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TABLE OF CONTENTS

Upcoming Features

- Anti-obesity drug therapy: Individualized, comprehensive

- Autoimmune encephalitis

- Teriparatide: Labeling changes, Long-term dosing

'Guidelines to Practice' series: Asthma in adults

In this issue, Kommaraju and Latifi summarize highlights from the 2020 GINA (Global Strategy for Asthma Management and Prevention) guidelines for the management of asthma in adult patients. This article is part of our ongoing series "Guidelines to Practice," shepherded by CCJM deputy editor Dr. Pelin Batur.

Recent years have seen a proliferation of practice guidelines put forth by specialty societies and various working groups. Practicing clinicians have found some to be useful in that they represent an evidence-based list of diagnostic and management suggestions, providing a summary of data on topics that we may not have had the opportunity to review ourselves. But there have been concerns that payers may use guidelines to limit payment for tests or therapies that were not specifically recommended or were specifically discouraged. Physicians bristle at this, but theoretically, and hopefully in reality, the reasonable exceptions to published guidelines for specific patient circumstances can be justified and resolved. As almost all guidelines state somewhere in small print, guidelines are only guidelines and are not meant to encompass all scenarios.

The goal of the "Guidelines to Practice" series is to briefly and concisely outline how a specific guideline fits in the context of current clinical practice and how it compares with previous guidelines. This is important, because not all guidelines on the same topic are in agreement. Publication of new studies and availability of new therapies necessitate revisiting older guidelines. Sometimes the rules for generating a new set of guidelines differ from older ones. Some consider cost while others do not, arguing that regional economies differ and the marketplace changes. Some have strict rules regarding the incorporation of data used in the writing of the guideline, allowing only prospective randomized trials and excluding observational and preclinical data. So not all guidelines are created equal, and we ask authors of "Guidelines to Practice" articles to point out these differences, when relevant, and to highlight the practical and newer conceptual aspects of the guidelines.

The GINA document emphasizes a key concept in the management of asthma in adults: asthma is an inflammatory syndrome, with bronchospasm manifesting as wheezing or cough. Hence, for moderate disease activity or even for mild intermittent disease with flares, inhaled corticosteroid therapy should be considered in conjunction with a long-acting beta-agonist. We have all had patients in whom very intermittent use of short-acting beta-agonists has been sufficient to control their symptoms over many years, and this approach may remain reasonable for some of these patients. But as highlighted in the reasoned summary of the GINA report, the goal of co-therapy with inhaled corticosteroids and long-acting bronchodilators is to prevent severe exacerbations and even death from asthma, particularly in newly diagnosed patients in whom a track record of response to therapy has not been established.

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Tuberous sclerosis complex
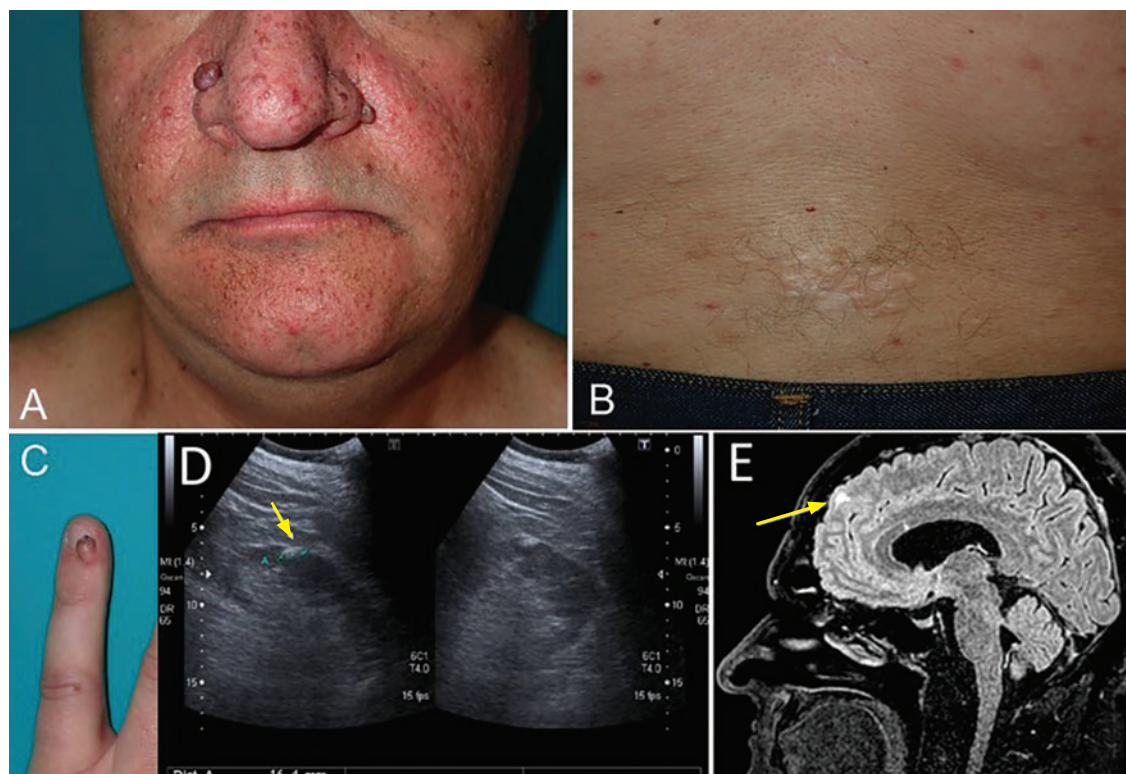
Figure 1. (A) Multiple erythematous papules in the malar and nasal regions were judged to be angiofibromas. (B) Linear hypopigmented macules and shagreen patches were noted over the lower back, as well as (C) a periungual fibroma on a fingernail. (D) Ultrasonography showed a hyperechoic solid lesion compatible with renal angiomyolipoma (arrow). (E) Brain magnetic resonance imaging detected cortical tubers (arrow) as well-circumscribed frontal and occipital areas of high signal intensity on axial fluid-attenuation inversion-recovery.

Tuberous sclerosis complex is a rare disorder caused by mutations of tumor-suppressor genes

A 45-year-old man with an unremarkable medical history was referred to the dermatology department because of facial lesions. On examination, he had multiple erythematous papules in the malar and nasal regions of the face that were judged to be angiofibromas (**Figure 1A**). He also had linear hypopigmented macules and shagreen patches on the lower back (**Figure 1B**) and a periungual fibroma on a fingernail (**Figure 1C**).

Although skin lesions such as these can be found in the general population, they can also be associated with certain syndromes. Having 1 or 2 angiofibromas is common in the general population, but multiple facial angiofibromas are present in 80% of patients who have tuberous sclerosis complex (TSC), for which at least 3 lesions are required as a diagnostic criterion. Angiofibromas can also be observed in Birt-Hogg-Dubé syndrome and in multiple endocrine neoplasia type 1.[1] Shagreen patches,

a type of collagenoma, are present in Cowden syndrome and in approximately half of patients with TSC. Over 90% of patients with TSC have hypopigmented macules, and the differential diagnosis includes postinflammatory hypopigmentation, piebaldism, and vitiligo.[1]

A genetic test was requested because we suspected TSC detected deletion of the *TSC1* gene, and this finding along with findings on the physical examination confirmed the diagnosis of TSC.

Because people with TSC tend to develop tumors in multiple organs of the body, the patient underwent an extensive workup. Ultrasonography of the kidneys showed a hyperechoic solid lesion compatible with renal angiomyolipoma (**Figure 1D, arrow**), although the patient's blood test results detected no renal impairment.

Although the patient did not manifest neurologic or neurobehavioral abnormalities, which are common in patients with TSC, brain magnetic resonance imaging detected cortical tubers as well-circumscribed frontal and occipital areas of high signal-intensity on axial fluid-attenuation inversion-recovery images (**Figure 1E, arrow**), and low signal-intensity on T1-weighted images, interpreted as cortical tubers. An ophthalmic examination, chest radiography, and echocardiography revealed no abnormalities.

SIGNS AND SYMPTOMS

TSC is a rare disorder with an incidence of 1 in 10,000 live births. It is caused by mutations of tumor-suppressor genes, which can lead to benign hamartomas in the brain, eyes, heart, lung, liver, kidney, and skin.[2] The most frequent clinical manifestations are dermatologic lesions such as focal hypopigmentation, angiofibroma, ungual fibroma, and shagreen patches,[3] but neurologic manifestations such as epilepsy, neuropsychiatric disorders, and behavioral problems are also common. Renal impairment is seen but is not among the most common early clinical manifestations.

Even though benign tumors are more common, there is a risk of malignancy, especially in the brain and kidney.

DIAGNOSIS AND TREATMENT

Appropriate evaluation is important to limit the morbidity and mortality of TSC. Neurologic and renal involvement are the principal causes of morbidity.[2] The evaluation should include brain, lung, and abdominal imaging, a complete blood cell count, and pulmonary function testing. The physical examination includes auscultation for heart murmur or lung crackles and identification of eye disorders or abdominal mass.[4]

Treatment depends on the clinical features. Inhibitors of the mammalian target of rapamycin pathway are a therapeutic option and can be used as adjuvant therapy for large tumors before surgery.[5] Other medical treatments depend on the manifestation (eg, antiepileptic drugs in epilepsy). Surgery is considered for solitary lesions that cannot be controlled with conservative treatment in patients without high surgical risk.

OUR PATIENT'S COURSE

The patient was followed by several specialists to monitor for the appearance of complications, occasionally requiring resection of a skin lesion with local complication. ∎

DISCLOSURES

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Fever, rash, pruritus: Sweet syndrome

Figure 1. On the patient's back were multiple firm erythematous nodules with pustular heads, as well as several erythematous plaques.

Figure 2. The patient's lower extremities.

Figure 3. The patient's right arm.

The patient presented with a 5-day history of fever, rash, and pruritus

A 40-YEAR-OLD man with a history of diabetes mellitus and hypertension, but taking no medications, presented to the hospital with a 5-day history of fever, rash, and pruritus. The patient initially presented to an urgent care center, where he received intramuscular and oral antibiotics, but his symptoms continued to worsen.

On physical examination, his temperature was 39.6°C, heart rate 138 beats per minute, blood pressure 93/70 mm Hg, and respiratory rate 18 breaths per minute. He had elevated, tender, inflammatory plaques, nodules, and pustules distributed throughout his upper and lower extremities, back, chest, abdomen, scalp, and dorsal aspects of both feet (**Figures 1–3**).

His white blood cell count was 15.2×10^9/L (reference range $3.7–11.0 \times 10^9$/L) with 60% neutrophils and 22% bands; the erythrocyte sedimentation rate was 48 mm/hour (0–15 mm/hour), and the C-reactive protein level was 10.4 mg/dL (< 0.9 mg/dL).

Diagnostic criteria for classic Sweet syndrome

The diagnosis requires both major and minor criteria:

Major criteria (both are required)

Abrupt onset of painful erythematous plaques or nodules

Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis

Minor criteria (2 of 4 are required)

Temperature > 38°C (100.4°F)

Association with an underlying hemoproliferative disorder, inflammatory disease, or solid tumor
OR
Preceded by an upper respiratory or gastrointestinal infection

Excellent response to treatment with systemic corticosteroids or potassium iodide

Abnormal laboratory values at presentation (3 of 4 are required):
• Erythrocyte sedimentation rate > 20 mm/hour
• Elevated C-reactive protein
• White blood cell count > 8.0×10^9/L
• Neutrophils > 70%

Adapted from information in references 7 and 8.

Because of concern for infectious dermatitis, his initial hospital treatment consisted of pain management, intravenous fluids, and intravenous vancomycin. However, a thorough infectious disease workup was unrevealing. Other considerations included a drug eruption, vasculitis, and various neutrophilic dermatoses (including pyoderma gangrenosum and Sweet syndrome). As a result, a skin biopsy was performed and revealed neutrophilic dermatitis without organisms, consistent with Sweet syndrome.

The patient began a 4-week course of prednisone in tapering doses (60 mg for 5 days, 40 mg for 5 days, 20 mg for 5 days, 10 mg for 5 days, then discontinued) and clobetasol 0.05% ointment twice daily for 7 days. He experienced rapid improvement of symptoms, which was noted during outpatient dermatology and primary care follow-up visits.

■ SWEET SYNDROME: KEY FEATURES

In 1964, R. D. Sweet, MD, first described acute febrile neutrophilic dermatosis, originally known as Gomm-Button disease, by its 4 cardinal features: fever; neutrophil polymorphonuclear leucocytosis of the blood; raised painful plaques on the limbs, face, and neck; and histologically, a dense dermal infiltration with mature neutrophil polymorphs, with no evidence of infection and prompt response to corticosteroids.[1]

There are 3 subtypes of Sweet syndrome:
• Classic or idiopathic
• Malignancy-related, most commonly hematologic but also observed in solid tumor malignancies[2–5]
• Drug-induced.[1,6,7]

In this patient's case, the abrupt appearance of fever, cutaneous lesions, and histopathologic findings, in the absence of malignancy or drug exposure and satisfaction of both major and 3 of 4 minor diagnostic criteria, were congruent with classic Sweet syndrome (**Table 1**).[1,6-8] Notably, the patient did not have preceding symptoms suggestive of gastrointestinal or upper respiratory illness, was not on medications associated with Sweet syndrome, and never had signs or symptoms of hematologic or solid tumor malignancy.

The pathogenesis of Sweet syndrome is multifactorial, but studies have suggested a hypersensitivity reaction that promotes neutrophil activation[9] and higher serum levels of granulocyte colony-stimulating factor[10] leading to increased circulating neutrophils, both of which may explain this patient's leukocytosis with increased left shift.

Skin biopsy is the technical standard for diagnosis, but this patient's response to systemic steroids and resolution of leukocytosis (his initial white blood cell count of 15.2×10^9/L came down to 9.25×10^9/L over 4 days) also supports the typical response to treatment.

■ STEROIDS ARE FIRST-LINE THERAPY

Systemic corticosteroid therapy is the first-line treatment, but some case reports[11,12] have also noted accelerated improvement in cutaneous lesions and reduced dependence on systemic steroids with adjunct topical glucocorticoid use, although the efficacy has not been formally studied.

Given their low potential for harm, topical steroids were used as adjuvant therapy, and the

patient had rapid overall clinical improvement and resolution of his rash. Colchicine and potassium iodide are also considered first-line treatment choices. Indomethacin, cyclosporine, dapsone, and clofazimine have all been used as second-line treatments.

■ **DISCLOSURES**

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Aspiration of a partial denture after an ischemic stroke

A 65-year-old man with numerous medical comorbidities presented with left-sided hemianopsia, hemineglect, weakness, and sensory loss lasting 1 day.

Results of computed tomography of the head were consistent with an acute ischemic stroke in the right-middle cerebral artery distribution. Perfusion imaging demonstrated minimal penumbra and a perfusion mismatch ratio of 1.0, a ratio suggesting that revascularization would not likely be beneficial.

In view of the duration of symptoms and the results of imaging, thrombolysis and acute neurointervention were deferred. Secondary stroke prevention was deemed the goal of care, and the stroke-care pathway was initiated.

