

# SAD HEART

by

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- Introduction
- Bible verses
  - Isaiah 43:2 – When you pass through the waters, I will be with you; and through the rivers, they shall not overflow you. When you walk through the fire, you shall not be burned, nor shall the flame scorch you.
  - II Chronicles 16:9 – For the eyes of the Lord run to and fro throughout the whole earth, to show Himself strong on behalf of those whose heart is loyal to Him.
- depression and heart disease
  - Heart disease is the number one cause of death in America.
  - Depression is a risk factor for heart disease (2-fold risk of coronary heart disease with depression).
  - Depression and heart disease are related.
  - Depression is one of the leading causes of disability.
  - Depression is a risk factor for cardiac arrhythmia from increased ANS (autonomic nervous system) activity.
  - Depression is a risk factor for blood clots (↑ platelet aggregation), and MI's (myocardial infarction).
  - Depression is a risk factor for arteriosclerotic heart disease (ASHD); ↑C-reactive protein and thus ↑arteriosclerosis; read further for details on interleukin 1, 2, and 6, and TNF (tumor necrosis factor)
  - Depression is a risk factor for cardiac arrest (dysfunction of ANS); 4 fold risk increase of recurrent cardiac events and death with depression.
  - Depression is a risk factor for myocardial infarction (MI) from ↑inflammatory cytokines and C-reactive proteins.
  - Depression is a risk factor for indirect suicide through indirect self-destructive behavior (ISDB):
    - smoking
    - physical inactivity
    - medical noncompliance
  - Depression is a risk factor for direct suicide:
    - 35,000 suicides per year in the USA; suicide is the 12<sup>th</sup> leading cause of death.
    - Indirect suicide through indirect self-destructive behavior (ISDB) causes many more deaths than direct suicide.
  - Depression is a risk factor for coronary heart failure (CHF) from
  - neurohormonal activation.
  - Depression is a risk factor for coronary heart disease (CHD) at 35% and, CHD is a risk factor for depression; bidirectional activity.
  - 20% - 30% of patients with CHF (chronic heart failure) are depressed.
  - Depression is a risk factor for ↑cortisol which ↓BDNF (brain derive neurotropic factor), and thus neuronal death.

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- Depression is a risk factor for hyperactivity of hypothalamic-pituitary axis (HPA).
- Depression is a risk factor for adrenal hypertrophy and thus ↑cortisol (adrenal cortex) and ↑NE (adrenal medulla).
- Depression is a risk factor for ↑sympathetic activity and thus, ↑NE (norepinephrine) and thus ↑HR (heart rate) and ↑arrhythmias.
- Depression is a risk factor for ↑weight which ↑CHD.
- Suggestions for patients with depression and CHD:
  - Decrease negative intimate relationships (NIRs). A NIR ↑cardiac events by 1/3; work on conflict resolution.
  - Decrease stress at job if possible (high demand, low latitude jobs ↑cardiac events).
  - Consider SSRIs (Celexa, Lexapro, Zoloft); talk with your medical doctor.
  - Decrease stress which ↓inflammation in coronary arteries. Stress is a risk factor for MI (myocardial infarction).
  - Seek an accountability friend to decrease indirect suicide habits (smoking, low exercise, high cholesterol diet, high triglyceride diet, medical noncompliance)

#### Depression and coronary heart disease (CHD) – details

- Depression is an independent risk factor for CHD.
- CHD is the leading cause of death and disability in the USA.
- CHD patients have depression (35% - 15% MDD and 65% depressive symptoms).
- Thus, there is a bi-directional relationship between CHD and depression.
- Depression increases all courses of cardiac mortality – MI, CHF (congestive heart failure), SCD (sudden cardiac death).
- Depression ↑inflammatory processes.
  - ↑platelet activation → ↑platelet adhesiveness.
  - ↑CRP (Creative protein) → ↑plaques.
  - ↑interleukin 6
  - ↑tumor necrosis factor (TNF)
- Psychotherapy did not help according to CREAT (Canadian Cardiac Randomized Evaluation of Antidepressants and Psychotherapy Efficacy) and ENRICHD studies.
- Psychopharmacology may help (quality of life) according to SAD HART study; ENRICHD said it may ↓risk of death. Considerations from good to possibly dangerous include:
  - Citalopram (Celexa), and escitalopram (Lexapro) – low P450 involvement
  - Venlafaxine (Effexor) – low P450 involvement, low anticholinergic side-effects. Can ↑BP at higher doses
  - Zoloft (sertraline)
  - Trazadone (Desyrel) – can ↓BP but overall good drug for many
  - Mirtazepine (Remeron) – can ↓BP and ↑weight
  - Bupropion (Wellbutrin) – overall good but watch BP

