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Depression and the Risk of Coronary Artery Heart Disease in the Elderly

ABSTRACT & COMMENTARY

Source: Ariyo A, et al. Depressive symptoms and risks of coronary heart disease and mortality in elderly americans. *Circulation* 2000;102:1773-1779.

Depression occurs in 19-30% of all elderly patients and only 1% of those so effected receive the necessary treatment for this serious illness.[1,2] Many published studies have suggested that abnormally high depression scores may predispose an individual to an increased risk of developing coronary heart disease (CHD) especially in middle-aged populations, but data regarding the relationship between depression and CHD in the elderly have been sparse.[3,4]

Ariyo and colleagues in the Cardiovascular Health Study Collaborative Research Group have now published the results of a multicenter study that started in 1989 evaluating cardiovascular risk factors in 5888 Americans aged 65 and older. No evidence of CHD was present at baseline in the 4493 participants who subsequently provided annual information regarding their depressive tendencies, which were assessed by using the Depression Scale of the Center for Epidemiological Studies. These subjects were followed for six years and, in each case, the cumulative mean depression score was assessed and correlated with all cardiovascular events and/or CHD deaths. Among participants with the highest cumulative mean depression scores, the risk of CAD increased by 40% and risk of death by 60% compared with those individuals who had the lowest mean depression scores.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Many previously published studies have demonstrated that depressive symptoms constitute a risk factor for CHD[3-7] and CHD mortality.[4,6-8] However, the data presented by Ariyo et al differ from previously reported studies because they focused exclusively on the elderly. There now seems to be little question that depressive symp-

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toms constitute an independent risk factor for the development of CHD and total mortality in the elderly and, in addition, this risk appears to increase for those individuals who score higher on the Depression Scale.

The results of the reported study could have been influenced by depression produced by other events such as life-threatening illnesses, which are obviously more common in the elderly. Equally important, it should be noted that participants with prior cardiac disease were excluded at the onset so there appeared to be an independent relationship between the depressive symptoms and subsequent cardiovascular events. The prospective nature of this study, the large sample size, the duration of follow-up, and the blinded ascertainment of cardiac events all tend to make the final results even more impressive. As an aside, it should be noted that the results were similar in men and women even though women had higher depression scores at the beginning of the study.

Multiple theories have been advanced as to why depression would be associated with CHD risk. For example, it has been speculated that depressed individuals frequently exercise less, smoke more, and have a higher likelihood of indulging in anxiety-provoking behavior patterns, all of which may increase cardiovascular risk. It has also been speculated that depression produces anxiety, which may result in an increase in autonomic sympathetic activation.[9,10] Many published papers have suggested that there is an inter-relationship between depression and abnormal lipid/glucose metabolism,[11,12] which may encourage the earlier development of CHD. Finally, sudden deaths associated with depressive states have been attributed to an imbalance between the autonomic parasympathetic and sympathetic nervous systems resulting in increased sympathetic activity and induction of lethal ventricular arrhythmias.[13]

The importance of the data presented by Ariyo et al is obvious in that 31 million Americans are 65 or older and, in this group, 5 million are afflicted with depressive symptoms. Between 7-12% of men and 20-25% of women will develop a major depressive episode during their lifetime. The strong relationship between depression and CHD demonstrated in this study makes it mandatory for all primary care physicians to familiarize themselves with the relationship and to vigorously treat depression with drugs and/or psychotherapy early after the onset of depression, much before cardiovascular symptoms and/or sudden cardiac death occur. It would appear that treating this very important risk factor may be equally important as is treating an abnormal lipid panel, or as is advising patients to discontinue cigarette smoking, to bring their weight down to ideal levels, and/or to initiate a regular exercise program. In other words, treating depressive symptoms in the elderly should not be overlooked since such therapy is obviously incredibly important in preventing the onset of symptomatic CHD or even sudden cardiac death in the elderly. *(Dr. Karpman is Clinical Professor of Medicine, UCLA School of Medicine, Los Angeles, Calif.)* ❖

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Testosterone and Sexuality

ABSTRACT & COMMENTARY

Source: Shifren JL, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682-688.

