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INSIDE

Financial Disclosure:
Internal Medicine Alert's Editor, Stephen Brunton, MD, is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and Astra-Zeneca, and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

Don't Put Away Those Glucose Monitors: Glycemic Variability May Be Harming Our Diabetic Patients

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

Dr. Scherger reports no financial relationships to this field of study.

Synopsis: *Glycemic variability may be an independent cause of diabetic complications. Wide fluctuations of blood glucose may not be detected by HbA1c measurement. High blood glucose levels, even if brief, may cause oxidative damage to endothelial tissue leading to atherosclerosis.*

Source: Monnier L, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patient with type 2 diabetes. *JAMA*. 2006;295:1707-1708.

THE BIOCHEMICAL MECHANISM OF GLUCOSE TOXICITY IN DIABETICS is being elucidated. In this French study of 21 patients with type 2 diabetes, the investigators demonstrated that blood glucose fluctuations caused oxidative stress independent of HbA1c levels. Specifically, in patients with the same HbA1c levels, those with greater glucose fluctuations had more production of the reactive free radical molecule superoxide. The potential damage is directly related to high blood glucose levels, which triggers the oxidative free radical production in mitochondria. The authors call for interventional trials which not only target HbA1c levels, but also acute glucose swings.

In an accompanying editorial, Brownlee and Hirsch call these findings new, yet the study was too small to confirm that the increased free radical production was enough to cause clinically significant damage. They cite several studies which found that diabetic complications such as retinopathy varied among patients with similar HbA1c levels, and that these complications are reduced with more intensive control of blood glucose.[1] Self-monitoring of blood glucose (SMBG), especially postprandial levels, is likely to remain important in the monitoring of diabetic control. This is well established in type 1 diabetes. These data suggest that SMBG will remain important for type 2 diabetics also.

VOLUME 28 • NUMBER 8 • APRIL 29, 2006 • PAGES 57-64

COMMENTARY

In a previous issue of *Internal Medicine Alert*, I wrote an article entitled "Getting practical with monitoring type 2 diabetes."[2] A meta-analysis showed that self-monitoring of blood glucose by type 2 diabetics did not improve control of the disease compared with regular monitoring of HbA1c. Much time and expense is required for frequent blood glucose monitoring, and there are large numbers of patients with type 2 diabetes in our practices. The clinical implications of the decision how best to monitor this disease are enormous. Is regular monitoring of HbA1c good enough? What do these results do to the previous recommendation?

Nothing is clinical medicine is ever simple. It would have been nice to think that HbA1c measurement, as useful as it is, would be the whole story. The important new information from this data is that glycemic variability is important. High glucose levels, even if brief, may be harmful. Measuring postprandial glucose levels is still important. But how often?

What is not discussed in this study and editorial is the diet of the patients. The glycemic index of certain foods, how rapidly they cause a rise in blood glucose, becomes very important and may shift from the popular diet books to mainstream medicine. A wise approach to diabetic patient care is for patients to know their glucose response to eating certain meals. Self-monitoring of blood glucose postprandially may become more about understanding the patient's response to food than monitoring the disease.

As this knowledge develops, we may have more refined target postprandial glucose levels that we want patients to stay below. Armed with the knowledge of high glycemic foods to avoid or eat sparingly, patients may sporadically check their 1-2 hour postprandial glucose levels. The combination of regular HbA1c levels and periodic postprandial glucose levels to monitor fluctuations and response to certain meals may emerge as the best way to manage type 2 diabetes. This approach preserves patient empowerment in monitoring and managing their disease. ■

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1. Brownlee M, Hirsch IB. Glycemic variability: A hemoglobin A1c-independent risk factor for diabetic complications. *JAMA*. 2006;295:1707-1708.
2. Scherger J. Getting practical with monitoring type 2 diabetes. *Internal Medicine Alert*. 2005;27:163-164.

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Customer Service: 1-800-688-2421.

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United States
1 year *with* free AMA Category 1 credits: $289
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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

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Eat Your Vegetables! Avoid a Stroke?

ABSTRACTS & COMMENTARY

By Matthew E. Fink, MD

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Dr. Fink reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.

Synopsis: *Increased fruit and vegetable intake, at least 5 servings per day, is associated with a reduced risk of stroke.*

Sources: He FJ, et al. Fruit and Vegetable Consumption and Stroke: Meta-Analysis of Cohort Studies. *Lancet*. 2006;367:320-326; Howard BV, et al. Low-Fat Dietary Pattern and Risk of Cardiovascular Disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655-666.

