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HIGHLIGHTS NOVEMBER 1999

11-1 RANDOMISED TRIAL OF OLD AND NEW ANTI-HYPERTENSIVE DRUGS IN ELDERLY PATIENTS: Cardiovascular Mortality and Morbidity: The Swedish Trial in Old Patients with Hypertension-2 Study

Old (diuretic and beta-blockers) and new (ACE inhibitors and calcium blockers) anti-hypertensive drugs were equally effective in preventing cardiovascular mortality or major events over 5 years in elderly patients with hypertension. Lancet November 20, 1999; 354: 1751-56

11-2 CONVENTIONAL VERSUS NEWER ANTIHYPERTENSIVE THERAPIES – A DRAW

The prudent cost-effective prescriber who has decided that thiazide diuretics should be first-line treatment for elderly hypertensive people, will be further encouraged by this and other studies. LANCET November 20, 1999; 1744-45

11-3 EVALUATION OF PROGNOSTIC CRITERIA FOR DETERMINING HOSPICE ELIGIBILITY IN PATIENTS WITH ADVANCED LUNG, HEART, AND LIVER DISEASE.

For seriously ill patients with chronic obstructive pulmonary disease, congestive heart failure, and end-stage liver disease, the recommended clinical prediction criteria were *not* effective in identifying individuals with a survival prognosis of 6 months or less. JAMA November 3, 1999; 282: 1638-45

11-4 HOW GRAVELY ILL BECOMES DYING: The Key to End-of-Life Care

The preceding study concluded that we cannot accurately predict duration of remaining life in seriously ill persons, many of whom "never experience a time during which they were clearly dying of their disease". "The sickest patients are not necessarily the ones who die first." JAMA November 3, 1999; 282: 1670-72

11-5 FACILITATION OF BENZODIAZEPINE DISCONTINUATION BY MELATONIN

Controlled-release melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality. Archives Intern Med November 8, 1999; 159: 2456-60

11-6 MELATONIN THERAPY: FROM BENZODIAZEPINE-DEPENDENT INSOMNIA TO AUTHENTICITY AND AUTONOM

"Choosing benzodiazepine-free treatment for insomnia can help patients sleep, dream, remember, and continue to have access to both the continuity of autobiographical memories relevant to authenticity and the procedural memories essential to autonomy." Archives Int Med November 8, 1999; 159: 2393-95

11-7 PERNICIOUS PAPILLOMA INFECTION

"In sum, cervical cancer often begins with the sexual transmission of HPV infection to a woman who is susceptible to persistent infection. Over time, the HPV lesions progress to invasive cervical cancer." NEJM November 25, 1999; 341: 1687-88

11-8 ANTI-INFLAMMATORY AND UPPER GASTROINTESTINAL EFFECTS OF CELECOXIB IN RHEUMATOID ARTHRITIS: A Randomized Controlled Trial

Celecoxib (*Celebrex*, a COX-2 inhibitor) was efficacious in treatment of rheumatoid arthritis and did not affect COX-1 activity in the upper GI tract mucosa as evidenced by less frequent ulcers compared with naproxin. JAMA November 24, 1999; 282: 1921-28

11-9 COX-1-SPARING NSAIDs – Is the Enthusiasm Justified?

Costs are high for the new COX-1-sparing NSAIDs. The extra protection they offer the stomach must be balanced against the cost on an individual basis. JAMA November 24, 1999; 282: 1961-63

11-10 TWICE DAILY VERSUS FOUR TIMES DAILY INSULIN DOSE REGIMES FOR DIABETES IN PREGNANCY

Giving insulin four times daily rather than twice daily improved glycemic control in pregnancy and perinatal outcome without further risking the mother. BMJ November 6, 1999; 319: 1223-27

11-11 AN UPDATE ON PERIOPERATIVE MANAGEMENT OF DIABETES

A review of pre- intra- and post-operative care. Perioperative management is generally more of an art than a clinical science. There are many protocols for management. Homeostasis during this period is highly variable and often unpredictable. Clinical judgement remains the key. Archives Int Med November 8, 1999; 159: 2405-11

11-12 REVERSAL OF IRON DEFICIENCY ANEMIA AFTER *HELICOBACTER PYLORI* ERADICATION IN PATIENTS WITH ASYMPTOMATIC GASTRITIS

In this cohort of adult patients with iron deficiency associated with chronic pangastritis due to *H pylori*, cure of the infection cured the anemia. Annals Int Med November 2, 1999; 131: 668-72

11-13 ADVERSE CHILDHOOD EXPERIENCES AND SMOKING DURING ADOLESCENCE AND ADULTHOOD.

Smoking was strongly associated with adverse childhood experiences. Primary prevention of adverse childhood experiences and improved treatment of exposed children could reduce smoking among both adolescents and adults. JAMA November 3, 1999; 282: 1652-58

11-14 EARLY ONSET DRUNK DRIVING, VIOLENT CRIMINALITY, AND MENTAL DISORDERS

"The younger the drunk driver is, the greater the probability is of the driver being a violent offender with co-morbid mental disorder." Lancet November 20, 1999; 354: 1788

11-15 CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF EXERTION-RELATED MYOCARDIAL INFARCTION

Exertion-related MI occurs predominantly during unaccustomed physical activity in habitually inactive individuals with risk factors. These results should reassure individuals who exercise regularly, and public health advocates of physical activity. Habitually inactive adults with elevated cardiac risk factors should avoid unaccustomed vigorous exertion. JAMA November 10, 1999; 282: 1731-36

11-16 PLATELET ACTIVATION WITH EXERCISE AND RISK OF CARDIAC EVENTS

An individual unaccustomed to habitual physical activity has about a 50-fold increase in the risk of sudden death and a 100-fold increase in risk of acute myocardial infarction when undertaking vigorous exercise – as compared with remaining at rest. Although physical fitness does not completely remove the risk of an event associated with vigorous exertion, it greatly reduces risk. Lancet November 20, 1999; 354: 1747-48

11-17 NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

This article reviews epidemiology, pathology, genetic basis, risk factors, renal failure, and treatment. NEJM October 7, 1999; 341: 1127-33

11-18 EFFECT OF NITRIC-OXIDE-GENERATING SYSTEM ON MICROCIRCULATORY BLOOD FLOW IN THE SKIN OF PATIENTS WITH SEVERE RAYNAUDS'S SYNDROME

In Raynaud's syndrome topical application of a nitric-oxide-generating system can stimulate an increase in both microcirculatory volume and flux. The NO generating gel was formed by mixing a solution of KY jelly and sodium nitrate with a solution of KY jelly and vitamin C. Lancet November 13, 1999; 354: 1670-75

11-19 ANTIBIOTICS AND *CLOSTRIDIUM DIFFICILE*

In addition to the second- and third-generation cephalosporins and clindamycin, ampicillin and amoxicillin are associated with the highest incidence. Quinolones, aminoglycosides, macrolides (especially the newer agents clarithromycin and azithromycin), vancomycin, and extended spectrum penicillins (ticarcillin, mezlocillin, and piperacillin) are associated with the lowest risk. Trimethoprim, tetracycline, and imipenem seem to carry an intermediate risk. NEJM November 25, 1999; 341: 1690-91

11-20 CAFFEINE – FILTERING THE FACTS

Reports a risk of spontaneous abortion in women who consume up to 6 cups of coffee a day. NEJM November 25, 1999; 341: 1688-89

11-21 INJECTION WITH METHYLPREDNISOLONE PROXIMAL TO THE CARPAL TUNNEL: RANDOMIZED, DOUBLE BLIND TRIAL

A single injection of methylprednisolone close to (not into) the carpal tunnel may result in long-term improvement and should be considered before surgical decompression. BMJ October 2, 1999; 319: 884-86

11-22 THE YOUNG WOMAN WITH A WART ON HER NOSE

An Anecdote of a Tragedy "*A Memorable Patient"* A narrative of a poignant personal experience. BMJ November 20, 1999; 319: 1349

RECOMMENDED READING

11-22 THE YOUNG WOMAN WITH A WART ON HER NOSE

REFERENCE ARTICLES

11-3 EVALUATION OF PROGNOSTIC CRITERIA FOR DETERMINING HOSPICE ELIGIBILITY IN PATIENTS WITH ADVANCED LUNG, HEART, AND LIVER DISEASE.

11-4 HOW GRAVELY ILL BECOMES DYING: The Key to End-of-Life Care

11-11 AN UPDATE ON PERIOPERATIVE MANAGEMENT OF DIABETES

11-17 NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

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11-1 RANDOMISED TRIAL OF OLD AND NEW ANTI-HYPERTENSIVE DRUGS IN ELDERLY PATIENTS: Cardiovascular Mortality and Morbidity: The Swedish Trial in Old Patients with Hypertension-2 Study

Treating hypertension benefits elderly people by decreasing cardiovascular morbidity and mortality. The first STOP-Hypertension study[1] found a 40% decrease in major cardiovascular events and total mortality from treatment with beta-blockers, or a fixed-ratio of hydrochlorothiazide + amiloride (diuretic + antikaliuretic) compared with placebo.