The patient passed a bedside swallow examination with a mandibular removable partial denture in place, and was thus advanced to a level 2 mechanically altered dysphagia diet. The patient attempted to slowly self-feed for his first meal under close nursing supervision. After intake of a few bites of food, he complained of a cough and throat irritation, without symptoms of airway distress. Expeditious examination of his oral cavity revealed absence of his partial denture.

Soft-tissue radiography of the neck was urgently obtained (**Figure 1**) and revealed a metallic foreign body that looked like the patient's partial denture in the pharynx at the level of the epiglottis, effacing the epiglottis.

The patient was immediately placed on nothing-by-mouth status and underwent emergency direct laryngoscopy to remove the foreign body.

His postoperative hospital course was complicated by septic shock secondary to aspiration pneumonia, requiring broad-spectrum antibiotic therapy, mechanical ventilation, and vasopressor support. The patient ultimately died of these complications during this hospital stay.
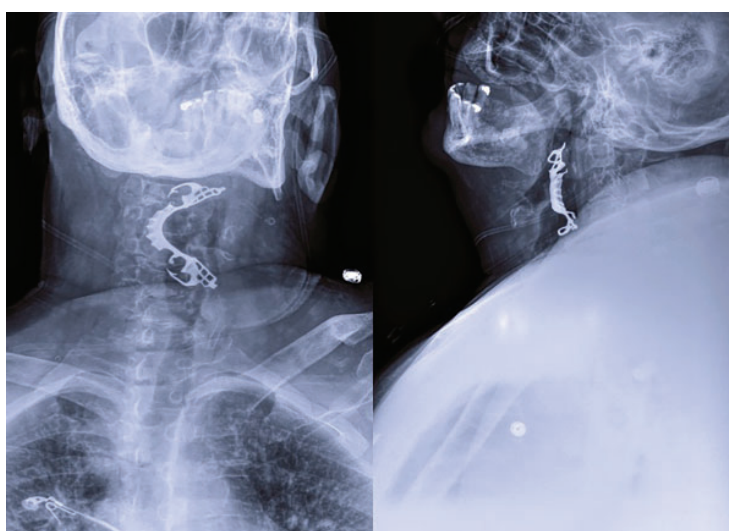
Figure 1. Anteroposterior (left) and lateral (right) views on soft-tissue neck radiography show a metallic foreign body—the patient's mandibular removable partial denture—within the pharynx at the level of the epiglottis, effacing the epiglottis.

◼ THE ROLE OF OROPHARYNGEAL SWALLOWING DEFICITS

In the United States, 800,000 people suffer a new or recurrent stroke each year, and stroke is the third leading cause of death after heart disease and cancer.

In patients with stroke, pneumonia is the medical complication causing the highest attributable proportion of deaths, accounting for nearly one-third of all deaths.[1] Oropharyn-

geal swallowing dysfunction significantly increases the risk of this complication: patients with stroke who have dysphagia are 3 times more likely to develop respiratory infections than their counterparts without swallowing deficits, and those with aspiration are nearly 12 times more likely.[2]

While overt aspiration may be suspected in patients with a history of pneumonia, posterior territory lesions, impaired palatal and gag reflexes, coughing or choking during oral feeding, and voice changes after swallowing, these findings are not ubiquitous.[3]

Removable dentures pose a unique consideration, as they have been correlated with increased oral transit time and may be associated with an increased risk of aspiration, possibly due to impairment in oral cavity sensory function.[4]

In addition, although silent aspiration has been observed more frequently in patients with a history of orotracheal intubation and impaired velopharyngeal reflexes, the risk of silent aspiration is typically difficult to predict on the basis of the clinical history and neurologic evaluation. In patients with severe stroke and suspected oropharyngeal dysphagia, bedside swallowing assessments and pulse oximetry have a low diagnostic yield compared with videofluoroscopic evaluation.[3,5]

In this patient with severe stroke and a removable denture, a bedside clinical evaluation inaccurately led to the conclusion that it was safe to advance to a dysphagia diet, and he aspirated the denture and subsequently developed aspiration pneumonia and died. ■

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Outpatient management of asthma in adults: A snapshot of the 2020 GINA report

ABSTRACT

The Global Strategy for Asthma Management and Prevention publishes an annual report on asthma management and prevention. The report reflects the most recent evidence on asthma and its treatment and provides recommendations for clinical practice. This article reviews the guidelines with a focus on what's new and clinically important for practitioners treating this patient population.

KEY POINTS

Adults with asthma should receive combination therapy with an inhaled corticosteroid and a long-acting beta-agonist on an as-needed basis for mild asthma or regular daily use for moderate or severe asthma.

The recommended option is low-dose budesonide-formoterol, or beclomethasone-formoterol as an alternative.

Monotherapy with a short-acting beta-agonist on an as-needed basis is no longer recommended as the initial therapy for mild asthma.

The preferred agent for rescue therapy is as-needed low-dose inhaled corticosteroid/long-acting beta-agonist.

ASTHMA, AS DEFINED BY the Global Strategy for Asthma Management and Prevention (GINA), is a heterogeneous disease characterized by chronic airway inflammation.[1] It is hallmarked by respiratory symptoms such as wheezing, shortness of breath, chest tightness, or cough that vary over time and in intensity, together with variable expiratory airflow limitation.

In adults, variable expiratory airflow limitation can be confirmed several ways:
- Postbronchodilator increase in forced expiratory volume in 1 second (FEV_1) by more than 12% and more than 200 mL from baseline 10 to 15 minutes after the patient takes 200 to 400 μg of albuterol
- Average daily diurnal peak expiratory flow variability of more than 10%
- FEV_1 increase by more than 12% and more than 200 mL from baseline after 4 weeks of anti-inflammatory treatment outside of respiratory infections
- Fall in FEV_1 of more than 10% and more than 200 mL from baseline with exercise
- Fall in FEV_1 of 20% or more from baseline with standard bronchial challenge (methacholine or histamine), or a fall of 15% or more with standardized hyperventilation or hypertonic saline or mannitol challenge).[1]

Recognized clinical phenotypes include allergic asthma, nonallergic asthma, adult-onset (late-onset) asthma, asthma with persistent airflow limitation, and asthma with obesity. Asthma severity (mild, moderate, severe) is classified based on frequency of day and night

symptoms, as well as on the level of stepwise treatment required to control symptoms and prevent exacerbations.

■ CLINICAL SETTING

The field of asthma has evolved significantly during the last several years. This review of the GINA 2019 update focuses on changes in the management of asthma in adult outpatients. We use the following abbreviations: short-acting beta-agonist (SABA), long-acting beta-agonist (LABA), inhaled corticosteroid (ICS), and oral corticosteroid (OCS).

■ INTENDED AUDIENCE

This review is intended for healthcare providers who manage adult patients with asthma in the outpatient setting.

■ WHO WROTE THE GUIDELINES?

The GINA Science Committee was established in 2002 and is composed of voluntary members who are leaders in both adult and childhood asthma research. The committee meets biannually with the American Thoracic Society (ATS) and European Respiratory Society (ERS) to review the latest in asthma research in order to release new recommendations annually.

For these recommendations, a PubMed literature search covering approximately 18 months yielded 1,137 clinical trials or meta-analysis publications of which 906 were screened out for duplicates, relevance, or quality. Each of the remaining 231 publications was reviewed by at least 2 committee members for overall scientific impact. Of those, 123 were subsequently discussed in the biannual GINA Science Committee meetings in 2018 for consideration of inclusion in the annual guidelines.

Of note, any new therapy or indication required regulatory approval by at least 1 agency and at least 2 good-quality studies in suitable populations before committee recommendation. Off-label recommendations were made for existing therapies if the committee found suitable supportive evidence. For these off-label recommendations, the committee emphasized that clinicians should use their

For off-label recommendations, the GINA committee urged professional judgment and consideration of existing local and national guidelines

professional judgment and take into account existing local and national guidelines.

■ WHAT ARE THE MAIN RECOMMENDATIONS?

Monotherapy with SABA on an as-needed basis is no longer recommended as the initial therapy for mild asthma because it increases the risk of severe exacerbations and asthma-related deaths. To decrease these risks, all adults with asthma should receive combination therapy with an ICS and an LABA on an as-needed basis for mild asthma or regular daily use for moderate or severe asthma. The recommended option is low-dose budesonide-formoterol, or beclomethasone-formoterol as an alternative. If an SABA is used, it should be simultaneously combined with a low-dose ICS.

■ WHAT IS DIFFERENT FROM PREVIOUS GUIDELINES?

- The preferred agent for rescue therapy is as-needed low-dose ICS-LABA (preferably budesonide-formoterol); prior guidelines recommended SABA as needed for first-line therapy.
- Replacement of "upper airway dysfunction" and "vocal cord dysfunction" with "inducible laryngeal obstruction," and the replacement of "fixed airflow limitation" with "persistent airflow limitation."
- Emergency room or hospital discharge follow-up after severe exacerbations should occur within 2 days.
- New add-on therapies for step 5 treatments include low-dose daily azithromycin (off-label), dupilumab (anti-IL4 receptor antibody), and tiotropium, based on specific drug indications.
- Trial use of high-dose ICS-LABA for 3 to 6 months is now limited to use in step 5 treatment (previously recommended in steps 4 and 5) owing to increased risk of side effects; for similar reasons, maintenance OCS is no longer a preferred treatment in step 5.
- Of note, the GINA 2020 guidelines address asthma and COVID-19; they emphasize continuing to take all prescribed asthma medications, having a clearly writ-

ten asthma action plan, and preferentially using metered-dose inhalers over nebulizers when possible.

WHAT IS THE EXPECTED CLINICAL IMPACT?

The expected clinical impact of the latest guidelines is a decreased incidence of severe asthma exacerbations and asthma-related deaths globally.

It should be noted that until 2017, ICS-LABA combinations had a boxed warning from the US Food and Drug Administration (FDA) based on early LABA trials (Serevent Nationwide Surveillance study and the Salmeterol Multicenter Asthma Research trial) that showed increased risk of serious adverse asthma outcomes (death, hospitalization, intubation).[2,3]

Due to these concerns, the FDA required manufacturer-conducted noninferiority post-market safety trials for ICS-LABA combinations vs ICS alone. Four trials (3 adult and 1 pediatric) enrolling approximately 45,000 participants were conducted and examined fluticasone-salmeterol vs fluticasone, budesonide-formoterol vs budesonide, and mometasone-formoterol vs mometasone for efficacy and the aforementioned serious asthma outcomes.

In summary, these trials found that the ICS-LABA combinations were effective in reducing asthma exacerbations requiring corticosteroids and did not significantly increase the risk of serious adverse asthma outcomes.[4–7] Despite the removal of the boxed warning, no ICS-LABA combination has an FDA-approved indication for treating acute bronchospasm on an as-needed basis, as the GINA 2019 guidelines recommended.[8]

DO OTHER SOCIETIES AGREE OR DISAGREE?

The annual GINA report is endorsed by the ATS and ERS. After the GINA 2019 report was published,[8] the ATS and ERS published a joint guideline on the management of severe asthma in January 2020.[9] Prior to this, their last independent publication was in 2014, which was also limited to the description of severe asthma. More recently, the National Heart Lung and Blood Institute (NHLBI) released updated guidelines in December 2020.[10] Though the full review of the evidence behind those guidelines is beyond the scope of this article, a key difference in recommendations should be noted. The NHLBI 2020 guidelines still recommend as-needed SABA as the preferred initial treatment for intermittent asthma, with as-needed or daily low-dose ICS-LABA reserved for step 3. The American College of Chest Physicians has no published asthma guidelines.

HOW WILL THIS CHANGE DAILY PRACTICE?

Combination ICS-LABA should be considered for all patients with asthma, and for select patients with mild asthma this should be considered on an as-needed basis replacing SABA as the sole therapy. The consideration for this change should be based on shared decision-making with each patient. Providers should discuss the risks and benefits of sole SABA therapy with patients, while acknowledging that symptoms may have been well controlled without exacerbations for many years on the patient's current regimen. Continued provider and patient education is a key for population-level success of any new society recommendations.

WHEN WOULD GUIDELINES NOT APPLY?

Availability and affordability of ICS-LABA combinations may limit widespread adoption of these recommendations. In these cases, GINA recommends that low-dose ICS be used when SABA is used. Timing of FDA approval for any ICS-LABA combination for an as-needed indication may influence medication coverage practices and, ultimately, affordability. ■

DISCLOSURES

The expected clinical impact of the guidelines is a global decrease in severe asthma exacerbations and asthma-related deaths

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Statin intolerance and new lipid-lowering treatments

CORONARY ARTERY DISEASE continues to be the leading cause of death in developed countries, and rates are rapidly rising in the developing world.[1] With the current obesity epidemic and growth of metabolic syndrome, its prevalence is likely to continue to climb. Along with hypertension, diabetes, and smoking, hyperlipidemia has consistently been shown to be one of the most significant and modifiable risk factors of coronary artery disease development and progression.[2]

Lipid-lowering therapy is important for secondary prevention for patients with known cardiovascular disease, as well as for primary prevention for those at increased risk. Although guidelines have historically focused on achieving specific levels of low-density lipoprotein cholesterol (LDL-C), there is increasing recognition that in many cases lower levels are progressively beneficial, making lipid-lowering therapies especially relevant.

■ STATINS STILL THE THERAPY OF CHOICE TO LOWER CHOLESTEROL

Several drug classes lower atherosclerotic risk by lowering circulating lipid concentrations and have been thoroughly tested. With a historically proven track record in reducing morbidity and mortality related to atherosclerotic disease, beta-hydroxy beta-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are first-line cholesterol-lowering medicationss. A large meta-analysis found that sustained moderate- or high-intensity statin therapy over 5 years reduced events related to atherosclerotic cardiovascular disease by 21% for every 1 mmol/L (approximately 40 mg/dL) decrease in LDL-C.[3]

However, many patients experience musculoskeletal side effects that either prevents them from using statins at all or limits their ability to tolerate a dosage necessary to achieve their cholesterol targets. As suboptimal control keeps them at continued cardiovascular risk, such patients should be thoroughly evaluated for true statin intolerance, and adjunctive or alternative therapies should be considered.

■ STATIN INTOLERANCE: MYOPATHY

While the benefits and safety profile of statin therapy are clear, adverse effects such as statin-related myopathy remain elusive, posing diagnostic and therapeutic challenges. Statin intolerance is widely reported in clinical practice, often leading to its discontinuation. Some estimate that up to 20% of patients are unable to tolerate statin therapy owing to muscle symptoms.[4]

Most of our current knowledge regarding statin intolerance originates from observational data, although randomized control trials have also been conducted evaluating drug discontinuation due to intolerance. One meta-analysis of randomized controlled trials found that patients taking a statin and those taking a placebo were not significantly different when discontinuing treatment (odds ratio [OR] 0.99; 95% confidence interval [CI] 0.93–1.06]).[5] The Self-Assessment Method for Statin Side-effects or Nocebo (SAMSON) trial[6] found that 90% of side effects experienced on statin therapy were also experienced while taking placebo. Discordant data between randomized controlled trials and observational data may be explained by the healthier and younger populations studied in randomized controlled trials,

Patients with muscle symptoms should be thoroughly evaluated for true statin intolerance

as well as lower dosages used during testing in the early statin randomized controlled trials compared with clinical practice.