DIETARY SUPPLEMENTATION TARGETED TO REDUCE the risk of stroke and other cardiovascular diseases

has been an area of much controversy in research, especially since the publication of negative results from The Vitamin Intervention for Stroke Prevention (VISP) randomized, controlled trial (*JAMA*. 2004;291:565-575), which studied the impact of high doses of folic acid, pyridoxine (vitamin B_6), and cobalamin (vitamin B_{12}) on vascular outcomes during 2 years of follow-up. In spite of the negative results from the VISP trial, folate/B_6/B_{12} supplementation is widely prescribed by neurologists as part of a stroke prevention protocol, with the belief that there were many methodological weaknesses of the VISP study. Another possible explanation is that the benefits of diet depend on the complex mixture of vitamins, minerals, antioxidants, and fiber that are present in whole fruits and vegetables, rather than from a few specific vitamins that are administered as supplements.

Two recently published studies have looked at the effects of healthy diets on the risk of stroke and other cardiovascular diseases. He and colleagues from St. George's University of London performed a meta-analysis of 8 prospective cohort studies that included 257,551 individuals followed for an average of 13 years, and compared individuals who consumed less than 3 servings of fruit and vegetables per day, with those that consumed either 3 to 5 servings per day, or more than 5 servings per day. The relative risk of stroke was reduced in the 2 groups that had a higher daily consumption of fruits and vegetables—0.89 (95% CI, 0.83-0.97) and 0.74 (95% CI, 0.83-0.97, respectively). In real terms, those that consumed more than 5 servings per day had a 26% reduction in their risk of stroke. What elements in whole fruits and vegetables contribute to a reduction in stroke risk? Is it a specific vitamin or mineral, or is it related to other lifestyle changes? Individuals who eat more fruit and vegetables will probably have lower rates of smoking, a lower intake of salt and saturated fat, higher levels of physical exercise, and are less likely to be overweight.

A second important study, just published by Howard and colleagues, as part of the Women's Health Initiative, reported the results of a randomized clinical trial of dietary modification in 48,835 postmenopausal women, aged 50 to 79 years, designed to reduce fat intake to 20% of calories and increase intake of fruits and vegetables to 5 servings per day. The control group received diet-related education materials. The patients were followed for a mean of 8.1 years, and the primary outcome measures were fatal and non-fatal coronary heart disease (CHD) and a composite (CVD) of heart disease and stroke. The numbers who developed CHD, stroke, and CVD (annualized incidence rates) were 1000 (0.63%), 434 (0.28%), 1357 (0.86%) in the intervention group and 1549 (0.65%), 642 (0.27%), and 2088 (0.88%) in the comparison group. The differences between the groups were not statistically significant, although there was a trend toward greater reduction in CHD risk in those with higher intakes of fruit and vegetables.

COMMENTARY

How do we interpret these large, well-designed, and well-executed studies? Does diet really have any impact on cardiovascular and stroke risk? The VISP study looked at recurrent stroke risk over a 2-year period of time, a very short period of time to evaluate the effects of a dietary manipulation. The Women's Health Initiative followed healthy women for a period of 8 years, and the He et al study looked at cohorts followed for an average of 13 years. It appears that the longer a dietary manipulation is followed, the more likely it is that a significant impact will be identified. Therefore, the preponderance of evidence still supports the benefits of increasing fruit and vegetable intake in order to reduce stroke risk. What specific vitamins or other nutrients are most important remains to be determined by further research, but certainly, we as neurologists can feel confident in advising our patients: "Eat your vegetables"! ■

Increased Internet Use for Health Information

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

Dr. Ferris reports no financial relationship to this field of study.

Synopsis: *A new national survey showed people of all ages increasingly using the Internet for initial health information, but physicians remain the most trusted source to validate their findings.*

Source: Hesse B, et al. Trust and sources of health information: the impact of the Internet and its implications for health care providers: findings from the first Health Information National Trends Survey. *Arch Intern Med*. 2005;165: 2618-2624.

THE HEALTH INFORMATION NATIONAL TRENDS SURVEY has been established by the National Cancer Institute using telephone interviews, with plans to repeat biennially. This article reports the initial findings from October 2002 to April 2003. A total of 6369 persons

were included in the final sample with methods used to ensure proportional representation of age, sex, race/ethnicity, education level, and household income.

