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Stroke: Rehabilitation and Recovery

Rehabilitation is a critical component of stroke treatment, as most stroke survivors are left with significant neurological impairments and other sequelae, such as spasticity and pain. Approximately 40% of stroke patients are left with moderate functional impairment and 15%-30% with severe disability.[1] Stroke rehabilitation aims to reverse these impairments to the extent possible, maximize functionality through the use of compensatory approaches, prevent complications, and manage comorbidities. This article will review the basic principles of rehabilitation, current practices, and evidence supporting various aspects of stroke rehabilitation.

Role of Primary Care Physician

With millions of stroke survivors in the United States, primary care physicians are often faced with providing care to these individuals and, thus, need to be able to identify common post-stroke rehabilitation issues. Post-stroke depression can occur at any time after stroke, and it is important that primary care physicians recognize this as a treatable and reversible condition, rather than a "natural" consequence of disability after stroke. Monitoring range of motion to identify developing contracture and/or spasticity is important so that referral can be made to a rehabilitation physician if these occur. Lastly, addressing the stroke survivor's mobility, ability to perform activities of daily living (ADL), and any deterioration in functional status are critical to making timely referrals to rehabilitation services when needed. When these issues are identified early, the primary care physician can prevent the progression of debilitating consequences by initiating treatment or referring to appropriate specialists for further evaluation and management.

Rehabilitation

Functional improvement in rehabilitation is accomplished through a combination of neurological recovery and adoption of compensatory techniques and equipment. Improved functional independence may be attained by reducing impairment directly (i.e., via neural recovery using cerebral plasticity to overcome neuronal loss) or through compensation for impairment by using remaining physical and cognitive abilities and strategies. Both recovery and compensation are crucial concepts in rehabilitation and key therapeutic approaches; interventions must be balanced to address patient goals and efficiently deploy the available rehabilitation resources.[2]

Over the last century, a significant amount of research has been conducted to further elucidate how best to provide comprehensive stroke rehabilitation. Currently, it is comprised of several key components, including assessment, goal setting, treatment of functional and psychosocial impairments, and prevention of complications. Patients are reassessed at regular intervals to evaluate progress, and treatment plans are adjusted accordingly. Ideally, rehabilitation begins immediately following stroke and often becomes a long-term element in the lives of these patients. Assessment and treatment should begin in the setting of acute hospitalization, and depending on the needs of the individual, continued

Executive Summary

With millions of stroke survivors in the United States, primary care physicians are often involved in providing post-stroke rehabilitation care, including recognizing common treatable and reversible conditions such as depression.

- Key components of rehabilitation include assessment, goal setting, treatment of functional and psychosocial impairments, and prevention of complications.
- A coordinated, multidisciplinary rehabilitation evaluation and treatment approach during the early post-stroke period is associated with improved clinical outcomes.
- Muscle weakness and impaired motor control are managed with various modalities such as repetitive task training, constraint-induced movement therapy, mirror therapy, and functional electrical stimulation.
- Spasticity is addressed through stretching and range of motion exercises, bracing, and medication, although benzodiazepines, if possible, should be avoided.
- Post-stroke depression and fatigue are common and underdiagnosed. Standard antidepressant psychotherapy and psychopharmacologic treatment including selective serotonin reuptake inhibitors, such as fluoxetine, have been found effective.

rehabilitation may transition to the appropriate inpatient or outpatient setting.