The present study compared efficacy of conventional anti-hypertensive drugs with some newer drugs on cardiovascular morbidity and mortality.

Conclusion; Old and new were similar.

STUDY

1. Prospective, randomized trial entered over 6500 patients (age 70-84; mean = 76). All with hypertension (Systolic BP > 180, diastolic > 105, or both; mean = 194/98).
2. Randomized to:
   A. Conventional drugs (beta blockers; diuretic): Atenolol (*Tenormin* ; generic) 50 mg, metoprolol (*Lopressor* ; generic) 100 mg, pindolol (generic) 5 mg, or hydrochlorothiazide 25 mg + amiloride 5 mg (*Moduretic* ; generic) , or

   Newer drugs:

   B. ACE inhibitors: enalapril (*Vaseretic*) 10 mg, lisinopril (*Prinivil*) 10 mg,, or

   C. calcium antagonist: isradipine (*DynaCirc*) 2.5 mg.
3. If target BP of < 160/95 was not reached on a single drug, patients started on beta-blockers were given hydrochlorothiazide + amiloride as additional treatment; patients started on diuretic or calcium antagonist were given any of the beta-blockers listed; and patients on ACE inhibitors were given hydrochlorothiazide 12.5 to 25 mg.
4. End points = fatal stroke, fatal myocardial infarction **(MI)**, or other fatal cardiovascular disease.
5. Follow-up = up to 6 years.

RESULTS

1. BP was reduced similarly in all groups – at 54 months mean = 158/80
2. Combined end point of fatal stroke, fatal MI, and other fatal cardiovascular disease = 2 events per 100 patients per year in both groups.
3. Combined endpoint of fatal and non-fatal stroke + fatal and non-fatal MI + other cardiovascular mortality occurred in 20.7% of group A and 20.1% of groups B + C.
4. Most common comparative adverse events: conventional drugs – cold hands and feet; ACE inhibitors – dry cough; calcium antagonists – ankle edema. Dizziness occurred in about a third of patients in each group.

DISCUSSION

1. All 3 therapies showed similar efficacy in preventing cardiovascular mortality and major morbidity.
2. The frequency of MI and of congestive heart failure was significantly lower in patients treated with ACE inhibitors than in those treated with calcium antagonists.
3. Calcium antagonists were *not* less effective in any other way than conventional drugs. This accords with the current opinion that calcium antagonists are safe when used appropriately.
4. Older and newer anti-hypertensive drugs are equally useful. The choice of agent will depend on other factors: cost, side-effects, co-existing disorders.

CONCLUSION

Old (diuretic and beta-blockers) and new (ACE inhibitors and calcium blockers) anti-hypertensive drugs were equally effective in preventing cardiovascular mortality or major events over 5 years in elderly patients with hypertension. Decreasing in BP is of major importance for prevention.

Lancet November 20, 1999; 354: 1751-56 Original investigation by the STOP-Hypertension-2 study group, first author Lennart Hansson, University of Uppsala, Sweden.

1 Lancet 1991; 338: 1281-85

11-2 CONVENTIONAL VERSUS NEWER ANTIHYPERTENSIVE THERAPIES – A DRAW

(This editorial comments and expands on the preceding study.)

Each of the regimens in STOP-2 can be considered an effective means of reducing morbidity and mortality among elderly hypertensive people.

Some facts in the report should be noted:

At last visit half of the patients were on more than one drug.

At last visit, only 2/3 of patients were still taking the original drug allocated to them.

The slightly lower risk of myocardial infarction and heart failure with ACE inhibitors (compared with calcium antagonists) was statistically significant, and perhaps expected. ACE inhibitors have an established role in post-MI and heart failure patients.

The reported 25% incidence of dizziness in all 3 drug regimens was of particular concern. Were some of these patients over-treated and at risk of falls?

Many elderly people have serious life-shortening disorders (cancer, dementia, end-stage respiratory disease). For many of these antihypertensive therapy would be inappropriate. Others have serious concomitant disorders and are already on several drugs, increasing potential for additional adverse effects. "Nevertheless, for the fit elderly hypertensive patient, drug therapy is clearly indicated."

The prudent cost-effective prescriber who has decided that thiazide diuretics should be first-line treatment for elderly hypertensive people, will be further encouraged by this and other studies.

LANCET November 20, 1999; 1744-45 Editorial by Martin J Kendall, Queen Elizabeth Hospital, Birmingham, UK

11-3 EVALUATION OF PROGNOSTIC CRITERIA FOR DETERMINING HOSPICE ELIGIBILITY IN PATIENTS WITH ADVANCED LUNG, HEART, AND LIVER DISEASE.

Chronic obstructive pulmonary disease **(COPD),** congestive heart failure **(CHF),** and end-stage liver disease **(ESLD)** are among the most common chronic diseases. In contrast to incurable metastatic cancer, diseases involving chronic organ failure tend to have a more erratic course, and to produce death at a time difficult to predict. As a result, many patients with these chronic diseases never experience a time during which they are clearly dying of the disease. This has important implications, especially with regard to hospice care.

Medicare hospice benefits cover comprehensive services. Use of hospice is widespread and favored. Patients and families are satisfied with the care, hospice patients have fewer regrets than non-hospice patients, and they are more likely to die in a way consistent with their wishes.

Under Medicare regulations, a beneficiary is eligible for hospice care only if both the patient's attending physician and the medical director of the hospice certify that prognosis for life expectancy is 6 months or less. (*The great majority are patients with terminal cancer.)* Only 15% of patients receiving Medicare hospice benefits survive for longer than 6 months. The median survival is 40 days. For individuals dying of diseases other than cancer, access has been limited, in part because they rarely manifest a discrete phase of inexorable decline at the end of life.

Despite its advantages, hospice care serves a small portion of the dying population for only a short time. Regulators may not understand the uncertainty inherent in projecting survival. Indeed. . . "The National Hospice Organization **(NHO)** has pointed out that the Office of the Inspector General's intense scrutiny has a chilling effect on appropriate referrals of terminally ill beneficiaries."

In an effort to clarify eligibility for hospice for other serious illnesses, the NHO has drafted guidelines for determining prognosis in selected non-cancer diseases. (*See p 1641 for NHO Guidelines for Determining Prognosis and the criteria used in this study*.)

This study applied a variety of potential criteria, among seriously ill patients with advanced chronic disease, for determining prognosis to evaluate accuracy in predicting death within 6 months.

Conclusion: The recommended clinical criteria are *not* effective in predicting survival of 6 months or less.

STUDY

1. Entered over 2600 seriously ill patients with CHF, COPD, and ESLD who survived to hospital discharge.
2. Applied the NHO guidelines for determining prognosis, attempting to identify patients with a survival prognosis of 6 months or less. Three sets of criteria were used, aimed at providing low, medium, and high thresholds for hospice eligibility.

RESLTS

1. Forty four percent of patients expressed a preference for palliative care.
2. Seventy five percent of individuals survived for more than 6 months after hospital discharge.
3. Low threshold inclusion criteria identified 923 (35%) eligible for hospice care. Of these 70% survived longer than 6 months.
4. High threshold inclusion criteria identified 19 patients (less than 1%). Of these, 53% survived longer than 6 months.

DISCUSSION

1. The prognostic criteria used to simulate NHO guidelines were largely ineffective in predicting which seriously ill patients had a prognosis of survival of 6 months or less.
2. The criteria used, even the most restrictive, excluded the vast majority of patients they were supposed to identify as living less than 6 months.
3. "The goal of determining in advance – with a high degree of accuracy – which individual patients with COPD, CHF, or ESLD will die within 6 months is unrealistic."
4. If a high degree of predictive accuracy is demanded by those who interpret the 6-month prognosis requirement for hospice enrollment, few patients who die of these chronic diseases will be eligible for hospice care. Stipulating that only 20% of patients should outlive their 6-month prognosis would eliminate hospice access for these patients almost entirely. The sickest patients are not necessarily the ones that die first.

CONCLUSION

For seriously ill patients with chronic obstructive pulmonary disease, congestive heart failure, and end-stage liver disease, recommended clinical prediction criteria were *not* effective in identifying individuals with a survival prognosis of 6 months or less.

JAMA November 3, 1999; 282: 1638-45 Original investigation, first author Ellen Fox, George Washington University School of Medicine, Washington DC, for the SUPPORT Investigators (The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments JAMA 1995; 274: 1591-98)

11-4 HOW GRAVELY ILL BECOMES DYING: The Key to End-of-Life Care

(This editorial comments and expands on the preceding study.)