Shifren and colleagues report the results of a multi-center trial examining the effect of transdermal testosterone treatment in 75 women who had undergone oophorectomy and hysterectomy. All of the subjects were receiving daily estrogen therapy. They were randomized to placebo and patch treatment with either 150 mg testosterone or 300 mg testosterone daily. Duration of the study was 12 weeks. Outcome measurements were determined for sexual functioning and psychological well-being. Results were available for 65 women after 18 withdrawals. The 300 mg transdermal dose of testosterone was associated with a statistically significant increase in the scores for sexual functioning in the following categories: composite score, frequency of sexual activity, and pleasure-orgasm. The psychological well-being scores significantly increased with the 300 mg dose in the following categories: composite score, depressed mood, and positive well-being. Hirsutism and acne scores did not change during treatment, but one would not expect to see an effect within 12 weeks. There were no significant effects on the lipid profile, but again, this was only a short-term study. Shifren et al concluded that transdermal testosterone improves sexual function and psychological well-being.

COMMENT BY LEON SPEROFF, MD

For a long time, there has been no doubt that pharmacologic amounts of testosterone can increase sexuality and perhaps psychological well-being in women who have experienced surgical menopause. An important unanswered question has been whether treatment with testosterone to produce relatively normal testosterone levels, that is, normal for reproductive age women, would produce any beneficial effects. Shifren et al concluded that transdermal testosterone improves sexual function and psychological well-being. However, it is clear to me that this observation was limited to the high-dose treatment. Within the paper, Shifrin et al argues that the 300 mg transdermal treatment, the high-dose treatment, increased free testosterone levels to what they called high normal values. This is derived from their interpretation of the free testosterone levels as being within the normal range. Both the 150 mg and 300 mg transdermal treatments increased free testosterone levels. The average free testosterone level with the 150 mg treatment was 3.9 pg/mL, and it was 5.9 pg/mL with the 300 mg transdermal treatment. Total testosterone levels increased to a normal range with the 150 mg dose, but exceeded the normal range of 20-80 ng/dL with the 300 mg dose.

The sexual and psychologic effects achieved with the lower dose, 150 mg, were equal to those achieved with placebo. This emphasizes two things: the need for placebo controls in studies of this nature, and the powerful placebo response most individuals experience.

A statistically significant beneficial effect was demonstrated only with the higher dose that, in my view, produced pharmacological levels of circulating testosterone. The long-term consequences of such levels are at this time unknown, but presumably one would expect an effect on cardiovascular disease. There also exists a concern that aromatization of testosterone within breast tissue might produce exceptionally high estrogen levels and affect the risk of breast cancer. I would expect with time that the higher dose treatment would be associated with a significant percentage of hirsutism and acne. In the discussion, Shifren et al attribute the elevated testosterone levels to the effect of the concomitant treatment with estrogen raising sex hormone-binding globulin (SHBG). However, the increase in free testosterone levels indicates the SHBG effect was overwhelmed by the treatment.

In most women, sexual dysfunction is due to psychological problems. In those women in whom clinician and patient decide testosterone treatment is worthwhile, data thus far indicate that only super physiological testosterone can produce sexuality and psychological effects. In the absence of data on long-term consequences, I am reluctant to promote this pharmacologic use of testosterone. I have used an approach in my own patients in which we agree to monitor testosterone levels and to maintain levels within the normal reproductive range of 20-80 ng/dL. This study would support the contention that treatment associated with those levels is yielding mainly, if not totally, a placebo response. There is nothing wrong with that, especially if the patient is happier, and I am certainly happier in being comfortable that long-term adverse consequences would be less likely at those levels. The transdermal testosterone method of treatment helps provide us with an option that is easily monitored by testosterone levels. *(Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health sciences University, Portland, Ore.)* ❖

Death Be Not Proud

ABSTRACT & COMMENTARY

Source: Wilson KG, et al. Attitudes of terminally ill patients toward euthanasia and physician-assisted suicide. *Arch Intern Med* 2000;160:2454-2460.

Wilson and associates carefully recruited a group of patients who were dying of cancer. Because many of the potential patients for this study were too ill or died before they could be interviewed, they were able to offer participation to 150 subjects, 80 of whom declined to be interviewed. Their final sample was 70 patients. This group of 70 had a mean age of 64.5 years, consisted of 32 men, and was highly educated. A total of 41% were Roman Catholic, 41% were Protestant, and 17% were "none" or "other." As would be expected, the leading kind of cancer was lung (21%), followed by GU (19%), female breast (13%), gastrointestinal (13%), and head and neck (10%). The mean survival of this group was 44.5 days after the interview; only 15% lived as long as six months.