Overall use of the Internet was 63.7%, generally more common among persons younger than 65 years, women, those who were white or Asian, and who had higher levels of education and income. For persons older than age 65, 48.2% used the Internet. The difference between men and women of all ages was 69.8% women and 57.5% men. Race/ethnicity divisions varied from 65.2% for whites and 56.5% for Hispanics. The majority (86.8%) were using the Internet from home.

Respondents expressed a high level of trust for information obtained from physicians, with 49.5% reporting a desire to ask their physicians first for health information, but only 10.9% reported actually doing it. Overall, 48.6% went to Internet first for health information. Persons 18-34 years old were 9 times more likely to access the Internet before physician contact (61.1% vs 7.1%). For ages older than 65 years, there was a more equal split with 21.4% actually using the Internet first vs 20.9% contacting their physicians first.

COMMENTARY

The authors describe these findings as a "tectonic shift" in the ways our patients access health information, and indeed past surveys have shown a rapidly increasing use of the Internet: 22% in 1997, 44% in 2000, up to 63% recently. They point out that the increasing availability of high-speed connections (33% in 2003, now estimated at 50%) leads to even more frequent use of the Internet to quickly locate answers to their enquiries.

A recent study in a family medicine clinic supports these conclusions, with 65% of 1300 patients surveyed reporting access to the Internet.[1] Interestingly, a survey of 92 of their physicians underestimated this use; the majority thought less than half of patients were using the Internet. The top 4 topics for patients were diseases, medications, nutrition, and exercise.

It appears that the patient visiting us with their computer printout is unlikely to disappear anytime soon, although a significant group still do not use the Internet, particularly the elderly. The challenge for us will be to steer patients to reliable websites for information, but fortunately the survey showed they continue to trust our knowledge as the final authority. ■

Reference

1. Schwartz KL, et al. Family medicine patients' use of the Internet for health information: a MetroNet study. *J Am Board Fam Med*. 2006;19:39-45.

Fibromyalgia, Depression, and Sexual Dysfunction

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

Dr. Ling reports no financial relationship to this field of study.

Synopsis: *Sexual dysfunction, most commonly low libido, is more common in patients with fibromyalgia than in healthy controls.*

Source: Aydin G, et al. Relationship between sexual dysfunction and psychiatric status in premenopausal women with fibromyalgia. *Urology*. 2006;67:156-161.

The authors sought to determine the relationship between psychiatric and sexual status of premenopausal women with fibromyalgia compared to a control group of healthy women. Forty-eight women with fibromyalgia and 38 control patients completed Female Sexual Function Index (FSFI), the State-Trait Anxiety Inventory (STAI), and the Beck Depression Inventory (BDI).

The average BDI was significantly greater in the fibromyalgia patients and the mean FSFI was significantly lower. The incidence of sexual dysfunction was 54% in the study population compared to only 16% in the control group. The most common sexual problem encountered in both groups was sexual desire.

COMMENTARY

Do you treat fibromyalgia in your practice? Do you even believe that it exists? The answer to the first question is a resounding "yes" whether you realize it or not, ie, you are likely seeing patients with fibromyalgia whether they are labeled as such or not. The answer to the second question is up to you. If you don't believe that it is a real clinical entity, then you need to have some explanation for the myriad of pains and symptoms that so many women have. Personally, I'm a big believer, but my bias is that of someone who has an office practice that focuses on pelvic pain disorders. Consider the following:

1. Fibromyalgia occurs in 2-4% of the general population, but it is estimated that up to 90% of patients are female. (That's our practice, by definition).
2. The most characteristic symptoms are generalized pain, stiffness, fatigue, and poor sleep. (Sound familiar?)

3. Fibromyalgia symptoms often follow an episode of infection, trauma, or mental stress. (I think a few of our patients may have some of those episodes, don't you?)
4. Up to 50% of patients with fibromyalgia have a current or past history of depression.

In the generic practice that focuses on women's health, sexual functioning is a major focus, either overtly or at least just beneath the surface. Just asking about it often brings forth an unexpected flood of emotions. In the routine visit, just asking whether the patient has any sexual concerns allows her to discuss it now or gives her permission to ask at a later time. It is well-known that sexual functioning can be compromised by pain syndromes but also poor body image and/or suboptimal health overall.