The preceding study concluded that we cannot accurately predict duration of remaining life in seriously ill persons, many of whom "never experience a time during which they were clearly dying of their disease". "The sickest patients are not necessarily the ones who die first." Indeed, on the day before death, patients with congestive failure were predicted to have a mean chance of 62% to survive 2 months. Patients with dementia are an even more heterogeneous group and have a more unpredictable course. Identifying a patient as "terminal" is no more than a guess until death is near.

One factor that makes it difficult for patients to give up their fight is medicine's inability to predict the future. This leads to a persistence of hope. "For many, hope persists and surrender is excruciating."
Hope often springs, then diminishes gradually and haltingly.

In the SUPPORT study of patients who were seriously ill with metastatic cancer, 20% to 40% preferred a plan of care that focused on extending life even if it meant having more pain and discomfort. Most patients were willing to accept intensive chemotherapy for a very small chance of benefit. Another study reported that about two thirds of oncology patients and the public found euthanasia and physician-assisted suicide acceptable for patients with unremitting pain. But, patients actually experiencing pain were more likely to find euthanasia or physician-assisted suicide unacceptable.

In caring for a severely, progressively ill patient, what may be most difficult is moving through the transition from gravely ill and fighting death to seeking peace, shifting the goals of treatment from cure or longer survival to preservation of comfort and dignity.

The physician's central task in caring for a gravely ill person near death is to accompany and guide the patient, who as a rule does not want to be dead, through the critical transition. "A cornerstone of the relationship is to understand and respect a patient's desire to fight and stay alive, even if treatment is burdensome, expensive, and unlikely to succeed."

But, . . ."Do everything you can Doctor" in life often becomes "Why did this have to drag on so long?" after death.

JAMA November 3, 1999; 282: 1670-72 Essay by Thomas E Finucane, Johns Hopkins Bayview Medical Center, Baltimore MD.

11-5 FACILITATION OF BENZODIAZEPINE DISCONTINUATION BY MELATONIN

Insomnia is particularly troublesome in the elderly. Treatment with benzodiazepines is considered safe. But, short term therapy (eg, 2-weeks) and intermittent therapy is recommended. Some patients use the drugs for prolonged periods. This may be associated with impaired functional status. Dependence and rebound insomnia seem to interrupt attempts at discontinuation.

Melatonin, a natural hormone produced by the pineal gland and released into the circulation at night, plays a major role in induction and regulation of sleep.

Benzodiazepines suppress the nocturnal rise in melatonin and shift the day-night rhythmicity.

This study assessed whether melatonin could facilitate discontinuation of benzodiazepine in long-term users.

Conclusion: Melatonin may be effective.

STUDY

1. Entered 34 patients (25 women; mean age 68) who had been taking a benzodiazepine daily for at least 6 months. None had cognitive impairment or liver or renal disease. Study divided into 2 periods:
   - Period 1: Patients received (double-blind) 1) 2 mg controlled-release melatonin nightly, or 2) placebo for 6 weeks. They were encouraged to reduce the benzodiazepine dosage by 50% during week 2, and discontinue completely by week 5 or 6.
   - Period 2: Melatonin administered (single blinded) for a second 6 weeks to all subjects again with attempts to discontinue the benzodiazepine.

RESULTS

1. By the end of period 1:	Received melatonin	Placebo
Had discontinued benzodiazepine	14 of 18 (75%)	4 of 16 (25%)

Sleep-quality scores were significantly higher in the melatonin group.

2. By end of period 2:

   Six additional patients had discontinued the benzodiazepine

3. At 6-months, of the 24 who had discontinued benzodiazepine and received melatonin, 19 maintained good sleep quality while melatonin was continued.
   - A. Five of 24 who had discontinued benzodiazepine later resumed taking it.
   - B. Safety and tolerability were good and identical in both groups. Two melatonin patients reported headache. None were withdrawn.

DISCUSSION

1. Controlled-release melatonin significantly favored discontinuation of benzodiazepine in these long-term users.

2. Melatonin use was associated with good sleep quality.

3. No tolerance to melatonin developed. No withdrawal effects were experienced.

CONCLUSION

Controlled-release melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality.

Archives Intern Med November 8, 1999; 159: 2456-60 Original investigation, first author Doron Garfinkel, E Wolfson Medical Center, Tel Aviv, Israel

Comment

The Israelis have been enthusiastic about use of melatonin. The study was supported by Neurim Pharmaceuticals, Tel Aviv, manufacturers of melatonin. It is a simple amino-acid derivative, not an herbal compound. It can be made available in pure form.

I abstracted the article as an example of a transfer from what might be termed "alternative" or "complementary" medicine to the mainstream of traditional Western medicine. Traditional Western bioscience-based medicine will welcome any contribution from "alternative" medicine which is found effective by usual scientific study. I believe there will be more examples forthcoming.

Melatonin is available at my pharmacy over-the-counter only, not by prescription. It comes in 2 strengths – 3.0 mg and 0.2 mg. It is not FDA approved. Dose and purity are not supervised by the FDA. Nevertheless, I have heard of no serious adverse effects from its use. I believe it is an over-the-counter that many physicians may recommend for jet-lag, and now for benzodiazepine dependence. RTJ

11-6 MELATONIN THERAPY: FROM BENZODIAZEPINE-DEPENDENT INSOMNIA TO AUTHENTICITY AND AUTONOMY

(This editorial comments and expands on the preceding.)

The potential short-term benefits of benzodiazepine for insomnia relief are offset by vulnerability to both acute and long-term adverse effects or dependency. The study indicated that melatonin therapy is a hopeful adjunct in the weaning process. And a sleep-maintenance alternative.

For clinicians who treat patients who suffer from insomnia and are benzodiazepine-dependent, an informed consent process that offers melatonin as an alternative integrates good clinical care with effective risk management. It carefully navigates between the Scylla of addiction and the Charybdis of abandonment.

We must not overlook, however, the often neglected yet treatable causes of sleeplessness: chronic bereavement; chronic depression (dysthymia); posttraumatic stress. Symptoms of these disorders can include a mixture of hyper arousal; irritability; difficulty in concentration; demoralization; fatigue; loss of pleasure (anhedonia); obsessive rumination; phobias; and a sense of meaninglessness of life.

Intrusive memories are a hallmark of a variety of disorders, including post-traumatic stress and pathological grief. On the other hand, some kinds of memory, such as autobiographical memories, are important for a

meaningful life. Procedural memories (eg, how to drive) are essential for many tasks of daily living. "The inhibition of each by benzodiazepines is far too high a price to pay for sleep."

Even patients who deny persistent sad and anxious moods may offer physicians clues to hidden depressive or anxiety disorders by reporting sad or frightening dreams. They should be questioned tactfully. "How well do you remember your dreams" is a useful and long-overdue modification that may be used prior to, or at least concurrently with, prescribing memory-inhibiting or dream-suppressing agents.

Insomnia is rarely a volunteered problem. Patients with "closet insomnia" tend to have a much higher rate of interaction with heath care. A high percentage have depressive disorders. "Shying away from inquiring about sleep and dreams saves neither time nor cost, and undermines the treatment of these disorders." While benzodiazepine treatment may initially restore sleep, it does not treat occult psychiatric disorders or the symptoms or underlying causes of depressive and stress disorders. Indeed, benzodiazepine treatment may exacerbate depressive states as well as fostering dependency.

From an ethical perspective, the prescription of benzodiazepines for insomnia in the elderly can proceed only when accompanied by the informed consent process. Begin by informing the patient of the need for comprehensive diagnostic evaluation and the availability of alternative primary approaches, including melatonin and behavioral interventions. Inform the patient about the recognized risks of benzodiazepines. Even when a patient asks for benzodiazepines, or is already dependent on them, an informed consent process needs to be initiated. Once initiated, the informed consent process should be continued after the initial encounter. This allows physicians to add the benefit of performing ongoing informal Mini-Mental-like screening that is sensitive to early signs of diminished capacity or fluctuating competency in the face of progressive cognitive impairment exacerbated by benzodiazepines.

Melatonin is a promising treatment for patients with sleep disturbances related to Alzheimer disease when an increased sleep latency and a decrease in melatonin production seem to coincide. "Any patient with Alzheimer disease who is sleepless deserves the opportunity for a therapeutic trial of melatonin."

Patients with dementia are especially sensitive to the sedative-depressant effects of benzodiazepines. All too many premature nursing home placements, as well as accidents such as falls, occur as a result of patients with early Alzheimer disease being undertreated or overmedicated for insomnia.

Melatonin is no panacea. Nevertheless, both good clinical practice and ethics require treatment for sleeplessness beyond the benzodiazepine-therapy solution.

Melatonin may decrease sleep latency (reduce the time it takes to fall asleep) without improving total sleep time. Reducing the time it takes to fall asleep can have significant meaning to an elderly patient. It may help preserve a locus of control and autonomy as age advances. But, patients need to be informed that we do not know the long-term consequences of melatonin therapy. It is available as a choice for effective benzodiazepine-free treatment for insomnia.

