

ANXIOUS DEPRESSION: DIAGNOSTIC AND TREATMENT ISSUES

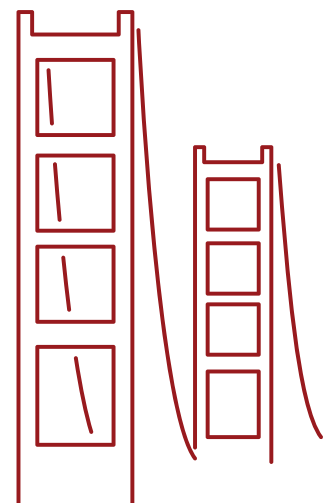
Welcome and Introduction

Maurizio Fava, MD (Chair)



Maurizio Fava, MD (Chair)

Dr. Fava obtained his medical degree from the University of Padova School of Medicine and completed a residency training in endocrinology at the same university. After completing a residency training in psychiatry at the Massachusetts General Hospital (MGH), he has been Director of the MGH Depression Clinical and Research Program since 1990 at the same hospital. Under Dr. Fava's direction, the MGH Depression Clinical and Research Program has become one of the most highly regarded depression programs in the country, conducting research projects in a variety of areas, including pharmacotherapy of resistant depression, neuroimaging, genetics, neurophysiology, neuroendocrinology, novel pharmacotherapies, alternative medicine, and psychotherapy. Dr. Fava has also been successful in obtaining funding for his program, as principal or co-principal investigator, from both the National Institutes of Health and industry for a total of more than \$23,000,000 in the past 18 years. Dr. Fava has authored or co-authored more than 400 original articles published in medical journals with international circulation. He has also edited five books, and published more than 50 chapters and 500 abstracts. Dr. Fava is also a well-known national and international speaker, having given more than 200 presentations at national and international meetings during his career in psychiatry. Dr. Fava has also been the recipient of many honors and awards. He is currently Executive Vice Chair for the MGH Department of Psychiatry, Executive Director, MGH Clinical Trials Network and Institute, Director of the MGH Depression Clinical and Research Program, and Professor of Psychiatry at Harvard Medical School.



Welcome and Introduction

Maurizio Fava, MD
Executive Vice Chair, Department of Psychiatry
Director, Depression Clinical and Research Program
Executive Director, MGH Clinical Trials Network and Institute
Massachusetts General Hospital
Professor of Psychiatry, Harvard Medical School

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2

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As Symposium Chair, I am responsible for ensuring that relevant disclosures are made by all presenters

Educational Goal for Our Presentation

To help psychiatrists and other mental health practitioners differentiate anxious depression from major depression and to develop treatment plans including psychotherapy and targeted pharmacotherapy to help manage individual patients and improve outcomes



The APA acknowledges support for this symposium from
H. Lundbeck A/S
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Agenda

- How Do We Define Anxious Depression?
John M. Zajecka, MD
- Neurobiology of Anxious Depression
Audrey R. Tyrka, MD, PhD
- Pharmacotherapeutic Strategies in the Treatment of Anxious Depression
Maurizio Fava, MD
- Psychotherapeutic Approaches to Anxious Depression
Amy Farabaugh, PhD
- Panel Discussion and Q&A



Learning Objective #1

Differentiate anxious depression from nonanxious depression and appreciate the neurobiological and phenomenological differences between these subtypes



Glossary of Terms

5HT	serotonin	hth	hypothalamus
aCg24	anterior cingulate	L/L	long/long
ACTH	adrenocorticotrophic hormone	MDD	major depressive disorder
a-ins	anterior insula	mF/ mF9/10	medial frontal
am	amygdala	MI	myocardial infarction
AUGM	augmentation	NE	norepinephrine
BDNF	brain-derived neurotrophic factor	OCD	obsessive compulsive disorder
bg	basal ganglia	oF11	orbital frontal
bs	brainstem	pACC	perigenual anterior cingulate cortex
BUP-SR	bupropion (sustained-release)	P40	inferior parietal
BUS	bupirone	pC, pCg	posterior cingulate
CBT	cognitive behavioral therapy	PD	panic disorder
Cg25	ventral subgenual cingulate	PF9	dorsolateral prefrontal
CGI-s	Clinical Global Impressions-Severity	PTSD	post-traumatic stress disorder
CHF	congestive heart failure	SAD	seasonal affective disorder
CIT	citalopram	SER	sertraline
CRF	corticotropin-releasing factor	S/L	short/long
CRH	corticotropin-releasing hormone	SNS	sympathetic nervous system
CSF	cerebrospinal fluid	SNRI	serotonin-norepinephrine reuptake inhibitor
CT	cognitive therapy	S/S	short/short
CVD	cerebrovascular disease	SSRI	selective serotonin reuptake inhibitor
DEX	dexamethasone	SR	sustained release
ELS	early life stress	STAR*D	Sequential Treatment Alternatives to Relieve Depression
GAD	generalized anxiety disorder	TCA	tricyclic antidepressant
HAM-A	Hamilton Anxiety Rating Scale	tha	thalamus
HAM-D/HDRS	Hamilton Depression Rating Scale	TSST	Trier Social Stress Test
HIV	human immunodeficiency virus	VEN-XR	venlafaxine (extended release)
HPA	hypothalamic-pituitary-adrenal		

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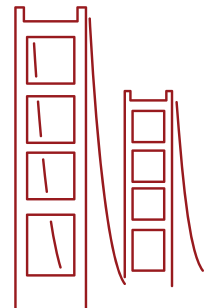
How Do We Define Anxious Depression?

John M. Zajecka, MD

There is a rapidly evolving paradigm shift in the diagnosis and management of mood disorders in order to achieve the expected rates of remission and recovery. Among the revisions that may have the greatest impact on long-term outcome is the recognition and acceptance that concurrent depression and anxiety is highly prevalent and may require a refined approach to diagnosis, differential diagnosis, and assessing outcome in a depressed population.

Various presentations of anxious depression occur in the majority of a depressed population at some time in the course of the illness. Depending on factors such as severity of anxiety, presence of somatic anxiety, and concurrent illness, anxious depression has been associated with lower rates of remission, reduced tolerance to treatment, and higher morbidity and mortality. The term anxious depression describes a range of possible clinical scenarios that may vary over time, even in the same individual. Therefore, it is important for the clinician to be aware of the various presentations and possible differential diagnosis in this population from time of initial diagnosis and through all phases of treatment. The general clinical presentation of anxious depression can range from co-occurrence of a full anxiety disorder and major depressive disorder to a treated depression with residual symptoms of intermittent anxiety symptoms. The signs and symptoms of anxious depression may also vary in intensity and over time, and include the traditional categories of psychic anxiety, somatic anxiety, and agitation. Other signs/symptoms that may signal anxious depression include nervousness, irritability, fear, insomnia, cognitive symptoms, motor movements, and others.

The differential diagnosis and consideration of concurrent factors are among the most important strategies to achieve and sustain remission in anxious depression. Assessing the onset, severity, and correlation of initial or new symptoms can help the clinician identify whether signs/symptoms are part of the underlying disorder(s) or are a result of a number of possible "modifiable factors" including psychosocial factors, iatrogenic causes, concurrent illness, or misdiagnosis.

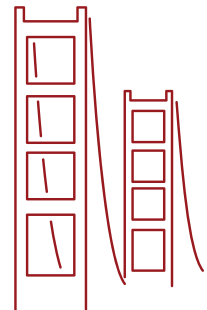


John M. Zajecka, MD

Dr. Zajecka is Associate Professor of Psychiatry and Director of the Depression Treatment and Research Center at Rush University Medical Center in Chicago, Illinois. Dr. Zajecka has also been in private practice since 1988. Dr. Zajecka earned his MD at Loyola University Chicago Stritch School of Medicine. After graduating, he completed his internship and psychiatric residency at Rush.