In this study, we are provided interesting insights into what appears in our practices very frequently. The interplay of chronic pain states and sexual functioning as well as clinical depression is an intricate web that can be overwhelming in a busy practice. The practitioner can be a great source for rational discussion and sort the issues out by recognizing that one often leads to the others. When we see patients who present with chronic pain, asking about depression or sexual functioning should be included. When a patient complains of sexual problems, inquire into depression and pain.

Remember, where there's smoke, there's fire. ■

GERD and Rabeprazole

ABSTRACT & COMMENTARY

By Malcolm Robinson MD, FACP, FACG

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Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca, and Centocor.

Synopsis: *In contrast to the findings from a recent esomeprazole study, these authors show that on-demand therapy with rabeprazole is a good alternative to continuous treatment.*

Source: Bour B, et al. Long-term treatment of gastro-oesophageal reflux disease patients with frequent symptomatic relapses using rabeprazole: on-demand treatment compared with continuous treatment. *Aliment Pharmacol Ther*. 2005;21:805-812.

SINCE MOST PATIENTS WITH GASTROESOPHAGEAL reflux disease (GERD) suffer intermittent rather than continuous symptoms, and since most patients don't have severe erosive esophagitis, the goal of GERD therapy is mainly to relieve symptoms. This study was done in patients with either nonerosive GERD or mild esophagitis (including grade 2 erosions). This segment of the GERD population probably includes more than 80% of all patients. The study began with a 4-week selection phase with 176 patients. Approximately 89% of these patients with mild-to-moderate GERD had relief of their symptoms in this study phase. Patients who immediately relapsed in the period during which treatment was interrupted were excluded from the study since they were felt to be "PPI-addicted" and thus not really suitable for an on-demand form of therapy. However, it appears that few patients were so excluded. 152 patients were randomized to either 10 mg of rabeprazole daily 9 (n = 81) or to on-demand treatment (n = 71). The on-demand group was told to take the rabeprazole for symptoms interfering with their quality of life and was urged to discontinue therapy after 48 hours without symptoms. Symptom relief slightly favored the continuous treatment with 86.4% symptom relief vs 74.6% for the on-demand group (NS). However, quality-of-life scores were similar for both groups, and the mean consumption of rabeprazole by the on-demand group was only 0.31 tablets daily.

■ COMMENTARY

In Europe, 10 mg of rabeprazole is approved for GERD maintenance therapy. Although less potent than the usual US dose of 20 mg, the 10 mg dose has been proven to be clinically effective. Unlike the recent study of esomeprazole in erosive esophagitis, this rabeprazole study did not follow these maintenance therapy patients with endoscopy. However, the likelihood of significant disease worsening in such a setting is generally accepted to be extremely low. Patients in this study had chronic illness, impaired quality of life, and almost all experienced numerous past symptomatic relapses. Almost half (45%) of the on-demand rabeprazole recipients took between one and three tablets per week during the study. Unlike other studies of PPIs for maintenance therapy, this one did not provide 'rescue' antacids. In general, the proportional results of this study with low-dose rabeprazole parallel those of other PPIs studied in on-demand settings where antacids were provided (thereby potentially lowering the likelihood of PPI consumption). It is recognized by most physicians that their patients often opt for on-demand therapy even when daily therapy is prescribed. This study is encouraging in its support for this approach to treating a very substantial proportion of our GERD patients. ■

Pharmacology Update

Selegiline Transdermal System (Emsam®)

By William T. Elliott, MD, FACP, and James Chan, PhD, PharmD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationships to this field of study.

THE FIRST TRANSDERMAL PATCH HAS BEEN APPROVED for the treatment of depression. Selegiline is an irreversible monoamine oxidase inhibitor (MAOI), which, because of the transdermal delivery system, avoids some of the dietary restrictions associated with oral MAOIs. It is marketed by Bristol-Myers Squibb and Somerset Pharmaceuticals as Emsam®.

Indications

Selegiline patch is indicated for the treatment of major depressive disorder.[1]

Dosage

The recommended initial dose is 6 mg/24 hours (one patch). The dose may be increased by 3 mg/24 hour (at no less than 2 week interval) to a 9 mg/24 hour patch and to a maximum of 12 mg/24 hours. Tyramine-rich food or beverages should be avoided with the first dose of the 9 mg/24 hour patch and should continue until 2 weeks after a dose reduction to 6 mg/24 hour. The patch should be applied to dry intact skin on the upper torso (between the neck and waist) or the upper thigh or the outer surface of the upper arm.[1]

Selegiline patch is supplied as 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours.

