Psychiatry for the Practicing Internist

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Disclosures

- Research: Principal Investigator/Clinical Trials-Alkermes, Neurocrine, Supernus
- Speakers Bureau: Janssen Pharmaceutical
- Stockholder: None
- Other Financial Interest: None

Objectives

- Discussing aspects of the pathophysiology of Depression and Anxiety Disorders.
- Discuss the role of inflammation in the pathophysiology of Depression and Anxiety
- Identify Depression as a risk of morbidity and mortality in Cardiovascular, Diabetes, and Gastrointestinal Illnesses.
- Discuss Treatment aspects in Depression and Anxiety to Reduce morbidity and mortality in patients with comorbid Chronic Medical Illnesses

Six in ten adults in the US have a chronic disease and **four in ten adults** have two or more.

















 Heart disease, cancer, and diabetes are the leading causes of death and disability in the United States.

National Center for Chronic Disease Prevention and Health PromotionNovember 19, 2018

90% of the nation's \$3.3 trillion in annual health care expenditures are for people with chronic and mental health conditions.^{1,2}



Page last updated: February 11, 2019

Content source: National Center for Chronic Disease Prevention and Health Promotion

Mental and Physical Health

- Mental and physical health are equally important components of overall health.
- Mental illness, especially depression and anxiety, increases the risk for many types of physical health problems, particularly longlasting conditions like stroke, type 2 diabetes, and heart disease.
- Similarly, the presence of chronic conditions can increase the risk for mental illness.

How common are mental illnesses?

- Mental illnesses are common health conditions in the US.
- More than 50% will be diagnosed with a mental illness or disorder at some point in their lifetime.
- 1 in 5 Americans will experience a mental illness in a given year.
- 1 in 5 children, either currently or at some point during their life, have had a seriously debilitating mental illness.
- 1 in 25 Americans lives with a serious mental illness, such as schizophrenia, bipolar disorder, or major depression.

Salud Mental En PR Antes del Huracan Maria







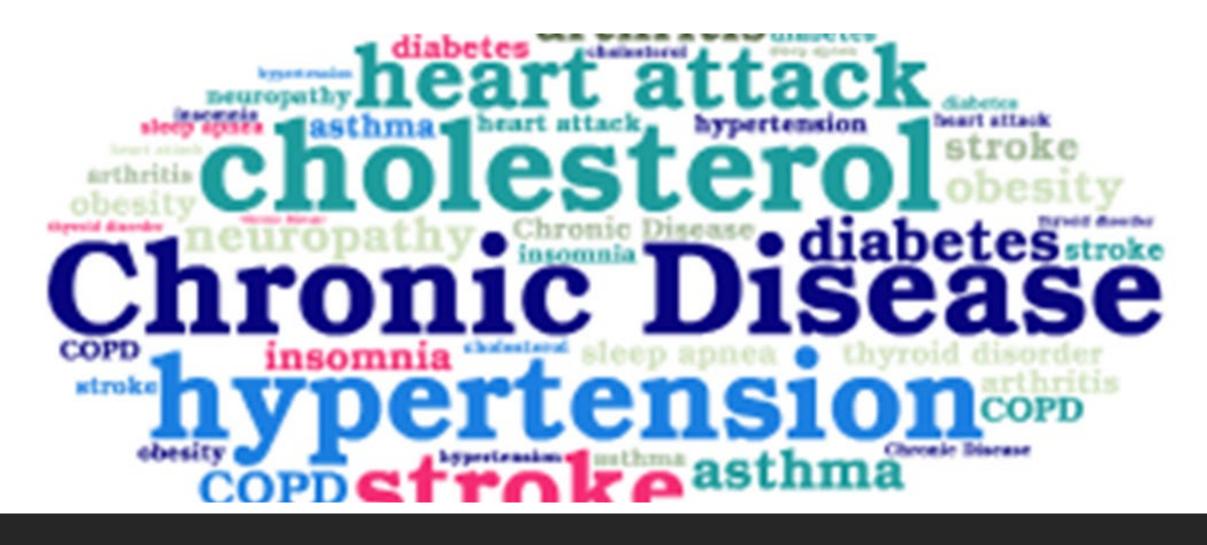
Estudio por la **investigadora Glorisa Canino**, del Instituto de Investigación de Ciencias de la Conducta del RCM, por encomienda de la Administración de Servicios de Salud y Contra la Adicción (ASSMCA).

El estudio fue realizado entre el año **2014 y 2016**

Los datos se revelaron en Enero 2017

DATOS REVELADOS POR EL ESTUDIO:

- 165,497 personas en Puerto Rico padecen alguna condición seria de salud mental.
- 7.3 % de los adultos puertorriqueños entre 18 y 64 años padece de una condición mental seria en Puerto Rico
- De ese total, el 23.7 % combina alguna condición mental con abuso de drogas y alcohol
- 18.8 % padece de alguna condición psiquiátrica
- 36.1 % no recibe servicios
- 9.7 % padece de algún trastorno depresivo severo
- 6.3 % cumplen con algún criterio de desorden de **fobia** social
- 5.2 % cumple con algún desorden generalizado de ansiedad



Chronic Illnesses and Mental Health

People with chronic medical conditions have a higher risk of depression

Depression is common among chronic illnesses such as:

- Cancer
- Coronary heart disease
- Diabetes
- Epilepsy
- Stroke
- Multiple sclerosis

- Alzheimer's disease
- HIV/AIDS
- Parkinson's disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Osteoporosis

The reverse is also true:

the risk of developing medical illnesses is higher in people with depression.