Dr. Zajecka's expertise includes the study and treatment of depression, bipolar disorder, treatment-resistant mood disorders, anxiety disorders, and sexual dysfunction. He has authored numerous publications and conducted research in affective disorders, anxiety disorders, schizophrenia, and sexual dysfunction. He has also done research and published extensively in the areas of treatment-resistant mood disorders, and safety and side effect issues related to psychotropic medications. He has a special interest in the management of treatment-resistant mood disorders, including the long-term outcomes of this population. He was the principle investigator in several pivotal trials resulting in the FDA approval of novel treatments including vagus nerve stimulation, and other pharmacological treatments for psychiatric disorders. He is a principle investigator for a three-site NIH-funded study assessing the effect of cognitive behavioral therapy on the prevention of recurrence in depressed patients treated with antidepressants.

Dr. Zajecka served as an Honorary International Advisor of the Chinese Psychopharmacology Algorithm Project and currently serves on the scientific advisory boards for the National Depression and Bipolar Support Alliance and the American Foundation for Suicide Prevention. He serves as an editor for several peer-reviewed journals. He was past Co-Chairman of the Scientific Advisory Board Member for the Obsessive-Compulsive Foundation of Metropolitan Chicago and past President of the MidWest Chapter of the American Foundation for Suicide Prevention. He received the Upjohn Young Investigators Award for Psychiatric Research and twice received the Special Recognition Award for Training Psychiatric Residents.



How Do We Define Anxious Depression?

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John M. Zajecka, MD Disclosures

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Major Depression Among the Most Treatable Illnesses

- Defined as complete resolution of symptoms *and* return to presymptomatic levels of functioning¹
- Adequate response can prevent all-cause morbidity and mortality²
- Assess for remission during all phases of treatment³

1. National Institutes of Mental Health. How is depression detected and treated? October 23, 2008.
2. Clinical Practice Guidelines Number 5: Major Depression in Primary Care. Available at: <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter.15593>.
3. Rush AJ, Trivedi MH. *Psychiatric Annals* 1995;25:704-705,709.



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Impact of Inadequately Treated Depression

- Depression is the fourth most disabling medical condition worldwide based on disability-adjusted life years
- Depression is predicted worldwide to be second only to ischemic heart disease with regard to disability by the year 2020
- Patients with MDD function more poorly than other outpatients with a variety of general medical conditions in terms of physical activity and occupational and social role responsibilities

Rush AJ, et al. *Clinical Controlled Trials* 2004;25:119-142.

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The Importance of Addressing Anxiety Symptoms of MDD

- A 2-year study of outpatients with MDD revealed that risk of relapse was significantly greater in nonremitters than in patients who achieved complete remission (69% vs. 15%)¹
- Strong correlation between anxiety symptoms and remission
 - Baseline anxiety symptoms have a significant impact on remission rates²
 - Early resolution of anxiety symptoms may be a predictor of remission and functional recovery^{2,3}

1. Pincus L, et al. *J Affect Disord* 2003;73:237-244.
2. Davidson JR, et al. *Depress Anxiety* 2002;16:4-13.
3. Silverstone PH, et al. *Int Clin Psychopharmacol* 2002;17:273-280.

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Risks Associated with Failure to Achieve and Sustain Remission

- Greater risk of relapse/recurrence¹⁻³
- More chronic depressive episodes¹
- Shorter durations between episodes¹
- Continued impairment in work and relationships⁴
- Increased association with mortality,⁵ morbidity and/or mortality with stroke,⁶ diabetes complications,⁷⁻⁸ MI,⁹ CVD,¹⁰ CHF,¹¹ and HIV¹²
- Ongoing risk of suicide¹³

References available in supplemental bibliography section of course guide.

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Anxious Depression: How Does It Differ from Depression of Similar Severity Without Anxiety?

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Anxious Depression Clinical and Demographic Characteristics

- Greater severity of illness¹
- Younger mean age²
- Earlier age of onset²
 - 20.6 ± 10.4 years in MDD with comorbid anxiety disorders
 - 28.4 ± 13.0 years in MDD alone

1. Joffe RT, et al. *Am J Psychiatry* 1993;150:1257-1258.
2. Fava M, et al. *Compr Psychiatry* 2000;41:97-102.



Anxious Depression Course of Illness

- Chronicity is common¹
- Greater functional impairment²
- Increased risk of suicide³
- Greater chance of treatment discontinuation⁴

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



How Does Anxious Depression Present in a Clinical Setting?

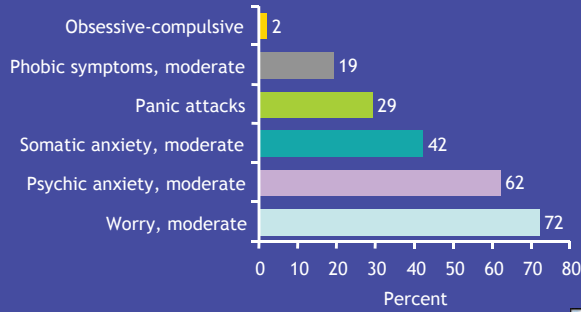
Anxiety May Be Prodromal Symptom in Various Mood Disorders

- Unipolar major depression
- Bipolar depression
- Psychotic mood disorders

Williamson DE, et al. *J Am Acad Child Adolesc Psychiatry* 2004;43:291-297.



Anxiety Symptoms in Major Depression



N = 200
Fawcett J, Kravitz HM. *J Clin Psychiatry* 1983;44(8 pt 2):8-11.
13

Most Depressed Patients Have Some Anxiety Symptoms

Psychic Anxiety	Somatic Anxiety	Other Symptoms
<ul style="list-style-type: none"> Worry Nervousness Fear Hypervigilance 	<ul style="list-style-type: none"> Autonomic hyperactivity Headache Backache Musculoskeletal pain Gastrointestinal distress 	<ul style="list-style-type: none"> Cognitive problems Individual target symptoms

Adapted from Fawcett J, Kravitz HM. *J Clin Psychiatry* 1983;44(8 pt 2):8-11.
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Anxiety ↔ Depression

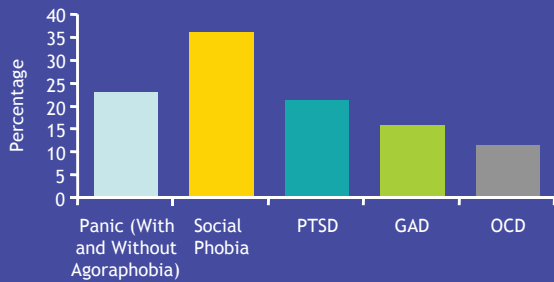
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Possible Clinical Presentation(s) of Patients with Coexistent Depression and Anxiety

Anxiety ↑	Subsyndromal depressive disorder + Anxiety disorder	Depressive disorder + Anxiety disorder
	Subsyndromal depressive disorder + Subsyndromal anxiety disorder	Depressive disorder + Subsyndromal anxiety disorder
	Depression →	

Zajacka JM, Ross JS. *J Clin Psychiatry* 1995;56(Suppl 2):10-13.
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Comorbidities Among Individuals Diagnosed with Major Depressive Disorder



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

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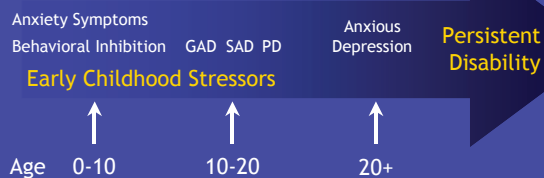
Major Depression with Comorbid Anxiety Disorders

- Anxiety disorders preceded the onset of depression in 40% of patients¹
- Both social phobia and GAD preceded the onset of MDD in 65% and 63% of the patients²
- Panic disorder, OCD, and agoraphobia followed MDD onset in 78%, 63%, and 86% of patients²

1. Sanderson WC, et al. *Am J Psychiatry* 1990;147:1025-1028.
2. Fava M, et al. *Compr Psychiatry* 2000;41:97-102.

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Hypothesized Model Sequence of Comorbidity



Fava M, et al. *Compr Psychiatry* 2000;41:97-102.

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Anxiety Disorders and MDD Gender Effects

- Women are twice as likely as men to have lifetime anxiety disorders
- Anxiety disorders are a risk factor for MDD in both sexes
- Anxiety disorder comorbidity accounts for much of the gender difference between men and women in MDD

Breslau N, et al. *Psychiatry Res* 1995;58:1-12.

