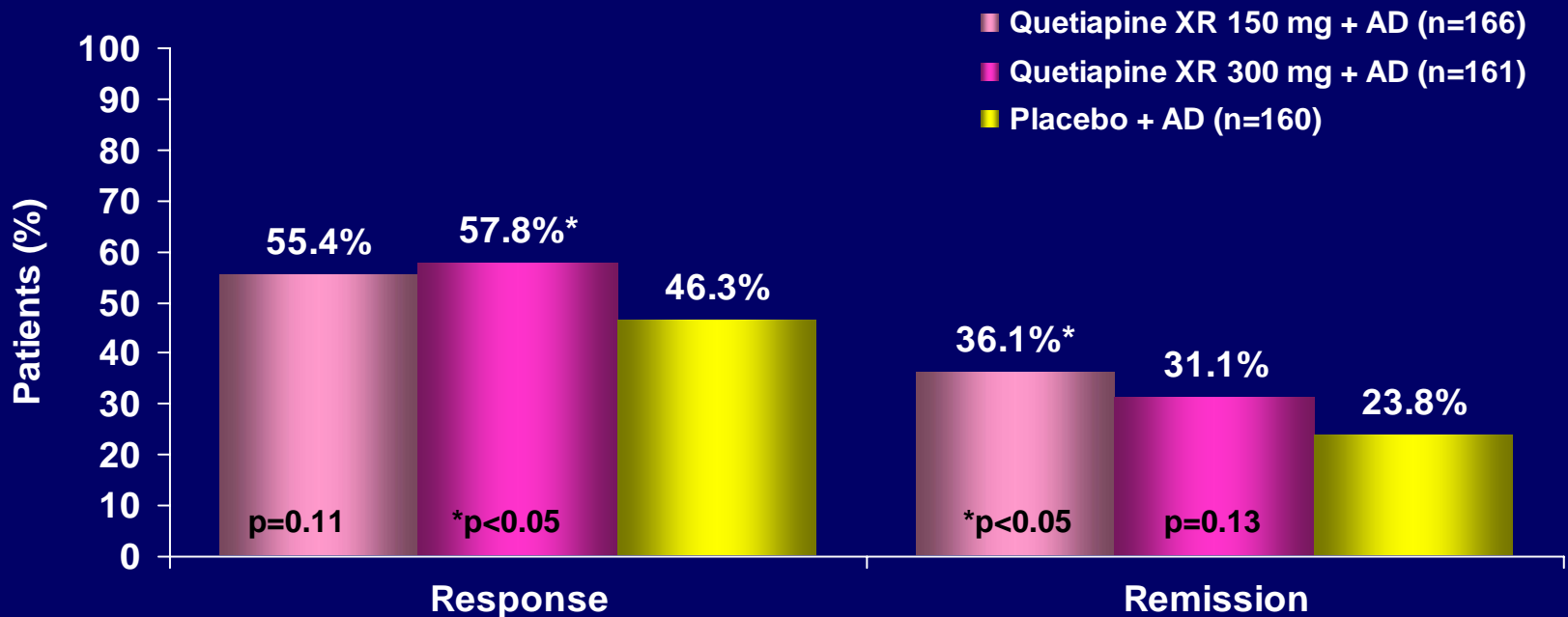
AD: antidepressant; FLX: fluoxetine; OLZ: olanzapine

Response: ≥50% reduction in MADRS from baseline; Remission: MADRS ≤10

Thase et al. *J Clin Psychiatry* 2007;68:224-36

Adjunctive AAPs in Patients With Inadequate Response to One Prior AD

6 week RCT of **quetiapine XR** as adjunct to antidepressant[†], response and remission rates (n=493)

