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Creating an Algorithm for Success

Key Factors Affecting Outcomes in
Respiratory Tract Infection Treatments

Improving Type 2 Diabetes Care:
When and How to Implement Insulin

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Pain Talk: Communicating With Patients in Pain



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A Case-Based Approach to Diagnosing and Managing Insomnia

Transient insomnia, lasting from 1 to 3 nights, affects approximately 30% to 40% of adults in a given year. As many of 50% of patients who are seen in primary care complain of chronic insomnia, which occurs more than 3 nights each week and lasts for a month or more. There is evidence that insomnia is significantly underdiagnosed in the United States, and that of those who are diagnosed with insomnia, only about one-half receive treatment. This symposium, developed in partnership with the American Academy of Physician Assistants, reviews the latest advances in sleep science and explains today's approaches for treating insomnia, which often combine behavioral and pharmacologic interventions on a patient-specific basis.

Speakers

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Introduction

Insomnia, which occurs at a prevalence in the general population of anywhere from 10% to 20% in the U.S., is on the increase, according to a survey conducted in 2005 by the National Sleep Foundation (Gallop Organization, 2005). Seventy-five percent of survey respondents reported experiencing at least one symptom of a sleep problem lasting a few nights each week or more in the past year and 28% said they had missed work activities or made errors in their work in the past three months due to sleepiness.

Sleep difficulties impair general functioning and interfere with many aspects of life and living (Table 1). Insomnia patients have problems with information processing, sequential tasks, and difficulty extrapolating from one piece of information to another — all executive functions. Impairment of cognitive functioning due to sleep loss can be reflected in decreased job performance and increased absenteeism. Persons who are deprived of sleep report increased bodily pain, and it has been demonstrated that the perception of pain is accentuated by insomnia (Roehrs et al. *Sleep* (Suppl). 2005). The coping skills of insomnia sufferers are reduced; not surprisingly, insomnia affects mood and personal relationships, and has impacts

on family and social life (Ancoli-Israel S, Roth T. *Sleep* 1999;22 (suppl 2):S347-S353). Persons afflicted with insomnia have a 4-fold increased risk of new onset depression.

Healthcare costs for people with insomnia are as much as 50% higher than for people without insomnia. Persons with sleep are also at increased risk of accidents and (Bixler EO. *Am J Psychiatry* 1979;136:1257-62). The National Highway Traffic Safety Administration reports that drowsiness was thought to be a factor in approximately 56,000 fatal automobile accidents (Vaca F. *Ann Emerg Med*.2005; 45(4):433-4).



Catherine R. Judd, MS, PA-C

The perception of pain is accentuated by insomnia; persons who are deprived of sleep report increased bodily pain.

**Table 1
 Consequences of Insomnia**

- Impaired cognitive functioning
 - Decreased job performance, increased absenteeism
 - Increased risk of accidents
- Negative impact on quality of life measures
- Increased incidence of bodily pain, poor general health
- Increased risk of psychiatric disorders, including a 4-fold increased risk of new onset depression
- Increased healthcare costs

Bixler EO. *Am J Psychiatry* 1979;136:1257-1262.
 Breslau N. *Biol Psychiatry* 1996;39:411-418.
 Mellinger GD. *Arch Gen Psychiatry* 1985;42:225-232.
 Zammit GK. *Sleep* 1999;22:S379-S385.

The science of insomnia, along with prevalence, risk factors, and consequences; its diagnosis and management, and a discussion of newer and more effective treatments, were the subject of this educational breakfast symposium held in Orlando, Florida, May 29, 2005 in association with the American Academy of Physician Assistants (AAPA) 33rd Annual Conference.

Insomnia in 2005: More is Known; More Suffer; But More Can be Done

Speaker Catherine Judd, MS, PA-C, a physician assistant associated with the Department of Psychiatry at the University of Texas Southwestern Medical Center in Dallas, pointed to the need for better identification and management of patients with insomnia. Often, patients do not discuss sleeplessness with their healthcare providers but instead self-medicate or simply endure. According to a study by Ancoli-Israel and Roth (*Sleep* 1999;22(suppl 2):S347-S353), nearly 70% of persons with insomnia had never discussed a sleep problem with their doctors. In this study, only 5% visited a doctor specifically to address a sleep problem.

In a study by Ancoli-Israel and Roth, nearly 70% of persons with insomnia had never discussed a sleep problem with their doctors. (*Sleep* 1999;22(suppl 2):S347-S353)

According to Ms. Judd, insomnia may be divided into short-term insomnia and long-term, or chronic, insomnia. Causes of short-term insomnia, lasting from 1 to 3 nights, may be illness or pain; adjustment to a new time zone; shift work; life stressors or grief; or a new sleep environment, such as a hospital or a hotel. Primary insomnia is actually considered a chronic disease. In one study to evaluate the chronicity of insomnia, 85% of patients reporting severe insomnia continued to report moderate

Table 2
Agents That May Contribute to Insomnia

Prescription Medications

- Anticholinergics
- Antidepressants
- Antihypertensives
- Antineoplastic agents
- Bronchodilators
- CNS stimulants
- Corticosteroids
- Decongestants
- Diuretics
- Histamine-2 blockers
- Smoking cessation aids

OTC Medications

- Alcohol
- Caffeine (including diet pills)
- Nicotine
- Various herbs and supplements

or severe insomnia at a 2-year follow up (Katz DA. *Arch Intern Med* 1998;158:1099-1107).

Patients with insomnia may say they have difficulty falling asleep, or staying asleep, and/or experience poor quality sleep or an inadequate duration of sleep despite adequate opportunity to sleep.

In the elderly, poor sleep is most often related to medical illness (Kupfer DJ. *N Engl J Med* 1997;336:341-346. Martinez-Gonzalez DM. *Primary Psychiatry* 2002;9:37-49). The list of medical illnesses that can cause insomnia is long and “body-system”-wide:

- Cardiac (angina, phrenic nerve dysfunction)
- Pulmonary (COPD, coughing)
- GI (nocturnal reflux, IBD)
- Musculoskeletal (pain)
- Endocrine (hypo/hyperthyroidism, diabetes, menopause)
- Neurological (dementia, Parkinson’s disease; CVA, migraine)
- Urological (nocturia, renal failure)

Chronic medical conditions and insomnia are frequently comorbid. In a study by Katz and colleagues (*Arch Intern Med* 1998;158:1099-1107), of 3,445 patients with chronic medical conditions, insomnia and severe insomnia occurred most frequently in persons who had undergone hip replacements; in those with obstructive airway diseases; and in patients with angina and congestive heart failure.

Insomnia and Depression

Insomnia and depression have a complex inter-relationship. (Benca R. Available at: <http://www.medscape.com/viewprogram/3317.pnt>. Accessed July 1, 2005). Insomnia is associated with an increased risk of psychiatric disorders, including a fourfold increase in new onset depression (Mellinger GD. *Arch Gen Psychiatry* 1985;42:225-32). Mellinger and colleagues found that 40% of insomniacs had psychiatric disorders, compared with 15% without insomnia. In another study, 33% of persons with insomnia had depression or anxiety disorders, compared with 11% of patients without insomnia (Ford DE. *JAMA* 1989;262:1479-84). Most of the time, according to a study from Dr. Roth’s laboratory, insomnia predates depression (Breslau N. *Biol Psychiatry* 1996;39:411-418). The Roth study, which evaluated a random population of adults and used a psychiatric interview at baseline and then re-interviewed the group 3 1/2 years later, found that subjects who had insomnia at the first interview had five times the risk of developing depression over the next three-plus years.

A long list of prescription and over-the-counter medications can contribute to insomnia (Table 2). Self-medication by patients with insomnia is common. According to one study of patients with insomnia, 23% reported using over-the-counter medications, many of which are of uncertain or unproven efficacy (Ford DE. *JAMA* 1989;262:1479-1484).

Caffeine and nicotine can also interfere with sleep, by decreasing total sleep time and via effects on REM (rapid eye movement) sleep. Chronic insomnia is a risk factor for substance abuse (Smith *Am J Psychiatry* 2002;159:5-11). Alcohol, the most commonly used aid to promote sleep, is a central nervous system depressant, but in terms of sleep/wake arousal centers in the brain, said Ms. Judd, it is actually a stimulant and may contribute to sleeplessness.

**Physician Assistant
Assessment of Insomnia**

In the PAs’ assessment of insomnia, an important goal is to identify an underlying cause — to determine whether the sleep disturbance is a symptom of another underlying disorder. Steps in an assessment include:

- a review of the patient’s medical and psychiatric history
- interview of bed partner (to assess snoring, movements, and behaviors during sleep)
- sleep diary (Accessible at <http://www.nhlbi.nih.gov/health/public/sleep/starslp/teachers/sleep-diary.htm>)

The sleep diary, a valuable tool, asks patients to report subjective, scaled ratings of sleep quality and quantity over a period of several weeks, as well as ratings of next-day functioning.

“The half-life of caffeine is approximately 6 hours. If you have a cup of coffee or a caffeinated soda at 3:00 in the afternoon, half of the caffeine is still on board at 9:00 at night.”

A patient history should explore functional impact; the severity of problem; duration; age on onset; any predisposing factors or lifestyle stressors (e.g., night work or travel over several time zones; a personal loss; financial or legal problems, birth of a child; use of caffeine, alcohol, prescribed medication, over-the-counter drugs, or street drugs).

Treatment Plan for Insomnia

Behavioral therapy should always be a component of the treatment plan for insomnia. Although behavioral change is not easy to implement, Ms. Judd explained, behavioral strategies for treating insomnia may be aided by positive reinforcement. She suggests that frequent, short visits with the insomnia patient may serve to spur the process along. Education regarding the principles of good sleep hygiene is impor-

tant, including maintenance of a regular sleep-wake cycle; exposure to light in the early morning in order to stimulate the arousal centers in the brain; avoidance of caffeine and nicotine from 4- to 6-hours before bed; avoidance of exercise too close to the time of sleep (3-4 hours); reserving the bed only for sleep and sex; and becoming comfortable and relaxed before bedtime.

Non-pharmacologic approaches are indeed successful. In a meta-analysis of studies to evaluate the efficacy of non-pharmacologic interventions for insomnia, Morin et al (*Am J Psychiatry* 1994;151:1172-1180) found a 50% decrease in sleep-onset latency versus controls in patients who had adopted non-pharmacologic approaches to treat insomnia, and a similar, 50% decrease in time awake after sleep onset.

In some instances, referral of patients to sleep labs or sleep disorder centers is in order. Examples of when referral may be advised are reports of lifelong sleep difficulty, to rule out narcolepsy, or unusual sleep behaviors, such as parasomnias. Referral to a sleep center is also indicated in instances where there is a high index of suspicion of a primary sleep disorder; when patients report falling asleep while driving; or of course, when standard care fails to result in improvement. ■

Regulation of Sleep and Wake

The regulation of sleep and wake, according to Tom Roth, PhD, whose work on the biological processes of sleep is widely known and published, involves homeostatic mechanisms, circadian rhythms, and ultradian processes. The basic rest/activity cycle is controlled in the brain by the superchiasmatic nucleus (SCN), a “biological clock” whose primary output is the stimulation of wakefulness. “It is theorized that wakefulness is in part achieved by CNS stimulatory output,” Dr. Roth said. At a specific point in the evening, endogenous melatonin, a sleep-related neurotransmitter, promotes inhibition of the stimulatory

**Table 3
FDA-Approved Benzodiazepine Receptor Agonists**

Drug (h)	Dose (mg)	Half-life
Triazolam	0.25	2-4
Temazepam	15-30	8-20
Estazolam	1-2	10-24
Quazepam	15	25-41
Flurazepam	15-30	24-100
Zaleplon	10	1
Zolpidem	5-10	1.5-2.5
Eszopiclone	1-3	6

output of the SCN, allowing the accumulated homeostatic influence of sleep to manifest. Important to the sleep-wake cycle — and thus to insomnia and its treatment by non-pharmacologic means — is light, which is transmitted via the retinal hypothalamic tract and registered at the suprachiasmatic nuclei, located next to the hypothalamus.

**Treatments for Insomnia:
Current and Emerging**

Over the years, as can be seen by a scan of the half-lives of the eight FDA-approved benzodiazepine receptor agonists used for the treatment of insomnia (Table 3), progress has been measured by shortened half-lives, to “... get to the right half-life of around 5 1/2 to 6 hours,” Dr. Roth said, in order to reduce daytime hangover from the hypnotic agent. Another dimension of progress was development of the more selective benzodiazepine receptor agonist agents such as zaleplon zolpidem, and eszopiclone.

The sleep system is governed by GABA, but the wake system is driven by multiple receptors, and these have become the targets of newer agents under development.

Emerging Treatments

The next step in the development of agents for sleep disorders has been enabled by the work of Dr. Roth and colleagues in explaining the action of neurotransmitters involved in sleep regulation. Emerging treatments thus aim to target specific receptors subtypes within sleep-related neurotransmitter systems and identify transmitter systems that will have an impact on both sleep and circadian processes. “It is very important to understand that sleep is an on/off system,” Dr. Roth explained. The sleep system is governed by GABA, but the wake system is driven by multiple receptors, and these have become the tar-

gets of newer agents under development.

Some strategies under development for insomnia treatment include an improved pharmacokinetic profile to address sleep maintenance insomnia. Sustained release Indiplon, and sustained release formulations of Zaleplon and Zolpidem (not FDA-approved yet) are examples of this. A handful of GABA-receptor agents are in development (gaboxadol, NGD 96-3, gabapentin, pregabalin, tiagabine). 5-HT2A antagonists under evaluation for possible future FDA approval for insomnia include eplivanserin, a selective 5-HT2A antagonist that increases slow-wave sleep, and M-100907, which is also an N-methyl-D-aspartate (NMDA) antagonist. Melatonin-receptor agonists include ramelteon, which is highly selective for, and has greater potency at MT1 and MT2 receptors, and agomelatine (MT1 and MT2 selective).

Roth and colleagues have studied ramelteon for its effect on increased sleep latency. They found in one investigation that latency to persistent sleep was significantly improved versus placebo with this agent and that its effects were not influenced by gender or age (Roth T. *Sleep* 2005;28(3):303-308). There was little or no dose-response relationship with ramelteon, an effect arising from the fact that its mechanism of action involves not CNS depression but instead action to permit sleep onset (Roth T. *Sleep* 2005;28(3):303-308). Ramelteon also increased total sleep time. Most importantly, it does not have a sedative effect, eliminating the daytime sleepiness that has characterized older agents, at low or high doses.

Case-Based Approach to Insomnia

In two theoretical patient cases, Dr. Roth made points that bear upon the evaluation of patients who have complaints of insomnia.

Case #1

Case #1 is a 78-year old sedentary retired man who recently lost his spouse of 55 years. The patient has arthritis and high blood pressure, and is taking multiple medications, including diuretics. His complaints are trouble falling asleep and

multiple arousals during the night.

Dr. Roth pointed out that in the elderly, pain is frequently associated with sleep difficulties, as is grief. As we age lower levels of endogenous melatonin make sleep difficulties more common. Also, many medications disrupt sleep. Diuretics, for example, require that persons get up during the night to go to the bathroom. Dr. Roth suggested that clinicians consider adjusting the timing of medication dosing in order to reduce its effect on sleep. He also emphasized the importance of patient education regarding the particulars of sleep hygiene, including conveying the value of instituting an exercise regimen and the fact that medication is only one part of the treatment paradigm for insomnia.

Behavioral change is as important as medical treatment for insomnia, just as it is with other chronic conditions like heart disease and hyperlipidemia.

Case #2

Case #2 is 45-year old businessman who travels between time zones frequently; has a poor diet, a limited opportunity for exercise, and regular heartburn and back pain. He complains of having trouble falling asleep at night and says that he often finds himself falling asleep at meetings.

This patient, said Dr. Roth, is a poster child for poor sleep practices (as well as other health problems). Before his is treated pharmacologically, or at the same time, he should be introduced to a program of behavioral changes, in part to separate out the sources of sleep problems from other problems. Behavioral change is a process, not an overnight fix, Dr. Roth added, but is as important as medical treatment for insomnia just as it is with other chronic conditions like heart disease and hyperlipidemia. ■

Early Aggressive Treatment of Type 2 Diabetes: Creating an Algorithm for Success

Type 2 diabetes greatly increases an individual's risk for arterial endothelial dysfunction leading to myocardial infarction and stroke, and for retinopathy, nephropathy, and peripheral neuropathy.

Epidemiological evidence supports the hypothesis that aggressive glucose control mitigates the vascular complications of diabetes. In the realm of macrovascular disease, however, not all clinicians are persuaded that clinical trial data support this hypothesis compellingly, although data do demonstrate a strong correlation between intensive treatment for both hyperglycemia and hypertension (where indicated) and improvement in microvascular outcomes.

These issues were the subjects of a symposium conducted during the 33rd Annual Conference of the American Academy of Physician Assistants (AAPA) on May 31, 2005.