- Duloxetine (Cymbalta) – moderate to potent inhibitor of P450 2D6 so caution with beta blockers and 1-c antiarrhythmic drugs, also watch BP
- TCAs – anticholinergic, antiadrenergic, antihistamine effects, sinus tachycardia, tachyarrhythmias, ventricular tachycardia, prolongation of PR, QRS, QT intervals, first, second, and third degree heart block, ST-T wave changes
- MAOI – fatal adrenergic crisis possible

#### ASHD (arteriosclerotic heart disease) and stress

- Psychological factors that increase ASHD are:
  - negative intimate relationships (NIR). Those with NIR are 1/3 more likely to have a cardiac event such as a MI or severe chest pain.
  - Job stress – high demand (amount of work and intellectual difficulty) jobs with low latitude (freedom to make decisions) increase cardiac risk.
  - Chronic stress increases inflammation in the coronary arteries resulting in blood clots that cause heart attacks. Chronic stress also increases unhealthy health habits and decreases healthy habits; both increase ASHD.

#### Depression and coronary heart disease (CHD)

- Depression often ↑CHD
- Depression is linked to ↑weight, ↑DM (diabetes mellitus), and ↑smoking all of which ↑CHD.
- Depression ↑noncompliance with heart medications and diet which ↑CHD.
- Depression is associated with a 2-fold increase risk for CHD.
- Depression, stress, and life events ↑risk of MI (myocardial infarction) more than ↑BP, DM, and obesity.
- Depression is associated with a 4-fold risk of recurrent cardiac events and death.
- Depression is associated with ↑5HT<sub>2</sub> receptor binding and ↑density of platelet 5HT<sub>2</sub> receptors, ↑platelet reactivity, ↑platelet aggregation with ↑thrombus formation; thus, depression and CHD are linked.

#### Depression ↑the inflammatory response with:

- ↑TNF (tumor necrosis factor)
- ↑interleukin (IL-1, IL-2, IL-6) – proinflammatory cytokines
- ↑C-reactive protein (CRP)
- the above inflammatory markers are linked to CHD (CHF or congestive heart failure, ASHD, MI, stroke).
- Statins ↓Creactive protein (CRP)

#### Depression ↑ HPA (hypothalamus, pituitary, adrenal) axis which:

- ↑CRF or corticotropin releasing factor (hypothalamus)
- ↑cortisol (adrenal cortex) increased cortisol is associated with CHD

- ↑catecholamines (NE and E) – catecholamine ↑vasoconstriction and volume expansion in acute state, but chronic vasoconstriction and volume expansion results in CHF.
- ↑sympathetic activity → ↓parasympathetic activity → ↑CHD → ↑vulnerability to arrhythmia and sudden death.

Depression – MDD (major depressive disorder) – various details

- 10% of men will have MDD.
- 20% of women will have MDD.
- MDD is usually recurrent.
- 30% of MDD people have an episode lasting > 2 years.
- MDD ↑ the morbidity and mortality of:
  - CVD (cardiovascular disease)
  - Chronic pain
  - DM (diabetes mellitus)
  - Respiratory illnesses
- MDD antidepressant remission rate is 30%.
- MDD antidepressant response rate is 50%-70%.
- Discontinuation of antidepressants is due to:
  - sexual dysfunction
  - weight gain
  - perceived lack of efficacy
- In Star D
  - 30% remission with citalopram 40mg in level 1
  - 70% remaining went to level 2
    - augmentation with bupropion or buspirane =30% response
    - switch to bupropion, venlafaxine, or sertraline =20% response
  - non-remitters in level 2 → level 3
    - augmentation with T3 = 25% remission or LiCo<sub>3</sub> = 16% remission
    - switch to nortriptylene =20% remission or mirtazepine = 12% remission
  - Thus, augmentation strategies were more effective than switching.
- Another augmentation strategy to consider is L-methylfolate
  - L-methylfolate is a trimonamine modulator
  - L-methylfolate acts as a regulator of B4 (tetrahydrobiopterin) important in D and NS synthesis
  - Low serum and red blood cell (RBC) folate levels are associated with ↓ response to antidepressant therapy.
  - L-methylfolate lowers homocysteine that is associated with depression, dementia, and stroke
  - L-methylfolate helps convert homocysteine to methionine then to SAMe the methyl donor of all 3 biogenic amines
- Low serum folate causes include:
  - A genetic polymorphism (C677T – the MTHFR gene) in 50% of the US population; the T/T genotype is in 22% of Hispanic or

Mediterranean, 10% of whites, and 70% of depressed patients; the C/T and T/T polymorphisms are less functional forms that result in less L-methylfolate.