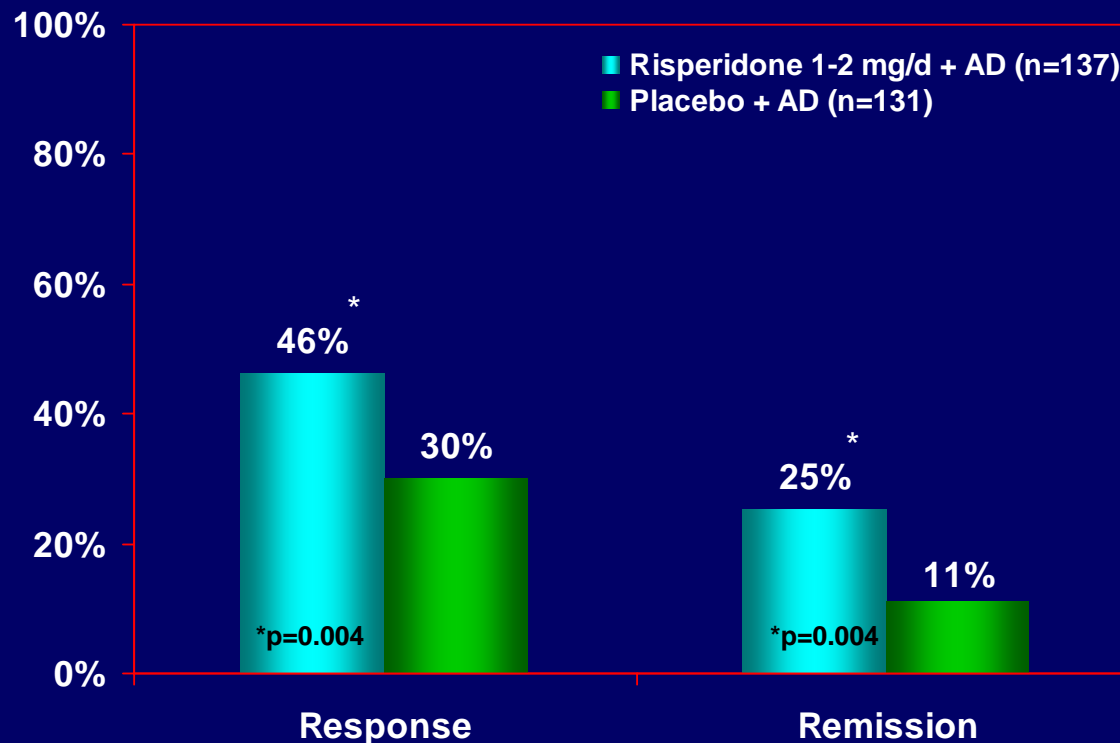


Inadequate response to one ≥ 6 week course of AD during current MDE

[†]Antidepressants (AD) included: SSRI, SNRI, TCA, bupropion
Response: $\geq 50\%$ reduction in MADRS from baseline; Remission: MADRS ≤ 8

Adjunctive AAPs in Patients With Inadequate Response to One Prior AD

6 week RCT of risperidone as adjunct to antidepressant[†], response and remission rates (n=274)