Implications of Comorbid Depression/Anxiety

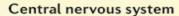
- Increased somatic symptoms, eg, multiple pain complaints
- Excess functional disability
- Increased morbidity/mortality
- Increased healthcare utilization and costs
- Poor self-care
- Decreased adherence to treatment regimens
- Higher drug interaction potential due to polypharmacy
- Increased use of substances



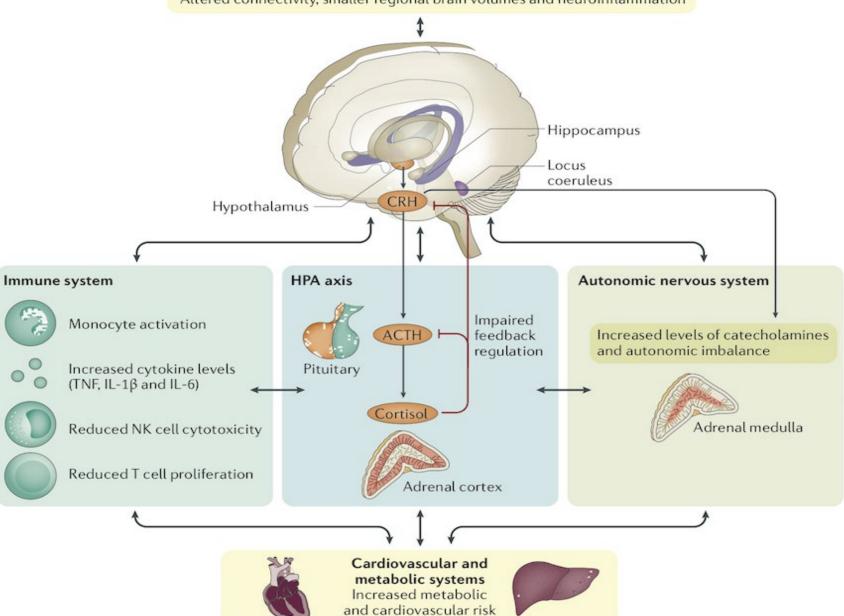
Neurobiology

Neurobiology of Anxiety and Depression

- Neurotransmitters Imbalance-Serotonin, NE, Dopamine
- Increased Glutamate/Decreased GABA
- Signs of increased inflammation
- Abnormalities in stress hormones-Cortisol
- Metabolic changes typical of those seen in people at risk for diabetes



Altered neurotransmission, reduced plasticity and impaired neurogenesis Altered connectivity, smaller regional brain volumes and neuroinflammation



HPA Axis

Temporal Lobe Trontal Lobe Amygdala Hippocampus Brain Stem

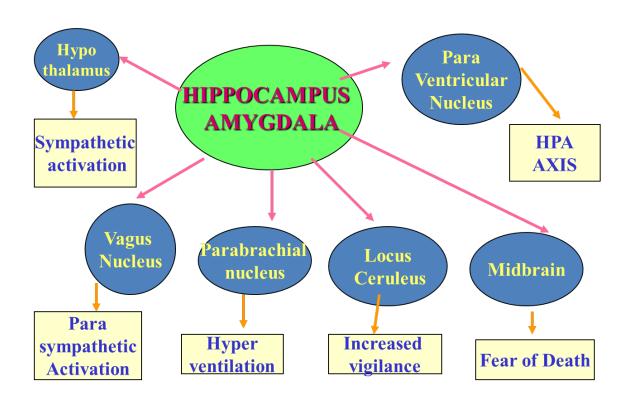
prefrontal cortex inhibits the amygdala

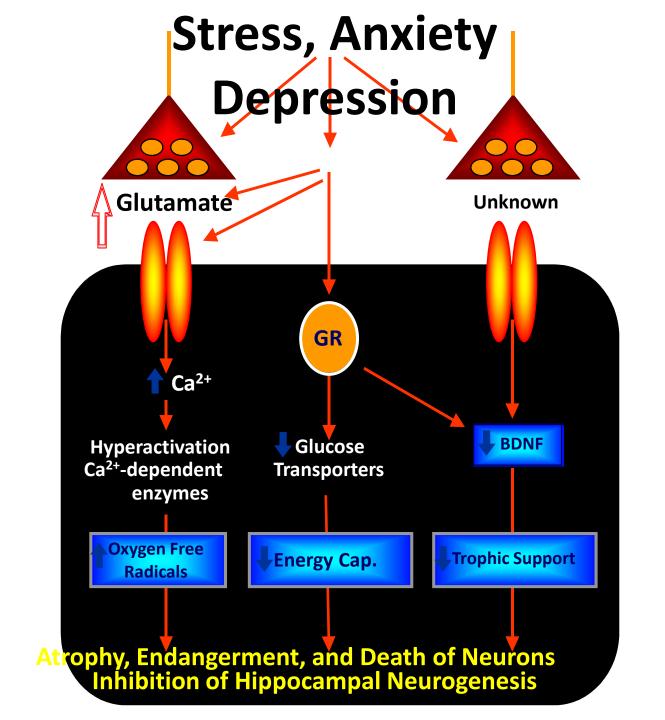


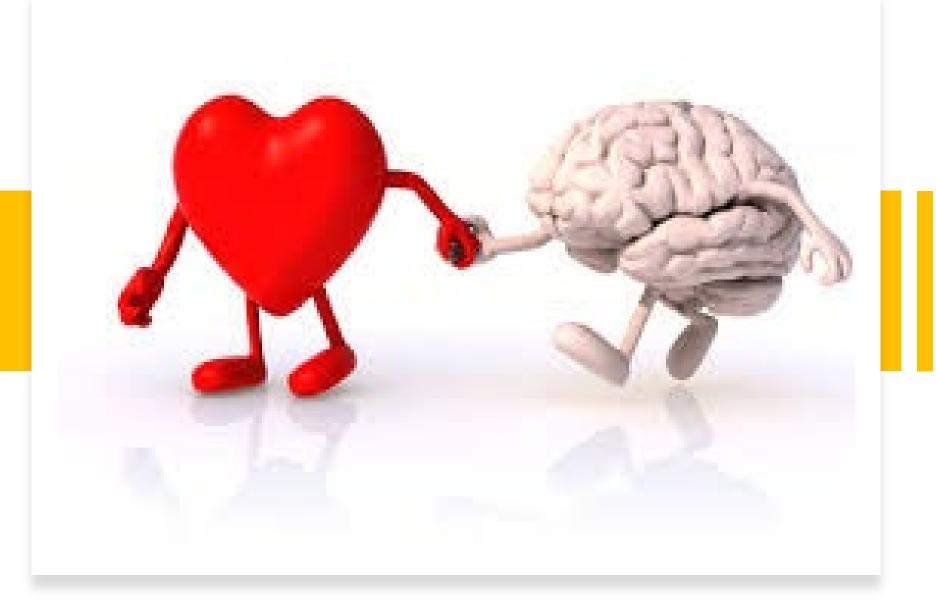
The mPFC, OFC, and ACC all inhibit amygdalar activity