National and international guidelines have been developed to provide resources for health care providers with the latest evidence-based practices, such as the American Heart Association (AHA) Guidelines in 2005 and the National Institute for Health and Care Excellence (NICE) Guidelines in 2013.[3,4] AHA guidelines incorporate the U.S. Preventive Services Task Force (USPSTF) grading system for level of evidence and are referenced in this article where applicable[5] (*see Table 1*). AHA rehabilitation guidelines currently are being updated, with release anticipated in 2014. Adherence to stroke rehabilitation guidelines is associated with improved patient functional outcomes.[6]

In an effort by the Joint Commission and the AHA, certification has been developed using current guidelines and established standards of care to identify Primary Stroke Centers and more recently Comprehensive Stroke Centers. The rehabilitation requirements for Primary Stroke Center certification include the ability to assess for rehabilitation needs and refer for appropriate post-acute care. Comprehensive Stroke Centers also must have a rehabilitation service led by a physician with expertise in neurorehabilitation, and the service must include therapists, nurses, and social workers with an expertise in addressing the rehabilitation needs of stroke patients.[7,8] Complete guidelines can be found on the Joint Commission's website.[7]

Services and Settings

A coordinated, multidisciplinary rehabilitation evaluation and treatment during the early post-stroke period is associated with improved clinical outcomes[9,10] (*USPSTF Level A*[1]). The multidisciplinary team typically consists of physicians, physical therapists, occupational therapists, speech therapists, recreational therapists, nurses, social workers, and psychologists who work closely with patients and their family members or caregivers to achieve rehabilitation goals. If these rehabilitation services are not available in the acute hospital, then patients with moderate or severe symptoms should be referred to a facility with these services (*USPSTF Level I*[1]).

Stroke patients should be assessed for rehabilitation needs, and rehabilitation should commence during the acute hospitalization. Upon discharge, rehabilitation (if required) may continue in either the inpatient, home, or outpatient setting. For patients who require inpatient rehabilitation prior to returning home, the two main options are acute inpatient rehabilitation (often referred to as Inpatient Rehabilitation Facilities, or IRFs) or subacute inpatient rehabilitation (also known as skilled nursing facilities). IRFs typically provide 3 or more hours of therapy per day, with subacute rehabilitation facilities providing a lesser (and more variable) amount. For patients who can be safely discharged home, rehabilitation may continue either through homecare services or in an outpatient rehabilitation program. Choice of rehabilitation setting depends on the patient's care needs, the team's assessment, goals of care, available resources, and patient's ability and willingness to participate in and tolerate a therapeutic exercise program (*USPSTF Level I*[1]).

Timing and Intensity

Initiation of rehabilitation during the acute hospitalization should

Table 1: USPSTF Recommendation Grading System[5]

A:	A strong recommendation that the intervention is always indicated and acceptable.
B:	A recommendation that the intervention may be useful/effective.
C:	A recommendation that the intervention may be considered.
D:	A recommendation that the procedure may be considered not useful/effective or may be harmful.
I:	Insufficient evidence to recommend for or against — the clinician must use clinical judgment.

occur once the patient is medically stable and safe to participate in therapy. Evidence supports early mobilization to prevent complications, such as venous thrombosis and contractures, and to begin the assessment and treatment process[3] (*USPSTF Level C*[1]). Early mobilization is currently being studied in A Very Early Rehabilitation Trial (AVERT), which is a single-blind, multicenter, randomized, controlled trial. Results from Phase 2 of this trial have shown that mobilization within 24 hours of stroke and at regular intervals is safe, is feasible, expedites return to unassisted ambulation, and is independently associated with long-term improved functional outcomes.[11,12]

Currently, there is wide acceptance of the hypothesis that a higher intensity of therapy is more beneficial than a lower intensity;[2,4,9,13-15] however, there is insufficient evidence to make specific recommendations regarding the optimal level of intensity of rehabilitation services (*USPSTF Level B*[1]). Ultimately, determining intensity level as well as duration of therapy is often greatly impacted by the mental and physical tolerance of the patient to participate in therapy, and therefore, programs must be individualized based on the multidisciplinary team's assessment and plan of care.[16]

Motor Rehabilitation

Many stroke patients suffer from muscle weakness and impaired motor control, with resultant functional deficits. Multiple therapeutic methods have been developed to aid stroke patients with improving motor function. These methods typically involve repeated practice of movements as a foundation, and vary greatly from simple task-specific training to more complex methods, using virtual reality or advanced robotics. Additional therapeutic options have emerged recently and are still currently being studied, including pharmacotherapy to facilitate plasticity and the use of non-invasive brain stimulation (*see Figure 1*). These novel therapies are likely to serve an adjunctive role to conventional physical and occupational therapy.