Speakers

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Correlating Early Therapeutic Intervention with Pathophysiology

When thought of in the simplest definition, type 2 diabetes is a hyperglycemic disorder consisting of three metabolic defects: (i) insulin resistance in skeletal muscles and adipose tissue that prevents the uptake of circulating glucose; (ii) increased hepatic glucose synthesis; and (iii) impaired insulin secretion by pancreatic beta cells. However, because this disorder typically occurs in the context of a constellation of disorders comprising the metabolic syndrome (also referred to as syndrome X and the cardiometabolic syndrome), it is more accurately described as a systemic vascular disorder of metabolic origin leading to impaired vascular endothelial function and both macro- and microvasculopathy. These phenomena place the patient at markedly increased risk for cardiovascular and cerebrovascular disease leading to myocardial infarction and stroke, as well as for microvascular complications including retinopathy and loss of vision, peripheral neuropathy, and chronic nephropathy potentially leading to end-stage renal disease (ESRD).

Because of the systemic character of type 2 diabetes, contemporary therapeutic guidelines call for aggressive treatment of hyperglycemia and related obesity, hypertension, and dyslipidemia to ambitious target levels (see ensuing sections) thought to be critical for preventing potentially life-threatening complications. Dwight M. Deter, PA-C, discussed the correlation of therapy to specific pathophysiologic mechanisms of hyperglycemia.

Because approximately 92% of patients with type 2 diabetes have insulin resistance (Haffner SM et al. *Diabetes Care*. 1999;22:562), insulin resistance is an important target of therapy. Obesity, and particularly intra-abdominal fat, contributes to insulin resistance via increased free fatty acids and subsequently to diabetic dyslipidemia characterized by increased triglycerides and small, dense, low-density lipoprotein



Dwight M. Deter, PA-C

cholesterol (LDL-C) particles (Bruzell JD et al. *Diabetes Care*. 1999;22(Suppl 3):C10). Insulin resistance is the first step on the pathway to type 2 diabetes, occurring initially as hyperinsulinemia with near-normal glucose tolerance (prediabetes) and later, as beta cell function declines, as insulin resistance with decreasing insulin levels and impaired glucose tolerance. Type 2 diabetes occurs as the functioning of beta cells declines. The decline in beta cell function leading to the onset of type 2 diabetes may take as long as 12 years or more.

The contributing factors in type 2 diabetes present multiple therapeutic targets for which pharmacologic therapies are now available for use in conjunction with behavioral modifications that reduce body fat, strengthen skeletal muscle, and limit glucose ingestion.

The contributing factors in type 2 diabetes present multiple therapeutic targets for which pharmacologic therapies are now available for use in conjunction with behavioral modifications that reduce body fat, strengthen skeletal muscle, and limit glucose ingestion. Specifically, the glitazones (e.g., pioglitazone and rosiglitazone) improve glucose uptake and reduce production of free fatty acids. These same agents and metformin improve insulin sensitivity, and they all reduce hepatic glucose output. Sulfonylurea agents such as glimepiride are insulin secretagogues that stimulate pancreatic beta cells. Repaglinide, a drug of the meglitinide class that is unrelated to the sulfonyl-

lureas, has a similar mechanism of action. Alpha-glucosidase inhibitors, such as acarbose and miglitol, delay the digestion of ingested carbohydrates, thus decreasing the typical postprandial hyperglycemic spike and lowering the mean glycosylated hemoglobin (Hgb_{A1c} or A1c).

The time line for introducing medications in patients with insulin resistance and type 2 diabetes remains unresolved. The traditional approach has been to postpone pharmacologic intervention until the onset of chronic hyperglycemia and then to initiate stepped care. Following nutritional therapy and behavioral changes, nonresponders were typically “treated to failure” with oral monotherapy before introducing combination treatment. Insulin therapy with or without oral medications was reserved for beta cell cessation. With the current emphasis on early aggressive intervention, however, there is increasing interest in the off-label treatment of prediabetes with metformin, alpha-glucosidase inhibitors, or thiazolidinediones. In addition, traditional stepped care for

Table 1
Goals for Glycemic Control

Biochemical Index	Normal	Goal
Fasting/Preprandial Capillary Glucose (mg/dL)	< 100	ADA: 80–120; Action at <80 or >140 ACE: <110
Bedtime Capillary Glucose (mg/dL)	< 110	ADA: 100–140; Action at <100 or >160 ACE: No Recommendation
Postmeal Glucose, 2-Hour (mg/dL)	< 140	ADA: No Recommendation ACE: < 140
A1c (%) Normal Range: 4–6%	< 6	ADA: < 7; Action at > 8 ACE: < 6.5

ADA Position Statement. *Diabetes Care*. 2001;24(suppl 1):SA33–S43.
ACE Consensus Conference on Guidelines for Glycemic Control. *Endocrine Practice*. 2001.

the patient with type 2 diabetes is now regarded as too limited, largely because the majority of patients are not adequately controlled and because newer classes of drugs offer reasonable expectation of better control at earlier stages in disease progression. Especially important is the widespread acceptance of

polypharmacy based on the various targets of opportunity among the underlying mechanisms of this disease. The glycemic control targets recommended by the American Diabetes Association (ADA) and the American College of Endocrinology (ACE) appear in Table 1. ■

Macrovascular Disease Risk Modification in Diabetes

Although there is evidence that lowering blood pressure, plasma glucose concentrations, and A1c levels may reduce the risk for macrovascular complications in diabetes, the current target levels are consensus figures based on evidence related to medications already subjected to extensive clinical testing. The optimum levels remain uncertain. Nor is it known whether direct modulation of insulin resistance will affect cardiovascular and cerebrovascular outcomes beneficially. These less well understood aspects of diabetes care were discussed by David M. Kendall, MD.

Atherogenic Dyslipidemia

Chronically elevated LDL-C is associated with an increased risk for cardiovascular events, and it is the first priority of lipid management for patients with type 2 diabetes. Both epidemiological data and outcome trials demonstrate a linear correlation between LDL-C reduction and a decrease in clinical events

rates. Based on this evidence, the consensus target level for LDL-C is less than 100 mg/dL. However, while clinical trials utilizing low to moderate dosages of statin therapy demonstrate that this strategy is effective for reducing cardiovascular disease rate, it does not ameliorate the risk of events. Consequently, aggressive LDL-C lowering, often requiring high-dose statin therapy, is recommended for many patients. Indeed, for the highest risk patient, an LDL-C target of 70 mg/dL should be considered. Alternatively, lowering LDL-C by 30% to 40% is very effective in reducing risk, perhaps as effective as treating to a specific target LDL-C level.

Epidemiologic data suggest that patients with diabetes frequently present with mixed lipid disorders characterized by high triglyceride (TG) and low HDL-C levels. Even in those patients with acceptably low levels of LDL-C, abnormal HDL-C and TG levels may affect risk significantly. Accordingly,

although the third version of the Adult Treatment Program of the National Cholesterol Education Program (NCEP-ATP III, 2001) cites LDL as “the primary target of therapy,” it is now recognized that fibrate or niacin therapy should be considered for diabetes patients with elevated TG and/or decreased HDL-C levels (Grundy SM. *Circulation*. 2004;110:227). The recommendation for the use of such agents is supported by epidemiologic data from the Framingham Heart Study indicating that individuals with HDL levels below 25 mg/dL have a three-fold greater risk for cardiac events than those who have very high LDL-C concentrations along with protective levels of HDL-C (Castelli WP. *Can J Cardiol*. 1988;4(Suppl A):5A). In addition, clinical trials utilizing gemfibrozil and fenofibrate as treatment for mixed dyslipidemia support a critical role for controlling TG and increasing HDL-C. In both the Veterans Administration High-Density Lipoprotein Cholesterol

Intervention Trial (VAHIT) and the Diabetes Atherosclerosis Intervention Study (DAIS), modest increases in HDL-C and modest reductions in TG resulted in an approximate 25% risk reduction for future cardiovascular events (Koskinen P. *Diabetes Care*. 1992;15:820; Rubins HB. *Arch Intern Med*. 2002;162:2597; DAIS Investigators. *Lancet*. 2001;357:905).

Hypertension

High blood pressure affects approximately two-thirds of individuals with diabetes, and lowering systolic blood pressure is of established benefit for significantly reducing risk for cardiovascular events. Clinical trials utilizing the major classes of antihypertensive therapies – thiazide diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and various combinations including beta-blockers – have consistently demonstrated the benefit of blood pressure control. Current treatment algorithms suggest a target systolic blood pressure of less than 130 mmHg. Despite these somewhat more intensive treatment targets for patients with diabetes, none of the large clinical trials, all of which used combination therapy, have consistently achieved such levels of blood pressure control. A retrospective review of selected trials indicates that blood pressure lowering to approximately 140 mmHg not only requires multidrug therapy but can significantly reduce cardiovascular disease risk (Bakris GL. *J Clin Hypertens*. 1999; 1:141). Thus, the desirable blood pressure target for optimally managing cardiovascular disease risk remains to be determined. Similarly, there does not appear to be a preferred agent, although the compounds that affect the angiotensin-renin-aldosterone system, along with thiazide diuretics, appear to have significant benefit.

Hyperglycemia

There is strong epidemiological support for the association between hyperglycemia and cardiovascular disease risk and some support for the hypothesis that rigorous glucose control may indeed reduce that risk. However, there are insufficient data from randomized clinical

trials to support the use of intensive glycemic control solely for purposes of reducing cardiovascular disease risk. A large body of epidemiological evidence demonstrates a relationship between glucose levels and the relative risk for cardiovascular disease (Khaw K-T. *BMJ*. 2001;322:15). Similarly, an analysis of data from the United Kingdom Prospective Diabetes Study (UKPDS) estimates that each increase of 1.0% in A1c is associated with a 16% increase in cardiovascular disease risk (Stratton IM. *BMJ*. 2000;321:405). However, clinical trials of aggressive glucose lowering have not demonstrated a conclusive benefit for reducing cardiovascular risk, although some studies have suggested a relative risk reduction ranging from 16% to 44%. Nevertheless, few if any of these trials have demonstrated a statistically significant benefit; and in one large trial (the Veterans Administration Cooperative Study of Diabetes Mellitus) aggressive glucose control was associated with an increase in cardiovascular events. Thus, the relationship between glucose reduction and long-term cardiovascular risk remains under study.

Insulin Resistance

It is well established that insulin resistance is associated with an increase in cardiovascular disease risk, but whether directly improving insulin resistance can reduce that risk has not been elucidated clearly. Weight control improves many of the myriad components of the metabolic syndrome including insulin resistance, but our ability to help patients sustain weight reduction is limited. Moreover, the full benefit of lifestyle modification, including weight reduction, on cardiovascular disease risk remains to be determined. Diabetes medications such as metformin secretagogues are of known value for improving glu-

ucose control, but their specific effect on cardiovascular risk remains controversial. Data from the UKPDS do suggest that metformin use may be associated with a reduced cardiovascular risk in obese patients with diabetes. Insulin is known to limit vascular inflammation. It has been shown to reduce mortality from myocardial infarction and to limit the risk of cardiovascular events following coronary artery bypass. One of the challenges for the future is to determine if direct modulation of insulin resistance by a combination of behavioral and pharmacologic therapy will affect rates of cardiovascular events in type 2 diabetes.

The broad array of potential therapeutic targets in type 2 diabetes suggests that aggressive multifactorial treatment regimens will provide substantial protection against cardiovascular events. Using that hypothesis, Danish investigators randomized patients to receive either conventional or intensive treatment for hyperglycemia, dyslipidemia, and hypertension. Intensive therapy resulted in statistically significant improvements relative to conventional treatment in total cholesterol, TG, and systolic blood pressure, and a trend toward significant improvement in A1c. This intensive multifactorial treatment was associated with a 53% reduction in combined cardiovascular events (Gaede P. *N Engl J Med*. 2003; 348:383). Although a small study (N=150), it provides promising evidence for a benefit from such an approach for patients with type 2 diabetes. A large trial of 10,000 patients is currently underway in the United States and Canada that will further illuminate the value of intensive multifactorial treatment for reducing cardiovascular disease risk in type 2 diabetes ([www.ACCORD trial.com](http://www.ACCORDtrial.com)). ■

Microvascular Disease Risk Modification in Diabetes

The pathogenic processes that give rise to macrovascular disease in diabetes also affect the microcirculation in multiple organs. Consequently, among the

most common sequelae of diabetes are retinopathy, nephropathy, and peripheral neuropathy. Because the retinae, glomeruli, and peripheral nerves are par-

ticularly vulnerable to glucose fluctuation, uncontrolled or poorly controlled hyperglycemia poses a threat to each of them. These issues were discussed by David E. Kelley, MD.

The entry of glucose into a cell is achieved through a protein channel in the lipid bilayer. In contrast to the glucose transporter in the central nervous system, which admits glucose at a constant low level, the protein channel of the vulnerable organs admits glucose without a shut-off mechanism, thus enabling glucose to overwhelm the cell. In essence, therefore, the cells of these organs have no defense against hyperglycemic influx. Intracellular glucose in the microvascular endothelium undergoes non-enzymatic glycosylation, the end products of which contribute to cell damage. These include altered ionic charges leading to abnormal function, oxidative stress and the highly reactive superions of oxidative burst, abnormal protein folding in DNA replication, and resistance to proteolysis. These, in turn, lead to structural changes, the trapping of macromolecules including LDL-C, leakage of proteins, changes in osmolality that alter cellular metabolism, and the induction of pro-inflammatory cytokines. Together, these phenomena are atherogenic. Because this cascade of events commences with glycosylation, A1c is a critical marker for cell damage in diabetes and an important measure of response to treatment.

Diabetic retinopathy

Diabetic retinopathy is the foremost cause of adult blindness in the United States, accounting for approximately 24,000 new cases per year. Up to 90% of vision loss may be preventable by early intervention, effective control of A1c, and treatment of macular edema. An annual eye examination with dilation is essential for each patient with type 2 diabetes, regardless of age, as a means of preventing diabetes-related blindness.

Diabetic nephropathy

Diabetic nephropathy is the number one cause of ESRD in the United States, accounting for approximately 28,000 new cases annually. Although there are ethnic variations, within 20 years of diagnosis of type 2 diabetes approximately 50% of patients given traditional stepped care have some evidence of proteinuria

(Knowles WC. *The Kidney and Hypertension in Diabetes Mellitus*. 1988;25), a marker for both glomerular degeneration and cardiovascular disease.

A review of data from the first National Health and Nutrition Evaluation Survey cohort (NHANES I) determined that the relative risk of death due to ESRD among patients with type 2 diabetes is greater than that for ischemic heart disease (Gu K et al. *Diabetes Care*. 1998;21:1138). Moreover, the risk of all-cause and cardiovascular mortality in type 2 diabetes correlates directly with increasing proteinuria over time (Miettinen H et al. *Stroke*. 1996;27:2033). Much of this renal damage may be preventable with appropriate care and repetitive monitoring of urinary protein.

A review of data from the first National Health and Nutrition Evaluation Survey cohort (NHANES I) determined that the relative risk of death due to ESRD among patients with type 2 diabetes is greater than that for ischemic heart disease.

Diabetic neuropathy

Diabetic neuropathy is the leading cause of non-traumatic lower-extremity amputation in the United States. Individuals with diabetes have a 15- to 40-fold greater risk of requiring amputation than the non-diabetic population. Of the approximately 67,000 patients with diabetes who undergo these amputations annually, the vast majority have both vascular disease and symptomatic peripheral neuropathy. Deterioration of the foot or lower leg typically begins with an insensitizing blister that progresses to an infected ulcer that the damaged vascular system fails to heal.

The key to diagnosing diabetic neuropathy is the foot examination, assisted by a screening device such as the Michigan Neuropathy Questionnaire. For symmetric polyneuropathy, a monofilament tests for sensation at the level of the foot and a 124 Hertz tuning fork for vibratory sensations and ankle reflexes. Clues to autonomic neuropathy include tachycardia unexplained by

hydration, fever, or exercise, orthostatic hypotension, urinary retention, and diarrhea.

For the prevention of complications in diabetes, the American Diabetes Association (ADA) recommends therapy targeting preprandial glucose levels of 90-130 mg/dL (normal <110 mg/dL) and A1c less than 7.0% (normal <6.0%). It has been established that the relative risk for microvascular complications in a combined population of patients with type 1 and type 2 diabetes is directly correlated with the A1c level, with each 1% increase above normal adding significantly to risk. However, data from the UKPDS indicate that controlling A1c decreases the incidence of retinopathy in type 2 diabetes by 17% to 21% and of nephropathy by 24% to 33% (UKPDS Study Group 33. *Lancet*. 1998;352:853). In that study, in which patients were randomized to receive either conventional treatment or intensive therapy for hyperglycemia, intensive therapy was associated with statistically significant decreases in albuminuria (33%; p=0.000054) and retinopathy (21%; p=0.015) (UKPDS Study Group. *Lancet*. 1998;352:352).