When these structures are dysregulated, amygdalar activity is less modulated by the prefrontal cortex: anxiety and emotional responses are less controlled; fear may be more easily aroused

Neurobiology of Anxiety



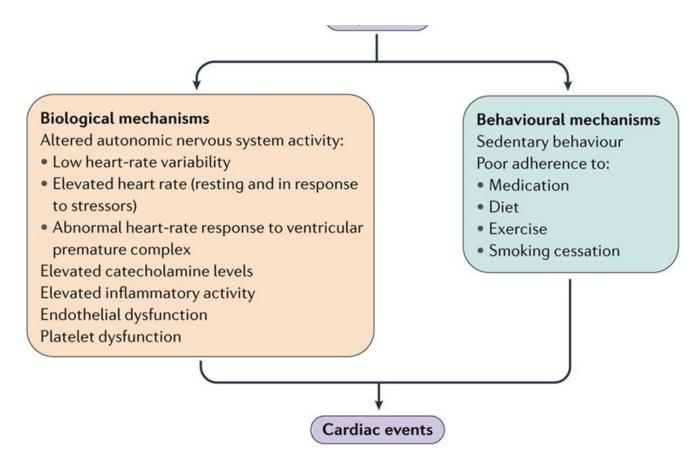


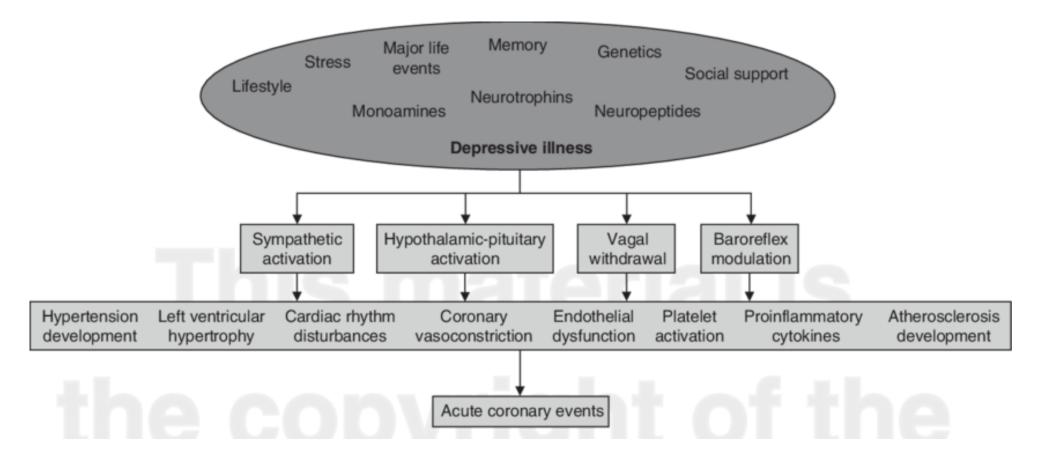


Mental Health and Cardiovascular Disease

The relationship between depression/anxiety and CVD is bidirectional

- Prevalence of depression in CVD pts is 3x than general population.
- 80% higher risk of developing new or worsening CVD and death from CVD in adults with depression with or without prior CVD.
- Depression is common in pts who have angina and can increase risk of developing myocardial infarction, stroke, sudden death, and atrial fibrillation





Cardiovascular Abnormalities in Patients with Major Depressive Disorder - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Depression-and-the-heart-possible-mechanisms-increasing-cardiac-risk-Recent fig4 26316903

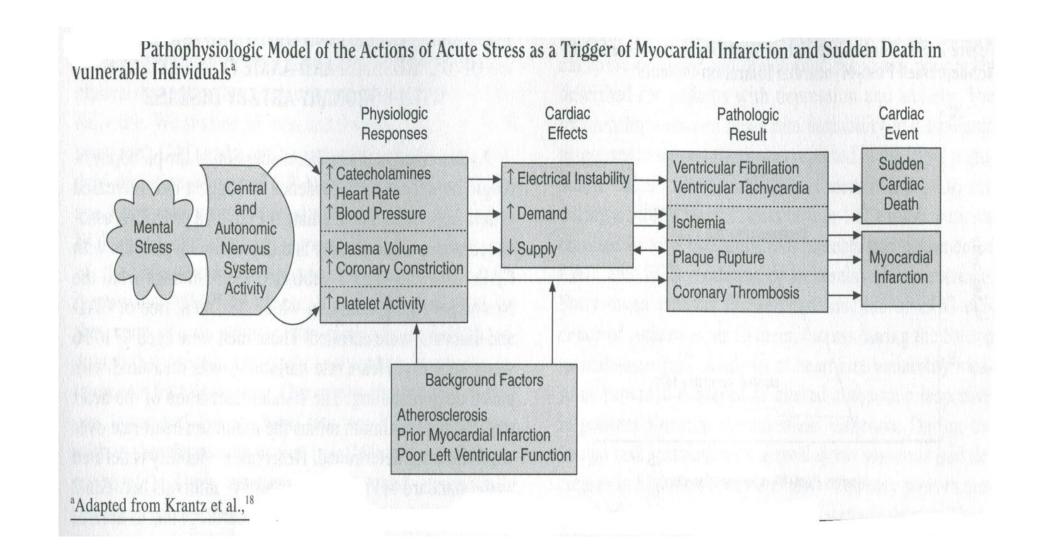
Depression and CAD

- The American Heart Association has concluded that **depression can** accelerate atherosclerosis.
- Depression promotes the onset and severity of the coronary risk factors of diabetes, hypertension, and high levels of low-density lipoprotein.
- The American Heart Association recognizes Depression as a major risk factor for coronary heart disease, similar to hyperlipidemia, diabetes, hypertension, and smoking.

