Depression Subtypes: Revisiting the Phenomenology of Depression

Psychiatrist-in-Chief, Massachusetts General Hospital (MGH)
Executive Director, MGH Clinical Trials Network and Institute (CTNI)

Associate Dean for Clinical and Translational Research
Slater Family Professor of Psychiatry, Harvard Medical School

Disclosures (lifetime): Maurizio Fava, MD

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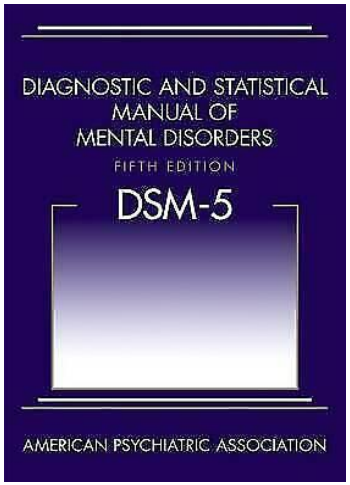
Stock/Other Financial Options	Equity Holdings: Compellis; PsyTherapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691). Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte.Ltd.

Major Depressive Disorder (MDD) Subtypes

MDD is characterized by its heterogeneity in behavioral, psychological, cognitive, and physical symptoms, severity, course and treatment response.



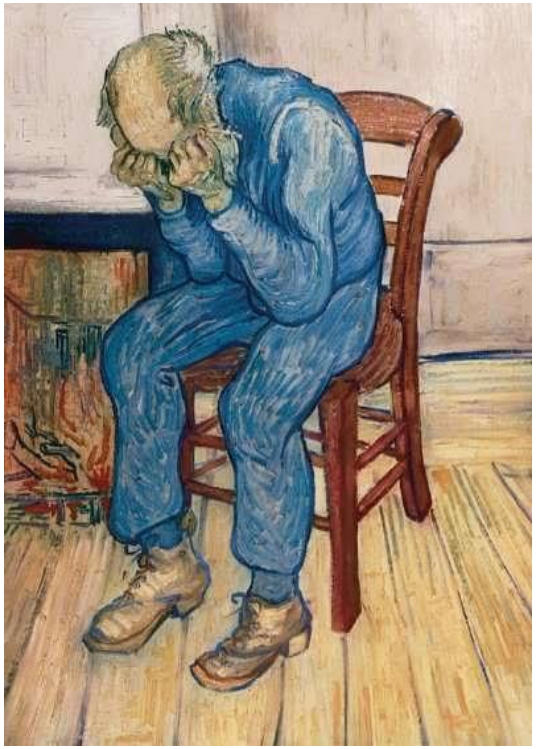
DSM-5 recognizes three common subtypes:

- Melancholic Depression
- Atypical Depression
- Anxious Depression

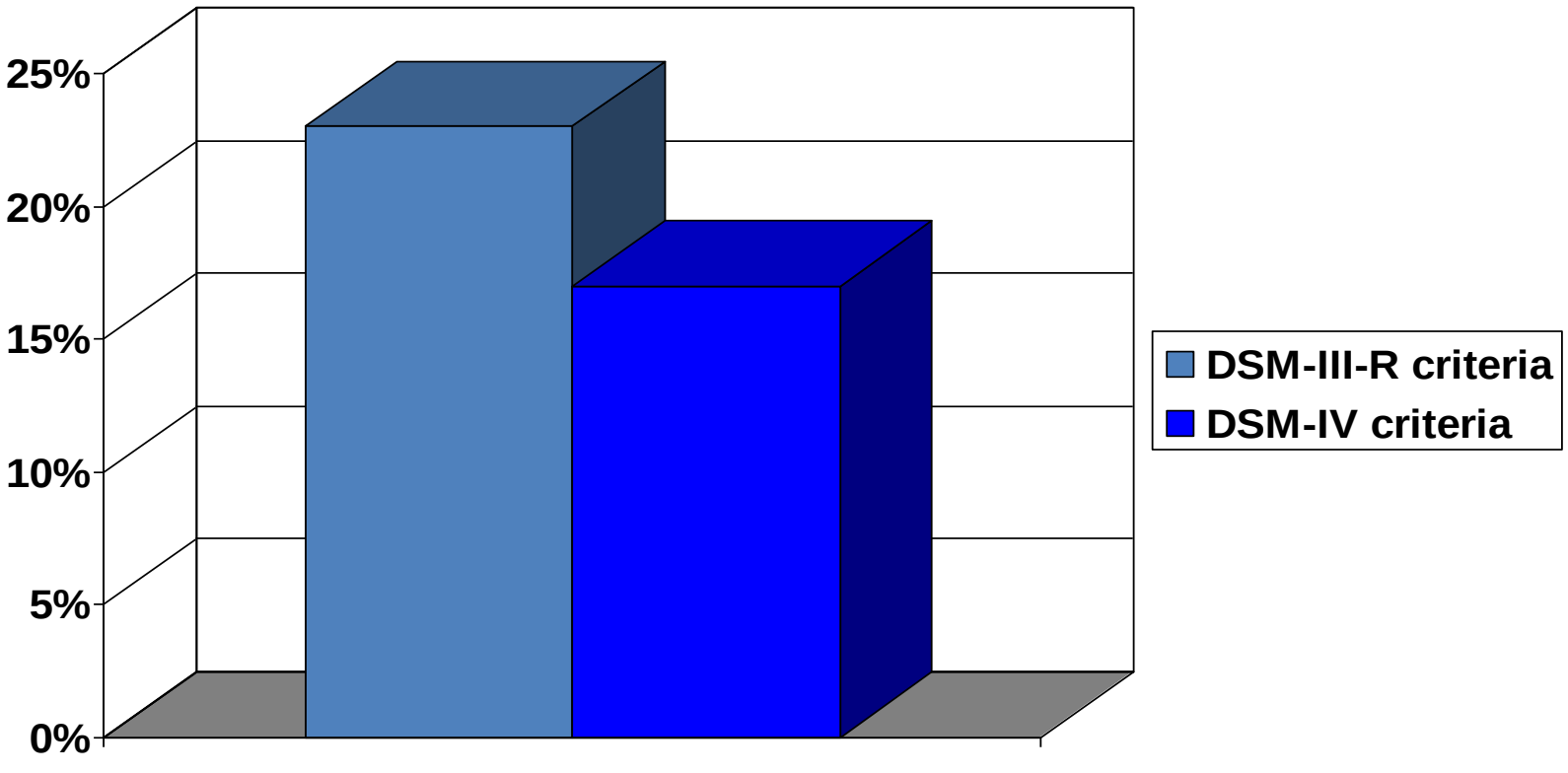
Another common subtype is MDD with anger attacks

Melancholic Depression (DSM-5)

- Loss of pleasure in almost all activities or loss of reactivity to usually pleasurable stimuli
- *Three* or more of the following:
  - Distinct quality of depressed mood (differing from bereavement)
  - Worse in the morning
  - Early morning awakening
  - Marked psychomotor changes (retardation or agitation)
  - Significant appetite loss/weight loss
  - Excessive or inappropriate guilt



Melancholic Depression: Prevalence



Lafer et al, Compr Psychiatry. Jan-Feb 1996;37(1):37-9.

Treatment Sample: Melancholic and Atypical Features in STAR*D Outpatients with Major Depressive Disorder (MDD)

Among depressed outpatients in Primary Care and Psychiatric Care settings (N = 3,671), slightly under 1/5th with MDD with melancholic features:

Melancholic Features	19.7%

Rush AJ et al. CNS Drugs 2009; 23(8)627-647.

Melancholic Depression: Characteristics

- Less likely to be associated with external precipitants
- Associated with greater illness severity/impairment
  - may require longer acute treatment to achieve remission
- More common among inpatients and elderly
- Lower likelihood of premorbid personality disorder
  - recent study challenged this view (Tedlow et al, Compr Psychiatry. 2002 Sep-Oct;43(5):331-5)
- High familial genetic loading

Amsterdam, J Psychopharmacol. 1998;12(3 Suppl B):S99-111

Melancholic Depression: Treatment Studies

- **Traditional view of melancholic vs. non-melancholic depression:**
  - Superior response to somatic (drug or ECT) treatments over psychotherapy
  - Low placebo response rates

Peselow et al. Am J Psychiatry 1992; 149:1324-1334.Brown WA: Acta Psychiatr Scand Suppl 2007; 115:125-129; Parker G: Current Opinion in Psychiatry 2007;20:197-201

Are TCAs and Dual Action Antidepressants Superior in Melancholic Depression ?

- Clomipramine > paroxetine (DUAG, J Affect Disord. 1990 Apr;18(4):289-99) and citalopram (DUAG, Psychopharmacology (Berl). 1986;90(1):131-8) in melancholic/endogenous depression
- Venlafaxine > fluoxetine (Clerc et al, Int Clin Psychopharmacol. 1994 Sep;9(3):139-43; Rudolph and Feiger, J Affect Disord. 1999 Dec;56(2-3):171-81) and sertraline (Mehtonen et al, J Clin Psychiatry. 2000 Feb;61(2):95-100.)
- Mirtazapine > fluoxetine (Wheatley et al, J Clin Psychiatry. 1998 Jun;59(6):306-12.)
- However, conflicting studies including:
  - Clomipramine = sertraline (Lepine et al, Int Clin Psychopharmacol. 2000 Sep;15(5):263-71)
  - Venlafaxine = fluoxetine (Diaz-Martinez et al, Clin Ther. May-Jun 1998;20(3):467-76)

Are Dual Action Antidepressants Superior in Melancholic Depression ?

Duloxetine Meta-Analysis

Pooled data from 8 double-blind, placebo-controlled efficacy trials of duloxetine (N = 1,913), duloxetine's advantage over placebo was similar for melancholic and non-melancholic patients.

No evidence for a treatment x melancholic features interaction that would have indicated a preferentially better response of melancholic depression to the SNRI.

Mallinckrodt et al. BMC Psychiatry. 2005 Jan 4;5:1. doi: 10.1186/1471-244X-5-1.

Are Dual Action Antidepressants Superior in Melancholic Depression? (cont.)

CO-MED Trial:

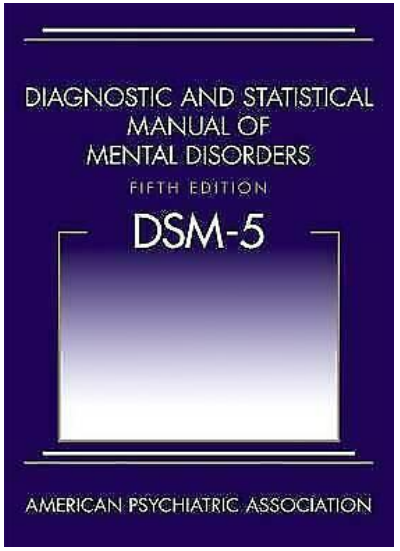
- Escitalopram + placebo (monotherapy)
- Escitalopram + Bupropion SR
- Venlafaxine ER + Mirtazapine

No evidence for differential response or remission rates between subjects with melancholic features (N=124) vs. non-melancholic features (N=481) based on antidepressant combination (dual action) vs. monotherapy as initial treatment

Babo et al. J Affect Disord 2011 May 19 [Epub ahead of print]

Atypical Depression (DSM-5)

- Mood reactivity to actual or anticipated positive events and exclusion of melancholic and catatonic subtypes in addition to 2 or more of the following for a period of at least 2 weeks
- *Two* or more of the following:
  - Increased appetite or significant weight gain
  - Increased sleep
  - Feelings of heaviness in arms or sensitivities of the legs that extend far beyond the mood disturbance episodes and result in significant impairment in social or occupational functioning
  - A pattern of longstanding interpersonal rejection sensitivity that extends far beyond the mood disturbance episodes and results in significant impairment in social or occupational functioning



Atypical Depression: Prevalence

- > 40% of outpatients with MDD (Fava et al, Biol Psychiatry. 1997 Oct 1;42(7):568-76)
- Among depressed outpatients in Primary Care and Psychiatric Care settings (N = 3,671), slightly under 1/5th of patients with MDD have atypical features (Rush AJ et al. CNS Drugs 2009; 23(8)627-647):
  - Atypical Features 17.1 %
- no significant difference in prevalence between unipolar and bipolar depression (Robertson et al, Acta Psychiatr Scand. 1996 Dec;94(6):421-7)

Atypical Depression: Clinical and Biological Correlates

- Greater comorbidity with anxiety including social phobia[a, e]
- Earlier age of depression onset[a,c,d]
- More chronic course in some but not all studies[a,f]
- Female preponderance in many studies[a]
- Greater comorbidity with bulimia, substance abuse and personality disorders in some but not all studies[a]
- Higher levels of perceived stress[g]

a. Novick et al. J Clin Psychiatry 2005; 66:1002-1011; b. Zimmerman and Posternak 2002;59:70-76; c. Stewart et al. Psychiatr Clin North Am 1993;16:479-495.; d. Nierenberg et al., J Clin Psychiatry 1998; 59(Suppl 18):5-9; e. Alpert et al. Psychol Med 1997;27:627-633; f. Thase Neuropsychopharmacology 2009;34:2633-2641. g. Farabaugh et al. Acta Psychiatr Scand. 2004; 110:465-470.