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Supplemental Bibliography

Slide Title: Risks Associated with Failure to Achieve and Sustain Remission

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11. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline and death in patients with heart failure. *J Am Coll Cardiol* 2001;38:199-205.
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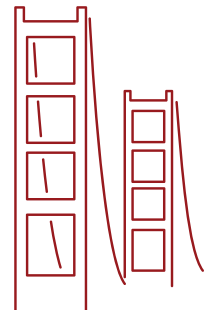
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ANXIOUS DEPRESSION: DIAGNOSTIC AND TREATMENT ISSUES

Neurobiology of Anxious Depression

Audrey R. Tyrka, MD, PhD

Anxious depression, defined as major depressive episodes with prominent or comorbid anxiety, is an important clinical entity. Depressive and anxiety disorders frequently co-occur, and evidence from behavioral genetics studies indicates that anxiety and depression may represent manifestations of a unified disorder. Recent work suggests that depressive and anxiety disorders may have common neurobiological origins. Stress and trauma, as well as temperamental sensitivity to stress, precede the development of depressive and anxiety disorders. Several genes that regulate monoamine pathways or activity of the hypothalamic-pituitary-adrenal (HPA) axis have been associated with both major depression and some anxiety disorders. Recently, a number of studies have also identified genes that interact with environmental stress to produce risk for major depression and for anxiety-related traits. Neuroimaging and neuroendocrine studies further reveal abnormalities of neural and hormonal function in association with depression and anxiety, and with anxious depression specifically. This presentation will discuss these emerging findings in genetics, neuroimaging, and neuroendocrinology as they relate to the pathophysiology of this important clinical condition.

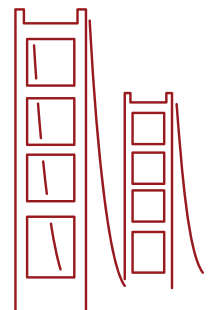


Audrey R. Tyrka, MD, PhD

Dr. Tyrka is Assistant Professor in the Department of Psychiatry and Human Behavior at Brown Medical School and Associate Chief of the Mood Disorders Program at Butler Hospital in Providence, Rhode Island.

Dr. Tyrka received her MD and PhD in medicine and psychology through a combined program at the University of Pennsylvania. She completed a psychiatry residency at Brown Medical School and further research training in clinical neuroscience at the Mood Disorders Research Program and Laboratory for Clinical Neuroscience at Butler Hospital and Brown University.

Dr. Tyrka's research is focused on the identification of endophenotypes, or latent risk factors, for psychiatric disorders. Her early prospective work identified behavioral and psychological markers of the later development of schizophrenia and eating disorders. More recently, Dr. Tyrka has focused on the effects of stress and adversity on neuroendocrine function, and how such influences may be moderated by genetic factors. The goal of this work is to understand how neurobiological and psychosocial processes interact to increase risk for mood and anxiety disorders.



Neurobiology of Anxious Depression

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Butler Hospital

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AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

Audrey R. Tyrka, MD, PhD Disclosures

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Introduction Neurobiology of Anxious Depression

- Genetic epidemiology studies show that comorbidity of depression and anxiety is due to shared genetic vulnerability
- Depression and anxiety disorders have both been linked to abnormalities in:
 - Norepinephrine (NE) signaling
 - Serotonin (5HT) activity
 - Corticotropin-releasing factor (CRF) and glucocorticoid stress response abnormalities

Ressler KJ, Nemeroff CB. *Depress Anxiety* 2000;12(Suppl 1):2-19.



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Introduction Neurobiology of Anxious Depression

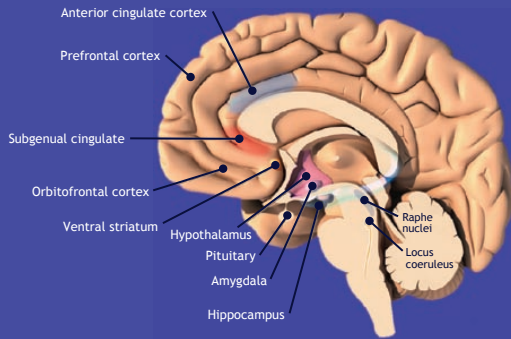
- Abnormalities of limbic and cortical brain regions implicated in both depression and anxiety
- Only a few studies have specifically examined the neurobiology of anxious depression
- Even fewer investigations have compared anxious depression with non-anxious depression or pure anxiety disorders

Ressler KJ, Nemeroff CB. *Depress Anxiety* 2000;12(Suppl 1):2-19.



4

Brain Regions Implicated in Major Depression and Anxiety Disorders



Adapted from aan het Rot M, et al. *CMAJ* 2009;180:305-313.

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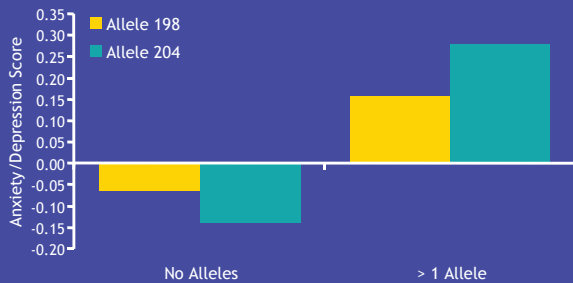
Genetic Epidemiologic Perspective on the Comorbidity of Depression and Anxiety

- Family and twin studies show that 30-40% of the liability for depression and for anxiety disorders is inherited¹
- The co-segregation of depression and anxiety disorders within families is strong and begins in childhood¹
- Twin studies indicate that comorbidity between depression and anxiety is due to a shared genetic vulnerability for both disorders^{2,3}
- Genetic risk for neuroticism, a trait that precedes depression and anxiety disorders, accounts for a portion of the genetic risk^{2,3}

1. Williamson DE, et al. *Child Adolesc Psychiatr Clin N Am* 2005;14:707-726.
2. Kendler KS, et al. *Psychol Med* 2007;37:453-462.
3. Middeldorp CM, et al. *Psychol Med* 2005;35:611-624.

6

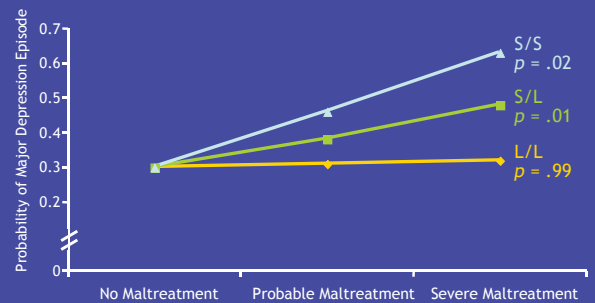
Anxiety/Depression Score by Tryptophan Hydroxylase Polymorphism Genotypes



n = 312
p < .05
Nash MW, et al. *Am J Med Genet B Neuropsychiatr Genet* 2005;135B:33-37.

7

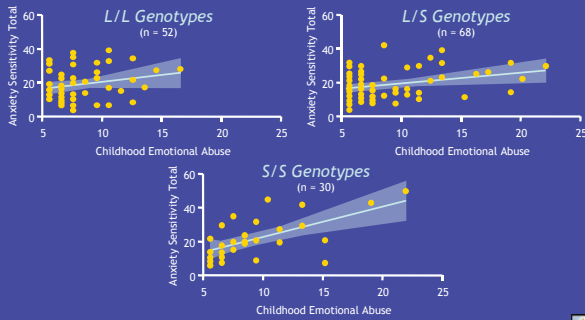
Influence of Life Stress on Depression Depends on the Serotonin Transporter Gene



Caspi A, et al. *Science* 2003;301:386.

8

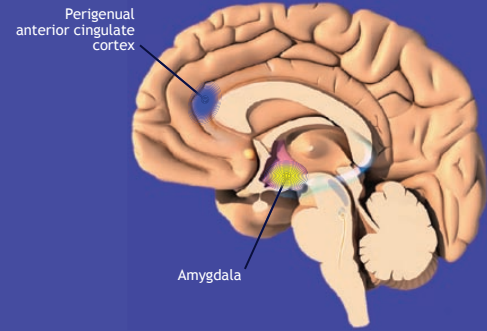
Interaction of Serotonin Transporter Gene and Childhood Emotional Abuse Predicts Anxiety Sensitivity



S/S vs. L/L or L/S genotypes grouped together: $p = .03$
Stein MB, et al. *Neuropsychopharmacology* 2008;33:312-319.