Anxiety and CVD

- General anxiety about daily tasks, even if criteria GAD are not met, and psychological distress, including anger and stress, promote and precipitate cardiovascular diseases.
- The effect may be progressive, more episodes of anxiety, anger, and stress are associated with higher risk of cardiovascular diseases.
- Symptoms include chest pain, despite normal coronary arteries and palpitations even in the absence of structural or functional heart diseases.

Conceptual Model of Pathophysiology of Stress in Coronary Artery Disease

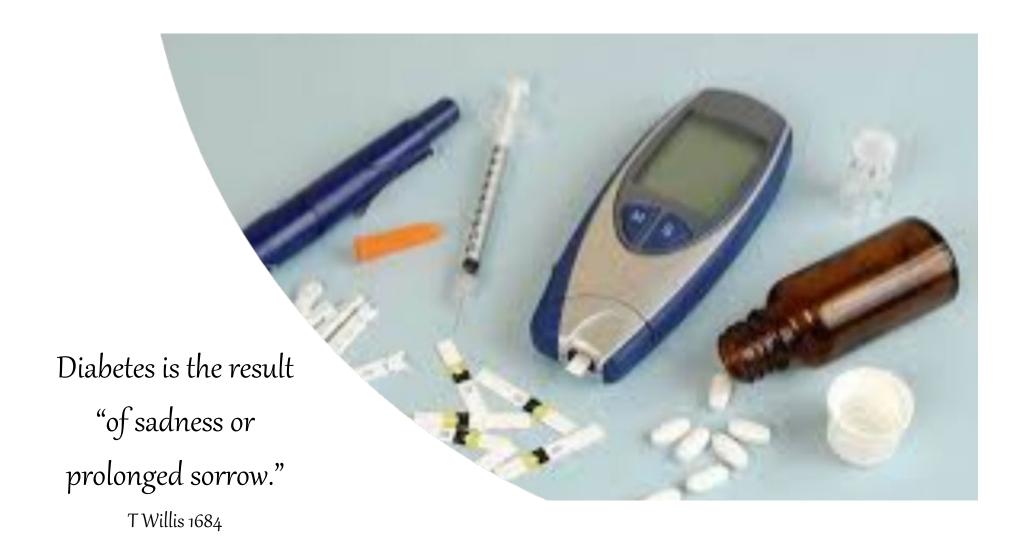


Panic Disorder is Not Benign

- Increases risk of **hypertension** by 1.91
- Increases risk of **heart attack** by 4.5
- Increase risk of **stroke** by 11.95



Diabetes and behavioral illnesses



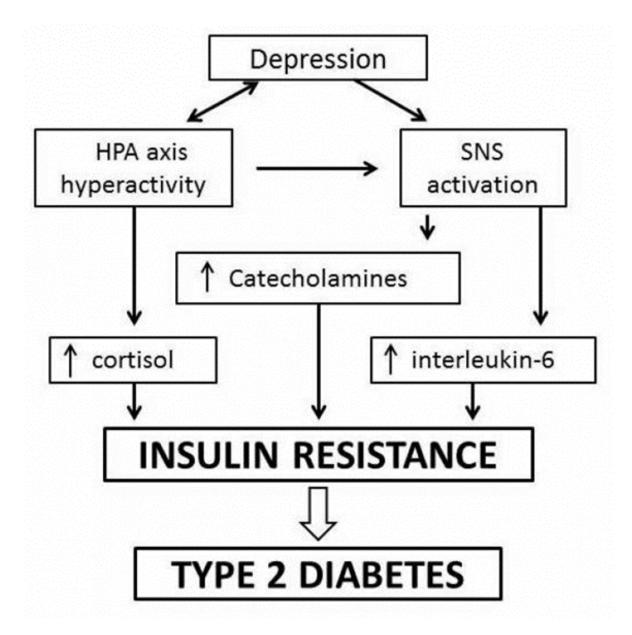
Cortisol dysregulation: the bidirectional link between

stress, depression, and type 2 diabetes mellitus

Joshua J. Joseph and Sherita H. GoldenANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: The Year in Diabetes and Obesity REVIEW ARTICLE 2017

- HPA axis dysfunction has been cross-sectionally associated with diabetes, independent of depression
- HPA axis abnormalities represent a shared pathogenic mechanism leading to both disorders.





Depression and Diabetes

- Depression and depressive symptoms increase risk for progressive insulin resistance and incident diabetes.
- Coexisting **MDD** and diabetes are high with 10–15% of individuals with diabetes suffering from depression.
- Depression in **diabetic individuals is 2x** those of the nondiabetic comparison groups.
- Prevalence of **comorbid depression** was significantly higher in: diabetic women (28%) vs. diabetic men (18%) uncontrolled (30%) vs. controlled (21%) studies clinical (32%) vs. community (20%) samples self-report questionnaires (31%) vs. standardized diagnostic interviews (11%)

Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus Joshua J. Joseph and Sherita H. Golden ANNALS OF THE NEW YORK ACADEMY OF SCIENCES Issue: The Year in Diabetes and Obesity REVIEW ARTICLE 2017

Diabetes and Depression

- 20 studies over past 10 years, prevalence rate of diabetics with major depression is 3-4x than in general population.
- A 2004 Johns Hopkins study tracking 11,615 initially nondiabetic adults aged 48-67 over six years found that "depressive symptoms predicted incident type 2 diabetes."
- Depression in diabetics is a greater risk factor for heart disease than high blood sugar.
- According to CDC, depressed adults have 37% increased risk of developing type 2 diabetes.
- ADA-Prevalence of clinically significant psychopathology diagnoses are considerably more common in people with diabetes than in those without the disease. .