"Choosing benzodiazepine-free treatment for insomnia can help patients sleep, dream, remember, and continue to have access to both the continuity of autobiographical memories relevant to authenticity and the procedural memory essential to autonomy."

Archives Int Med November 8, 1999; 159: 2393-95 Editorial by Harold J Bursztajn, Harvard Medical School, Cambridge, Mass.

Comment:

Some thoughts as I abstracted the 2 articles:

Dr Bursztajn wholeheartedly embraces melatonin as an effective treatment for insomnia. Likely with good reason. However, remember, in the US it is still an over-the-counter medication, not subject to purity and dosage requirements of the FDA. Indeed, the continuing-release formulation is not available, at least not in my pharmacy.

Dr Bursztajn also notes that we do not know the long-term effects of melatonin, despite the fact that it is entirely (at least in pure form) a natural hormone. This should be pointed out as part of any informed-consent process.

I believe the point that melatonin may help elderly persons fall to sleep more quickly is important. Many elderly will complain that their sleep period is short, despite the observation by others which indicates that sleep period was reasonably long. A short time to sleep after retiring may be very helpful, even if total sleep time is not increased. RTJ

11-7 PERNICIOUS PAPILLOMA INFECTION

"More than 100 years have passed since an association between sexual behavior and cancer of the cervix was reported."

There is now compelling evidence that human papillomaviruses **(HPV)** can cause cervical cancer. HPV is found in the majority of cervical cancers. HPV DNA is also frequently integrated into the host genome. HPV DNA has been detected in more than 90% of cervical cancers. The proteins produced can immortalize human cells in vitro and make the cell more susceptible to genetic instability.

In case-control studies, the odds ratio of presence of oncogenic HPV infections in patients with intraepithelial neoplasia and cervical cancer (compared with population-based controls) is more than 200.

A case-control study in the issue of NEJM[1] reported the rate of detection of HPV in Pap smears of women who developed cervical cancer years later (compared with women who did not develop cervical cancer) was 77% vs 3%.

Persisting infection appears to be the defining risk factor . In many women the infection is transient. In those with persistent infection (perhaps related to sexual activity), a 10 to 20 year period allows development of additional genetic changes and the progression of low-grade lesions to cancer.

False negative Pap smears are common – up to 50% originally read as negative are found to be positive for cytological abnormalities on re-examination. Cytological screening is imperfect. "Perhaps it is time to consider periodic screening for HPV in conjunction with Pap smears." However, blanket screening for HPV in young sexually active women will probably do more harm than good because of the high prevalence of HPV and the tendency for the infection to regress. The key is to identify persistent, type specific (HPV – 16) infection. But,

there is yet no consensus on what constitutes persistent infection. It seems rational to define persistent infection as present when the same type of HPV is detected at least twice over a period of one or more years. Twenty percent of new HPV infections persist for at least one year in young women. This definition may be useful in identifying those at high risk.

"In sum, cervical cancer often begins with the sexual transmission of HPV infection to a woman who is susceptible to persistent infection. Over time, the HPV lesions progress to invasive cervical cancer."

NEJM November 25, 1999; 341: 1687-88 Editorial by Robert D Burk, Albert Einstein College of Medicine, Bronx, NY

1 "Type-specific Persistence of Human Papilloma DNA before Development of Invasive Cervical Cancer" NEJM November 25,1999; 341: 1633-38

2 See also "Natural History of Cervicovaginal Papillomavirus Infection in Young Women" NEJM 1998; 338: 423-28

Comment:

So . . . cancer of the cervix turns out to be a venereal disease.

The editorialist's comment on blanket screening illustrates the serious adverse effects screening may produce. Detecting the virus in an asymptomatic woman with a normal cervix will bring additional burdens – anxiety, invasive procedures, costs, and inconvenience. What to do if positive? Will advice about sexual activity benefit? Do antiviral drugs eliminate the HPV in the cervix? RTJ

11-8 ANTI-INFLAMMATORY AND UPPER GASTROINTESTINAL EFFECTS OF CELECOXIB IN RHEUMATOID ARTHRITIS: A Randomized Controlled Trial

Prostanoic acids are produced during inflammatory processes. They mediate many of the symptoms of inflammation.

Two isoforms of the enzyme cyclo-oxigenase (COX-1 AND COX-2) catalyze the synthesis of prostanioc acids from arachidonic acid. COX- 1 is expressed in many tissues and produces prostanoic acids that predominantly regulate normal cellular responses (eg, maintaining homeostasis in the stomach). COX-2 activity is typically undetectable in most tissues. Expression of COX-2 activity can be rapidly induced by proinflammatory cytokines. The prostanoic acids produced cause some of the symptoms of inflammation – swelling, pain.

Celecoxib (*Celebrex*) inhibits COX-2, but not COX-1. Thus it may have anti-inflammatory and analgesic activity without adversely affecting the stomach.

This study tested whether celecoxib has efficacy as an anti-inflammatory and analgesic agent without the GI tract mucosal damage associated with nonsteroidal anti-inflammatory drugs (NSAIDs).

Conclusion: Celecoxib was effective in treatment of symptoms of rheumatoid arthritis and did not affect COX-1 activity on the stomach and duodenum.

Study

1. Multicenter, randomized, double-blind, placebo-controlled trial entered over 1100 patients with symptomatic RA.
2. Randomized to: 1) celecoxib 100, 200, or 400 mg twice daily, or 2) naproxin (*Naprosin*; generic) 500 mg twice daily, or 3) placebo.
3. Performed upper GI endoscopy in all before and at termination of treatment.
4. Follow-up = 12 weeks.

RESULTS

1. All doses of celecoxib as well as naproxin significantly improved symptoms as compared with placebo.
2. The incidence of endoscopically determined GI ulcers at 12 weeks: placebo – 4%; celecoxib -- 6% (not statistically different from placebo); naproxin – 26%.
3. Safety: All doses of celecoxib were well tolerated.

DISCUSSION

1. Celecoxib at therapeutic doses will inhibit COX-2 while sparing COX-1.
2. The analgesic effects of celecoxib were comparable with naproxin.
3. Celecoxib was associated with a lower incidence of GI ulceration than naproxin at a rate not significantly different from placebo.
4. Up to 30% of patients who take conventional NSAIDs develop persistent adverse effects. More than 10% discontinue treatment as a result.

CONCLUSION

Celecoxib was efficacious in treatment of rheumatoid arthritis and did not affect COX-1 activity in the upper GI tract mucosa as evidenced by less frequent ulcers compared with naproxin.

JAMA November 24, 1999; 282: 1921-28 Original investigation, first author Lee S Simon, Beth Israel Deaconess Medical Center, Boston, Mass.
See also "Adverse Upper Gastrointestinal Effects of Rofecoxib Compared with NSAIDs: JAMA November 24, 1999; 282: 1929-33 This meta-analysis of 8 trials of patients with osteoarthritis found a significantly lower incidence of peptic ulcer bleeding compare with standard NSAIDs.

11-9 COX-1-SPARING NSAIDs – Is the Enthusiasm Justified?

(This editorial comments and expands on the preceding.)

One large prospective trial of patients with rheumatoid arthritis found a rate of serious GI complications (bleeding, perforation, obstruction) of 1.5% per year. The rates are higher in some subgroups – the elderly and

those with prior ulcerations. While not a high absolute rate, thousands of patients are at risk each year because of the large numbers of NSAID users. **1**

The editorialist calculates that five hundred otherwise healthy patients need to be treated yearly (compared with standard NSAIDs) to prevent one GI complication, at an extra cost of $400 000.
For patients at higher risk (eg, a 75-year old with a prior history of ulcer) the NNT might be 40 at a cost of $30 000.

The yearly cost for an individual is over $700 (compared with generic naproxin).

Cox-1-sparing NSAIDs are not "super aspirins". They do not relieve symptoms any more effectively than standard NSAIDs. Nor are they related to any clinically significant reduction in incidence of dyspepsia.

JAMA November 24, 1999; 282: 1961-63 Editorial by Walter L Peterson and Bryon Cryer, University of Texas Southwestern, Dallas.

Comment:

1 Indeed, nationally, NSAID use is an important cause of hospitalization and death. I believe for chronic users, especially the frail elderly, an informed consent process (including costs) should be offered. RTJ

11-10 TWICE DAILY VERSUS FOUR TIMES DAILY INSULIN DOSE REGIMES FOR DIABETES IN PREGNANCY

Good glycemic control is the cornerstone of treatment of diabetes in pregnancy. It reduces both maternal and fetal morbidity. Measures to achieve glycemic control should be initiated before conception in individuals with pregestational diabetes, and as early as diagnosis in gestational diabetes.

The most widely used regimen for control is twice-daily insulin:

Morning dose contains 2/3 of the daily dose:

Two thirds intermediate insulin and 1/3 regular

Evening dose contains 1/3 of daily dose:

Equal amounts of intermediate and regular.

The disadvantages are relative fasting hyperglycemia, relative hyperglycemia after lunch, and possible nocturnal hypoglycemia. All have negative effects on fetal and maternal well-being.