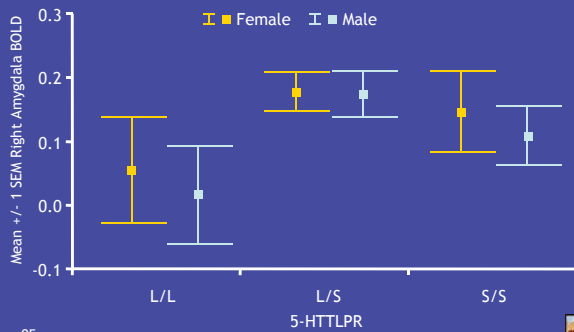
Brain Regions Implicated in Major Depression and Anxiety Disorders



Adapted from aan het Rot M, et al. *CMAJ* 2009;180:305-313.



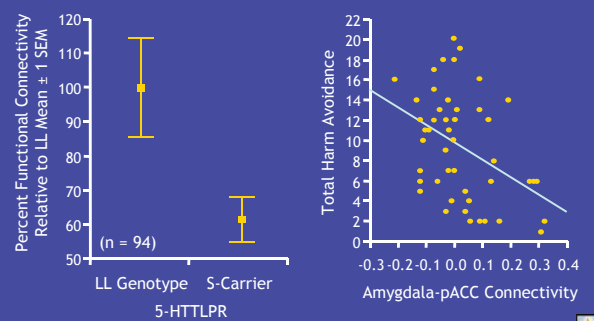
Regulatory Variant of 5-HTTLPR Effects on Amygdala Reactivity



$p < .05$
Hariri AR, et al. *Arch Gen Psychiatry* 2005;62:146-152.



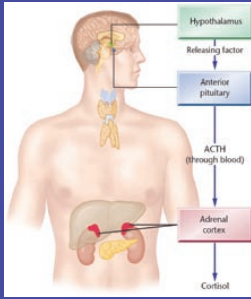
Regulatory Variant of 5-HTTLPR Effects on pACC Functional Connectivity



Pezawas L, et al. *Nat Neuroscience* 2005;8:828-834.
Hariri AR, et al. *Biol Psychiatry* 2006;59:888-897.



Hypothalamic-Pituitary-Adrenal (HPA) Axis

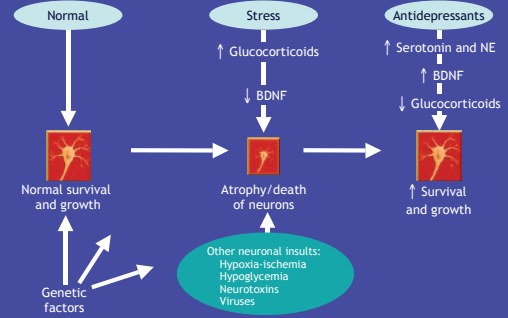


- Acutely mobilizes the body's resources to cope with stressor
 - Sympathetic nervous system activation
 - Mobilization of fuels: gluconeogenesis, lipolysis, proteolysis
- Deleterious effects of prolonged or excessive activation

Halasz B. *The Hypothalamus as an Endocrine Organ: The Science of Endocrinology*. In Conn PM, Freeman ME, eds. *Neuroendocrinology in Physiology and Medicine*. Totowa, NJ: Humana Press. 2000.

13

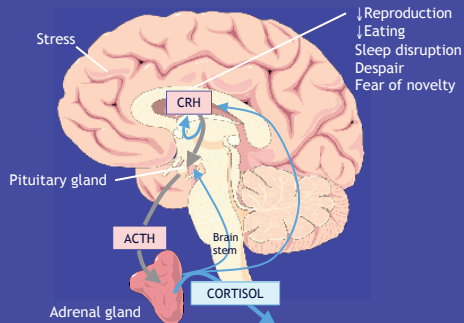
Excess Glucocorticoids Hippocampal Volume Loss



NE = norepinephrine; BDNF = brain-derived neurotrophic factor
Duman RS, et al. *Arch Gen Psychiatry* 1997;54:597-606.

14

HPA Axis Stress Response



ACTH = adrenocorticotrophic hormone; CRH = corticotropin-releasing hormone;
HPA = hypothalamic-pituitary-adrenal

15

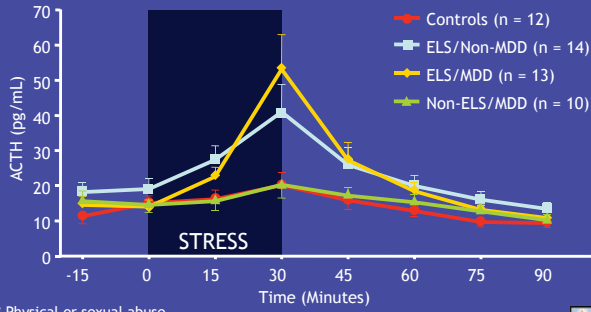
HPA Axis Abnormalities Seen in Depression and Some Studies of Anxiety Disorders

- Increased CSF CRH concentrations
- Increased or decreased basal cortisol concentrations
- Changes in negative feedback inhibition by glucocorticoids
- Increases or decreases in glucocorticoid receptor density (lymphocytes)

CSF = cerebrospinal fluid
Heim C, et al. *Arch Gen Psychiatry* 2009;66:72-80.
Risbrough VB, Stein MB. *Horm Behav* 2006;50:550-561.

17

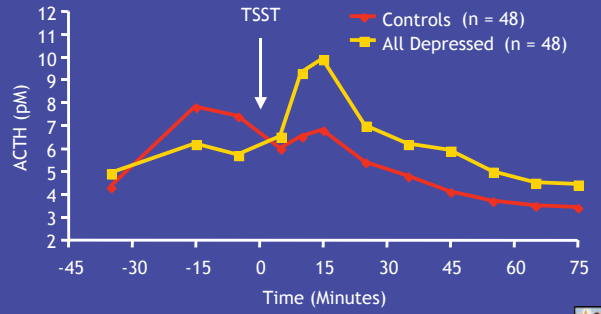
Women with Early Life Stress* and Depression/Anxiety Have Increased ACTH Responses to the Trier Social Stress Test (TSST)



* Physical or sexual abuse
 $p < .05$
Heim C, et al. *JAMA* 2000;284:592-597.



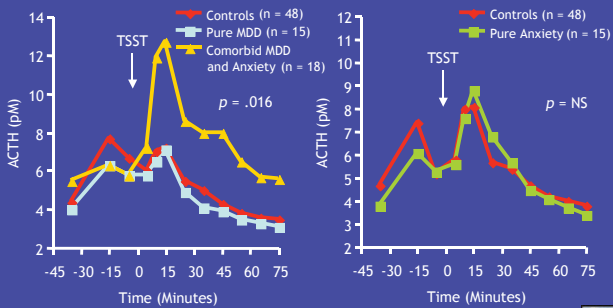
ACTH Response to the TSST



$p = .02$
Young EA, et al. *Biol Psychiatry* 2004;56:113-120.



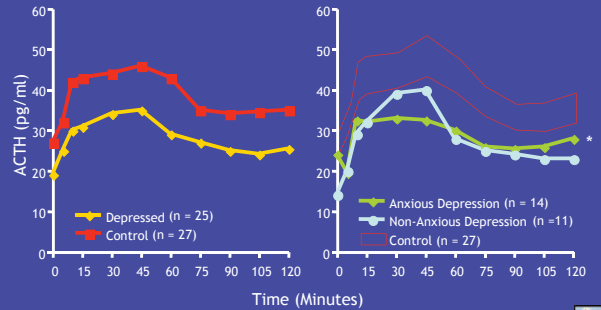
ACTH Response to the TSST



Young EA, et al. *Biol Psychiatry* 2004;56:113-120.



ACTH Response to CRH



* $p = .05$
Meller WH, et al. *Biol Psychiatry* 1995;37:376-382.