Rates of myalgia, myositis, and rhabdomyolysis are rare, according to the US Food and Drug Administration (FDA) Adverse Event Reporting system and other large, real-world databases.[7–9] However, not all studies evaluated myalgia or reported creatine kinase levels, and several trials included a run-in period, in which randomization and inclusion occurred only after preliminary trial exposure to statin therapy.

Anti-HMG-CoA reductase antibody-mediated myopathy is an infrequently occurring immunologic necrotizing myopathy, which causes widespread and profound muscle breakdown leading to permanent weakness. Patients report progressive muscle weakness and have persistently elevated creatine kinase levels. Recognizing it promptly is critical so that intravenous immunoglobulin treatment can be started.

STATIN INTOLERANCE: NONMUSCLE-RELATED SIDE EFFECTS

Nonmuscle-related side effects have also been attributed to statin therapy, several of which have been studied. Reports of peripheral neuropathies are rare. Neurologic cognition changes and memory loss do not appear to be associated with statins.[10,11] No increased risk of hemorrhagic cerebrovascular accidents with the use of statins for primary stroke prevention has been demonstrated, the literature is conflicting regarding their use for secondary prevention, but benefits appear to largely outweigh risks.[12,13]

Liver dysfunction, a rare finding in patients taking high-intensity statins, appears to be a laboratory side effect but is not clinically significant.[14] Liver failure is even more rare.[15] There is a slight increase in diabetes in patients taking statin therapy, but this should be weighed against far greater risk reductions in major cardiovascular events. Cataracts, renal dysfunction, malignancy, and tendonitis have not proven attributable to statin use.

STATIN-ASSOCIATED MYALGIA

Risk factors for statin-related myalgia have been identified, including older age, female sex, family history of statin-associated myalgia, alcohol use, and rheumatologic disease. Certain drugs can increase risk: colchicine, verapamil, diltiazem, fibrates, protease inhibitors, azoles, and antimicrobials such as clarithromycin and erythromycin.

Clinical diagnosis is difficult, as no definitive blood markers have been identified. Values for creatine kinase, thyroid function, inflammatory markers, and vitamin D are usually normal. Furthermore, definitions for myopathy, myalgia, myositis, and rhabdomyolysis vary among professional organizations.

Although standardized definitions are lacking, certain diagnostic criteria are consistent across published guidelines.[4,16] Factors favoring a clinical diagnosis of statin-related myopathy include:

- Symmetric, proximal large muscle pain or weakness, worsened by exercise
- Symptoms beginning 2 to 4 weeks after statin initiation
- Resolution of symptoms within 2 weeks of discontinuation
- Symptoms returning within 2 weeks after reintroducing statin
- Symptoms occurring with 2 or more different statins, at least one of which is prescribed at the lowest dosage.

DETERMINING STATIN INTOLERANCE

A major difficulty in establishing statin intolerance lies in distinguishing statin-associated from nonstatin-associated muscle symptoms. Many patients diagnosed with statin-associated muscle symptoms likely have nonspecific musculoskeletal pain, unrelated to statin therapy.[16] Although the Statin-Associated Muscle Symptom Clinical Index questionnaire was designed to facilitate diagnosis, it requires additional validation.[17]

Whereas previous trials have suggested an almost indistinguishable side-effect profile between low-dose statin therapy and placebo, more recently designed rechallenge crossover studies such as the Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3 (GAUSS-3)[18] and the ODYSSEY ALTERNATIVE[19] trials have been able to establish statin intolerance as a real and verifiable phenomenon.

Anti-HMG-CoA reductase antibody-mediated myopathy causes widespread and profound muscle breakdown leading to permanent weakness

TABLE 1

Nonstatin lipid-lowering medications

Medication	Mechanism of action	LDL-C reduction	Trials
Ezetimibe	Reduces absorption of cholesterol from small intestine	15%–25%	IMPROVE IT[27]
Bempedoic acid	Inhibition of adenosine triphosphate citrate lyase	15%–20% (alone) 25%–30% (with ezetimibe)	CLEAR Outcomes study (pending)
PCSK9 inhibitors	Inhibition of PCSK9 protein resulting in more LDL receptors available, and increased uptake of LDL-C into cells	45%–60%	FOURIER, 2015[30] ODYSSEY Outcomes 2015[19]

LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

The GAUSS-3 trial[18] used a double-crossover design with atorvastatin and placebo in 491 patients who were self-reported to be intolerant to 2 or more statins. They found a 43% rate of true statin intolerance, determined by symptoms present during atorvastatin therapy but absent during placebo therapy. Although similar rates of myalgia were reported initially in both atorvastatin and placebo groups (hazard ratio [HR] 1.34; 95% CI 1.05–1.71; P = .02), after full completion of the washout and double-crossover protocol, significantly more patients experienced muscle-related symptoms when taking atorvastatin than when taking placebo (HR 1.96; 95% CI 1.44–2.66; P < .001).

■ CONSEQUENCES OF STATIN INTOLERANCE

A diagnosis of statin intolerance comes with significant health and financial costs. Statin-intolerant patients who have their medication down-titrated or discontinued are at increased risk of future cardiovascular events.

A large retrospective cohort study found that patients who were statin-intolerant had a 36% higher rate of recurrent myocardial infarction than those adherent to statin therapy (HR 1.50; 95% CI 1.30–1.73; P < .001) and a 43% higher rate of coronary heart disease events (HR 1.51; 95% CI 1.34–1.70; P < .001).[20] Another study found significantly higher medical costs in patients with statin intolerance than in controls receiving statin therapy, with a cost ratio of 1.2 (95% CI 1.11–1.28; P < .0001).[21]

■ MANAGING STATIN INTOLERANCE

Confirm statin intolerance

In a patient suspected of having statin intolerance, statin therapy should be discontinued and symptoms monitored over 2 weeks to see if they resolve. Patients should be asked about alcohol intake and nutraceutical medications, as they potentially contribute to and confound muscle symptoms attributed to statins. After 2 weeks, if symptoms have resolved, the same statin can be restarted at a lower dose or an alternative statin prescribed.[22]

Strategies for treating statin intolerance include using an alternative statin, modifying dosage, changing diet, and using other medications.

Try another statin

Pharmacologic profiles can differ significantly among statins[23–25]:

- Lipophilic statins diffuse nonselectively into extrahepatic tissues such as muscle; simvastatin, the most lipophilic statin, is most associated with muscle symptoms
- Hydrophilic statins are actively transported into hepatocytes; examples are pravastatin and rosuvastatin, which are less associated with muscle symptoms.

Changing from a lipophilic to a hydrophilic statin is a reasonable first-line alternative drug strategy for patients experiencing myalgia.

Adjust dosage

Intermittent rather than daily dosing can also be considered for patients with statin-associated muscle symptoms and for patients who

Many patients diagnosed with statin-associated muscle symptoms likely have nonspecific musculoskeletal pain, unrelated to statins

TABLE 2

PCSK9 inhibitor trials

Trial[a]	PCSK9 inhibitor	Definition of statin intolerance	Statin rechallenge	LDL-C reduction with PCSK9 inhibitor	LDL-C reduction with ezetimibe[a]	Patients with muscle events during trial
GAUSS-2, 2014[32]	Evolocumab	Intolerable muscle-related side effects to ≥ 2 statins; most participants unable to tolerate ≥ 3 statins	No	56.1% (140 mg every 2 weeks) 55.3% (420 mg per month)	19.2%	12% (evolocumab) 23% (ezetimibe)
GAUSS-3, 2016[18]	Evolocumab	Intolerance to atorvastatin 10 mg and another statin at any dose; or 3 or more statins, with 1 at the lowest daily dose and 2 others at any dose	Yes	52.8% (420 mg per month)	16.7%	20.7% (evolocumab) 28.8% (ezetimibe) HR 0.68; 95% CI 0.39-1.19
ODYSSEY ALTERNATIVE, 2015[19]	Alirocumab	Inability to tolerate 2 or more statins because of unexplained skeletal muscle-related symptoms with one of the 2 statins at the lowest-approved daily starting dose.	Yes	45.0% (75 mg every 2 weeks)	14.6%	32.5% (alirocumab) 41.1% (ezetimibe) HR 0.71; 95% CI 0.47 to 1.06

[a]All trials used ezetimibe 10 mg daily as the nonstatin comparator.

CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

have a history of severe myotoxicities and marked creatine kinase elevation.

Studies have found that intermittent dosing can achieve LDL-C reductions of about 20% to 40%, although impacts on cardiovascular outcomes have yet to be established. A large single-center study of statin intolerant patients found a trend toward mortality benefit with intermittent dosing.[26] A statin with a long half-life, such as rosuvastatin, may be a good choice for intermittent dosing.

◼ NONSTATIN DRUG THERAPY

For patients with persistent symptoms even after trials of two different statins at their lowest dosages, categorical intolerance is likely, and nonstatin medications should be considered. These include ezetimibe, bempedoic acid, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The actions of these agents are summarized in **Table 1**.[18,19,27–32]

PCSK9 inhibitor therapy

Monoclonal antibody PCSK9 inhibitors belong to a novel class of lipid-lowering therapy that have been reported to reduce LDL-C concentrations by up to 60%[19,30–33] and reduce the risk of cardiovascular events.[34] PCSK9 inhibitor therapy prevents downregulation and destruction of cell membrane LDL receptors, thereby leading to lower circulating LDL particle concentrations. Several studies have evaluated the efficacy of PCSK9 inhibitors in patients with statin-associated muscle symptoms (**Table 2**).[18,19,32]

The GAUSS-2 trial[32] randomized more than 300 patients who experienced statin-associated muscle symptoms and discontinued two different statin medications to either evolocumab (a PCSK9 inhibitor), ezetimibe, or placebo. After 12 weeks of therapy, evolocumab was associated with the largest average reduction in LDL-C from baseline val-

ues (56.1%; 95% CI −59.7% to −52.5%; *P* < .001). None of the patients in the evolocumab group discontinued medication due to muscle-related events.

The GAUSS-3 trial[18] randomized confirmed statin-intolerant subjects to evolocumab or ezetimibe for 24 weeks. Evolocumab produced a more significant mean reduction in LDL-C of 52.8% from baseline values (95% CI −55.8% to −49.8%; *P* < .001). Discontinuation of therapy due to muscle-related symptoms occurred in 6.8% of the ezetimibe group vs 0.7% of the evolocumab group.

The ODYSSEY ALTERNATIVE trial[19] compared PCSK9 inhibitor therapy (using alirocumab) with ezetimibe in patients with confirmed statin intolerance. While ezetimibe reduced mean LDL-C by 14.6%, alirocumab reduced mean LDL-C levels by 45.0%. Muscle-related symptoms occurred less frequently with alirocumab (32.5%) than with ezetimibe (41.1%), but the difference was not statistically significant (HR 0.71; 95% CI 0.47–1.06; *P* < .096).

Their findings establish PCSK9 inhibitor therapy as a promising alternative LDL-C lowering strategy in patients with proven statin intolerance. It may ultimately prove superior to statin dosage reduction, dietary modification, and pharmaceutical alternatives.

Bempedoic acid

In 2020, the FDA approved bempedoic acid for treatment of hypercholesterolemia. It works by inhibiting adenosine triphosphate citrate lyase (ACL), an enzyme critical to the hepatic synthesis of cholesterol.

In the Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Tranquility phase 3 randomized placebo-controlled trial[29] of patients with a history of statin intolerance, bempedoic acid together with ezetimibe led to LDL-C reduction of 28.5% more than ezetimibe alone (*P* < .001), while bempedoic acid led to significant reductions in nonhigh-density lipoprotein cholesterol (23.6%), total cholesterol (18%), apolipoprotein B (19.3%), and C-reactive protein (31%) (*P* < .001).

The ongoing CLEAR Outcomes study is randomizing more than 14,000 patients who are statin-intolerant and at high risk for cardiovascular disease to treatment with bempedoic acid

vs placebo.[35] Results are expected in 2023 to address the effects on cardiovascular outcomes.

■ PROMISING NEW AGENTS

While PCSK9 inhibitor therapies and bempedoic acid will likely find their way into routine prescription use in the coming years, ongoing investigations continue to demonstrate promise in other advanced lipid-lowering approaches.

Inclisiran, currently under FDA review, is a small interfering RNA (siRNA) agent that inhibits translation of the PCSK9 protein and therefore its formation. This promotes LDL-C receptor recycling from cell membranes at a stage upstream from the PCSK9 inhibitor therapies. Trials of patients with elevated LDL-C levels despite maximally tolerated statin therapy found that adding inclisiran reduced LDL-C levels by about 50% compared with baseline levels of patients on statin therapy only.[36,37] Inclisiran is administered by subcutaneous injection, followed by a second dose after 90 days, then every 6 months thereafter.