The interviews were audiotaped for later content analysis, and were conducted by clinical psychologists, doctoral students in psychology, or research associates in palliative care. Interviewers solicited participants' views about euthanasia and physician-assisted suicide (PAS), both in general, and with regard to the subject's personal situation. Euthanasia was defined as a situation in which "a medical doctor gives an overdose of medication to purposely end a patient's life. This is only done with patients who have asked their doctor to help them die in this way. Usually, the patients involved are very ill with a life-threatening disease." PAS was defined as an action in which "a medical doctor provides drugs and advice, so that a patient could commit suicide. The doctor does not actually inject the drugs, but rather gives the patient the means to end his or her own life."

Seventy-three percent of the patients believed that euthanasia or PAS should be legalized, with pain and the individual's right to choose as the main reason. Those who thought these actions should not be legalized cited religious or moral reasons. Fifty-eight percent of the participants said that they might personally request such a procedure if it were legal, particularly if pain or physical symptoms became intolerable. Eight of the 70 participants would have made such a request at the time of the interview: four of these had major depression, two had comorbid anxiety disorders, and one had major depression in remission. Of those who would consider asking for hastened death, euthanasia was preferred to assisted suicide.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Like it or not, this is a hot topic. I found 4812 articles in the National Library of Medicine published since 1966 using the key word "euthanasia," limited to human subjects. I found 487 web sites using the keyword "euthanasia." Euthanasia and PAS are legal in The Netherlands, the Australian Northern Territory, and Oregon. In a recent national telephone survey, 15.8% of 56 oncologists had performed euthanasia or PAS.[1] In six of the patients involved in this report, the patient did not participate in the decision, and in only about one-third of cases did the physicians adhere to all three of the proposed safeguards: 1) having the patient initiate and repeat the request for euthanasia or PAS; 2) ensuring the patient was experiencing extreme physical pain or suffering (although all the patients were receiving narcotic analgesia); and 3) consulting with a colleague. In a mail questionnaire of 1902 physicians, Meier and colleagues found that 11% were willing to hasten a patient's death even with the current legal constraints, and 18.3% reported having received a request for assistance with suicide from a patient.[2] Approximately 3.3% reported writing at least one prescription and 4.7% reported administering at least one lethal injection.

In the current report, patients reported the following reasons that there should be at least limited legal access to euthanasia or PAS: individual's right to choose, pain, diminished quality of life, suffering, hopeless situation, mental symptoms, burden for others, physical symptoms other than pain, and knowledge of others' experiences.

In previous reports, pain has been a significant negative factor in studies of end-of-life care.[3-5] Bereaved family members cite inadequate pain control (and access to physician's time!) as significant problems with end-of-life care.[4] However, neither a specific nurse intervention[3] nor patient empowerment and feedback[5] improved pain control in clinical trials. I suspect that sometimes physicians balk at giving adequate pain control if they believe that the medicine will hasten death. However, the American Medical Association's Code of Ethics endorses doing exactly that, if the primary purpose is to relieve pain or suffering. In "official" parlance, "Physicians have an obligation to relieve pain and suffering and to promote the dignity and autonomy of dying patients in their care." This includes providing effective palliative treatment even though it may foreseeably hasten death.[6]

Depression is also a significant and frequent finding in the terminally ill,[7-9] and there is some evidence that

depression is undertreated in terminal patients.[8] In the current study, the eight patients who would have requested PAS/euthanasia at the time of study were significantly more depressed than the other study patients, but there was no difference in their report of pain as a symptom. The article does not include information on antidepressant treatment of this group, though 24% of the 70 patients were on antidepressants.

Fear of being a financial burden is listed as a reason for PAS/euthanasia in some studies of terminal patients.[10] However, in the current study, the Canadian patients had access to state-funded palliative care services, at no personal financial cost.

This study and others spotlight the fact that we do not do a very good job with end-of-life care. My reading to prepare this commentary turned up documentation that we are perceived as inaccessible to terminal patients and their families, that we undertreat pain and depression, and that we sometimes expend vast resources for little benefit. As a result, patients and their families feel that they have lost control at the most vulnerable time in their lives. No wonder they request that it be ended!

The American Medical Association is attempting to address this problem with a program called Education for Physicians on End-of-Life Care (EPEC). You can learn more about this program by visiting the AMA web site at www.ama-assn.org and clicking on or searching for EPEC. This educational program is divided into 12 Modules and four Plenary Sessions, and includes modules on Pain Management, Physician-Assisted Suicide, and Withholding/Withdrawing Treatment. *(Dr. Phillips is Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington, Ky.)* ❖

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Hypnotic Activity of Melatonin

ABSTRACT & COMMENTARY

Source: Stone BM, et al. Hypnotic activity of melatonin. *Sleep* 2000;23(5):663-669.