The Diabetes Control and Complications Group recommends an intensified 4-times daily insulin regimen for those who plan pregnancy and those who have conceived. But, during pregnancy no prospective comparison has been made between the two regimens.

This study compared glycemic control, maternal complications, and perinatal outcome between two insulin regimens.

Conclusion: Four-times daily insulin improved glycemic control and perinatal outcome.

STUDY

1. Defined gestational diabetes by a 100g oral glucose tolerance test. At least two serum glucose concentrations equaled or above 106 mg/dL fasting; 190 at 1 hour; 166 at 2 hours; and 146 at 3 hours. (National Diabetes Data Group criteria.)
2. Randomized, controlled open label study entered 274 patients with gestational diabetes and 118 patients with pregestational diabetes.
3. Randomized each group to: 1) 4-times daily insulin, or 2) 2-times daily insulin. The 2-times regimen as above; the 4-times consisted of 3 doses of regular insulin given a half hour before meals, and a dose of intermediate at bedtime.
4. Control was carefully assessed by glucose monitoring and monthly HbA1c determinations. The goal for blood glucose control was 54 to 95 mg/dL before meals, and 120 mg/dL 2-hours after meals. Insulin dosage was adjusted upward when values exceeded the upper limits. Goal for HbA1c was below 6%.

RESULTS

1. Gestational diabetes (4-times daily insulin compared with 2-times daily):
   A. Glycemic control was better in the 4-times daily regimen. Mean blood glucose decreased by 4 mg/dL and HbA1c decreased by 0.3%. Insulin dose increased an average of 22 units.
   B. Adequate glycemic control (mean blood glucose < 105 mg/dL) was achieved in 17% more women.
   C. The 4-times daily regimen resulted in a lower rate of overall neonatal morbidity; RR = 0.59
   Reduced the risk of hyperbilirubinemia (RR = 0.51 and hypoglycemia (RR = 0.12)
2. Pregestational diabetes (4-times daily insulin compared with 2-times daily):
   A. Mean blood glucose decreased by 8 mg/dL and HbA1c decreased by 0.5%. Insulin dose increased an average of 28 units.
   B. Adequate glycemic control was achieved by 31% more women.
   C. Relative risk of hypoglycemia in newborns was 0.17
   D. Severe maternal hypoglycemic events, caesarian section, preterm birth, macrosomia, and low APGAR scores were similar in both groups.

DISCUSSION

1. Maternal hyperglycemia results in hyperinsulinism in the infant, which in turn increases rates of perinatal death, macrosomia, early hypoglycemia, respiratory distress syndrome, polycythemia, hypocalcemia, and hyperbilirubinemia in the neonate.
2. Controlling the glucose is the cornerstone of treatment for diabetes in pregnancy and results in improving neonatal outcomes.
3. In this study, a 4-times daily insulin regimen (as compared with a 2-times daily regimen) significantly reduced neonatal morbidity . This was probably due to the increased mean dose of insulin.
4. The increased dose did not result in any increase in cases of maternal hypoglycemia.

5. "Our results show that a dose regimen that is neither more complicated nor more expensive than the conventional twice daily regimen provides a better outcome."

CONCLUSION

Giving insulin four times daily rather than twice daily improved glycemic control in pregnancy and perinatal outcome without further risking the mother.

BMJ November 6, 1999; 319: 1223-27 original investigation, first author Zohar Nachum, HaEmek Medical Center, Afula, Israel

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REFERENCE ARTICLE

11-11 AN UPDATE ON PERIOPERATIVE MANAGEMENT OF DIABETES

An estimated 25% of patients with diabetes will require surgery. Advances in operative care allow them to safely undergo the most complicated procedures. This article reviews preoperative, perioperative, and postoperative care.

Insulin secretory capability, insulin sensitivity, overall metabolism, and nutritional intake may change radically from the preoperative period through postoperative recuperation, and may also differ from one procedure to another. Physicians tend to be reactive as opposed to proactive in their management of hyperglycemia. Marked hyperglycemia should be prevented. It may lead to dehydration and electrolyte abnormalities and predispose to infection – and, in type 1 patients, to ketoacidosis.

Preoperative evaluation and preparation:

Table 1 p 2506 presents a check list for preoperative assessment. It is in general similar to that of any other patient in whom it is important to evaluate and treat underlying cardiac, pulmonary, and renal disease. Since cardiovascular disease is inordinately common in patients with diabetes, assessment of cardiac risk assumes a high priority. In patients with a history of myocardial infarction or unstable angina, postoperative cardiac complications may be decreased if coronary bypass or angioplasty, if warranted,[1] are performed before other elective surgery.

The effects of antecedent glucose control are not well established. Although in the past, near optimal control has been advocated in preparation for surgery, little evidence substantiates this approach. It is important to optimize nutritional status if time permits.

Hypertension should be well controlled before elective surgery.

Perioperative management:

Patients treated with diet and oral drugs:

In general the goal is to maintain blood glucose levels between 150 and 200 mg/dL to protect against hypoglycemia. For unstable patients, frequent glucose monitoring is needed.

For patients receiving diet therapy alone and those treated with diet plus oral agents, no perioperative therapy is usually recommended if preoperative glucose levels are within the glycemic goals. For patients poorly controlled on oral medication, insulin is often required during the perioperative period.

Patients with type 2 diabetes treated with diet alone usually abstain from oral intake overnight. Hydration may be maintained by IV fluids. Blood glucose may be measured before and after surgery, and during surgery if the procedure is long. Hyperglycemia is treated with short acting insulin.

Antidiabetic drugs are usually administered on the day before surgery and withheld the day of surgery. If marked hyperglycemia occurs, insulin is given.

Currently, metformin is discontinued on the day of surgery and for several days after because alterations of renal function arising intraoperatively may potentiate the risk of lactic acidosis.

See figure 2 p 2408 for an algorithm for oral agents.

Type 1 and 2 diabetes treated with insulin:

Glucose should be monitored intensively and dextrose infusion rate adjusted appropriately to prevent hypoglycemia or substantial hyperglycemia. *See figure 3 p 2408 for a summary of perioperative management.*

For patients previously on insulin, intravenous regular insulin is indicated during the perioperative period for patients undergoing long, complex procedures, for patients with unstable type 1 diabetes, and in patients with type 1 diabetes who are pregnant.

The glucose-potassium-insulin infusion is widely used in Europe. It has advantages of simplicity and single-solution technique, simultaneously infusing both glucose and insulin. *See algorithm p 1409 for management by GKI intravenous infusion.)*

Postoperative management:

During the postoperative period, control may be markedly unstable. Oral intake may be limited for prolonged periods because of side effects of anesthesia, or ileus. These patients may require continued infusions of glucose. Insulin requirements are dependent on the rate of glucose administration and the patient's metabolic stress. Compensatory subcutaneous short-acting insulin may be given according to the blood glucose levels. *See algorithm p 2410.*

Perioperative management is generally more of an art than a clinical science. There are many protocols for management. Homeostasis during this period is highly variable and often unpredictable. Clinical judgement remains the key.

Archives Int Med November 8, 1999; 159: 2405-11 Review article by Scott J Jacober and James R Sowers, Wayne State University School of Medicine, Detroit, MI

Comment:

1. The decision for these interventions is based solely on the usual indications for the interventions themselves, and not on whether elective surgery is planned.

11-12 REVERSAL OF IRON DEFICIENCY ANEMIA AFTER *HELICOBACTER PYLORI* ERADICATION IN PATIENTS WITH ASYMPTOMATIC GASTRITIS

Recent studies have suggested an association between *H pylori* infection and iron deficiency. Peptic ulcer disease and gastric cancer are related to the infection. Both can bleed and cause anemia. But, most individuals infected have chronic gastritis not associated with bleeding. Can the gastritis impair iron absorption or increase demand?

This study investigated the effect of eradication of *H pylori* on iron deficiency anemia in patients with *H pylori*-associated gastritis.

Conclusion: Cure of the infection reversed the anemia.

STUDY

1. Entered 30 patients (median age = 35; 24 women) with a long-standing history of iron deficiency anemia. None were taking NSAIDs. None had been on a iron deficient diet; 80% had chronic pangastritis.
2. Defined iron deficiency anemia as a hemoglobin concentration less than 14 g/L for men and less than 12 g/L for women, a mean corpuscular volume < 80 fL, and a serum ferritin less than 30ug/L. Mean hemoglobin was 10 g/L; mean corpuscular volume – 73 fL; serum ferritin – 6 ug/L.
3. Excluded patients with obvious source of bleeding. Gastritis was the only GI finding detected.
4. Patients were instructed to discontinue all iron medication. Treated with combined antibiotics + omeprazole for 2 weeks.