Diabetes and Depression Recommendations

- **Annual screening** of all patients with diabetes, especially those with history of depression recognizing further evaluation for individuals who have a positive screen.
- Routine screening for depressive symptoms in gestational diabetes mellitus, and postpartum diabetes.
- At diagnosis of complications or when there are significant changes in medical status, consider assessment for depression.
- Referrals for treatment of depression should be made to mental health providers.
- History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes, especially if the individual has other risk factors such as obesity and family history of type 2 diabetes.
- Regardless of diabetes type, women have significantly higher rates of depression than men.



Why is Depression in Diabetes Serious?

Depression in diabetes is very concerning for several reasons:

- Individuals who are depressed may have more difficulty following the medical treatment. For example, depressed persons might not take their medication as prescribed or monitor their glucose levels as recommend.
- Individuals who are depressed **might adopt unhealthy behaviors**, such as a sedentary lifestyle and/or a poor diet.
- **Social isolation** is also common for people who are depressed, which decreases opportunities for social support that is often needed for self-management of diabetes.

Untreated depression in diabetes can result in

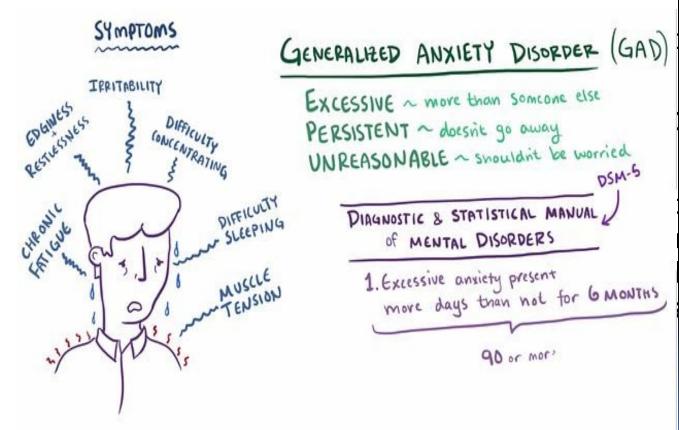
- Hyperglycemia
- Poor metabolic control
- Decreased quality of life
- Increased health care usage and costs
- Increased risk of mortality

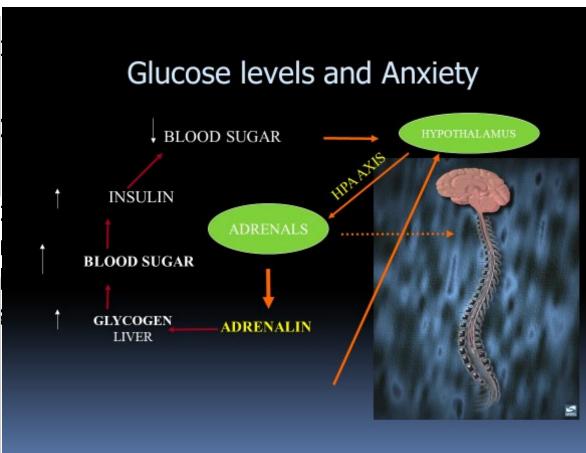




Anxiety Disorders and Diabetes

Anxiety Disorders







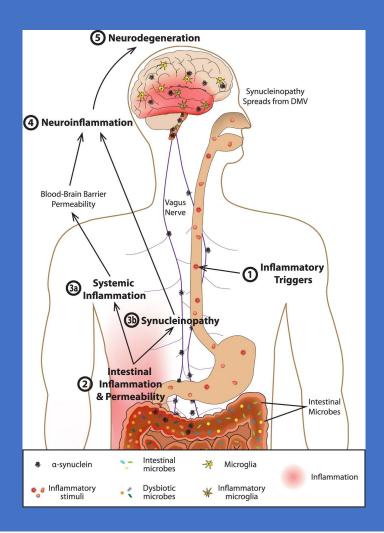
Anxiety and Diabetes

- Common diabetes-specific concerns include fears related to hypoglycemia, not meeting blood glucose targets, and insulin injections or infusion.
- Onset of complications presents another critical point when anxiety can occur.
- People with diabetes who exhibit excessive diabetes self-management behaviors well beyond what is prescribed or needed to achieve glycemic targets may be experiencing symptoms of obsessivecompulsive disorder.



The brain and the immune system continuously signal each other, often along the same pathways, which may explain how state of mind influences health