Figure 1: Transcranial Magnetic Stimulation

This technique is used both as a tool for investigating brain physiology during stroke recovery, and also as a potential therapy to enhance motor recovery.

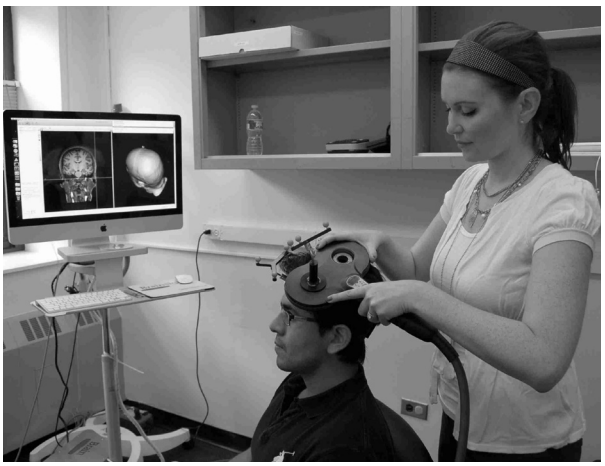


Photo courtesy of Dr. Joel Stein.

Conventional stroke rehabilitation includes repetitive task training; however, effects of specific interventions may generalize poorly to related tasks and emphasis should be placed on task- or context-specific training, which may be referred to as meaningful task-specific training.[17,18] This type of therapeutic exercise has been found effective in improving upper and lower extremity motor function.[18]

Constraint-induced movement therapy (CIMT) is another type of repetitive task training, involving forced use of the affected limb by "constraining" use of the non-paretic limb. A randomized trial found benefit in upper limb use after CIMT training.[19] The durability of this benefit is unknown, however, and additional research is required to define optimal dosing and timing of CIMT.[20,21,22]

In mirror therapy, a mirror is placed in the patient's midsagittal plane while performing bilateral exercises, providing the patient with the visual illusion of successfully moving the affected limb. In a Cochrane review, mirror therapy was shown to improve upper extremity motor function, ADLs, and pain; however, data are limited.[23,24] Mirror therapy may be used as an adjunct to conventional therapy.[24]

More than half of stroke patients are unable to walk independently during the acute phase of recovery and may benefit from intensive gait training, which can significantly improve gait function.[25,26] Gait training may include assisted ambulation, treadmill training, and body-weight-supported treadmill training (BWSTT).[27,26] A recent large, multicenter, randomized trial found that BWSTT compared to a home exercise program with physical therapy found no incremental benefit for BWSTT on walking speed, motor recovery, balance, and functional status, with patients participating in the home exercise program experiencing fewer falls.[28]

Functional electrical stimulation (FES) involves stimulating specific muscle groups to cause a muscle contraction. FES may lead to a short-term increase in motor strength and reduction in impairment severity, but without evidence of improved function.[29,30,31] This method is recommended for use in ankle, knee, or wrist motor impairment, shoulder subluxation, and for gait training (*USPSTF Level B*[1]). Several FES devices have been designed to aid in ambulation for patients with foot drop, including the Bioness L300 (Bioness Inc., Valencia, CA) and the WalkAide (Innovative Neurotronics Inc., Austin, TX). Kluding et al compared use of the FES (Bioness L300) with a traditional ankle-foot orthosis (AFO) and found that use of both FES and AFO with physical therapy training significantly improved gait speed and functional outcomes, with no significant difference between groups.[32]

Electrical signals also can be

detected in the muscle using surface electromyographic electrodes and translated into visual or auditory signals to provide biofeedback during therapeutic exercises.[33,34] The benefits of this therapy remain unproven.