RESULTS

1. *H pylori* infection was cured in 25 patients.
2. At 6 months 75% of patients had recovered from anemia; mean ferritin increased from 6 ug/L to 24 ug/L; mean hemoglobin to 13 g/L; mean corpuscular volume to 86 fL. Mean transferrin saturation index increased from 6% to 19%.
3. At 12 months, 92% had recovered from the anemia.
4. At further follow-up, in 2 of the patients who had remained anemic, hemoglobin returned to normal.
5. Three patients remained anemic.

DISCUSSION

1. In this group of patients with iron deficiency anemia in whom *H pylori*-positive pangastritis was the only GI pathology found, cure of the infection reversed the iron deficiency anemia within 1 to 2 years.
2. Ferritin levels increased by 300% over baseline, indicating a progressive build-up of iron stores.
3. Most of the cohort were premenopausal women. The presence of a factor that impairs iron absorption added to regular menstrual blood loss can unbalance an already unsteady equilibrium.

4. In most patients with *H pylori* infections the gastritis is more prominent in the antrum. In the present cohort, the pan-gastritis was present.
5. Poor iron absorption is the suspected mechanism; or possibly increased demand. (Iron is an essential growth factor for *H pylori*..)

CONCLUSION

In this cohort of adult patients with iron deficiency associated with chronic pangastritis due to *H pylori*, cure of the infection cured the anemia.

Annals Int Med November 2, 1999; 131: 668-72 Original investigation, first author Bruno Annibale, Universitario Umberto I, Rome, Italy

Comment: Something to keep in the back of your mind. RTJ

11-13 ADVERSE CHILDHOOD EXPERIENCES AND SMOKING DURING ADOLESCENCE AND ADULTHOOD.

In recent years, smoking among adolescents in the U.S. has increased, and the decline of adult smoking has slowed to nearly a halt. These disturbing trends have occurred amidst efforts to reduce access to cigarettes, and to counter the effects of tobacco marketing, parent and sibling smoking, and peer pressure to smoke.

About 2 out of every 3 adults who have ever smoked regularly began smoking by age 18.

Long-term use of nicotine has been linked with self-medicating efforts to cope with the negative emotional, neurobiological, and social effects of adverse childhood experiences.

This study assessed the relationship between adverse childhood experiences and smoking behaviors.

Conclusion: Smoking was strongly associated with adverse childhood experiences.

STUDY

1. Used data from the Adverse Childhood Experience (ACE) study[1] which included 8 categories of adverse childhood experiences: emotional, physical, and sexual abuse; a battered mother; parental separation or divorce; growing up with a substance-abusing, mentally ill, or incarcerated household member.
2. Entered over 9000 adults (mean age – 56) who responded to a survey questionnaire asking about adverse childhood experiences, smoking initiation by age 14, or after 18, and status of smoking – ever, current, and heavy.

RESULTS

1. At least one of the categories of adverse childhood experiences was reported by 2 out of every 3 respondents.
2. After adjusting for age, sex, and education, each category showed an increased risk of smoking behavior.
3. Compared with those reporting no adverse childhood experiences, persons reporting 5 or more

had substantially higher risk of early smoking initiation, ever smoking, current smoking, and heavy smoking. (Odds ratios 2.1 to 5.4)

4. Each relationship between smoking behavior and the number of adverse childhood experiences was strong and graded.
5. For any number of adverse childhood experiences, recent problems with depressed affect were more common among smokers than among non-smokers.

DISCUSSION

1. "Our data indicate that if a person reports one of these adverse childhood experiences, there is an 85% chance of experiencing a second, and a 70% chance of experiencing a third."
2. The adverse experiences antedate the smoking behavior.
3. The mean age at smoking initiation was inversely related to the number of adverse experiences. This supports a causal relationship.
4. How might a person exposed to adverse childhood experiences benefit from use of nicotine? Nicotine has psychoactive benefits. These persons might use nicotine to regulate their mood. Nicotine is a coping device for the negative emotional, neurobiological, and social effects of adverse experiences. Recurrent use could occur unconsciously in situations of chronic distress.
5. Children of abuse may be victims on several levels:
   A. By finding that nicotine provides pharmacological relief.
   B. Because of resulting problems with affect, socialization, and self-esteem, they may be more likely to fall prey to both peer pressure and seductive marketing.
   C. They may be fined or criminalized by state law which prohibits purchase or possession of tobacco.
6. "Although some form of negative consequence for youth who purchase or possess tobacco might be useful, the effectiveness of current state sanctions is unproven and, in some cases, seems excessive. Youths whose smoking may be a consequence of adverse childhood experiences, are victimized by legislation that fines or criminalizes them. . . "
7. Smokers who consciously or unconsciously use nicotine as a pharmacological tool to alleviate the long-term emotional and psycho-biological wounds of adverse childhood experiences may need special assistance to help them quit.

CONCLUSION

Smoking was strongly associated with adverse childhood experiences. Primary prevention of adverse childhood experiences and improved treatment of exposed children could reduce smoking among both adolescents and adults.

JAMA November 3, 1999; 282: 1652-58 Original investigation, first author Robert F Anda, Centers for Disease Control and Prevention, Atlanta GA.

1 Am J Prev Med 1998; 14: 245-58

Comment: Teen-age smokers may be crying for help. RTJ

11-14 EARLY ONSET DRUNK DRIVING, VIOLENT CRIMINALITY, AND MENTAL DISORDERS

This study examined whether the age at first conviction for drunk driving was associated with severe psychiatric morbidity and violent criminality.

Extracted records of all people in the 1966 birth cohort in Northern Finland convicted at least once of drunk driving. (In Finland the legal blood alcohol limit is 50 mg/dL.) Obtained data on diagnosis of any hospital treated mental disorder before 1995. Obtained relevant criminality data from the Ministry of Justice for those between ages 15 and 25. Violent crimes included: homicide, assault, robbery, arson, sexual crime, or violation of domestic peace.

Correlated the age at first conviction due to drunk driving among violent and non-violent criminal cohort members.

Of all cohort members, 333 subjects had been convicted of at least one drunk-driving offense by the age of 25.

The probability of being an early-onset drunk driver was significantly related to being a violent offender and having a mental disorder. Of the drunk drivers who were violent offenders and mentally ill, 43% had their first conviction for drunk driving before the age of 18.

"The younger the drunk driver is, the greater the probability is of the driver being a violent offender with co-morbid mental disorder."

Lancet November 20, 1999; 354: 1788 Original investigation, first author Pirkko Rasanen, University of Oulu, Finland.

Comment: Another group of teen-agers crying for help. RTJ

11-15 CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF EXERTION-RELATED MYOCARDIAL INFARCTION

Vigorous exertion can acutely and transiently increase the risk of myocardial infarction **(MI)** and cardiac death. Up to 15% of MIs occur during, or soon after, vigorous exertion – one of the most common triggers. These events occur more often in patients with diabetes and in individuals who are habitually sedentary.

This study compared the clinical characteristics of patients who experienced an exertion-related MI with those who experienced an MI not related to exertion.

Conclusion: Most exertion-related MIs occurred in habitually inactive persons with multiple cardiac risk factors.

STUDY

1. Compared characteristics of 640 patients with acute MI who were selected for primary angioplasty. Of these 64 (10%) had experienced an exertion-related MI.
2. Determined clinical characteristics of those with and those without exertion related MI.

RESULTS

1. Clinical characteristics (Means)	Exertion-related MI	Non-exertion-related MI
Age	59	61
Male	86%	68%
Hyperlipidemic	62%	40%
Smokers	59%	37%
BMI ≥ 30	48%	28%
Presented with ventricular fibrillation	20%	11%
Heart Failure class III or IV	44%	22%
Single vessel disease	50%	28%
Large thrombus in artery	64%	35%
Low or very low physical activity	84%	66%

2. The relative risk **(RR)** of experiencing an MI during exertion was 10 times greater than the risk at other times, with the highest risk among those with habitually very low or low physical activity.

DISCUSSION

1. In this study, 10% of the MIs treated with primary angioplasty occurred during or within an hour of vigorous exertion.
2. A total of at least 6% of all acute MIs evaluated in this institution were exertion-related. The RR of experiencing an MI associated with vigorous exertion was 10 times higher than at other times. Risk was greatest for sedentary individuals. Risk was not significantly increased among those classified as moderately or highly active.
3. Definition of an exertion-related MI required exertion of at least 6 METs. Only 17% of persons who sustained an exertion-related event routinely performed a similar level of sustained effort.
4. Subjects who had an exertion-related MI had higher levels of exertion than comparison subjects during the 24 hours prior to the event. This suggests that the MI occurred during unaccustomed physical activity.
5. One study reported that joggers were 7 times more likely to die while jogging than during other activities. In another study, the RR of a cardiac arrest during exercise (vs when resting) among the habitually least active subjects was 56. Among the most active persons – 5.
8. Nevertheless, among fit and active persons, a cardiac event may occur more frequently when they are active than when not active. This does not impugn the benefits of regular exercise.
7. Possible mechanisms causing or contributing to the acute event during exertion: plaque fissuring

and rupture due to increased shear forces, increased BP and heart rate, increased bending, twisting, and flexing motions of the coronary arteries. Smoking and hyperlipidemia-related increase in platelet aggregation might be potentiated during exercise.