The purpose of this study was to establish the effect of melatonin on sleep. Stone and colleagues conducted two experiments. In the first experiment, varying doses (0.1-10 mg) of melatonin were administered to eight healthy volunteers at 23:30. Sleep time was from 23:30 to 07:30. Core body temperature, sleep structure, and dim light melatonin onsets (DMLO) were measured. This study was placebo-controlled, double-blinded, and included a crossover comparison with temazepam (20 mg). Melatonin had no significant effect on sleep compared with placebo, but temazepam resulted in classic benzodiazepine-induced changes of increased sleep efficiency, increased stage 2 sleep, and increased rapid eye movement (REM) sleep latency compared with placebo.

In the second experiment, varying doses of melatonin were administered at 18:00, and sleep time was from 18:00 to 24:00. Core body temperature, sleep structure, and DMLO were measured. This study was also placebo-controlled and double-blinded, and included a crossover comparison with temazepam (20 mg). In this study, all doses of melatonin (range, 0.1-10 mg) increased total sleep time, sleep efficiency, and stage 2 sleep. There was an absence of dose response over the range of 0.5-10.0 mg. These changes were similar to those induced by temazepam.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH & CARL BOETHEL, MD

Melatonin is a pineal hormone that is secreted during darkness. In people with normal sleep-wake schedules, melatonin levels begin to rise approximately two hours before sleep, and begin to decline prior to the termination of sleep. There is a strong correlation between the time course of endogenous melatonin production and sleep propensity.[1] Further, daytime exogenous melatonin administration increases subjective sleepiness but impairs cognition.[2] Because melatonin is a "food supplement" not regulated by the FDA, rigorous testing of safety, efficacy, and dose-response curves has not been done. It appears that the dose response curve may be flat, with effects noted at extremely low doses (< 1 mg), and little increase in toxicity at extremely high doses (> 1000

g). Because of these properties, melatonin has been recently touted in the lay press as a cure for insomnia and sleep disorders associated with abnormal daytime sleep schedules such as shift work and jet lag.

In this report, Stone et al produce evidence that melatonin given at 23:30 has no significant clinical effect on nocturnal sleep in healthy good sleepers. However, they found that melatonin given at 6 pm (presumably before endogenous levels begin to rise) has immediate hypnotic activity similar to 20 mg temazepam. This suggests that melatonin is unlikely to result in useful hypnotic activity in healthy people when taken around the normal time of sleep, but may be beneficial for sleep induction for "out-of-phase" sleeping.

Another finding of this study is that doses of melatonin above 0.5 mg did not further improve sleep. We have learned something useful about dosing melatonin.

This study's findings may not be extrapolated to all populations. It is notable that Stone et al studied healthy young men, who had high baseline sleep efficiencies (92%) to begin with. But it strongly suggests that 0.5 mg of melatonin has an effect comparable to temazepam for sleep induction in the evening, which could be very beneficial to time zone travelers and shift workers. *(Dr. Boethel is a Fellow in Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Ky.)* ❖

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Special Feature

Screening for Domestic Violence: Who, What, When, Why, and How?

By Ellen L. Sakornbut, MD

Although the reported incidence of domestic violence varies, the literature indicates that violence issues are a common problem in women's health, as common (or more so) than other lifestyle and health problems that are a part of routine health screening. Despite this, domestic violence remains an area of silence between most patients and their physicians. A study of female patients in a Veterans' Administration ambulatory setting found 40% of women had experienced emotional or physical abuse by a partner and 7% were currently in abusive relationships, yet only 12% report being asked about violence by their physicians.[1] The majority of these women reported a willingness to talk about partner violence with their physician and an expectation that the physician would be an advocate.

Domestic violence is not confined to urban or low-income settings. Studies of women seen at family practice clinics in rural and medium-sized communities in the Midwest find a 34-39% lifetime rate of physical abuse, with 8-23% reporting abuse within the past year.[2,3] Although domestic violence may be more common in young women of low educational background, a relatively high rate (25%) of violence with the current partner has been found in an older population of women in a rural area.[4] Other identified risk factors are partner violence in the family of origin and substance abuse by the partner.[5] Domestic violence is a common finding in women treated for depression.[6]

Pregnancy health is affected by domestic violence. A study of women in public prenatal clinics found a 17% incidence of physical or sexual abuse during pregnancy; abused women were twice as likely as nonabused women to enter prenatal care in the third trimester.[7] Physical abuse during pregnancy has also been associated with poor outcomes such as preterm birth and placental abruption.