Evinacumab is a monoclonal antibody that blocks angiopoietin-like 3 (ANGPTL3), a protein that inhibits lipoprotein lipase and thereby increases plasma LDL-C levels. Gene mutations resulting in loss of function of this protein are associated with hypolipidemia. A phase 3 clinical trial with 65 patients with homozygous familial hypercholesterolemia found that evinacumab infusion every 4 weeks reduced LDL-C by 49 percentage points vs the placebo group at 24 weeks, with both groups also on maximum lipid-lowering therapy.[38]

Finally, recent evidence from nonhuman primates shows promise in the field of gene editing, a form of next-generation alteration of the biological blueprint that underlies serum lipoprotein concentrations. Gene therapy to mimic natural cardioprotective variants (such as targeted reduction in PCSK9 and ANGPTL3 protein production) have shown reduction in serum cholesterol levels.[39]

■ NUTRACEUTICALS

Nutraceuticals are natural food-derived substances that are generally well tolerated and provide health benefits, including the preven-

A diagnosis of statin intolerance comes with significant health and financial costs

tion or treatment of medical conditions. Two of the most widely studied in cardiovascular medicine are red yeast rice (which contains monacolin K, the active ingredient of lovastatin) and berberine. Other plant sterols, soluble fibers, probiotics, polyunsaturated fatty acids, and antioxidants have also been evaluated.[40,41] Lipid-lowering effects occur via multiple mechanisms (eg, inhibition of the intestinal absorption of cholesterol, inhibition of cholesterol synthesis, and enhanced excretion of LDL-C).[42]

Nutraceuticals have been found to lower LDL-C when used alone or combined with ezetimibe[43] or a reduced statin dosage[41,42] and can help patients with statin intolerance

achieve their LDL-C goal. Red yeast rice was found to reduce LDL-C by up to 27% compared with placebo after 1 to 3 months.[44]

However, LDL-C reductions are modest compared with pharmacologic therapy, and the long-term effect on cardiovascular outcomes with nutraceutical therapy has not been formally evaluated. Therefore, nutraceuticals should be reserved only for patients who are truly statin-intolerant as an adjunct to nonstatin pharmacologic therapy. ■

■ DISCLOSURES

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2021

JULY

**MIDWEST MELANOMA
AND HIGH-RISK SKIN CANCER
SYMPOSIUM**
July 16
Live stream

AUGUST

HOSPITAL MEDICINE 2021
August 5–6
Live stream

**NEUROLOGY UPDATE: A COMPREHENSIVE
REVIEW FOR THE CLINICIAN**
August 7–8
Live stream

INTENSIVE REVIEW OF CARDIOLOGY
August 14–15
Live stream

**TRANSTHYRETIN CARDIAC AMYLOIDOSIS
IN AFRICAN AMERICANS:
WHAT PHYSICIANS NEED TO KNOW**
August 24
Live stream

**INTENSIVE REVIEW OF ENDOCRINOLOGY
AND METABOLISM**
August 27–29
Live stream

SEPTEMBER

**STATE-OF-THE-ART DIAGNOSIS
AND TREATMENT OF DEMENTIA**
September 9–November 4
Live stream

**DIABETES, OBESITY,
AND CARDIOVASCULAR DISEASE
VIRTUAL SUMMIT**
September 9–11
Live stream

**THE PRACTICE OF ECHOCARDIOGRAPHY
AT CLEVELAND CLINIC 2021**
September 11
Live stream

**COMPREHENSIVE LIFELONG
EXPEDITIOUS (CLE) CARE
OF AORTIC DISEASE**
September 17–18
Cleveland, OH

**INTENSIVE REVIEW
OF GASTROENTEROLOGY
AND HEPATOLOGY**
September 17–20
Virtual stream and webcast

**PRIMARY CARE WOMEN'S HEALTH:
ESSENTIALS AND BEYOND**
September 18
Live stream

GLOBAL EP
September 24
Live stream

**GENETICS EDUCATION SYMPOSIUM –
GENETICS AND GENOMICS:
APPLICATIONS FOR THE PREVENTION,
DETECTION, AND TREATMENT OF CANCER**
September 30
Live stream

OCTOBER

VIRTUAL NEPHROLOGY UPDATE
October 1
Live stream

PRACTICAL MANAGEMENT OF STROKE
October 1
Live stream

**ADVANCES IN CONGENITAL
HEART DISEASE SUMMIT**
October 1–2
Live stream

**IMPROVING END-OF-LIFE CARE
IN THE ICU: CHALLENGES
AND OPPORTUNITIES**
October 6–November 23
Virtual webcast

**WAKE UP TO SLEEP DISORDERS 2021:
A CLEVELAND CLINIC SLEEP DISORDERS
CENTER UPDATE**
October 9–10
Live stream

PRIMARY CARE UPDATE
October 15–16
Live stream

**CARDIOVASCULAR UPDATE
FOR THE PRIMARY CARE PROVIDER**
October 28–29
Live stream

NOVEMBER

**GASTROENTEROLOGY UPDATE:
CONTROVERSIES, INNOVATIONS,
RESEARCH**
November 6
Live stream

**WASOG/AASOG 2021:
MULTIDISCIPLINARY MEETING
FOR SARCOIDOSIS AND ILD**
November 29–December 2
Hollywood, FL

DECEMBER

**MASTERING THE MANAGEMENT
OF THE AORTIC VALVE**
December 3–4
New York, NY

**RESUSCITATING A DYING MARROW:
EMERGING CONCEPTS AND TREATMENT
ADVANCES IN MYELOID MALIGNANCIES**
December 10
Atlanta, GA

2022

JANUARY

**SHAPING THE MANAGEMENT
OF PARKINSON DISEASE: DEBATING
THE MOST CONTROVERSIAL ISSUES
AND DISCUSSING THE LATEST
BREAKTHROUGHS**
January 22–23
Lake Tahoe, NV

FEBRUARY

**MULTIDISCIPLINARY APPROACH
TO THE CONTEMPORARY MANAGEMENT
OF HEART FAILURE**
February 25
Cleveland, OH

**BASIC AND CLINICAL IMMUNOLOGY
FOR THE BUSY CLINICIAN**
February 26–27
Scottsdale, AZ

MARCH

**VALVE DISEASE, STRUCTURAL
INTERVENTIONS,
AND DIASTOLOGY/IMAGING SUMMIT**
March 4
Live stream

FOR SCHEDULE UPDATES AND TO REGISTER, VISIT: WWW.CCFCME.ORG/LIVE

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ONE
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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What antithrombotic therapy should I use for my patient with atrial fibrillation who underwent percutaneous coronary intervention or had an acute coronary syndrome?

A: Double therapy (ie, an oral anticoagulant and a P2Y12 inhibitor such as clopidogrel) is reasonable for most patients, ie, those with average risk of ischemia, elevated risk of bleeding, or both. However, in certain patients, particularly those with atrial fibrillation who undergo percutaneous coronary intervention or those at higher risk of ischemia, triple therapy (ie, an oral anticoagulant, a P2Y12 inhibitor, and low-dose aspirin) may be reasonable initially.

The current (2019) guidelines on atrial fibrillation from the American College of Cardiology, American Heart Association, and Heart Rhythm Society (ACC/AHA/HRS) recommend that, if triple therapy is used initially, double therapy (ie, discontinuing the aspirin) can be considered after 4 to 6 weeks.[1] The 2017 guidelines from the European Society of Cardiology (ESC)[2] are slightly different: triple therapy for at least 1 month after percutaneous coronary intervention and up to 6 months if the patient is at high risk of ischemia. The risk of thrombosis with double therapy must be weighed against the risk of bleeding with triple therapy.

■ NEED FOR COMBINED ANTITHROMBOTIC THERAPY

Combined antithrombotic therapy—a regimen that includes an oral anticoagulant and antiplatelet agents—is indicated for patients with atrial fibrillation requiring anticoagulation and coronary artery disease requiring antiplatelet therapy (for example, after acute

coronary syndrome or percutaneous coronary intervention).

Both atrial fibrillation and coronary artery disease are common in the elderly, they share important risk factors, and they often occur concomitantly. Before direct oral anticoagulants were developed, patients with atrial fibrillation were often given triple therapy after experiencing acute coronary syndromes or undergoing percutaneous coronary interventions. This consisted of a vitamin K antagonist (eg, warfarin) and dual antiplatelet therapy. While oral anticoagulation and antiplatelet therapy separately increase the risk of bleeding, the risk is even higher when they are combined, and higher still with triple therapy.[3]

■ DOUBLE VS TRIPLE THERAPY

The safety and efficacy of double vs triple therapy has been evaluated in several randomized controlled trials.[4–8]

The WOEST trial[4] (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting?) compared double vs triple therapy, with a vitamin K antagonist as the anticoagulant, in patients with atrial fibrillation requiring percutaneous coronary intervention. It found that double therapy was safer and more effective than triple therapy, as measured at the end of 1 year.

Other trials[5–8] subsequently showed that double therapy using a direct oral anticoagulant posed a lower risk of bleeding and was not inferior in efficacy (in general, a composite

The risk of thrombosis should be balanced with the risk of bleeding

outcome of mortality and ischemic events) compared with triple therapy using a vitamin K antagonist as the oral anticoagulant.

Gargiulo et al,[9] in a meta-analysis of these trials,[5–8] found that double therapy posed a lower risk of bleeding, defined as International Society on Thrombosis and Haemostasis major or clinically relevant nonmajor bleeding (risk ratio 0.62, 95% confidence interval [CI] 0.47–0.81, number needed to treat 14). However, the trials were not specifically powered to detect a difference in ischemic event rates. While there was no difference in the rates of all-cause mortality, cardiovascular mortality, or trial-defined major adverse cardiac events, there was a small but significant increase in the risk of stent thrombosis with double therapy (risk ratio 1.59, 95% CI 1.01–2.50, number needed to harm 273).[9]

■ DIRECT ORAL ANTICOAGULANTS VS VITAMIN K ANTAGONISTS

Comparing the type of anticoagulant, direct oral anticoagulant therapy was at least noninferior to vitamin K antagonist therapy in regard to bleeding outcomes, and noninferior in regard to ischemic outcomes.[5–8] The numbers needed to treat with a direct oral anticoagulant to prevent 1 bleeding event from a vitamin K antagonist ranged from 10 to 24. There were no significant differences in ischemic outcomes between the 2 types of anticoagulants. However, as we said, these trials were not specifically powered to detect differences in ischemic events; the primary outcome of interest was bleeding.

■ CURRENT GUIDELINES

Current ACC/AHA/HRS guidelines[1] recommend anticoagulation in atrial fibrillation if the CHA_2DS_2-VASc score is 2 or higher in men and 3 or higher in women. (To calculate the CHA_2DS_2-VASc score, 1 point each is given for **c**ongestive heart failure, **h**ypertension, **a**ge greater than 65 [or 2 points for age > 75], **d**iabetes, **s**troke [2 points], **v**ascular disease, and female **s**ex **c**ategory, for a maximum of 9 points.)

First-line oral anticoagulation therapy has traditionally consisted of a vitamin K antagonist but now includes the direct oral anticoagulants, such as dabigatran, rivaroxaban, apixaban, and edoxaban,[1] which have become the preferred agents due to safety data.

For patients with atrial fibrillation requiring combined antithrombotic therapy for acute coronary syndromes or percutaneous coronary intervention, the ACC/AHA/HRS,[1] American College of Chest Physicians (ACCP),[10] and ESC[2] guidelines recommend double or short-term triple therapy with an oral anticoagulant (vitamin K antagonist, rivaroxaban, or dabigatran) and clopidogrel, tailored on the basis of thrombotic risk and bleeding risk (discussed further below).

The ESC guidelines[2] specifically recommend against the combination of a direct oral anticoagulant plus prasugrel or ticagrelor, given a lack of evidence and potential for increased bleeding based on registry data. The ACC/AHA/HRS guidelines[1] allow ticagrelor as an alternative to clopidogrel in dual therapy with a vitamin K antagonist but not a direct oral anticoagulant.

The ACCP guidelines[10] further recommend that direct oral anticoagulants be used at licensed dosing levels, particularly important with rivaroxaban and dabigatran, which were given in lower, nonapproved doses in their respective clinical trials.[5,6]

The current guidelines regarding direct oral anticoagulants do not include apixaban or edoxaban. However, based on recent trials of these newer agents,[7,8] double therapy with apixaban or edoxaban and clopidogrel may soon be formally recommended.

■ PATIENTS AT HIGH THROMBOTIC RISK

In their 2017 guidelines,[2] the ESC recommended triple therapy for at least 1 month and up to 6 months in the subset of patients who underwent percutaneous coronary intervention or who had a high thrombotic risk. The ESC[2] and ACCP[10] guidelines enumerate these risk factors, which include:
- Prior stent thrombosis while receiving antiplatelet therapy
- Stenting of the last remaining patent coronary artery
- Diffuse multivessel disease, especially in patients with diabetes
- Chronic kidney disease

For most patients, double therapy (an oral anticoagulant and a P2Y12 inhibitor) is reasonable

- At least 3 stents implanted
- At least 3 lesions treated
- Bifurcation with 2 stents implanted
- Total stent length greater than 60 mm
- Treatment of a chronic total occlusion
- Left main stenting.

■ PATIENTS AT HIGH BLEEDING RISK

The risk of thrombotic events should be balanced with the risk of bleeding. The most commonly used tool for assessing bleeding risk is the HAS-BLED score, in which points are given for **h**ypertension, **a**bnormal kidney or liver function, **s**troke, **b**leeding, **l**abile international normalized ratio, **e**lderly status, and use of **d**rugs that predispose to bleeding or use of alcohol. A HAS-BLED score of 3 or more indicates a higher risk of bleeding.

The 2018 ACCP atrial fibrillation guidelines[10] recommend using the HAS-BLED score, particularly in patients taking vitamin K antagonists, to tailor discussion of risk of bleeding while on anticoagulant therapy. While rarely a reason to avoid anticoagulation, a high HAS-BLED score should prompt clinicians to aggressively treat the modifiable aspects of the score to reduce the risk of bleeding.[10] This is particularly important to consider when additional antiplatelet therapy is required after percutaneous coronary intervention.

■ DURATION OF COMBINED ANTITHROMBOTIC THERAPY

The overall duration of antiplatelet therapy is based on the indication for it (stable ischemic heart disease with percutaneous coronary intervention, acute coronary syndrome, and type of stent used). Patients who have stable ischemic heart disease who undergo percutaneous coronary intervention with bare-metal stents require at least 1 month of antiplatelet therapy. Those who receive drug-eluting stents require at least 3 months of antiplatelet therapy if they have a high risk of bleeding; otherwise, 6 months is preferred. In those with acute coronary syndrome with or without percutaneous intervention, antiplatelet therapy is recommended for at least 6 months if there is a high risk of bleeding; otherwise, 12 months is preferred.[11]

Whether to start patients on triple therapy and its duration is another consideration. The duration of initial triple therapy is tailored on the basis of individual thrombotic and ischemic risk, and the guidelines[1,2,10] offer multiple strategies. In summary:

- For patients at low thrombotic risk, double therapy alone (ACC/AHA/HRS)[1] or 1 to 6 months of triple therapy (ACCP[10] and ESC[2]) can be considered, with shorter durations of triple therapy if bleeding risk is high (HAS-BLED score ≥ 3).
- For those at high thrombotic risk, all guidelines recommend triple therapy for 1 to 6 months, again tailored to bleeding risk.[1,2,10]

■ TAKE-HOME MESSAGES

Combined antithrombotic therapy in patients with atrial fibrillation with acute coronary syndrome or percutaneous coronary intervention requires a balanced consideration of bleeding risk vs ischemic risk.

For most patients with average ischemic risk, double therapy with a vitamin K antagonist or a direct oral anticoagulant—specifically rivaroxaban, dabigatran, and, probably soon, apixaban and edoxaban— with clopidogrel is reasonable. Direct oral anticoagulants, at licensed dosing, have become the preferred agents for many patients due to the lower risk of bleeding.

For patients at increased ischemic risk and average or lower bleeding risk, triple therapy for 1 to 6 months may be considered. The duration of triple therapy is tailored to the risk of bleeding, with a shorter duration if bleeding risk is high (eg, HAS-BLED score ≥ 3, recent bleeding).

Given the current evidence, clopidogrel should be used in combined antithrombotic therapy. Ticagrelor can be considered for double therapy with a vitamin K antagonist.

This is a complex and evolving field, and as new evidence comes out and technology improves, our practice of using combined antithrombotic therapies in these high-risk patients will undoubtedly continue to change. ■

■ DISCLOSURES

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The current state of tobacco cessation treatment

ABSTRACT

Nicotine addiction and dependence is a chronic relapsing disease driven by addiction to nicotine. Proactive treatment for all tobacco users, regardless of their readiness to quit, is recommended. First-line tobacco cessation medications include nicotine replacement therapy, bupropion, and varenicline. Comprehensive treatment with behavioral interventions and pharmacologic therapy increases success rates of smoking cessation. Although there are many popular alternative treatments, they should not replace or delay the use of known effective therapies.

KEY POINTS

An individualized treatment for tobacco cessation is necessary and should be based on severity of nicotine dependence, probability of developing withdrawal symptoms, comorbidities, local resources, and patient preferences.