Importantly, the combined effects of glucose control and blood pressure control may be profound in some patients with diabetes. In the UKPDS, for example, intensive antihypertensive treatment with a goal of reducing systolic pressure by 10 mmHg was associated with a 13% reduction in symptomatic microvascular disease (Adler AI et al. *BMJ*. 2000;321:412).

Although trial data suggest that aggressive treatment of hyperglycemia and hypertension in patients with diabetes significantly decreases the risk for microvascular complications, only one-seventh of diagnosed patients are treated to maintenance A1c levels of less than 7.0%. Early diagnosis and tight glucose control are essential for avoiding or delaying loss of beta cell function and for reducing the development or progression of macrovascular and microvascular complications. (In the UKPDS, half of patients already had evidence of microvascular disease at diagnosis.) Progression of microvascular complications may begin at fasting blood glucose levels as low as 110-120 mg/dL, thus explaining the current interest in the off-label treatment of prediabetes. ■

Key Factors Affecting Outcomes in Respiratory Tract Infection Treatments

Respiratory tract infections (RTIs) account for 116 million office visits yearly. Many physician assistants must deal with this problem on a daily basis and it is important that they become aware of new developments in the diagnosis and management of these infections.

At a symposium held at the annual meeting of the American Academy of Physician Assistants in Orlando, Florida, two experts in RTIs discussed the important role physician assistants have in treating them.

Speakers

Theresa Fontenot, PA-C
Family Practice Physician Assistant
Family Medical Group of Texarkana
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Gregory A. Volturo, MD, FACEP
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Ensuring Proper Treatment through Accurate Diagnosis and Management

Respiratory tract infections (RTIs) are responsible for millions of antibiotic prescriptions and billions of dollars in healthcare costs. Unfortunately, antibiotics are often prescribed improperly and it is important for physician assistants to be familiar with the different types of RTIs, their different pathophysiologies, and their different treatment options. The pathophysiology of common RTIs and diagnostic procedures used to properly identify RTIs were discussed by Theresa Fontenot, PA-C, Family Practice Physician Assistant at Family Medical Group of Texarkana, in Texarkana, TX.

Acute Sinusitis

Acute sinusitis is a condition manifested by an inflammatory response involving mucous membranes of the nasal cavity, paranasal sinuses, fluids within these cavities, and the underlying bone. Sinusitis can be further subgrouped into acute, subacute, recurrent and chronic sinusitis. Ms. Fontenot said, “acute is anything that lasts less than four weeks and the symptoms completely resolve after appropriate antibiotic therapy has been performed.”

Differential diagnosis is essential for properly diagnosing RTIs and this is especially true with acute sinusitis which is used to rule out viral and allergic

***D*uring an acute migraine headache, the superior salivatory nucleus is activated and the associated nerves go directly over the frontal and maxillary sinuses that can often create symptoms similar to sinusitis.**

rhinitis, tumors, presence of foreign bodies, and migraines. Ms. Fontenot briefly discussed the fact that migraines are often mistaken for a ‘sinus headache’. During an acute migraine attack, the superior salivatory nucleus is activated and the associated nerves go directly over the frontal and maxillary sinuses that can often create symptoms similar to sinusitis and Ms. Fortenot advised PAs to ask their patients if they have a history of migraines.

Ms. Fontenot told the audience that a diagnosis can be made based on ‘factors’ (Table 1) and acute sinusitis occurs if the patient has 2 or more major factors or 1 major and 2 minor factors.

Table 1
Factors Commonly Associated with Diagnosis of Acute bacterial Sinusitis

Major Factors	Minor Factors
<ul style="list-style-type: none"> • Facial pain/pressure • Facial congestion/fullness • Nasal obstruction/blockage • Nasal discharge/purulence • Hyposmia/anosmia • Purulence in nasal cavity on examination • Fever 	<ul style="list-style-type: none"> • Headache • Halitosis • Fatigue • Dental pain • Cough • Ear pain, pressure, and/or fullness

Other observations used to diagnose sinusitis include:

- ≤ 4 weeks' duration
- URI symptoms worsening after 5 days and/or persisting more than 10 days
- Purulence in the nasal cavity on examination
- Resolves completely after appropriate medical therapy.

Acute Bronchitis

Acute bronchitis is an inflammation of the tracheobronchial tree. It is generally a self-limited condition with return to normal pulmonary function and complete healing usually occurring. Ms. Fontenot noted, "it primarily happens in the winter months, typically to healthy adults who suffer some sort of predisposing factor, such as allergies, or a viral URI." Acute bronchitis is consistently one of the top 10 reasons for outpatient visits to primary care providers. Approximately 5% of adults report some sort of episode of acute bronchitis each year and 90% of these people seek medical treatment.

"Your differential diagnosis includes anything that makes you wheeze: such as reactive airway disease, COPD, allergies, asthma, or predisposing factors such as sinusitis, common cold, pneumonia, foreign body or other medical causes such as congestive heart failure, GERD, bronchogenic tumor, or some sort of aspiration syndromes," stated Ms. Fontenot.

Acute bronchitis is usually caused by a viral infection (95%). "This is a very important point, as we all tend to over treat bronchitis with antibiotics," said

Ms. Fontenot said, "if we go back to what we learned in school, if you get a good physical and a good history, especially with a good history, these people are going to tell you what their diagnosis is, just based on what they've been telling you."

Ms. Fontenot. Only 5% of cases are caused by bacteria and Ms. Fontenot urged the audience to prove that it's one of the other five percent before initiating antibiotic therapy.

A diagnosis of acute bronchitis is based on a good history and physical exam. A chest x-ray may be indicated if you hear rales or an area of consolidation (i.e., crackle heard or lung engorgement felt) in order to rule out pneumonia, and sputum cultures if a bacterial cause is suspected.

Acute Exacerbation of Chronic Bronchitis

A good medical history can easily differentiate acute exacerbations of chronic bronchitis from acute exacerbations of chronic obstructive pulmonary disorder (COPD). The definition of chronic bronchitis is an increase in mucous production and recurrent cough for at least three months in two consecutive years for whom all other causes of chronic cough have been excluded. The prominent symptoms are intermittent cough, dyspnea, cyanosis, and purulent sputum production.

Patients experiencing acute exacer-

bations of chronic bronchitis tend to seek medical treatment. Ms. Fontenot stressed the importance of the pulmonary function tests and encouraged their use to help differentiate reversible from irreversible pulmonary diseases.

Community-Acquired Pneumonia

Cardinal symptoms of pneumonia are pleuritic chest pain, fever, chills, and increased production of purulent sputum "On a physical exam, you're going to hear decreased breath sounds, usually in an area of consolidation," said Ms. Fontenot. Ms. Fontenot also noted that chest x-rays, a complete blood count and sputum smears are also important to determine the etiology.

Concluding Remarks

Ms. Fontenot ended her presentation by saying, "we have the ability to accurately diagnose respiratory tract infections from other causes and establish treatment paradigms to support our patients," adding, "if we go back to what we learned in school, if you get a good physical and a good history, these people are going to tell you what their diagnosis is, just based on what they've been telling you." ■

Key Factors Affecting Outcomes in Respiratory Tract Infection Treatments

Gregory A. Volturo, MD, FACEP, Associate Professor of Emergency Medicine and Vice-Chairman in the Department of Emergency Medicine at the University of Massachusetts Medical Center in Worcester, MA concluded the symposium with an overview of treatment options available for patients with RTI.

Treatment – Prescription Trends and Concerns

The treatment prescribed for any given RTI is dependent on many factors (Table 2).

"We're thinking about the patient's age, allergies, renal function, hepatic

function and comorbid conditions," said Dr. Volturo. For example, Dr. Volturo said, "we think about drug dosing frequency because none of us can take a pill more than once or twice a day." Also important is the development of antibiotic resistance but Dr. Volturo warned the audience not to be too concerned about resistance and to remember that there are two different types of resistance: high and intermediate resistance. "In 2000, the CDC looked at this resistance problem and said, all those patients with intermediate resistance get better, maybe it's not the bug that's resistant, maybe the fact is, we haven't defined resistance correctly," noted Dr. Volturo. In 2002,

Table 2
Important Factors in Antibiotic Selection

Patient	Etiology	Resistance	Drug	Cost
Age	Bacterial	Geography	Dosing frequency	Formularies
Allergies	Viral	Nosocomial	Side effects	Hospitalization
Renal Function	Mixed	Multiple	Interactions	Length of treatment
Hepatic function			Formulation	
Comorbidities				

Dr. Volturo said, “we think about drug dosing frequency because none of us can take a pill more than once or twice a day.”

the National Commission of Clinical Laboratory Standards also reexamined how they defined resistance and changed the breakpoints for non-meningeal isolates. The net result is that the ‘breakpoint’ for an antibiotic such as ceftriaxone is now 95% susceptible against non-meningeal *S. Pneumoniae* isolates (not 82% as previously measured) and this is comparable to the more expensive fluoroquinolones (99%). Dr. Volturo said, “there’s no reason, in most cases, when we’re dealing with pneumococcal infection, to go right to a fluoroquinolone, no reason.” The recent overuse of fluoroquinolones adds to the resistance problem and in most cases, a less expensive antibiotic is effective.

The major driving force for resistance is increased number of antibiotic prescriptions. “If you look at antibiotic resistance, no matter what antibiotic you look at, if we’re looking at staph, if we’re looking at pneumococcus, if we’re looking at things like klebsiella, if we’re looking at pseudomonas, the major contributor to resistance, the major driver of resistance happens to be antibiotics,” stated Dr. Volturo, adding, “as health-care providers, we own it because we overprescribe antibiotics.”

To illustrate the overuse of antibiotics, Dr. Volturo discussed a Canadian study which found that 50% of levofloxacin use was inappropriately prescribed based on the Canadian Thoracic Society Guidelines (*Arch Intern Med.* 2003;163:797-802). Similarly, a study from the University of Pennsylvania observed that one third of the patients who received antibiotic treatment showed no evidence of infection (*Arch Intern Med.* 2003;163:601-605). Dr. Volturo said, “all of us in this room would agree, somebody who comes into the office with a common cold has a viral infection, right?” adding, “yet seventy percent of those patients leave with a prescription for an antibiotic. That’s something we have to stop if we want to get a handle on resistance.”

In regard to fluoroquinolone use, Dr. Volturo suggested we should adhere to the CDC’s guidelines and limit fluoroquinolone use due to concern for increased resistance with their overuse. Dr. Volturo added, “the Infectious Disease Society of America (IDSA) is so concerned about fluoroquinolone overuse that they’ve stated that continued unabated use of these agents may result in the demise of the entire class of fluoroquinolone antibiotics within the next five to 10 years.”

Community-Acquired Pneumonia

Treatment options for persons with CAP are dependent on many factors, including the patients’ recent medical history. For example, persons who have recently been on an antibiotic (i.e., < 3 months) should be given a given a different class of antibiotic. “If they’ve been on fluoroquinolones, don’t use fluoroquinolones

as part of primary therapy, use macrolides as part of primary therapy,” noted Dr. Volturo.

To maximize compliance and reduce resistance, Dr. Volturo said the recent trend is to give short-term, high-dose antibiotics such as 1-day azithromycin, 3-day azithromycin, or once a-day ceftriaxone. Dr. Volturo said this treatment regimen promotes patient compliance and may reduce resistance. With longer treatment regimens (i.e., 10 days), patients compliance often is poor once the symptoms go away yet the bacteria may still be present and allowed to develop resistance.

The Antibiotic Selection for Community-Acquired Pneumonia (ASCAP) Consensus Panel meets annually to recommend treatment options for CAP and this past year, the ASCAP meeting was chaired by Dr. Volturo. The panel tabulated an excellent summary of first-line and alternative first-line therapies for a number of patient profiles and can be read at: www.ahcpub.com/ahc_root_html/hot/archive/cap2005.html.

For example, the ASCAP Panel recommends azithromycin as first-line therapy and telithromycin as alternative first-line therapy for treatment of outpatient CAP. In patients with comorbid conditions (i.e., elderly, COPD) who are at greater risk for resistant organisms, moxifloxacin or telithromycin is recommended. In CAP patients from nursing homes requiring hospitalization, dual administration of ceftriaxone and azithromycin is recommended as first-line therapy. Monotherapy with a fluoroquinolone is an alternative but Dr. Volturo stated that dual therapy usually is more effective.

Acute Bacterial Sinusitis

Ninety percent of patients with common colds have symptoms similar to acute sinusitis. “The problem is, only about one half to two percent of the patients actually develop a bacterial infection,” said Dr. Volturo, adding, “if you have a cold, symptomatic treatment is needed: no antibiotic is needed and you have to wait it out.” If bacterial infection is diagnosed, the patient has several treatment

options available. First-line antibiotic therapy options include:

- Amoxicillin 875 mg
PO BID x 10-14 days
- Amoxicillin/clavulanate extended release
 - 500 mg/125 mg PO TID x 10 days
 - 2000 mg/125 mg PO BID x 10 days
- Azithromycin 500 mg
PO QD x 3 days

If the patient is allergic to the first line antibiotics, alternative first-line antibiotics include:

- Moxifloxacin 400 mg
PO QD x 10 days
- Levofloxacin 500 mg
PO QD x 10-14 days
- Clarithromycin 500 mg
PO BID x 14 days
- Doxycycline 100 mg
PO BID x 10 days

Other first-line alternatives include cefpodoxime, cefuroxime, and ceftibuten. Dr. Volturo said, “my bias here is really to go either with azithromycin or telithromycin as initial therapy in patients with mild to moderate bacterial sinusitis.” If the patient has not improved after two treatments, ceftriaxone or com-

bination therapy is a third option.

In addition to antibiotic treatment, Dr. Volturo also reminded the audience that adjunctive therapy is helpful and should be encouraged (i.e, rest, fluids, nutrition, antihistamines, decongestants, expectorants, saline nasal sprays, anti-tussives, analgesics, humidifiers, and nasal steroids).

Acute Exacerbation of Chronic Bronchitis

A recent report indicates that management of acute exacerbations of COPD or chronic bronchitis is difficult. For example, 43% of patients who go to an emergency room for acute exacerbations of COPD relapse or are still symptomatic 2 weeks later (*J Am Ger Soc.* 2003;51:908-916). Treatment options for acute exacerbations include beta-agonists, anticholinergics, home oxygen, systemic corticosteroids, and antibiotics. Treatment will be dependent on the patients history and current condition but according to Dr. Volturo, “all patients should be receiving beta-agonists or anticholinergics and probably both in acute exacerbations,” adding, “there’s a little bit of debate over which one is better and which one should come first.”

Dr. Volturo said that steroids are

good for the initial exacerbation but should not be given for long periods of time and studies indicate there is no benefit from steroid use after two weeks. The role of antibiotics in acute exacerbation treatment has been controversial, however, a study by Adams et al (*Chest.* 2000;117:1345-1352) showed improved relapse rates in patients given antibiotics, especially in moderate or severe patients.

Dr. Volturo discussed the Canadian Thoracic Society Guidelines on acute exacerbation of chronic bronchitis which categorized patients into three groups, simple chronic bronchitis, complicated chronic bronchitis, and chronic suppurative (at risk for *P aeruginosa*). As shown in Table 3, initial antibiotic treatment in simple bronchitis is fairly straight-forward and a macrolide or a 2nd /3rd generation cephalosporin agent can be used. In contrast, patients with complicated chronic bronchitis usually require a fluoroquinolone.

Guidelines are available to help physician assistants choose the best treatment option.

**Table 3
Canadian AECB Therapy Guidelines**

Simple Chronic Bronchitis	Complicated Chronic Bronchitis	Chronic Suppurative (at risk for <i>P aeruginosa</i>)
<ul style="list-style-type: none"> • Any age • < 4 exacerbations/yr • No cardiac disease • FEV₁ > 50% 	<ul style="list-style-type: none"> • > 64 years • ≥ 4 exacerbations/yr • Serious cardiac disease • FEV₁ < 50% • Home oxygen • Chronic oral steroids • Antibiotic within 3 months 	<ul style="list-style-type: none"> • Patients with chronic bronchial sepsis • Need for chronic corticosteroid therapy and frequent (> 4/yr) course in antibiotics • FEV₁ < 35%
<p>Macrolide (azithromycin, clarithromycin), or 2nd or 3rd generation cephalosporin, doxycycline</p> <p>Amoxicillin, TMP/SMX</p>	<p>Fluoroquinolones or Amoxicillin/clavulanate</p>	<p>Target to cultures Empiric for <i>P aeruginosa</i>: Ciprofloxacin Consider parenteral treatment in hospital</p>

Concluding Remarks

RTIs are very common but remain a challenge to diagnose and treat. In many patients, an antibiotic is unnecessary but if an antibiotic is required, then the physician assistant’s choice of antibiotic is dependent on many factors. Guidelines are available to help physician assistants choose the best treatment option. If possible, a treatment regimen that promotes compliance and attenuates resistance is also important. ■

Improving Type 2 Diabetes Care: When and How to Implement Insulin

Type 2 diabetes is a disease in which both insulin resistance and decreased insulin secretion play major roles. The standard of care for patients with type 2 diabetes is to attempt to normalize blood glucose levels. Although oral agents are effective at controlling fasting and postprandial blood glucose levels as well as Hgb_{A1C} in the short-term, more than half of the patients with type 2 diabetes will eventually need insulin due to the progression of their disease. Today, clinicians have a number of choices by which to individualize insulin therapy to address patients' impaired beta-cell function and their ability to achieve and maintain glycemic targets. This symposium, presented in conjunction with the American Academy of Physician Assistants (AAPA) annual conference, addressed important issues regarding insulin use for physician assistants who regularly care for and manage patients with type 2 diabetes.