Trait Markers Linked to Depression/Anxiety

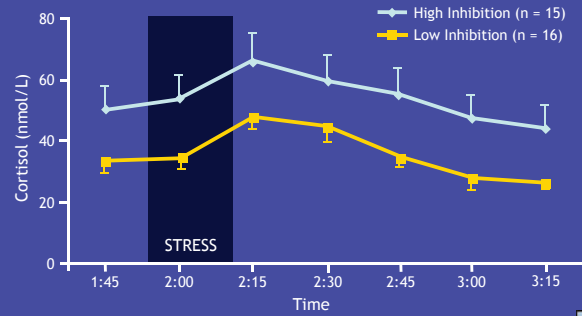
- Behavioral inhibition
 - Tendency to withdraw and avoid novel situations
 - Stable over time
 - Predicts the later development of anxiety disorders and depression
 - Linked to the CRH gene
- Neuroticism
 - Characterized by a global tendency to experience negative affect
 - Heritable and shares common genetic risk factors with MDD and GAD
 - Predicts the later development of depression and is a risk factor for anxiety disorders

- Kendler KS, et al. *Am J Psychiatry* 2004;161:631-636.
- Kendler KS, et al. *Arch Gen Psychiatry* 1993;50:863-870.
- Fox NA, et al. *Annu Rev Psychol* 2005;56:235-262.
- Smoller JW, et al. *Biol Psych* 2005;57:1485-1492.



22

Inhibited Temperament Linked to High Cortisol Response to the TSST



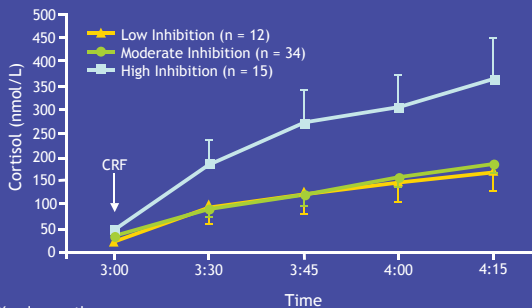
$p < .05$

Tyrka AR, et al. *Acta Psychiatr Scand* 2007;115:395-402.



23

Inhibited Subjects Have High Cortisol Response to the Dex/CRH Test



DEX = dexamethasone

$p < .05$

Tyrka AR, et al. *Horm Behav* 2008;53:518-525.



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Summary Neurobiology of Anxious Depression

- Comorbidity of anxiety and depression is due to shared genetic vulnerability
- Limbic and frontal brain circuits are implicated in anxiety and depression
- Risk genes may influence the abnormalities in brain signaling underlying depression and anxiety



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Bibliography

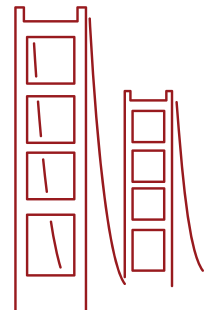
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- Kendler KS, Kuhn J, Prescott CA. The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *Am J Psychiatry* 2004;161:631-636.
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ANXIOUS DEPRESSION: DIAGNOSTIC AND TREATMENT ISSUES

Pharmacotherapeutic Strategies in the Treatment of Anxious Depression

Maurizio Fava, MD

The presence of anxious depression has typically been associated with poorer treatment outcome compared to non-anxious depression. In fact, in most but not all studies, individuals with anxious depression were also found to be less likely to respond to antidepressant treatment than those without anxious depression, regardless of the type of antidepressant used. In addition, no significant differences in efficacy have typically been shown among antidepressants of the same or different class, with the exception of a pooled analysis showing significantly higher rates of remission with a serotonin norepinephrine reuptake inhibitor compared to a selective serotonin reuptake inhibitor. The association between anxious depression and poorer response to antidepressant treatment may account for the results of a recent study showing that the concomitant use of anxiolytics/hypnotics was a significant predictor of treatment resistance in older adults with depression. This presentation will review the various therapeutic strategies that clinicians use in the treatment of anxious depression, including monotherapy with antidepressants and augmentation and combination therapies. In particular, polypharmacy is used quite commonly to treat anxious depression. Although many of these treatments have not yet been approved for anxious depression, augmenting agents such as benzodiazepines, nonbenzodiazepine hypnotics, anticonvulsants, atypical antipsychotics, and bupropion are common pharmacological options. This presentation will review the empirical evidence in support of these therapeutic interventions in anxious depression and will discuss their limitations.



Pharmacotherapeutic Strategies in the Treatment of Anxious Depression

Maurizio Fava, MD

Executive Vice Chair, Department of Psychiatry
 Director, Depression Clinical and Research Program
 Executive Director, MGH Clinical Trials Network and Institute
 Massachusetts General Hospital
 Professor of Psychiatry, Harvard Medical School

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Maurizio Fava, MD Disclosures

- **Research Support:** Abbott Laboratories; Alkermes, Inc.; Aspect Medical Systems, Inc.; AstraZeneca Pharmaceuticals LP; Bio Research Laboratories, Inc.; BrainCells Inc.; Bristol-Myers Squibb Company; Cephalon, Inc.; Clinical Trial Solutions; Eli Lilly and Company; Forest Laboratories, Inc.; Geneden Biotech, Inc.; GlaxoSmithKline; Johnson & Johnson Pharmaceutical Research & Development, LLC; Lichtwer Pharma; Lorex Pharmaceuticals; NARSAD; NCCAM; NIDA; NIMH; Novartis Pharmaceuticals Corporation; Organon Pharmaceuticals USA Inc.; PamLab, LLC; Pfizer Inc.; Pharmavite LLC; Roche Labs; Sanofi-aventis; Sanofi-synthelabo; Shire Pharmaceuticals; Solvay Pharmaceuticals, Inc.; Wyeth-Ayerst
- **Speaking:** Advanced Meeting Partners Corporation; American Psychiatric Association; AstraZeneca Pharmaceuticals LP; Boehringer Ingelheim Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Cephalon, Inc.; Eli Lilly and Company; Forest Laboratories, Inc.; GlaxoSmithKline; Imedex, LLC; Novartis Pharmaceuticals Corporation; Organon Pharmaceuticals USA Inc.; Pfizer Inc.; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed-Elsevier; United BioSource Corporation; Wyeth-Ayerst



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Maurizio Fava, MD Disclosures

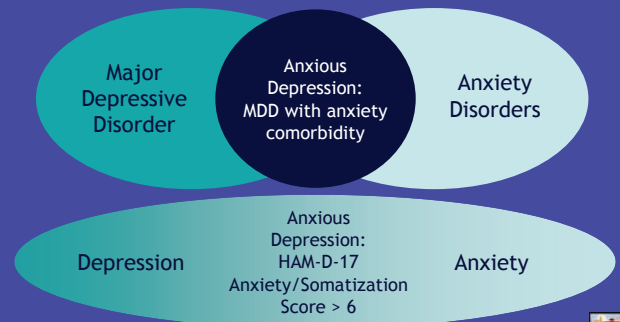
- **Advisory/Consulting:** Abbott Laboratories; Amarin Corporation plc; Aspect Medical Systems, Inc.; AstraZeneca Pharmaceuticals LP; Auspex Pharmaceuticals; Bayer AG; Best Practice Project Management, Inc.; Biovail Pharmaceuticals, Inc.; BrainCells Inc.; Bristol-Myers Squibb Company; Cephalon, Inc.; Clinical Trial Solutions; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DOV Pharmaceutical Inc.; Eli Lilly and Company; EPIX Pharmaceuticals, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Laboratories, Inc.; GlaxoSmithKline; Grunenthal GmbH; H. Lundbeck A/S; Janssen LP; Jazz Pharmaceuticals, Inc.; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceutical Company; Labopharm Inc.; Lorex Pharmaceuticals; MedAvante, Inc.; Merck & Co., Inc.; Methylation Sciences, Inc.; Neuronetics Inc.; Novartis Pharmaceuticals Corporation; Nutrition 21, Inc.; Organon Pharmaceuticals USA Inc.; PamLab, LLC; Pfizer Inc; Pharmavite LLC; Precision Human Biolaboratory Inc.; Roche Labs; Sanofi-aventis; Sanofi-synthelabo; Sepracor Inc; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Takeda Pharmaceuticals North America, Inc.; Tetraxenex Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; United BioSource Corporation; VANDA Pharmaceuticals; Wyeth-Ayerst
- **Equity Holdings:** Compellis Pharmaceuticals
- **Royalty/Patent, Other Income:** Patent applications for SPCD and for a combination of azapirones and bupropion in MDD; copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER



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Anxious Depression Categorical vs. Dimensional Definitions



HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder



4

An Illustrative Case

- 62-year-old divorced man
 - “I am feeling down a lot, and I worry all the time, I cannot relax”
 - Fragmented sleep and daytime fatigue
 - Diminished appetite and concentration
 - “I used to be a shy kid and I don’t go out very often”
 - “I have tried an SSRI (citalopram) for 3 months, but it’s not helping much”
 - On adjunctive melatonin for sleep



5

How Does Anxious Depression Respond to Antidepressant Treatment?