- Poor dietary intake
  - DM (diabetes mellitus)
  - Various GI disorders
  - Hypothyroidism
  - Nicotine dependency
  - Coffee
  - Alcoholism
  - Cigarette smoking
  - Renal failure
  - Medications – lamotrigine (Lamictal), methylprednisone, sulfasalazine (Asulfidine), cholestyromine (LoCholest, Questran), colchicines, colestipol, isotretinoin (Accutane), panalatic enzymes, pentamidine, triamterene, trimethoprim (Primisol), pyrimethamine, first generation anticonvulsants, oral contraceptives, NSAID for pain, metformin (Glucophage) for diabetes, LiCO<sub>3</sub>
  - L-methylfolate is a cofactor in the synthesis of the monoamine neurotransmitters (serotonin, norepinephrine, dopamine).
  - Folate is a water soluble B vitamin (B9); it is one of the 13 essential vitamins: it transfers methyl and formyl groups; it is essential for cell reproduction, the utilization of proteins, the formation of nucleic acids, and several CNS reactions.
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    - ↑ sympathetic activity → ↓ parasympathetic activity → ↑ CHD → ↑vulnerability to arrhythmia and sudden death.
  - Depression impaired arterial endothelial function; impaired endothelial function is a marker of CHD.
  - Treatments of comorbid depression and CHD have been studied in:
    - SADHART (Sertraline Antidepressant Heart Attack Randomized Trial)
    - ENRICH (The Enhancing Recovery in Coronary Heart Disease Patients)
    - CREATE (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficiency)
    - MIND-IT
  - The best treatments tried in comorbid depression and CHD have included:
    - sertraline (Zoloft)
    - paroxetine (Paxil)
    - citalopram (Celexa)
  - TCAs are often not chosen because they:
    - ↑ orthostatic hypotension
    - ↓ cardiac conduction
    - ↑ ventricular arrhythmias with OD
    - ↑ widening of QT, QRS, P-R on EKG
  - Conclusions of antidepressives in CHD:
    - they are reasonably safe
    - they are reasonably effective
    - they have not been shown to improve cardiac outcomes
    - they improve functioning and quality of life
  - In summary, depression increases CHD by increasing inflammatory markers (TNF, interleukins, or CRP) and increasing hormones/neurotransmitters (cortisol, CRF, catecholamines).
- Conclusion
- Bible verses
  - Isaiah 43:2 – When you pass through the waters, I will be with you; and through the rivers, they shall not overflow you. When you walk through the fire, you shall not be burned, nor shall the flame scorch you.
  - II Chronicles 16:9 – For the eyes of the Lord run to and fro throughout the whole earth, to show Himself strong on behalf of those whose heart is loyal to Him.

# Resources

- Minirth Clinic – for outpatient care and **individualized retreats**  
[www.minirthclinic.com](http://www.minirthclinic.com)  
972-669-1733 or 1-888-MINIRTH (646-4784)
- Hearts of Love International Ministry (for pastors and Christian workers)  
[www.holinternational.org](http://www.holinternational.org)
- Hope Line – for inpatient and partial hospitalization care in Denton and El Paso, Texas  
1-888-789-HOPE (4673)
- Celebrate Recovery – local Churches  
[www.celebraterecovery.com](http://www.celebraterecovery.com)
- AACC – American Association of Christian Counselors  
[www.aacc.net](http://www.aacc.net)
- [www.2ndfiddleentertainment.com/maggiespassage](http://www.2ndfiddleentertainment.com/maggiespassage)
- Retreat for Women and Girls  
[www.christmascreekvillage.com](http://www.christmascreekvillage.com)
- To obtain books written by Frank Minirth:
  - Books available only through the Minirth Clinic:
    - Psychopharmacology 2010, 600 pages
    - The Reflective Genius (obsessive compulsive disorder) 225 pages
    - Grace In Salvation (difficult to understand Bible passages on salvation) 250 pages
  - Other Minirth books available through [www.amazon.com](http://www.amazon.com)