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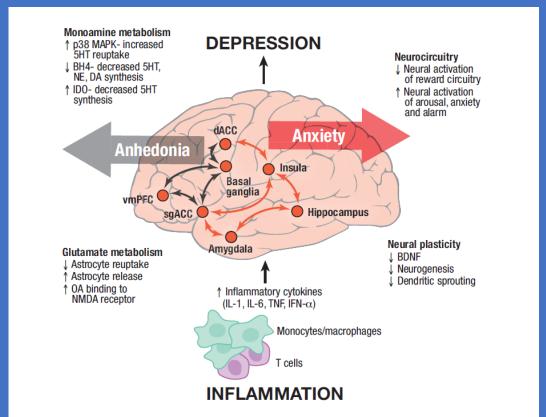
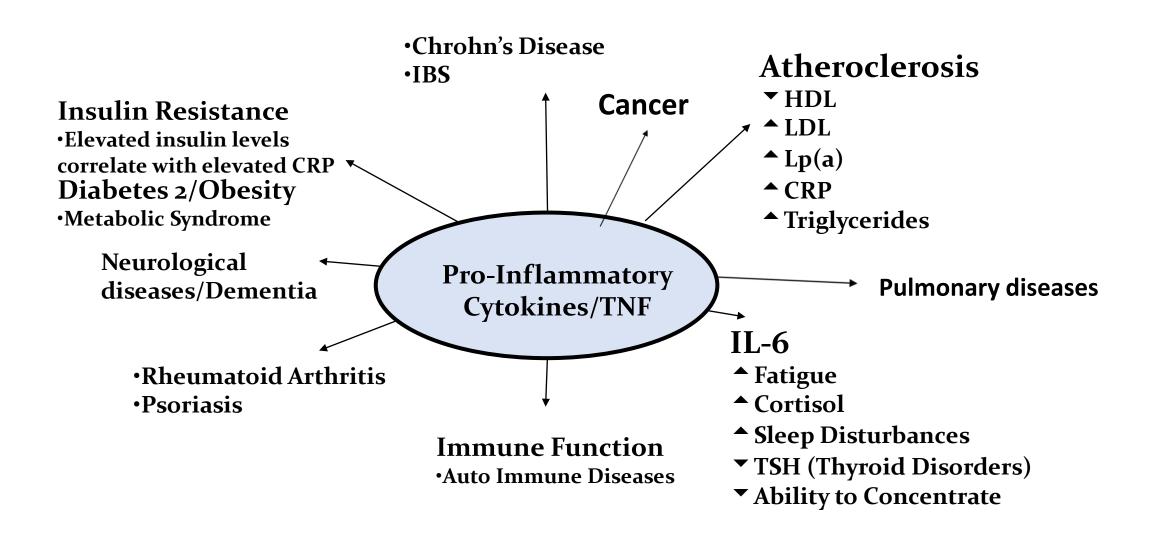


Figure Impact of inflammation on the brain and behavior

5HT, serotonin; BDNF, brain derived neurotrophic factor; BH4, tetrahydrobiopterin; DA, dopamine; dACC, dorsal anterior cingulate cortex; IDO, indoleamine 2,3 dioxygenase; IFN-interferon; IL, interleukin; MAPK, mitogen activated protein kinase; NE, norepinephrine; NMDA, N-methyl-D-aspartate; QA, quinolinic acid; sgACC, subgenual anterior cingulate cortex; TNF, tumor necrosis factor.



Cytokines and HPA Axis Alteration

Mental Health and Inflammation

- Negative mental states can trigger inflammation, thereby increasing the risk of disease.
- Depressive sxs are associated with increases in IL-6, an inflammatory protein that predicts cardiovascular events.
- Effects of pro-inflammatory cytokines on neurogenesis in the hippocampus have direct action of pro-inflammatory cytokines on the serotonin system
- Action of cytokines on the HPA Axis
- Potential anti-inflammatory effects of antidepressant and antidepressant effects of antiinflammatory treatments.

Inflammation is elevated in depressed people



Depressed pts have elevated inflammatory markers-- interleukin-6 and C-reactive protein.



Levels of proinflammatory cytokines correlate with the severity of depressive symptoms in studies.



Inflammatory cytokines released peripherally might reach the brain through active transport, passage through leaky regions in the blood-brain barrier, or transmission through afferent nerve fibers (vagus nerve).

Inflammation and Depression

- Chronic inflammation damages endothelium and increases coagulability, thereby increasing depressed people's risk of heart attack and stroke (Kop & Gottdiener, 2005; Robles et al., 2005).
- Researchers induced behavioral changes that resemble Major Depression in human and animal studies with administration of proinflammatory cytokines.
- Some therapeutic cytokines cause **depression**. **Interferon-**[alpha] is a potent inducer of the inflammatory cytokine network, especially IL-6.

Inflammation and Anxiety

- Animal studies suggest stress-induced increase in catecholamines stimulate release of monocytes from bone marrow.
- These monocytes encounter danger- or microbial-associated molecular patterns derived from **stress-induced alterations in metabolism or microbial products from the gut that in turn activate inflammatory signaling** pathways such as nuclear factor κB (BF-κB) leading to TNF and IL-6 as well as the inflammasome, which leads to the production of IL-1.
- TNF activate microglia to produce MCP-1, attracting monocytes to the brain notably in areas that regulate fear and anxiety including the amygdala.

Strong link seen between depression, inflammation
Clinical Psychiatry News June 2006 Andrew H. Miller, MD professor
Dpt of Psychiatry and Behavioral Sciences at Emory University
Five Things to Know about Inflammation and depression, Andrew Miller Psychiatric Times April 2018

Proinflammatory Cytokines Induce Sickness Behaviour

- Fatigue
- Loss of appetite
- Sleep disturbance
- Social withdrawal
- Decreased libido
- Depressed mood
- Decreased Cognition
- General malaise
- Aches and pains



Chronic Medical Illnesses and Psychiatry

Diagnosis And Treatment Considerations



Depression is underdiagnosed in the medical setting

2 Questions to Screen for Depression

- In the past month, have you felt down or depressed?
- In the past month, have you lost interest in things you usually do?

PHQ-9

Patient Health Questionnaire PHQ-9

Nine Symptom Checklist (Spanish)