Robots have been used in stroke rehabilitation to provide reliable, reproducible, high-intensity exercise therapy (*see Figure 2*).[35,36,37] A 2012 Cochrane review found that patients who received robot-assisted arm training were more likely to improve arm function and ADLs but not muscle strength.[17] Overall, data regarding efficacy of robot-assisted rehabilitation are limited and its cost-effectiveness may pose a barrier to implementation.[36,38] Other systems, including computer games and virtual reality, have been studied as standalone therapies to provide guidance and a motivating environment as well as in combination with robot-assisted therapy.[39] Although some benefit has been demonstrated, further research is needed to optimize these treatments and determine their clinical utility and cost-effectiveness.

Multiple drugs have been studied as potential facilitators of motor recovery. The Fluoxetine for Motor Recovery in Acute Ischemic Stroke (FLAME) study found that patients with moderate-to-severe motor deficits experienced enhanced motor recovery with combined fluoxetine and physical therapy after 3 months.[40] However, larger, more definitive studies are needed before fluoxetine can be routinely recommended for this indication.

Non-invasive cortical stimulation is currently being studied to assess its impact on motor recovery, but it is not yet routinely used in clinical practice.[41,42] The two main types of non-invasive cortical stimulation are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).[16] In rTMS, electric current is induced in the underlying cortex using pulses of high-intensity magnetic fields. Depending on the stimulation parameters, rTMS can either augment or inhibit cortical excitability. In tDCS, surface electrodes on the scalp deliver direct current that can similarly modulate excitatory or inhibitory effects on the underlying cortex. In a 2012 meta-analysis, Hsu et al found that rTMS had a positive effect on motor recovery, especially for those with subcortical stroke.[43] Non-invasive cortical stimulation is generally safe and well tolerated and is a potentially useful future therapeutic option when paired with exercise therapy.[16]

Approximately one-third of stroke patients develop muscle spasticity, which may further impair motor function and quality of life. However, treatment of spasticity is not necessary unless it causes impaired function, pain, deforming contractures, or limits skin hygiene. Treatment options include stretching and range of motion exercises, bracing, oral medications, and intramuscular injections. The most frequently used oral medications include baclofen, tizanidine, benzodiazepines, and dantrolene.[1] If possible, use of benzodiazepines should be avoided during the stroke recovery period because of possible deleterious effects on recovery[44] (*USPSTF Level D*[1]). Intramuscular injection is most commonly performed with botulinum toxins and less commonly with phenol or ethanol, and should be considered for disabling or painful spasticity, particularly if localized (*USPSTF Level B*[1]). Occasionally, patients may require more invasive treatments, such as intrathecal baclofen (ITB) or surgical correction of contractures.

Figure 2: Hand Robotic Device

The Amadeo robot (Tyromotion Inc., Graz, Austria) is one of a growing number of robotic devices for providing exercise therapy for the upper limb after stroke. This device provides finger flexion and extension training.