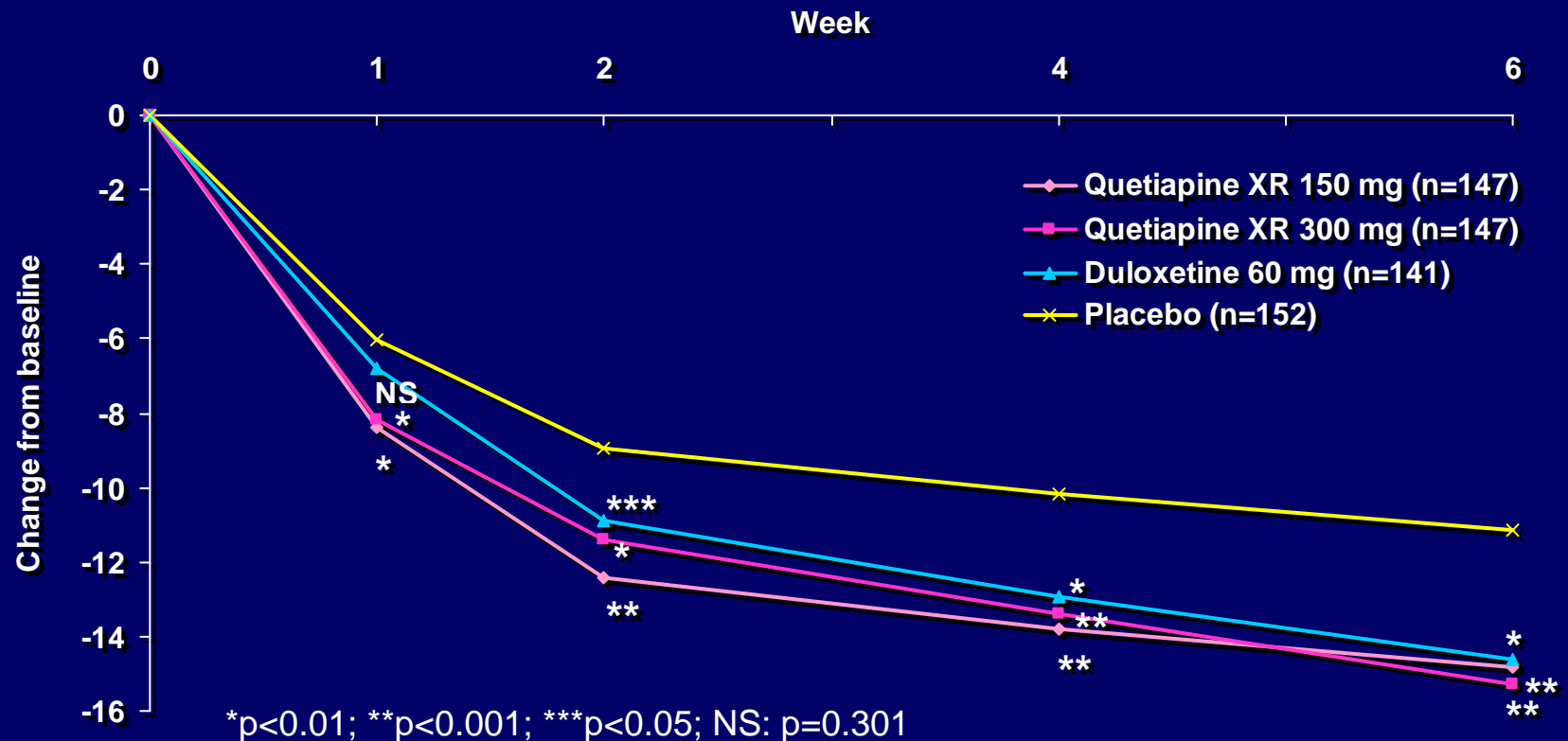


Inadequate response to one ≥ 4 week course of AD during current MDE

[†]Antidepressants (AD) included: SSRI, SNRI, bupropion, other AD
Response: $\geq 50\%$ reduction in HRSD-17 from baseline; Remission: HRSD-17 ≤ 7