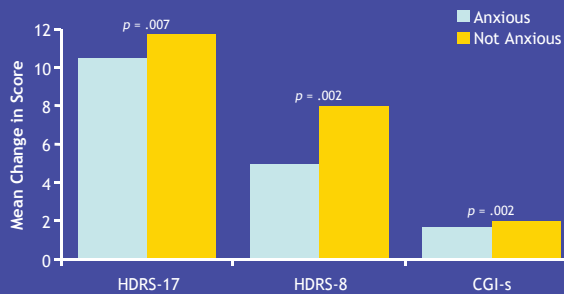
- Lesser likelihood to respond to antidepressant treatment
 - In adults¹
 - In elderly²
- When anxiety persists despite response, greater likelihood of relapse³

1. Fava M, et al. *Biol Psychiatry* 1997;42:568-576.
2. Flint AJ, Rifat SL. *Am J Geriatr Psychiatry* 1997;5:107-115.
3. Flint AJ, Rifat SL. *Psychiatry Res* 1997;66:23-31.



6

Change in Depression Severity for Patients With and Without Anxious Depression Treated with Fluoxetine

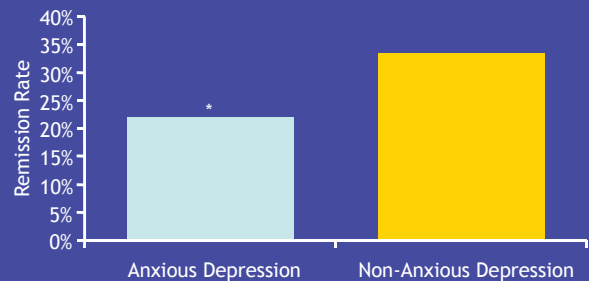


N = 294
Fava M, et al. *Biol Psychiatry* 1997;42:568-576.



7

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

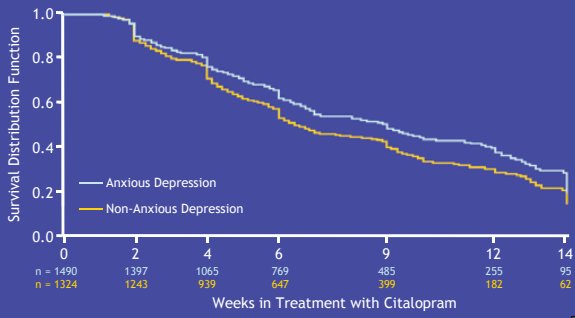


N = 2876
* p < .05
Fava M, et al. *Am J Psychiatry* 2008;165:342-351.



8

Time to Response in Level 1 of STAR*D Anxious vs. Non-Anxious Depression



* Log-rank Statistic = 22.7, $p < .0001$
Fava M, et al. *Am J Psychiatry* 2008;165:342-351.



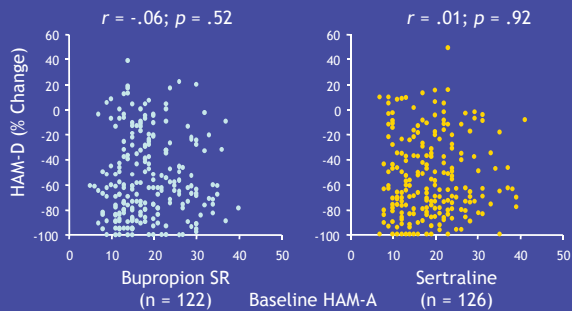
Anxious Depression Treatment Approaches

- Monotherapy with antidepressants
 - Sedating vs. nonsedating
- Augmentation with:
 - Benzodiazepines
 - Eszopiclone
 - Bupropion
 - Gabapentin or other anticonvulsants
 - Antipsychotics

10



Relationship Between Baseline Anxiety (HAM-A) and Percentage Change in the HAM-D-21

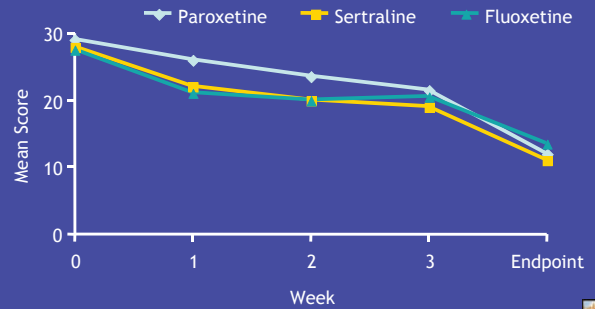


Rush AJ, et al. *Neuropsychopharmacology* 2001;25:131-138.

11



HAM-D-17 Scores Before and After Double-Blind Treatment with SSRIs in Anxious Depression

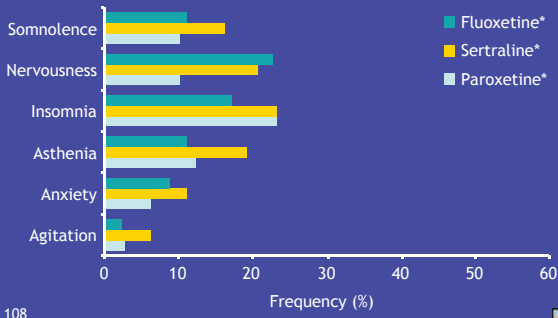


N = 108
Fava M, et al. *J Affect Disord* 2000;59:119-126.

12



Rates of Adverse Events During Double-Blind Treatment with SSRIs in Anxious Depression



N = 108
* p = ns
Fava M, et al. *J Affect Disord* 2000;59:119-126.
13

Use of Anxiolytics and Hypnotics During SSRI Treatment

Drug	No. of Patients	Hypnotic %	Hypnotic/Anxiolytic %
Paroxetine	5704	18	42
Sertraline	13,558	16	36
Fluoxetine	12,607	14	33

From the Texas Medicaid Database

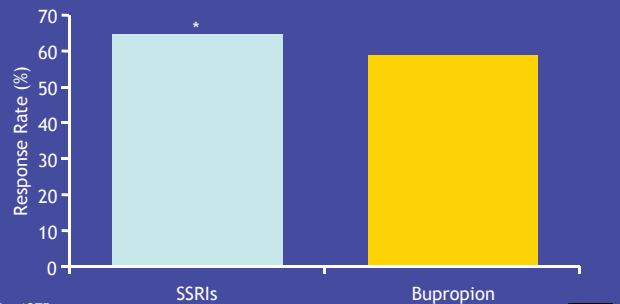
Rascati K. *Clin Ther* 1995;17:786-790.
14

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.
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 - Sheehan D, et al. *Psychopharmacol Bull* 1992;28:139-143.
 - Sertraline
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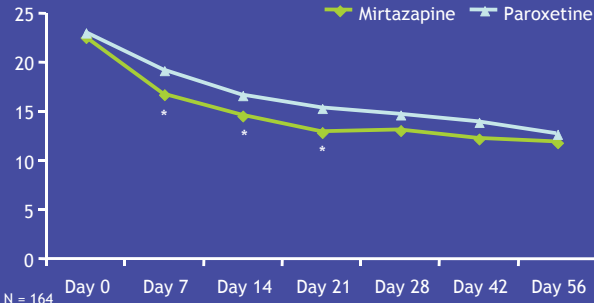
15

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.
16

HAM-D-17 Scores in Double-Blind Study of Mirtazapine vs. Paroxetine in Anxious Depression

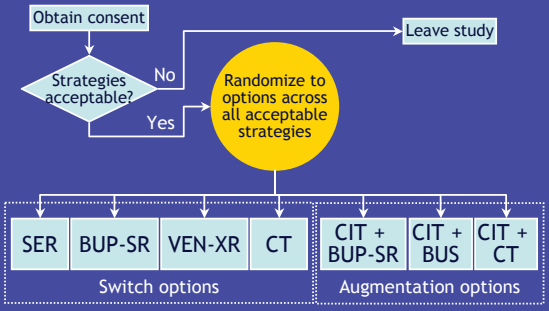


N = 164
* p < .05

Fava M, et al. Presented at 15th Congress of the European College of Neuropsychopharmacology; 2002 October 5-9; Barcelona, Spain.