Atypical Depression: Treatment Studies

STAR*D

- Although associated with lower remission rates with acute treatment, this apparent association with poorer treatment outcome did not hold when other associated baseline characteristics were adjusted for.
- Unlike melancholic depression or anxious depression, atypical depression was not independently associated with lower remission rates

Stewart et al. Int J Neuropsychopharmacol 2010(13):15-30.

Atypical Depression: Treatment Studies (cont.)

- Quitkin (1993) meta-analysis: MAOIs > TCAs preceded DSM-IV
- In general support, meta-analysis with DSM-IV-based studies showed superiority of MAOI (phenelzine) > TCA (imipramine) in 3 of 4 studies (Henkel et al., 2006) with an effect size in the medium range (0.27; 95% CI:0.16-0.42).
- The superiority of MAOIs in atypical depression is attributable to the *inferiority of TCAs* for this condition *not to greater effectiveness of MAOIs* for atypical vs. other forms of depression.

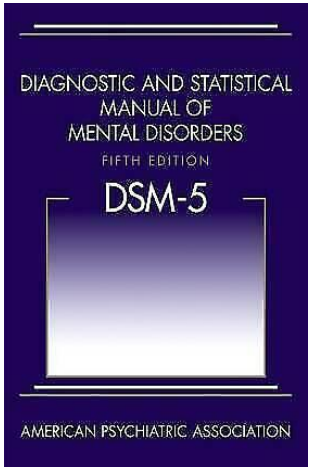
Quitkin et al., Br J Psychiatry 1993; 163(suppl 21):30-34. Henkel et al. Psychiatry Res 2006; 14:89-101

Atypical Depression: Management Issues

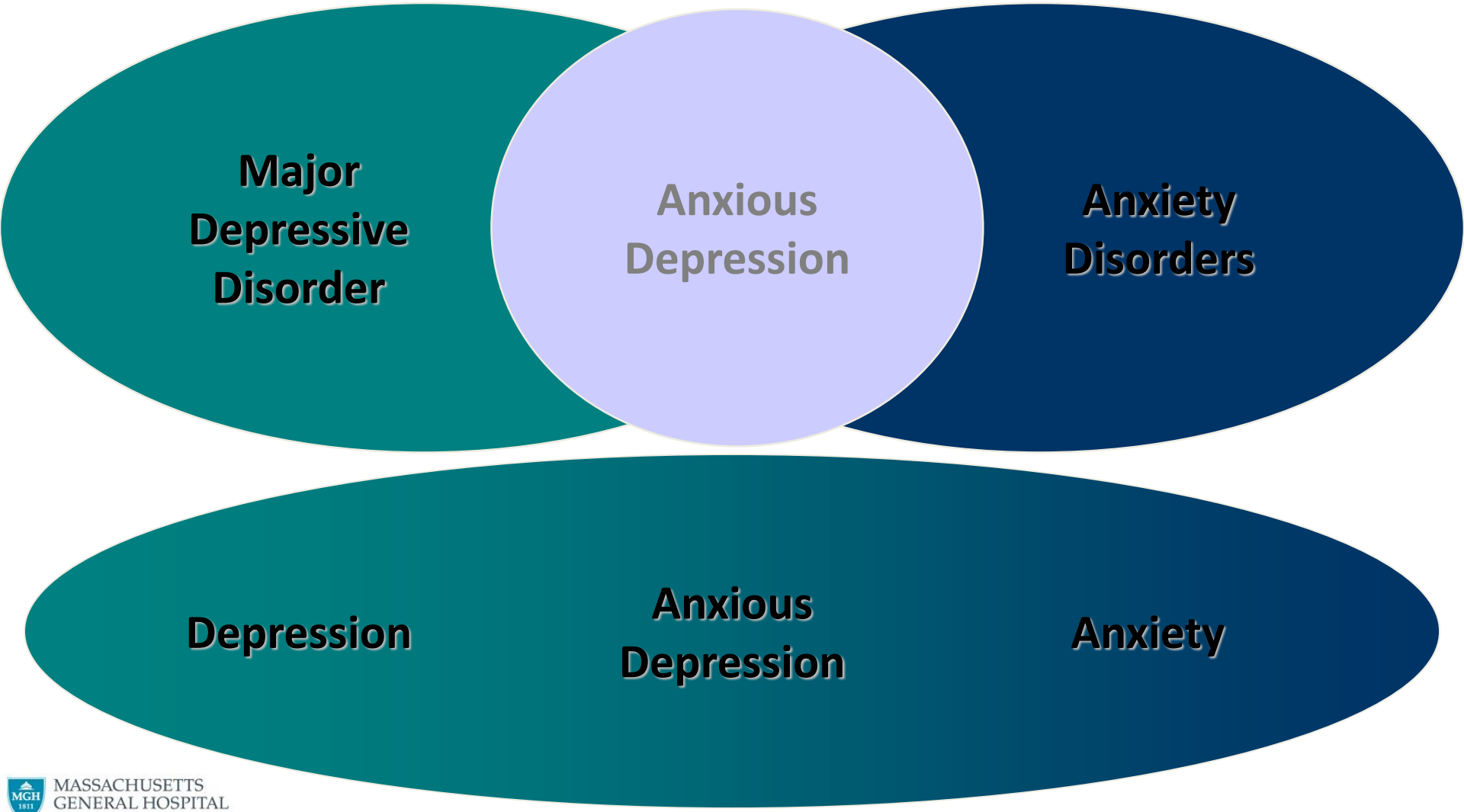
- Concerns about safety and risk of weight gain often make use of MAOIs as first-line treatment unfeasible
- Concomitant use of antianxiety drugs is common because of comorbid anxiety and social phobic behavior
- Psychotherapy (e.g., IPT and CBT) may be helpful in dealing with interpersonal difficulties due to hypersensitivity to rejection
- Augmentation with dopaminergic agents (e.g., bupropion 150-300 mg/day, pramipexole 0.25-0.5 mg b.i.d.-t.i.d.)

Major Depressive Disorder with Anxious Distress (Anxious Depression)

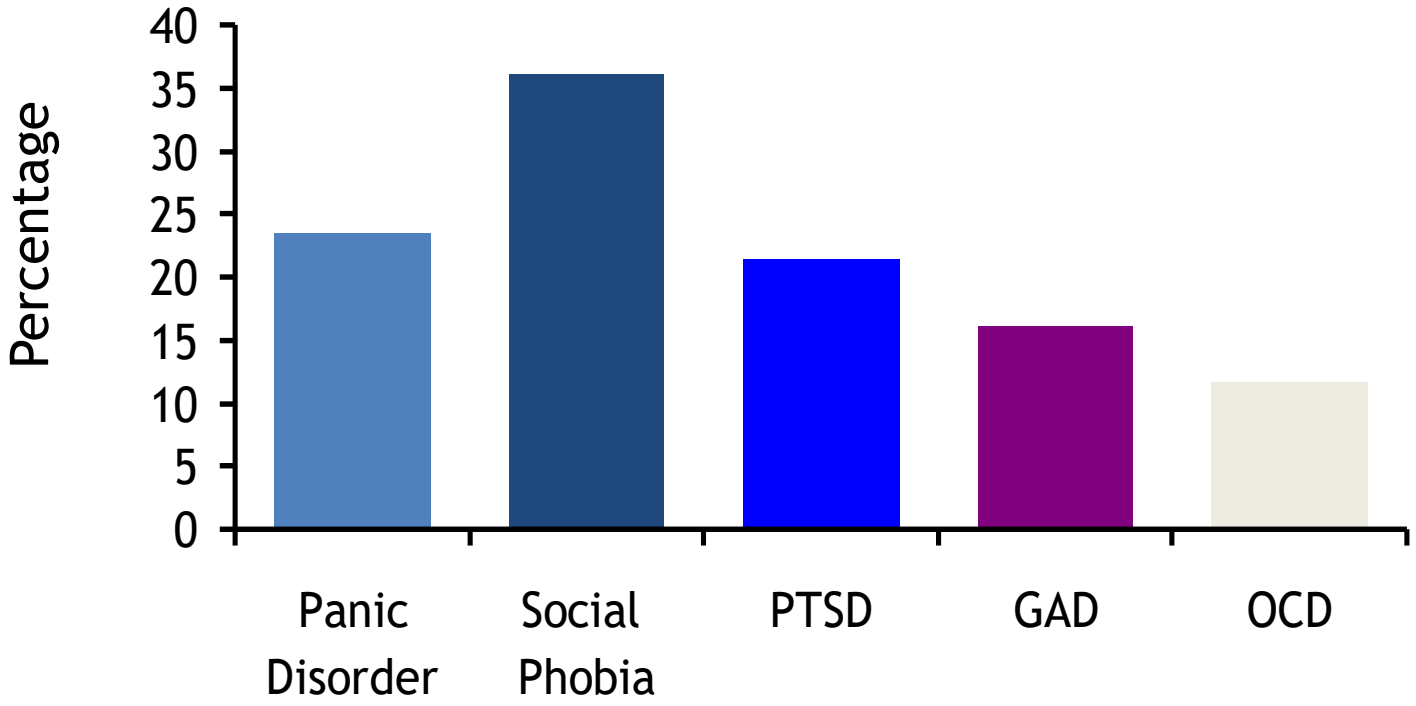
- According to DSM-5, for patients to meet the criteria of the anxious distress specifier, they must have at least 2 of the following 5 symptoms across a major depressive episode:
  - 1) feeling keyed up or tense
  - 2) feeling unusually restless
  - 3) difficulty concentrating because of worry
  - 4) fear that something awful might happen
  - 5) a feeling that one might lose control of himself/herself



Anxious Depression: Categorical vs Dimensional Definitions



Comorbidities Among Individuals Diagnosed with Major Depressive Disorder



Zimmerman M, et al. *J Clin Psychiatry* 2002;63:187-193.