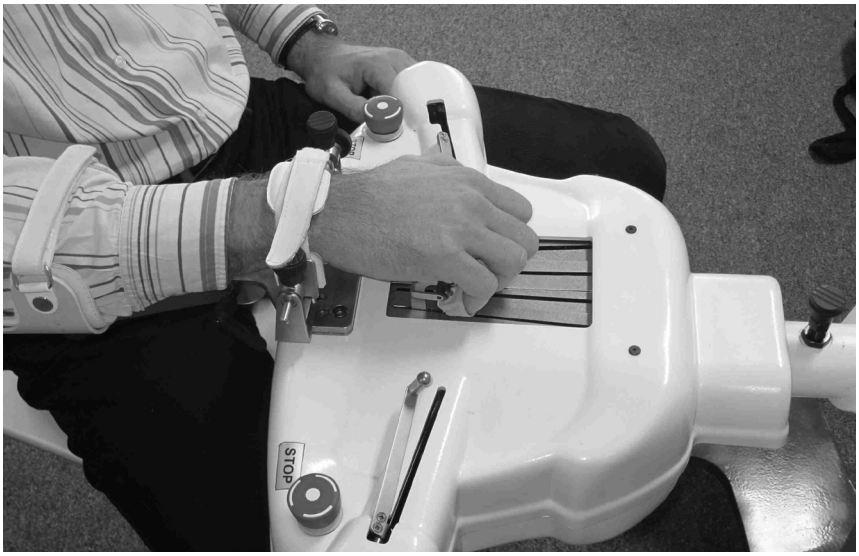


Photo Courtesy of Dr. Joel Stein

Speech and Language Rehabilitation

Disorders of communication, which may occur in as many as 40% of stroke patients, most commonly include aphasia, dysarthria, or apraxia. Aphasia results from damage to the regions of the central nervous system that affect language reception, expression, or both. Apraxia is caused by impairment in the patient's ability to plan and organize commands for muscle movement. Dysarthria results from neuromuscular damage, causing impairment in muscle movement and subsequent alterations in speech production. Speech and language rehabilitation involves careful assessment of the patient's abilities and deficits, as many patients suffer from a complex combination of these communication disorders. Therapy includes working on the affected system (e.g., phonation, articulation, prosody,

etc.) along with use of compensatory strategies and potential use of augmentative or alternative communication devices.[1] Patient and caregiver education is a critical component of speech therapy. Currently, no guidelines exist for use of specific therapeutic modalities in speech and language therapy. Nonetheless, treatment can aid in recovery and prevent ineffective or inappropriate compensatory behaviors[45] (*USPSTF Level A, B*[1]). Several novel therapeutic approaches are currently being investigated and include constraint-induced aphasia therapy, where use of compensatory strategies (such as communicating using gestures) is not permitted; use of non-invasive brain stimulation; and use of medications, such as memantine, an NMDA receptor antagonist.[46]

Dysphagia

Dysphagia is seen in approximately 45% of hospitalized stroke patients; therefore, early assessment is critically important due to the risk of aspiration.[1] Bedside dysphagia screening assessment should be performed before initiating oral intake for all stroke patients (*USPSTF Level B*[1]). If the bedside screening assessment is abnormal, then a complete bedside swallow evaluation is warranted (*USPSTF Level I*[1]). Additional measures, including modified barium swallow studies (*see Figure 3*) and flexible endoscopic evaluation of swallowing and sensory testing, also may be necessary in evaluating patients at high risk for aspiration. Treatment of dysphagia includes use of dietary texture modification, compensatory strategies, exercises, and postural advice.[4,47,48] In some cases, a feeding tube may be needed temporarily or long-term to support a patient's nutrition. Malnutrition affects approximately 30% of stroke patients during the first week of hospitalization and nutritional status should be carefully monitored and appropriate supplementation provided when necessary.[1]

Cognitive Rehabilitation

Cognitive deficits are very common after stroke, may be quite complex, and may affect multiple aspects of cognition such as attention, executive function, memory, and insight. Screening for alterations in cognition is important, as sustained cognitive deficits may result in poor outcomes. These deficits may impact a patient's ability to perform therapeutic exercise, and may affect one's ability to recognize one's own impairments, known as anosognosia. When possible, sedating medication that may exacerbate cognitive difficulties should be avoided, such as benzodiazepines, neuroleptics, barbiturates, and anticonvulsants. Severe cognitive impairments may pose significant obstacles in community and home reintegration.