Potential Advantages

Selegiline transdermal provides an alternative delivery system of MAOIs to the central nervous system without extensive inhibition of MAO-A in the gastrointestinal system.[2] Typical side effects associated with MAOI are not seen with the patch.[3] Avoidance of tyramine-rich food and beverage is not required for the initial recommended dose (6 mg/24 hrs).[4] There is also less exposure to the metabolites of selegiline, l-amphetamine and l-methamphetamine, which are the less active isomers of amphetamine and methamphetamine.[5,6]

Potential Disadvantages

As with oral MAOIs, concomitant use of other antidepressants are contraindicated with selegiline the patch including SSRIs, SNRIs (eg, venlafaxine), and tricyclic antidepressants. Carbamazepine, oxcarbazepine, and sympathomimetic amines are also contraindicated. Selegiline patch should be discontinued 10 days before elective surgery. If not possible, benzodiazepine, neuromuscular blockers (eg, mivacurium), fetanyl, morphine, and codeine should be used with caution.[1]

Comments

Selegiline is an inhibitor of MAO-A and MAO-B isoenzymes. Transdermal delivery of selegiline provides sufficient drug concentration to inhibit MAO activity in the central nervous system while minimizing inhibition of MAO activity in the liver and intestines. Tyramine dietary restriction is not required for the initial dose (6 mg/24hrs). The efficacy of the transdermal patch was shown in placebo-controlled, 6- or 8-week studies.[1,3,4] Selegiline was found to be more effective than placebo based on standard assessment methods such as the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scales (HAM-D 17, HAM-D 28), and Clinical Global Impression. Greater improvement was seen with selegiline, although one study characterized the benefit of a fixed dose of 6 mg/24 hour as modest.[4] In 2 fixed-dosed studies (6 mg/24 hr), a 50% or greater reduction in MADRS total score was achieved in 33.1% for selegiline patients compared to 20.8% for placebo patients in one study (n = 289). In the other (n = 177), a 50% reduction in HAM-D total score of 37.5% and 22.7% were achieved respectively.[3,4] The patch is generally well tolerated with 30-40% experiencing application site reactions.[3,4] Sixteen percent (16%) of patients required symptomatic treatment with topical corticosteroid or an oral antihistamine.[3] Sexual side effects were not significantly different from placebo. The wholesale cost of selegiline patch is $385.50 for 30 days.

Clinical Implications

The American Psychiatry Association Guidelines indicate that MAO inhibitors are useful in atypical major depressive symptoms, anger, hostility, and impulsivity in patients with borderline personality disorder.[7] Oral MAO inhibitors have limited use due to adverse events and need for diet restriction. The transdermal system provides delivery of a MAO inhibitor with less restrictive diet requirement and better tolerance compared to oral agents. ■

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CME Questions

16. What is the mechanism by which high blood glucose levels may cause diabetic complications?

a. By a prothrombotic effect increasing the risk of thrombus formation in blood vessels
b. By causing the overproduction of oxidative free radicals
c. By raising LDL-C and lowering HDL-C
d. By raising blood pressure

17. What is the approximate current percentage found in surveys of patient use of the Internet for health information?

a. 25%
b. 45%
c. 65%
d. 85%
e. 100%

18. The study of daily rabeprazole 10 mg vs on-demand rabeprazole 10 mg showed which of the following:

a. Patients randomized to on-demand therapy had dramatically worse quality of life vs. those who received daily therapy.
b. Adverse events and patient drop-outs from the study were quite common.
c. Nearly half of the patients on on-demand rabeprazole 10 mg took between 1 and 3 tablets per week of the study.
d. The primary goal of therapy in GERD must always be the healing of all erosive esophagitis lesions.
e. Response to 10 mg of rabeprazole is relatively low in patients with mild-to-moderate GERD as compared to those reported with more potent PPIs.