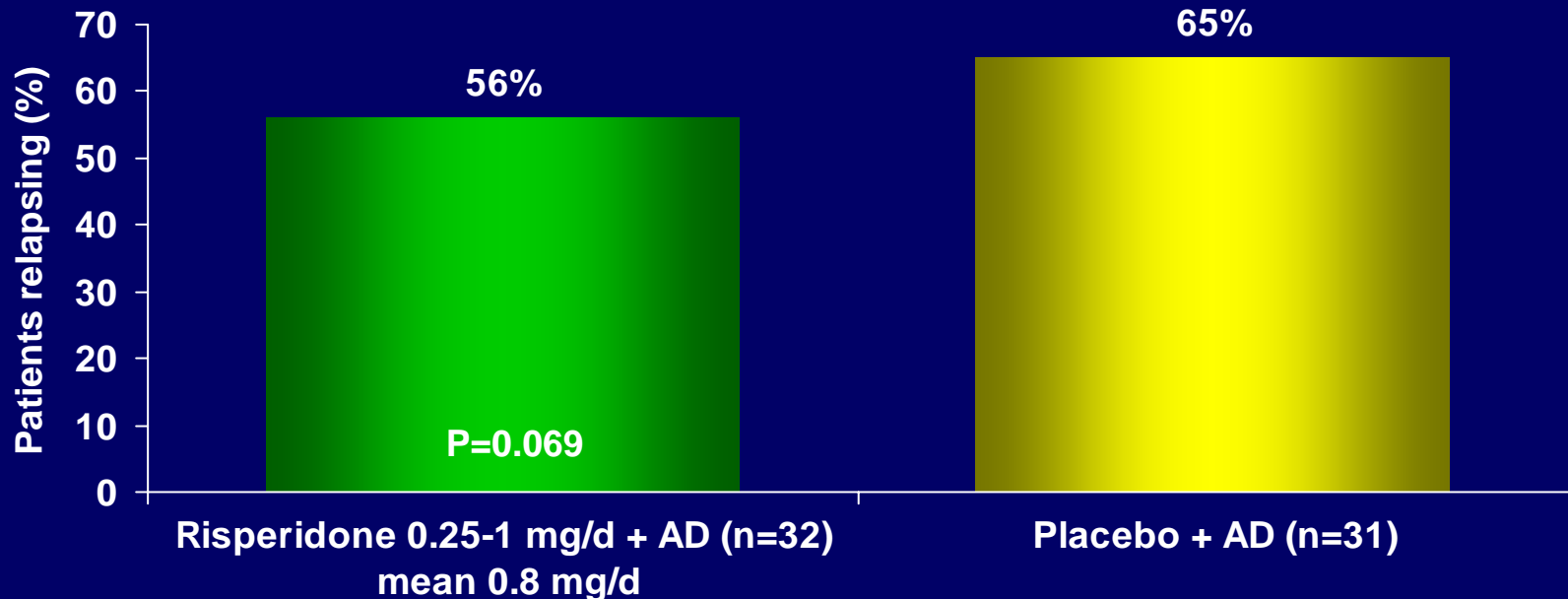
Similar Efficacy as Antidepressants in MDD and Fast Onset of Action

Monotherapy - 6 week RCT of quetiapine extended release (XR) or duloxetine vs. placebo, change in MADRS total score (n=612)



Maintenance with Adjunctive AAPs in TRD

24 week RCT of risperidone as adjunct to antidepressant*,
relapse rates (n=63)