Temporal Relationship Between Onset of Major Depressive Disorder and Comorbid Anxiety Disorders

- **Anxiety disorders preceded the onset of depression in 40% of patients[1]**
- **Both social phobia and GAD preceded the onset of MDD in 65% and 63% of the patients[2]**
- **Panic disorder, OCD, and agoraphobia followed the MDD onset in 78%, 63%, and 86% of the patients[2]**

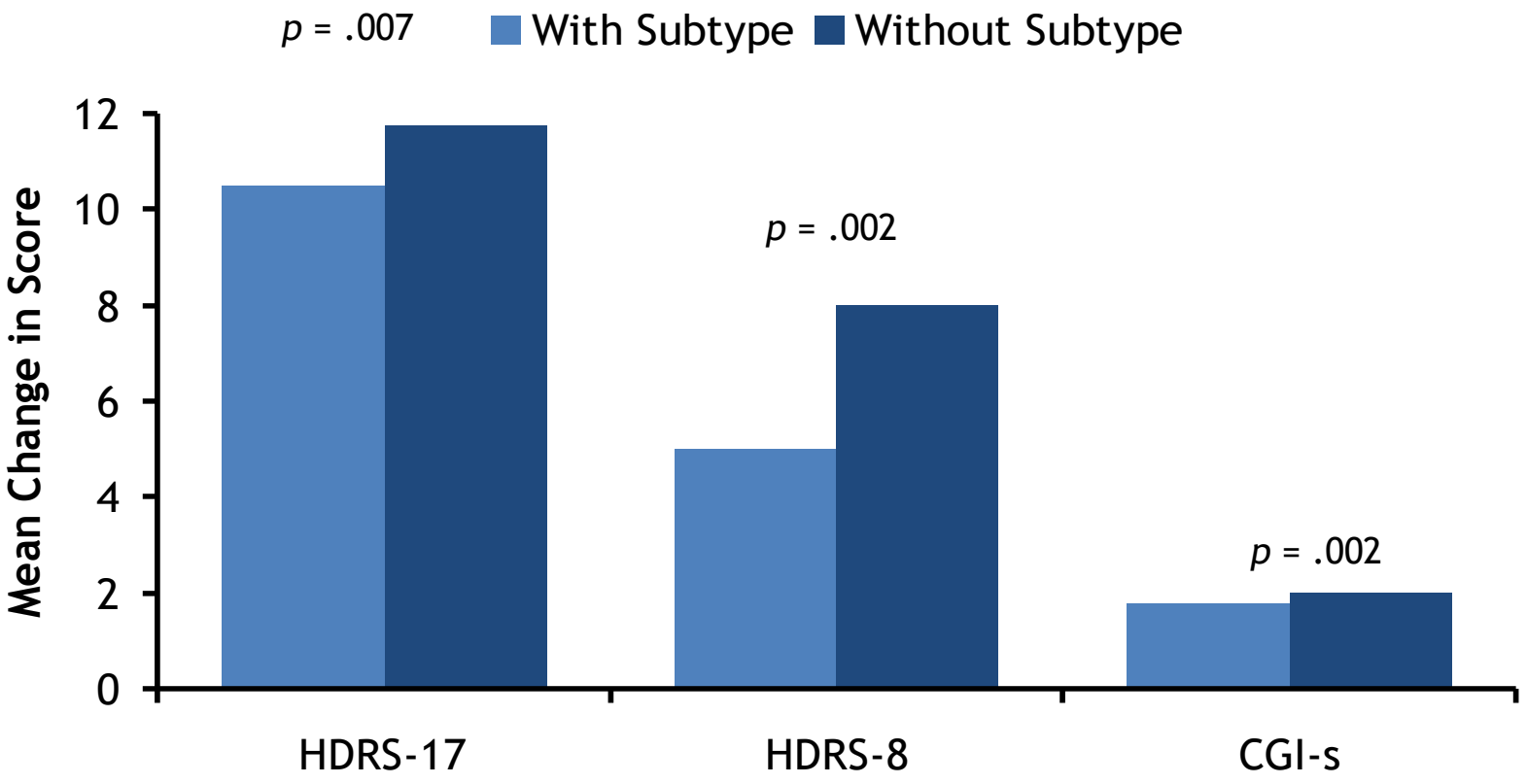
[1]Sanderson WC et al. *Am J Psychiatry*. 1990;147:1025-28.
[2]Fava M et al. *Compr Psychiatry*. 2000;41:97-102.

Anxious Depression
Clinical and Demographic Characteristics

- Greater severity of illness[1]
- Younger mean age[2]
- Earlier age of onset[2]
  - 20.6 ± 10.4 years in MDD with comorbid anxiety disorders
  - 28.4 ± 13.0 years in MDD alone
- Chronicity is common[3]
- Greater functional impairment[2]
- Increased risk of suicide[4]
- Greater chance of treatment discontinuation[5]

1. Joffe RT, et al. *Am J Psychiatry* 1993;150:1257-1258.
2. Fava M, et al. *Compr Psychiatry* 2000;41:97-102.
3. Van Valkenburg C, et al. *J Clin Psychiatry* 1984;45:367-369.
4. Clayton P, et al. *Am J Psychiatry* 1991;148:1512-1517.
5. Flint AJ, Rifat SL. *Am J Geriatr Psychiatry* 1997;5:107-115.

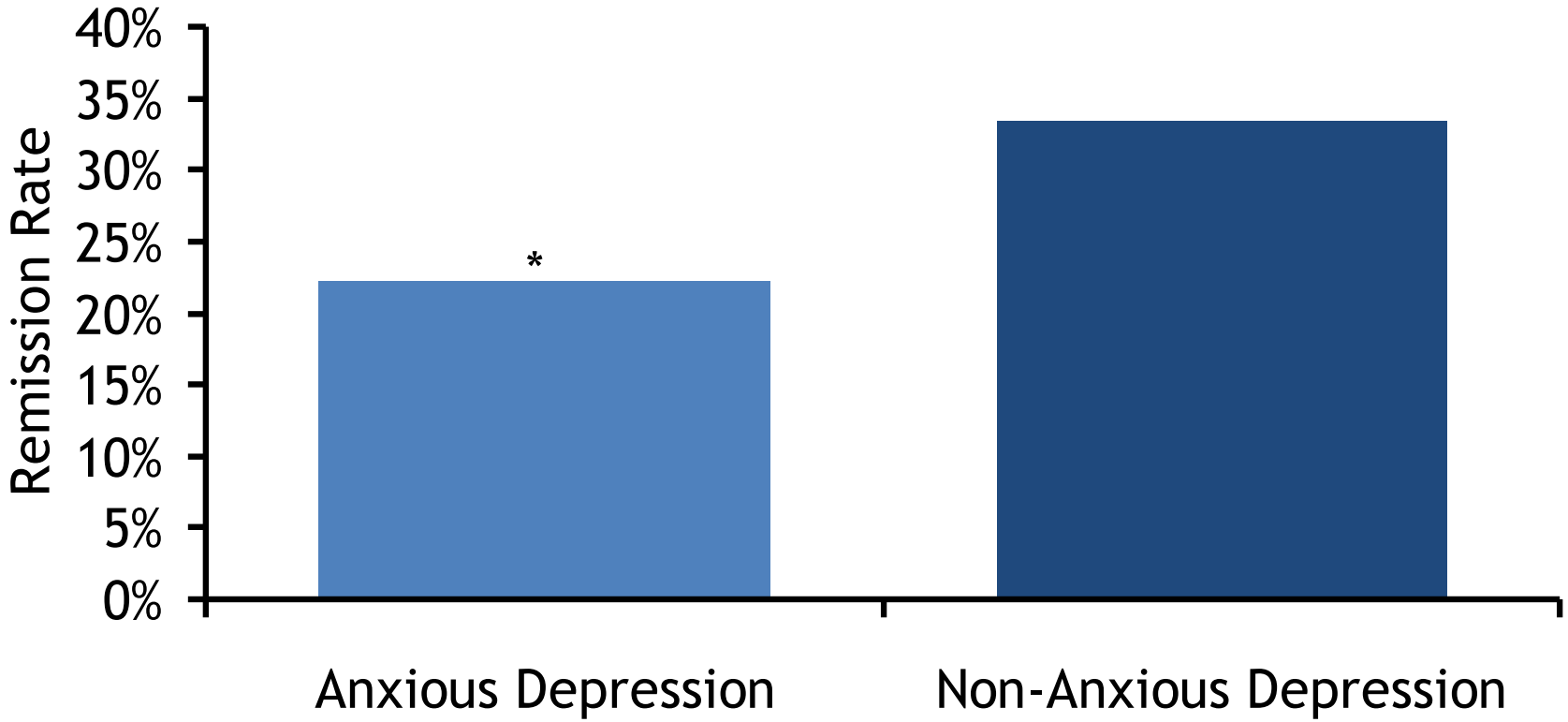
Change in Depression Severity for Patients With and Without Anxious Depression



N = 294

Fava M, et al. *Biol Psychiatry* 1997;42:568-576.

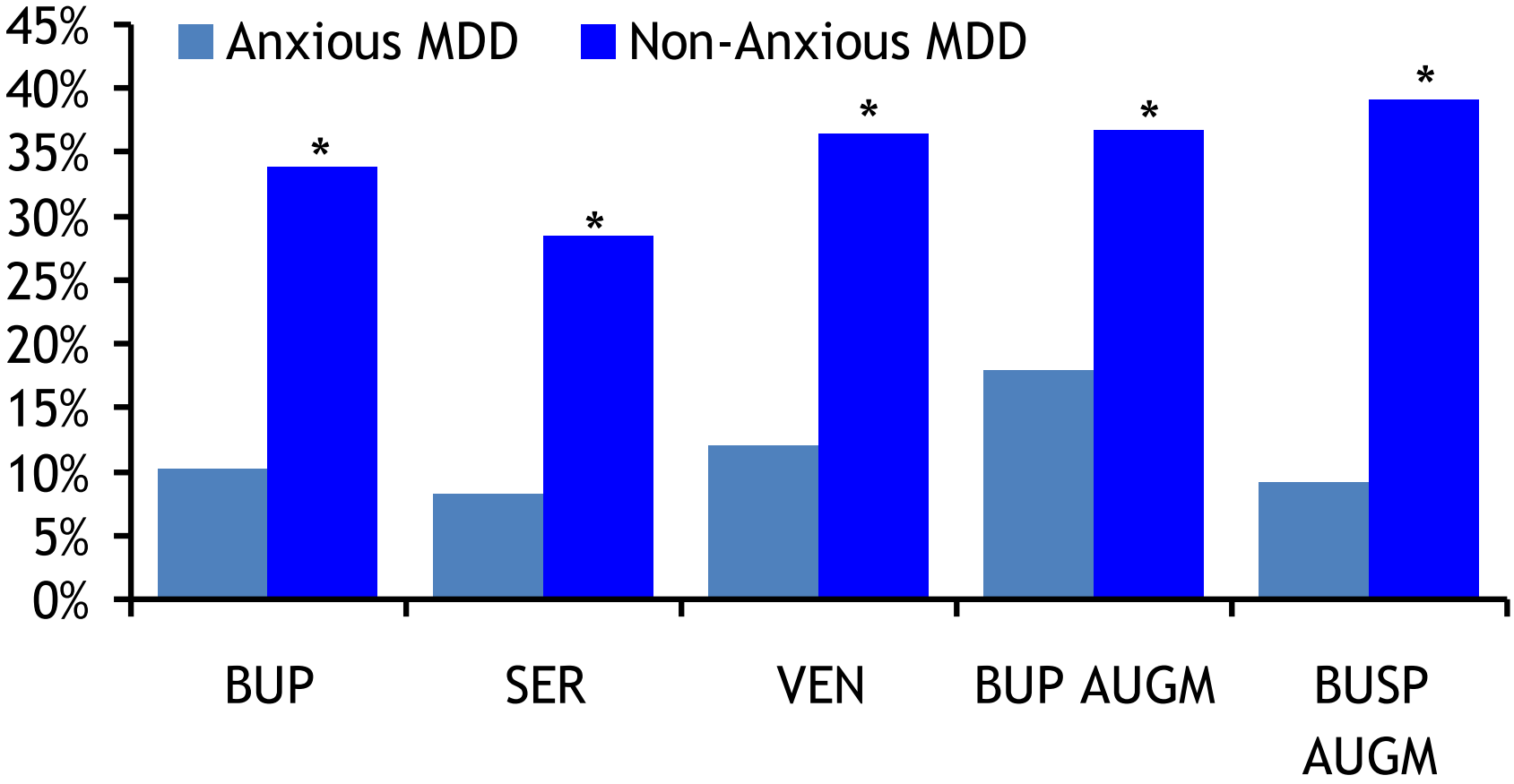
Remission Rates Following Citalopram Treatment in Level 1 of STAR*D



N = 2876
* $p < .05$

Fava M, et al. *Am J Psychiatry* 2008;165:342–351.

Remission Rates (HAM-D-17 < 8) in Level 2 of STAR*D
Anxious vs. Non-Anxious MDD



* $p < .05$

Fava M, et al. *Am J Psychiatry* 2008;165:342-351.