Speakers

Dwight M. Deter, PA-C (Moderator)
Southwest Endocrine Consultants
El Paso, TX

David M. Kendall, MD
International Diabetes Center
Minneapolis, MN

Christopher E. Sadler, MA, PA-C, CDE
Diabetes and Endocrine Associates
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Introduction

In the United States and worldwide, diabetes has reached epidemic proportions. The highest incidence is in China and India, but the incidence is also increasing in the U.S. It is estimated that by the year 2025, more than 300 million persons worldwide will have diabetes, making this disease an urgent management issue for all healthcare professionals.

Type 2 diabetes is a “dual defect” disease, with both insulin resistance and decreased insulin secretion contributing to its long-term effects. Progressive beta-cell failure may begin as many as ten years before hyperglycemia reaches a threshold consistent with a diagnosis of type 2 diabetes (Lebovitz HE. *Diabetes Rev.* 1999;7:139-153). Large studies, such as the United Kingdom Prospective Diabetes Study (UKPDS), have established this fact and shown as well that beta-cell function continues to decline long after treatment begins. Per the UKPDS (*Diabetes.* 1995;44:1249-1258) up to 50% of beta-cell function had been lost by the time subjects in the study were diagnosed with diabetes, according to speaker Dwight M. Deter, PA-C, from

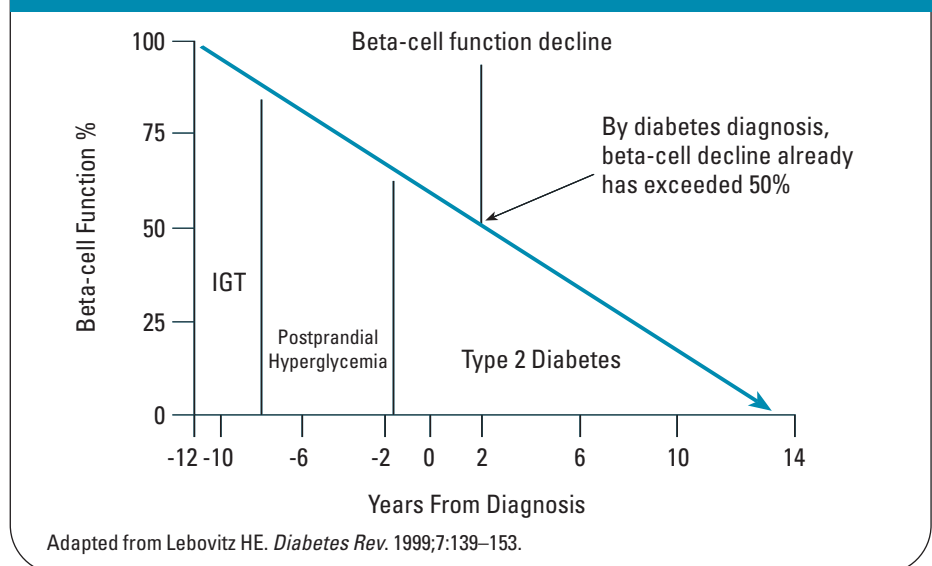
Southwest Endocrine Consultants in El Paso, TX (Figure 1).

Most oral agents, such as metformin or sulfonylureas, improve glycemic control in the short-term, but do not prevent progressive islet beta-cell failure or long-term deterioration of glycemic control (although there has been recent evidence for beta-cell preservation with thiazolidinediones [TZD]). More than 10 years after the start of the study, investigators reexamined some UKPDS patients and found that their beta-cell function had continued to decline after diagnosis and treatment. The decline correlated to loss of response to oral therapy (Turner RC, et al. *JAMA.* 1999;281: 2005-2012). In order for secretagogues to work, as Mr. Deter explained, “...you have to have beta cells [functioning well enough] to respond.” In the UKPDS, patients increasingly required insulin as response to oral therapy signaled continuing beta-cell decline over the years.



Dwight M. Deter, PA-C

Figure 1
Appreciable, Progressive Loss of Beta-Cell Function From Time of Diagnosis



Insulin will lower blood glucose in patients with diabetes in a dose-dependent manner, and its use should be considered early in the care of patients with type 2 diabetes. Today, aided by the availability of a number of insulin formulations, healthcare professionals can customize insulin regimens for patients based upon beta-cell function, patient lifestyle, and the ability of a patient to achieve and maintain glycemic targets. Increasingly, physician assistants accept the opportunity to play an important role in diabetes healthcare teams, allowing them to facilitate the highest quality of care in their patients with type 2 diabetes.

Principles of Insulin Therapy

Achieving tight blood glucose control is considered the standard of care for patients with type 2 diabetes. More intensive treatment targets have been established over the past two decades (Figure 2). Current ADA (American Diabetes Association) targets for A1C are set at < 7% while the ACE (American College of Endocrinology) has established even lower targets of ≤ 6.5%. These targets may be destined to go even lower, particularly if current studies such as the ACCORD trial (targeting A1C values <6%) confirm a benefit of even lower blood glucose values. While very diffi-

cult for patients to achieve, especially without insulin, these targets have been established based on unequivocal evidence that lower A1C values are associated with a lower risk for complications such as retinopathy and neuropathy. (No threshold was found in the UKPDS).

A1C targets, currently < 7% (ADA) and ≤ 6.5% (ACE) could go lower if studies such as the ACCORD trial confirm a benefit.

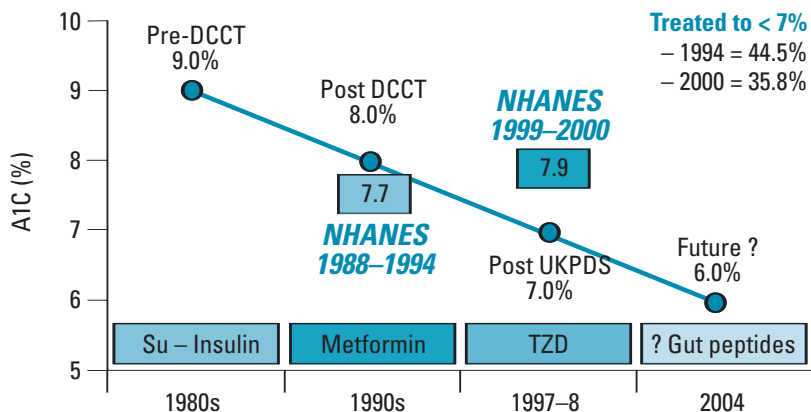
Unfortunately, insulin therapy is often delayed in patients who would likely benefit. The reasons for this delay are numerous and include provider reluctance, the need for continued titration and adjustment and/or patient fears associated with insulin use. Regardless, insulin therapy does have a critical role to play, even in type 2 diabetes, given that up to 50% of patients may ultimately require insulin to achieve current treatment goal, stated David M. Kendall, MD, Chief of Clinical Services and

Medical Director at the International Diabetes Center at the University of Minnesota. “Absolute insulin deficiency in type 1 diabetes necessitates insulin use. The relative insulin deficiency that characterizes type 2 diabetes, when paired with significant insulin resistance, will often necessitate that insulin be considered as a therapeutic option in these patients,” he added. Furthermore, according to Dr. Kendall, the use of insulin should be considered early if treatment targets are not achieved. Instead of the traditional stepwise approach to diabetes treatment, he suggests basing therapeutic choices on a given patient’s clinical characteristics.

Insulin therapy in type 2 diabetes is known to significantly improve glucose control, and with today’s insulin treatment options, the variety of insulin regimens available is extensive. Basal insulin provides excellent control of fasting glucose levels, whereas pre-mixed insulin formulations provide both basal and prandial glucose coverage. Ideally, Dr. Kendall stated, multiple daily injection (MDI) could be used to improve control, provide flexibility and limit the risk of hypoglycemia. However, some patients express a reluctance to use multiple injections due to its demands. For many patients, the use of 1- or 2-injection insulin regimens can be very effective and is particularly useful for those individuals with consistent mealtimes and an interval between breakfast and dinner of less than 12 hours. Such an approach is also practical for patients who may be unprepared or unwilling to utilize multiple injections. Pre-mixed insulin and insulin pens may be appropriate for patients in whom the daily titration, or adjustment, may be difficult or a limiting feature to their lifestyle. In patients who have not responded to other therapies (whether diet, exercise or oral drugs, and particularly if fasting blood glucose is the primary concern) a single daily injection of basal insulin is often used in combination with continued oral therapy.

A single daily injection of basal insulin (such as glargine or NPH) is a good option for starting patients who are resistant to initiating insulin. For

Figure 2
Using the Newest Therapies in Type 2 Diabetes: Is There a Need?



Data adapted from Koro CE. *Diabetes Care*. 2004;27:17–20.

patients with elevated fasting glucose, combining this with continued oral therapy is generally recommended. A pitfall of this approach is that mealtime insulin needs are not generally covered with basal insulin only, and over time many of these patients may also benefit from mealtime insulin. In such patients, rapid-acting insulin analogs are generally recommended to improve postprandial coverage, provide greater flexibility in dose timing and limit the risk of hypoglycemia (when compared to regular insulin).

"Absolute insulin deficiency in type 1 diabetes necessitates insulin use. The relative insulin deficiency that characterizes type 2 diabetes, when paired with significant insulin resistance, will often necessitate that insulin be considered as a therapeutic option in these patients."

Data from recent clinical trials provide insight into the use of each of these insulin treatment regimens. The Treat-to-Target study (Riddle MC, et al. *Diabetes Care*. 2003;26:3080-3086) compared use of a basal insulin analog (insulin glargine) with a bedtime injection of NPH-insulin using a titration schedule in order to achieve fasting prandial glucose targets of ≤ 100 mg/dL. With this titration protocol, A1C levels dropped to values of less than 7% in almost two-thirds of patients, independent of the type of insulin used. Both insulins were equally effective, Dr. Kendall pointed out. The study clearly demonstrated that it was possible to titrate insulin glargine effectively while significantly reducing the risk of nocturnal hypoglycemia.

In the INITIATE study, which evaluated insulin aspart 70/30 BID versus insulin glargine once daily (Raskin P, et al. *Diabetes Care*. 2005;28:260-265), all patients continued oral agents (except secretagogues or α -glucosidase inhib-

itors) during the 28 weeks of the study. Algorithm-based adjustments in insulin were used in both treatment groups. A1C for the group treated with twice-daily insulin aspart 70/30 was significantly lower in those treated with twice-daily analog mixed insulin. The results of this trial suggested that two daily injections increased the likelihood of getting patients to target, with 66% of insulin aspart 70/30 treated subjects achieving the ADA A1C target of $<7\%$, compared to 40% of those treated with insulin glargine ($P<0.001$). A similar result was seen in terms of AACE (American Association of Clinical Endocrinologists) targets, (42% versus 28% of patients treated with insulin aspart 70/30 versus glargine) ($P<0.05$).

Malone and colleagues reported similar results using an algorithm-based initiation and adjustment with insulin lispro 75/25 BID versus insulin glargine once daily in insulin-naive subjects (Malone JK, et al. *Clin Ther*. 2004;26:2034-2044). Results from this trial showed that both premixed and basal insulin analogs were associated with improvements in A1C, but as in the INITIATE trial, a greater percentage of patients reached target with insulin lispro 75/25 (42% reached A1C $<7\%$ with insulin lispro 75/25 versus 18% of those treated with insulin glargine, $P<0.001$).

In his summary comments, Dr. Kendall pointed out that once- or twice-daily injections have the advantage of being a simpler (and for many patients more practical) starting point than multiple daily injections. Pre-mixed regimens are useful for initiation, for promoting earlier and more aggressive insulin use, and for achieving better control in most patients. One must, however, take into consideration the relative lack of flexibility with pre-mixed regimens. Meal timing remains an important consideration, and in some instances, there may be continued need for snacks to account for continued intermediate insulin effects between meals. For maximal effectiveness, flexibility of dosing and improved post-meal glucose control, most clinicians consider multi-dose insulin to provide both consistent basal insulin as well as mealtime injections, adjusted based

Clinical Pointers: Insulin Use in Type 2 Diabetes

- Initiation of insulin is often delayed due to patient and provider reluctance
- Insulin is safe and effective and appropriate
 - Its use is required in $>50\%$ of patients to achieve A1C $<7\%$
 - A1C reduction of $>3\%$ are achievable
 - Hypoglycemia risk in patients with type 2 diabetes is one-tenth that of type 1 diabetes
 - High-dose therapy is often needed: TITRATE!
 - Average dose is about 100+ U/d

Once- or twice-daily injections have the advantage of being a simpler and more practical starting point for many patients.

on both current blood glucose values and for carbohydrate intake and exercise. "All of this provides improved flexibility but requires a motivated, educated patient to utilize it most effectively," Dr. Kendall said.

Special circumstances apply for treating patients who have persistent post-meal hyperglycemia, erratic schedules both for eating and activity, and variable carbohydrate intake, as well as an extended interval between major meals, or varying work times. "Fit the insulin to the patient" is the rule, he said, and with this type of patient, rapid-acting insulins combined with basal insulin coverage may be the most appropriate approach to insulin therapy. ■

Intensive Insulin Therapy

Intensive insulin therapy may be called for in some patients, not because there has been a failure in treatment or necessarily in adherence, but for reasons of inevitable disease progression, said speaker Christopher E. Sadler, MA, PA-C, CDE. Consisting of a basal-bolus MDI regimen, or continuous subcutaneous insulin infusion (CSII, or insulin pump therapy), intensive insulin therapy has the greatest potential among all regimens to reduce blood glucose levels to target values. Of the options for intensive therapy, CSII can often achieve the best glycemic control with less hypoglycemia, in patients who are highly motivated and can adhere to the requirements associated with the pumps. MDI is the next preferred method, but one which also requires a certain degree of strict adherence to rigorous treatment algorithms, said Mr. Sadler.

When should patients be advanced to basal/bolus insulin? It's indicated when patients are not reaching A1C targets on basal therapy alone, Sadler said, and/or when SMBG pre-dinner is greater than 140 mg/dL (Table 1). One elegant intensive insulin management regimen, according to Sadler, involves using a long-acting insulin analog like insulin glargine to provide a basal level of

insulin, or NPH several times a day (a less optimal choice due to insulin peaks); then adding a rapid-acting insulin analog such as aspart, glulisine, or lispro to provide 'bolus' or mealtime coverage. Another option is a "three-shot" regimen — insulin aspart 70/30 in the morning; a rapid-acting insulin analog at dinner, whenever that should occur; and then a bedtime dose of NPH insulin. In spite of the complexity that is implied in intensive therapy such as MDI, the trend of newer insulins and insulin delivery systems, along with glucose sensors, will "revolutionize our care of diabetes," Mr. Sadler said.

"... Most patients are surprised at how good they feel after starting insulin."

Typically, when bolus therapy is added, the secretagogues are stopped, but metformin is continued for weight control and glitazone continued for



Christopher E. Sadler,
MA, PA-C, CDE

glycemic stabilization (Watch for edema and tailor the glitazone dose as needed, Sadler added).

Whatever the basal/bolus strategy, the concept is to employ basal insulin to suppress glucose production between meals and overnight. This addresses 40% to 50% of patients' daily needs. Bolus (mealtime) insulin serves to limit hyperglycemia after meals, when there is an immediate rise and sharp peak at 1 hour. Typically, this supplies about 10% to 20% of total daily insulin needs.

In diabetes care, some of the newer technologies are:

- Continuous Glucose Monitoring System, which records glucoses on a continuing basis, and automatically communicates with an implanted or external pump, providing a "closed loop — an artificial pancreas." This technology will become available within the next few years.
- "Smart pumps" which allow for input of the actual carbohydrate being eaten along with blood sugar values. The pump then determines the insulin dose based on predetermined calculations. In some instances, glucose meters can communicate with the pumps to avoid errors in calculation.

Each of these devices and regimens involves focused effort on the part of patients, even while they aim at simplification. Nevertheless, they are able to more accurately approach correct dosing and physiologic insulin secretion. In practice, despite the greater demands on patients, Sadler says, most are surprised at how good they feel after starting insulin. "People don't realize that their lack of energy was not just that they were getting older, it was poor glycemic control." ■

Table 1
Advancing to Basal/Bolus Insulin

Indicated when FBG is acceptable but...