Spatial neglect and visual deficits may result from damage to the non-dominant parietal lobe or to various areas of the visual system. Patients should be screened for visual deficits and spatial neglect. Use of prisms, education, functional training, compensatory strategies, and sensory stimulation may be employed in the treatment of spatial neglect or visual deficits.[4,49,50,51]

Psychological

Psychological disorders after stroke, including depression and fatigue, are very common and under-diagnosed, and can have a negative impact on rehabilitation. Signs or symptoms of depression warrant thorough assessment by a specialist and frequently require treatment. Standard antidepressant therapeutic modalities, including psychotherapy and psychopharmacologic treatment (e.g., selective serotonin reuptake inhibitors, such as fluoxetine),[4] have been found effective for post-stroke depression.[52]

Psychosocial Issues

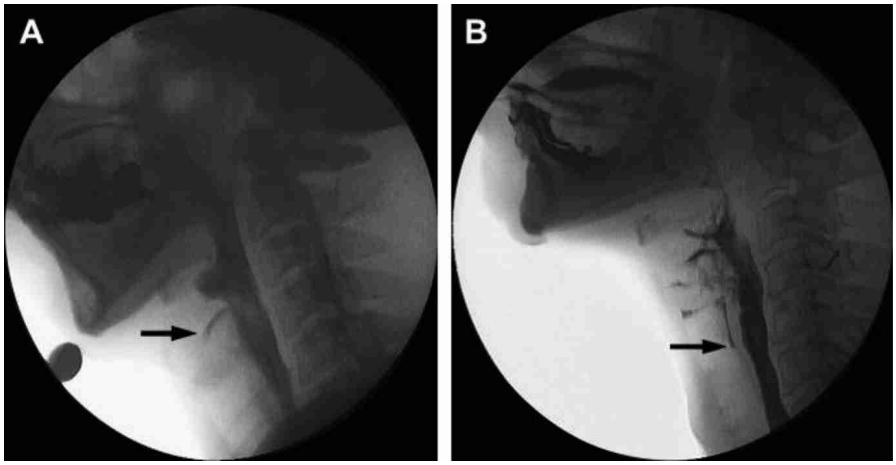
Rehabilitation not only should assess and treat motor, sensory, and cognitive deficits, but also should address issues of social support and caregiver stress early and at regular intervals. Living with disability after stroke is a lifelong challenge and adequate support from family and caregivers is critical to successful outcomes.

Conclusion

Stroke is one of the most common causes of acquired disability worldwide. The field of stroke rehabilitation is ever changing and evolving to better meet the needs of stroke survivors. Novel techniques and technology are being developed and studied with the ultimate goal of improving patient function and quality of life.

Figure 3: Modified Barium Swallow (MBS) Study

Static images from MBS studies show laryngeal penetration (A) and aspiration of barium into the trachea (B)



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CME Questions

1. Neurological recovery after stroke:
   a. is a typical part of the post-stroke course.
   b. is frequently incomplete.
   c. is influenced by sensorimotor activities.
   d. frequently needs to be combined with compensatory training to achieve functional goals.
   e. All of the above
2. Post-stroke depression:
   a. is uncommon, affecting less than 20% of stroke survivors.
   b. does not respond to conventional antidepressant therapies.
   c. is a normal reaction to the losses associated with stroke and doesn't require treatment.
   d. responds well in most cases to SSRIs and other pharmacotherapies.
   e. does not impact functional recovery.
3. A bedside dysphagia screening assessment should be performed before initiating oral intake for ***all*** stroke patients.
   a. True
   b. False
4. All of the following are used to treat spasticity in stroke survivors, ***except***:
   a. range of motion exercises.
   b. desensitization therapy.
   c. tizanidine.
   d. botulinum toxin intramuscular injections.
   e. intrathecal baclofen.
5. When can rehabilitation assessment and treatment begin after stroke in a medically stable patient?
   a. within 24 hours
   b. within 72 hours
   c. within 1 week
   d. within 2 weeks

In Future Issues: Obesity

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a. Total Number of Copies *(Net press run)*	352	284
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g. Total Distribution *(Sum of 15c. and 15f)*	300	268
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AHC Media

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 18, NUMBER 11 PAGES 21-22 NOVEMBER 2013

Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

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Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

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Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

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