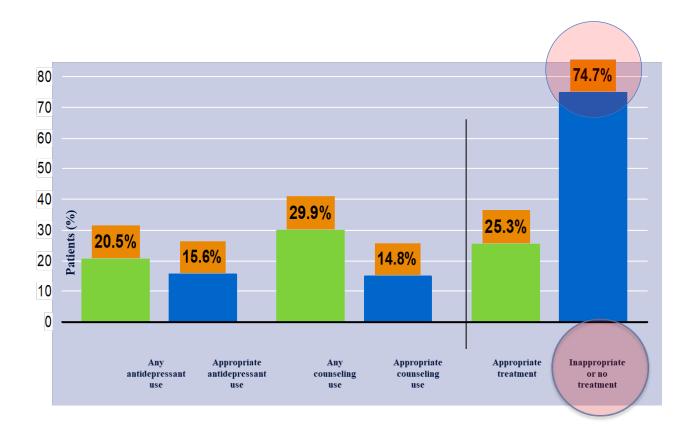
No	mbre Médico		Fecna L	е ноу	_
1.	Durante las últimas 2 semanas, ¿cuan qué frecuencia le han	molestado	los sigui	entes probler	nas?
		Nunca 0	Varios dias	Más de la mitad de los dias 2	Casi todos los dias 3
a.	Tener poco interés o placer en hacer las cosas				,
	Sentirse desanimado/a, deprimido/a, o sin esperanza	П	П	П	П
	Con problemas en dormirse o en mantenerse dormido/a, o en dormir demasiado				
d.	Sentirse cansado/a o tener poca energía				
e.	Temer poco apetito o comer en exceso				
f.	Sentir falta de amor propio – o que sea un fracaso o que decepcionara a si mismo/a su familia				
g.	Tener dificultad para concentrarse en cosas tales como leer el periódico o mirar la televisión				
h.	Se mueve o habla tan lentamente que otra gente se podria dar cuenta – o de lo contrario, esta tan agitado/a o inquieto/a que se mueve mucho más de lo acostumbrado				
i.	Se le han ocurrido pensamientos de que sería mejor estar muerto/a o de que haría daño de alguna manera*				
2.	Si usted se identificó con cualquier problema en este cues con su trabajo, atender su casa, o relacionarse con otras Nada en absoluto Algo difícil Muy difícil	tionario, ¿c personas d	cuan difíc ebido a es	il se le ha hec tos problema	cho cumplii
3.	Si estos problemas le han causado dificultad, ¿le han causa Sí, he tenido dificultad con estos problemas por dos			s años o más	s?
	\square No, no he tenido dificultad con estos problemas por	dos años c	más.		
	tiene pensamientos de que es major estar muerto/a o hacerse daño en a a de emergencia o llamar al 911.	ilguna manei	ra, favor de	hablar con su	médico, ir a u
	Number of symptoms:	T-4-1 -	core:		

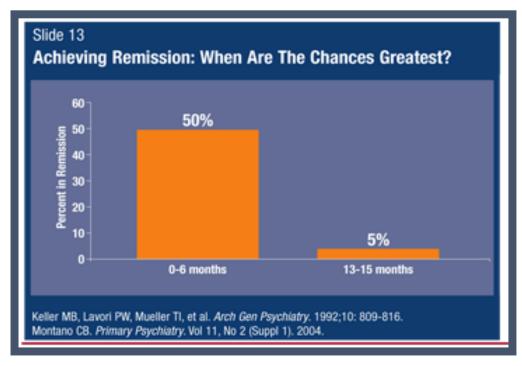
PHQ9 Copyright © Pfizer Inc. All rights reserved. Reproduced with permission. PRIME-ME ® is a trademark of Pfizer Inc May be photocopied for non-commercial use in physicians' offices.

Escala de Trastorno de Ansiedad GAD7

	Cuestionario de síntomas del Trastorno de Ansiedad Generalizada	SI		
1.	¿Se encuentra usted más nervioso y tenso de lo habitual?			
2.	¿Se encuentra usted más inseguro, aprensivo o irritable que de costumbre?			
3.	¿Ha estado preocupado por situaciones cotidianas o simples que antes no le importaban?			
4.	¿Es usted incapaz de relajarse o tiene demasiada inquietud interna que no logra controlar?			
5.	¿Ha sentido miedo de situaciones que normalmente no se lo provocaban?			
6.	¿Ha tenido dificultades para conciliar o mantener el sueño durante la noche?			
7.	¿Ha tenido últimamente problemas de concentración o memoria?			
8.	¿Ha sentido sus músculos más tensos, rígidos o dolorosos?			
9.	¿Se ha sentido más fatigado y débil que de costumbre?			
10.	¿Ha sentido palpitaciones, sensación de ahogo, temblores u hormigueos en su cuerpo?			
11.	¿Ha tenido molestias digestivas pasajeras o episodios de diarrea que usted relacione con los estados de ansiedad?			







Earlier Antidepressant Treatment Yields Higher Remission Rates

Pooled analysis of original data from the initial 8 double-blind, randomized registration RCTs* of 2,045 depressed patients

Kelsey JE, Entsuah R. Int J Neuropsychopharmacol. 2002;5(suppl 1):S207. Abstract P.4.W.031.

[†]Fluoxetine, paroxetine, fluvoxamine.

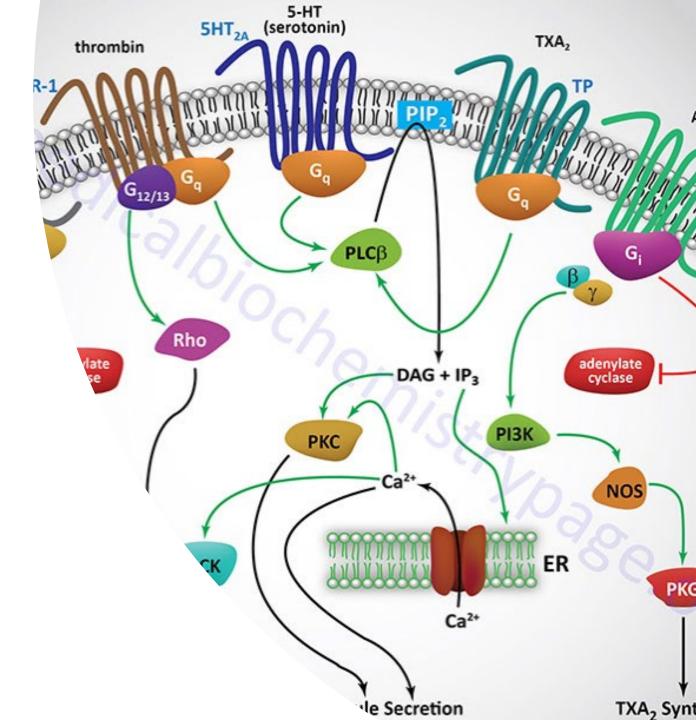
 $^{^{\}ddagger}P$ □ 0.05 drug vs. placebo.

P = 0.05 venlafaxine/venlafaxine XR vs. SSRI.