- A1C >7% or >6.5%, and/or
- SMBG before dinner >140 mg/dL

Insulin options

- To glargine or NPH, add mealtime aspart/lispro
- To dinnertime 70/30, add morning 70/30
- To morning 70/30, add dinnertime aspart/lispro and hs NPH
- Consider insulin pump therapy

Oral agent options

- Usually stop sulfonylurea
- Continue metformin for weight control
- Continue glitazone for glycemic stability?

The Value of the Physician Assistant in the Recognition and Management of Neuropathic Pain

Standard treatment options for patients with nociceptive pain are ineffective in patients with neuropathic pain. Medical personnel must recognize the difficulty in managing this problem and are encouraged to develop a team approach to treatment that takes into account the physical as well as psychological and social problems associated with neuropathic pain.

At a symposium held at the annual meeting of the American Academy of Physician Assistants in Orlando, Florida, two experts in pain management discussed the important role physician assistants have in diagnosing and treating neuropathic pain.

Speakers

Roy Freeman, MD
 Professor of Neurology
 Harvard Medical School
 Director of the Center for Autonomic and Peripheral Nerve Disorders
 Beth Israel Deaconess Medical Center
 Boston, MA

Charlene M. Morris, PA-C, MPAS
 Physician Assistant
 Cumberland County Hospital
 BF Taylor Medical Arts Clinic
 Burkesville, KY

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Recognizing Neuropathic Pain, Key Considerations in Appropriate Patient Assessment

The 80/20 rule states that 80% of a physician assistant's time is spent on 20% of the patients. In many practices, these patients are the ones with unspecified neuropathic pain. Unlike nociceptive pain which has a known pain source, "neuropathic pain may come from nociceptive origins, but not necessarily be because of it," began Charlene M. Morris, PA-C, MPAS, Physician Assistant at Cumberland County Hospital, BF Taylor Medical Arts Clinic in Burkesville, KY (Table 1).



Charlene M. Morris, PA-C, MPAS

To introduce the topic of neuropathic pain, Ms. Morris showed the audience several types of neuropathic pain (Table 2) with two of the most common being diabetic peripheral neuropathy and postherpetic neuralgia zoster.

Diabetic Peripheral Neuropathy

One method to distinguish the array of diabetic peripheral neuropathies is to group them into acute focal pain or slow

**Table 1
 Nociceptive vs Neuropathic Pain**

Nociceptive	Neuropathic
<ul style="list-style-type: none"> Actual cause defined Usually self-limiting Treatment options varied and many Arises from stimulus outside the nervous system 	<ul style="list-style-type: none"> May have nociceptive origins but not etiologies Unclear, unproven, or misunderstood causes Treatment may be difficult Arises from a primary lesion or dysfunction in the nervous system

Wallace MS. *Curr Pain Headache Rep.* 2001;5:138-150; Galer BS, Dwokin RH. *A Clinical Guide to Neuropathic Pain.* Minneapolis Minn: McGraw-Hill;2000:33-36.

**Table 2
 Neuropathic Pain Types**

<ul style="list-style-type: none"> Painful (poly) neuropathy (PNP) <ul style="list-style-type: none"> – Diabetic peripheral neuropathy (DPN) Mononeuropathy <ul style="list-style-type: none"> – Postherpetic neuralgia (PHN) zoster ("shingles") – Trigeminal neuralgia (TGN) Central poststroke pain *(CPSP) Spinal cord injury Multiple sclerosis Complex regional pain syndrome
--

Lacere M, Shah RV. *Arch Phys Med Rehabil.* 2003;84(3 suppl 1):S35-S38.

onset pain. The acute focal, also called quick onset pain, is generally short-lived while the slow onset type generally worsens over time and is more difficult to treat. Slow onset pain is also the most common form.

Physician assistants should routinely screen for neuropathy in their diabetic patients and develop a strategy to monitor and treat the pain appropriately.

From a physician assistant's perspective, the best treatment option for diabetic peripheral neuropathy is prevention. Ms. Morris encouraged physician assistants to monitor and manage blood glucose levels in patients susceptible for diabetes and to teach their patients the consequences complications associated with this disease. Furthermore, physician assistants should routinely screen for neuropathy in their diabetic patients and develop a strategy to monitor and treat the pain appropriately. For example, when the diabetic patient starts to complain about tingling in their feet and asks for a referral to a podiatrist, this may be the first stage of diabetic peripheral neuropathy and they should be evaluated and monitored closely.

Herpes Zoster and Postherpetic Neuralgia

Herpes zoster is primarily diagnosed by a clinical assessment. "Lesions appear as a maculopapular rash that often follow a dermatomal distribution. The rash evolves into fluid-filled vesicles on a hyperemic base. They look like little water-filled blisters on a red section of skin," stated Ms. Morris, adding, "and they are usually very painful." Postherpetic neuralgia is the neuropathic pain that occurs approximately three months after the lesion. According to Ms. Morris, the patient's age is an important factor in the development of this complication. The probability of having

postherpetic neuralgia increases sharply after 60 years of age. On a more positive note, Ms. Morris reminded the audience to tell their patients that there are treatment options available to treat the pain and that they most likely will recover from the outbreak. Reports have shown that 96-98% of herpes zoster patients show improvement by 12 months (*BMJ*. 2000;321:794-6) and over half the patients with chronic postherpetic neuralgia were 'coping well' after 2 years (*Pain*. 1991;46:195-199).

"If they're not able to go to work, go to church, do what they used to like to do, then they are ostracized and shunned from doing what they want to do," said Ms. Morris, adding, "in their own minds — not necessarily by the rest of society."

Nonpharmacologic Treatment Options

Several components of the patient's pain need to be addressed when diagnosing and managing it. In addition to the biological aspects of the pain, the physician assistant must also address the psychological and social components of pain. "If they're not able to go to work, go to church, do what they used to like to do, then they are ostracized and shunned from doing what they want to do," said Ms. Morris, adding, "in their own minds — not necessarily by the rest of society." The pain can have a cascade effect on other problems as well. For example, the pain will lead to less activity, less exercise, less sleep and so forth, and this in turn leads to poorer health, reduced work performance, anxiety, and depression. In some cases, the patients may benefit from psychological counseling. "I tell people, don't just send this patient to any psychologist or therapist. Make sure it's somebody that knows how to deal with pain issues because, otherwise you're going to get into a whole situation where this patient's difficulties are not addressed," stated Ms. Morris.

"I tell people, don't just send this patient to any psychologist or any therapist. Make sure it's somebody that knows how to deal with pain because, otherwise you're going to get into a whole situation where this patient's difficulties are not addressed," stated Ms. Morris.

Ms. Morris also recommended that physician assistants can help the patient by 'prescribing' various tasks to keep the patient active such as "today I want you to go walk the dog" or "I want you to go food shopping for 10 minutes".

Ms. Morris encouraged physicians assistants to keep an open mind about treatment and informed the audience that some patients benefit from nontraditional methods such as t'ai chi (*Psychosom Med*. 2003;65:824-30) and/or acupuncture (*Spinal Cord Med*. 2003; 26:21-6). Ms. Morris ended her presentation by stating that there are more effective medical therapies for neuropathic pain becoming available and she encouraged physicians assistants to become more familiar with current and emerging treatment strategies (see following article) to help improve the patient's quality of life. ■

Physician assistants can help the patient by 'prescribing' various tasks to keep the patient active such as "today I want you to go walk the dog" or "I want you to go food shopping for 10 minutes".

Exploring Current and Emerging Treatment Strategies for Optimal Patient Outcomes

Neuropathic pain is neither a uni-dimensional entity nor merely a sensation. Neuropathic pain is a precept that comes from a variety of sites within the central and peripheral nervous system. “The reason why there are so many agents to treat neuropathic pain is because there are such a large number of pathophysiological mechanisms that are functional at different points in the neuropathic pain continuum,” stated Roy Freeman, M.D., Professor of Neurology at Harvard Medical School and Director of the Center for Autonomic and Peripheral Nerve Disorders at Beth Israel Deaconess Medical Center in Boston, MA. An excellent example to illustrate the complexity of neuropathic pain is postherpetic neuralgia. The pain in these patients doesn’t develop until approximately three months after the rash has healed. During those three months,

“The reason why there are so many agents to treat neuropathic pain is because there are such a large number of pathophysiological mechanisms that are functional at different points in the neuropathic pain continuum,” stated Dr. Freeman.

changes in the periphery such as sensitized pain fibers to stimuli and neural fiber sprouting, and/or changes in the central nervous system such as reorganization of the neural synaptic array can all result in a pain that is multidimensional and difficult to treat (Table 3).

Pharmacologic Treatment Options

Placebo Effect

All clinical trials with neuropathic pain show a very high placebo effect and Dr. Freeman stressed the fact that when examining any clinical trial for neuropathic pain, a placebo control group must be included. To illustrate his point, Dr. Freeman mentioned that specific serotonin reuptake inhibitors (SSRIs) were examined as possible treatment options for painful diabetic neuropathy but in a clinical trial, the high percentage of patients that improved (48%) following fluoxetine treatment were not significantly different from the percentage of patients improving in a placebo-treated group (41%) (*N Engl J Med.* 1992;326: 1250-1256).

Tricyclic antidepressants

The most frequently used tricyclic antidepressants for treating neuropathic pain are amitriptyline, nortriptyline and desipramine (Elavil, Aventyl, Norpramin). These medications have been extensively studied and although they are not indicated for treatment of

neuropathic pain, they are effective and fairly inexpensive. Unfortunately, they are often poorly tolerated and the high doses needed to be effective also lead to several anticholinergic (i.e., drowsiness, anxiety, agitation, cognitive difficulties, dry mouth, constipation, urinary retention, visual blurring) and cardiovascular side effects (tachycardia, and orthostatic hypotension). “There are several studies suggesting there is a risk of cardiovascular death associated with the use of these agents,” said Dr. Freeman, adding, “it behooves us to do a good cardiovascular work-up before using these agents and being careful about the use of these agents in the elderly.” Of the three tricyclic antidepressants, amitriptyline is the most effective but it also has the highest incidence of side effects.

Selective serotonin/norepinephrine reuptake inhibitors (SSNRIs)

As stated earlier, SSRIs such as fluoxetine and paroxetine (Prozac, Paxil) have not been shown to be any better than placebo at treating neuropathic pain. In contrast, the newer SSNRIs such as venlafaxine (Effexor) and duloxetine (Cymbalta) have a good efficacy rate for treating some forms of neuropathic pain and duloxetine has been approved by the FDA for the treatment of neuropathic pain in diabetes. Dr. Freeman warned that although these drugs appear to be effective and well tolerated (GI adverse events are common), more data are needed on these two drugs in regard to their safety and efficacy for different types of neuropathic pain.

Anticonvulsants

First-generation anticonvulsants such as phenytoin and carbamazepine (Dilantin, Tegretol) have not been well studied for the treatment of neuropathic pain but there is a plethora of data available on second-generation anticonvulsants. Among these agents, the two most

**Table 3
Peripheral and Central Mechanisms of Chronic Pain**

Peripheral	Central
<ul style="list-style-type: none"> • Sensitization of peripheral neurons • Spontaneous ectopic discharge • Ephaptic communication • Collateral sprouting 	<ul style="list-style-type: none"> • Central sensitization • Reorganization • Disinhibition

Table 4
Pregabalin and Gabapentin Pharmacology Facts

	Pregabalin	Gabapentin
FDA-approved Indication	Neuropathic pain associated with diabetic peripheral pain and postherpetic pain	Postherpetic pain
Mechanism of action	Selectively binds to the $\alpha 2\delta$ site in CNS tissue	Selectively binds to the $\alpha 2\delta$ site in CNS tissue
Pharmacokinetic profile	Linear (plasma concentration is dose proportionate)	Nonlinear (plasma concentration increases disproportionately to dose)
Oral bioavailability	$\geq 90\%$, all doses	60%(900 mg); 47%(1200 mg); 34%(2400 mg); 33%(3600 mg)
Dosing (PHN)	b.i.d. or t.i.d.	t.i.d.
Time to effective dose (PHN)	1 day (effective starting dose of 150 mg/day)	≥ 9 days (titrate to effective dose of 1800 mg/ day)

studied are gabapentin (Neurontin) and pregabalin (Lyrica). Dr. Freeman stated that these two medications do not affect GABA neurotransmission, as their names imply, but they act on a subunit of the calcium channel that interferes with transport of calcium into the neuron. As a result, the reduced influx of calcium attenuates the release of neurotransmitters from neurons. It is this reduced synaptic neurotransmitter release which allows these two drugs to be effective in the treatment of neuropathic pain (Table 4).

Gabapentin requires a large dose (usually > 1800 mg) to be effective and needs to be titrated slowly to minimize adverse events; in contrast, the newer

drug pregabalin is effective within a day. In regard to side effects, these two drugs are well tolerated with the predominant side effects being dizziness and somnolence. Interestingly, a recent study with pregabalin indicates it can improve sleep in patients with diabetic peripheral neuropathy (*Pain*. 2004;110:628-38).

Other anticonvulsant agents studied for their efficacy in treating neuropathic pain include topiramate, lamotrigine and oxcarbazepine (Topomax, Lamictal, Trileptal). To date, four studies with topiramate have been published with only one study showing a positive effect. In regard to lamotrigine and oxcarbazepine, Dr. Freeman stated that promising data have been presented at pain conferences

but to date, no peer-reviewed published data is available.

Topical agents

“The data on topical agents are not as good as they are for the orally ingested agents with the exception of Lidoderm in the treatment of postherpetic neuralgia,” said Dr. Freeman. Studies with the lidocaine patch have shown it to be effective (*Drugs*. 2000;59:245-259) and it is the only topical agent to be FDA approved for the treatment of postherpetic neuralgia. Dr. Freeman noted that the other topical agents have not been well studied and results are inconsistent.

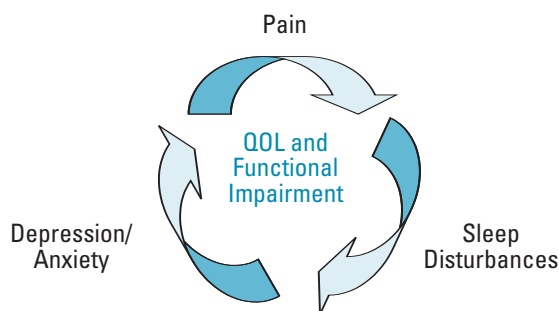
Opioids

Dr. Freeman told the audience that opioids are effective for the treatment of neuropathic pain and if prescribed properly can be safe. Dr. Freeman said, “you need to be comfortable with their use and have an approach to using opioids that suits your practice.” The two most commonly prescribed opioids for neuropathic pain are oxycodone (OxyContin) and tramadol (Ultram), both of which have been shown to be effective in the treatment of neuropathic pain (*Neurology*. 2003;60:927-934; *Neurology*. 1998;50:1842-1846). Dr. Freeman added, “obviously, opioids have an array of side effects and for that reason, in my practice, they are not first line but they are useful supplements in the treatment of neuropathic pain.”

Concluding remarks

The complex interactions between the periphery, the spinal cord and the central nervous system in regard to pain sensation make it necessary that numerous treatment options be available for treating neuropathic pain. Dr. Freeman added, “don’t give up on agents before reaching an effective dose and certainly use agents in combination.” Dr. Freeman ended his presentation by reminding the audience that neuropathic pain is part of a triad and that pain can lead to sleep disturbances and that in turn can lead to depression/anxiety. Unless the pain, sleep and mental concerns are all addressed, the quality of life of the patient will continue to deteriorate (Figure 1). ■

Figure 1
The Comorbidity Triad



Contemporary Treatment Options for Overactive Bladder

Overactive bladder (OAB) is an age-related disorder in both women and men that decreases the quality of life and may lead to a variety of pathologic and psychological complications if untreated. Although most of the research on this disease, and on the medications that are now available for its treatment, has been conducted in women, it is now recognized that men may experience OAB either independent of or concomitant with bladder outlet obstruction (BOO) associated with benign prostatic hyperplasia (BPH).

Although bladder training and pelvic floor rehabilitation by way of exercise (such as kegels) may improve the symptoms of OAB, they must always be accompanied by pharmacologic therapy. At present this consists of drugs of the antimuscarinic class, all of which have been shown to decrease bladder contractions and to decrease both the frequency and severity of urge incontinence. They vary widely in side effects due to their differing affinities for the 5 muscarinic receptor subtypes that are variously located.

OAB and clinical data pertaining to current medications were the subjects of a symposium conducted in conjunction with the 33rd Annual Conference of the American Academy of Physician Assistants on May 31, 2005.