Acute injuries from domestic violence constitute from 15-35% of all emergency room visits by women. Up to 50% of all homicides in women are committed by a current or former partner. Many of these women have been seen in an emergency room setting within a year or two prior to the homicide.[8]

Physician Awareness and Behavior

Domestic violence education has become a requirement in undergraduate and graduate, medical education (postgraduate in some states), but domestic violence screening is not a routine part of practice for most physicians providing primary care to women. The U.S. Preventive Services Task Force did not recommend universal screening on the basis of clear evidence of benefit.[9] A large study in California suggested that physicians routinely screen injured patients for intimate partner abuse, but that most do not screen during routine checkups, prenatal care, or new patient visits.[10] This study found no difference in screening by gender of physician or recent training in partner violence. A physician survey about factors affecting screening rates cited lack of physician education in screening (34%) as a deterrent. Other factors that may affect the behavior of physicians include a belief that domestic violence is not an issue in one's patients (46%), a lack of time to deal with abuse (39.2%), and frustration at not being able to

help victims (34.2%). Physicians may mistakenly believe that domestic violence does not occur in patients of higher socioeconomic status, but a study of medical school students and faculty found that 17% of female faculty and students and 3% of male faculty and students have experienced partner violence during their adult life.[11]

Short-term physician behavior may be altered by education. An educational intervention for internal medicine residents resulted in significant increases of patients being asked about domestic violence.[12] Whether such an intervention will be effective in establishing a change in practice patterns is not clear. At the current time, there is no evidence that mandatory CME affects physician awareness and response to domestic violence. In one study of mandatory CME, the only positive predictor for likelihood of screening was the presence of a female physician in the practice.[13]

What do Patients Want?

The literature indicates that abused and nonabused women believe health care providers should screen for abuse. Less than 50% of victims have been screened by medical providers for partner violence.[14] Patients who have been abused believe that clinicians should ask more specific questions than women who have not experienced abuse.

Screening Methods

Structured screening methods may improve the detection rate of domestic violence. A study of pregnant women screened using a five-question Abuse Assessment Screen found significantly improved rates in detection of domestic violence as compared to standard interview at prenatal intake visits.[15]

A number of brief screening tools have been developed and validated in primary care settings. The HITS questionnaire is a four-item questionnaire that asks how frequently the patient was physically Hurt, Insulted, Threatened with harm, and Screamed at by the partner.[16] Other brief screening tools include the single question "Have you been hit, slapped, kicked, or hurt during this pregnancy?"[17] The WAST (Women Abuse Screening Tool) uses an initial shortened form that asks two questions about how much tension is present in the relationship and how much difficulty is experienced in resolving conflict with the partner. Positive responses to these questions are followed by administration of the other six questions in this screening instrument.[18]

Structure of a Screening and Treatment Plan

Universal screening for domestic violence may be adopted, although no outcome data are available on the effect of screening. If a strategy of selective screening is used, multiple clinical problems, including depression, unexplained symptoms, injuries, delayed prenatal care, and other psychosocial red flags should prompt more thorough inquiry. A screening tool is likely to be helpful, used in the same way that the CAGE instrument has been used in screening for alcoholism. Clinicians and office personnel should develop routine signals for separating patients and their partners briefly to facilitate screening. The first step in dealing with partner violence is to create a safe environment where patients may tell their story.

A study of physicians working with abuse victims identified these key components of care: giving validating messages that identify abuse as abuse; acknowledging that abuse is not justified; labeling abuse as wrong; listening in a nonjudgmental way to the woman's story; and documenting the history and physical signs of abuse.[19] Patients benefit from referral to community resources; it is unlikely that an individual physician has as much to offer as a team approach. A small business card with important contact numbers should be provided to patients (and may be displayed discreetly in the women's bathroom). In settings where the physician treats both the woman and her partner, ethical and strategic considerations may make it advisable for the physician to refer the partner to another clinician. ❖

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CME Questions

20. The following statements are true regarding sexuality and testosterone *except*:

a. Women who undergo surgical menopause have a more abrupt decrease in testosterone levels compared to women undergoing natural menopause.
b. Restoring reproductive age testosterone levels improves sexuality.
c. Possible long-term consequences of testosterone treatment include increased risks of coronary heart disease, breast cancer, hirsutism, and acne.
d. Circulating testosterone levels reflect the dose of testosterone administered by the transdermal method.

21. In terminal patients, pain control is:

a. rarely a problem.
b. enhanced by a nurse educator intervention.
c. improved by patient empowerment and feedback.
d. cited as a reason to consider physician-assisted suicide.
e. supposed to be limited if adequate pain control would hasten death.

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