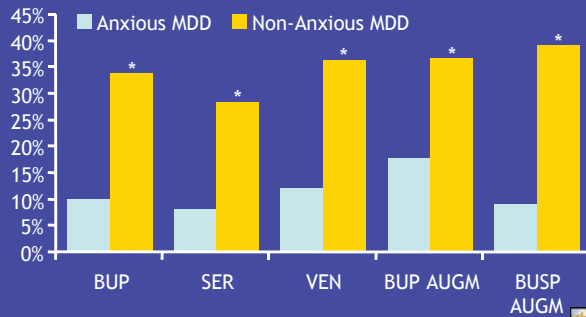
STAR*D Level 2 Switching Treatments for Citalopram Nonremitters



BUP-SR = bupropion (sustained-release); BUS = buspirone; CIT = citalopram; CT = cognitive therapy; SER = sertraline; VEN-XR = venlafaxine (extended release)
Rush AJ, et al. *Am J Psychiatry* 2003;160:237.

18

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

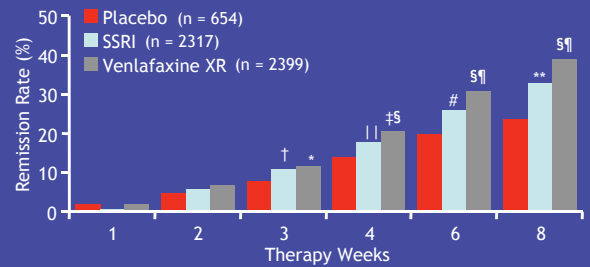


* p < .05

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



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

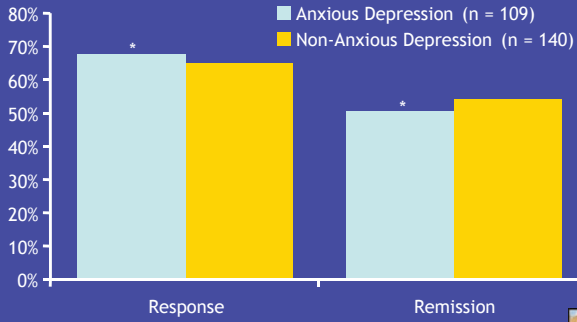


* p < .01 vs. placebo; † p < .05 vs. placebo; ‡ p < .05 vs. SSRI; § p < .001 vs. placebo; || p < .05 vs. placebo; ¶ p < .001 vs. SSRI; # p < .01 vs. placebo; ** p < .001 vs. placebo

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

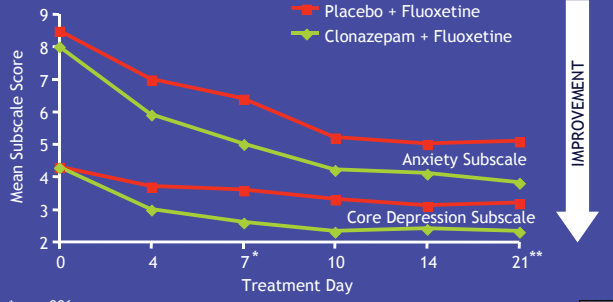
20

Response & Remission Rates in Open Trial of Duloxetine in Anxious and Non-Anxious MDD



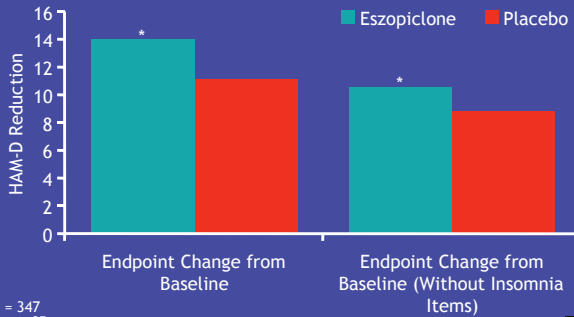
* p = ns
Fava M, et al. *Ann Clin Psychiatry* 2007;19:187-195.
21

Mean Scores of the HAM-D Anxiety Cluster with Benzodiazepine Augmentation



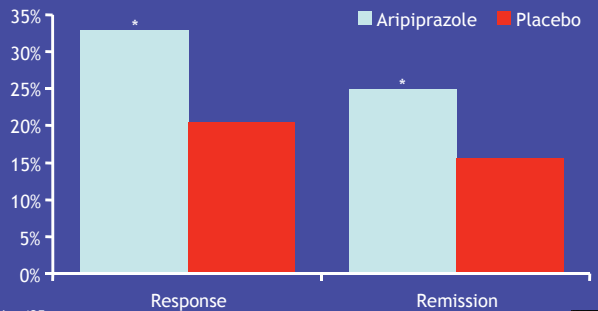
* p < .006
** p < .01
Londborg PD, et al. *J Affect Disord* 2000;61:73-79.
22

Pooled Analysis of Trials Comparing Eszopiclone Added to SSRI and Placebo in Anxious Depression



N = 347
* p < .05
Fava M, et al. Presented at the 47th Annual Meeting of the American College of Neuropsychopharmacology 2008 December 7-11; Scottsdale, AZ. Poster No. 146.
23

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.
24

Follow-Up with Our Illustrative Case

- A trial with a bupropion augmentation of citalopram was poorly tolerated
- Patient was started on a combination of antidepressant plus benzodiazepine and showed partial response
- The SSRI was replaced with an SNRI and patient had full response



25

Anxious Depression Management Issues

- Antidepressant monotherapy works well in efficacy trials
- Concerns about agitation/activation often lead to the use of:
 - Relatively more sedating antidepressants
 - Lower starting doses
 - Polypharmacy (e.g., combination of an antidepressant and a benzodiazepine)
- Higher antidepressant doses may be required in some patients



26

Anxious Depression Management Issues (cont.)

- Anxiety sensitivity may predict poorer treatment adherence¹
- Side effect management very important
- Concomitant **antianxiety drugs** can be **started with the antidepressant** or **added later**
- What is the role of psychotherapy?



1. Tedlow JR, et al. *Biol Psychiatry* 1996;40:668-670.

27

Summary

- Antidepressants are typically equally effective in anxious depression
- However, SNRIs may be better than SSRIs
- Overall efficacy of currently available therapies is modest
- Anxiolytics may be indicated as adjuncts in nonresponders
- Novel therapies targeting this population are needed



28

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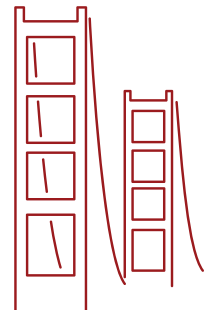
ANXIOUS DEPRESSION: DIAGNOSTIC AND TREATMENT ISSUES

Psychotherapeutic Approaches to Anxious Depression

Amy Farabaugh, PhD

Anxious depression, a subtype of depression, appears to be quite prevalent, is often challenging to treat, and likely represents a complex interplay of biological and psychosocial factors. The relationship between depression and anxiety is not well understood and there has been limited attention to the optimal use of psychosocial interventions, such as cognitive behavior therapy (CBT) for anxious depression. Although psychopharmacological treatment for anxious depression are effective, there are often high rates of nonremission and of subsequent relapse and recurrence. Premature discontinuation of medication by patients with anxious depression is also a common clinical challenge. Moreover, antidepressants do not provide an individual with strategies and skills for coping with associated functional impairment. Quality of life impairments, such as underachievement, occupational and economic status issues, and relationship difficulties, appear to require skills training over and above medication management. Psychosocial interventions potentially offer the advantage of providing specific skill sets to individuals to help them address both anxiety and depressive symptoms, ideally increasing the likelihood that they will respond/ remit with antidepressant treatment and decreasing their chances of relapse.