Speakers

David O. Sussman, DO
School of Osteopathic Medicine
University of Medicine And Dentistry
Newark, NJ

Paul H. Taylor, PA-C
Emory University
Atlanta, GA

This program was supported by an unrestricted educational grant from Pfizer, Inc.

Overactive Bladder: The Differential Diagnosis

The International Continence Society (ICS) defines OAB as a condition consisting of urinary urgency (i.e., a sudden and strong desire to urinate), with or without urge incontinence, usually with frequency and nocturia. Frequency is characterized as eight or more urinations in a 24-hour period, and nocturia by one or more visits to the toilet during the sleep cycle. Urge incontinence manifests as a sudden, involuntary loss of urine typically occurring as leakage of small amounts of urine in advance of reaching a toilet. This spontaneous loss of urine is in contrast to provoked leakage, which may occur in association with sudden bladder pressure resulting from coughing, sneezing, laughing, or lifting, or from a mechanical change in bladder orientation such as occurs when bending at the waist. This phenomenon is referred to as stress incontinence, or mixed incontinence. Some individuals suffer from the combination of urge and stress incontinence. Nonetheless, approximately two-thirds of patients with OAB rarely or never experience incontinence, and are thus said to have “dry” OAB.

Paul Taylor, PA-C noted that although OAB is commonly thought of as a disorder of older women, it is actually an age-related disorder of both women and men, affecting approximately 20% of each gender by age 75 years. Importantly, however, OAB with incontinence is significantly more common among women at virtually all adult ages, but especially after age 45 years. From ages 65 years and above, approximately 9.3% of American women suffer from “wet” OAB compared with 2.4% of men (Stewart WF et al. *World J Urol.* 2003;30:327). These epidemiological findings are important reminders that inquiring about urinary habits is an important part of taking histories from all adult patients, and especially for women over age 40. As many as 10% of women in their 40s may have OAB symptoms that are easily overlooked if they are not reported explicitly. Moreover, because some women are reluctant to discuss these symptoms with male practitioners, it may be helpful to



Paul H. Taylor, PA-C

have this issue raised routinely by female office personnel.

In addition to the discomfort and potential embarrassment associated with OAB, this disorder increases risk for urinary tract infections, skin disorders, chronic depression, sexual dysfunction, and sleep disturbance. Daytime drowsiness associated with disturbed sleep increases risk for accidents and misjudgments. Similarly, nocturia increases risk of falling and fractures, especially in postmenopausal women who have osteopenia or osteoporosis.

Fear of embarrassment from an incontinence episode often induces a spectrum of avoidance behaviors ranging from voiding without urge and wearing panty liners or incontinence pads to social withdrawal and fear of leaving home. Some patients also intentionally limit fluid intake, further increasing the risk for urinary tract infections, endangering electrolyte balances, aggravating bladder function, and inviting constipation. Indirect cost consequences of OAB include the costs of dry cleaning, detergent, bed linens, incontinence pads, garments, and even home and auto upholstery. This disorder can have a severely negative impact on quality of life, and effective treatment may help substantially. Yet a recent report claims that only 17% of individuals with OAB symptoms seek pharmacologic treatment (Consumer Segmentation Study, 2002).

Some patients also intentionally limit fluid intake, further increasing the risk for urinary tract infections, endangering electrolyte balances, aggravating bladder function, and inviting constipation.

Under-diagnosis and under-treatment of OAB result from barriers among both patient and clinician barriers. Patient barriers may involve the misconceptions that OAB is a natural part of aging and that treatment will not help. Some patients, especially those who find OAB embarrassing to discuss, may convince themselves that their symptoms are not sufficiently frequent or severe to merit treatment. Others avoid the subject because they fear that surgery is the only effective intervention. For their part, clinicians may not include questions concerning bladder condition in screening patients, and may assume that the patient will report OAB symptoms when they become sufficiently troublesome. Some clinicians may not adequately appreciate the impact of comorbidities and may fear that they will not be reimbursed for treating OAB except as a specific diagnosis during a separate appointment.

This disorder can have a severely negative impact on quality of life, and effective treatment may help substantially. Yet a recent report claims that only 17% of individuals with OAB symptoms seek pharmacologic treatment.

The diagnosis and evaluation of OAB can be easy and efficient. Patients can fill out a validated screening questionnaire such as the Overactive Bladder—Validated 8-Question Awareness Tool (OAB-V8), which screens with high accuracy for OAB symptoms of urge, frequency, nocturia, and urgency incontinence. For each symptom, the patient scores the frequency or severity on a six-point scale (0 to 5) and totals the result. Any score over 8 is indicative of OAB, but scores in symptomatic patients are usually much higher. In the validation study that involved 1,260 patients during regularly-scheduled appointments, 12% of patients screened had symptoms consistent with OAB, and patients with scores of 8 or more were 95 times more likely that those scoring less than 8 to have OAB (Data on file. Pfizer, Inc.).

Table 1 Urinary History	
<ul style="list-style-type: none"> • Signs and symptoms • Current management • Strategies • Number and type of pads • Fluid intake • Impact – QOL • Previous evaluation and treatment 	<ul style="list-style-type: none"> • Medical history <ul style="list-style-type: none"> – Medications – Hormonal status – Bowel history – Functional status – Diet • Goals for treatment • Social situation

Table 2 Differential Diagnosis	
<ul style="list-style-type: none"> • Benign prostatic hyperplasia • Pelvic organ prolapse • Atrophic vaginitis • Pelvic floor dysfunction • Interstitial cystitis • Diabetes <ul style="list-style-type: none"> – Excessive fluid intake 	<ul style="list-style-type: none"> • GU malignancy • Urinary tract infection (UTI) • Other forms of incontinence • Medication induced

Table 3 Red Flags: Consider Referral	
<ul style="list-style-type: none"> • Abnormal neurologic exam • Hematuria without infection • Recurrent UTIs • Uncertain diagnosis • Abnormal postvoid residue (PVR) (200 mL) 	<ul style="list-style-type: none"> • Difficult bladder emptying • Unsuccessful treatment • Previous surgery • Symptomatic pelvis prolapse • Prostate nodules

Details of a 2-week bladder diary that includes intake and output voiding volumes further refine the patient’s symptoms and assist in the diagnosis of OAB. Because of the correlation between decreased intravascular volume and bowel activity, a bowel history should be part of the diary. Note also that just as fluid restriction may lead to constipation, the unemptied rectum may affect bladder capacity and increase urinary frequency and/or incontinence.

With these details in hand, the clinician should secure a thorough urinary history (Table 1), perform a urinalysis and physical examination, and conduct urodynamic studies including post-void residual urine volume where indicated. The objective is to rule out potential secondary causes of OAB as summarized in Table 2. A patient meeting any of the criteria enumerated in Table 3 should be referred to a urologist or a urogynecologist. ■

Update on Treatment Options and Rationale for Use

David Sussman, DO reviewed clinical data regarding current dietary, behavioral, and pharmacologic interventions for OAB.

Because caffeine is both a diuretic and bladder irritant, its intake should be restricted or eliminated. Alcohol is also a bladder irritant, as are some spicy foods. Thus they, too, should be limited or removed from the diet. For patients whose OAB is accompanied by constipation, stool softeners may contribute significantly to relief.

The principal behavioral therapies for OAB are bladder training and pelvic floor rehabilitation. Bladder training has been shown to reduce incontinent episodes by 57% in patients with OAB and genuine stress incontinence. Additionally, it has been shown to reduce the quantity of urine lost by 54%, although the response in OAB is superior to that in stress incontinence (Fantl JA et al. *JAMA*. 1991;265:609). Pelvic floor rehabilitation by way of muscle exercise may increase the patient's muscle tone and thereby decrease bladder instability. It has been shown to induce complete resolution of OAB in 20% of patients and to improve symptoms in most patients by 50% to 75% (Payne CK. *Urol*. 1998;51(Suppl 2A):3; Fantl JA. *Urol*. 1998;51:30). Many patients find that rapid, active pelvic muscle contractions ("quick flicks") may inhibit an unstable bladder contraction after its onset.

Despite the apparent benefits of behavioral therapies, they have several limitations. First, they require a motivated patient, one who will accept responsibility for his/her own symptom relief and is willing to maintain a regular schedule of exercise once training is completed in order to prevent the recurrence of symptoms. Second, the success of behavioral therapy depends in large measure on the intensity of the program, thus testing the patient's commitment. Third, training time is expensive, with greater cost associated with more intensive training. One important study comparing behavioral with pharmacologic intervention concluded that whether they are introduced simultaneously or sequentially, "the evidence from the present study is that [these] two interventions

combined have a greater potential to enhance outcome than could be achieved by either intervention alone" (Burgio KL et al. *J Am Geriat Soc*. 2000;48:370). Consequently, for optimum clinical benefit, pharmacologic intervention should always accompany behavioral treatment of OAB.

The primary pharmacologic treatments for OAB are in the antimusaranic class. Agents approved by the Food and Drug Administration (FDA) with specific indication for the treatment of OAB appear, together with their respective dosing schedules, in Table 4. As a class, these agents stabilize the bladder's detrusor muscle, increase bladder capacity, diminish the frequency of involuntary bladder contractions, decrease urge incontinence episodes by 65% to 70%, and delay the initial urge to void.

*A*s a class, these agents stabilize the bladder's detrusor muscle, increase bladder capacity, diminish the frequency of involuntary bladder contractions, decrease urge incontinence episodes by 65% to 70%, and delay the initial urge to void.

They do not, however, change the individual's warning time, so urgency may remain a problem.

Currently, tolterodine LA is considered the gold standard of treatment for OAB. It is the most frequently prescribed medication for this disorder and, conveniently, it is available in one dosage. In a pivotal placebo-controlled trial involving 986 patients, tolterodine LA was shown to reduce the number of urge incontinence episodes by 71% in all patients significantly ($p=0.0023$) and by 68% ($p=0.0221$) in the most severe patients having 21 to 168 urge incontinence episodes per week (Lands et al. *J Urol*. 2004;171:752; Data on file. Pfizer, Inc., subset analysis from the registration trial), with dry mouth the only adverse effect with significantly higher incidence than placebo. There were no significant differences between tolterodine LA and placebo regarding the most common adverse effects on the central nervous system (CNS): somnolence, dizziness, and anxiety. This is due to the fact that the active metabolite of tolterodine has a bulky molecular structure, is positively charged, and has low lipophilicity, thus sharply restricting its ability to cross the blood-brain barrier and cause CNS side effects (Todorova A et al. *J Clin Pharmacol*. 2001;41:636).

Prior to the introduction of tolterodine, oxybutynin was the preferred med-

Table 4
Treatment Options

Drug	Dose	Frequency
Tolterodine LA	4 mg	once daily
Oxybutynin XL	5–15 mg	once daily
Oxybutynin	5–30 mg	BID or TID
Oxybutynin Trans	3.9 mg/day	1 patch BIW
Trospium	20 mg	BID
Solifenacin	5–10 mg	once daily
Darifenacin	7.5–15 mg	once daily

Adapted from: *Medical Letter*. 2005;47:23–24.

ication for OAB, but its side-effects profile and three-times-per-day dosing schedule both contributed to poor compliance by many patients. More recently, however, an extended-release formulation (oxybutynin XL) and a transdermal formulation have been approved by the FDA. In an efficacy trial comparing the immediate-release and extended-release formulations of oxybutynin, both medications were associated with statistically significant percentage reductions in number of urge incontinence episodes at week 12, with superior performance from oxybutynin XL (83% vs. 76%) (Versi E et al. *Obs Gyn.* 2000;95:718). Unlike tolterodine LA, however, the high lipophilicity, neutral polarity, and small molecular structure of oxybutynin XL enable it to cross the blood-brain barrier relatively freely, resulting in much higher incidents of dry mouth (60.8%), somnolence (11.9%), headache (9.8%), and nausea (8.9%). Constipation and diarrhea are also reported by the manufacturer's package insert to be of high prevalence (13.1% and 9.1%, respectively).

Trospium has been shown to induce a statistically significant percentage reduction in urge incontinence episodes per 24 hours (59%) in a trial in which the placebo effect was a high 44.2% (Zinner N et al. *J Urol.* 2004;171:2311). The trial drug was associated with a higher frequency of dry mouth and constipation than placebo, consistent with the class effect. Theoretically, this molecule should not cross the blood-brain barrier freely, and other CNS effects, including the high incidence of headache in this trial, result from unusually efficient absorption in the gastrointestinal tract. Typically, less than 10% of this medication is absorbed, and the bioavailability is approximately 9.6%. Trospium is taken twice daily 1 hour prior to meals. Because it is eliminated by tubular secretion, it may cause interaction with other drugs such as digoxin and morphine.

Solifenacin and darifenacin joined the FDA-approved armamentarium for treating OAB in 2005. In a three-arm trial of solifenacin involving 857 patients randomized to take solifenacin 5 mg, solifenacin 10 mg, or placebo, both dosages reduced urge incontinence episodes per 24 hours relative to controls (Cardozo L et al. *J Urol.* 2004;172:1919). Although the 10 mg dose has not been shown conclusively to be more

effective than the 5 mg starting dose, solifenacin is associated with dose-dependent increases in constipation, dry mouth, dyspepsia, and blurred vision. Pharmacokinetic studies indicate that the half-life of this agent is 45 to 68 hours, and that after a single 10-mg dose, only 92% of the drug was excreted after 26 days. These findings raise concerns about drug accumulation and potential CNS toxicities with long-term exposure, particularly in older patients and those with renal or hepatic impairment.

While M₃ inhibition appears to decrease detrusor contractions in OAB, it also leads to constipation because of the abundance of M₃ receptors in the colon. This may explain the increased prevalence of constipation in OAB patients taking antimuscarinics that have the greatest affinity for M₃ receptor subtypes.

Darifenacin at doses of 7.5 mg and 15 mg have also been shown to reduce the frequency of urge incontinence per week after 12 weeks of treatment significantly compared with placebo (Haab F et al. *Eur Urol.* 2004;45:420), but with high dose-related incidences of dry mouth, constipation, and dyspepsia. Because of its metabolic pathways, patients may encounter adverse drug reactions with a wide spectrum of other medications including calcium channel blockers and beta-blockers, antiviral agents, antihistaminics, antidepressants, antipsychotics, estradiol, and glucocorticoids.

The clinical effectiveness of any muscarinic agent may be attributed to its affinity for each of the five muscarinic receptors subtypes (M₁-M₅). These are located virtually throughout the body including at various sites in the brain as well as the bladder, colon, stomach, gallbladder, salivary glands, and iris. Human bladder smooth muscle contains primarily the M₂ and M₃ receptor subtypes in an approximate ratio of 3:1.

Activation of M₃ receptors evokes direct smooth muscle contraction, and stimulation of M₂ receptors may reverse sympathetically-mediated smooth muscle relaxation (Chapple CR. *Urol.* 2000;55:33; Chapple CR et al. *Urol.* 2002;60:S82). Thus, while M₃ inhibition appears to decrease detrusor contractions in OAB, it also leads to constipation because of the abundance of M₃ receptors in the colon. This may explain the increased prevalence of constipation in OAB patients taking antimuscarinics that have the greatest affinity for M₃ receptor subtypes, with darifenacin having the greatest affinity and the highest prevalence of constipation and tolterodine having the lowest of each.

Before concluding his presentation, Dr. Sussman turned to the subject of OAB in men. Although OAB is just as prevalent in men as in women, male patients are less frequently diagnosed. This may be in part because men are less likely to experience incontinence than women and because bladder complications in men are often casually attributed to benign prostatic hyperplasia (BPH). Moreover, even among men whose symptoms are recognized as those of OAB either independent of or concomitant with BPH, only 24% of these men currently take antimuscarinic therapy. Since previous thinking was that anticholinergic agents put men at risk for urinary retention, the debate continues as to whether to treat men with OAB but no bladder outlet obstruction (BOO) or men with both OAB and BOO. For those who have both, can antimuscarinic therapy be administered safely in combination with antiadrenergic BPH medications?

In an effort to resolve this issue, Lee and colleagues undertook a trial involving 144 men, 53% of whom had BOO only and 47% had both BOO and detrusor overactivity diagnosed by urodynamics. All patients were treated with doxazosin 4 mg per day for 3 months. For patients who had no symptomatic improvement (65%), tolterodine 2 mg twice daily was added to doxazosin. Combination therapy was associated with symptom relief in 73% of those patients (Lee JY et al. *BJU Int.* 2004;94:817), indicating its efficacy in men with OAB and co-existing BOO. Additional trials in male patients with OAB with and without BOO are currently in progress. ■

New Insights in the Treatment of Hepatitis C Infections: Evaluation for Appropriate Therapy

An estimated 200 million people worldwide and 3.9 million Americans are infected with hepatitis C virus. Damage caused by this virus can be both direct and immunologically mediated. The liver is the primary organ affected, but other organ systems can also be injured primarily through immunologic mechanisms.

At a symposium held at the annual meeting of the American Academy of Physician Assistants in Orlando, Florida, three experts in the treatment of patients with hepatitis C virus showed a series of posters illustrating recent developments in the management of HCV.