Comprehensive smoking cessation treatment provides counseling, assesses the patient's readiness to quit, offers treatment options, and arranges follow-up.

Evidence is lacking to support the use of smart phone "apps" for smoking cessation as monotherapy.

E-cigarettes are not used in tobacco cessation treatment as they can also cause nicotine addiction and other concerns.

TOBACCO USE CONTINUES TO BE a major public health problem and a major risk factor for deaths from heart disease and several types of cancer such as lung, head and neck, and colorectal cancers.[1] The prevalence of smoking has declined over the last 6 decades, to an all-time low of 13.7% in adults in 2018.[2] However, nicotine dependence is still considered a common and significant clinical problem.

A number of effective therapies exist, yet treating patients for tobacco cessation remains a challenge, not only for patients, but also for clinicians, who may not be aware of effective therapies available and may fail to offer treatment. Therefore, it is important for clinicians to familiarize themselves with treatment options they can offer to every smoker.

In this article, we review behavioral interventions and pharmacotherapy to treat nicotine dependence associated with tobacco use. We also discuss the role of e-cigarettes.

■ A PROACTIVE APPROACH TO TOBACCO CESSATION

The 2008 US Public Health Service guidelines outlined an evidence-based behavioral intervention to manage tobacco treatment in primary care called the 5-A (ask, advise, assess, assist, and arrange) framework, which is still used today.[3] Its aim is to identify every smoker, provide counseling, assess readiness to quit, offer treatment options, and arrange follow-up.

Nicotine dependence is a chronic, relapsing disease driven by addiction to nicotine. A proactive approach is needed, offering treatment to all smokers regardless of their level of readiness to quit. Treatment should be in-

TABLE 1
The Heaviness of Smoking Index

How many cigarettes do you smoke a day?

	Score
10 or fewer	0
11–20	1
21–30	2
31 or more	3

How soon after waking up do you smoke your first cigarette of the day?

	Score
60 minutes	0
31–60 minutes	1
6–30 minutes	2
Within 5 minutes	3

Level of nicotine dependence by total score:

0–2 = low

3–4 = moderate

5–6 = high

Based on information in reference 4.

The Heaviness of Smoking Index is a simple way to assess the level of nicotine dependence

dividualized based on the severity of nicotine dependence and the probability of developing withdrawal symptoms, as well as on comorbidities, local resources, and patient preferences.[3]

Pharmacotherapy for tobacco treatment is based on alleviating symptoms of nicotine withdrawal with nicotine replacement therapy (NRT) and on optimal use of medications such as varenicline and bupropion. The best results are obtained when pharmacotherapy is combined with behavioral interventions.[3]

◼ EVALUATION OF NICOTINE DEPENDENCE

The severity of nicotine dependence, risk of developing withdrawal symptoms, and risk of relapse should be determined. The Heaviness of Smoking Index is a simple and validated test to assess the strength of a smoker's nicotine dependence. It consists of 2 questions, making it a quick and practical tool to administer (**Table 1**).[4] Other indicators of nicotine dependence include early initiation of tobacco use, difficulty attaining prolonged abstinence from smoking, history of withdrawal symptoms, and continued use despite knowledge of harm.

Nondaily smokers may use cigarettes compulsively in certain situations but may not have withdrawal symptoms. Factors that influence the risk of relapse include the degree of motivation to quit, presence of comorbid psychiatric disorders, other substance use (eg, heavy alcohol use), and living with other smokers. Nondaily smokers should be advised to quit smoking completely and should be offered assistance to do so. The need for pharmacotherapy should be evaluated on a case-by-case basis.

On the other hand, daily smokers with high nicotine dependence benefit from combination therapies including pharmacotherapy and behavioral interventions.

◼ BEHAVIORAL INTERVENTIONS

Behavioral support can be provided in face-to-face meetings, group sessions, and text messages. It is typically provided by specialists in tobacco cessation counseling. Interventions that combine pharmacotherapy and behavioral support increase tobacco cessation rates compared with minimal intervention or usual care.[5,6] Intensive support, especially when it involves in-person contact, increases the chance of abstinence by about 10% to 20%.[7]

Advice and counseling

Providing advice about quitting is the most common form of behavioral intervention. Even a brief verbal exchange can increase cessation rates.[8] Ideally, the advice should be tailored to individual circumstances.

Self-help materials with additional advice and information may also be beneficial. Standardized, print-based, self-help materials increase quit rates compared with no intervention.[9] However, individual counseling is more effective than self-help materials in promoting smoking cessation, and a more intensive counseling intervention is more effective than a less intensive intervention.[10] **Table 2** lists messages that can be used when giving advice to quit.

Motivational interviewing

Motivational interviewing is a more intense form of behavioral intervention,[11] though less commonly used due to lack of knowledge or training. The aims are to increase motivation

TABLE 2

Suggested messages to use when giving advice on tobacco cessation

Brief advice:
"Quitting is the best way to improve your health."

Develop discrepancy:
"How do you think your smoking is affecting your loved ones?"

Express empathy:
"Many people worry about managing without cigarettes."

Manage resistance:
"You are worried about how you would manage withdrawal symptoms."

Personalized messages:
"The best way to prevent lung cancer is to quit smoking."
"The best way to prevent another heart attack is to quit smoking."

Connect to resources:
"There are many effective options. I can help you find the best effective treatment for you."

Support self-efficacy:
"Would you like information about the benefits and strategies of quitting?"

in smokers who do not intend to quit, to enhance self-control over smoking behavior, and to assist in structuring a plan and techniques to control urges and cues.

Motivational interviewing is a collaborative, patient-focused counseling technique. It is designed to help people to explore and resolve ambivalence about behavior change.[11]

Group therapy or classes

Group therapy or classes offer individuals the opportunity to learn behavioral techniques and provide them with mutual support.[12]

■ FIRST-LINE THERAPEUTICS

Nicotine replacement therapy

NRT delivers nicotine in place of smoking or tobacco use to reduce the urge to smoke, as well as associated withdrawal symptoms.[13]

Clinical guidelines recommend NRT as a first-line treatment for tobacco cessation.[14] All commercially available forms (gum, transdermal patch, nasal spray, inhaler, and lozenges) are effective in helping smokers increase their chance of quitting successfully.[15] Each product has about the same efficacy, increasing quit rates by 50% to 70% compared with placebo. However, NRT is most effective when the nicotine patch is used in conjunc-

tion with a more rapidly absorbed form of NRT (eg, gum).[15]

In the United States, nicotine replacement products are available over the counter or by prescription (**Table 3**). The initial dosing of most products is based on the number of cigarettes smoked daily or on the time to the first cigarette after waking.

Nicotine patches deliver nicotine in a sustained manner throughout the day.[16] More rapidly absorbed forms of NRT such as gum, lozenges, inhalers, and spray relieve withdrawal symptoms more quickly than patches. None of the available nicotine delivery systems reproduces the rapid and high levels of arterial nicotine achieved when cigarette smoke is inhaled.[16] This partially explains why nicotine replacement does not completely eliminate the symptoms of withdrawal. A rapid-release of nicotine gum has been formulated and may achieve faster withdrawal relief.[17,18]

In general, NRT is recommended for 2 to 3 months after smoking cessation. However, it may be used through the period when patients are at high risk for relapse. Some smokers may need to use nicotine replacement products indefinitely. There is no evidence to show that gradual withdrawal of NRT is better than abrupt withdrawal.

Motivational interviewing is a collaborative, patient-focused counseling technique

TABLE 3

First-line pharmacologic options for tobacco cessation

Drug, available doses	Dosing	Administration [a]	Common side effects	Comments
Nicotine patch (7 mg, 14 mg, 21 mg)	≤ 10 cigarettes/day: start with nicotine patch 14 mg/day > 10 cigarettes/day: start with nicotine patch 21 mg/day	Apply one patch each morning to any non-hairy, clean, dry skin on upper body or outer arm. Rotate the site daily to avoid skin irritation. After 6 weeks, taper to lower doses for 2–4 weeks.	Skin irritation Insomnia Vivid dreams	Consider removing patch at bedtime in case of insomnia and vivid dreams.
Nicotine gum (2 mg, 4 mg)	Smokers wait > 30 min after waking to smoke: use 2 mg Smokers smoke within 30 min of waking: use 4 mg	"Chew and park" is recommended: chew until tingling sensations occurs, then "park" until tingling disappears. Then chew again to repeat. Chew one piece of gum every 1–2 hours or whenever there is an urge to smoke. Use up to 24 pieces of gum/day per day for 6 weeks. Gradually reduce use over a second 6 weeks, for a total duration of 3 months.	Mouth irritation Esophageal and gastric irritation Hiccups Jaw pain Nausea/vomiting Excess salivation Headache Palpitations	Avoid acidic beverages (eg, coffee, carbonated drinks) 15 minutes before and during gum use, as they reduce nicotine absorption.
Nicotine lozenge (2 mg, 4 mg)	Smokers wait > 30 min after waking to smoke: use 2 mg Smokers smoke within 30 min of waking: use 4 mg	Place lozenge in the mouth and allow it to dissolve for 30 minutes. Use 1 lozenge every 1–2 hours for 6 weeks. Maximum five lozenges every six hours or 20 lozenges per day. Gradually reduce number of lozenges used per day over a second 6 weeks.	Mouth irritation Mouth ulcers Abdominal pain Hiccups Nausea/vomiting Diarrhea Headache Palpitations	Do not chew lozenge. Avoid acidic beverages (eg, coffee, carbonated drinks) 15 minutes before and during gum use, as they reduce nicotine absorption.
Nicotine inhaler (10 mg/cartridge)	Puff into mouth as needed; use 6–16 cartridges per day (at least 6 cartridges per day for the first 3–6 weeks) for up to 12 weeks	Inhale deeply into back of throat or puff in short breaths. Maximum 16 cartridges per day. Gradually reduce dose over 6–12 weeks	Mouth irritation Throat irritation Cough	Required frequent use. Each cartridge lasts about 20 minutes if continuously puffing. Inhaled nicotine may cause bronchospasm.
Nicotine nasal spray (10 mg/mL)	Use 1 spray in each nostril 1–2 times per hour	Maximum of 10 sprays per hour or 80 spray per day. Adjust dose as needed based in response. Gradually reduce dose after 12 weeks.	Side effects are common (headache, throat irritation, cough, rhinitis). Nasal irritation may be a reason to stop.	Provides a more rapid rise in plasma nicotine concentration than that produced by agents absorbed via the oral mucosa.
Bupropion SR (sustained release) (150 mg)	150 mg once daily for 3 days, then increase to 150 mg twice daily	Begin at least 1–2 weeks before target quit date. May use longer than 12 weeks if needed for maintenance. Consider combination therapy, discontinuation, or alternative agent if no progress is made by seventh week.	Insomnia Headache Dizziness Diaphoresis Weight loss Xerostomia Nausea/vomiting	Consider lowering dose to 150 mg daily if full dose not tolerated. Decreases seizure threshold.
Varenicline (0.5 mg, 1 mg)	Days 1–3: 0.5mg once daily Days 4–7: 0.5 mg twice daily Day 8 and later: 1 mg twice daily	Treatment should be continued for 12 weeks but can be extended. Consider dose reduction if usual dose is not tolerated.	Insomnia Nausea/vomiting Abnormal dreams Headache Nasopharyngitis Xerostomia	Varenicline does not increase the risk of depression, suicidal ideation, or cardiovascular disease.

[a] Nicotine replacement therapy is recommended for 2 to 3 months after smoking cessation. However, it may be used through the period when the patient is at high risk for relapse. Some smokers may need to use nicotine replacement products indefinitely.

Side effects of nicotine replacement products include nausea, vomiting, abdominal pain, diarrhea, headache, and local irritation depending on the delivery method.[13] These can be managed by titrating or changing products. Long-term use is not associated with any serious harmful effects, and the risk of dependence on nicotine replacement products is small.[13]

Bupropion

Bupropion is an antidepressant. Its mechanism of action in the treatment of nicotine dependence is not well understood.[19] The main hypothesized effect is the attenuation of withdrawal symptoms (eg, irritability, anxiety) by mimicking nicotinic effects on dopamine and noradrenaline receptors.[20]

Sustained-release bupropion is an effective aid to help smokers quit with or without depression.[21] It is effective as monotherapy and comparable to the nicotine patch in efficacy.[3,22] However, the combination of bupropion with NRT is more effective than bupropion or NRT alone.[23]

Bupropion is typically started 1 to 2 weeks before a patient's planned quit date, at a dose of 150 mg daily. After 3 days, the dose should be increased to 150 mg twice daily for 7 to 12 weeks. After this period, bupropion can be continued for up to 12 months, as long as abstinence is attained (maintenance dosage 300 mg/day).[14]

Common side effects are insomnia (decreased if medication given at least 8 hours before bedtime), headache, dizziness, diaphoresis, weight loss, xerostomia, nausea and vomiting, and pharyngitis.[24] There is no increase in the incidence of neuropsychiatric adverse events with bupropion compared with placebo in psychiatric and nonpsychiatric cohorts.[21]

Bupropion is contraindicated in patients with seizure disorder and high-risk conditions such as brain arteriovenous malformation, severe head injury, severe stroke, and central nervous tumor or infection. Other contraindications include the presence of anorexia or bulimia; abrupt discontinuation of ethanol; current use of benzodiazepines, barbiturates, or antiepileptic drugs; use of monoamine oxidase inhibitors in the previous 2 weeks; and as concomitant use of linezolid or intravenous methylene blue, a reversible monoamine oxidase inhibitor.

Varenicline

Varenicline is a partial agonist on 2 nicotinic acetylcholine receptors.[25,26] These receptors mediate the release of dopamine, the main neurotransmitter underlying nicotine addiction. The partial agonist action decreases the intensity of withdrawal symptoms. It also reduces nicotine binding to nicotinic acetylcholine receptors that generates rewarding effects, thus reducing the perceived pleasure generated by nicotine consumption. This explains why patients on this medication reduce their cigarette consumption even before their quit date.[14]

Although it is recommended to start varenicline dosing at least 1 to 2 weeks before the target quit date (the "fixed target quit date" approach), other approaches are acceptable:
- Medication preloading: ie, starting pharmacotherapy while the smoker is still smoking
- Flexible quit date: patient chooses a quit date within 1 month of starting medication
- Reduce-to-quit approach: gradual smoking reduction with the goal of eventually quitting completely.[27]

Dosing titration starts with 0.5 mg orally once daily for 3 days, with up-titration every 3 days to 1 mg orally twice daily until the end of treatment. In patients who develop adverse effects, lower doses of varenicline (eg, 0.5 mg twice daily) can be used. If well tolerated, varenicline may be used up to 6 months for continued abstinence.[28]

Efficacy. Varenicline is effective in helping smokers achieve tobacco abstinence. It is superior to placebo, bupropion, and NRT.[29] Clinical guidelines recommend varenicline as first-line treatment in conjunction with behavioral therapy for a minimum of 12 weeks.[3,14,30] It may be used in combination with NRT to achieve higher rates of abstinence.[31]

The additive efficacy of combining varenicline and NRT may be due to the partial agonism of individual drugs leading to synergistic effects when combined, or to NRT binding to different or additional receptors not stimulat-

Bupropion is an effective aid to tobacco cessation in smokers with or without depression

ed by varenicline. It is also possible that short-acting nicotine replacement products add to the effect by allowing as-needed dosing and relief of withdrawal symptoms.[32]

Contraindications are a history of severe hypersensitivity reactions and skin reactions to varenicline. Seizure disorder is not a contraindication, though occurrence of seizures during therapy warrants medication cessation.