Answers: 16 (b); 17 (c); 18 (c)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances; and
- to describe cost-effective treatment regimens.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

HbA1c Following Successful Initial Metformin Therapy

APPROPRIATE INITIAL TREATMENTS for type 2 diabetes (DM2) include a diversity of oral agents and/or insulins. One of the most popular current initial treatments is metformin (MET), due to its efficacy, tolerability, and weight-neutrality. Because diabetes is typically a progressive disorder, most patients progress to require intensification of treatment. Nichols et al studied a large cohort of DM2 patients (n = 1,288) who had received MET as their initial treatment, and had achieved an A1c level of < 8%. Subjects were followed to evaluate which factors predicted loss of control of DM2, defined as the addition of other agents for glucose control, or finding an A1c > 8%.

MET failure occurred within 36 months in 50% of individuals who initially attained an A1c 7-7.9% on MET alone. In comparison, there was a steep linear relationship between degree of initial control and likelihood of secondary drug failure: those who initially attained better control on MET monotherapy (A1c 6-6.9%) did not experience drug failure until at least 60 months, and those with the best degree of control (A1c < 6%), maintained MET as successful monotherapy for greater than 84 months. Another critical factor discerned amongst this population was that weight gain had a major impact upon failure. As little as 1 kg increase in weight was associated with a 4-6% increased likelihood of treatment failure. Hence, vigilance in glucose control combined with maintenance of weight both factor significantly into long-term treatment success. ■

Nichols GA, et al. Diabetes Care. 2006; 29:504-509.

Triple Therapy in Type 2 Diabetes

THE MOST COMMONLY USED AGENTS for the treatment of type 2 diabetes are metformin and a sulfonylurea. Despite adequate doses of both of these medications, many patients remain uncontrolled, or progress to inadequate control over time. The next best step after dual therapy fails is indeterminate. It is tempting to place patients on a third oral agent, usually a thiazolidinedione (TZD), but this enthusiasm must be tempered by two cold realities: 1) that usual A1c reductions rarely exceed 1.4-1.7% on triple therapy, hence patients with baseline above 8.7% are unlikely to achieve their goal, and 2) the expense of adding a TZD is not inconsiderable. On the other hand, there is a substantial resistance to utilization of insulin, or any other injectable medications (eg, exenatide) for that matter.

To compare the utility of adding a TZD (rosiglitazone) vs insulin (glargine) to the regimen of persons uncontrolled with dual oral therapy, Rosenstock et al randomized 217 patients. In the glargine group, dose was titrated to a fasting glucose less than 120 mg/dL; in the TZD group, rosiglitazone was increased up to 8 mg/d if fasting glucose was above 120 mg/dL.

The overall reduction in A1c was similar in both groups, averaging a 1.7% reduction from baseline. However, in the group further from goal (A1c > 9.5%), the reduction in A1c with insulin was far greater than with TZD: 3.6% vs 2.6%. Although hypoglycemic events were more frequent with insulin, weight gain and lipid changes were more favorable with insulin. When faced with a challenge of best next-step treatment, there is solid evidence to provide guidance, dependent upon the degree of baseline control, risk of hypoglycemia, weight control, and cost issues. ■

Rosenstock J, et al. Diabetes Care. 2006;29:554-559.

Calcium, Vitamin D, and Fractures

CALCIUM (CAL) AND VITAMIN D (VITD) are commonly considered a cornerstone of customary treatment for postmenopausal women to prevent osteoporosis and fractures. In placebo-controlled trials of other osteoporosis therapies such as bisphosphonates and selective estrogen receptor modulators, inclusion of CAL and VITD supplementation has been standard.

The Women's Health Initiative, the same trial from we learned the limitations of postmenopausal hormone replacement therapy, included a large cohort of postmenopausal women (n = 36,282) between the ages of 50-79 who were randomly assigned to CAL/VITD or placebo, and followed for 7 years.

Although bone density was favorably affected by CAL/VITD, fractures were not. Neither hip fracture, spine fracture, nor total fractures achieved statistical significance when CAL/VITD was compared with placebo. Discouragingly, the incidence of kidney stones was increased by 17%. This data would suggest that healthy women do not experience a clinically beneficial reduction in fractures from CAL/VITD. Sensitivity analysis indicated that the subgroup of women with the highest adherence to the treatment regimen did experience a fracture reduction, but the absolute benefit was small: 4 fewer hip fractures per 10,000 women. ■

Jackson RD, et al. N Engl J Med. 2006;354:669-683. Erratum in: N Engl J Med. 2006;354:1102.

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