Speakers

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Introduction

Three experts in the management of patients with hepatic C virus (HCV) presented a series of posters to show the pathophysiology of HCV as well as the safety and efficacy concerns when treating this condition. The three experts were: Elizabeth K. Goacher, PA-C, MHS, Physician Assistant at the Duke Liver Center, Department of Medicine, Duke University Medical Center in Durham, NC; Brent D. Peterson, RPA-C, Physician Assistant at the Recanati/Miller Transplantation Institute of Mount Sinai Medical Center in New York, NY; and Fred Poordad, MD, Chief of Hepatology and Liver Transplantation, Comprehensive Transplant Center at Cedars-Sinai Medical Center, in Los Angeles, CA.

Hepatitis C virus or HCV is a single-stranded RNA virus with a genome of approximately 9,600 nucleotides. It is a very quiescent virus early in infection, but leads to advanced liver disease in a significant number of people. If infected, most patients will show no signs or symptoms until liver damage occurs many years later. In the United States, an estimated 3.9 million people are infected with HCV and approximately 70% of them have chronic liver disease. It is estimated that 200 million people worldwide have HCV.

HCV is transmitted through contact with infected blood and blood products. HCV RNA appears in blood within two weeks of exposure. Table 1 outlines people at risk for HCV and in whom HCV antibody testing is recommended. If an antibody is present, further testing is required and HCV genotyping should



Fred Poordad, MD

be performed to determine which of the 6 HCV genotypes is present. In the United States, 75% of infections are genotype 1 (either a or b) and the rest are mostly genotypes 2 or 3. Genotypes 4 and 6 may occasionally be seen in the U. S. but are more commonly observed elsewhere (e.g., in Egypt, genotype 4 is common while in parts of Southeast Asia, genotype 6 predominates) (www.cdc.gov; www.who.int; *Rev Gastroenterol Disord.* 2004;49 (Suppl 1):S8-S15.).

The treatment of choice for HCV is pegylated interferon-alpha (pegIFN- α) plus ribavirin. In certain special cases, pegIFN- α alone, interferon alpha (IFN- α) alone, or IFN- α plus ribavirin is used. Patients should be considered for treatment if they are viremic (virus in blood) and have the following characteristics:

- Patients at increased risk for developing cirrhosis
- 18 years of age or older (younger patients need evaluation by pediatric hepatologist)
- Liver biopsy with significant fibrosis, inflammation, and necrosis
- Evidence of compensated liver disease
- Acceptable hematological and biochemical indices
- Non-response/relapse to non-pegylated regimens
- Willingness and compliance with treatment ■

Table 1
CDC Recommendations for Testing Based on Risk of HCV Infection

Persons at Risk	Risk of infection	Testing Recommended?
Injection drug user	High	Yes
Pre 1987 clotting factor recipient	High	Yes
Hemodialysis patient	Intermediate	Yes
Pre-1992 blood and/or transplant recipient	Intermediate	Yes
Undiagnosed liver problems	Intermediate	Yes
Infant born to infected mother	Intermediate	>12–18 months
Healthcare/public safety worker	Low	Only after known exposure
Sex with multiple partners	Low	No
Sex with infected steady partner	Low	No

Structure and Function of Pegylated Interferons

Interferon reduces viral load by attaching to cell-surface receptors that initiate a series of events within the target cell that result in production of cytokines that lead to: suppression of cell proliferation and enhanced phagocytic activity of macrophages, improved cytotoxicity of lymphocytes against target cells and inhibition of viral replication in virus infected cells. Pegylation (see definition below) of the interferon molecule leads to sustained serum concentrations of drug with longer half-life and less proteolytic degradation. This, and the use of ribavirin, results in higher response rates over standard interferon.

Pegylation is the attachment of a polyethylene glycol (PEG) polymer to a protein. The attachment of PEG to IFN- α (PegIFN- α) increases the size of the molecule, improves the pharmacokinetic profile, and improves viral response rates. The prolonged drug elimination time allows for once-weekly dosing (*Clin Liver Dis.* 2003;7:139-158; *Dig Liver Dis.* 2004;36(Suppl 3)S334-S338; *Ailment Pharmacol Ther.* 2004;20:825-830; *Hepatology Rev.* 2005;2:3-9).

There are two pegylated IFNs: PegIFN- α -2a and PegIFN- α -2b. The difference in the size of the Peg moiety and linkage to the PEG polymer of the two compounds translates into different *in vitro* activity and pharmacological properties, with the PegIFN- α -2b showing more potency and antiviral activity. To assess clinical efficacy differences, a head-to-head clinical trial (IDEAL) is underway in a homogenous population infected with genotype 1 virus. ■

AASLD Guidelines for the Management and Treatment of Hepatitis C Patients

In 2004, the American Association for the Study of Liver Disease (AASLD) published guidelines for the diagnosis, management and treatment of hepatitis C (*Hepatology.* 2004;39:1147-1171). The primary goal of therapy is to eradicate the virus. Infection is considered eradicated when treatment results in 'sustained virological response' (SVR). SVR is defined as the absence of HCV RNA in serum at the end of treatment and six months later. Weekly subcutaneous injection of pegIFN- α plus daily oral ribavirin provides the highest overall SVR rates and is considered the current standard of care. There are two licensed pegIFN- α products in the United States — pegIFN- α 2a [PEGASYS] and pegIFN- α 2b [PEG-INTRON].

Genotype is a factor in determining the dosing regimen used. For example, 48 weeks of treatment is generally required in genotype 1 patients while 24 weeks of treatment is adequate in patients with genotypes 2 or 3 (Figures 1 and 2) (*Hepatology.* 2004;39:1147-1171).

Approximately 75% of treated patients will experience at least one systemic side effect associated with treatment (e.g., IFN- α based-neutropenia, thrombocytopenia, depression, hypo- or hyper-thyroidism, irritability, concentration/memory disturbances, visual disturbances, fatigue, muscle aches, headaches, nausea/vomiting, skin irritation, low grade fever, weight loss, insomnia, hearing loss, tinnitus, interstitial fibrosis, hair thinning. Ribovirin based-hemolytic anemia, fatigue, itching, rash, sinusitis, birth defects, gout). Adverse events may be more severe in the initial weeks of treatment but can often be managed with analgesics, antidepressants and, and growth factors (*Hepatology.* 2004;39:1147-1171). Due to the possibility of birth defects associated with ribovirin, persons who receive treatment should use strict contraceptive methods during treatment as well as 6 months after treatment. ■

Figure 1
Sequential Steps for Managing and Treating Patients with Chronic HCV Infection, Genotype 1.

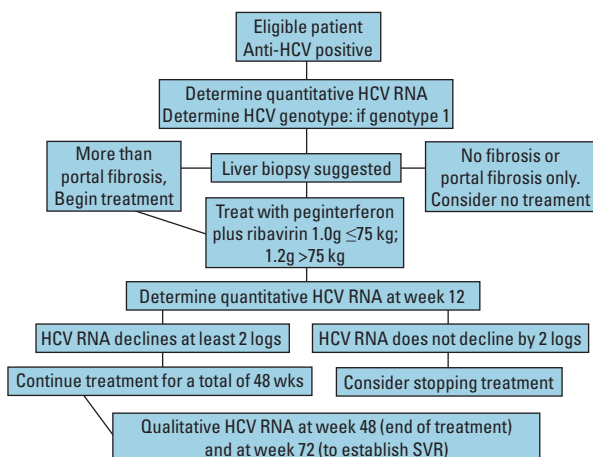
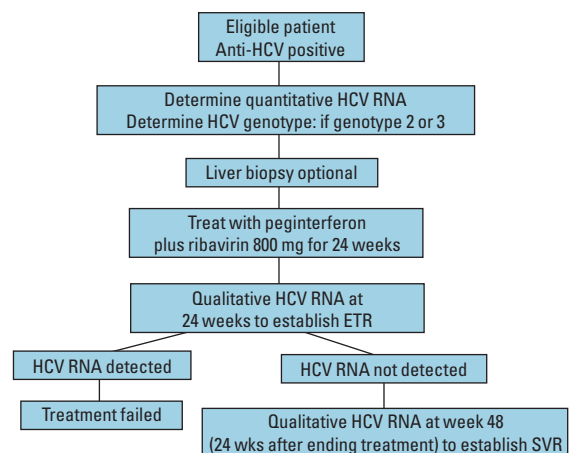


Figure 2
Sequential Steps for Managing and Treating Patients with Chronic HCV Infection, Genotype 2 or 3.



Challenges in the Treatment of Special Populations: AASLD Guidelines

The AASLD Guidelines also includes a section on special populations (*Hepatology*. 2004;39:1147-1171). Since comorbidities and complications are common in HCV patients, it is important that treatment options for special populations be understood. The guidelines provide detailed recommendations for the following special populations:

- Nonresponders
- Relapsers
- Normal serum ALT values
- Children
- HIV coinfection
- Renal disease
- Decompensated cirrhosis
- Solid organ transplant recipients
- Acute hepatitis C
- Active injection drug users

Treatment recommendations for these populations are available at www.aasld.org. In most cases, treatment with pegIFN- α plus ribavirin is recommended (ribavirin is contraindicated in the renal failure patient). ■

Treatment of Hepatitis C in Nonresponders and Relapsers

Patients whose chronic hepatitis C either does not respond to treatment or relapses may be at risk for progressive liver disease or hepatocellular carcinoma. Currently, there are four clinical trials underway that are examining the efficacy of PegIFN- α in nonresponders or relapsers: the Copilot Trial, TARGET Trial, HALT-C Trial and EPIC3 Trial.*

Preliminary results from these studies indicate that some patients do respond to retreatment and may achieve SVR. Preliminary results with the EPIC3 Trial indicated that it is possible that outcomes can be better predicted. To date, overall positive outcome has been achieved in 21% of nonresponders/relapsers with outcomes favoring patients with genotype 2 or 3 (56% of patients achieving SVR compared to 14% of genotype 1 patients), relapsers (41% of patients achieving SVR compared to 14% of nonresponders), and/or with mild to moderate fibrosis (26% of patients achieving SVR compared to 15% of patients with advanced fibrosis). In the majority of patients who achieved SVR, undetectable HCV RNA was achieved by week 12 of treatment. These preliminary results are very promising and may alter the way we treat nonresponders and relapsers in the future. Final outcomes from these important studies are expected over the next few years. ■

*Afdhal et al. Poster presented at the AASLD Annual Meeting in Boston, MA, 2004; Melet et al. Poster presented at AASLD Annual Meeting in Boston, MA, 2004; Shiffman et al. Poster presented at AASLD Annual Meeting in Boston, MA, 2004; *Gastroenterology*. 2004;126:1015-23. Poynard et al. Presented at the European Association for the Study of the Liver (EASL) Annual Meeting, Paris, France, 2005.

Predicting Sustained Virological Response in Hepatitis C Virus Infection

Improved methods for identifying patients destined to not respond to treatment are necessary to change strategies as early in the treatment course as possible. Serum HCV RNA quantification is an important tool for monitoring HCV response to therapy and allows for accurate prediction as to who will be a nonresponder. Indeed, studies have shown if HCV RNA has not decreased by 2 log units at week 12 then treatment should be terminated. This treatment recommendation may be further refined in the future. For example, one study has shown that over half of nonresponders could be identified by week 4 of treatment (*Can J Gastroenterol*. 2003;17:483-487). In this study, a log unit fall in HCV RNA of less than or equal to 1.05 at week 4 may identify non-responders.

In another study, whole blood samples of HCV RNA were found to be superior to serum or plasma specimens for predicting an early viral relapse and provides a new tool for predicting SVR (*Clin Infect Dis*. 2004;39:1754-1760). Another possible predictive tool is to measure HCV core antigen levels which may predict outcome in genotype 1 patients receiving combination therapy (*J Hepatol*. 2004;40:527-532; *J Viral Hepatitis*. 2003;10:318-323). ■

Challenges in the Treatment of HCV Infection in Liver Transplant Patients

Hepatitis C almost universally recurs in HCV-positive patients following liver transplantation and disease progression is accelerated in liver transplant patients when compared with immune-competent patients. Treating HCV recurrence after liver transplantation should be done by experienced transplant hepatologists. Interferon acts by up-regulating the immune system and rejection rarely occurs during treatment.

Results from one study indicate that both pre-emptive therapy (within 3 weeks of transplant) or treatment (6 to 24 months after transplant) of liver transplant patients with pegIFN- α can lead to viral response (i.e., nondetectable HCV) (*Hepatology*. 2005;41:289-298). Another study examining the safety and efficacy of combination therapy in transplant patients found that it is effective in treating recurrent HCV (*Transplantation*. 2004;78:1303-1307). Growth factors are often coadministered in this population due to renal dysfunction and high incidence of anemia. Dose modifications are also frequently required. ■

Treating HCV Infection in African American Patients

African-American patients with HCV have generally responded poorly to treatment compared to Caucasians. This disparity was believed to be because African Americans had a higher prevalence of genotype 1 HCV compared to Caucasian patients (96% vs 75%), but studies directly comparing treatment efficacy in genotype 1 between these two populations have shown a difference in response rates. A recently published study showed treatment with pegIFN- α -2b plus ribavirin therapy resulted in 19% of African Americans achieving SVR compared with 52% of non-Hispanic whites (*N Engl J Med.* 2004;350:2265-2271). The difference in response rates, however, could not be explained by differences in HCV genotype and remain unclear. Another study using pegIFN- α -2a plus ribavirin showed an overall lower response rates in Caucasians (39%) but still superior results to that achieved in African Americans (26%). The study also concluded that the differences could not be explained by genotype differences in the two populations. (*Hepatology.* 2004;39:1702-1708) Further studies are needed to determine if immunologic differences between races accounts for responsiveness to IFN.

Improvement in outcome for African-American patients may occur using weight-based dosing of ribavirin. In the WIN-R Trial, patients' body weight was used to adjust the dose of ribavirin (e.g., < 65 kg received 800 mg, 65-85 kg received 1000mg, 86-104 kg received 1200 mg, 105-124 kg received 1400 mg) in combination with a fixed dose of pegIFN- α -2b (Jacobson et al. Poster presented at the AASLD Annual Meeting in Boston, MA, 2004). Using this method, higher SVR rates and significantly lower relapse rates were observed with higher doses of ribavirin without compromising safety (compared to the group receiving standard 800 mg dose).

In conclusion, the high genotype 1 prevalence in African Americans cannot explain lower SVR rates. Weight-based dosing of ribavirin offers a significant advantage in treating African-American patients infected with HCV genotype 1. ■

Managing HCV Infection in Patients with Concomitant HIV or HBV Infection

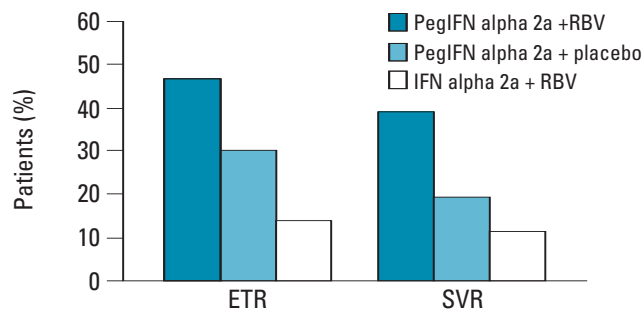
Approximately one-third of HIV infected patients in Europe and the United States are co-infected with HCV. HIV infection is associated with higher HCV RNA viral load and a more rapid progression of cirrhosis, liver failure, and hepatocellular carcinoma.

A retrospective analysis of 351 HIV/HCV co-infected patients (119 patients treated with IFN, 106 patients treated with IFN plus ribavirin, and 126 patients treated with pegIFN- α -2b plus ribavirin) found that SVR was achieved in 18.5% of the IFN monotherapy patients, 16% of the IFN plus ribavirin treated patients and 30.2% of the pegIFN- α -2b plus ribavirin treated patients. During follow-up (mean 56-58 months), none of these patients relapsed (*Antiviral Ther.* 2004;9:987-992). This study indicates that SVR can be achieved in this population, though response rates are lower than those in mono-infected patients.

Another study compared pegIFN- α -2a plus ribavirin with pegIFN- α -2a plus placebo (versus standard IFN plus ribavirin) and found the pegIFN- α -2a + ribavirin combination to be superior (Figure 3) (*N Engl J Med.* 2004;351: 438-450).

In conclusion, the current regimen used for the treatment of chronic HCV infection can be applied to HIV/HCV co-infected patients as well. PegIFN- α plus ribavirin is the treatment of choice for HIV/HCV co-infected patients. This treatment regimen is also optimal for hepatitis B viral/ HCV co-infected patients; however, more data are needed about the optimal treatment regimen. ■

Figure 3
Response to Treatment in HIV/HCV Coinfection



ETR = end of treatment response
 SRV= sustained virological response
N Engl J Med 2004;351:438-450.