Common side effects of varenicline use are nausea, insomnia, abnormal dreams, headache, nasopharyngitis, and xerostomia.[21]

Postmarketing reports of neuropsychiatric adverse effects have included suicidal ideation and behavior, completed suicide, changes in mood, psychosis, aggression, and hostility; these have been reported in smokers with and without previous psychiatric conditions, prompting drug label warnings in many countries.[33,34] Observational studies, randomized clinical trials, and meta-analyses have not confirmed these concerns, leading the US Food and Drug Administration to remove the boxed warning in 2015 for both varenicline and bupropion.[34,35]

In summary, varenicline does not increase the risk of depression, suicidal ideation, or cardiovascular disease.[36,37]

Preoperative counseling and nicotine replacement therapy can improve surgical outcomes

■ SECOND-LINE THERAPEUTICS

Nortriptyline and clonidine are second-line pharmacotherapies. Nortriptyline is a tricyclic antidepressant that has a beneficial effect in smoking cessation.[38] As with bupropion, its effect on smoking cessation is unrelated to its antidepressant activity. It should be used carefully in patients with chronic heart disease due to potential for QT-segment prolongation.[19,38]

Clonidine is a selective alpha-adrenergic receptor agonist used to treat hypertension. It has been used off-label to treat withdrawal symptoms due to its effect in the central nervous system. It is effective for smoking cessation when compared with placebo, but side effects such as dry mouth and sedation limit its use.[19,39]

It is not clear whether one second-line therapy is more effective than the other. Second-line therapies can be considered when first-line treatments fail or are contraindicated.

■ DRUG INTERACTIONS

When prescribing a tobacco cessation drug, it is important to consider the potential for drug interactions (**Table 4**).[24,40,41]

Nicotine

Nicotine from NRT is generally absorbed more slowly and gradually than nicotine from cigarettes, leading to lower nicotine blood levels.[42] Nicotine may cause tachycardia regardless of the source, so it is possible that nicotine could enhance the tachycardic effect of certain drugs with similar effects on heart rate, such as adenosine.[43] Drugs that inhibit cytochrome P450 enzymes (eg, cimetidine), which participate in nicotine metabolism, could decrease the clearance of nicotine, thereby increasing the physiologic effects of nicotine.[44]

Varenicline

Because varenicline is a substrate of the kidney transport protein organic cation transporter 2 (OCT2), medications that inhibit OCT2 could increase the serum concentration of varenicline and therefore increase the risk for adverse effects, especially in patients with renal disease.[24]

Neuropsychiatric adverse effects such as aggressive behavior and amnesia have been reported with the combination of alcohol and varenicline.[33] Because varenicline may increase the intoxicating effect of alcohol, patients should be counseled to reduce their alcohol intake while on varenicline until they know how varenicline affects their alcohol tolerance.[33]

Bupropion

Bupropion should not be prescribed for tobacco cessation in patients taking drugs that lower the seizure threshold. The combination may enhance neuroexcitatory effects, thereby increasing the risk of seizures.[40] Alcohol should be used with caution in patients taking bupropion: it not only lowers the seizure threshold, but also may reduce alcohol tolerance. Patients should be advised to minimize or avoid alcohol consumption while taking bupropion.[40]

Bupropion is a strong inhibitor of the enzyme cytochrome P450 2D6 (CYP2D6), which increases the concentration of drugs that are CYP2D6 substrates and the risk for

TABLE 4

Drug interactions to consider in tobacco cessation treatment

Agent	Potential drug interactions
Nicotine replacement therapies	Adenosine, cimetidine, varenicline
Varenicline	Alcohol, nicotine, OCT2 inhibitors (eg, histamine-2-receptor blockers, quinolones, tafenoquine, trimethoprim)
Bupropion	Drugs that lower seizure threshold (eg, alcohol, selective serotonin reuptake inhibitors, tricyclic antidepressants, systemic steroids)
	CYP2D6 substrates (eg, aripiprazole, atomoxetine, brexpiprazole, clozapine, codeine, duloxetine, fesoterodine, galantamine, hydrocodone, iloperidone, metoprolol, metoclopramide, nebivolol, pimozide, primaquine, selective serotonin reuptake inhibitors, tamoxifen, tamsulosin, thioridazine, tramadol, tricyclic antidepressants, valbenazine, vortioxetine)
	Dopaminergic medications (eg, amantadine, levodopa)
	CYP2B6 inducers (eg, carbamazepine, efavirenz, nelfinavir, nevirapine, phenobarbital, phenytoin, primidone, rifampin, ritonavir)
	CYP2B6 inhibitors (eg, clopidogrel, mifepristone; ticlopidine)
	Digoxin, monoamine oxidase inhibitors
Cigarette smoke	CYP1A2 substrates (eg, clozapine, fluvoxamine, olanzapine, tacrine, theophylline)

OCT2 = organic cation transporter 2

Based on information in references 24, 43, and 49.

adverse effects for many of these agents.[43] However, certain CYP2D6 substrates such as codeine, tramadol, hydrocodone, and tamoxifen rely on CYP2D6 for the metabolic conversion of these drugs to their active metabolites.[45,46] Concurrent use of bupropion may lead to an inadequate therapeutic response to these agents that are activated by CYP2D6.

Bupropion is contraindicated in patients taking monoamine oxidase inhibitors, which can enhance the hypertensive effect of bupropion. These drugs should not be used concomitantly or within 14 days of one another.[47]

Selective serotonin reuptake inhibitors. Reports suggest that concurrent use of selective serotonin reuptake inhibitors with bupropion may increase the risk for serious toxicity such as serotonin syndrome; however, the mechanism is unclear because the antidepressant effects of bupropion are largely dopamine-based, with less-pronounced effects on serotonin activity.[48] Antiparkinson agents may enhance the adverse effects of bupropion through cumulative dopamine agonist effects.

Patients taking bupropion for tobacco cessation who are currently taking other dopaminergic agents should be monitored for evidence of central nervous system toxicities such as restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness.[40]

Digoxin. Bupropion may decrease the serum concentration of digoxin. Thus, digoxin levels should be monitored if these drugs are used concomitantly.

Finally, drugs that inhibit or induce CYP2B6, the major enzyme involved in the metabolism of bupropion, can interact with bupropion by increasing or decreasing its concentration, respectively.[24]

Effects on drug metabolism after quitting

In addition to considering the potential drug

Bupropion may lower serum digoxin levels; monitor digoxin levels if these drugs are used concomitantly

interactions between a selected smoking cessation product and a patient's current medications, it is also important to note that successful smoking cessation can alter the metabolism of medications once the effects of cigarette smoke are eliminated.

Tobacco smoke is known to induce cytochrome P450 enzymes, particularly CYP1A2. Therefore, smokers more rapidly metabolize certain medications that are substrates of this enzyme.[41,49] When tobacco use ceases, the concentration of these drugs can increase, raising the potential for adverse drug events.

Clozapine, olanzapine, and theophylline may cause clinically significant adverse effects upon smoking cessation, including seizures with clozapine, extrapyramidal effects with olanzapine, and tachycardia with theophylline.[49,50] Thus, it is important to closely monitor patients taking these drugs when they quit smoking and adjust the dosage.

■ OTHER INTERVENTIONS

Smart phone app-based interventions
The widespread use of smart phones and the advent of health-related apps have the potential to make smoking cessation interventions more accessible. Smart phone apps offer the opportunity to provide tailored behavioral support and real-time responses to smoking urges and cues.[51] They may help adolescents and young adults adhere to treatment. However, there are concerns regarding their quality and effectiveness,[52,53] as most apps do not follow existing smoking-cessation treatment guidelines, and the quality of the content is variable.[51,53,54]

While apps could be a successful strategy for specific patients, evidence is lacking to support their use as monotherapy, and they should not replace interventions known to be effective. More research and innovation are needed to evaluate the role and efficacy of mobile apps as a smoking cessation intervention.

Alternative interventions
Hypnotherapy is widely promoted as a method for aiding smoking cessation. However, there is currently insufficient evidence to determine whether hypnotherapy is effective.[55] Electrostimulation is not effective for smoking cessation.[56]

Phone apps may encourage adherence to treatment, but most do not follow current guidelines on smoking cessation

Acupuncture is promoted as a treatment for smoking cessation that can control withdrawal symptoms.[56] Acupuncture combined with counseling and an educational smoking cessation program may be beneficial.[57] However, there is very limited high-quality evidence to support acupuncture as monotherapy in smoking cessation.[56] Well-designed research into these alternative therapies is necessary, especially since these are popular interventions.

■ OPPORTUNITIES TO ENCOURAGE TOBACCO CESSATION

Pregnancy
Female patients of childbearing age and pregnant patients represent an opportunity for clinicians to encourage smoking cessation. All pregnant patients should be counseled to quit. Patients should be counseled about the adverse effects of tobacco use and about effects such as subfertility and miscarriage risks.[58,59]

The American College of Obstetricians and Gynecologists recommends that NRT be considered for pregnant women with a strong resolution to quit. Bupropion is also a reasonable first-line therapy.[60] However, there is limited evidence supporting the subsequent addition of bupropion in patients as a first-line treatment in female patients unable to tolerate NRT or as an addition to counseling and NRT. Varenicline is typically not used in this setting due to the limited data supporting its safety.[60]

Inpatients
Hospital admission requires temporary tobacco abstinence, providing an opportunity to initiate treatment. The primary reason for hospitalization may serve as an opportunity to provide personalized advice and motivation to quit, especially if surgery is undertaken during the same admission.[61]

Smokers are far more likely to quit if they are provided close follow-up after inpatient discharge (eg, during follow-up appointments) vs traditional provision of postdischarge pharmacotherapy and recommendations alone.[62]

Cardiovascular disease
The increased risk of cardiovascular disease from tobacco use is well known. In patients

with known atherosclerotic cardiovascular disease, the approach to tobacco cessation is the same as for patients without cardiovascular disease. Data show that NRT, bupropion, and varenicline do not significantly increase the risk of adverse cardiovascular events.[63]

The lack of evidence regarding the efficacy and safety of NRT in acute coronary syndrome and the theoretical concern for nicotine's vasoconstrictive properties may explain why clinicians tend to avoid recommending it. However, NRT is a first-line therapy for the relief of withdrawal symptoms in inpatients with acute coronary syndrome, according to expert consensus.[14] NRT or varenicline can be prescribed at hospital discharge.[14]

Preoperative evaluation

Because cigarette smoking increases the risk for poor postoperative outcomes, formal preoperative counseling and use of NRT are recommended because they result in greater rates of preoperative cessation and lower rates of postoperative complications than no treatment.[64]

Concerns that quitting shortly before surgery could increase the risk of pulmonary complications have been found to be unsubstantiated.[65] Patients should be advised to quit at any time before surgery. Although the optimal duration of abstinence is not known, a greater reduction in risk of complications is associated with longer periods of abstinence.[66] As with hospitalized patients undergoing surgical procedures, postdischarge cessation rates were found to be highest in those who received formal perioperative counseling and pharmacotherapy.[67]

Psychiatric and mental health considerations

Nicotine dependence is known to exacerbate concurrent mental illnesses and psychiatric disorders. However, patients with psychiatric needs are less likely to be provided with tobacco cessation counseling or pharmacotherapy.[68] Recent studies have shown that the safety of NRT, varenicline, and bupropion are comparable between patients with and without psychiatric disorders.[21] It is reasonable to offer varenicline and NRT alongside formal tobacco cessation counseling, followed by use of bupropion as a second-line agent in the ab-

sence of a documented seizure history.[69]

■ ELECTRONIC CIGARETTES

E-cigarettes have been proposed as a method to reduce the harms of tobacco use and as a nicotine replacement product.[70] However, e-cigarettes can also cause nicotine dependence, so users may need treatment for nicotine dependence similar to that for tobacco users.[71]

Studies in tobacco cessation

E-cigarettes have been promoted as safe alternatives to combustible cigarettes, and they have been studied in randomized controlled trials as a treatment for tobacco cessation.[72]

One randomized trial compared nicotine-containing e-cigarettes with NRT.[72] The e-cigarette group abstinence rate was 18% at 12 months, though 80% continued use of e-cigarettes, compared with a 9% abstinence rate in the NRT group and a 9% rate of continued use of NRT.[72]

Although e-cigarettes were beneficial in achieving abstinence, the concern is that individuals continued to use them. It is not clear whether e-cigarettes truly reduce harm as they are not as safe as they are promoted to be. While nicotine inhalation with e-cigarettes is thought to release fewer toxic by-products than combustible cigarettes, there are concerns regarding their safety.[73] Carcinogens and toxins have been found in the liquid used for vaporization and in the aerosols emitted, and e-cigarettes have been associated with an outbreak of cases of acute lung injury that caused hospitalizations and even deaths.[74,75]

The long-term consequences are unknown, but several studies have shown the potential of e-cigarettes to cause chronic lung and heart disease and to increase the risk of infection and of cancer.[76]

The potential for nicotine addiction with e-cigarettes is also concerning. Pod systems (eg, JUUL brand) are popular devices that can deliver high concentrations of nicotine through the use of nicotine salts.[77,78] For example, each JUUL pod may contain a nicotine concentration of 3% (equivalent to 35 mg/mL) or 5% (equivalent to 59 mg/mL).[79] A combustible cigarette has a nicotine concentration between 1.5% and 2%.[80] It is worrisome that e-cigarette users are often unaware

Several studies have shown the potential of e-cigarettes to cause chronic lung and heart disease and to increase risk of infection and cancer

of or underestimate the nicotine content.[81,82]

Managing nicotine dependence related to e-cigarettes

It is not clear whether nicotine dependence from e-cigarette use should be managed differently than that from combustible cigarette smoking. Because the addiction is to the same substance, it is likely that the same strategies and tools could be applied with careful attention to the unique aspects of e-cigarette use.

The pattern of use with e-cigarettes is different. An e-cigarette does not need to be lit; it can be used any time and with a potentially higher frequency than combustible cigarettes; and nicotine concentrations can be higher in e-cigarettes. Thus, this pattern of use can pose a higher risk of withdrawal symptoms.

This highlights the need for clinicians to familiarize themselves with different e-cigarette products and their nicotine content, as well as the need for further investigation into whether higher doses of NRT are necessary in these patients.

E-cigarettes use by adolescents: A public health concern

Another important aspect is the high prevalence of e-cigarette use among adolescents. Adolescent e-cigarette usage is now a major public health concern, with 1 in every 6 high school students reporting current e-cigarette use.[83,84]

Treatment options for adolescents are more limited than those for adults. Neither varenicline nor bupropion has shown benefit in the adolescent population based on limited studies of nicotine dependence associated with combustible cigarettes.[85] NRT combined with cognitive-behavioral interventions has been shown to be effective in adolescent cigarette smokers.[86] However, further research is needed to determine the most effective treatment of nicotine dependence in adolescents, especially when it is associated with e-cigarette use.