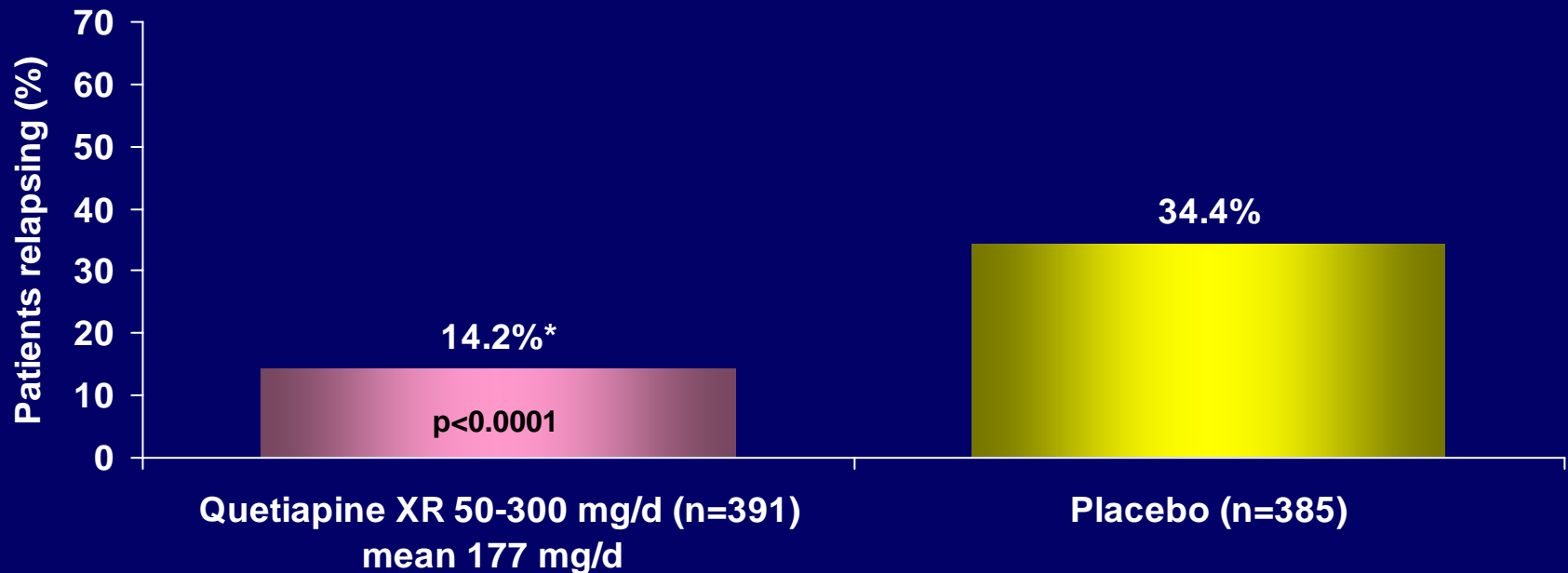


TRD: Incomplete response to 1 historical and 1 prospective course of antidepressants during current MDE
Remitted patients (HAM-D ≤ 7 or CGI-S 1 or 2) after 4-6 weeks of open-label risperidone augmentation
were randomized to risperidone or placebo

*Antidepressant (AD) was citalopram

Maintenance With AAPs in MDD

52 week RCT of quetiapine extended release (XR) or placebo, relapse rates (n=787)



Patients initially received open-label quetiapine extended release XR: 4-8-week run-in and 12-18-week stabilization
Remitted patients (MADRS ≤ 12 ; CGI-S ≤ 3) were randomized to quetiapine extended release XR or placebo

Generalized Anxiety Disorder

Role of AAPs

- Patients with anxiety who may benefit from atypical antipsychotic therapy
 - Treatment-resistant/refractory GAD
 - Comorbid bipolar disorders
 - Comorbid anxiety disorders
 - Psychosis
 - Severe agitation
 - Need for fast onset of action