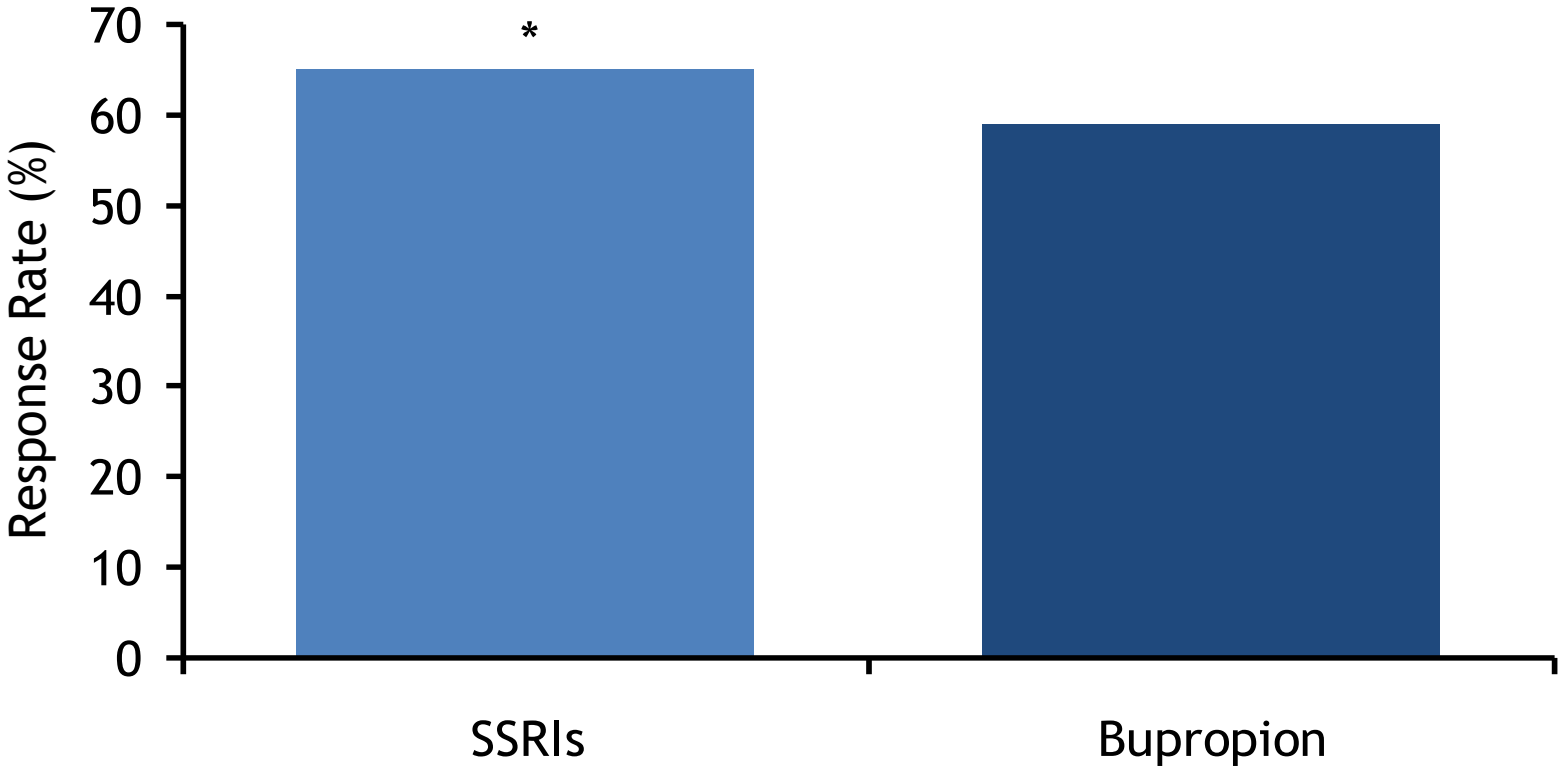
Anxious Depression
Treatment Approaches

- Monotherapy with antidepressants
  - Sedating antidepressants vs. non-sedating antidepressants
- Augmentation with:
  - Benzodiazepines
  - Eszopiclone
  - Buspirone
  - Gabapentin or other anticonvulsants
  - Antipsychotic drugs

SSRIs vs. TCAs Treatment Studies

- In anxious-agitated depressed patients, TCAs were equally effective to:
  - Fluoxetine
    - *Montgomery SA. Int Clin Psychopharmacol 1989;4(suppl 1):113-119.*
    - *Tollefson GD, et al. J Clin Psychopharmacol 1994;14:385-391.*
    - *Marchesi C, et al. Pharmacopsychiatry 1998;31:216-221.*
    - *Versiani M, et al. Int Clin Psychopharmacol 1999;14:321-327.*
  - Paroxetine
    - *Sheehan D, et al. Psychopharmacol Bull 1992;28:139-143.*
  - Sertraline
    - *Russell JM, et al. Depress Anxiety 2001;13:18-27.*
    - *Moon CAL, et al. J Psychopharmacol 1994;8:171-176.*

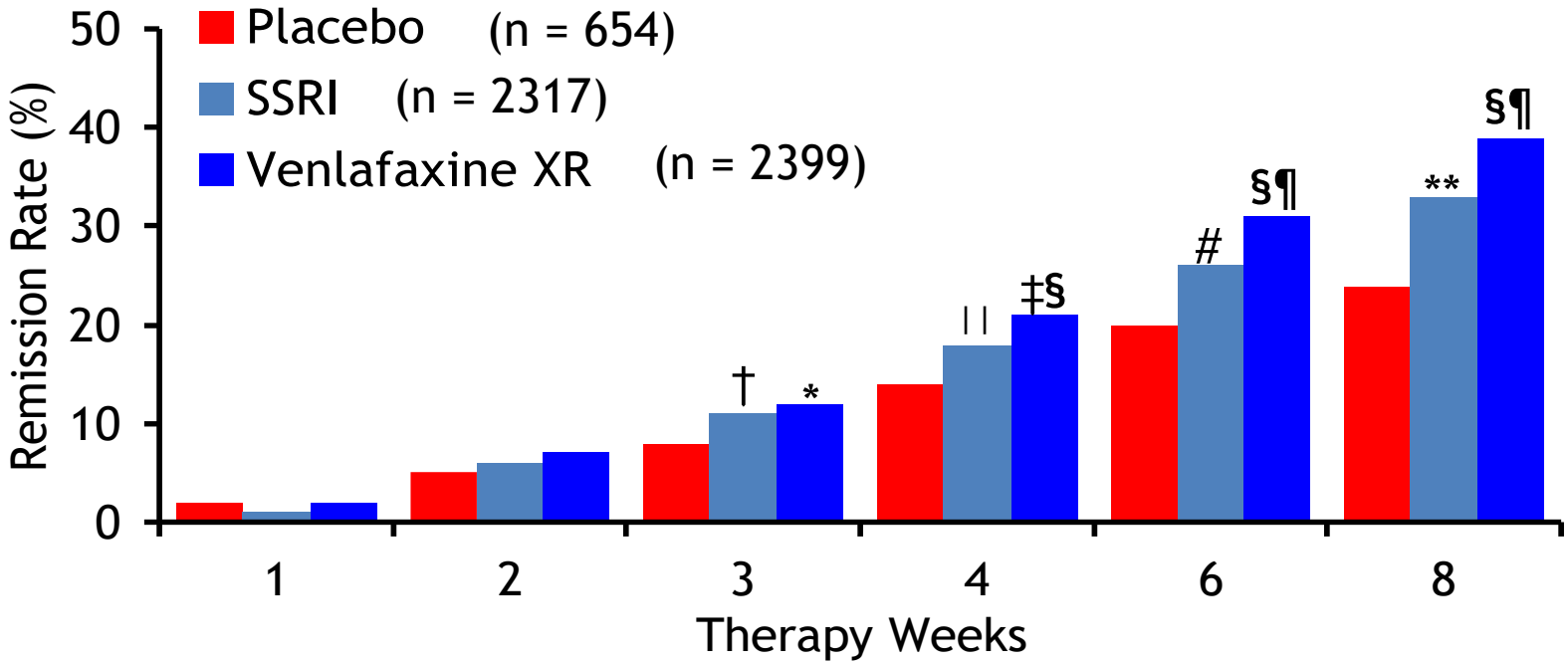
Pooled Analyses of Response Rates in Trials Comparing Bupropion and SSRIs



N = 1275
* $p < .05$

Papakostas GI, et al. *J Clin Psychiatry* 2008;69:1287-1292.

Pooled Analysis of Remission Rates Across 31 Studies of Venlafaxine vs. SSRIs vs. Placebo



* $p < .01$ vs. placebo; † $p < .05$ vs. placebo; ‡ $p < .05$ vs. SSRI;
§ $p < .001$ vs. placebo; || $p < .05$ vs. placebo; ¶ $p < .001$ vs. SSRI;
# $p < .01$ vs. placebo; ** $p < .001$ vs. placebo

Fava M, et al. Presented at the 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA.

Pooled Analyses of Duloxetine Studies in Anxious and Nonanxious Depression

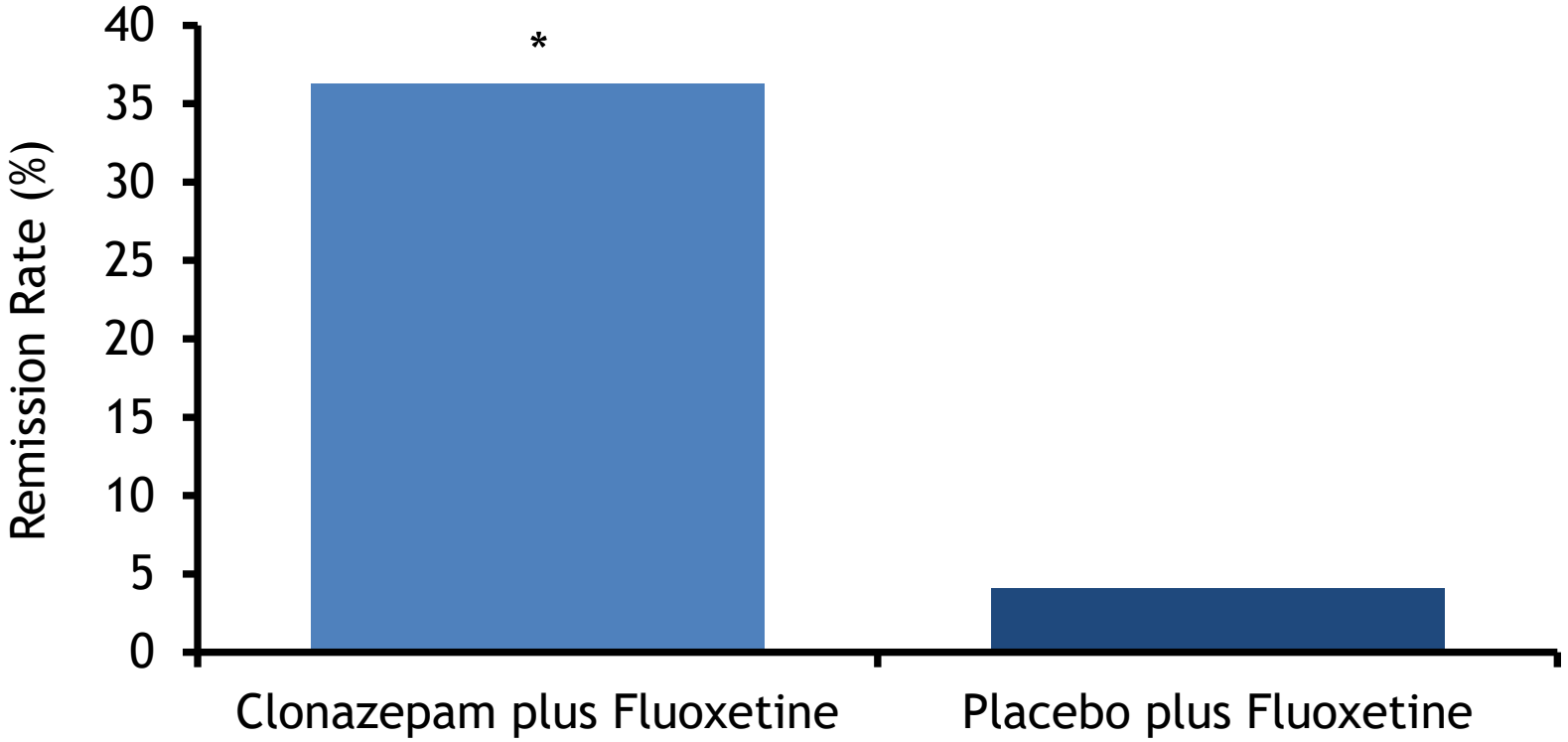
TABLE 1. Logistic Regression With Remission Entered as the Dependent Variable, With Treatment Group (Duloxetine and Placebo) and Anxious and Nonanxious Subgroups Entered as Independent Variables While Controlling for Treatment Study

Anxious Subgroup	Treatment Group	Remission, n (%)	Within Subgroup, Duloxetine vs Placebo, *P*	Between Anxious Subgroups, *P*	Treatment Group by Anxious Subgroup Interaction, *P*
A. Without Controlling for Baseline Severity on HDRS					
Anxious	Duloxetine, n = 805	259 (32)	<0.001	<0.001	0.50
	Placebo, n = 521	106 (20)			
Nonanxious	Duloxetine, n = 905	353 (39)	0.001		
	Placebo, n = 610	173 (28)			
B. Controlling for Baseline Severity on HDRS					
Anxious	Duloxetine, n = 805	259 (32)	<0.001	0.12	0.35
	Placebo, n = 521	106 (20)			
Nonanxious	Duloxetine, n = 905	353 (39)	0.001		
	Placebo, n = 610	173 (28)			

Regressions performed with and without controlling for baseline depression severity. Anxious depression defined by an anxiety-somatization HDRS factor score of 7 or greater.