Accurately diagnosing anxious depression and integrating psychosocial and pharmacological approaches to establish remission is likely to yield significant benefits in terms of reducing risks of prolonged functional impairment, medication noncompliance, relapse and suicide among patients with anxious depression.



Psychotherapeutic Approaches to Anxious Depression

Amy Farabaugh, PhD
Director, Psychotherapy Research
Depression Clinical and Research Program
Massachusetts General Hospital
Assistant Professor, Harvard Medical School

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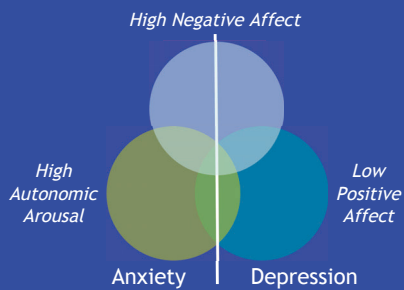
Amy Farabaugh, PhD Disclosures

- *Research/Grants:* None
- *Speakers Bureau:* None
- *Consultant:* None
- *Stockholder:* Pfizer Inc.
- *Other Financial Interest:* None
- *Advisory Board:* None



2

Comorbidity and Tripartite Theory Clark and Watson, 1991



Otto MW, et al. Panic disorder and social phobia. In MA Whisman (Ed). *Cognitive Therapy for Complex and Comorbid Depression: Conceptualization, Assessment, and Treatment*. New York: Guilford Press, 2008, pp.185-208.
Clark LA, Watson D. *J Abnorm Psychol* 1991;100:316-336.



3

Why Use Psychotherapy for Anxious Depression

- Enhance treatment adherence
- Improve likelihood of remission
- May reduce risk of relapse



4

Why Use Psychotherapy for Anxious Depression

- Does not add to drug-drug interactions
- Target specific symptoms
- Provide coping mechanisms



5

Evidence for Efficacy of CBT for MDD

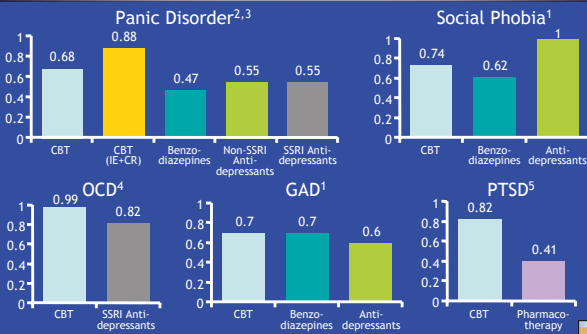
- Shown to be more effective than placebo/wait list
- Shown to be as effective as medications, especially in mild to moderate depression
- May be as effective as medications in severe MDD
- Shown to have relapse prevention effects
- ALONE or COMBINATION
- Though effective, many will not reach remission

Gloaguen V, et al. *J Affect Disord* 1998;49:59-72.
DeRubeis RJ, et al. *Arch Gen Psychiatry* 2005;62:409-416.



7

Evidence for Efficacy of CBT for Anxiety Disorders

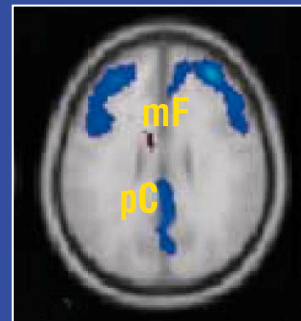


References available in supplemental bibliography section of course guide.



8

Brain Changes and CBT

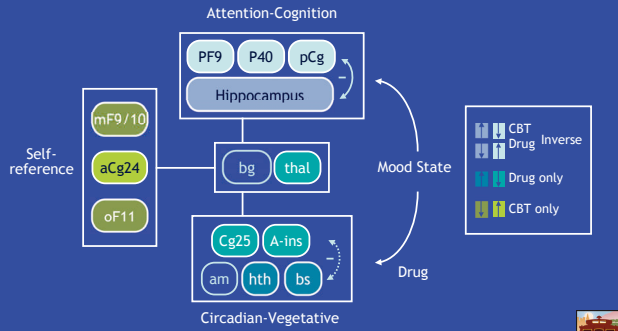


Goldapple K, et al. *Arch Gen Psychiatry* 2004;61:34-41.



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Brain Changes and CBT



Goldapple K, et al. *Arch Gen Psychiatry* 2004;61:34-41.

10

Cognitive Behavioral Therapy (CBT)

- Bi-directional relationship
- Test the accuracy of thoughts
- Behavioral component
- Cognition, behavior, and biochemistry are all important components of MDD and anxiety

Beck JS. *Cognitive Therapy: Basics and Beyond*. New York, NY: Guilford Press, 1995.

11

Are Anxiety Disorders More Disruptive to CBT for Depression than Depressive Disorders Are to CBT for Anxiety?

12

In Anxiety Treatment, We Could Imagine that Depression Would:

- Reduce motivation
- Impair concentration
- Impact habituation patterns
 - New learning associated with exposure

Otto MW, et al. Panic disorder and social phobia. In: Whisman MA, ed. *Cognitive Therapy for Complex and Comorbid Depression: Conceptualization, Assessment, and Treatment*. New York: Guilford Press; 2008: pp.185-208.
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Abramowitz JS, et al. *Behav Ther* 2000;31:517-528.
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13

Yet, This Might Not Be the Case

- Many studies suggest a resilience
- Depression often improves with CBT for anxiety disorders
- Improvements in anxiety mediate improvements in depression

Otto MW, et al. Panic disorder and social phobia. In: Whisman MA, ed. *Cognitive Therapy for Complex and Comorbid Depression: Conceptualization, Assessment, and Treatment*. New York: Guilford Press; 2008: pp.185-208.



14

Anxiety Impacts Depression Treatment

- Makes it more challenging to treat¹
- In one study, patients with a history of anxiety disorders were less likely to complete psychotherapy compared to patients with MDD alone²

1. Fava M, et al. *Psychol Med* 2004;34:1299-1308.
2. Brown C, et al. *Am J Psychiatry* 1996;153:1293-1300.



15

Tailoring CBT for Anxious Depression

17

Start With...

- A detailed, thorough clinical interview
- Remember, misclassification of symptoms can lead to failed treatment
- High risk for personality pathology

Farabaugh A, et al. *Compr Psychiatry* 2005;46:266-271.



18

Conceptualization

- Over the course of treatment, attempt to frame for the patient the anxiety and depressive symptoms per their relationship with one another



19

Conceptualization (cont.)

- Is the anxiety or avoidance contributing to the core beliefs?
- Is the depression interfering with exposure and increasing avoidance?
- Patient's attributions are key



20

Things to Consider...

- Treat concurrently or sequentially
- Measurement-guided care
- Track suicidal ideation
- Track side effects



21

Summary

- Make early gains
- Consider skills that are helpful to both conditions
- Collaborate with the patient
- Don't overlook anxiety

Otto MW, et al. Panic disorder and social phobia. In: Whisman MA, ed. *Cognitive Therapy for Complex and Comorbid Depression: Conceptualization, Assessment, and Treatment*. New York: Guilford Press; 2008: pp.185-208.



22

Summary (cont.)

- Accurate diagnosis
- Conceptualization
- Integration of psychosocial and pharmacological approaches to establish remission
- Don't forget, depression and anxiety typically go hand in hand and will indeed influence the treatment!



23

Panel Discussion/Q&A



Maurizio Fava, MD
(Chair)

Amy Farabaugh, PhD

Audrey Tyrka, MD, PhD

John M. Zajecka, MD



24

Supplemental Bibliography

Slide Title: Evidence for Efficacy of CBT

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