Efficacy of Antidepressants in GAD

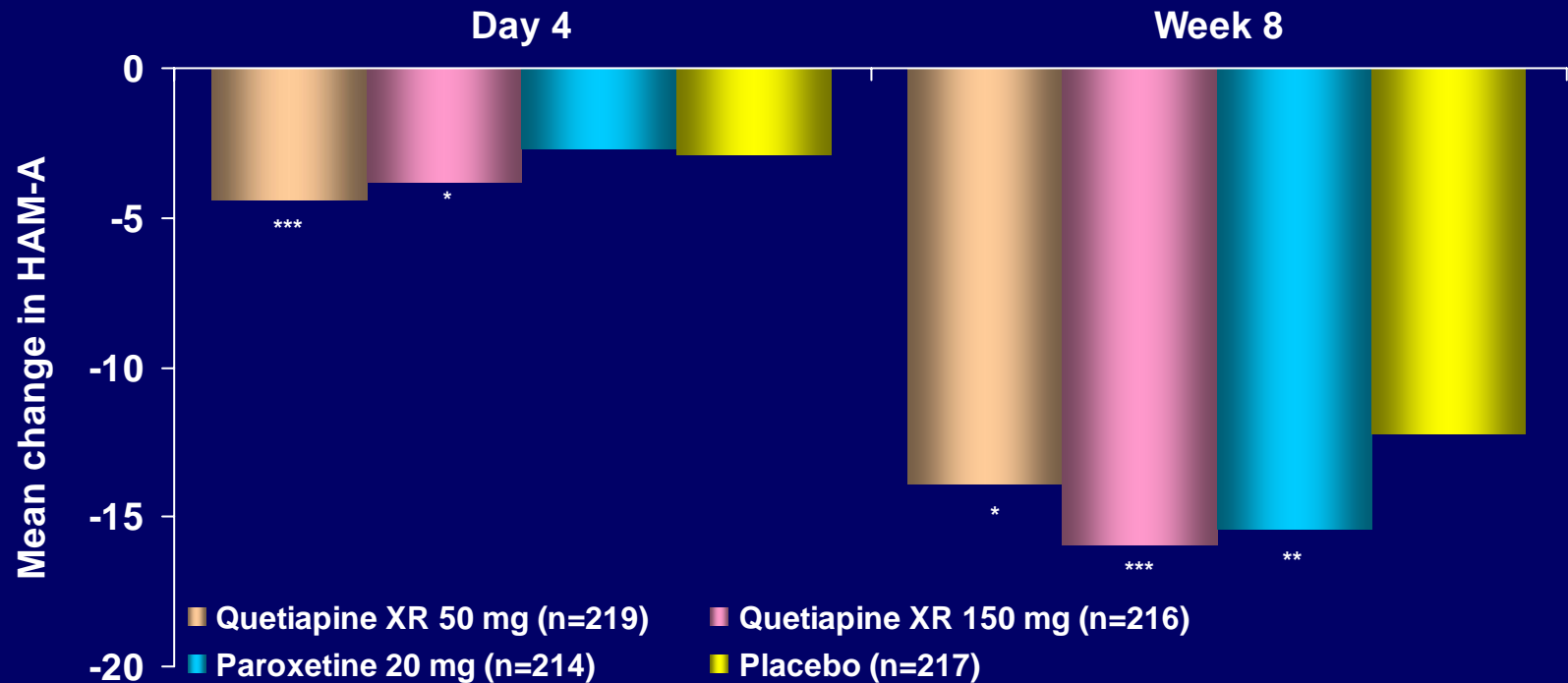
- Response to first-line agents may be inadequate
 - Dose optimization, compliance assessment
 - Consider switch, augmentation

	Antidepressants*	Placebo
Response rates	58-68%	37-47%
Remission rates	30-63%	9-22%