◼ THE BOTTOM LINE

Nicotine dependence is a chronic relapsing disease. Every tobacco user should be offered treatment for tobacco cessation regardless of their level of readiness to quit.

Treatment should be based on the severity of nicotine dependence, the probability of developing withdrawal symptoms, risk of relapse, comorbidities, local resources, and patient preferences.

Comprehensive tobacco treatment that combines pharmacologic and behavioral therapy significantly increases successful tobacco cessation. Although there are many popular alternative treatments, they should not replace or delay the use of known effective therapies.

E-cigarettes have been proposed as a method of reducing the harms of tobacco use, but they also can cause nicotine addiction. Moreover, their effectiveness in tobacco cessation treatment has not been determined, and concerns related to their safety preclude their use in tobacco cessation treatment at this time. ◼

◼ DISCLOSURES

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Promoting physical activity in older women to maximize health

ABSTRACT

Physical activity can maximize health by improving disease-oriented and patient-oriented outcomes in women age 60 and older. General activity levels are low in the United States. Promoting physical activity in clinical practice is limited by time constraints and knowledge deficits. Understanding the benefits of the specific type of physical activity, the intensity, and the level in older women helps clinicians provide focused, time-efficient counseling in primary care. This review details the benefits of physical activity in older women by disease state.

KEY POINTS

Sex-specific differences in diseases exist for older women.

The leading causes of disability and death in women over age 60 are cardiovascular disease, stroke, hypertension, diabetes mellitus, hyperlipidemia, cancer, cognitive decline, chronic obstructive pulmonary disease, depression, musculoskeletal disorders, osteoporosis, and falls, all of which are improved by physical activity.

Primary care counseling on routine physical activity and exercise can increase the level of activity in women age 60 and older and improve clinical outcomes.

THE WORLD'S POPULATION is rapidly aging, particularly women, who have a life expectancy 10 years longer than that of men.[1] By 2050, the number of women age 60 is expected to double, and the number of women age 80 is expected to triple.[1]

The leading causes of disability and death in women over age 60 are cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cancer, back pain, arthritis, osteoporosis, falls, depression, and dementia.[1] Approximately 20% have more than one health condition.[1] Improving outcomes in these conditions is crucial to health as women age.

Physical activity is a safe way to improve health and to promote healthy aging. Important differences exist between men and women in the degree of benefit derived from physical activity, especially for stroke risk, hypertension, and diabetes and, thus warrant special attention.[2–5] While it is generally accepted that physical activity is a healthy behavior and that any activity is better than none, the optimal type, intensity, and level required to achieve specific health outcomes depends on the disease the patient and clinician are trying to prevent or manage.

Physical activity is defined as "any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level."[2] Exercise is "a form of physical activity that is planned, structured, repetitive, and performed with the goal of improving health or fitness."[2] The distinction between the two is important as clinical outcomes vary depending on the type, intensity, and level of activity. Definitions and examples of physical activity, with estimates of metabol-

TABLE 1

Physical activity and exercise: Definitions and durations

Physical activity	Bodily movement from skeletal muscle contraction resulting in energy expenditure above baseline.	
Exercise	Planned, structured, repetitive physical activity performed to improve health or fitness.	
MET (metabolic equivalent of task)	A measure of energy expenditure for an activity with a reference of 1 MET being rest.	
Intensity	**Low intensity:** Nonsedentary activity ≤ 3 METs	Leisurely walking (≤ 2 mph) Light household chores
	Moderate intensity: 3–5.9 METs	Golfing (walking, carrying bag) Dance Pickleball Brisk walk (2.5–4 mph) Gardening Playing with grandchildren
	Vigorous intensity: ≥ 6 METs	Hiking Swimming Water aerobics Fast walk (≥ 4.5 mph) Stationary cycling Strenuous fitness classes
Activity level	**Inactive:** No moderate to vigorous physical activity	
	Low: Almost completely inactive	
	Moderate: Some physical activity >4 hr/wk or about 12 MET hr/week or more	Brisk walk 4 hr/wk Pickleball 2.5 hr/wk Golfing (walking, with bag) 3 hr/wk
	High: Vigorous activity >3 hr/week or about 18 MET hr/wk or more	Hiking 3 hr/wk Swimming 2.5 hr/wk Strenuous fitness class 2.5 hr/wk
Types of exercise	**Aerobic:** Rhythmic movement of large muscles for sustained periods of time	Walking Swimming Stationary cycling
	Resistance: Activity that increases skeletal muscle strength, power, endurance and mass	Lifting weights Using resistance bands Body movement underwater
	Combined: Activity with aerobic and resistance components	Fitness classes with weights Circuit training

Adapted from reference 2.

Knowing the type and intensity of activity that benefits each disease helps clinicians make specific recommendations

ic equivalents, a measure of energy output, are presented in **Table 1**.

Levels of physical activity are low in US women, and 80% do not meet the US Department of Health and Human Services mini-mum recommendation for adults, including older adults, of at least 150 minutes a week of moderate-intensity activity or 75 minutes a week of vigorous-intensity activity.[2]

Evidence supports population-wide pro-

motion of physical activity to improve health,[2] yet counseling on this by primary care providers remains inadequate with only about 21% of patients receiving counseling.[6] Barriers to this counseling include a lack of training and knowledge among providers on the benefits of physical activity, as well as time constraints and inadequate counseling skills.[6]

This review presents outcomes from systematic reviews and meta-analyses published through December 2019 that describe optimal type, intensity, and level of physical activity to improve outcomes for the most common causes of morbidity and death in women age 60 and older (**Table 2**).[3–5,7–21] This information can help clinicians provide practical, specific, and time-efficient counseling in the primary care setting.

While some studies report outcomes specifically for women, most include both men and women, and thus we have generalized the combined data to women. This is discussed in more detail below in the section, "Limitations of current literature on physical activity."

■ DISEASE-SPECIFIC FINDINGS

Cardiovascular disease
This is the leading worldwide cause of premature death in people age 60 and older.[1] Studies have shown that physical activity improves cardiovascular disease mortality rates and major cardiovascular events including myocardial infarction and stroke, the development of coronary artery disease, and most modifiable cardiovascular risk factors.

In a systematic review, Kraus et al[7] found that moderate to vigorous activity significantly reduced cardiovascular disease-related mortality rates compared with inactivity, and the greater the quantity, the greater the reduction. Performing the US Department of Health and Human Services' recommended 150 minutes per week accounted for 75% of the total estimated cardiovascular disease mortality reduction associated with physical activity. In women, Sattelmair et al[8] found that leisure-time physical activity reduced the risk coronary heart disease by 33%.

Patient counseling suggestion. Brisk to fast walking—and even walking at moderate intensity—for about 4 hours a week may prevent heart disease and death from heart disease.

Stroke
Reducing stroke risk in women requires high levels of physical activity. In a meta-analysis by Diep et al,[3] women achieving high but not moderate activity levels had a 24% lower stroke risk than women achieving only low activity levels. For women participating in moderate vs low activity levels, the stroke risk was not significantly different (relative risk [RR] 0.99).[3]

Patient counseling suggestion. Fast walking or other vigorous-intensity exercise for 3 hours per week may prevent stroke.

Hypertension
Physical activity has been shown to improve blood pressure in people with and without hypertension. A systematic review by Pescatello et al[4] found that in normotensive adults, increasing activity levels was associated with decreases in the incidence of hypertension. Compared with people engaging in low-level physical activity, those engaging in moderate-level activity had an 11% reduced risk; those engaging in high-level activity had a 19% reduced risk. Each 10 MET hour/week of physical activity, equivalent to brisk walking for 2 to 3 hours a week, was associated with an additional 6% risk reduction in incident hypertension.[4]

In people with hypertension, physical activity improves blood pressure control and reduces cardiovascular disease mortality rates. Exercise has been associated with reductions of 5 to 17 mm Hg in systolic pressure,[4,14] similar to reductions achieved with pharmacotherapy.[14]

In women with hypertension, increasing levels of activity is associated with significant reductions in mortality regardless of the severity of hypertension.[4,22] A meta-analysis by Pescatello et al[4] reported that highly active women with resting systolic blood pressures of 140 to 159 mm Hg had a 24% relative risk reduction, while highly active women with baseline systolic pressures above 160 mm Hg had a 27% relative risk reduction in cardiovascular mortality compared with inactive women with the same systolic pressures.

Patient counseling suggestion. Participat-

Counseling by primary care practitioners in partnership with exercise professionals results in better long-term adherence to physical activity

TABLE 2

Benefits of exercise for common causes of morbidity and death in women [a]

CONDITION	INTERVENTION	END POINT	COMPARATOR GROUP	EFFECT SIZE (95% CI)
CVD	7.5–14.9 MET hr/wk LTPA[7]	All-cause mortality	No LTPA	HR 0.68 (0.66–0.69)
	150 min/wk MVPA[8]	CHD incidence	No LTPA	RR 0.86 (0.77–0.96)
Stroke	High PA[3]	Stroke incidence	Low level PA	RR 0.76 (0.64–0.89)
HTN	High PA[4]	HTN incidence	Low level PA	RR 0.81 (0.76–0.85)
	Moderate PA[4]	HTN incidence	Low level PA	RR 0.89 (0.85–0.94)
	Any exercise (exercise in general)[14]	SBP reduction	Control	−8.96 mm Hg (−10.27 to −7.64)
Diabetes	150 min/week MVPA[5]	Type 2 DM incidence	Inactivity	RR 0.74 (0.69–0.80)
	Supervised aerobic exercise[9]	HbA1c reduction	No exercise	−0.30 (−0.60 to −0.45)
	Supervised resistance exercise[9]	HbA1c reduction	No exercise	−0.30 (−0.38 to −0.15)
	Combined exercise[9]	HbA1c reduction	No exercise	−0.53 (−0.68 to −0.45)
Breast cancer	High-level MVPA[10]	Breast cancer incidence	Low level PA	HR 0.90 (0.87–0.93)
Cancer [b]	Supervised exercise[11]	Health-related QOL	Control	SMD 0.48 (0.16–0.81)
Cognitive decline	Physical activity[15]	Alzheimer disease incidence	Inactivity	RR 0.61 (0.52–0.73)
	Moderate to high-intensity aerobic exercise[16]	Global cognition	Control	SMD 0.60 (0.21–0.98)
COPD	Pulmonary rehabilitation[17]	Dyspnea	Usual care	MD 0.79 (0.56–1.03)
Depression	Moderate to high intensity combined exercise[18]	Depression severity [c]	Control	SMD −0.34 (−0.52 to −0.17)
Hip OA	Land-based exercise[12]	Pain (3–6 mo)	No exercise	SMD −0.38 (−0.58 to −0.18)
	Land-based exercise[12]	Physical function	No exercise	SMD −0.37 (−0.57 to −0.16)
Knee OA	Land-based exercise[13]	Pain	No exercise	SMD −0.49 (−0.39 to −0.59)
	Land-based exercise[13]	Physical function	No exercise	SMD −0.52 (−0.39 to −0.64)
Falls	Exercise[19]	Number of fallers	Control	RR 0.85 (0.81–0.89)
	Exercise[19]	Falls	Control	RaR 0.77 (0.71–0.83)
Osteoporosis	Combined exercise[21]	Lumbar spine bone density	Usual care	SMD 0.349 (0.064–0.634)
	Exercise[20]	Overall fracture	No exercise	RR 0.49 (0.31–0.76)

[a] Most studies cited here included both men and women.
[b] Breast, colorectal, head and neck, lymphoma, others.
[c] Severity determined by self-report on depression scales.

CHD = congestive heart disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DM = diabetes mellitus; HbA1c = hemoglobin A1c; HR = hazard ratio; HTN = hypertension; LTPA = leisure-time physical activity; MD = mean difference; MET = metabolic equivalent of task; MVPA = moderate to vigorous physical activity; OA = osteoarthritis; PA = physical activity; QOL = quality of life; RaR = rate ratio; RR = relative risk; SBP = systolic blood pressure; SMD = standard mean difference

ing in 2.5 hours a week of moderate-intensity exercise such as pickleball, golf, or dancing may lower blood pressure, prevent hypertension, and reduce mortality risk from heart disease in women with hypertension. Swimming 2.5 hours per week is even more beneficial as it is a vigorous-intensity exercise.

Diabetes mellitus

Diabetes is a leading cause of both morbidity and death in older people worldwide. Physical activity has been associated with significant benefits in reducing incident diabetes and in improving outcomes for diabetic patients.[5,9,23,24]

In a meta-analysis by Smith et al,[5] higher levels and intensity of physical activity led to a lower incidence of diabetes, especially for women. Compared with inactivity, 150 minutes of moderate to vigorous activity per week reduced the risk of diabetes by 26%. Long-term prospective cohort studies showed higher reductions in incident diabetes for every 10 MET hours per week of activity, equivalent to 3.5 hours of slow walking, for women compared with men (RR 0.83 vs 0.89). And more intense activity was associated with an even larger reduction in diabetes incidence. Participating in 10 MET hours per week of vigorous activity, equivalent to 100 minutes of fast walking, reduced the risk by 56%.[5]

Improvements in outcomes in patients with diabetes depended on the type and setting of exercise. Supervised exercises associated with reductions in hemoglobin A1c included aerobic exercise (−0.30 reduction), resistance training (−0.30 reduction), and combined exercise (−0.53 reduction).[9] However, unsupervised aerobic exercise such as walking did not improve hemoglobin A1c levels compared with no exercise at all,[9] although it may prevent worsening of hemoglobin A1c levels.[23]

However, despite the minimal impact on hemoglobin A1c reduction, walking has been shown to benefit several patient-oriented outcomes in those with diabetes, including quality of life, sleep, vitality, physical health, and mental health.[24]

Patient counseling suggestion. Stationary bicycling 2 hours per week may prevent diabetes. Supervised exercise improves diabetes control.

Lipids

A systematic review found no significant reduction in levels of low-density lipoprotein (LDL) cholesterol with low-intensity or moderate-intensity exercise.[25] Another review found LDL cholesterol was reduced in women engaging in resistance exercise (minus 16.2 mg/dL) and combined aerobic and resistance exercise (minus 23.2 mg/dL).[26] The level of high-density lipoprotein (HDL) cholesterol was increased with high-level, vigorous-intensity aerobic exercise (4.3 mg/dL to 15.2 mg/dL).[26]

Patient counseling suggestion. Resistance training with weights can lower LDL levels. Hiking 3 hours per week may raise HDL levels.