Nelson JC. J Clin Psychopharmacology 2011; 31: 682-684

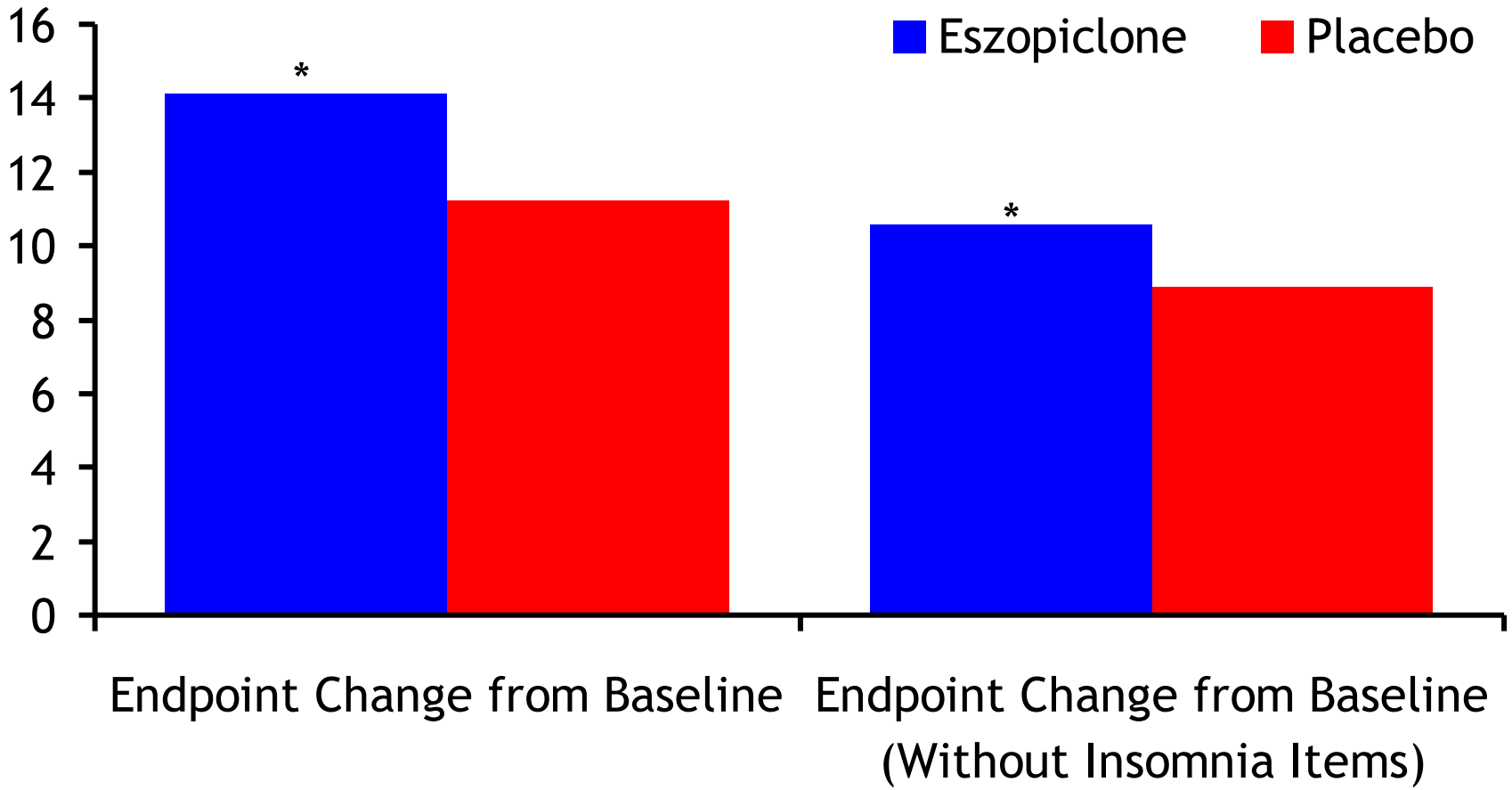
Remission Rates in Clonazepam plus Fluoxetine vs Placebo plus Fluoxetine in Anxious Depression (n=46)



* p =0.008

Papakostas GI, et al. *Int Clin Psychopharmacol. 2010 Jan;25(1):17-21. doi: 10.1097/YIC.0b013e32833205a4..*

Pooled Analysis of Trials Comparing Eszopiclone and Placebo in Anxious Depression



N = 347
* $p < .05$

Fava M, et al. J Clin Psychiatry. 2011 Apr;72(4):473-9.

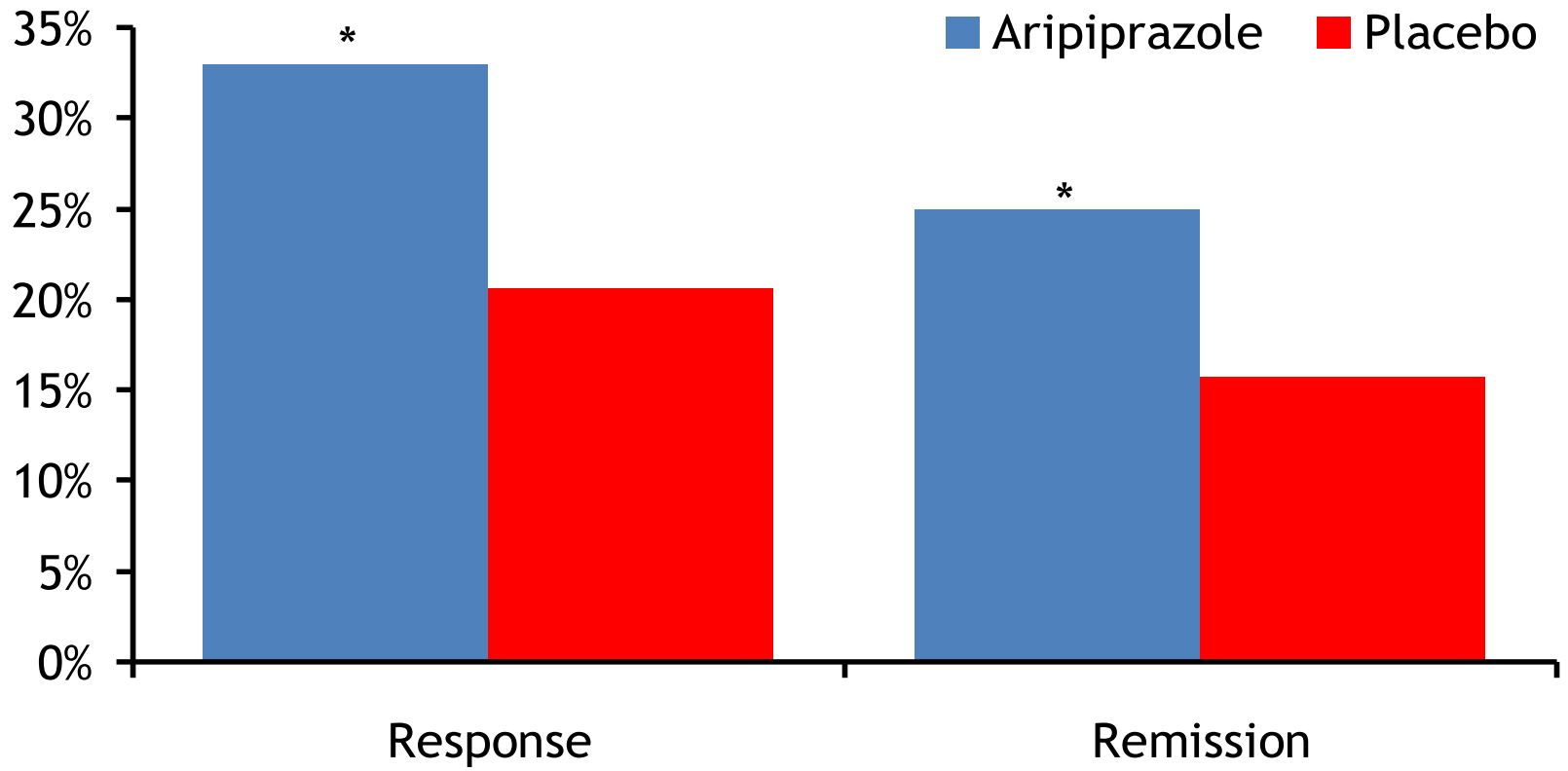
Adjunctive Pregabalin in Partial Responders With Major Depressive Disorder and Residual Anxiety

TABLE 2. Clinical Outcomes at Week 9 and After Pregabalin Augmentation at Week 17

Variable	Week 9	Week 17	*P*
HDRS-17 scores	13.5 ± 3.1	9.1 ± 2.9	<0.000
HDRS-AS scores	6.3 ± 2	3.6 ± 1.7	<0.000
HDRS total − AS scores	7.2 ± 2.3	5.5 ± 1.9	0.003
Responders, n (%)	0	13 (65)	
Remitters, n (%)	0	7 (35)	

Vitali et al, J Clin Psychopharmacol 2013;33: 95-98)

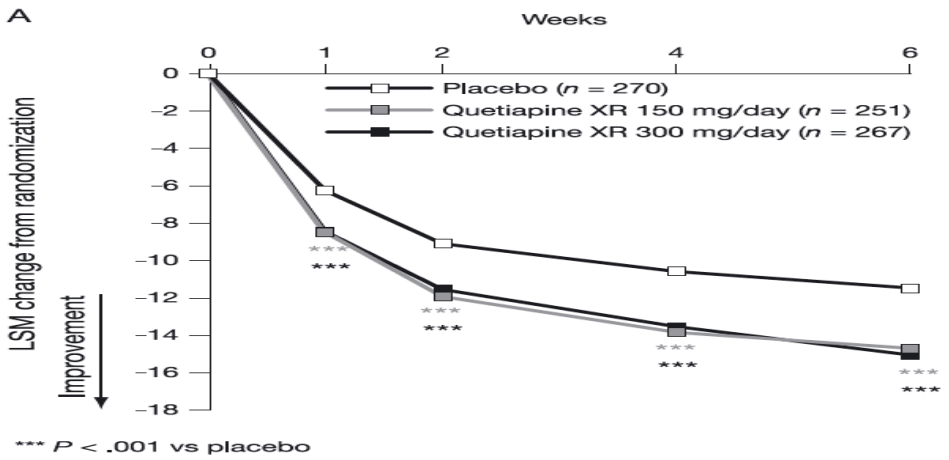
Response & Remission Rates in Double-Blind Study of Aripiprazole vs. Placebo in SSRI Non-Responders with Anxious Depression

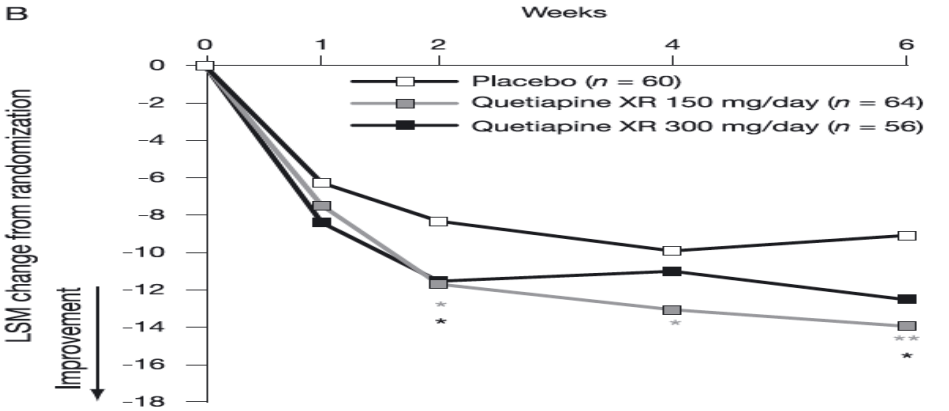


N = 435
* $p < .05$

Trivedi MH, et al. *J Clin Psychiatry* 2008;69:1928-1936.

Extended-Release Quetiapine in Anxious and Non-Anxious Depression





*P < .05; **P < .01 vs placebo
HAM–D, Hamilton Rating Scale for Depression; LOCF, last observation carried forward;
LSM, least squares means; MADRS, Montgomery Åsberg Depression Rating Scale;
MITT, modified intention-to-treat; XR, extended release

Thase et al. DEPRESSION AND ANXIETY 29:574–586 (2012)

Figure 1. Change in MADRS total score from randomization over time for patients with (A) anxious depression and (B) nonanxious depression according to HAM-D anxiety/somatization factor score at baseline (LOCF; pooled MITT population).

Cognitive Therapy (CT) and Medications (Meds) in Level 2 of STARD: Anxious vs Nonanxious Depression

Table 3
Response and remission percentages for switch and augment.

		Anxious depression		Non-anxious depression	
	QIDS-C L2	Meds % (*n*)	CT % (*n*)	Meds % (*n*)	CT % (*n*)
Switch (*n*=696)	Remit	15% (41)	21% (3)	36% (127)	51% (22)
	Response	18% (50)	14% (2)	36% (125)	36% (15)
Augment (*n*=577)	Remit	21% (30)	14% (4)	43% (150)	38% (19)
	Response	28% (40)	31% (9)	31% (108)	38% (19)

Farabaugh et al, Journal of AffectiveDisorders142(2012)213–218

Onset and Course of Irritable and Nonirritable DSMIV/CIDI MDD

	Irritable		*Nonirritable MDE*		
	Est	*(s.e.)*	*Est*	*(s.e.)*	F/χ^2
Mean age of onset	26.7[a]	(0.7)	31.3	(0.9)	13.7[a,b]
Mean years in episode	5.7	(0.5)	5.1	(0.9)	0.1[b]
12-month: lifetime prevalence	40.3[a]	(2.7)	28.8	(1.6)	9.0[a,c]
(n)[d]	(497)		(480)		

Abbreviations: Est, ; MDE, major depressive episode.
[a]Significant difference between irritable and nonirritable cases at the 0.05 level, two-sided test.
[b]F-test with 1 and 953 degrees of freedom.
[c]χ^2-test with 1 degree of freedom.
[d]The reported sample sizes are unweighted and assessed in the part I sample.

Fava et al, Molecular Psychiatry (2010) 15, 856–867

Symptom Profiles of Irritable and Nonirritable DSM-IV/CIDI MDE

	Irritable		*Nonirritable*		
	%	*(s.e.)*	*%*	*(s.e.)*	χ^2
Sad mood	99.1	(0.5)	98.6	(0.7)	0.3
Loss of interest	88.2	(2.0)	85.0	(1.8)	1.5
Appetite of weight disturbance					
Appetite/weight gain	18.6	(2.3)	15.8	(2.1)	1.3
Appetite/weight loss	68.9	(2.7)	72.7	(2.5)	1.4
Sleep disturbance					
Hypersomnia	16.7	(1.8)	17.5	(1.5)	0.1
Insomnia	78.0	(2.1)	73.9	(1.7)	2.3
Activity disturbance					
Psychomotor agitation	8.7	(1.6)	7.3	(0.9)	0.5
Psychomotor retardation	41.8	(2.6)	37.2	(2.5)	1.9
Fatigue	89.5[b]	(1.4)	83.5	(1.9)	11.5[b]
Self-reproach or guilt	81.3[b]	(1.5)	65.9	(1.9)	27.8[b]
Poor concentration or indecisiveness	91.3	(1.4)	87.4	(1.9)	2.3
Morbid thoughts of death	71.5	(2.8)	65.5	(2.4)	3.6
(*n*)[c]	(497)		(480)		

[a]Refers to symptoms in persons with a major depressive episode in the last 12 months.
[b]Significant difference between irritable and nonirritable MDE at the 0.05 level, two-sided test.
[c]The reported sample sizes are unweighted and assessed in the part I sample.

Fava et al, Molecular Psychiatry (2010) 15, 856–867

Anger Attacks in Depression

(Fava, Anderson, & Rosenbaum, Am J Psychiatry. 1990 Jul;147(7):867-70)

- Sudden spells of anger
- Associated with sweating, trembling, tachycardia, hot flashes, tightness of the chest, & shortness of breath
- Inappropriate to the situation
- Responded well to treatment with antidepressants
- Postulated to be variants of MDD
- We developed the Anger Attacks Questionnaire to assess the presence of these attacks
- Anger attacks were significantly more common among 31 outpatients with MDD than in 29 healthy volunteers with no known psychiatric history

Fava M et al, Psychopharmacol Bull. 1991;27(3):275-9.

Anger Attacks Criteria

- Irritability over previous 6 months
- Overreacting with anger to minor annoyances
- Occurrence over the past month of one or more anger attacks
- During the anger attack, the person becomes angry and enraged with other people in an inappropriate way

Fava M et al, Psychopharmacol Bull. 1991;27(3):275-9.

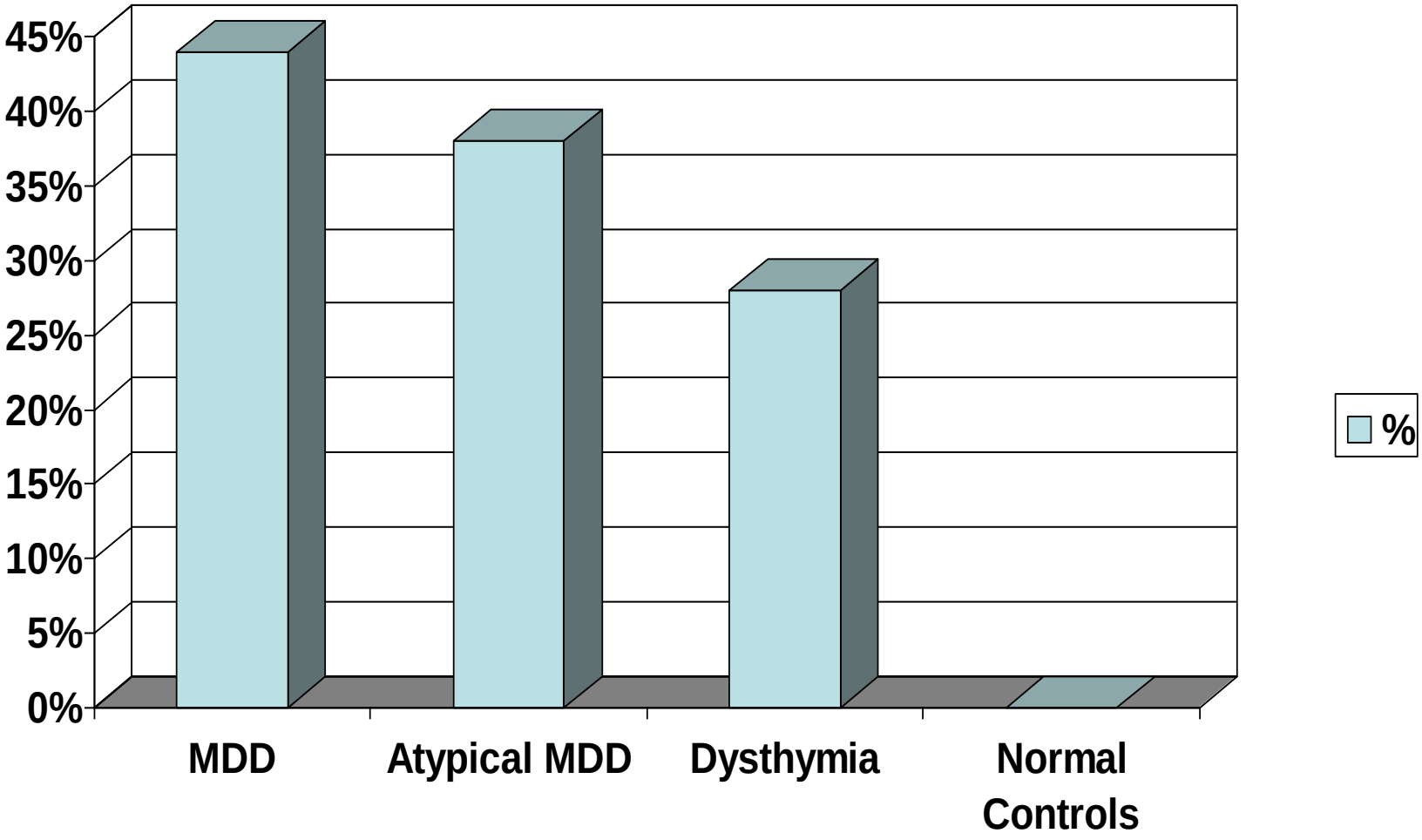
During at least one of the attacks, patient has 4 or more of the following:

- heart palpitations
- flushing
- chest tightness or pressure
- paresthesias
- lightheadedness or dizziness
- excessive sweating
- shortness of breath
- shaking/trembling

- intense fear or anxiety
- feeling out of control
- feeling like attacking others
- physically/verbally attacking others
- throwing or destroying objects

Fava M et al, Psychopharmacol Bull. 1991;27(3):275-9.

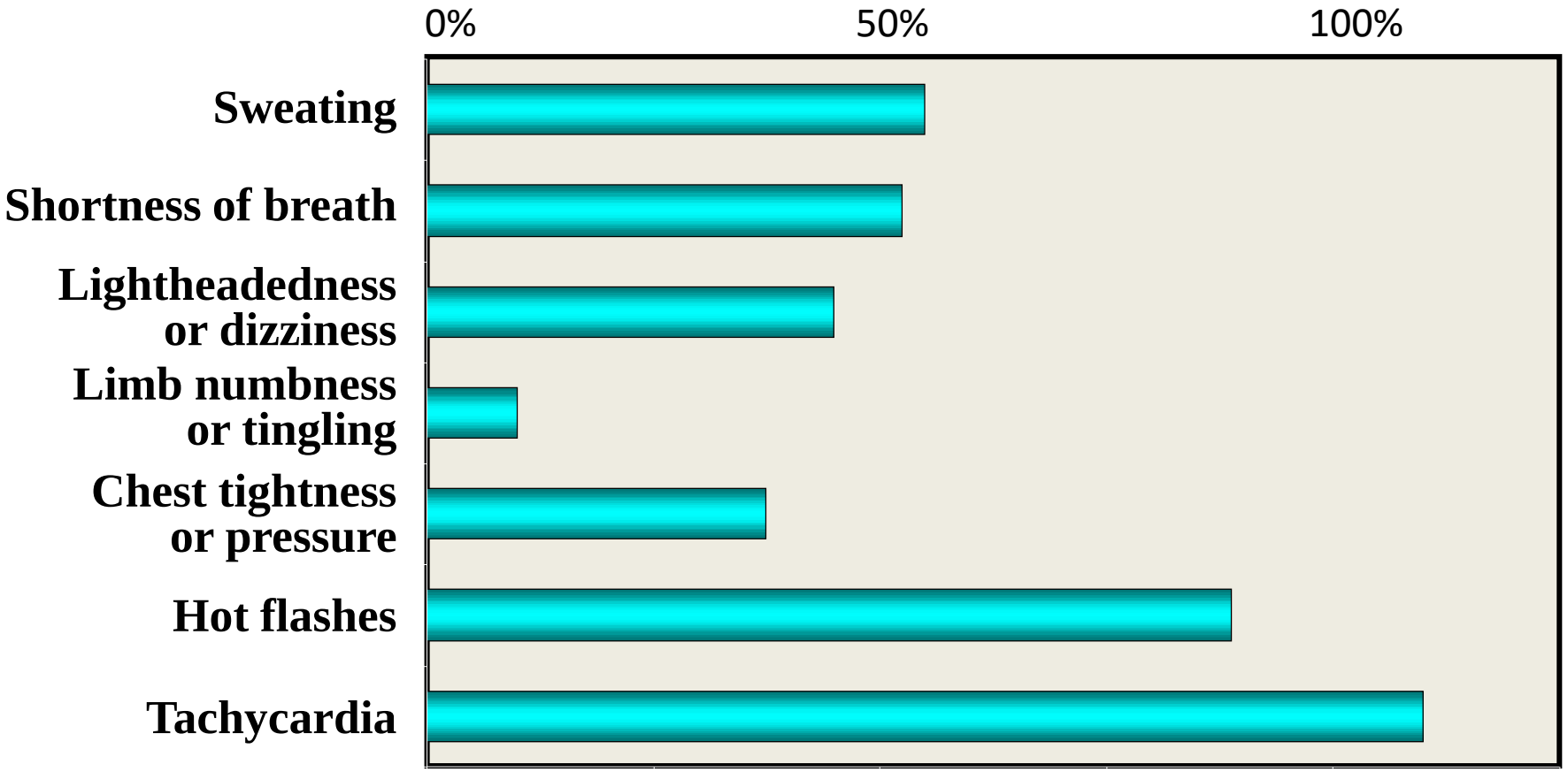
Anger Attacks: Prevalence Studies



Fava M and Rosenbaum JF, J Clin Psychiatry. 1999;60 Suppl 15:21-4.

Anger Attacks in MDD:

Frequency of Autonomic Arousal Symptoms & Behavioral Outbursts (N=56)



Fava M, et al, Am J Psychiatry. 1993 Aug;150(8):1158-63.

Anger Attacks in MDD:

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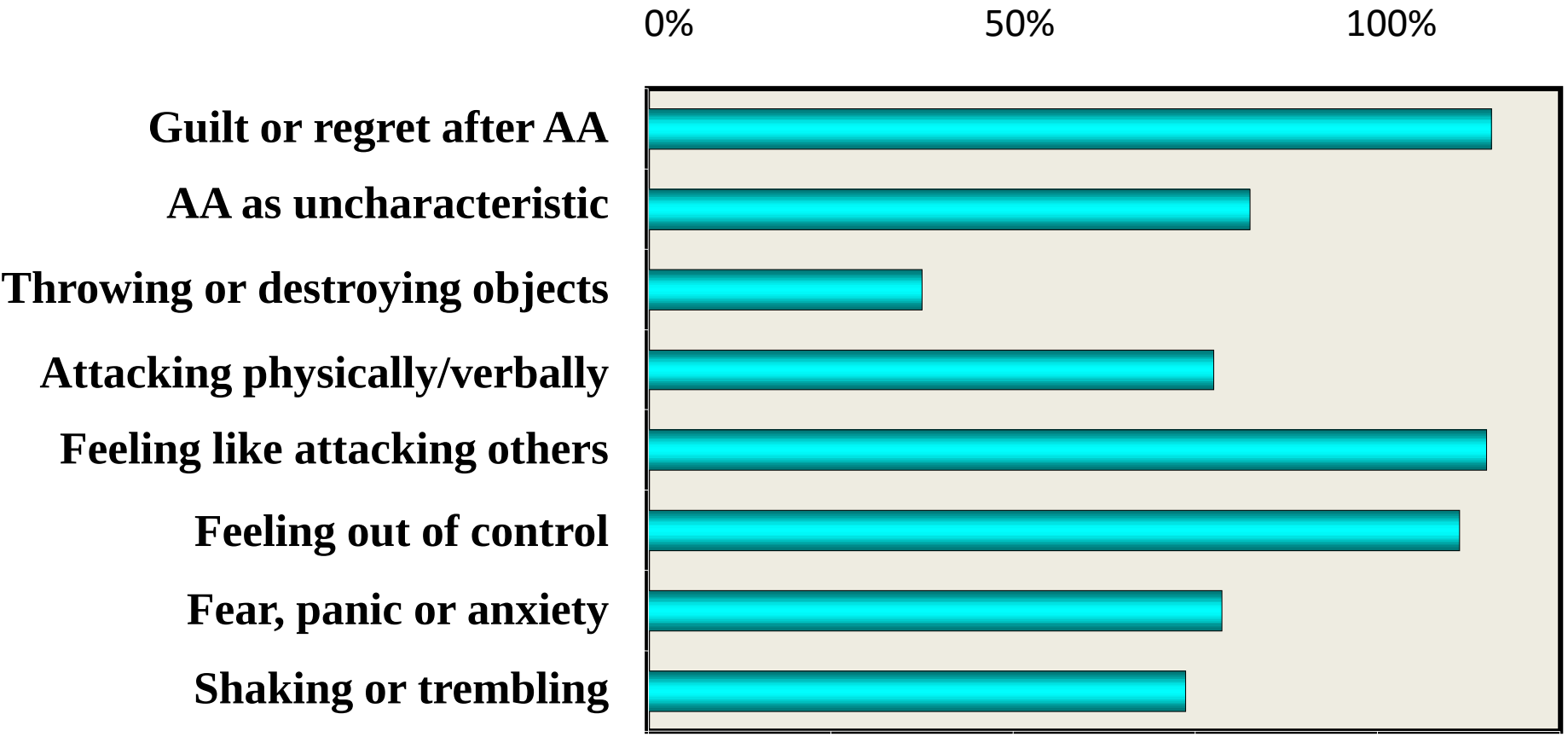
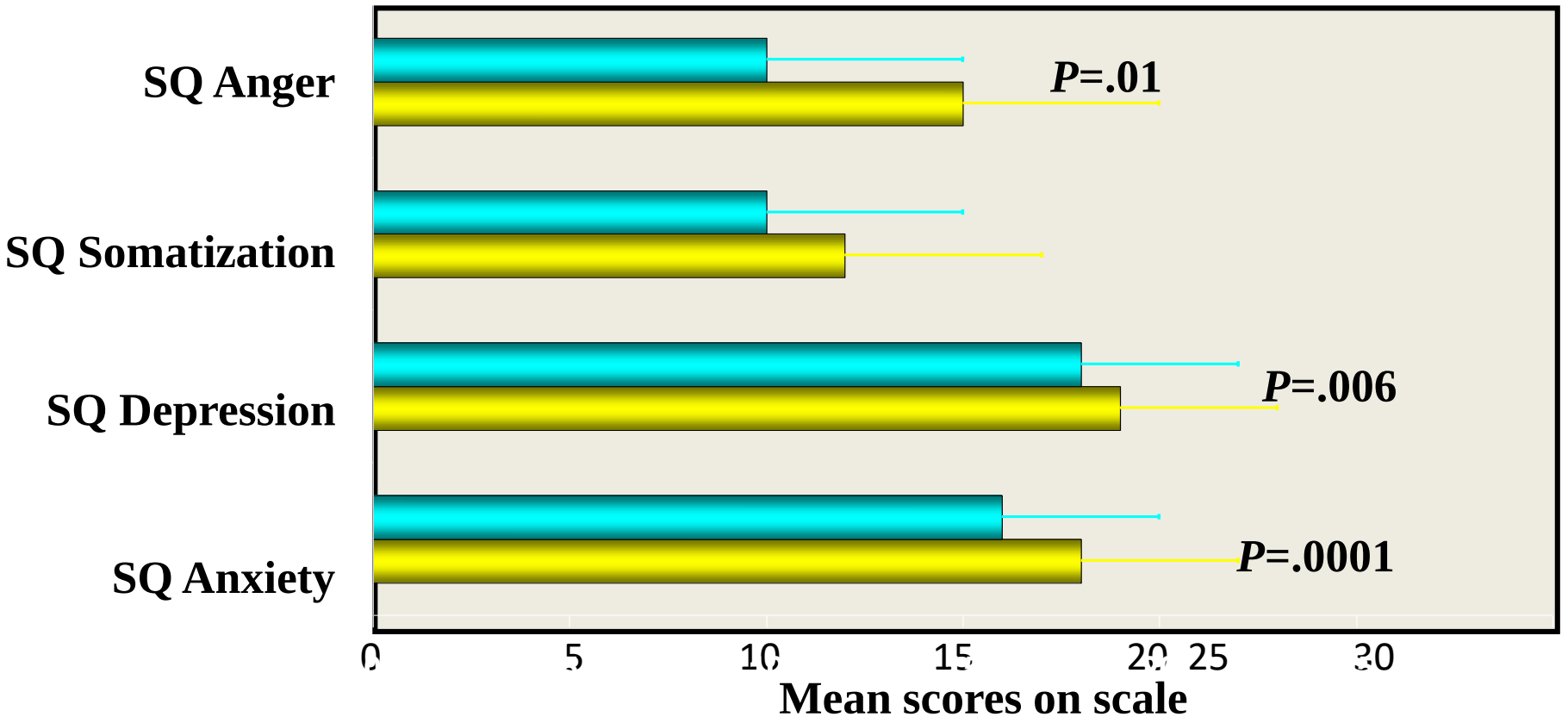


Fava M, et al. Am J Psychiatry. 1993 Aug;150(8):1158-63.

Scores on Symptom Questionnaire (SQ) of MDD with & without Anger Attacks



Fava M, et al. Am J Psychiatry. 1993 Aug;150(8):1158-63.

EMBARC STUDY:
Baseline clinical features and Anger Attacks

	No Anger Attacks (n=184)		Anger Attacks Present (n=109)			
Continuous variables	Mean	SD	Mean	SD	p Value	Cohen's d
HAMD-17	18.43	4.25	18.70	4.57	0.620	0.06
QIDS-SR	17.93	2.65	18.26	2.95	0.350	0.12
Irritability (CAST-IRR)	15.23	3.83	18.19	3.46	**<0.0001**	**0.80**
Anxiety (CAST-ANX)	8.52	2.64	9.37	2.63	**0.008**	0.32
Hostility—Friendly Visual Analogue of Mood Scale	74.39	20.62	66.93	22.61	**0.005**	0.35

Jha, Fava et al. Psychol Med. 2020 Mar 6:1-9.

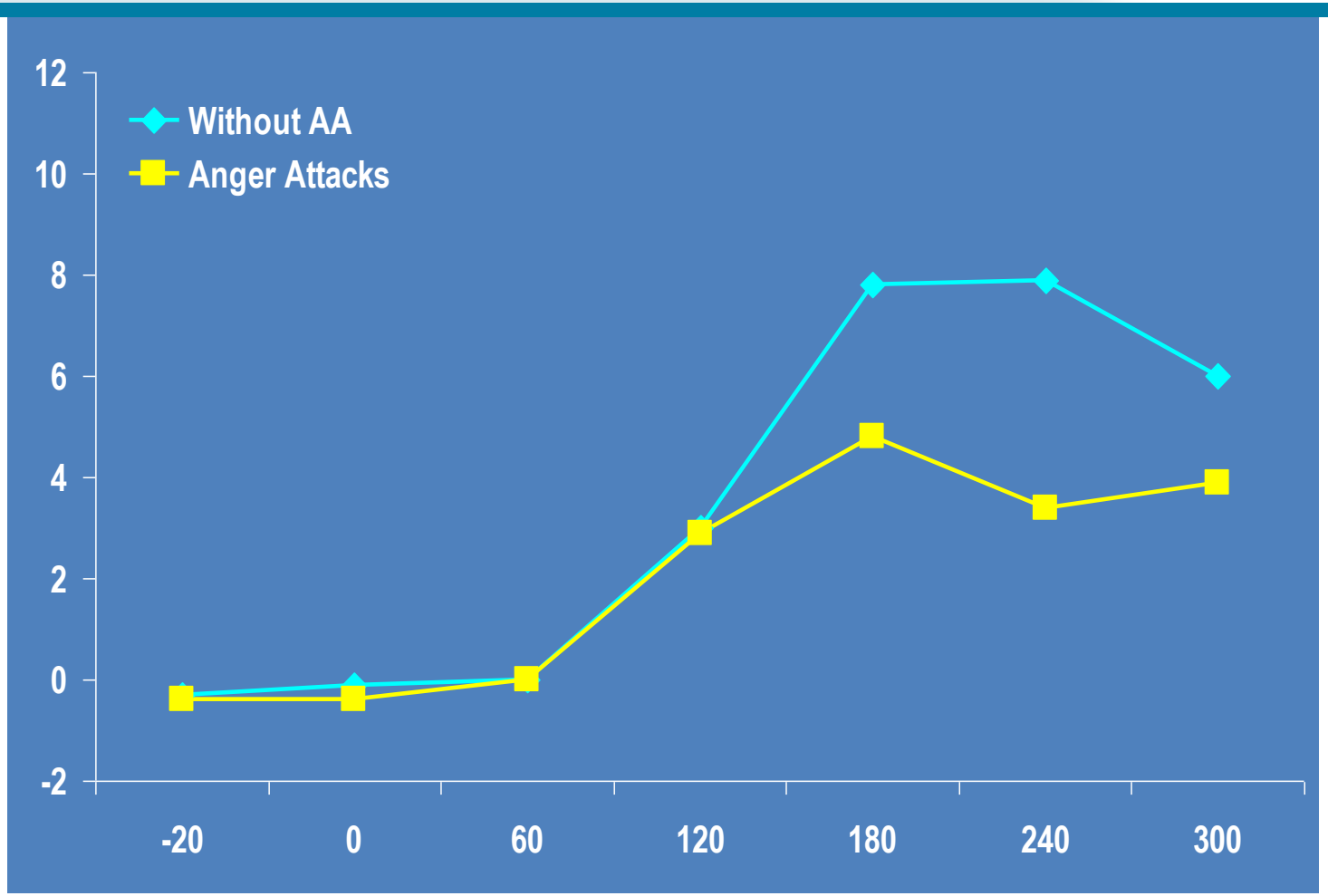
Anger Attacks in Bipolar vs. Unipolar Depression

- Rate of anger attacks in bipolar major depression > unipolar major depression[1]
  - Difference unipolars vs bipolars statistically significant ($P < .05$)[1]
- Rates of switch into mania in MDD patients with anger attacks = MDD patients without anger attacks[2]

[1]Perlis RH et al, J Affect Disord. 2004 Apr;79(1-3):291-5.

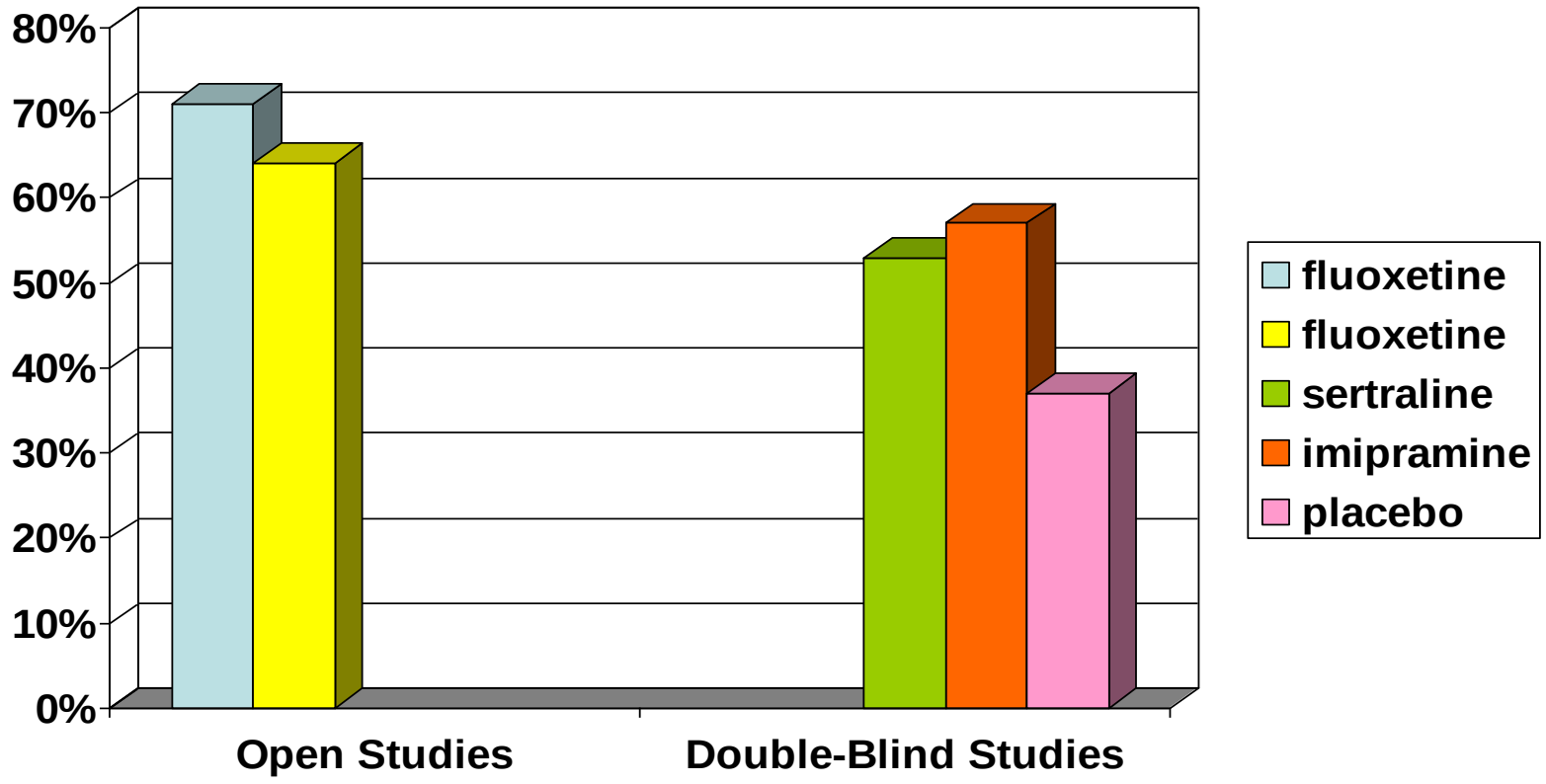
[2]Tedlow J, et al. J Affect Disord. 1999 Jan-Mar;52(1-3):217-23.

Fenfluramine-Placebo Difference in Prolactin Response in MDD with & without Anger Attacks



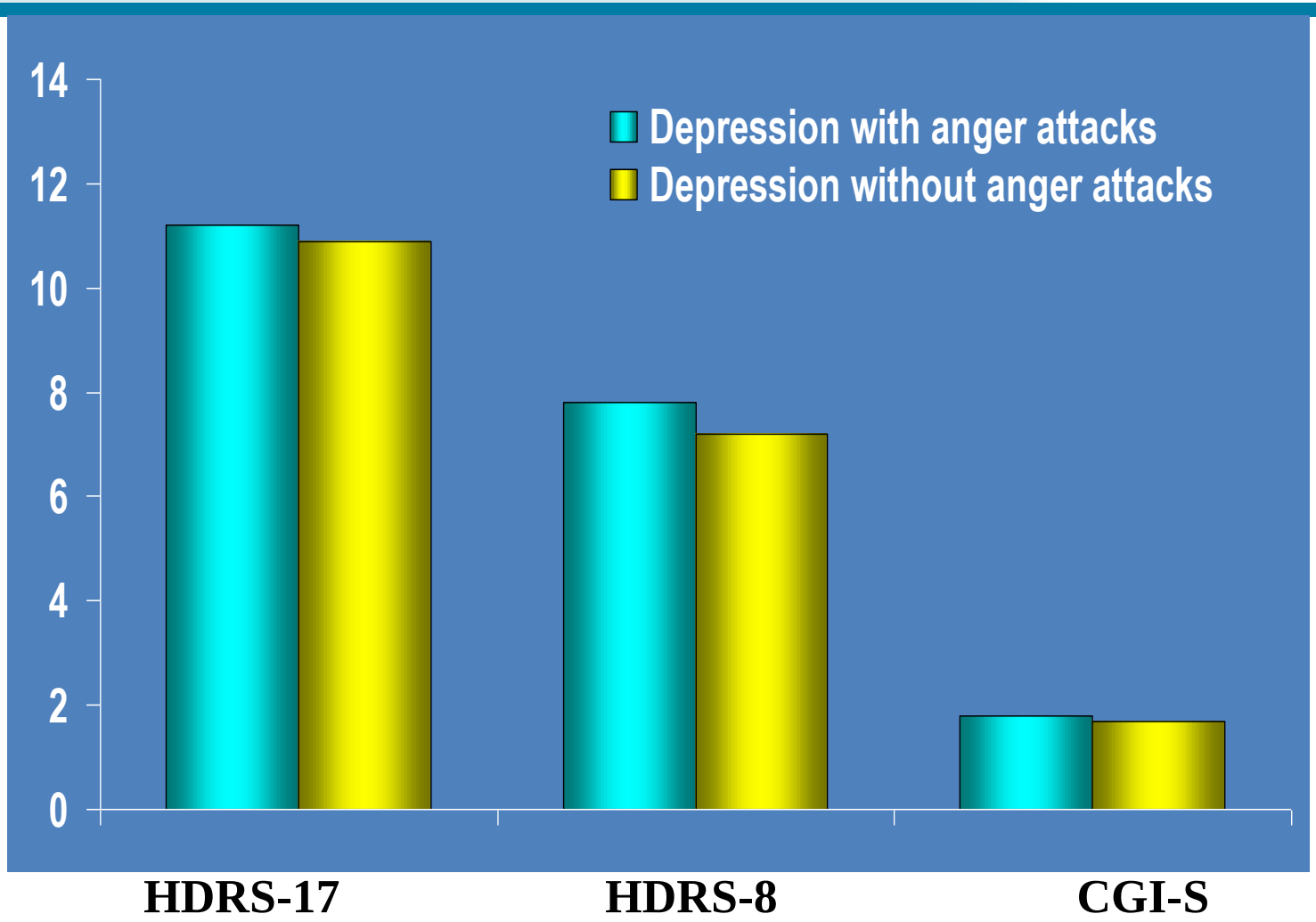
Fava M et al., Psychiatry Res. 2000 Apr 24;94(1):9-18

Anger Attacks & Their Response Rates to Antidepressants



[1]Open Study; Fava M, et al. Am J Psychiatry. 1993 Aug;150(8):1158-63; [2]Open Study; Fava M, et al. Ann Clin Psychiatry. 1996 Mar;8(1):7-10; [3]Double-Blind Study; Fava M, et al. Psychopharmacol Bull. 1997;33(1):101-3.

Changes in Depression Severity after Fluoxetine Treatment (20 mg/day)



Fava, et al. Biol Psychiatry. 1997 Oct 1;42(7):568-76.

CONCLUSIONS

- Major depressive disorder is highly heterogenous
- There is significant overlap among its most common subtypes (melancholic, atypical, anxious, and irritable)
- Distinctive responsiveness to antidepressants occurs in some but not all subtypes
- Further studies are needed