*First-line antidepressants include SSRIs and venlafaxine

GAD: Comparing Efficacy

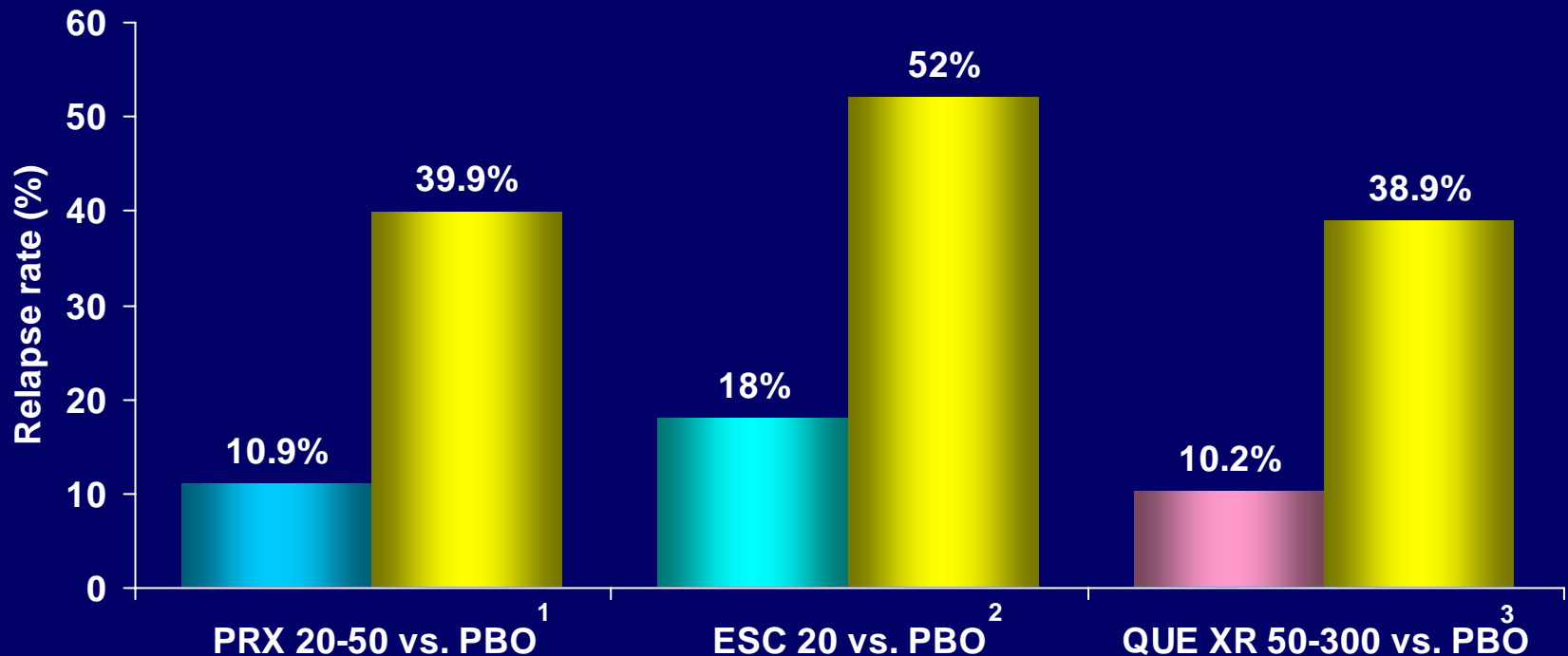
8 week, RCT of quetiapine XR or paroxetine vs. placebo
mean change in HAM-A total score (n=873)



*p<0.05; **p<0.01; ***p<0.001 vs. PBO

Summary of Relapse Prevention Trials in GAD

Relapse rates over 24-30 weeks, with paroxetine, escitalopram, quetiapine vs. placebo



Patients initially received open-label active treatment and those who responded were randomized to continued active treatment or placebo. Direct comparison cannot be made as data derived from different clinical trials