8. The observation that exertion-related events occur in persons with more cardiac risk factors, but less multivessel disease raises the possibility that modifying risk factors, specifically smoking and hyperlipidemia, is especially important in inactive people before they participate in vigorous exercise.

CONCLUSION

Exertion-related MI occurs predominantly in habitually inactive individuals during unaccustomed physical activity. These results should reassure individuals who exercise regularly, and public health advocates of physical activity. Habitually inactive adults with elevated cardiac risk factors should avoid unaccustomed vigorous exertion.

JAMA November 10, 1999; 282: 1731-36 Original investigation, first author Satyendra Giri, Hartford Hospital, Hartford, Conn.

Comment:

Increased physical activity lowers risk of MI. Fortunately the degree of exertion need not be great. Individuals who walk regularly and briskly at a MET level of 3 to 5 lower their risk just as much as individuals who jog or perform aerobics regularly, provided they expend the same number of extra MET-hours in purposeful exertion. The total weekly additional exertion required to lessen risk is the same, be the activity strenuous or moderate. Thus to burn an extra 1000 k/cal a week (a reasonable amount), the moderate exercisers need spend about twice as much time exerting themselves as the strenuous exercisers. RTJ

11-16 PLATELET ACTIVATION WITH EXERCISE AND RISK OF CARDIAC EVENTS

(This editorial comments and expands on the preceding study.)

An individual unaccustomed to habitual physical activity has about a 50-fold increase in the risk of sudden death and a 100-fold increase in risk of acute myocardial infarction when undertaking vigorous exercise – as compared with remaining at rest.

Training (becoming physically fit) greatly reduces the risk.

How does physical fitness reduce the risk of an event associated with vigorous exertion?

Fitness has beneficial effects on the principle risk factors of cardiovascular disease: hypertension; lipids; diabetes. A substantial benefit results from an increase in work capacity (higher exercise tolerance). At a given level of exertion, training results in less hemodynamic stress and in lower concentrations of catecholamines; platelet activation may be lessened.

How does vigorous exertion increase risk of an event?

Activating platelets, increasing platelet aggregation; increasing platelet counts; increasing some coagulation factors, shortening coagulation times, and increasing tendency to coagulation; increasing

catecholamine concentrations; increased shear stress in the coronary arteries leading to plaque fissuring and rupture.

Although physical fitness does not completely remove the risk of an event associated with vigorous exertion, it greatly reduces risk.

Lancet November 20, 1999; 354: 1747-48 Editorial by Peter Bartsch, University of Heidelberg, Germany

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REFERENCE ARTICLE

11-17 NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

This article reviews epidemiology, pathology, genetic basis, risk factors, renal failure, and treatment. I enjoy review articles such as this which gather up and condense much scattered data. I abstracted a few highlights. Ed.

The risk of nephropathy with progression to end-stage renal disease is similar in both groups of diabetes (type 1 and type 2). Encouraging evidence indicates that this is to a certain extent preventable. Paradoxically, because of effective treatment of hypertension and coronary heart disease, patients with type 2 diabetes are living long enough to develop end-stage renal disease. "Hence, end-stage renal disease in patients with type 2 diabetes may be viewed as a disease of medical progress."

Renal lesions

Patients with type 2 diabetes and microalbuminuria frequently have classic Kimmelstiel-Wilson lesions. A sizable number have non-specific vascular and interstitial lesions with minimal glomerular changes, or none at all. Some have atherosclerotic renal artery stenosis or cholesterol microembolism. Approximately 20% of patients with type 2 diabetes have a non-diabetic form of end-stage renal disease

Factors that increase risk of progression to end-stage disease:

Elevated BP

Both hypertension and high circadian BP are strongly correlated with albuminuria, and are strongly correlated with the presence of albuminuria and cardiovascular and renal events. Questions remain about the target BP for therapy and the most appropriate drug therapy. The National Kidney Foundation recommends a clinic target of 125/75. Lowering BP is more important than the type of antihypertensive drug used.

It is prudent to rule out presence of stenotic lesions, especially of the carotid arteries before treatment is begun. BP should be lowered slowly and patients monitored closely. (*Recall the adverse effects of ACE inhibitors on renal function in patients with renal artery stenosis. Ed.)*

Patients with diabetes tend to retain sodium and are exquisitely volume sensitive. It is advisable to restrict sodium intake and use thiazides with a potassium-sparing agent before renal failure begins, and a loop diuretic after.

Failure to use diuretics in appropriate doses are common causes of a poor response to ACE inhibitors. Impressive evidence suggests that ACE inhibitors and possibly angiotensin II blockers have specific renoprotective properties in diabetic patients with proteinuria.

A combination of agents is often necessary to achieve target BP levels.

Albuminuria or proteinuria

Microalbuminuria (urinary albumin 30 to 300 mg/d) is an indicator for need of antihypertensive treatment. Patients should be tested regularly for it. Antihypertensive treatment (preferably ACE inhibitors) reduces albuminuria and diminishes risk of progression even in normotensive patients with diabetes. Decreasing the level of proteinuria is a desirable therapeutic goal in and of itself.

Poor glycemic control (high level of insulin resistance)

The risk of development and progression of albuminuria can be substantially reduced by improving glycemic control. The goal is to achieve a HbA1c close to 7%, no matter whether by insulin or oral drugs.

Smoking

The adverse effects of smoking on renal disease (diabetic or non-diabetic) are well established but not widely appreciated. Rate of progression in smokers is about twice as fast. Stop smoking!

High dietary intake of protein?

Evidence of benefit is tenuous. The effect of restriction is not impressive. In advanced nephropathy reduction of protein carries risk of catabolism. Nevertheless, the authors suggest restricting protein intake to 0.8 g/kg preferably by reducing intake of animal protein, except among patients with preterminal renal failure.

Genetic predisposition

The risk of nephropathy is strongly determined by genetics. Familial clustering of diabetic nephropathy has been described in relatives of patients with type 2 diabetes, along with high rates of hypertension and cardiovascular events. Several genes have been linked to diabetic nephropathy.

NEJM October 7, 1999; 341: 1127-33 "Primary Care" Review article by Eberhard Ritz and Stephan Rheinhold Orth, Ruperto Carola University, Heidelberg, Germany.

11-18 EFFECT OF NITRIC-OXIDE-GENERATING SYSTEM ON MICROCIRCULATORY BLOOD FLOW IN THE SKIN OF PATIENTS WITH SEVERE RAYNAUDS'S SYNDROME

Various treatments for Raynaud's syndrome have been proposed: cessation of smoking; keeping warm; administration of slow-acting calcium-blockers and derivatives of nicotinic acid; intravenous prostanoids. Some have intrusive side effects. Effectiveness varies.

Endothelial dysfunction plays a part in the pathogenesis of Raynaud's syndrome. Decreased synthesis or accelerated inactivation of endothelium-derived relaxing factor (nitric oxide – NO) is one proposed pathogenic mechanism. NO is a potent vasodilator, synthesized and released by endothelial cells. It has an important role in regulating local vascular resistance and blood flow.

NO can be generated by mixing sodium nitrite with vitamin C. Large amounts of NO can be generated by the topical application of the mixture.

This study assessed effects of the use of this non-invasive topical gel on the microcirculation of the skin in normal persons as well as those with Raynaud's syndrome

Conclusion: The gel stimulated an increase in both microcirculatory volume and flux.

STUDY

1. Single-blind, randomized, placebo-controlled, cross-over study entered 20 patients with severe Raynaud's syndrome. And 10 normal volunteers.
2. The NO generating gel was formed by mixing a solution of KY jelly and sodium nitrate with a solution of KY jelly and vitamin C. (*See text for details*.) Mixing occurred by use of a cotton bud after each solution was separately applied to the skin.
3. KY jelly was used as a control.

RESULTS

1. When applied to the forearm, the active gel resulted in a large vasodilator response in both normal subjects and those with Raynaud's syndrome. Microcirculatory blood volume and blood flux (velocity X number of erythrocytes) were markedly increased. (*See figure 4 p 1674 for illustration of the erythema-producing effects in the forearm produced by various concentrations of the gel.)*
2. Both blood flow and flux were also markedly increased when the active gel was applied to the fingers of patients with Raynaud's syndrome. No effect from placebo.

DISCUSSION

1. Most patients with Raynaud's syndrome have mild symptoms of short duration. They require only advice on smoking cessation and strategies to protect their fingers from cold.
2. A few have critical digital ischemia in whom various vasodilatory drugs have proved only partly effective. Nifedipine [*Procardia*; a calcium-blocker] is generally accepted therapy of choice and may be effective. Adverse effects occur in about a third of patients.
3. Most patients require a simple treatment that is reliably effective when vasospasm is most severe. "The application of a nitric-oxide generating gel at the appropriates time seems to meet this requirement."
4. The gel can be used at the time of the attack. It seems to have no adverse effects. There are no systemic effects as with glyceryal trinitrate cream. And no adverse local effects. Development of tolerance is improbable.