American Academy of Physician Assistants Pain Talk: Communicating With Patients in Pain

Pain, the most commonly reported reason for medical appointments, accounts for about 40 million medical office visits annually. In spite of this, according to the American Pain Society, patients in pain are undertreated and report sub-optimal levels of pain relief, suggesting that they are not benefiting from the full spectrum of available approaches to pain management. In today's healthcare delivery systems, the Physician Assistant (PA) plays a key role in the diagnosis and management of chronic and persistent pain syndromes. Managed well, using a rational, multimodal plan, pain from a variety of sources can be relieved. Effective communication with patients is vital, as is employment of one or more of a number of pain assessment instruments. This symposium, presented in conjunction with the 33rd Annual Conference of the American Academy of Physician Assistants, arrays the latest knowledge regarding the clinical management of pain using a mix of didactic presentation and role-play.

Speakers

Allan F. Platt, Jr, PA-C (Chair)
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Introduction

Pain conditions are widely underdiagnosed and undertreated in this country, despite a number of effective medications and proven non-pharmacological treatments. (Am Pain Society; Available at: <http://www.ampainsoc.org>). Poor communication between healthcare providers and patients is an important underlying cause, as are factors such as patients' reluctance to admit to having pain, and difficulty in finding words to express their quality and level of pain. On the other side of the communication gap are clinicians, who may lack specific knowledge about pain; not listen well to patients or not take pain complaints seriously. Also, there is a significant overestimation of the risk of addiction to some pain medications. According to one study by the American Pain Society, among a group of physicians, 27% reported an unwillingness to treat pain aggressively. (Am Pain Society; Available at: <http://www.ampainsoc.org>).

In many practices, physician assistants play a key role in the diagnosis and management of patients with chronic or persistent pain. Physician assistants teach that with the appropriate use of communication, pain assessment tools, and programs that employ both pharmacologic and non-pharmacologic interventions, pain can be greatly improved in all sufferers.

The Size of the Pain Problem

Patients in search of pain relief account for 40 million medical office visits annually. Direct healthcare costs and lost productivity due to the suffering from pain amounts to \$100 billion annually (American Pain Foundation. Available at: <http://www.painfoundation.org>). Untreated or undertreated pain can reduce patients' quality of life; compromise immune function; hamper sleeping and eating; impact daily activities, including work; and lengthen hospital stays, among many other effects, both personal and societal (American Pain Society. Available at: <http://www.ampainsoc.org>).

The American Pain Society has determined that 4 out of 10 patients with chronic non-cancer pain do not obtain relief at more than a level of 5 on a scale

of 0-10. The frustration patients experience is reflected in their patterns of health care usage: 47% of patients with complaints of pain have changed doctors at least once. Twenty-two percent have switched health care providers three or more times (Available at: www.ampainsoc.org).

A number of misperceptions and mismanagement issues were illustrated by a dramatization, directed by speakers Allan Platt, Jr, PA-C, from the Physician Assistant Program in the Department of Family and Preventive Medicine at Emory University School of Medicine in Atlanta, GA; and John F. Byrnes, Jr, PA-C, Clinical Research Director and President at the Southeastern Clinical Research Consultants in Orlando, FL. They were assisted in their dramatic skit by professional actors.



Allan F. Platt, Jr, PA-C

The American Pain Society has determined that 4 out of 10 patients with chronic non-cancer pain do not obtain relief at more than a level of 5 on a scale of 0-10.

Case Study: Patient T. Smith

T. Smith is a 32-year-old female secretary who presents with the chief complaint of having lost her pain medication. Her medical history includes insulin-dependent Type 2 diabetes; diabetic neuropathy; and chronic neuropathic pain. In his exchange with the patient, the PA made immediately clear that he was skeptical of the patient's claim of having lost her medication. "I see in your chart you've had multiple prescriptions for Tylenol® 3 and they've been called in to multiple pharmacies," he said. "Additionally, you have diabetic neuropathy; if you would take care of your blood sugar you wouldn't be in this sit-

uation,” “You don’t look like you’re in pain.”

“What did the PA do wrong in this exchange?” asked speaker and moderator Allan Platt. Everything, he said, beginning with setting the stage and by not applying the ground rules of good communication. “Before you see the patient, make sure you are prepared. Communicate at eye level with the patient, and maintain eye contact. Give patients the benefit of the doubt — even if there is doubt”, he said. Also, “implement the GRE rule — be Genuine, give Respect, and show Empathy toward the patient.” Above all, Platt added, do not pre-judge.

Program speaker John F. Byrnes referred to the mnemonic ABCDE of pain evaluation and management as an aid to remembering these points.

- A** = Ask and assess the pain
- B** = Believe the patient
- C** = Choose the appropriate therapy (using the safest route and dose for pain level)
- D** = Deliver therapy in a timely manner (Use long-acting agents; dose according to half-life)
- E** = Empower and enable the patient (Partner with the patients in their treatment.)

A number of standardized pain assessment tools are available, and presently the JCAHO (Joint Commission on Accreditation of Healthcare Organizations), AHA (American Heart Association) and ACEP (American College of Emergency Physicians) are each developing guidelines for pain assessment. In each patient encounter, even before the physical exam, and before the laboratory studies, Mr. Platt emphasized, conduct an appropriate and thorough pain history.

LOCATES is an acronym developed by Mr. Platt to remember each aspect of a pain history (Platt A. Differential Diagnosis Mnemonics and the Medical History. Available for Palm Pilot download at www.EmoryPA.org):

- L** = Location
- O** = Other associated symptoms
- C** = Characteristics
- A** = Alleviating and aggravating factors
- T** = Timing
- E** = Environment
- S** = Severity (use a pain scale)

Pain intensity tools, for various patient populations, are available as well. These include the Adolescent Pediatric Pain Tool, “Oucher”, Poker Chip, the Visual Analog Scale — VAS, the McGill Pain Questionnaire (Graham C, et al. *Pain* 1980;8:377-387), and the “Faces” scale, which uses images of facial expressions linked to pain ratings (Wong D, Baker C. 1995)

Pain is multidimensional, and its effect on patient function in a larger sense may be assessed via mood assessment tools. “Faces” qualifies as both a mood and pain assessment tool, but there is also the Missouri Children’s Behavior Checklist; the Symptom Checklist 90-R; the Brief Symptoms Index (BSI); the well-known Hamilton Rating Scale for Depression (HRSD); and the Memorial Pain Assessment Card. The Multidimensional Pain Score (MPS) is a new tool which measures pain intensity, relief, mood as well as other side effects, and records and calculates responses via a PDA or computer template (Platt A, et al. *Annals of Emergency Medicine* 2005. In press).

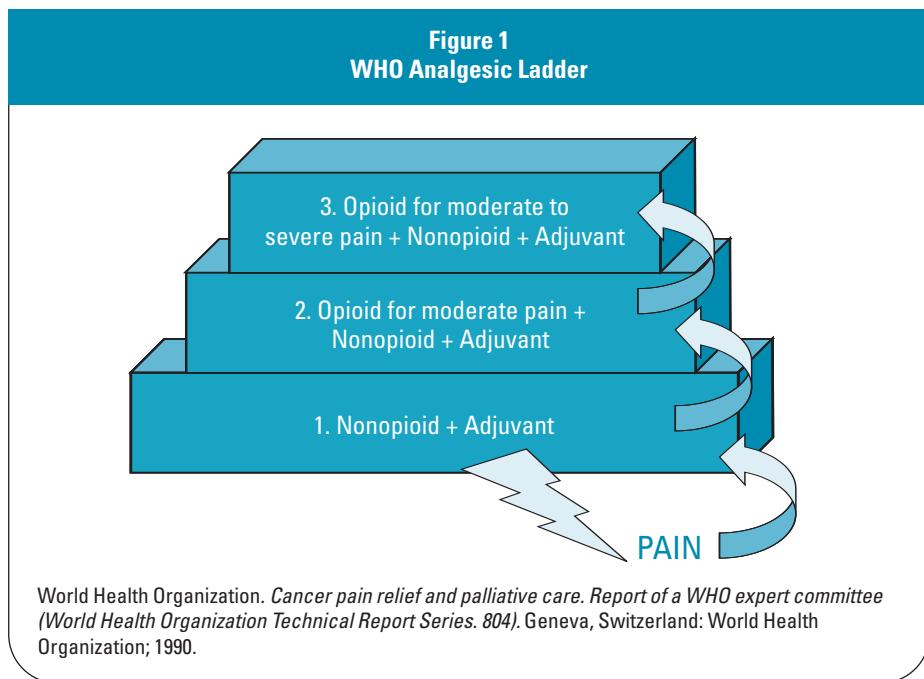
Matching the Treatment to the Pain in a Graduated, Step-wise Fashion

Pain may be managed via a number of methods — pharmacologic disease-specific therapy, pharmacologic nonopioid or opioid therapy, and/or by surgery

and anesthesia, in addition to non-pharmacologic approaches. Whatever the approach, say experts, “match the appropriate treatment with the corresponding pain in a stepwise and graduated fashion.” (The Sidebar illustrates how a comprehensive pain management plan may look.)

The World Health Organization, in an effort to guide the appropriate selection of analgesia for pain, developed the WHO Analgesic Ladder (Figure 1) According to the WHO Ladder, patients at Level 1 (with a VAS score of 1-3), should be treated with a nonopioid, with an adjuvant added, as needed. At level 2, with moderate pain and a VAS score of 4-7, an opioid may be added in addition to the non-opioid plus an adjuvant agent. For the most severe level of pain — Level 3 on the WHO scale, and represented by a VAS score of 8-10, a stronger opioid may be needed in addition to a nonopioid plus an adjuvant agent.

In pain management, the goal is always to match the appropriate treatment with the corresponding pain in a stepwise and graduated fashion.



NSAIDs — Non-steroidal anti-inflammatory drugs — are the most commonly used class of agents for pain and most are available over the counter. “The efficacy of these agents is often underestimated,” Mr. Platt said, “but their side effects and cautions — including renal impairment, GI bleeding, and platelet dysfunction — may be overlooked.” However, he added that with foresight, the side effects may be ameliorated. COX-2 inhibitors, formerly well-known and heavily prescribed for their efficacy, are now better known for their risks. But, said speakers Platt and Byrnes, they remain a potent treatment for pain, measuring the risks against the benefits.

Opioids, despite the concern they provoke, are safe if administered properly, and have an important role to play

For patients with continuous pain who have developed a tolerance to opioids, the longer-acting, sustained-release forms would be a logical choice to manage the pain and avoid the peaks and valleys [that occur] with intermittent pain management.

in alleviating intractable pain. There are oral, rectal, parenteral, and transdermal routes of administration to choose from,

depending on patient-specific considerations. In an opiate-naive patient, therapy should be initiated using an agent with a short half-life. For patients with continuous pain who have a tolerance to opioids, Mr. Platt said, longer-acting, sustained-release forms would be a logical choice to manage the pain and avoid the peaks and valleys [that occur] with intermittent pain management. Cautions regarding opiate treatment include respiratory depression, said Platt, and for this reason especially, he avoids prn dosing of opioids. Besides the danger of respiratory depression, he said, “You are never going to get a continuous blood level to maintain the pain coverage you want.” It is also important to remember to start therapy by titrating the medication. ■

Tolerance, Physical Dependence, and Addiction

Tolerance and dependence can certainly develop with opioids. But these problems should not be confused with addiction. “Physical dependence, an expected response to chronic opioid administration, and tolerance, are reversible physiological effects.” To prevent symptoms associated with acute opiate withdrawal, Byrnes said, downward titration is necessary (decrease the dose by 15% to 20% daily before stopping) (Foley KM. *N Engl J Med* 1985; 313:84-95). At the same time, a careful PA watches for side effects of constipation, histamine release (such as runny nose), nausea, and vomiting.

Although it should always be the last item on a differential diagnosis list, a PA should watch for such things as losing medications repeatedly and reports of multiple drug allergies except for one “favorite” drug.

Table 1
Pain Management — Adjuvants

- Antidepressants
- Anticonvulsants
- Anxiolytics
- Topical Agents
- Laxatives
- Antihistamines
- Antiemetics

Addiction

By contrast with physical dependence and tolerance, addiction is a brain disease characterized by dysfunctional behavior patterns such as craving; an overwhelming involvement in obtaining the drug; and use despite the range of negative consequences that appertain (Foley KM *N Engl J Med* 1985;313:84-95). PAs are advised to watch, monitor, and document patients’ behavior for evidence of addiction. In chronic pain management patients, “behavior observation is extremely important — much more so than with someone who has a broken leg” or another type of physical problem. “Although it should always be the last



John F. Byrnes, Jr, PA-C

Antidepressants, anticonvulsants, anxiolytics and topical pain agents may be appropriate adjuvants to a chronic pain treatment plan and should be considered when you prescribe other medications [for pain].

item on a differential diagnosis list, a PA should watch for such things as losing medications repeatedly and reports of multiple drug allergies except for one “favorite” drug. Still, many patients and clinicians fear the prospect of addiction to an unnecessary degree. In one study, only about four in 12,000 patients

have been documented to have become addicted by medication (Foley KM. *N Engl J Med* 1985;313:84-95).

Adjuvant therapies are a key aspect of pain management. The list of adjuvants includes antidepressants, anticonvulsants, anxiolytics, topical pain agents, laxatives, antihistamines, and antiemetics. The top four of these — antidepressants, anticonvulsants, anxiolytics

and topical pain agents — “are excellent adjuvants to your chronic pain treatment plan and always should be considered when you prescribe other medications.”

In pain management cases, Mr. Byrnes said, consider nonpharmacologic treatment. “If a patient is receptive to exploring one of many non-drug options (TENS; relaxation/biofeedback; heat/cold and massage; exercise; acupuncture,

and physical and occupational therapy), he or she has a much better chance of receiving benefit, compared with a medication they don’t like, doesn’t taste good, and has side effects. The main thing is compliance.” Finally, he added that it is important to reassure the patient that life will go on, and that there is a plan that will work. “Relief is on the way!” ■

Case Study

Bradley Jones: Back Pain Out of Control for 1 Week

History

Brad Jones, age 56, is a loading dock supervisor whose chief complaint is out-of-control back pain for a week. He has a history of chronic low back pain from a herniated disk. Jones has been treated with conservative therapy, including NSAIDs and weak opioids in the past. He is currently self-medicating with ibuprofen 200 mg every 8 hours and hydrocodone/acetaminophen, 2 tablets every 4 hours.

Pain Assessment

- Pain intensity: 9 out of 10 on a 0-10 scale
- Mood: Depressed, 5 on a scale of 0-10
- Side effects: Abdominal pain, 4 on a scale of 0-10
- Function: 3 on a scale of 0-10

Physical Exam Findings

- Vital Signs: Pulse 100, Respirations. 16, Blood pressure 130/85, Temperature 37.2
- General Inspection: Moderate distress.
 - Back: limited ROM with lumbosacral spasm and tenderness
 - + straight leg raise on left
- Lower extremity motor, sensory, pulses, reflexes all normal. Rectal: good sphincter tone, normal prostate, guaiac negative for occult blood

Comprehensive Pain Management Plan

- Stop ibuprofen (OTC, self-prescribed)
- Naprosyn 500 mg twice daily with food
- Omeprazole 40 mg once daily
- Morphine controlled-release 30 mg, every 12 hours
- Stool softener + stimulant
- Nortriptyline 10 mg once daily at bedtime for depression, sleep, and synergistic pain
- Alternating hot packs (10 mins) and cold packs (5 mins), as needed

- Back exercises (started a few days after medications)
- Graduated exercise program: short, 10 minute walks 4 times daily, increased to 15-20 minutes on a schedule

Case Comments:

Naproxen 500 milligrams is prescribed for long-acting, round-the-clock pain analgesia. Omeprazole provides stomach protection against the naproxen. Prior hydrocodone is replaced with long-acting morphine at 30 milligrams every 12 hours. Stool softener and stimulant are prescribed to address the constipation side effect of morphine. Nortriptyline is prescribed to address mood and sleep, often synergistic with pain. Non-pharmacologic approaches — hot/cold packs, back exercises, and general exercise — are prescribed as part of a regimen of general physical and back health and strengthening. Mr. Jones is scheduled for a return visit in 2 weeks. If pain persists, an MRI may be ordered to further evaluate the source of pain.

The risk of addiction using the opioids for pain as prescribed is very low. The expected outcome for Mr. Jones is recovery to full function in 2 weeks time.

Mr. Jones is counseled about the risks, side effects, and benefits of the treatment plan. He is warned about the potential for GI bleeding with the NSAID, the drowsiness that may occur with the opioid, and the need to avoid operating dangerous machinery at work. He is further advised to keep the morphine and all medications out of contact of any children in the house and to use the medication as directed. The risk of addiction using the opioids for pain as prescribed is very low. The expected outcome for Mr. Jones is recovery to full function in 2 weeks time. ■