Antidepressants in CVD

- Most studies on cardiovascular effects of different types of SSRIs have emphasized neutralized or even beneficial cardioprotective effects of SSRIs especially newer generations on cardiovascular system. (Nezafati MH, Vojdanparast M, Nezafati P. Antidepressants and cardiovascular adverse events: A narrative review. ARYA Atheroscler. 2015;11(5):295-304).
- Sertraline Antidepressant Heart Attack Randomized Trial (SADHART)
 demonstrated sertraline improved depression in acute coronary syndrome.
 Safety of sertraline in the CHD group was evidenced in this study.
- The ENRICHD trial showed that antidepressant treatment improved CHD prognosis

- The SADHART platelet sub study showed a decreased platelet activation in those patients who had suffered an MI, were depressed, and had it treated with a SSRI (sertraline).
- Paroxetine has also been shown to decrease platelet hyperactivity.
- SSRIs have been shown to decrease sympathetic hyperactivity and, as a consequence, potentially reduce cardiac morbidity and mortality.



- In the review by Skala et al, it was shown that antidepressant medication can positively alter physiological pathways linking MDD and CHD. (Coronary heart disease and depression: a review of recent mechanistic research Skala JA, Freedland KE, Carney RM 2006 Oct; 51(12):738-45).
- Sympathetic over activity is important in causality of CHD, and reductions in sympathetic activity have been shown following SSRI treatment.
- SSRIs are not without their flaws, and it has been noted that some induce weight gain and metabolic abnormalities.



- Venlafaxine-Ho et al.35 reviewing records of 48,876 elder patients receiving venlafaxine showed low to moderate doses had no adverse cardiovascular events. (Coronary heart disease and depression: a review of recent mechanistic research Skala JA, Freedland KE, Carney RM 2006 Oct; 51(12):738-45).
- Duloxetine-Xue et al. showed no difference in the rate of AEs between depressed patients treated with duloxetine and untreated ones. (Coronary heart disease and depression: a review of recent mechanistic research Skala JA, Freedland KE, Carney RM 2006 Oct; 51(12):738-45).
- Bupropion-8058 smokers w/ or w/o psychiatric diagnoses. No significant AE's reported in blood pressure, heart rate, or other cardiovascular events. (Published in Primary Care)



- The **TCAs**(amitriptyline, imipramine, doxepin) and **MAOIs** are generally **avoided** in those who have comorbid cardiac conditions because of their toxic cardiac side effects.
- TCAs associated with **elevated relative risk of 1.24 for CHD** and increased mortality rates in CHD.
- Amitriptyline usage is associated with significant prolongation of QRS and QTc as well as increased in heart rate while little change in BP. (Coronary heart disease and depression: a review of recent mechanistic research Skala JA, Freedland KE, Carney RM 2006 Oct; 51(12):738-45).

Antidepressants in Diabetes

- Antidepressant use is associated with improved glycemic control in type 2 diabetes pts and receiving treatment for depression, according to a cohort study(2008-2013) by Brieler et al (U of saint Louis published in Family Practice).
- The average A1c was lowest among patients with treated depression and was highest among those with untreated depression.
- The percentage of patients who achieved good glycemic control (ie, hemoglobin A1c <7.0%)
 was highest in the treated depressed group and lowest for the untreated depressed group.

Antidepressants and Diabetes

- In depressed DM type2 pts, SSRIs are favorable effects on glycemic control.(Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults Deuschle, Michael Current Opinion in Psychiatry: January 2013 - Volume 26 - Issue 1 - p 60–65)
- SSRIs-some studies suggest contribute to Type 2
 Diabetes.(Antidepressant Medication as a Risk Factor for Type 2
 Diabetes and Impaired Glucose Regulation Systematic review
 Katharine Barnard, PHD, Diabetes Care)
- Bupropion-no increased appetite, can improve sexual function.(Bupropion Improves Sexual Function in Type 2 Diabetes OBGYN.net Staff Mar 2, 2011)
- TCAs appear to increase cravings and increase FBG levels.(Use of Antidepressants in Treatment of Comorbid Diabetes Mellitus and Depression as Well as in Diabetic Neuropathy Paul J. Goodnick Annals of Clinical Psychiatry 2001)

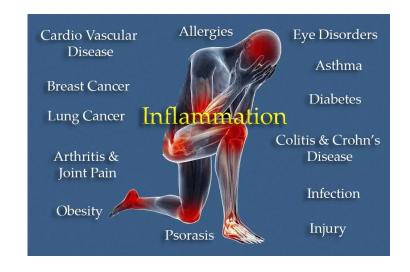
Antidepressants in Youths and Diabetes

In cohort study of youths insured by Medicaid who initiated treatment with antidepressant medications, indicates that there was a greater risk of incident type 2 diabetes for those currently using SSRIs or SNRIs than for those who formerly used these medications.

The risk of type 2 diabetes intensified with increasing duration of use, cumulative dose, and average daily dose. (Burcu M, Zito JM, Safer DJ, et al. Association of antidepressant medications with incident type 2 diabetes among Medicaid-insured youths. JAMA Pediatr. 16 Oct 16 2017. doi:10.1001/jamapediatrics.2017.2896)

Antidepressants and Inflammation

- Statistical analysis revealed significant decreases of IL-4, IL-6, and IL-10 in MDD subjects after antidepressant treatment.
- In case of IL-1ß the decrease was significant exclusively for SSRI drugs.





- Chronic depression may increase risk of cardiovascular diseases and diabetes.
- Depressive illness is an important cause of morbidity and disability in CVD and Diabetes.
- Brain states that produce mental illness also tend to activate inflammation which worsens CVD and Diabetes.
- Inflammation is equally capable of producing depression, anxiety, fatigue, and cognitive difficulties.
- Antidepressants are safe and effective in CVD and Diabetes.
- Antidepressant could decrease inflammatory factors.
- Depression and Anxiety should be screened in patients with CVD and Diabetes and Inflammatory Diseases.