CONCLUSION

In Raynaud's syndrome topical application of a nitric-oxide-generating system can stimulate an increase in both microcirculatory volume and flux.

Lancet November 13, 1999; 354: 1670-75 Original investigation, first author A T Tucker, St Bartholomew's Hospital, London, UK

Comment:

The authors did not comment on the clinical effects and acceptance by patients using the gel during an attack. It seems to be a simple gel to prepare, and worth a try if a patient with severe Raynaud's syndrome is encountered.

The remarkable discovery of NO, the endothelial-relaxing factor is leading to clinical applications. The first being *Viagra*. We await more. RTJ

11-19 ANTIBIOTICS AND *CLOSTRIDIUM DIFFICILE*

"It is hard to remember a time in the past decades when *Clostridium difficile* was not a scourge in our hospitals."

In the 1960s, the infection was termed "staphylococcal colitis". Subsequently, because of its association with clindamycin, it was called "clindamycin colitis".

The cause (*C. difficile*) was discovered in 1978. Frequency of the disease thereafter increased because increasing use of cephalosporins, in addition to clindamycin and lincomycin. Prevalence of *C difficile* in hospital patients increased to over 25%. Diarrhea developed during hospitalization in about 1/3 of newly infected patients. The infection is now acknowledged to be the chief cause of nosocomial diarrhea in the US.

The organism is endemic not only in hospitals, but in long-term care institutions.

In the issue of NEJM [1] a study reported an epidemic strain of clindamycin-resistant *C difficile.* The suppressive effect of the drug on the patient's bowel flora facilitated overgrowth of the organism.

Although use of clindamycin has declined over the years, *C difficile* associated diarrhea has increased even in hospitals where clindamycin is rarely used. The chief risk factor is prior exposure to antibiotics. The term "antibiotic-associated *C difficile* diarrhea" is still appropriate. Prolonged use of antibiotics, and the use of two or more antibiotics in combination increases risk. Nevertheless, a brief exposure to a single antibiotic can cause the condition.

Now, the antibiotic mainstays in hospitals, cephalosporins, especially the second and third generation, are the leading instigators of *C difficile* diarrhea. In one study at a large urban hospital, 85% of affected patients had received ceftriaxone [*Rocephin*] or ceftazidime [*Ceftaz; Fortaz*] in the preceding 6 weeks. The most common antibiotic used – ticarcillin-clavanate [*Timentin*] – was not associated with any cases.

When other antibiotics (eg, penicillin G, trimethoprim, and gentamycin, depending on the suspected pathogen) were substituted incidence fell by 50%.

In addition to the second- and third-generation cephalosporins and clindamycin, ampicillin and amoxicillin are associated with the highest incidence. Quinolones, aminoglycosides, macrolides (especially the newer agents clarithromycin and azithromycin), vancomycin, and extended spectrum penicillins (ticarcillin, mezlocillin, and piperacillin) are associated with the lowest risk. Trimethoprim, tetracycline, and imipenem seem to carry an intermediate risk.

Altering antibiotic-prescribing patterns is worthy of consideration when standard isolation and environmental policies are unsuccessful.

NEJM November 25, 1999; 341: 1690-91 Editorial by Sherwood L Gorbach, Tufts University School of Medicine, Boston, Mass

1 "Epidemics of Diarrhea Caused by a Clindamycin-resistant Strain of *Clostridium difficile* in 'four Hospitals" NEJM November 25, 1999; 341: 1645-51

11-20 CAFFEINE – FILTERING THE FACTS

A study in this issue of NEJM[1] reports an association between spontaneous abortions, primarily in the second trimester, and unusually high levels of consumption of caffeine, equivalent to 6 or more cups of coffee daily.

A recent meta-analysis concluded that there is a small increase in the crude risk of both spontaneous abortion (odds ratio = 1.4) and low birth weight (odds ratio = 1.5) in women who consume more than 150 mg of caffeine per day – roughly equal to one or two cups of coffee.

The most obvious effects of caffeine are cardiovascular and neurobehavioral. Indeed, coffee is the most widely consumed behaviorally active substance in the world. Caffeine, like nicotine, albeit to a lesser extent, meets some of the criteria of the WHO for a drug of dependence.[2] It acts on the dopaminergic system in the same way as amphetamines and cocaine.

Caffeine and its metabolites cross the blood brain barrier in adults and fetuses alike. It readily passes through the placenta. It is present in breast milk. The half-life in infants (up to 100 hours), the small body mass, and the inability of the fetus and neonate to detoxify caffeine make it likely that more profound effects occur on their cardiovascular and neurobehavioral systems, especially the premature – much more than on the mother.

Up to 75% of pregnant women consume coffee. Health care providers should counsel pregnant women to limit their caffeine intake.

NEJM November 25, 1999; 341: 1688-89 Editorial by Brenda Eskenazi, University of California, Berkeley.

Comment:

1 "Maternal Serum Paraxanthine, a Caffeine Metabolite, and the Risk of Spontaneous Abortion" NEJM November 25, 1999; 341: 1639-44

2 I suspect almost all devoted coffee drinkers have experienced a withdrawal headache at times when their intake is interrupted. Caffeine withdrawal symptoms are real. RTJ

11-21 INJECTION WITH METHYLPREDNISOLONE PROXIMAL TO THE CARPAL TUNNEL: RANDOMIZED, DOUBLE BLIND TRIAL

The carpal tunnel syndrome (CTS) is caused by compression of the median nerve at the wrist. Corticosteroid injection is only one of many recommended treatments.

One of the techniques entails injection just proximal (not into) the carpal tunnel. The rationale is that there is often a swelling at the volar side of the forearm, close to the carpal tunnel. This might contribute to compression of the nerve.

The risk of damaging the nerve by injection at this site is lower than by injection directly into the narrow carpal tunnel.

Lidocaine is added to the injection to reduce pain and to indicate, by diminished sensation after the injection to show that the injection was properly carried out.

Conclusion; A single injection resulted in long-term improvement.

STUDY

1. Entered 60 patients with CTS symptoms for over 3 months. All confirmed by electrophysiological testing.
2. Randomized to: 1) injection of 10 mg lidocaine, or 2) 10 mg lidocaine + 40 mg methylprednisolone. Injections were placed 4 cm proximal to the wrist crease between the tendons of the radial flexor muscle and the long palmar muscle. (See illustration p 884.)
3. This site was chosen because swelling is common close to the tunnel (in this study 3/4 of patients). Injections here are simpler and less likely to damage the nerve.
4. Improved wasdefined as no symptoms requiring further treatment

RESULTS

1. At one month	Methylprednisolone (n=30)	Placebo (n=30)
Improved	77% (23)	20% (6)

2. At one year, 15 of the 30 methylprednisolone patients were considered improved; 15 were non-responders and needed surgery.
3. No side effects from the injections.

DISCUSSION

1. The study found a beneficial effect of injection with methylprednisolone near the tunnel. A single injection was still effective at one year in half the patients.
2. These injections were safe.

CONCLUSION

A single injection of methylprednisolone close to (not into) the carpal tunnel may result in long-term improvement and should be considered before surgical decompression.

BMJ October 2, 1999; 319: 884-86 Original investigation,first author J W H H Dammers, Medical Centre, Alkmaar, Netherlands.

Read the Original!

11-22 THE YOUNG WOMAN WITH A WART ON HER NOSE

An Anecdote of a Tragedy

This is a story of a plain, simply dressed young woman who consulted her physician, asking "I want you to take this wart off my nose".

The physician could see nothing except through a magnifying glass. A tiny circular area was just a little paler than the surrounding skin. "I don't think I should touch that. If I do anything it will leave a very visible scar."

The woman walked out. The busy physician forgot about her.

The next day he was called by the local police (he was county coroner) about a woman who had been found dead. He went to the address and found the patient with the wart on her nose lying dead on her bed, an empty bottle of sedatives nearby.

"I sat buy her bedside with my head on my hands as I realized I had failed her. When she asked me to do something about an all but non-existent lesion on her nose, she was crying out for help, and I didn't hear her. If I had sensed her anguished plea for attention, for someone to listen and to show some concern for her, would it have made a difference? Perhaps not. On the other hand, if I had been sufficiently alert about how she was feeling, I might have been able to persuade her to see a psychiatrist."

"I would rather not remember that my lack of sensitivity may have led to her premature death."

BMJ November 20, 1999; 319: 1349 "*A Memorable Patient"* A narrative of a poignant personal experience by Donald W MacCorquodale, Washington, USA

Comment:

Personal experiences have powerful effects on us all. They can change the way we practice. Narratives of individual experiences are the next best way to lead us to increased sensitivity. RTJ