My perspective on the clinical utility of AAPs in the treatment of MDD and GAD

Treating MDD with AAPs: Safety and Tolerability

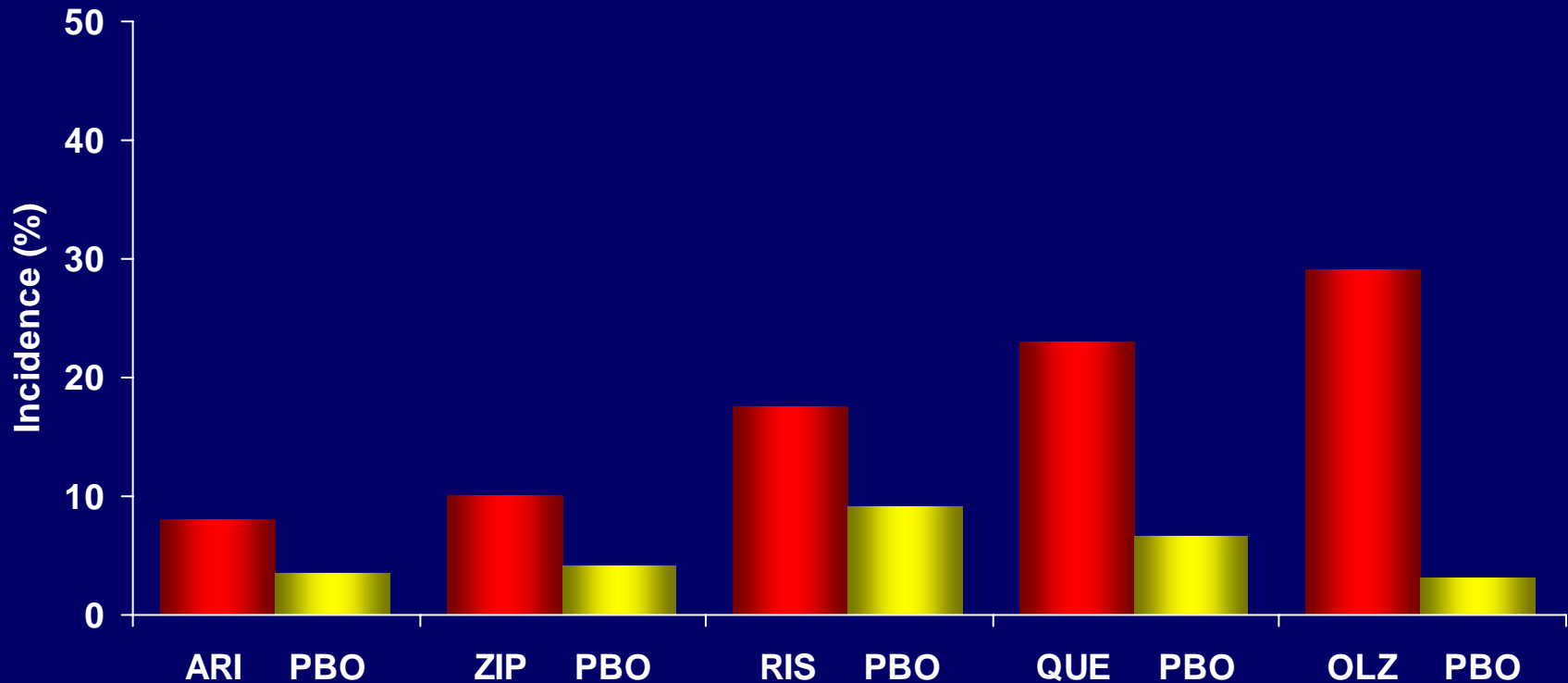
AAPs:

Receptors and Possible Associated Side Effects

Receptor	Weight Gain	Diabetes	Sedation	EPS	Endocrine Effects	Anticholinergic (dry mouth, blurred vision, constipation)
Serotonin 5-HT _{2C} antagonism	✓	✓				
Serotonin 5-HT _{1A}	✓					
Histamine H ₁ antagonism	✓	✓	✓			
Dopamine _{D2} antagonism	✓			✓	✓	
Muscarinic _{M1} antagonism						✓
Muscarinic _{M3} antagonism		✓				

AAPs and Weight Gain

Clinically significant ($\geq 7\%$) weight gain during antipsychotic treatment in schizophrenia trials



Data from package inserts

ARI: aripiprazole; ZIP: ziprasidone; RIS: risperidone; QUE: quetiapine; OLZ: olanzapine

Recommended Metabolic Monitoring

ITEM	Baseline	1 mth	2 mth	3 mth	Quarterly	Yearly
PHx / FHx	X					
Weight (BMI)	X	X	X	X	X	x
Waist Circum	X				X	x
BP	X			X		X
Fasting BS	X			X		X
Lipid Profile	X			X		X
Prolactin	x			x		x



**My perspective on
weighing benefits and
risks of AAP therapy for
MDD**

Summary

- MDD and GAD are common and have significant economic impact
- Common symptoms across psychiatric disorders (schizophrenia, bipolar disorder, GAD and MDD)
- AAPs and SSRIs share many common receptor targets
- AAP efficacy shown across many symptom domains in mood disorders (BPD, MDD and GAD)
- Treatment with AAPs may be an effective and well tolerated option for some patients with MDD