Cancer

Lung and colon cancers are 2 of the top 10 causes of death in people over age 60,[1] and breast cancer is the most frequent cause in women. Physical activity has been shown to reduce the incidence of cancer and improve patient-oriented outcomes such as fatigue and depression in those with cancer both during and after treatment.[10,11,27–29]

Compared with low levels of moderate to vigorous leisure-time activity, high levels are associated with significant reductions in the incidence of common cancers affecting women, including breast cancer (hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.87–0.93), lung cancer (HR 0.74, 95% CI 0.71–0.77), and colon cancer (HR 0.84, 95% CI 0.77–0.91).[10] Observational studies consistently demonstrate reductions in overall and cancer-related mortality associated with increasing levels and intensity of physical activity.[27]

Different types of exercise are associated with benefits on patient-oriented outcomes for breast cancer survivors after treatment. Moderate- to high-intensity aerobic, resistance, and combined exercise are all associated with improvements in quality of life.[28] Walking improves sleep, depression, anxiety, and cancer-related fatigue.[29] Exercise, particularly if supervised by a professional, may have lasting, although small to moderate, benefits compared with usual care for improving pain, emotional well-being, social functioning,

Regular moderate to vigorous activity is required for maximal benefit for many health outcomes

sleep disturbance, and fatigue.[11]

Patient counseling suggestion. About 3 hours of vigorous exercise per week, such as water aerobics or fitness classes, may prevent cancer. Most exercise improves quality of life after breast cancer treatment.

Cognitive decline

Dementia is a leading cause of disability in aging populations, and the number of people living with dementia is expected to triple by 2050.[1] A meta-analysis of physical activity in adults age 65 and older found it to be associated with a significant 39% reduced risk of developing dementia.[30]

However, exercise (as opposed to physical activity) does not appear to reduce the incidence of dementia or mild cognitive impairment. A systematic review of adults age 60 and older with normal baseline cognitive function showed no reduction in risk of dementia, mild cognitive impairment, or cognitive decline associated with exercise for longer than a year.[15] Another review analyzed the effect of activities with combined physical and cognitive components, such as line dancing and tai chi, that require body motion and memorization of sequences of movement.[31] Results showed that combined physical and cognitive activities improved cognitive function compared with control and physical activity alone, but not compared with cognitive activities such as computer-based games, memorization, and visual search tasks alone, suggesting that cognitive activity is the primary driver of the observed benefit.

In patients with known cognitive decline, including mild cognitive impairment and dementia, systematic reviews have found variable outcomes of exercise on quality of life. A systematic review by Law et al found that exercise of moderate to high intensity significantly reduced cognitive decline by 40% (mean age 68 to 86) but had minimal effect on behavioral problems such as agitation.[32] Another systematic review found no benefit to exercise programs on either cognition or depression in patients with dementia.[16] Home-based walking programs in patients with dementia showed improvements in patient-oriented outcomes including behavioral symptoms, activities of daily living, health-related quality

Even low-level, low-intensity physical activity has benefits

of life, and caregiver burden.[33]

Patient counseling suggestion. Physical activity may prevent dementia, but exercise likely does not. Brisk walking may slow the progression of dementia and improve quality of life.

Chronic obstructive pulmonary disease

COPD is the third leading cause of disability and death in the aging population worldwide.[1] A review comparing functional and psychological outcomes in patients with COPD over age 64 found similar benefits in both sexes.[34] A meta-analysis of 8 studies[35] found that the benefits of exercise in COPD are primarily from formal pulmonary rehabilitation programs, which improve functional outcomes and quality of life, but the programs may be underused in women. For those over age 60, pulmonary rehabilitation improved forced expiratory volume in 1 second, 6-minute walk distance, health-related quality of life, perceived dyspnea, and physical and emotional impacts of COPD measured by the Chronic Respiratory Questionnaire score.

Dyspnea is most consistently improved by formal pulmonary rehabilitation but not by other forms of physical activity. A Cochrane review found that hospital-based pulmonary rehabilitation improved dyspnea by 21% in patients with COPD.[36] Some evidence suggests home-based pulmonary rehabilitation can improve health-related quality of life, fatigue, and 6-minute walk distance.[17] Types of exercise other than pulmonary rehabilitation can improve functional outcomes but not dyspnea. Active mind-body movement therapy with tai chi improved forced expiratory volume in 1 second and 6-minute walk distance compared with usual care,[37] and therapy with yoga, tai chi, or qigong improved quality of life compared with pulmonary rehabilitation.[38]

Patient counseling suggestion. Formal pulmonary rehabilitation improves shortness of breath, and active mind-body exercise improves quality of life in patients with COPD.

Depression

Depression is the fourth leading cause of disability in those over age 60.[1] In general, high-quality trials of physical activity in patients of all ages with depression have shown no significant effect compared with control groups,

medications, or therapy.[39] In patients over age 60, however, exercise has shown consistent positive effects.[18,40,41]

In a systematic review of predominantly women age 60 and older with clinical depression,[40] mixed moderate-intensity and high-intensity exercise was associated with significant reductions in the severity of depressive symptoms (standard mean difference [SMD] −0.34). The observed effect size was similar to that with prescription medications and was correlated with a 20% reduction in total symptom burden. In another systematic review,[18] the reduction of depressive symptoms was more robust (SMD −0.61, 95% CI −0.88 to −0.33). Furthermore, the benefits of exercise on older patients with depression occurred even in patients not responsive to medications.[41]

Patient counseling suggestion. Fitness classes using weights improves depression symptoms as much as medications.

Musculoskeletal disorders

The combination of osteoarthritis and back pain is the leading cause of disability worldwide.[1] A systematic review found low-quality evidence that in women age 65 and older with more than 6 weeks of low back pain, physical therapy is associated with small to moderate pain reduction and small improvement in function.[42] High-quality evidence of the benefits of exercise exists for hip and knee osteoarthritis.[12,13] In patients with hip osteoarthritis, exercise was associated with sustained moderate reductions in pain and improvement in physical function.[12] For patients with knee osteoarthritis, there was a moderate reduction in pain and moderate improvement in physical function.[13]

The positive effects of exercise on hip and knee osteoarthritis are not dependent on the intensity of exercise.[43] In fact, in a systematic review, any form of exercise was better than usual care for older women, with the most substantial pain and function benefits from aerobic and mind-body exercise such as tai chi.[44] Similarly, aquatic exercise was associated with improved quality of life (SMD −0.25, 95% CI −0.49 to −0.01) and moderate pain reduction (SMD −0.31, 95% CI −0.47 to −0.15) in older women compared with controls.[45]

Patient counseling suggestion. Walking, tai chi, and water aerobics improve function and reduce pain from knee and hip osteoarthritis.

Osteoporosis and fall prevention

Falls are the fifth leading cause of morbidity and account for up to 40% of injury-related deaths in older adults.[1] Older women may have multiple risk factors for falls, including decreased visual acuity, sarcopenia, postural hypotension, and frailty. A Cochrane systematic review found that physical activity significantly reduced the number of falls by 23%, the number of people suffering at least 1 fall by 15%, and falls requiring medical attention by 39%.[46] The average age of study participants was 76, and 77% were women.

The beneficial effects of physical activity in fall reduction are most notable when it includes a balance component and is performed regularly. Data from community-dwelling people with a mean age of 65 or older showed a significant 39% reduction in fall rate for those performing exercises that challenged balance for more than 3 hours a week.[19] Similarly, a meta-analysis of studies of tai chi, which has a balance component, found it was significantly more effective at reducing fall rates when performed at least 3 times a week compared with once a week (RR 0.36 vs 0.95).[47]

Osteoporosis is a significant risk factor for fall-related fracture. Strength training has consistently been shown to improve or preserve bone density at the hip in postmenopausal women,[48,49] and physical activity can reduce fracture risk.[50] Combined strength and aerobic training is most effective for preserving bone density at the spine in women over age 60 (SMD 0.349, 95% CI 0.064–0.634).[20] Importantly, walking by itself typically does not preserve bone density in postmenopausal women.[49,21] In a systematic review of older women, exercise was associated with a significant reduction in total fracture risk (RR 0.49, 95% CI 0.31–0.76) and vertebral fractures (RR 0.58, 95% CI 0.35–0.95) after adjusting for quality of included studies.[50]

Patient counseling suggestion. Exercises that require balance, such as tai chi and yoga, prevent falls in older women. Exercising with weight or resistance bands prevents fractures.

In osteoporosis, physical activity can reduce fracture risk after menopause, and strength training can preserve bone density

■ THE BENEFITS OF PHYSICAL ACTIVITY: TAKE-HOME MESSAGES

The benefits of physical activity on common diseases in women age 60 and older depends on the intensity of the activity, the type of activity, the setting, and the frequency. Generally, regular physical activity of moderate to vigorous intensity is required to maximize benefit for health outcomes. Benefits include reductions in the incidence of cardiovascular disease, hypertension, diabetes, and cancer; reduced risk of stroke, falls, and death from cancer or cardiovascular disease; and fewer symptoms of depression. However, even low-level, low-intensity physical activity can improve diabetes-related quality of life and osteoarthritis-related pain, function, and quality of life.

The type of activity is important for reduction in the risk of osteoporosis and falls. The setting of physical activity is important for reducing hemoglobin A1c and improving COPD symptoms.

Importantly, exercise does not universally benefit the most common diseases in older women: moderate-intensity exercise does not improve LDL, walking does not significantly improve bone density, and exercise alone does not reduce the rate of dementia or mild cognitive impairment.

Physical activity benefits conditions beyond the most common causes of morbidity and death in older women. Frailty, the combination of weakness, decreased activity, slow walking speed, unintentional weight loss, and exhaustion are associated with increases in nursing home admissions, hospital length of stay, and death. Physical activity has been shown to prevent frailty,[51] which in turn may prevent nursing home admissions and prolonged hospital stays.

Sarcopenia is also common in older women. Though not directly prevented by physical activity, its associated conditions, including frailty and falls, are benefited, as discussed above. Exercise-based cardiac rehabilitation benefits patients with newly diagnosed heart conditions.

Selecting the exercise
Knowing which type, intensity, and level of physical activity benefits each disease enables clinicians to make specific, accurate exercise recommendations for older women. Formulating specific recommendations for women with comorbidities is complex, requiring clinicians to consider the functional capacity and general mobility of the patient.

Exercise is a generally safe practice that benefits women of all ages. Safer forms include walking, water aerobics, and seated resistance exercises. Women desiring the health benefits of more frequent and vigorous activity should increase their activity level gradually.

Although safety is important, clinicians should recognize that functional capabilities vary widely in older women. For some women, brisk walks are challenging, whereas others can easily participate in high-intensity exercise such as tennis and group fitness classes.

By applying knowledge of the specific benefits of physical activity, clinicians can direct women to appropriate exercise resources in their community. Retirement communities and senior centers offer access to safe indoor exercise facilities for unsupervised aerobic and resistance training, as well as scheduled, supervised, mobility-appropriate exercise including line dancing, Zumba, chair yoga, water aerobics, seated strength training, and tai chi. Medicare Advantage programs also offer beneficiaries membership in exercise programs.

Offer additional help
Clinicians can further support women's physical activity goals through evidenced-based strategies such as motivational interviewing. But barriers to counseling in primary care exist related to time constraints and perceived ineffectiveness of counseling. The Exercise is Medicine campaign[52] of the American Medical Association and the American College of Sports Medicine aims to overcome these barriers by providing practical, versatile, and time-effective strategies for physical activity counseling in primary care. The campaign advocates for promoting activity to every patient at every outpatient visit using 1 of 4 strategies:
- Assess current activity level using the 2-question Physical Activity Vital Sign
- Recommend exercise with optimism
- Counsel and prescribe a specific exercise plan including frequency, intensity, time, and type

> **In women with comorbidities, recommending physical activity requires consideration of the patient's functional capacity and general mobility**

- Refer the patient to a clinical or community-based exercise professional.

Counseling provided in partnership between primary care providers and exercise professionals results in better long-term adherence and reduces time demands on practitioners. Referral to an exercise professional is an evidence-based strategy supported by the US Department of Health and Human Services. Local exercise professionals can be found using the searchable online directories from the US Registry for Exercise Professionals (http://www.usreps.org) and the International Federation of Registers for Exercise Professionals (https://icreps.org).

LIMITATIONS OF CURRENT LITERATURE ON PHYSICAL ACTIVITY

The literature on physical activity in older women has several limitations. Large, long-term, randomized controlled trials of exercise interventions are challenging to perform. Thus, most data on exercise in primary prevention are from population-based, observational studies, which have inherent limitations. Systematic reviews and meta-analyses include studies with considerable heterogeneity, as participants are often men and women, and subgroup analyses of women participants are uncommon. Intervention lengths vary and rarely exceed 12 months. Interventions often include multiple exercise types, intensities, frequencies, and durations that are combined into broad categories such as low, moderate, and high activity levels, based on energy expenditure.

Heterogeneity in control group definition, commonly either inactive or participating in low-level physical activity, is another limitation. When low-level activity is used as the control, the observed benefits may be attenuated, as even low levels of activity have health benefits compared with inactivity.

Studies include women in a wide range of ages, from the 60s to the 90s. Outcomes may vary based on the participant's decade of life, and sample sizes are often too small to allow subgroup analyses of relatively young and very old participants. Lack of diversity of study participants in terms of race, ethnicity, socioeconomic status, and geographic setting limits the generalizability of the results of physical activity studies to all women.

In addition, translation of findings from the literature to clinical practice has limitations. For some women, social and environmental obstacles to regular activity exist, including characteristics of the environment, neighborhood safety, and caregiver responsibilities. For example, the benefits of hospital-based pulmonary rehabilitation for COPD or aquatic exercise for osteoarthritis can only be realized if the patient has access to a hospital or swimming pool. Similarly, the benefits of walking can only be achieved if the environment is convenient and safe for walking. And leisure-time activity can only be pursued if adequate social support exists to allow time away from family and work responsibilities.

All of these limitations should be considered when counseling patients.

FINDING THE RIGHT STRATEGY

As the population of women over age 60 grows, it is important to identify strategies to maximize health and minimize disease burden. Physical activity benefits the most common disease states in women. Knowing the type, intensity, and level of activity needed to achieve desired health outcomes can help the clinician make specific, individualized recommendations for exercise in the context of multimorbidity, functional abilities, and available resources. Routine counseling on exercise in partnership with an exercise professional may improve the patient's level of physical activity and is strongly recommended. ■

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Most data on exercise in primary prevention are from population-based, observational studies, which have inherent limitations

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MOC/CC PART II ACCREDITATION:

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to:

- **American Board of Anesthesiology (ABA) MOC:** 1.0 Lifelong Learning MOC points in the ABA MOCA 2.0® Maintenance of Certification in Anesthesiology Program®.
- **American Board of Internal Medicine (ABIM) MOC:** 1.0 Medical Knowledge MOC points in the ABIM MOC Assessment Recognition Program.
- **American Board of Pathology (ABPath) CC:** 1.0 Lifelong Learning credits in the ABPath Continuing Certification Program.
- **American Board of Pediatrics (ABP) MOC:** 1.0 Lifelong Learning & Self-Assessment MOC points in the ABP Maintenance of Certification Program.
- **American Board of Surgery (ABS) CC:** 1.0 Accredited CME & Self-Assessment credits toward ABS Continuous Certification Program.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity.

It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABA, ABIM, ABPath and ABP credit. Credit will be reported within 30 days of claiming credit.

ABS: It is the participant's responsibility to self-report their participation per current board policy.

Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps.