Efficacy and Safety of Naproxen for Acute Pain

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ABSTRACT

Acute pain often is treated with over-the-counter (OTC) therapeutics, including non-steroidal anti-inflammatory drugs (NSAIDs). However, not all NSAIDs are equally effective for treating different types of acute pain. In this article, we review the data supporting the use of OTC naproxen to effectively treat a variety of types of acute pain, including dysmenorrhea, headache, and dental pain, as well as review adverse effects. This information can be used to provide appropriate treatment for patients experiencing acute pain and help prevent progression to chronic pain.

ACUTE PAIN

Acute pain refers to pain that has been present for less than 3 to 6 months. Acute pain is a non-chronic symptom associated with surgery, trauma, or acute illness that ends when the underlying condition resolves.[1] Acute pain often can be managed with OTC pain medications. A US health statistics survey of adults reported that a substantial percentage of the adult population experiences conditions associated with acute pain. During a 3-month period, 29% of survey respondents reported that they experienced low back pain, 17% experienced a migraine or severe headache, 15% experienced neck pain, and 5% experienced facial or jaw pain.[2] NSAIDs are very effective for low back pain, migraine, neck pain, and facial or jaw pain.[3] Several other types of acute pain and discomfort, including dysmenorrhea, common cold symptoms, and acute musculoskeletal conditions, also can be managed with NSAIDs.[4,5] For these acute pain conditions, OTC NSAIDs generally are preferred over opioids, which have a significant risk of dependency or addiction, dose-dependent constipation, and respiratory depression.

Prompt non-prescription management of acute pain has been shown to prevent development of chronic pain.[6-10] Acute pain that transitions to chronic pain can lead to unhealthy behaviors, including alcohol and drug abuse, overeating, and opioid use or abuse.[11-13] Similarly, inadequate management of post-operative pain is associated with higher rates of morbidity and mortality and is a risk factor for transitioning to chronic pain.[6-8,14]

Acute Pain Progressing to Chronic Pain

Acute pain that has transitioned to chronic pain can impact mortality and creates a social and economic burden.[15] The etiology of the transition has been hypothesized to be related to the direct injury of cutaneous nerves. Peripheral nerve injury can be accompanied by structural changes, such as alterations in the electrochemical gradient and action potential, and physiological adaptations to these changes such as new expression of sodium channels, which creates a hypersensitized state. Tissue damage, especially from surgery, triggers a cascade of physiologic adaptions in response to the increased risk of infection: inflammation, immune activation, and chemokines to promote healing and protect the area from further injury.[16] Because stimulus from these hypersensitized nociceptors is constantly being transmitted to central nerves, it is thought that this primary hyperalgesia results in secondary hypersensitization when the peripheral pain is persistent.[17] The hypothesis that the central nervous system plays an important role in chronic pain is supported by experimental studies. A study of rats found that acute pain after spinal nerve ligation did not progress to chronic pain when specific central nerves were blocked.[16] In humans, this concept has led to the practice of preventative analgesia, where preoperative analgesia is used to avoid the transition from acute to chronic pain. A randomized controlled trial demonstrated

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that, although analgesia given before thoracic surgery did not result in a significant difference in acute pain over the 7-day post-surgical period compared with post-surgical analgesia, the technique did result in a significant reduction in pain after 3 (P =.035) and 6 (P =.0086) months.[19] A similar finding was observed in a study that showed intraoperative analgesia in colon resection did not result in significantly improved pain at the 2-week follow-up compared with post-operative analgesia, but a significant improvement was found 1 year after treatment.[20] Although the current evidence is not conclusive of the proposed mechanism, it provides some basis to support effective management of acute pain.

NAPROXEN

History

Following the US introduction of ibuprofen as an alternative to steroids for treating rheumatoid arthritis,[21] naproxen (free acid) was introduced a year later with additional data supporting its use for managing ankylosing spondylitis and acute gout.[22] Later data supported the drug for managing primary dysmenorrhea, bursitis, osteoarthritis, generalized pain, and more.[23]

Further advances led to development of a new formulation of naproxen. Naproxen is a weak acid (pKa=4.15) with pharmacokinetics that limit the rate of absorption in the highly acidic environment of the gastrointestinal (GI) tract; adding an alkali salt improves absorption. Naproxen sodium formulation has been shown to reach peak therapeutic index more rapidly than naproxen (P<.01), had a significantly higher concentration in the first 2 hours (P<.01),[24] and was FDA-approved in 1981.[25]

Naproxen sodium remained a prescription-only drug in the United States until the FDA approved an OTC dose and duration in 1994, supported by safety and efficacy evidence for self-management.

Efficacy

Indications

Naproxen free acid and naproxen sodium are FDA-approved at prescription doses for treating rheumatoid arthritis, osteoarthritis, ankylosing spondylitis (500 to 550 mg/d, up to 1500 mg/d), polyarticular juvenile idiopathic arthritis (10 mg/kg in 2 divided doses), bursitis, tendonitis, pain, primary dysmenorrhea (starting dose of 550 mg then 550 mg every 12 hours or 275 mg every 6 to 8 hours as required; the initial daily dose should not exceed 1375 mg; thereafter, the daily dose should not exceed 1100 mg), and acute gout (starting dose 750/825 mg then 250/275 mg every 8 hours until the attack has subsided). As an OTC product available in the United States, naproxen sodium is available at single doses of 220 to 440 mg (loading dose) with a maximum daily dose of 660 mg and a dosing frequency of 8 to 12 hours.[26] OTC dosing regimens and maximum daily doses vary in countries outside the United States.[27] Naproxen sodium is indicated for minor aches and pains due to arthritis, muscular aches, backache, menstrual cramps, headache, toothache, and the common cold, as well as the temporary reduction of fever.[23] Naproxen sodium provides a faster onset of action compared with the base naproxen (free acid) form, making it more suitable for treating acute pain. Clinical practice guidelines recommend naproxen as first-line treatment for a number of acute pain conditions, including dysmenorrhea and headache (**TABLE**).[28-39]

DYSMENORRHEA

Primary dysmenorrhea refers to painful menstrual cramps without underlying pathology. Nonprescription doses of naproxen have been evaluated for the treatment of this condition, which is estimated to affect more than 50% of women.[40] NSAIDs, including naproxen, dosed before and during menses, are recommended by clinical guidelines as a first-line treatment for primary dysmenorrhea.[41] A Cochrane review found that naproxen, 250 mg to 275 mg (sometimes with a loading dose of 500 mg to 550 mg), was more effective for relieving pain associated with dysmenorrhea compared with placebo and was associated with a small increase in adverse effects.[42] A recent crossover trial compared single doses of naproxen sodium, 440 mg, and acetaminophen, 1000 mg, for treating pain associated with primary dysmenorrhea (N = 189; per-protocol assessment). Participants were randomized to either therapy—1 dose for 12 hours, then switched to the other therapy—and were evaluted for total pain relief and pain intensity differences over a 12-hour period. Individuals taking the naproxen sodium regimen reported better total pain relief during therapy (difference of least squares means: 4.31; 95% confidence interval [CI]: 2.06 to 6.56; P <.001) and summed pain intensity difference during 6 to 12 hours (difference of least squares means: 8.27, 95% CI: 5.76 to 10.78, P <.001).[43]

POST-DENTAL SURGERY PAIN

Dental pain (toothache) is a manifestation of a number of acute facial conditions including dental caries, soft tissue disease, and post-surgical pain.[44] The American Dental Association recommends NSAIDs as first-line therapy for acute dental pain.[45] Post-surgical pain is a frequently used model for measuring analgesic efficacy for toothache because of the high predictability for symptom onset.

A systematic review of the literature found that NSAIDs were significantly more effective than placebo for relieving pain after endodontic treatment. This review included

an indirect comparison of ibuprofen and naproxen, which found that naproxen was more effective for relieving pain than ibuprofen, although the data did not reach significance (*P*=.052). The authors concluded that there is insufficient evidence to recommend a specific NSAID regimen, but stated that naproxen might be more effective than ibuprofen for acute endodontic pain.[46] Naproxen demonstrated efficacy for treating dental pain after third molar extraction evaluated in previous previously published studies.[47,48]

A 2019 randomized trial compared maximum single OTC doses of 440 mg naproxen sodium, 400 mg ibuprofen, and placebo for total and summed pain intensity difference over a 24-hour period (N = 385; per-protocol assessment). Total pain relief over 24 hours and pain intensity differences over 12 hours were significantly better with naproxen compared with ibuprofen or placebo (*P* <.05 for all comparisons). The time to rescue medication was significantly improved (*P*<.001) with naproxen compared with ibuprofen and placebo, and the number of individuals in the naproxen group requiring rescue medication (34.9%) was significantly lower than the ibuprofen (83.0%) and placebo groups (81.5%). Additionally, significant differences in pain intensity favoring naproxen manifested between 4 and 6 hours, which is earlier than the recommended re-dosing time for acetaminophen, underscoring the benefit of naproxen's longer duration of action.[49]

MUSCLE ACHES

Myalgia is pain originating from the muscles. Lower back pain is a common manifestation of myalgia and acute exacerbations can be managed with NSAIDs. Short-term treatment with naproxen and other NSAIDs is supported by several guideline recommendations. The American Academy of Family Physicians guidelines conclude that naproxen and other NSAIDs are more effective than placebo in the short-term treatment of non-specific chronic low back pain (evidence rating A2). These guidelines do not distinguish between NSAIDs, but do not recommend acetaminophen.[28] The American College of Physicians and the Pain Society Joint Clinical Practice Guidelines strongly recommend either an NSAID or acetaminophen as first-line treatment options for acute, subacute, or chronic treatment if baseline severity and risks are properly assessed.[29]

HEADACHE

NSAIDs are recommended for treating acute headaches and exacerbations of migraines. The American Headache Society and American Academy of Neurology concluded in their clinical practice guidelines that naproxen has established efficacy for acute migraine treatment.[50] These guidelines recommend naproxen as a nonprescription oral analgesic for acute migraine treatment in adults and children.

Naproxen is recommended as an adjunct to the serotonin agonist sumatriptan for acute relief when a migraine is unresponsive or only partially responsive to a triptan alone. The authors concluded with a high level of confidence that the combination of sumatriptan and naproxen effectively relieves pain 2 hours after treatment. At doses ranging from 60 to 500 mg, naproxen in combination with sumatriptan 10 to 85 mg was significantly better than placebo with an efficacy ratio ranging from 2.17 to 2.95 and statistically significant at all dosages. Additionally, the combination of naproxen and sumatriptan effectively relieved migraine symptoms of photophobia and phonophobia at 2 hours.[50]

Naproxen, 250 mg twice daily for 6 weeks, was tested for efficacy in individuals experiencing migraine headaches. The 28 participants taking naproxen experienced a reduced number of migraine attacks (1.0 ± 0.17 per week for naproxen compared with 1.3 ± 0.18 placebo, *P*<.03). Migraine index (frequency times severity) also was significantly reduced with naproxen (3.0 ± 0.51 for naproxen compared with 4.1 ± 0.50 placebo, *P*<0.01).[51]

Data on the efficacy of naproxen for headache are further supported at prescription dosages. A comprehensive literature review of placebo-controlled trials of naproxen aimed to evaluate the efficacy of different dosages of naproxen for treating acute headache of moderate to severe intensity. The pooled analysis only involved prescription dosages (500 and 825 mg) but found naproxen was significantly more effective than placebo in relieving headache (relative risk [RR]: 1.58; 95% CI: 1.41 to 1.77; *P*<.00001) and achieving complete pain relief at 2 hours (RR: 2.22; 95% CI: 1.46 to 3.36; *P*=.0002). Additionally, naproxen showed increased sustained relief of headache, nausea, and photophobia over a 24-hour period.[52]

THE COMMON COLD

Prostaglandins may be among the inflammatory mediators that play a role in the pathogenesis of symptoms of rhinovirus colds. Similar to all NSAIDs, naproxen inhibits cyclooxygenase (COX) resulting in decreased prostaglandin synthesis. Naproxen does not alter virus shedding or serum neutralizing antibody responses in rhinovirus colds but relieves symptoms of headache, malaise, myalgia, and cough.[53] A systematic review evaluated controlled trials of the efficacy of NSAIDs in relieving pain associated with the cold. Although neither duration nor respiratory symptoms were improved, outcomes relating to pain and sneezing were significantly reduced with NSAID treatment. For naproxen, daily sneezing scores were significantly reduced during days 1 and 4 of therapy. The score of headache associated with cold was sig-

TABLE. **Summary of Clinical Practice Guidelines and Recommendations of Naproxen**

Guideline Name	Recommendation
General Pain Management	
HHS Pain Management-Best Practices 2019[30]	For non-neuropathic, non-cancer pain, use NSAIDs and acetaminophen as first-line medications.
Arthritis	
ACR 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in OA of the Hand, Hip, and Knee[31]	Oral NSAIDs are recommended (based on patient preference) as first-line pharmacologic management of knee, hand, and hip OA.
AAFP 2012: Osteoarthritis: Diagnosis and Treatment[32]	NSAIDs are superior to acetaminophen for treating moderate-to-severe OA. (Evidence rating A)
AAOS 2013 Evidence-Based Guideline for Treatment of OA of the Knee (2nd Edition)[33]	Oral or topical NSAIDs should be used with symptomatic knee OA (Recommendation strength: strong).
OARSI 2014 Guidelines for the Non-Surgical Management of Knee Osteoarthritis[34]	Oral non-selective NSAIDs are recommended as a first-line pharmacologic therapy for knee only OA or for multi-joint OA in individuals without comorbidities. (Quality of evidence: good)
Low Back Pain	
AAFP 2018 Recommendations for Mechanical Low Back Pain[28]	Use short-term NSAIDs in non-specific chronic low back pain. (Evidence rating: A) No difference among types of NSAIDs.
American College of Physicians and American Pain Society Joint 2001 Guidelines for Low Back Pain[29]	NSAIDs are recommended as first-line therapy for acute, sub-acute, or chronic treatment for most low back pain.
Migraine	
American Headache Society 2019 Consensus Statement[35]	For acute treatment of migraines, use NSAIDs, or non-opioid analgesics for mild-to-moderate attacks. (Established efficacy)
AAFP 2019 Acute Migraine Headache: Treatment Strategies[36]	NSAIDs are first-line treatment for mild-to-moderate migraine. (Evidence rating A) Strong evidence supports the use of oral acetaminophen, aspirin, diclofenac, ibuprofen, or naproxen for mild-to-moderate migraine attacks.
Dysmenorrhea	
AAFP Guidelines 2014: Diagnosis and Initial Management of Dysmenorrhea[37]	NSAIDs should be used as first-line treatment for primary dysmenorrhea. (Evidence rating A)
ACOG 2018 Opinion on Dysmenorrhea and Endometriosis in the Adolescent[38]	Most adolescents with dysmenorrhea will respond to empiric treatment with NSAIDs, hormonal suppression, or both. NSAIDs are a first-line treatment option.
Dental Pain	
ADA 2019 Oral Health Topics: Oral Analgesics for Acute Dental Pain[39]	NSAIDs are more effective than opioid analgesics; recommended as first-line therapy for acute pain management.

Abbreviations: AAFP, American Academy of Family Physicians; AAOS, American Academy of Orthopedic Surgeons; ACOG, American College of Obstetricians and Gynecologists; ACR, American College of Rheumatology; ADA, American Dental Association; HHS, Department of Health and Human Services; NSAIDs, Nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

nificantly lower in the NSAID groups compared with the placebo groups (mean difference: –0.65; 95% CI: –1.11 to –0.19). Myalgia score also was significantly reduced with naproxen use and NSAIDs overall significantly reduced pain in both myalgia and joint pain (mean difference: –0.40; 95% CI: –0.77 to –0.03).[54]

SAFETY

General

Naproxen generally is well tolerated and safe at OTC dosages and durations indicated for use without physician monitoring. However, the mechanism of action of NSAIDs has a known link to GI, cardiac, and renal adverse effects.

Naproxen, similar to other NSAIDs, is a non-specific inhibitor of COX, an enzyme that is a required catalyst for the conversion of arachidonic acid from plasma membranes into prostaglandins, a family of hormone-like molecules that mediate inflammatory responses.[55] There are 2 COX isoforms, COX-1 and COX-2, that exist as homodimers. COX-1 inhibition could reduce prostaglandin synthesis, but also has the effect of promoting gastric protection. Inhibition of COX-1 can lead to GI issues such as bleeding or ulcers. COX-2 inhibition also reduces prostaglandin synthesis but prevents the kidney from performing homeostatic functions related to water retention, leading to blood pressure and kidney injury concerns. Traditional NSAIDs are nonspecific and do not

highly favor one isoform over the other. This could lead to GI, cardiac, or renal adverse effects, although with a lesser incidence or severity compared with an inhibitor of a specific COX isoform.[56]

In 2004 the FDA raised concerns about potential cardiovascular adverse effects with NSAIDs after the selective COX-2 inhibitor rofecoxib was withdrawn from the market. COX-2 specific inhibitors had demonstrated a significant elevation in cardiovascular risk, and there was concern that this risk would be present with NSAID use. Advisory committees convened in 2005 and 2014 noted that there is a lower cardiovascular risk profile for naproxen compared with ibuprofen, a risk that is further lowered at low dosages or shorter durations of use. However, the committee concluded that NSAIDs as a class are associated with an elevated cardiovascular risk, and the FDA required a label warning for all NSAIDs and did not make an exception for naproxen.[57]

Recently, joint recommendations from the Asian Pacific Association of Gastroenterology, Asia Pacific League of Associations for Rheumatology, Asia-Pacific Society for Digestive Endoscopy, Asia Pacific Society of Hypertension, Asian Pacific Society of Nephrology, and Pulse of Asia on the use of NSAIDs in patients with hypertension, cardiovascular, renal, or GI comorbidities includes naproxen as one of the preferred drugs for patients with high cardiovascular risk if NSAID treatment cannot be avoided.[58]

Cardiac and Renal

COX-2 inhibition can lead to cardiac and renal adverse effects with elevated concern for patients with underlying cardiovascular (CV) or renal disease. Because of the wide overlapping prevalence of OTC NSAID use and cardiovascular/renal disease, many large cohort studies have been conducted to understand if there is an association between NSAID use and cardiovascular or renal events. A 2018 review article by White et al[56] summarized these studies. In general, increased dosage and duration of NSAID therapy was associated with an increased risk of cardiovascular and renal events across observational studies. Many trials noted that, although prescription doses generally were safe in the absence of underlying cardiac and renal conditions, cardiovascular events were significantly reduced with OTC dosages and durations compared with prescription regimens. For example, an observational study with more than a million patients found that prescription dosages of ibuprofen were associated with an increased risk of major CV events (RR: 1.78; 95% CI: 1.35 to 2.34), while OTC use was not (RR: 1.05; 95% CI: 0.96 to 1.15). Although prescription naproxen use was not associated with an increased risk of major CV events (RR: 1.05; 95% CI: 0.89 to 1.24), the risk was numerically lower with non-prescription dosages (RR: 0.97; 95% CI: 0.87 to 1.08).[46] Although these studies provide substantial evidence to suggest the cardiac and renal safety of OTC naproxen, they are susceptible to confounding factors inherent to all observational trials. Recently, the PRECISION randomized controlled trial concluded that prescription doses of naproxen were not associated with a significantly increased risk of major adverse cardiac events compared with celecoxib (Hazard ratio [HR]: 0.97; 95% CI: 0.83 to 1.12, *P*=.64). However, prescription dosages of ibuprofen were associated with a significantly increased risk of major cardiac events compared with naproxen (HR: 1.39; 95% CI: 1.01 to 1.91; *P*=.04).[59]

GASTROINTESTINAL

COX-1 inhibition can lead to GI adverse effects. In a large meta-analysis (N=48,706) prescription naproxen 500 mg twice daily was associated with a significantly increased risk of upper GI events compared with placebo (RR: 4.22, 95% CI: 2.71 to 6.56).[60] OTC naproxen also is associated with elevations in mild GI adverse effects (constipation, diarrhea, dyspepsia, and nausea) but, in contrast with prescription dosages, the elevation is not significantly or clinically different. In a pooled analysis of naproxen studies with OTC dosages (N=7282), GI adverse events were elevated with naproxen (11.6%) vs placebo (9.5%), but the difference was not significant.[61] Also, ibuprofen and acetaminophen at non-prescription dosages in multiple-dose, multi-day (7 to 10 days) duration clinical trials did not show increased risk of adverse events compared with placebo or other OTC analgesics.[62] Similar to cardiovascular risk, evidence suggests that the risk of GI complications is minimized when naproxen is used at OTC dosages and durations.

CONCLUSIONS

Naproxen is an effective medication recommended for first-line use in many types of pain, particularly dysmenorrhea, headache, toothache, and acute musculoskeletal conditions such as back and neck pain. Efficacy is supported by randomized controlled trials, and secondary measures such as use of rescue opioids or the time to complete resolution of pain were significantly improved. Many clinical guidelines recommend naproxen use to achieve a clinical benefit and prevent development of chronic pain. Safety concerns include GI, renal, or cardiovascular risk primarily at prescription dosages and durations. At OTC dosages, the risk may be elevated, but does not reach statistical significance in many large cohort studies, even in participants with elevated baseline risk. Patients should consult their physicians regarding the use of naproxen for self-medicating their acute pain or discomfort.

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Managing the Burden of Dementia-Related Delusions and Hallucinations

Gary W Small, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Identify the burden experienced by patients with dementia-related delusions and hallucinations.
- Assess patients with dementia for the presence of delusions and hallucinations.
- Individualize treatment in patients with dementia-related delusions and hallucinations.
- Align treatment of patients with Parkinson's psychosis with current recommendations.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of dementia-related delusions and hallucinations.

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INTRODUCTION

Dementia is defined as a clinical syndrome that involves a cognitive impairment severe enough to impair the patient's ability to function independently.[1] Many different conditions can cause dementia, which is often characterized by a decline in memory, language, problem-solving, or other thinking skills. The most common form of dementia, occurring in up to 70% of the estimated 8 million people living with dementia in the United States, is Alzheimer's disease (AD).[2] Other subtypes include vascular dementia (20%), dementia with Lewy bodies (5%), Parkinson's disease (PD) dementia (4%), and frontotemporal dementia (1%).[2-4] Many patients with dementia have several different causes, eg, combined vascular dementia and AD.[5] Although dementia may occur in younger adults, the prevalence of dementia increases with age, affecting 2% of those age 65 to 69 years and 33% pf those age ≥90 years.[6] Due to the aging US population, the prevalence of dementia is expected to grow, with some estimates indicating a tripling of AD dementia prevalence by 2050.[7]

Neuropsychiatric symptoms are commonly experienced by people with dementia.[8] Symptoms that typically occur earlier in the course of dementia, often before diagnosis, include social withdrawal, suicidal ideation, depression, paranoia, anxiety, diurnal rhythm disturbances, and/or mood changes.[9] Symptoms that generally first appear shortly after diagnosis include irritability, delusions and hallucinations, agitation and aggression, wandering, and/or sexually inappropriate behavior.[9]

Delusions and hallucinations are among the signs and symptoms associated with a loss of contact with reality, or psychosis. A delusion is a false, fixed belief despite evidence to the contrary, whereas a hallucination is a perception-like experience that occurs without an external stimulus and is sensory in nature.[10] An estimated 2.4 million people in the United States have dementia-related delusions and hallucinations.[11,12] The prevalence of delusions and hallucinations vary based on the type of dementia. They are most common in patients with dementia with Lewy bodies or PD, occurring in 75% and 50%, respectively, and least common in patients with AD or vascular dementia (<30%).[11,12] Older adults with dementia may experience delusions and/or hallucinations 2 to 6 times per week.[13] Delusions persist longer than 3 months in 82% of patients with dementia and hallucinations in 52%.[14,15]

BURDEN OF DEMENTIA-RELATED DELUSIONS AND HALLUCINATIONS

Patient burden

Dementia-related delusions and hallucinations contribute to a wide variety of behavioral and psychological symptoms. These symptoms include insomnia, confusion, agitation, personality change, self-care problems, and cognitive and functional impairment.[16] Dementia-related delusions are associated with a 2- to nearly 3-fold increased risk of aggression, and dementia-related hallucinations with up to a 1.4-fold increased risk of aggression.[17,18] A prospective analysis of patients with early-stage AD (N=456) at baseline followed for 14 years showed that delusions were associated with an increased risk of cognitive (relative risk [RR] 1.50; 95% confidence interval [CI], 1.07-2.08) and functional (RR 1.41; 95% CI, 1.02-1.94) decline.[19] The effect of AD-related hallucinations is even greater, as the analysis showed greater risk of cognitive (RR 2.25; 95% CI, 1.54-2.27) and functional (RR 2.25; 95% CI, 1.13-2.28) decline. Moreover, patients who experienced hallucinations were at increased risk for institutionalization (RR 1.60; 95% CI, 1.13-2.28) and death (RR 1.49; 95% CI, 1.03-2.14).

By contrast, a case-control study that examined the association between the Neuropsychiatric Inventory (NPI) score in older adults with AD (N=641) showed no increased risk of nursing home placement in persons with dementia-related hallucinations.[20] However, persons with AD and agitation/aggression, disinhibition, irritability, delusions, sleep disorder, or appetite disorder were significantly more likely to be placed in a nursing home. Overall, a 10% increase in the total NPI score was associated with a 30% increased odds of nursing home placement.

A population-based study of older adults with possible or probable AD dementia indicated that those with dementia-related psychosis were twice as likely to progress to severe dementia and 1.5 times more likely to die during the 3 to 5 years of follow-up.[21] The presence of psychosis appears to portend a more severe disease course, particularly for patients with both delusions and hallucinations compared with patients with only delusions or hallucinations.[22]

The occurrence of delusions also appears to be associated with a severe disease course compared to people with dementia who do not experience delusions. A 2-year longitudinal analysis of older adults with AD showed that a delusion of theft was related to the degree of cognitive dysfunction and functional impairment, while a delusion of abandonment was related to the severity of cognitive impairment.[23] By contrast, hallucinations were not associated with the degree of cognitive or functional impairment.

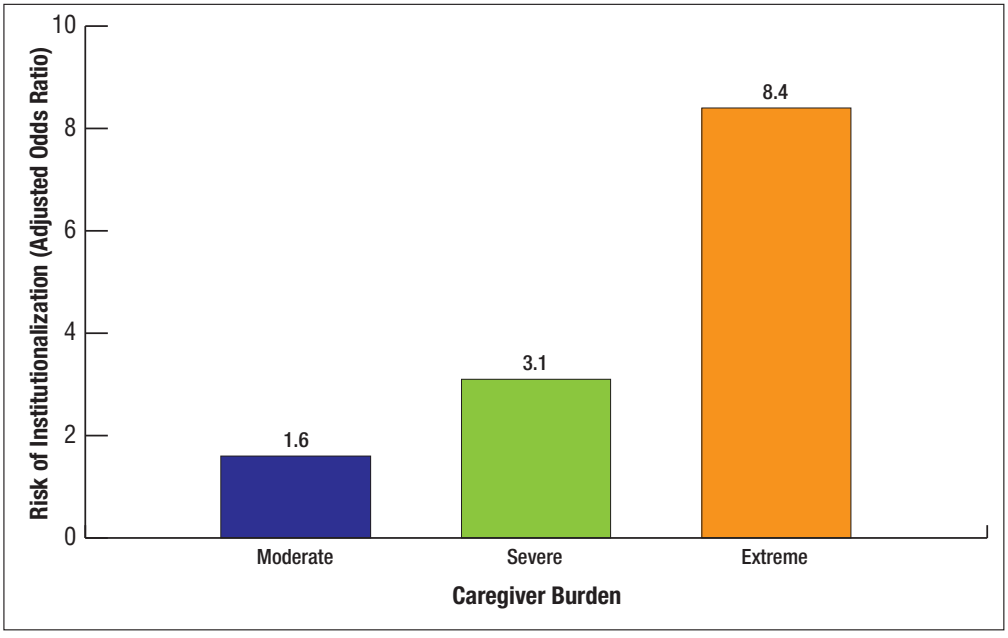
> For patients with dementia, the occurrence of delusions appears to be associated with a severe disease course compared to people with dementia who do not experience delusions.

Caregiver burden

The burden of psychosis-related dementia extends beyond patients to their caregivers.[24] Because two-thirds (64%) of older adults with dementia require assistance with ≥2 self-care or mobility activities and 70% of older adults with dementia receive help from family caregivers, the patient's family is particularly affected.[6] Delusions, irritability, and agitation/aggression in people with dementia are among the most distressing neuropsychiatric symptoms for family caregivers.[25] Common delusions that target the caregiver relate to accusations of theft, abandonment, and spousal infidelity.[13,26] The stress experienced by caregivers – family as well as professional – can even impair their memory abilities.[27] Behavioral problems in older adults with dementia often lead to caregiver depression and a greater sense of burden.[28]

Heightened caregiver burden is a major reason for earlier institutionalization of the individual with dementia.[26,29]

FIGURE 1. **Association of caregiver burden with risk of institutionalization of patients with dementia[26]**



One investigation showed that, over a 5-year period, patients with dementia were more likely to be institutionalized when their caregivers reported moderate, severe, or extreme burden by a factor of 1.6, 3.1, and 8.4, respectively (**FIGURE 1**).[26] Professional caregivers in long-term care facilities also report high levels of emotional exhaustion and burnout, particularly when caring for residents with agitated behavior.[29]

DIAGNOSTIC CRITERIA OF DEMENTIA-RELATED PSYCHOSIS

Diagnostic criteria for psychosis have been proposed for patients with dementia due to AD and related dementias.[30] Key criteria include requiring that patients must have had visual or auditory hallucinations and/or delusions for a month or more, but those symptoms of psychosis must not have been present continuously prior to the onset of dementia symptoms. The onset of the hallucinations and/or delusions is generally insidious rather than acute as might be observed with delirium secondary to underlying dehydration, urinary tract infection, or acute pain syndrome.[31] The hallucinations and/or delusions must be severe enough to cause some disruption in functioning of the patient and/or others.[30] Psychotic symptoms often occur with associated features, such as agitation, apathy, or depression.[30]

As implied by these proposed criteria, a key initial objective in assessing the patient with dementia who exhibits psychotic symptoms is to identify any underlying medical condition or risk factor for psychosis, such as chronic bed rest, sensory impairment, or social isolation.[31] Psychosis that occurs for the first time in late life is likely due to dementia or some neurologic condition such as PD or stroke. Psychosis that occurs earlier in life is more likely due to schizophrenia, mood disorder, or some other primary cause.[31] For confirmation that dementia is the cause of the psychosis, it is also necessary to determine that the psychotic symptom does not occur exclusively during the course of a delirium.[30] Consideration also should be given to a substance of abuse as a reason for the symptoms, or an iatrogenic cause such as medications. For example, dopaminergic and anticholinergic medications are common causes of psychosis in patients with PD.[32]

TREATMENT OF DEMENTIA-RELATED PSYCHOSIS

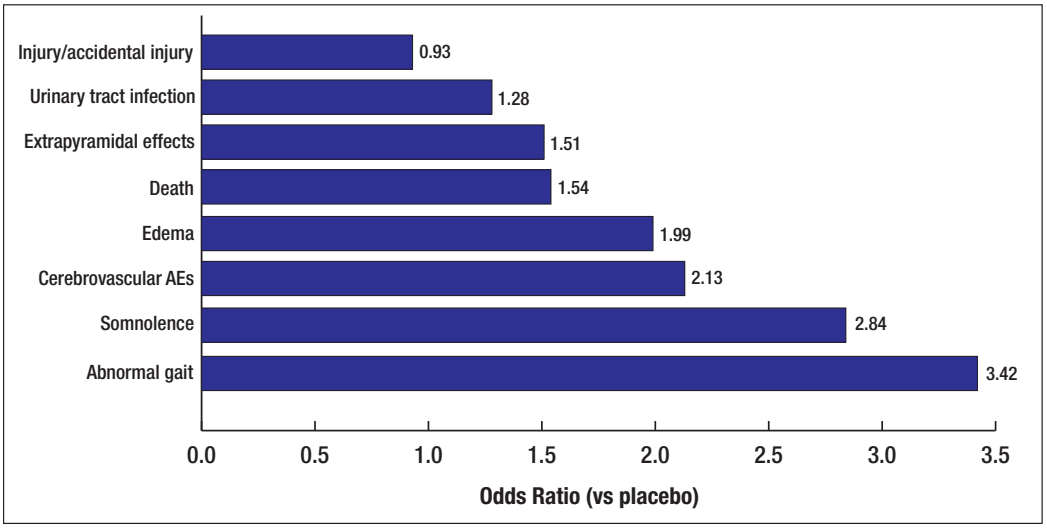
The treatment of psychosis in patients with dementia is multifaceted and is guided by the findings from the diagnostic evaluation. In addition to treating the symptoms of dementia, symptoms caused by underlying medical conditions, medications, or environmental and psychosocial triggers are important targets.

Nonpharmacological treatment

The Alzheimer's Association and the American Psychiatric Association recommend nonpharmacological approaches as first-line therapy for nonemergency dementia-related psychosis.[33,34] The use of nonpharmacological approaches is reasonable as an initial intervention unless the patient's psychotic symptoms pose a high safety risk to themselves or others, in which case hospitalization is appropriate. Nonpharmacological approaches typically focus on the caregiver strategies and the environment in which care is provided, because patient and caregiver burden is so strongly linked to the likelihood of patient institutionalization.[34] Consequently, caregiver distress is important to identify and address.

Caregivers should be educated to provide a variety of psychosocial interventions that might be helpful to the patient. These interventions include[33,34]:

FIGURE 2. **Adverse events associated with atypical antipsychotics in patients with dementia**[39]



Abbreviations: AE, adverse event.
Note: The odds ratio for all events (except injury/accidental injury) is statistically significant compared to placebo.

- Providing routine activities, including exercise
- Providing cues to heighten orientation
- Maintaining a calm environment by reducing environmental clutter and ambient noise, optimizing lighting and walkways, and playing music
- Separating the patient from environmental triggers of symptoms, eg, background noises
- Avoiding responses that contradict the patient's perception of reality and respecting their ideas about and explanation for their perceptions, even if incorrect
- Speaking slowly and calmly in a normal tone of voice
- Redirecting the person to participate in an enjoyable activity or offering comfort food or comforting comments

Caregiver resources are available through the Alzheimer's Association (www.alz.org) and Parkinson's Foundation (https://www.parkinson.org/Living-with-Parkinsons/For-Caregivers).

Pharmacological treatment

Antipsychotics

Antipsychotic therapy plays a central role in the treatment of psychosis, but the US Food and Drug Administration (FDA) has not approved a pharmacological treatment for dementia-related psychosis. Nonetheless, off-label use of atypical, or second-generation, antipsychotics has been the mainstay of pharmacological treatment for psychotic symptoms and agitation in patients with dementia. Antipsychotics are most effective for improving positive psychotic symptoms, eg, delusions and hallucinations, with less benefit for negative symptoms, eg, flat affect.

The use of antipsychotics for dementia-related psychotic symptoms is not without risk. A 2005 FDA analysis concluded that the use of atypical antipsychotics is associated with increased mortality in older adults with dementia.[35] Subsequent investigations confirmed these findings and extended the increased mortality risk to include conventional, ie, first-generation, antipsychotics.[36-38] Moreover, in patients with dementia, atypical antipsychotics have been shown to be associated with cognitive decline and increased risk of metabolic events such as glycemic abnormalities and elevated lipids, as well as an increased risk of adverse events, including abnormal gait, somnolence, edema, extrapyramidal symptoms, and urinary tract infections (**FIGURE 2**).[38-40]

Consequently, most antipsychotics are not approved for the treatment of psychotic symptoms in patients with dementia. In addition, all antipsychotics carry a black box warning indicating that elderly adults with dementia-related psychosis treated with antipsychotic medications are at an increased risk of death.

The FDA analysis and subsequent investigations led the American Geriatrics Society to recommend against the use of conventional and atypical antipsychotics in older adults, particularly those with dementia, as described in their updated "2019 Beers criteria for potentially inappropriate medication use in older adults."[41] In fact, the Beers criteria recommend avoiding the use of all antipsychotics (except quetiapine, clozapine, and pimavanserin) in older adults with PD, as their use may worsen parkinsonian symptoms.

Nonemergency use of antipsychotics may, however, be considered for patients with behavioral problems of dementia or delirium, if such patients have not achieved an adequate response to nonpharmacological therapy and pose a risk to themselves or others, or when the symptoms are of significant distress to the patient.[34,41] A decision to use antipsychotics in such situations should be based on a discussion of the potential risks and benefits from antipsychotic

medication with the patient, family, or others involved with the patient. Antipsychotic treatment should be initiated at a low dose and titrated to the minimum effective dose as tolerated.[34]

Pimavanserin

While no medications have been approved by the FDA for dementia-related psychosis, one atypical antipsychotic, pimavanserin, may be useful in these patients. Pimavanserin has a unique pharmacological profile that acts through a combination of inverse agonist and antagonist activity at serotonin type 2A receptors and, to a lesser degree, serotonin type 2C receptors. This is in contrast to atypical antipsychotics that are thought to exert their effects largely through antagonism of the dopamine type 2 and serotonin type 2A receptors. Pimavanserin is approved for the treatment of hallucinations and delusions associated with PD psychosis.

The approval of pimavanserin was based on a double-blind, placebo-controlled study of 199 patients with PD age ≥40 years. Patients could not have been diagnosed with dementia concurrent with or before PD.[42] After a 2-week lead-in phase to limit the placebo response, patients were randomized to pimavanserin 40 mg/d or placebo. Improvement of the primary outcome, as assessed using the Scale for Assessment of Positive Symptoms adapted for PD (SAPS-PD), was significantly greater with pimavanserin compared with placebo. From a baseline score of 15.9, the SAPS-PD score for patients given pimavanserin decreased to 10.1 after 6 weeks of treatment, while treatment with placebo led to a decrease from a baseline score of 14.7 to 12.0 (P=.001). Significant improvement with pimavanserin was also observed with respect to separate measures of hallucinations and delusions. Treatment-emergent adverse events occurring in ≥5% in either group (pimavanserin vs placebo) included urinary tract infection (13% vs 12%), falls (11% vs 9%), hallucinations (7% vs 4%), peripheral edema (7% vs 3%), nausea (6% vs 6%), confusion (6% vs 3%), and headache (1% vs 5%). There was no evidence of treatment-related impairment of motor function in either group. Ten patients in the pimavanserin group (6 because of psychosis) and 2 patients in the placebo group discontinued because of an adverse event.

The safety and efficacy of pimavanserin also have been investigated in a phase 2 trial involving 181 nursing home patients with possible or probable AD and psychotic symptoms.[43] Following 6 weeks of treatment, significantly greater improvement in the NPI-Nursing Home version was observed in patients treated with pimavanserin vs placebo.[43] No adverse effect on cognition or motor function was observed; more patients treated with pimavanserin experienced agitation.

The phase 2 SERENE (NCT02992132) and phase 3 HARMONY (NCT03325556) trials have evaluated the safety and efficacy of pimavanserin in patients with psychosis and either AD or various common subtypes of dementia, respectively. The extension phase of SERENE was completed in February 2019, but no data have been published. HARMONY was recently stopped early after the planned interim efficacy analysis showed pimavanserin to demonstrate a significantly longer time to relapse of psychosis compared with placebo.

SUMMARY

Neuropsychiatric symptoms such as delusions and hallucinations are commonly experienced by the estimated 8 million persons with dementia in the United States. Dementia-related delusions and hallucinations result in a wide variety of behavioral and psychological symptoms that contribute to substantial patient and caregiver burden and portend a more severe disease course of dementia. The diagnosis of dementia-related psychosis is based on clinical findings, with a key objective to rule out medical and other causes of the psychosis. Nonpharmacological approaches are generally first-line treatment, except when urgent symptom control is needed. None of the antipsychotics currently available are approved for dementia-related psychosis; in fact, antipsychotics are associated with increased mortality in older adults with dementia. Pimavanserin is an atypical antipsychotic with a unique mechanism of action that is approved for the treatment of hallucinations and delusions associated with PD psychosis; some evidence indicates the safety and effectiveness of pimavanserin for patients with dementia-related psychosis. ●

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Overcoming Barriers to the Diagnosis and Treatment of Insomnia

Thomas Roth, PhD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Apply evidence-based diagnostic guidelines for patients who have clinical features consistent with insomnia
- Use evidence-based guidelines to develop comprehensive treatment plans that include cognitive-behavioral therapy, pharmacologic treatment, and combination therapies to achieve optimal outcomes
- Identify basic elements of cognitive-behavioral therapy for insomnia
- Differentiate among medications FDA-approved for treating insomnia by discussing mechanism of action, safety, efficacy, and use

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of insomnia.

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SUPPORTER

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CASE SCENARIO

A 72-year-old woman describes difficulty staying asleep and daytime fatigue for the past 8 months. Initially, she only had difficulty staying asleep 2 to 3 nights per week, but over the past 5 months, these symptoms have increased in severity and frequency. She notes increased irritability and lack of motivation during the day associated with her disturbed sleep.

EPIDEMIOLOGY

Insomnia, defined as difficulty initiating or maintaining sleep with associated daytime consequence, is 1 of 7 sleep-wake disorders according to the International Classification of Sleep Disorders, 3rd edition (ICSD-3).[1] Insomnia is common, particularly among older adults.[2] The estimated prevalence varies based on the criteria, ranging from 22% using DSM-IV-TR, 15% using Research Diagnostic Criteria/ICSD-2, and 4% using ICD-10 criteria.[3]

TABLE 1. **Assessment of sleep history**[16-18]

Sleep Problem	Sleep Times	Consequences of Disturbed Sleep	Symptom Duration
Number of awakenings Duration of awakenings Duration of the sleep problem	Bedtime Duration until sleep onset Final awakening time Nap time(s) Nap length(s)	Fatigue or malaise Poor attention or concentration Social/vocational/educational dysfunction Motor disturbance or irritability Daytime sleepiness Reduced motivation or energy Increased errors or accidents Behavioral problems Ongoing worry	<3 months or ≥3 months

Insomnia can lead to complications, such as psychiatric disorders,[4-8] falls,[9-12] cardiovascular disorders,[13,14] and metabolic syndrome.[15] Psychiatric complications include depression and anxiety, and cardiovascular disorders include ischemic heart disease, ischemic (but not hemorrhagic) stroke, hypertension, and heart failure.[13,14] Recent evidence indicates severe insomnia is associated with increased risk of metabolic syndrome in women age ≥50, but not men.[15]

DIAGNOSIS

Insomnia is diagnosed clinically based on history and characterizing the nature and severity of the sleep problem (**TABLE 1**).[16-18] Asking the patient to talk through a typical 24-hour day can provide valuable insight. A sleep diary could be helpful for patients with substantial variability in the sleep problem.

Well-rested adults fall asleep within 10 to 20 minutes of attempting to sleep and spend <30 minutes awake during the night. Adults with chronic insomnia, however, usually take ≥30 minutes to fall asleep (for those with sleep initiation difficulty), spend ≥30 minutes awake during the night (for those with sleep maintenance difficulty), and/or terminate sleep ≥30 minutes prior to the desired wake-up time. It is not uncommon for patients to report 1 or more nights of poor sleep followed by a night of better sleep or to have minimal sleep over several consecutive nights. Patients often overestimate the amount of time it takes to fall asleep and underestimate total sleep time.

Asking patients why they are experiencing the sleep problem often identifies contributing factors and comorbid psychiatric or medical disorders, such as depression, anxiety, pain, restless leg syndrome, and obstructive sleep apnea.[16] The Epworth Sleepiness Scale is useful to identify patients with daytime sleepiness. Question patients about the use of prescription and non-prescription medications, such as central nervous system stimulants or depressants, antidepressants, beta-agonists, diuretics, opioids, and glucocorticoids. Ask patients about their consumption of caffeine, alcohol, and complementary and alternative medicines. Actigraphy could be considered to characterize circadian rhythm patterns or sleep disturbances.[16] Other laboratory testing, such as blood, radiography, or polysomnography, is needed only to investigate suspected comorbid disorders.[16]

Because insomnia is a component of many psychiatric and medical conditions, an insomnia diagnosis should be considered only when the symptoms are prominent and require further evaluation and treatment. If an associated comorbidity is identified, consider that it is sometimes difficult to determine whether the insomnia or the comorbidity occurred first. Due to this uncertainty, insomnia is no longer classified as primary or secondary, and treatment targets both insomnia and the comorbid disorder.[1,19]

An insomnia diagnosis requires that the patient experiences difficulty initiating or maintaining sleep despite adequate opportunity and circumstances for sleep that results in daytime consequences.[1] Insomnia differs from sleep deprivation in that insomnia occurs despite adequate opportunity and circumstances for sleep, whereas sleep deprivation does not. Those with chronic insomnia experience symptoms ≥3 times per week for ≥3 months. Daytime consequences include fatigue or malaise, poor attention or concentration, social/vocational/educational dysfunction, increased errors or accidents, motor disturbance or irritability, daytime sleepiness, reduced motivation or energy, or behavioral problems such as hyperactivity, impulsivity, or aggression. Patients with chronic insomnia might have ongoing worry that insufficient sleep could lead to daytime dysfunction, thereby creating a cycle that worsens insomnia.

TREATMENT

Overview of clinical guidelines

Several guidelines for managing patients with insomnia have been developed. Based on growing understanding of the often bi-directional association between insomnia and

comorbid disorders, these guidelines increasingly have emphasized the importance of identifying and treating comorbid condition(s) as well as the insomnia itself.[16,19,20] Discussion regarding the treatment of comorbid disorders associated with insomnia is beyond the scope of this review.

Based on growing understanding of the often bi-directional association between insomnia and comorbid disorders, these guidelines have increasingly emphasized the importance of identifying and treating comorbid condition(s) as well as the insomnia itself.

Treatment options

The goal of therapy is to improve sleep and alleviate distress or dysfunction caused by insomnia.[21] Psychotherapy and pharmacologic therapy, alone or in combination, are recommended most often for insomnia; referral to a sleep specialist, if available, also could be considered.[20,21] Psychotherapies include cognitive-behavioral therapy for insomnia (CBT-I), brief behavioral therapy, stimulus control, relaxation, and sleep restriction.

Cognitive-Behavioral Therapy for Insomnia

Based largely on moderate-quality evidence showing benefit on sleep onset, wake after sleep onset, and sleep efficiency, the American College of Physicians recommends CBT-I as initial therapy for all adults with chronic insomnia.[21] The American College of Physicians panel noted that evidence related to the harms of CBT-I is limited and concluded that CBT-I can be used for long-term treatment of insomnia.

CBT-I consists of a combination of cognitive therapy, behavioral interventions (eg, sleep restriction and stimulus control), and educational interventions (eg, sleep hygiene) to address thoughts and behaviors that interfere with optimal sleep. CBT-I traditionally has been offered one-on-one in the office setting, but is limited by the time required, the need for multiple training sessions, and the availability of trained providers. Telephone- and web-based platforms have shown evidence indicating benefit.[21] Two recent meta-analyses showed that CBT-I delivered via the internet produced clinically significant benefits for 1 year after the end of therapy.[22,23] One of these was restricted to CBT-I delivered in primary care (generally by a non-physician) over 4 to 6 sessions.[23]

Pharmacologic Therapy

Pharmacologic therapy plays a key role in treating chronic insomnia, particularly because not all patients achieve adequate benefits with CBT-I and long-term adherence can be challenging.[20,21] Approved medications include benzodiazepines, nonbenzodiazepine hypnotics, melatonin agonist, doxepin, and orexin receptor antagonists.

Benzodiazepines

Benzodiazepines, such as estazolam, lorazepam, temazepam, and triazolam, bind to several gamma-aminobutyric acid (GABA) type A receptor subtypes.[24] Benzodiazepines reduce the time to sleep onset, prolong stage 2 sleep, prolong total sleep time, and might reduce the length of rapid eye movement sleep.[25] Additionally, benzodiazepines have anxiolytic as well as anticonvulsant properties and produce anterograde amnesia. Although tolerance to the sedative effects could develop, next-day performance can be impaired depending on the elimination half-life of the benzodiazepine.[25] Withdrawal and rebound insomnia could occur with abrupt discontinuation.

Nonbenzodiazepine benzodiazepine receptor agonists

Nonbenzodiazepine benzodiazepine receptor agonists are more selective for a specific GABA type 1 receptor subtype and exert less anxiolytic and anticonvulsant effects than benzodiazepines. This class includes eszopiclone, zaleplon, and zolpidem (immediate- and extended-release). Nonbenzodiazepines decrease sleep latency and number of nighttime awakenings and improve sleep duration and sleep quality.[26-31] Headache and dizziness are common adverse events.[25] Low dosages are recommended to reduce the risk of impaired next-day performance.

Melatonin receptor agonist

Ramelteon binds to melatonin receptors in the suprachiasmatic nucleus with higher affinity than melatonin.[32,33] Short-term use of ramelteon is associated with small improvements in sleep onset and total sleep time.[34] The most common adverse effects are somnolence, fatigue, and abnormal dreams.[35]

Orexin receptor antagonists

Orexin receptor antagonists, suvorexant and lemborexant, which block the neuropeptides orexin A and B from binding in the hypothalamus are the newest class of medications for insomnia. Orexin A and B play a key role in promoting wakefulness and regulating the sleep-wake cycle.[36] Somnolence, fatigue, headache, and abnormal dreams are the most common adverse events.[25] Suvorexant and lemborexant have a reduced addictive potential than other FDA-approved medications for insomnia and are classified as schedule IV controlled substances.

Suvorexant

The safety and efficacy of suvorexant were demonstrated in a pooled analysis of 2 identical randomized, double-blind, placebo-controlled, parallel-group 3-month trials in nongeriatric (age 18 to 64) and geriatric (age ≥65) patients with insomnia.[37,38] At dosages of 15 or 20 mg/d (N = 493) and 30 or 40 mg/d (investigational) (N=770), suvorexant significantly improved most sleep onset and sleep maintenance endpoints compared with placebo (N = 767) beginning with the first treatment.[37] For example, placebo-corrected subjective time to sleep onset was 5.2 to 7.6 minutes and 8.4 to 13.2 minutes shorter with suvorexant 15 or 20 mg/d and 30 or 40 mg/d, respectively, at 3 months in the 2 trials.[37,38] Placebo-corrected subjective total sleep time increased from 10.6 to 19.7 minutes and 22.1 to 25.1 minutes with suvorexant, 15 or 20 mg/d and 30 or 40 mg/d, respectively.[37] Rates of discontinuation because of an adverse event were ≤4.7% for suvorexant and ≤6.0% for placebo.[37]

Lemborexant

Lemborexant has demonstrated safety and efficacy in nongeriatric and geriatric patients with insomnia. In a phase II, dose-ranging study, lemborexant improved both objective and subjective measures of sleep, which were apparent during the first 2 nights of treatment and persisted for the 15 nights of the trial.[39] A phase III trial compared lemborexant, 5 or 10 mg/d, zolpidem extended-release, 6.25 mg/d, and placebo over 1 month in 1008 patients with insomnia.[40] Compared with zolpidem, treatment with both dosages of lemborexant led to significant improvement in latency to persistent sleep, sleep efficiency, and wake-after-sleep onset during the first 2 nights of treatment and continued through the 1 month of the trial. For example, at 1 month patients treated with lemborexant experienced significantly greater reduction in wake-after-sleep onset in the second half of the night with the 5 and 10 mg/d dosages of lemborexant vs zolpidem (–6.7 and –8.0 minutes vs zolpidem, respectively). Similar significant improvements with lemborexant were observed vs placebo. Rates of discontinuation because of an adverse event were 0.4%, 0%, 0.8%, and 0.5% for lemborexant 5 and 10 mg/d, zolpidem, and placebo, respectively.

Guideline recommendations

The most recent guideline on pharmacotherapy for chronic insomnia in adults was developed by the American Academy of Sleep Medicine (AASM) in 2017.[20] The AASM recommendations are based on a systematic review of published literature, including meta-analyses. The AASM panel recognized the critical role of CBT-I because of its favorable benefit-to-risk ratio, but affirmed the need for pharmacotherapy, either alone or in combination with CBT-I, for many patients with chronic insomnia.

TABLE 2. **Recommendations regarding medications for insomnia[20]**

Medication	Recommended Use	
	Sleep Onset	Sleep Maintenance
Benefits outweigh harms		
Ramelteon Zaleplon	✓	
Doxepin Suvorexant		✓
Eszopiclone Temazepam Zolpidem	✓	✓
Benefits approximately equal to harms		
Triazolam	✓	
Diphenhydramine Melatonin	None	None
Harms outweigh benefits		
Tiagabine Trazodone l-Tryptophan Valerian	None	None

Note: Lemborexant is not included because it was approved for use in the United States after publication of the AASM guidelines in 2017.

The AASM panel provided recommendations regarding pharmacotherapy at FDA-approved dosages for sleep onset and/or sleep maintenance (**TABLE 2**).[20] Medications that are relatively short-acting are preferred for patients experiencing difficulty with sleep onset, while longer-acting medications are preferred for those with difficulty maintaining sleep. Lemborexant was not included because it was approved by the FDA after the AASM published their recommendations.

All recommendations were classified as weak, but the AASM panel noted that this reflects the limitations of the evidence as much as the relative benefits and risks of the treatments *per se*. The panel recommended that several agents commonly used for insomnia be avoided, including diphenhydramine, melatonin, tiagabine, trazodone, l-tryptophan, and valerian. Other medications that generally should not be used for chronic insomnia include antidepressants, antipsychotics, and barbiturates. An exception is doxepin at dosages ≤6 mg/d, which is FDA-approved for insomnia. The sedating antidepressants amitriptyline and trazodone should be limited to those with comorbid depression. Recommendations by the AASM panel for the following were not possible because of inadequate data for statistical analysis: estazolam,

flurazepam, gabapentin, oxazepam, paroxetine, quazepam, quetiapine, and trimipramine.

Recommendations regarding the use of medications for insomnia also are included in the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. The Beers Criteria were developed by the American Geriatrics Society to provide guidance regarding the use of medications in older adults based on a systematic review of clinical trials, observational studies, and meta-analyses involving adults age ≥65. According to the 2019 Beers Criteria,[41] several medication classes commonly used to treat insomnia should be avoided in older adults, often because of their anticholinergic properties, prolonged sedation, and/or risk of falls. These include first-generation antihistamines, some antidepressants, barbiturates, short- and long-acting benzodiazepines, benzodiazepine receptor agonists, and first- and second-generation antipsychotics. Lemborexant and suvorexant were not included in the list, and doxepin ≤6 mg/d was deemed acceptable.

Risk of Falls

The risk of falls, and the associated morbidity and mortality, is an important consideration when selecting a hypnotic agent for insomnia, especially in older adults. However, several investigations and meta-analyses provide conflicting conclusions.[42-49] A 2005 retrospective analysis of a database of nursing home residents (N = 34,163) found that hypnotic use did not predict falls (adjusted odds ratio [OR]: 1.13; 95% confidence interval [CI]: 0.98 to 1.30), but that the presence of insomnia did (adjusted OR: 1.52; 95% CI: 1.38 to 1.66). Results were not categorized by type of hypnotic, however.

A recent investigation of 331 nursing home residents found a significantly increased risk of falls with regular use of non-benzodiazepine benzodiazepine receptor agonists, particularly in adults age ≥85, but not with benzodiazepines, antidepressants, or antipsychotics.[50] A systematic review and meta-analysis involving 1.1 million patients found that the risk of fractures in patients treated with zolpidem was nearly twice that of other hypnotics, suggesting a greater risk of falls.[48] A prospective analysis involving 6882 community-dwelling older adults followed for 2 years showed that insomnia symptoms and use of prescription sleep medications independently predicted falls.[51]

CASE SCENARIO (CONTINUED)

Cognitive-behavioral therapy for insomnia is recommended as initial therapy for this woman, as well as all adults with chronic insomnia. If CBT-I does not provide adequate benefit or she is unable to adhere long term, pharmacologic therapy is recommended. Since sleep maintenance is her primary difficulty, medications recommended by the AASM are: doxepin (dose ≤6 mg/d), eszopiclone, suvorexant, temazepam, and zolpidem. Lemborexant, the other orexin receptor antagonist recently approved by the FDA, would also be an option. According to the Beers Criteria, doxepin ≤6mg/d is deemed acceptable, while lemoborexant and suvorexant were not included in the list of medications to avoid.

SUMMARY

Insomnia is common among US adults and, when chronic, increases the risk of other disorders, such as incident and recurring depression and cardiovascular diseases, and diminishes functioning and quality of life. The diagnosis is based primarily on a detailed sleep history and includes assessment of comorbidities. Cognitive-behavioral therapy is first line for patients with insomnia. A variety of medication classes have been used to treat patients with insomnia, but few, mostly newer agents, are recommended in current guidelines because of limited efficacy and/or safety concerns, particularly in older adults. Individualizing treatment is important. ●

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Overweight: The Overlooked Risk Factor

Robert F. Kushner, MD; Craig Primack, MD, FACP, FAAP, FOMA

LEARNING OBJECTIVES

At the conclusion of this activity, the family physician should be able to:

- Describe the epidemiology of overweight and obesity in the United States.
- Describe the disease burden associated with being overweight (body mass index 25-30 kg/m^2) and how to broach the topic of weight management with patients.
- Differentiate the safety and efficacy of 2 nonprocedural device treatments for people with overweight.

INTRODUCTION

Trends in body weight

Thirty percent. That's the estimated projected prevalence of adults with overweight in the United States in 2030.[1] Overweight, also called pre-obesity, is defined as having a body mass index (BMI) from 25.0 to <30.0 kg/m^2. Thirty percent is actually a reduction from the 33.1% of US adults who had overweight in 1988-1994 and the 31.6% in 2015-2016. The unfortunate reason for the continued projected decline in the prevalence of adults with overweight is their transition into the obesity classification. Without comprehensive treatment, adults with overweight continue to gain weight, moving steadily into the obesity (BMI 30-39.9 kg/m^2) and severe obesity (BMI ≥40 kg/m^2) categories.[2,3] One of the primary reasons for this transition lies in our dietary habits, eg, overconsumption of highly processed, energy-dense, and palatable foods and beverages in place of naturally fiber-rich foods, and reduced physical activity.[4]

Comparing 1960-1962 with 2015-2016, the mean BMI among US adults increased from 25.1 kg/m^2 to 29.1 kg/m^2 in men and from 24.9 kg/m^2 to 29.6 kg/m^2 in women.[2,5] In fact, despite an increase in mean height of <1 inch in both men and women, the mean body weight among US adults rose sharply, rising from 166.3 pounds in 1960-1962 to 197.9 pounds in 2015-2016 in men and from 140.2 pounds to 170.5 pounds in women.[2,5] By 2030, estimates are that 1 in 2 US adults (48.9%) will have obesity, nearly double the prevalence of 25.7% in 1988-1994.[1,3] Similar trends are observed in youth, particularly those age 5 to 19 years, as the prevalence of obesity increased from 13.9% in 1999-2000 to 18.5% in 2015-2016.[6]

Targeting people with overweight

Among the key trends noted above, one seems to be especially important. That is, people in the overweight category are more likely now than 30 years ago to continue to gain weight and develop obesity. These trends make it clear that early intervention efforts are needed, at lower BMI ranges before patients cross into the obesity classification. Put differently, patients who have overweight represent an important group for targeted treatment to prevent progression to obesity. In fact, patients who are classified as having a healthy weight, ie, BMI from 20 to <25 kg/m^2, are also an important target for preventive measures, because evidence indicates that many of the chronic diseases observed in people with obesity begin to emerge in people who have a healthy weight.

Understanding consequences of excess body weight

Beyond the enormous economic consequences of over-

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DISCLOSURES

Dr. Kushner discloses that he serves on the advisory board for Novo Nordisk and WW (formerly Weight Watchers).

Dr. Primack discloses that he serves as a consultant for Nestle Nutrition, Contrave, on the advisory board for Phenomix and Gelesis, and as a speaker for Novo Nordisk. He also owns stock in Vivus.

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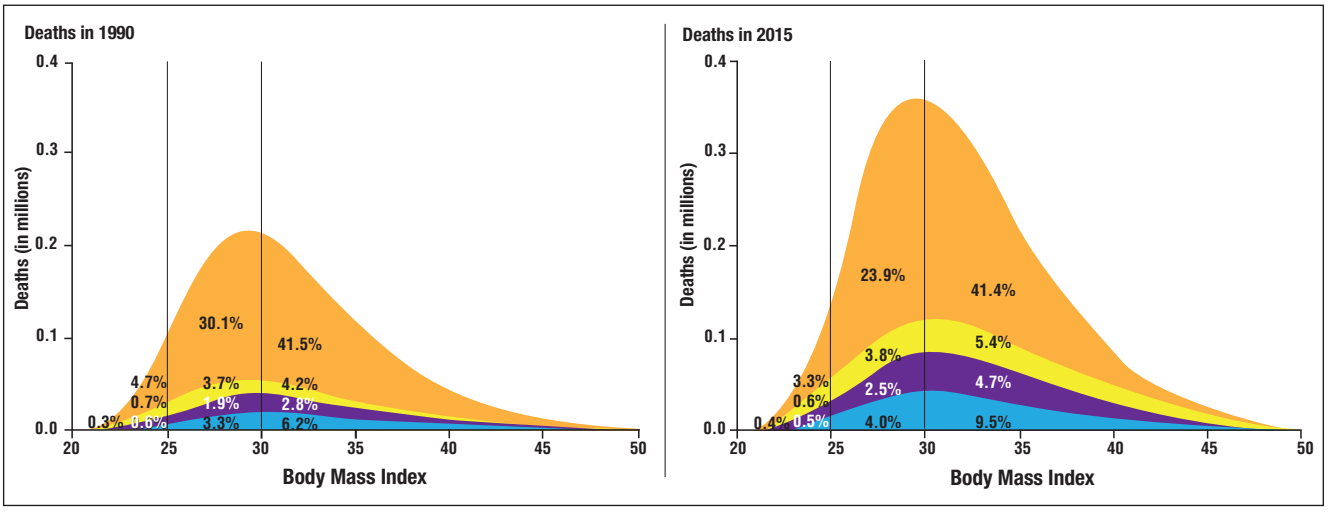
FIGURE 1. **Global deaths by body mass index**



Notes: Number of global deaths (millions) in 1990 (left) and 2015 (right). The 2 vertical lines mark the BMI thresholds for overweight and obesity. The percentages indicate the proportion of the total number of deaths that were contributed by diabetes mellitus (blue), chronic kidney disease (purple), cancers (light orange), and cardiovascular diseases (dark orange).

weight and obesity,[7,8] multiple chronic medical conditions are associated with weight gain and excess adiposity. These include dyslipidemia, type 2 diabetes mellitus, hypertension, coronary heart disease, stroke, gallbladder disease, gastroesophageal reflux disease, respiratory problems, sleep apnea, osteoarthritis, several cancers, urinary incontinence, and depression, as well as higher mortality rates and, most recently observed, an increased risk of complications from COVID-19.[9-19] Many of these chronic comorbidities are observed in children and adolescents with obesity.[20]

DISEASE BURDEN

BMI cutoff of 25 kg/m^2

The upper limit of a healthy BMI, ie, 25 kg/m^2, was established decades ago and reaffirmed in 1995 by the Dietary Guidelines Advisory Committee. This cutoff was based on epidemiological data showing that mortality increased significantly with a BMI >25 kg/m^2.[21,22] In establishing this cutoff, less consideration was given to the evidence showing that the incidence of diabetes, hypertension, and coronary heart disease began to increase well below a BMI of 25 kg/m^2.[23-28]

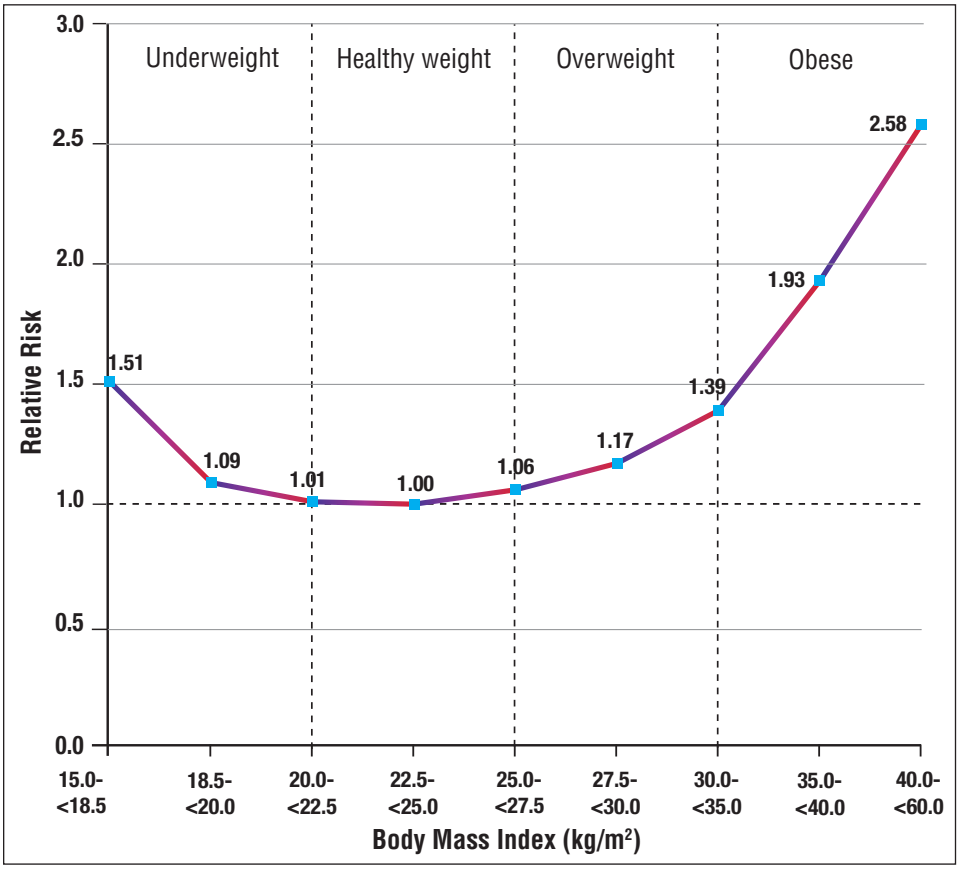
A factor contributing to the committee's decision was that designating a BMI cutoff lower than 25 kg/m^2 for the upper limit of healthy weight (and the lower limit of overweight) would have labeled >50% of US adults as having unhealthy weight. Moreover, the cutoff of 25 kg/m^2 was consistent with then-current recommendations of the American Institute of Nutrition[29] and the World Health Organization.[30]

Mortality burden in overweight

A recent analysis by the Global Burden of Disease (GBD) Obesity Collaborators reinforces that the mortality burden is not restricted to people with obesity.[15] The analysis included data from 68.5 million children and adults in 195 countries between 1980 and 2015. In 2015, 4.0 million weight-related deaths occurred in people with a BMI ≥25 kg/m^2; 39% of these deaths occurred in people with a BMI <30 kg/m^2 (**FIGURE 1**). In people with BMI-related death due to diabetes, for example, 4.5% occurred at a BMI <30 kg/m^2. Similar trends in BMI-related disability were observed.

Details regarding the association of BMI with mortality were provided by a similar analysis by the GBD BMI Mortality Collaborators.[31] The analysis was restricted to never-smokers and excluded preexisting disease and the first 5 years of follow-up. Data involving 1.42 million adults from North America showed that BMI was nonlinearly associated with all-cause mortality, with the overall nadir at BMI from 20.0 kg/m^2 to <25.0 kg/m^2 (**FIGURE 2**). The nadir was age dependent, identified at BMI 22 kg/m^2 for age 35-49 years, BMI 23 kg/m^2 for age 50-69 years, and BMI 24 kg/m^2 for age 70-89 years. These findings confirm the mortality risk in people with overweight and suggest that targeting a BMI well below the cutoff of 25 kg/m^2 may be advisable, particularly in younger adults. These findings also confirm an earlier investigation showing that the relative risk of all-cause and cardiovascular death associated with greater body weight is higher among younger adults than older adults.[32]

FIGURE 2. **Relative risk of all-cause mortality by BMI category in North America[31]***



Abbreviation: BMI, body mass index.

*BMI category from 22.5 to <25.0 kg/m² is set as the reference category. Data are in never-smokers, excluding people with chronic disease at baseline and 5 years of follow-up in geographic regions with >1 million participants.

The GBD BMI Mortality Collaborators analysis also showed that, compared with BMI from 22.5 to <25.0, increasing BMI was strongly positively related to death due to coronary heart disease (hazard ratio [HR] 1.42 per 5 kg/m² increase in BMI), stroke (HR 1.42 per 5 kg/m²), and respiratory disease (HR 1.38 per 5 kg/m²), and moderately positively related to cancer mortality (HR 1.19 per 5 kg/m²).[31] Another analysis showed a reduction in the expected age at death of 0.8 to 1.0 year in a 40-year-old, never-smoker with underweight.[14]

SCREENING

The 2012 guidelines developed by the American Heart Association/American College of Cardiology/The Obesity Society underscore the importance of measuring height and weight and calculating BMI at annual visits or more frequently for all patients.[33] For patients found to have overweight or obesity, measuring the waist circumference at annual visits or more frequently is also recommended. North American waist circumference cutpoints to identify high-risk patients are >40 inches for males and >35 inches for females.[33]

Recently, a task force of The Obesity Society assessed available evidence and concluded that weight history is an essential component of the medical history for patients presenting with overweight or obesity.[34] The weight history should assess the patient's life stage at which unhealthy weight occurred, duration of exposure to obesity, and maximum BMI, as each factor may help predict risk for developing many obesity-related comorbidities. As is often used for ascertaining a patient's chief complaint and history of present illness, the mnemonic "OPQRST" (onset, precipitating events, quality of life, remedy, setting, and temporal pattern) can be used to form an understanding of how and when a patient gained weight, which management efforts have been attempted, and the effect of unhealthy weight on the patient's health and well-being.

Having the conversation about weight

Family physicians are well positioned to address overweight with their patients, in part because patients want and expect weight-loss guidance from their health care providers. Nonetheless, as family physicians prepare for and have these conversations with their patients, it is important to realize that most patients with excess weight, particularly those with obesity, have often been stigmatized as a result of having the disease, including by physicians and other health care providers.[35-37] Consequently, treating the patient with respect and using appropriate language are important. Words such as overweight, unhealthy or excess weight, and increased BMI should be used instead of heaviness, obesity, or excess fat.[38,39]

The conversation about weight should begin by asking for the patient's permission to talk about his or her weight.

If the patient is not interested or ready, acknowledge the importance of discussing weight, but defer the discussion until a future visit. When the patient is ready for the discussion, start with an empathetic statement followed by listening, which can be helpful to avoid the patient feeling embarrassed and to build a trusting relationship. This exchange can be augmented by using a shared decision-making model to find a weight management plan the patient is willing and able to adopt. Inquiring about the patient's experience with weight loss is helpful to establish realistic expectations and inform the treatment plan. These and other suggestions are embodied in the FRAMES model for communicating with patients, which can be found in a discussion guide developed by the STOP Obesity Alliance (http://whyweightguide.org/docs/STOP-Provider-Discussion-Tool.pdf).

TREATMENT OPTIONS FOR OVERWEIGHT

Lifestyle management

Lifestyle management consisting of a calorie-controlled healthy diet and engagement in daily physical activity is a foundational treatment recommendation for weight loss[33] and improved health. After 1 year of treatment, the Look AHEAD trial showed a reduction in mean body weight of 8.6%, which resulted in improved glycemic control, improved lipid profile, and a reduced requirement for medications for diabetes, dyslipidemia, and hypertension.[40] Additional benefits such as improved symptoms of depression and sleep apnea also were observed.[41,42]

A recent analysis of data from the National Health and Nutrition Examination Survey showed that the proportion of overall participants (N=48,026) who had attempted to lose weight increased from 34.3% in 1999-2000 to 42.2% in 2015-2016.[43] The most commonly reported weight-loss strategies were reduced food consumption, exercise, and frequent water intake, used by 31.9%, 31.5%, and 26.3%, respectively, in 2015-2016.

Unfortunately, short- and long-term achievement of 5% to 10% weight loss with lifestyle management alone is difficult.[44-48] The inclusion of behavioral therapy results in modest additional health benefits, with evidence of a dose-response effect with higher intensity interventions resulting in greater improvement.[49,50]

Pharmacologic therapy

With the recent withdrawal of lorcaserin from the US market due to cancer concerns, there are now 4 medications approved for long-term use.[33] Liraglutide, naltrexone/bupropion extended-release, phentermine/topiramate extended-release, and orlistat are approved for weight loss and weight maintenance in patients with obesity or overweight (BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity). In randomized controlled trials, medications currently approved for long-term weight loss have yielded an average weight loss ranging from approximately 3% to 9% relative to placebo at 1 year, and are generally associated with improvements in blood glucose, lipids, and blood pressure.[51]

Although beneficial, use of medications approved for long-term weight loss is low, with 1% to 2% of eligible patients receiving weight-loss medication.[52,53] Several factors may underlie the low prescription rates, including concern about safety and long-term efficacy, failure to recognize obesity as a disease, lack of training, and limited insurance coverage. Furthermore, their approved indications do not include patients with BMI ranging from 25 kg/m^2 to <30 kg/m^2 without comorbidities. Recent investigations show that less than one-quarter of prescribers account for nearly all prescriptions for these medications.[52,53] Suboptimal adherence also appears to contribute. One real-world analysis (N=26,522) showed that 6-month persistence rates ranged from 16% to 42%, while another real-world analysis (N=2.2 million) showed the 4-month and 1-year persistence rates were 52% and 34%, respectively.[53,54] Modest weight reduction may also contribute to the low use and suboptimal persistence, as weight loss over 3 to 6 months is often <5%.[55-58]

Devices

Two nonprocedural devices are approved by the US Food and Drug Administration (FDA) for weight management and may fill a treatment gap, particularly in patients with overweight. One is an ingested, transient, space-occupying device, or oral superabsorbent hydrogel, and the other an oral, removable, palatal space-occupying device. Neither of these devices requires a procedure for use.

Nonsystemic, oral superabsorbent hydrogel

The nonsystemic, oral superabsorbent hydrogel (Plenity™) is indicated for use in conjunction with diet and exercise to aid in weight management in adults with overweight and obesity with a BMI from 25 kg/m^2 to 40 kg/m^2.[59] The availability of Plenity in the US has been delayed until 2021 due to the COVID-19 pandemic.

The oral hydrogel product, which is technically considered a device, is delivered in a capsule taken by mouth that consists of 2 building blocks, cellulose and citric acid.[59] Each capsule (1 dose=3 capsules) contains thousands of salt grain-size particles, which can hydrate up to 100 times their original weight. After oral ingestion with water, each capsule disintegrates in the stomach and releases the particles, which are then hydrated. The hydrated gel particles form a 3-dimensional matrix with viscoelastic properties similar

to solid ingested vegetables and superior to common processed functional fiber supplements such as psyllium.[60] The hydrogel matrix occupies about one-quarter of the average stomach volume, thereby promoting satiety and fullness. The matrix passes through the stomach and small intestine before breaking down in the colon, where the water is released and reabsorbed by the body. The particles are not absorbed and are eliminated in the feces. Consequently, the product has no nutritional or caloric value.

The safety and efficacy of the oral superabsorbent hydrogel product were investigated in a 24-week multicenter, randomized, double-blind, placebo-controlled trial in adults with BMI ≥27 kg/m^2 and ≤40 kg/m^2 and fasting plasma glucose (FPG) ≥90 mg/dL and ≤145 mg/dL (N=436).[61] At baseline, the mean BMIs were 33.5 kg/m^2 and 34.1 kg/m^2 in the oral hydrogel and placebo groups, respectively, with 11.7% and 9.9% classified as overweight. Weight loss ≥5% was achieved by 59% vs 42% of patients, respectively, while weight loss ≥10% was achieved by 27% vs 15%, respectively. Patients treated with the oral superabsorbent hydrogel lost 6.4% body weight compared with 4.4% with placebo (*P*=.0007). In patients with FPG ≥100 mg/dL or drug-naïve type 2 diabetes mellitus at baseline, the mean percentage decrease in body weight was 8.1% with the oral hydrogel and 5.6% for placebo (*P*=NS).

The overall incidence of adverse events (AEs) in the oral superabsorbent hydrogel treatment group was no different from placebo. An AE probably or possibly related to treatment occurred in 39.5% of the oral hydrogel group and 30.3% of the placebo group; most were mild. No serious AEs were reported with the oral superabsorbent hydrogel product. The most common gastrointestinal AEs probably or possibly related to treatment in the oral superabsorbent hydrogel vs placebo groups were diarrhea (10.3% vs 7.6%), abdominal distension (10.8% vs 5.7%), infrequent bowel movements (9.0% vs 4.7%), flatulence (8.5% vs 4.7%), constipation (4.5% vs 4.7%), nausea (3.6% vs 3.8%), and abdominal pain (4.9% vs 2.8%).

Extended treatment was offered to the last 52 patients of the study who lost ≥3% body weight over the 24 weeks. These patients were treated for an additional 24 weeks, with all continuing patients receiving the oral superabsorbent hydrogel. Over weeks 25 to 48, patients in the oral hydrogel–oral hydrogel group lost an additional 0.5% of body weight (7.6% from baseline to week 48), while patients in the placebo–oral hydrogel group lost an additional 2.3% of body weight (9.4% from baseline to week 48). The safety results over weeks 25 to 48 were similar to weeks 0 to 24.

Oral, removable, palatal space-occupying device

The sensor monitored alimentary restriction therapy (SMART) device was approved by the FDA in 2016 as a class II device for weight management or weight loss.[62] It is an oral, removable, upper palatal space-occupying device that is worn during meals to limit bite size and slow the intake of food, thereby reducing the amount of food that is consumed. The device is indicated for people with BMI from 27 kg/m^2 to 35 kg/m^2 in conjunction with behavioral modification instruction.[63] A heat sensor in the device automatically records usage; the data can be uploaded to a secure website for adherence monitoring. The device is made from a mold of the patient's upper oral cavity by a trained health care provider using a mold kit included with the device.

The safety and efficacy of the oral palatal device were assessed in a 16-week, prospective, single-arm, nonrandomized multicenter trial in combination with a video-delivered lifestyle program in adults with BMI 27 kg/m^2 to <35 kg/m^2.[64] Mean weight loss was 2.1% among the 76 intent-to-treat (ITT) subjects and 2.9% among the 40 per-protocol (PP) subjects. PP subjects were required to use the device ≥7 times per week for 14 of 16 weeks, have an overall device usage rate ≥33%, and complete the trial. Weight loss ≥5% at 16 weeks was achieved by 19.7% of the ITT subjects and 30.0% of the PP subjects. Two ITT subjects reported mild/moderate device-related AEs (1 a hard palate abrasion and 2 tongue lacerations).

SUMMARY

While treatment of people with unhealthy weight has typically focused on patients with obesity, evidence indicates that the detrimental effects of excess weight on morbidity and mortality begin at lower BMI categories. Therefore, identifying at-risk patients who have overweight (BMI from 25.0 to <30.0 kg/m^2) and initiating treatment earlier may interrupt the progression toward further weight gain and the development of obesity-related comorbidities. The first step in treatment is broaching the topic of weight with the patient in an empathic and respectful manner. All patients should be provided guidance on following a calorie-controlled healthy diet and engaging in daily physical activity. For some patients, prescription of a medication approved for weight loss may be warranted after reviewing the risks and benefits of the available agents. With the FDA clearance of 2 nonprocedural devices, we now have additional therapeutic options for patients who have a lower BMI, with evidence of modest weight loss and good patient tolerability. ●

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Recognition and Management of a Less Common Cause of Chronic Kidney Disease: Autosomal Dominant Polycystic Kidney Disease

Matthew Weir, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this review article on ADPKD, participants should be able to:

- **Identify** people at high risk for ADPKD
- **Conduct** a diagnostic evaluation
- **Initiate** evidence-based therapy to slow kidney progression and treat extra-renal manifestations

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of chronic kidney disease.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder with an incidence of 1 in 1000 live births in the United States.[1] The progressive development and enlargement of renal cysts results in an exponential increase in total kidney volume. Some polycystic kidneys grow to be as large as a football and weigh as much as 30 pounds. Despite destruction of renal parenchyma, normal renal function usually is maintained for decades because of compensatory hyperfiltration in surviving glomeruli. However, when the majority of nephrons have been destroyed, typically during the fourth decade of life, renal function begins to decline, often leading to end-stage kidney disease (ESKD).[2] This is in sharp contrast to the much rarer autosomal recessive form of polycystic kidney disease that often is apparent at birth or in early infancy, frequently leading to death early in life.[1]

ADPKD is caused by mutations in the *PKD1* and *PKD2*

genes. These genes provide instructions for making proteins thought to be involved in normal kidney development, organization, and function.[1] Approximately 90% of individuals with ADPKD inherit a *PKD1* or *PKD2* mutation from 1 affected parent. The other 10% of cases are acquired, resulting from a new mutation in 1 of the genes in people with no family history of the disorder.[1] Historic evidence indicates that the *PKD1* mutation occurs in 85% of people with ADPKD and the *PKD2* mutation in 15%. Recent evidence in individuals from Canada and the United States suggests that the prevalence of *PKD2* could be approximately 30%.[3]

Variants in other genes linked to PKD, as well as environmental factors such as acute kidney injury, can influence cyst formation and disease progression.[4] Compared with *PKD2*, *PKD1* mutation is associated with greater cyst number and volume at a given age and results in more severe disease.[5] People with the *PKD2* genetic mutation generally experience milder kidney disease with fewer kidney cysts, delayed onset of hypertension and ESKD by nearly 2 decades, and longer overall survival.[6-8] However, because the renal prognosis differs according to the type of mutation in both *PKD1* and *PKD2,* the renal prognosis of patients with a *PKD2* mutation is not always favorable compared with patients with a *PKD1* mutation.[6]

DIAGNOSIS

Case scenario

A family physician sees a 28-year-old female for a preventive health visit. She appears healthy. Vital signs: BP 146/92 mm Hg (132/78 mm Hg 6 years ago); HR 74/min; RR 15/min; T 36.8°C. Her liver appears slightly enlarged. She reports that her belly generally feels full.

The diagnosis of ADPKD typically occurs in common clinical settings, such as routine evaluation in an asymptomatic patient with a positive family history of ADPKD, incidental finding during an imaging study conducted for pregnancy, trauma, surgery, or some other unrelated reason, initial evaluation for hypertension, or evaluation for hematuria, cyst rupture, kidney stones, or some other potential symptom related to ADPKD. Consideration should be given to non-ADPKD causes of hematuria and back pain, such as cancer, particularly in patients age >50. Asymptomatic at-risk people usually are not screened until adulthood because there is a lack of disease-specific treatment for this group. However, in children and adolescents, recent guidelines recommend ongoing surveillance or immediate diagnostic screening in those who are asymptomatic but at risk of ADPKD.[9]

Because 90% of patients with ADPKD have a genetic cause, obtaining a detailed family history is the first step in the diagnostic evaluation. The family history should elicit the number and relationship of affected family members, age at diagnosis, age at ESKD development, and known genetic mutations. If the family history is positive, diagnosis is confirmed primarily through imaging.[2,4] For those without a family history of ADPKD, the history should elicit information to assess the presence of other acquired disorders such as multiple benign simple cysts, autosomal dominant tuberous sclerosis complex, and von Hippel-Landau disease.

Imaging with ultrasound generally is used first because of its low cost and widespread availability, but is less sensitive than magnetic resonance imaging (MRI) or computed tomography (CT). If the ultrasound is positive, MRI or CT is appropriate and more useful for determining prognosis. If MRI or CT is positive for ADPKD, referral to a nephrologist is recommended. Imaging might not be definitive in those with manifestations of mild disease such as low cyst size and/or burden (not unusual in some children with ADPKD), in which case genetic testing could be helpful. Otherwise, genetic testing often is limited to patients with atypical presentation, the presence of a few cysts but negative family history, or to rule out ADPKD in a young potential kidney donor.[2,4,10,11]

The diagnostic evaluation should assess for complications. Some involve the kidneys and urinary tract, such as gross hematuria in one-third of individuals, recurrent urinary tract infections in 30% to 50%, and kidney stones in 10% to 35%.[12] Beyond the kidneys, cysts often occur in the liver and less commonly in the pancreas, seminal vesicles, and arachnoid membrane.[4] Cardiovascular disorders often occur, including hypertension, heart valve abnormalities, and aortic and intracranial aneurysms.[13] Arterial hypertension occurs in approximately 50% to 70% of individuals when kidney function is still normal and might be the presenting sign.[13,14] Metabolic complications include insulin resistance and dyslipidemia.[15]

PROGNOSIS

Once an ADPKD diagnosis has been established, a key step is to identify individuals who are at high risk of progressing to chronic kidney disease because this informs prognosis and guides therapy. Measures of kidney function usually are already available, but could remain within normal ranges for several decades.[2] To more accurately assess risk of progression to ESKD, either the PROPKD score or Mayo classification system often is used. The PROPKD score is based on sex, hypertension onset before age 35, urologic complications before age 35, and genotype.[16] Because genetic testing is not routinely done outside of a clinical trial, use of PROPKD is limited.

TABLE. **Basic optimized treatment of adults with ADPKD[20]**

Intervention	Goal	Methods to achieve goal
Intensive BP control	≤110/75 mm Hg in: 18- to 50-year-olds eGFR >60 mL/min/1.73 m^2 Particularly: Mayo Clinic class 1 C-E Intracranial aneurysm Valvular heart disease ≤130/85 mm Hg in: Other adult with hypertension	Early detection is essential[a] By order of preference: 1. ACEI/ARB 2. α/β or cardioselective β-blocker 3. Dihydropyridine CCB 4. Diuretic Dietary Approaches to Stop Hypertension (DASH)-like diet at early stages
Sodium	Moderate restriction (2.3 to 3 g/d) Adjust for extrarenal losses (hot climate, runners, sauna, bowel disease) if appropriate	Counseling Dietitian follow-up Monitor 24-hour urine sodium
Hydration	Moderately enhanced hydration spread out over 24 h (during the day, at bedtime, and at night if waking up) Maintain urine osmolality ≤280 mOsm/kg	Counseling Monitor first morning urine osmolality, plasma copeptin if available Water prescription (L) = [24-h urine solute load (mOsm) ÷ 280] + insensible loss (∫ 0.5L)
Protein	0.8 to 1 g/kg of ideal body weight	Dietitian Monitor protein intake: 6.25 x (UUN in g/d + [0.03 x weight in kg])
Phosphorus	Moderate diet phosphate restriction (800 mg/d)	Dietitian Read food labels and watch for food additives containing phosphates Use of phosphate binders not different from other advanced CKD when needed
Acid base	Maintain plasma bicarbonate within the normal range (≥22 mEq/L)	Increase fruits/vegetables (2 to 4 cups/day) Oral sodium bicarbonate if needed
Caloric intake	Maintain normal BMI Moderation in caloric intake	Dietitian Regular exercise
Lipid control	Aim for serum LDL-C ≤100 mg/dL	Dietitian Regular exercise Statin if needed (ezetimibe if intolerant to statin)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomular filtration rate; LDL-C, low density lipoprotein cholesterol; UUN, urine urea nitrogen.

[a]Screen children at risk every 3 years starting at age 5. Children with hypertension should be referred and managed by experts in pediatric hypertension

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The Mayo classification system categorizes patients with typical ADPKD into 5 prognostic classes.[17] Required data are the patient's age, height, and total kidney volume, as well as a single representative coronal image of the kidneys. The total kidney volume can be determined using an online calculator (available at: https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754). A benefit of the Mayo classification system is that it allows estimation of a patient's glomerular filtration rate (GFR) at any point in the future. However, it is not applicable to the approximately 5% of patients with ADPKD with an atypical presentation, ie, unilateral, asymmetrical, or segmental cyst burden.

TREATMENT

Goals

The focus of treatment is to slow disease progression and reduce the need for renal replacement therapy. Not to be forgotten, however, is the need to address the diminished quality of life experienced by patients with chronic kidney disease, particularly as the disease progresses.[18] In patients

with ADPKD, the physical burden caused by pain, abdominal fullness, cardiovascular disease, and urinary issues adds to the psychological burden stemming from treatment complexity and the hereditary nature of the disorder with its potential effect on family. Poor quality of life in patients with chronic kidney diseases has been shown to be associated with increased hospitalization and mortality rates.[19] Addressing quality-of-life issues beginning at the time of diagnosis and continuing over the patient's lifetime is a critical part of patient management and often requires involvement from other healthcare providers.

GENERAL MEASURES

The systemic consequences of ADPKD require a comprehensive treatment approach that includes a healthy lifestyle to enhance hydration, limit dietary sodium and protein intake, maintain a healthy weight, and reduce cardiovascular risk (**TABLE**).[20]

HYPERTENSION

Early in the course of ADPKD, before loss of kidney function, the activity of the renin-angiotensin-aldosterone system (RAAS) often increases and extracellular volume expands. These changes are thought to contribute to increased blood pressure observed in 50% to 70% of patients with ADPKD, with an average onset at age 30.[21-23]

An angiotensin converting enzyme inhibitor (ACEI) is generally recommended as first-line antihypertensive therapy based on the results of the HALT-PKD trials.[24,25] These trials were designed to determine the effect of intensive blockade of the RAAS and blood pressure control on the progression of kidney disease in individuals with an early or moderately advanced stage of ADPKD. In early ADPKD (eGFR >60 mL/min/1.73 m^2), the annual percentage increase in total kidney volume was not significantly different with the combination of the ACEI lisinopril and the angiotensin receptor blocker (ARB) telmisartan vs lisinopril plus placebo.[24] Similarly, there was no significant difference in change in eGFR between the 2 medication groups.[24] Lisinopril monotherapy resulted in greater decline in the left ventricular mass index and greater reduction in urinary albumin excretion. Similarly, in patients with ADPKD and stage 3 chronic kidney disease (eGFR 25 to 60 mL/min/1.73 m^2) monotherapy with lisinopril was sufficient to achieve blood pressure control (110/70 to 130/80 mm Hg); adding telmisartan offering no extra significant benefits.[25]

A key finding of the HALT-PKD trial is that rigorous blood pressure control (95/60 to 110/75 mm Hg), compared with standard blood pressure control (120/70 to 130/80 mm Hg), slowed the increase in total kidney volume with no overall change in the eGFR.[24] Secondary analysis confirmed that the kidney benefits were related to the degree of blood pressure control rather than pharmacologic intensity of RAAS blockade.[26]

PAIN

Pain associated with ADPKD could be acute or chronic.[2] Acute pain often is caused by kidney cyst hemorrhage, infection, or stones, while chronic pain generally is because of stretching or pulling of the kidney capsule caused by the enlarged kidneys or marked enlargement of the kidneys or liver that causes musculoskeletal back pain.[4] The pain etiology must be identified because some causes such as cyst infection could lead to severe systemic illness. Nonopioid analgesics, including short-term use of non-steroidal anti-inflammatory drugs, often are sufficient to provide relief for acute pain. Usual recommendations regarding analgesic use must be followed, such as dosing based on renal or liver function, age ≥65. Reserve opioids, often in combination with another analgesic, may be used for acute moderate-to-severe pain.

PREGNANCY

Women with ADPKD of reproductive potential should be advised that exogenous estrogen or progesterone exposure could aggravate ADPKD.[2] Family planning, which includes genetic counseling and preimplantation genetic diagnosis/*in vitro* fertilization access, could be offered.

CHILDREN

Current recommendations indicate that off-label use of vasopressin antagonists should be limited to children at high risk of early disease progression.[9] The use of somatostatin analogues and mTOR inhibitors (eg, sirolimus and everolimus) is not recommended, while the safety and efficacy of statin therapy are unclear. A low dietary salt intake is recommended.

TREATMENT OF RAPIDLY PROGRESSIVE DISEASE

Tolvaptan

Plasma levels of vasopressin and its precursor copeptin generally are increased in patients with ADPKD.[27,28] The plasma level of copeptin correlates with ADPKD severity and the rate of disease progression.[29] Therefore, the vasopressin system was identified as a therapeutic target, leading to development and FDA-approval of tolvaptan, a vasopressin V2-receptor antagonist.

FDA-approval of tolvaptan was based on the results of the TEMPO 3:4 phase III clinical trial involving 1445 adults age 18 to 50 with ADPKD, total kidney volume ≥60 mL, and creatinine clearance ≥60 mL/min.[30] After 3 years of treatment, tolvaptan significantly reduced the increase in total kidney volume and decline in kidney function compared with pla-

cebo. The rate of discontinuation was higher with tolvaptan vs placebo (23% vs 14%, respectively), primarily because of events related to aquaresis, ie, excretion of electrolyte-free water, such as thirst, polyuria, nocturia, polydipsia, as well as increases in liver enzyme levels >3 times the upper limit of normal.

The safety and efficacy of tolvaptan also have been demonstrated in patients with later-stage ADPKD (eGFR 25 to 65 mL/min/1.73 m^2 if age 18 to 55 or eGFR 25 to 44 mL/min/1.73 m^2 if age 56 to 65).[31] The adjusted mean change in eGFR over 1 year was significantly lower in the tolvaptan vs placebo group (-2.3 vs -3.61 mL/min/1.73 m^2, respectively; $P < .001$). The benefits of tolvaptan were maintained across subgroups, including sex, baseline eGFR, and stage of chronic kidney disease (except stage 2). Aquaretic and other adverse events led to 8.4% of patients withdrawing during a single-blind tolvaptan period before randomization. After randomization, the overall rates of new or worsening adverse events did not differ between the tolvaptan and placebo groups. After randomization, patients treated with tolvaptan had higher rates of polyuria, nocturia, thirst, polydipsia, dry mouth, diarrhea, and fatigue.

Tolvaptan is approved to slow decline in kidney function in adults at risk of rapidly progressing ADPKD. Patients at risk of rapid disease progression are those with Mayo class 1C, 1D, or 1E disease or PROPKD score ≥6. Most experience is in adults age ≤55 and eGFR ≥25 mL/min/1.73 m^2. The decision to prescribe tolvaptan should be made using a shared decision-making discussion with the patient based on risks (eg, liver toxicity, polyuria, polydipsia), benefits, and affordability. Assess for potential drug interactions. The morning and afternoon dosages are titrated over several weeks based on tolerability as well as alanine transferase and aspartate transaminase levels remaining <2 to 3 times the upper limit of normal.

Investigational therapies

Several medications are being investigated for treating ADPKD. These include tesevatinib, metformin, pioglitazone, nicotinamide, lixivaptan, and somatostatin analogs such as lanreotide. None is FDA-approved for ADPKD.

COLLABORATING WITH A NEPHROLOGIST

Managing patients with ADPKD should involve a nephrologist, ideally one in an ADPKD center of excellence.[2] Because of the complex treatment of these patients, close communication between nephrologist and family physician is critical. It is important to reach agreement as to who will assume responsibility for treating the extra-renal complications of ADPKD, such as hypertension. Integrating the management of these disorders into the holistic management of the ADPKD is a key role of the family physician.

PATIENT EDUCATION RESOURCES

- American Association of Kidney Patients [https://aakp.org/]
- American Kidney Fund [https://www.kidneyfund.org/kidney-disease/other-kidney-conditions/polycystic-kidney-disease.html]
- Genetic and Rare Diseases Information Center [https://rarediseases.info.nih.gov/diseases/10413/autosomal-dominant-polycystic-kidney-disease]
- National Human Genome Research Institute [https://www.genome.gov/Genetic-Disorders/Autosomal-Polycystic-Kidney-Disease]
- National Institute of Diabetes and Digestive and Kidney Diseases [https://www.niddk.nih.gov/health-information/kidney-disease/polycystic-kidney-disease/autosomal-dominant-pkd]
- National Kidney Foundation [https://www.kidney.org/atoz/content/polycystic]
- National Organization for Rare Disorders [https://rarediseases.org/rare-diseases/autosomal-dominant-polycystic-kidney-disease/]
- Polycystic Kidney Disease Foundation
  - ADPKD [https://pkdcure.org/what-is-adpkd/]
  - Patient Handbook [https://pkdfoundation.salsalabs.org/infopacketandpatienthandbook/index.html] ●

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Recognition and Management of Hypoglycemia

Jay H Shubrook, DO, FAAFP, FACOFP

"Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes."

—American Diabetes Association[1]

This statement by the American Diabetes Association (ADA) comes as no surprise to family physicians. People with diabetes, their families, and physicians all regularly share concerns about hypoglycemia. These concerns are well founded. More than 30% of patients with type 1 diabetes mellitus (T1D) annually experience 1 to 3 episodes of severe hypoglycemia, ie, low blood glucose characterized by altered mental and/or physical status requiring assistance.[2] For people with type 2 diabetes mellitus (T2D), approximately 50% experience hypoglycemia, and 20% have ≥1 episode of severe hypoglycemia per year.[3] In 2016, hypoglycemia was the reported cause for 235,000 emergency department (ED) visits.[4] Of these, 22.3% were admitted to the hospital and <0.1% died. Another study found that, in patients with T1D since childhood who died over 24 years of follow-up, hypoglycemia was the cause in 10%.[5]

Wider use of continuous glucose monitoring (CGM) provides for a more accurate assessment compared with relying on symptom recognition or self-monitored blood glucose and has resulted in greater insight into the true frequency of hypoglycemia.[6,7] A recent analysis of 2 trials involving 307 adults with T1D treated with multiple insulin injections per day, and with glycated hemoglobin (A1C) ≤9% to 10%, showed that patients were hypoglycemic >1 hour per day.[8] Patients spent a median of 22 minutes/day with a blood glucose <54 mg/dL, and 72 minutes/day with a blood glucose <70 mg/dL. In patients with T2D (N=108) treated with insulin and/or oral medications, a prospective evaluation showed that 49% experienced ≥1 hypoglycemic episode (mean 1.74 episodes) over a 5-day period.[9] Of these patients, 75% experienced ≥1 asymptomatic hypoglycemic episode.

Hypoglycemia may not be recognized if it occurs during the night or in patients with hypoglycemic unawareness. Similarly, episodes are likely to be missed despite periodic daily monitoring using finger sticks, especially in persons with wide glycemic variability. Moreover, the risk of severe hypoglycemia occurs similarly, across the range of A1C levels, although the reason for this is unclear. The Diabetes and Aging Study showed that the prevalence of severe hypoglycemia was 12% in persons with A1C <6%, 11% in persons with A1C 7% to 7.9%, and 14% in persons with A1C ≥9%.[10]

A wide variety of patient factors contribute to an increased risk of hypoglycemia. These include longer duration of diabetes, older age, history of recent severe hypoglycemia, chronic kidney disease, and tight glycemic control.[11-13] Medications such as sulfonylurea, meglitinide, and basal insulin, particularly at doses >0.5 units/kg per day, are common causes of hypoglycemia.[14] Lifestyle factors such as a variable eating, administering insulin after meals, drinking alcohol, and vigorous or unexpected exercise also increase the risk of hypoglycemia.[11,13]

The consequences of hypoglycemia extend well beyond ED visits and increased health care resource utilization. People feel bad when they are hypoglycemic and these spells may lead to suboptimal treatment adherence, resistance to intensifying treatment, diabetes distress and reduced quality of life among patients and families/caregivers, higher mortality rate, diminished academic performance, and possibly diminished cognition.[5,15-28] A key consequence of suboptimal treatment or scheduled adherence, as well as resistance to intensifying treatment, is that patients remain on suboptimal glucose-lowering therapy. Thus, patients are exposed

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TABLE 1. **Physiologic responses to hypoglycemia**[1,30]

Plasma glucose (mg/dL)	Physiologic response	Function in hypoglycemia
80-85	Primary: Decreased insulin secretion Secondary: Increased glucose production; decreased glucose uptake by insulin-sensitive tissues	First physiologic defense against hypoglycemia. Primary glucose regulatory factor
65-70	Primary: Increased glucagon secretion Secondary: Increased glucose production	Second physiologic defense against hypoglycemia. Primary glucose counterregulatory factor
	Primary: Increased epinephrine secretion Secondary: Increased glucose production; increased renal gluconeogenesis; decreased insulin secretion; decreased glucose uptake by insulin-sensitive tissues	Third physiologic defense against hypoglycemia. Critical when glucagon is deficient
	Primary: Increased cortisol, growth hormone secretion Secondary: decreased glucose uptake by insulin-sensitive tissues	Not critical, slower counterregulatory factor
50-55	Neurogenic symptoms	Prompt behavioral defense of food intake
<50	Neuroglycopenic symptoms	Compromised behavioral defense

to frequent postprandial hyperglycemia, prolonged basal hyperglycemia, reduced blood glucose time-in-range, and increased glucose variability that may further accelerate the dire clinical consequences of diabetes.

DEFINITIONS & SYMPTOMS

CASE SCENARIO

KT is a 64-year-old woman diagnosed with T2D 7 years ago. She presents today with her husband after having experienced an episode of severe hypoglycemia during the night 2 days ago that awakened her husband. She was making unusual sounds and when her husband tried to wake her, she was incoherent; her blood glucose was 50 mg/dL. She was transported to the local ED where she was treated, held for observation, then released. Her husband is worried that this may be happening more often and wonders if he should be checking her blood glucose during the night.

Hypoglycemia criteria were reclassified in 2017 by a panel of medical, patient, and charitable organizations.[29] Level 1 hypoglycemia is a blood glucose level < 70 mg/dL, and is a threshold generally recognized for the activation of neuroendocrine responses to decreasing blood glucose levels (**TABLE 1**).[30] If blood glucose levels <70 mg/dL recur, some patients with diabetes mellitus begin to experience hypoglycemia unawareness around this level. Level 2 hypoglycemia is a blood glucose <54 mg/dL, and is a threshold when neurogenic (autonomic) and neuroglycopenic symptoms may increase in severity and at which immediate treatment is required. Level 3 hypoglycemia is a severe event characterized by altered mental and/or physical functioning requiring assistance from another person, or who are unable to take fast-acting oral carbohydrate during hypoglycemia.[1,29] It is important to note that level 3 hypoglycemia is not defined by a specific blood glucose level, and it should be considered a life-threatening event that requires both prompt and definitive intervention.

Signs and symptoms of hypoglycemia are categorized as neurogenic or neuroglycopenic (**TABLE 2**).[1,29,31] Neurogenic symptoms, which largely manifest as increased sympathetic neural activity, trigger increased serum epinephrine levels and exhibit symptoms such as palpitations, anxiety, tremors, tachycardia, and behavioral defense mechanisms for hunger and immediate food ingestion. As the blood glucose further declines, neuroglycopenic symptoms such as drowsiness and cognitive dysfunction appear, which can impair behavioral defenses.

The presentations of hypoglycemia symptoms are heterogeneous and individual to patients, and are correlated only loosely with the blood glucose level. For example, older adults and patients with long-term diabetes may exhibit fewer neurogenic symptoms and instead manifest more neuroglycopenic manifestations of hypoglycemia. Longstanding diabetes and recent episodes of any hypoglycemia may attenuate the neurogenic response, which can further contribute to hypoglycemia unawareness[32-34]; in these patients the first actual sign of hypoglycemia may be the clinical presentation of severe hypoglycemia. However, hypoglycemia unawareness is generally reversible if hypoglycemia can be avoided

TABLE 2. **Signs and symptoms of hypoglycemia**[1,29,31]

Neurogenic (autonomic)	Neuroglycopenic
Sweating	Confusion
Palpitations	Drowsiness / Lethargy
Tachycardia	Slurred speech / Difficulty speaking
Tremors	Unable to follow commands / Unresponsive
Anxiety	Inappropriate behavior
Hunger	Headache
Irritability	Blurred vision
Tingling	Cool skin
	Unconsciousness
	Seizures
	Coma

for 2 to 3 weeks, as this time allows inborn mechanisms to become active again.

SELF-MANAGEMENT

Diabetes mellitus is a chronic disease, the management of which is determined by numerous decisions the patient makes daily. It is critical, therefore, that patients with T1D or T2D are educated and supported so that they are able to optimally self-manage their diabetes mellitus. In this regard, a key role for the family physician is to individualize therapy over the course of the disease to best meet the patient's health and other needs. This strategy includes balancing the benefits of glucose control while minimizing the risk of hypoglycemia.

Identifying and addressing patient concerns and barriers to treatment, including hypoglycemia, is especially important. Among the various strategies that can be employed, perhaps those most important may be to build on the established and trusting relationship with the patient and to provide ongoing education and support to both the patient and the family/caregiver, eg, shared decision-making and using open-ended questions. Establishing good rapport combined with open patient provider communication, regular screening, education, and training should help ease patient (and family/caregiver) concerns and help to build the confidence needed to manage the everyday risks of hyperglycemia and hypoglycemia.

At every visit, patients should be assessed for the occurrence of symptomatic and asymptomatic hypoglycemia. In addition to asking the patient about such episodes, a review of the patient's blood glucose log is helpful—but often inadequate because episodes of hypoglycemia, particularly those occurring during sleep, may not be captured through routine blood glucose monitoring. This is especially important to consider in patients treated with daily doses of basal insulin > 0.5 units/kg (particularly when given with sulfonylureas),[14] and in patients who use continuous glucose monitoring and/or insulin pumps[35] regardless of their A1C levels.

HYPOGLYCEMIA MANAGEMENT IN CLINICAL PRACTICE

CASE SCENARIO

A 23-year-old man with T1D is being seen for a routine visit. His family physician notes that his A1C has increased over the past 11 months, rising from 6.8% to 7.2%. Upon questioning, the patient admits that he is no longer increasing his insulin dose based on his blood glucose monitoring because a friend of his was recently hospitalized after a severe hypoglycemic episode. The patient notes that he has frequently experienced symptomatic hypoglycemia through the years and is now especially fearful of a severe hypoglycemic episode. He finds hypoglycemia to be untimely and embarrassing.

The patient's growing concern about hypoglycemia emphasizes the importance of routinely assessing concerns and barriers to treatment. Partners and family members are routinely more distressed and concerned about hypoglycemia and severe hypoglycemia than the person with diabetes.[36] This emphasizes the importance of providing ongoing patient and family education and training, and the critical role for a written and executable action plan for patient self-management. A key part of the action plan is how to identify and acutely respond to adverse events such as hypoglycemia in any situation (eg, exercise, work, school, home, travel). The action plan also should include how patients can prevent hypoglycemia by adjusting medications, meals, and exercise based on blood glucose monitoring. Patient understanding and ability to follow the action plan should be assessed, particularly when changes are made.

A patient resource related to the recognition and self-management of hypoglycemia has been developed by the ADA (see https://professional.diabetes.org/sites/professional.diabetes.org/files/pel/source/sci-advisor_2018_low_blood_glucose_hypoglycemia-newb-final.pdf). For hypoglycemia that can be self-managed, the ADA recommends implementing the "15-15 rule."[37] To raise the blood glucose, 15 g of fast-acting oral carbohydrate should be ingested and the blood glucose level checked 15 minutes later. If the blood glucose remains <70 mg/dL, another 15 g of fast-acting oral carbohydrate should be ingested. These steps are repeated as necessary until the blood glucose is ≥70 mg/dL, at which time a meal or snack is to be eaten to ensure the blood glucose level does not decrease again. Carbohydrate options

TABLE 3. **Selected glucagon products for outpatient use**

	Baqsimi[40]	GlucaGen[41,42]	Gvoke[43]
Approved age group	≥4 years	Children, adults	≥2 years
Route of administration	Intranasal	IM, IV, SC	SC
Dosage form, strength	Intranasal device containing glucagon powder 3 mg	Single-dose vial containing glucagon 1 mg with 1 disposable syringe or vial containing 1 mL SWFR	Single-dose prefilled autoinjector or prefilled syringe containing glucagon 0.5 mg/1 mL or 1 mg/0.2 mL
Reconstitution needed?	No	Yes	No
Contraindications	Pheochromocytoma, insulinoma, known hypersensitivity to glucagon/excipients		
Adverse reactions	[a]Nausea, headache, vomiting, URTI	Nausea, vomiting	[a]Nausea, vomiting, injection site edema raised ≥1 mm, headache
Mean time to peak plasma glucagon level	Adults: 15 minutes Children: 15-20 minutes	12.5 minutes[b]	Adults: 50 minutes Children: 34-51 minutes
Onset of rise of plasma glucose level	<10 minutes	<10 minutes (IM)	<10 minutes
Mean time to peak plasma glucose level	NR	~30 minutes (IM) 30-45 minutes (SC)	NR
Mean maximum glucose increase from baseline	Adults: 140 mg/dL Children: 102-138 mg/dL	—	Adults: 176 mg/dL Children: 123-145 mg/dL

Abbreviations: IM, intramuscular; IV, intravenous; NR, not reported; SC, subcutaneous; SWFR, sterile water for reconstitution; URTI, upper respiratory tract irritation.
[a]Incidence ≥2%
[b]Median

include glucose tablets, gel tube, hard candies, jellybeans, or gumdrops in the amount needed to provide 15 g carbohydrate. Other options include 4 ounces of juice or regular (not diet) soda; 1 tablespoonful of sugar, honey, or corn syrup; or 8 ounces of nonfat or 1% milk.

Glucagon

When a hypoglycemia episode occurs and (1) the patient is unable to take oral carbohydrate, (2) the blood glucose level has not recovered to normal levels despite using the 15-15 rule and the patient's status is deteriorating, or (3) the blood glucose level is very low (ie, <54 mg/dL), then the prompt administration of glucagon is required.

Glucagon is a hormone normally secreted by the pancreas that stimulates glycogenolysis and the release of glucose from the liver. Recent ADA guidelines recommend that glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, ie, blood glucose <54 mg/dL, so the medication is available should it be needed.[1] However, despite these guidelines, few patients who are eligible for a glucagon prescription, including persons who have experienced level 3 hypoglycemia, receive such a prescription.[38,39]

More than 60 glucagon products are available in the United States; several products are shown in **TABLE 3**.[40-43] Historically, glucagon products required reconstitution immediately prior to use, contributing to frequent dosing and administration errors. Now there are 2 exceptions. One is a prefilled syringe or autoinjector (Gvoke) and the other an intranasal formulation (Baqsimi).

All glucagon products provide an onset of rise of the plasma glucose level in <10 minutes. If there has been no response 15 minutes after administration, a second dose may be administered while waiting for emergency assistance. When the patient responds to glucagon treatment, oral carbohydrate should be given to restore liver glycogen and prevent the recurrence of hypoglycemia.

Glucagon administration is not limited to health care professionals; the formulation is generally administered by an individual other than the person experiencing severe hypoglycemia. Because the complexity of standard powder glucagon kits can be intimidating if the person administering them is not properly trained,[28] it is essential to educate family members, friends, and coworkers of patients at risk of hypoglycemia about the importance of glucagon, when and how to administer the glucagon product, and what to do after glucagon administration.[44] Fortunately, the newer intranasal and stable soluble glucagon formulations available in autoinjector pens make this task simpler.[1]

Gvoke PFS and Gvoke HypoPen (glucagon injection)

Gvoke is a concentrated, liquid stable glucagon for subcutaneous injection, indicated for the treatment of severe hypo-

glycemia in pediatric and adult patients with diabetes age ≥2 years. It is provided in a premixed, premeasured, and prefilled device in both adult (1 mg) and pediatric (0.5 mg) dosages.

Two phase 3, randomized, blinded, 2-way crossover trials compared a powder glucagon product available as a Glucagon Emergency Kit (GEK) requiring manual reconstitution with the liquid stable glucagon product available as a prefilled premeasured autoinjector (Gvoke HypoPen).[45] Adults with T1D (N=161) were subjected to induced level 2 hypoglycemia by intravenous administration of regular insulin, followed by treatment with a single dose of 1 of the 2 glucagon products. After a 7- to 28-day washout period, patients were crossed over to the other glucagon product. The primary outcome, increase in the plasma glucose concentration from <50 mg/dL to >70 mg/dL or ≥20 mg/dL rise in plasma glucose within 30 minutes of glucagon administration, was achieved by 99% of patients when treated with Gvoke and 100% of patients when treated with GEK.[43] The mean time to successful plasma glucose recovery was 13.8 minutes in the Gvoke group and 10 minutes in the GEK group. Comparing common adverse events between Gvoke and GEK, nausea occurred in 29.8% and 22.9% of patients, respectively, and vomiting in 16.1% and 9.6%, respectively.[43]

The safety and efficacy of the concentrated, liquid stable glucagon product has been evaluated in a phase 3 single-arm, open-label trial in children with T1D, ages 2 to <18 years (N=31).[43]

Baqsimi (glucagon nasal powder)

Baqsimi is an intranasal glucagon powder indicated for the treatment of severe hypoglycemia in patients with diabetes age ≥4 years. It is provided in a premeasured and prefilled device in a 3 mg dosage, for both adults and children.

The safety and efficacy of the intranasal glucagon product (Baqsimi) was compared with intramuscular (IM) administration of glucagon in a randomized, crossover, non-inferiority study involving adults with T1D (N=75).[46] Hypoglycemia was induced by intravenous insulin, followed by treatment with a single dose of 1 of the 2 glucagon products. After a 7- to 28-day washout period, patients were crossed over to the other glucagon product. The primary outcome, increase in the plasma glucose concentration from the nadir (mean 48-49 mg/dL) to >70 mg/dL within 30 minutes of glucagon administration, was achieved by 100% of patients when treated with the IM product and 98.7% of patients when treated with the intranasal product. The mean time to success was 13 minutes and 16 minutes for the IM and intranasal products, respectively. Nausea with or without vomiting occurred during 38% and 35% of visits, respectively. Head/facial discomfort was reported during 9% and 25% of IM and intranasal visits, respectively.

The safety and efficacy of the intranasal glucagon product have been shown to be similar to an IM product in children with T1D, ages 4 to <17 years (N=48).[47]

SUMMARY

Hypoglycemia is serious and a common experience among patients with diabetes mellitus, yet the condition is often underscreened, unrecognized, and underreported. Although hypoglycemia serves as a common barrier to optimal diabetes treatment, particularly in patients who use insulin, most patients do not receive the regular ongoing screening, education, and training support needed to prevent and self-manage hypoglycemia when it occurs.

The ADA recommends that all patients with diabetes who are at increased risk of clinically important hypoglycemia should have glucagon prescribed. To support this practice, family physicians should provide applicable screening, education, and training for both patients and caregivers on a regular basis. While most glucagon products are in powder form and require manual reconstitution immediately prior to injection, 2 exceptions improve the simplicity of glucagon administration. One is a prefilled syringe or autoinjector and the other is an intranasal product. The safety and efficacy of these 2 glucagon products are similar to products requiring manual reconstitution. ●

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Review of LDL-C Lowering with Focus on New and Emerging Agents

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- **Identify** the benefits and limitations of statin therapy as a treatment option for lowering LDL-C.
- **Intensify** treatment in appropriate patients or refer for intensification.
- **Describe** the safety and efficacy of ezetimibe, bempedoic acid, PCSK9 inhibitors, LDL apheresis.
- **Describe** the safety and efficacy of medications in late-stage development or under review by the FDA for LDL-C reduction.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of hyperlipidemia.

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Dr. Brinton serves on the advisory board for Esperion, Amarin, 89bio, AstraZeneca, Kowa and Novartis, and on the speakers' bureau for Amarin and Esperion. He is a grant recipient for Kowa. Dr. Backes, editorial support, discloses that he serves on the speakers' bureau for Kowa Pharmaceuticals. Dr. Scott, editorial support, discloses that he has no real or apparent conflicts of interest to report.

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INTRODUCTION

There is growing consensus that the "LDL Hypothesis" has been proven. First, essentially every well-conducted cardiovascular outcomes trial (CVOT) with low-density lipoprotein cholesterol (LDL-C)-lowering has also shown reduction in atherosclerotic cardiovascular disease (ASCVD). This is true not only for the many CVOTs with statins, but also for at least 5 other classes of medications as well as 3 non-pharmacological treatments.[1-3] Meta-analyses of these trials show a log-linear relationship between on-treatment LDL-C and ASCVD risk.[4-8] Further, extensive mechanistic data strongly support a causal role for LDL in atherogenesis.[9] Causation is further supported by several Mendelian randomization studies of a wide variety of genetic conditions, which have consistently reported decreased or increased ASCVD risk related to genetically decreased or increased LDL-C, respectively.

This first section of this review will discuss familial hypercholesterolemia (FH), the most important disease of elevated LDL-C levels, in the context of other causes of LDL-C elevations. Next, it will discuss risk assessment and stratification,

relevant to decision-making for LDL-C lowering treatment. Next, LDL-C lowering medications will be covered, beginning with statins, which are by far the best-established agents and which are universally used as first-line treatment for LDL-C lowering and ASCVD prevention. Finally, existing and emerging statin adjuncts will be discussed, regarding their use in management of patients who cannot achieve appropriate LDL-C control with a statin alone.

FAMILIAL HYPERCHOLESTEROLEMIA

FH may be the single most common monogenic disease,[10] with the prevalence of heterozygous FH (HeFH) estimated to be ~1/200 patients in the general population,[11] and homozygous FH (HoFH) being rare, at roughly 1/300,000.[12] HeFH typically presents with untreated LDL-C levels ≥190 mg/dL, Achilles tendon xanthomas (after ~40 years old), and a positive family history of LDL-C >190 mg/dL and premature ASCVD. In contrast, patients with HoFH typically present with LDL-C levels >500 mg/dL and widespread xanthomas or even a CV event in childhood.[13]

The 2018 American College of Cardiology (ACC)/American Heart Association (AHA)/National Lipid Association (NLA) Multi-Society Guideline on the Management of Blood Cholesterol recommends that patients age 20 to 75 years without ASCVD but with an LDL-C ≥190 mg/dL should be treated with maximally tolerated statin therapy to achieve an LDL-C reduction >50%. Further, statin adjuncts are to be considered for secondary prevention if LDL-C remains above a treatment threshold of 70 mg/dL for very high-risk and 100 mg/dL for high-risk patients.[14] The addition of ezetimibe is the first of statin-adjunct. In patients failing to achieve an LDL-C decrease of 50%, or with LDL-C remaining above 100 mg/dL, with both a statin and ezetimibe, use of a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) may then be considered.[15] For HoFH, early identification and referral to a lipid specialist is needed. Treatment is more aggressive than for HeFH in that more than 1 statin adjunct is always required, and usually also LDL-apheresis (also used for more severe HeFH) and sometimes lomitapide (indicated only for HoFH) as well.

RISK STRATIFICATION AND PATIENT SELECTION FOR STATINS AND STATIN ADJUNCTS

Risk stratification is crucial, first, to identify which patients warrant consideration of statin therapy, then to determine the appropriate level of statin intensity, and finally, to direct any needed use of statin adjuncts.

For patients with prior ASCVD ("secondary prevention"), the 2018 Multi-Society Guidelines[14] classify patients as "very high-risk ASCVD" if they have a history of 2 or more major ASCVD events (acute coronary syndrome within the past 12 months, heart attack, ischemic stroke, or symptomatic peripheral arterial disease) or one such event plus ≥2 high-risk conditions (age ≥65 years, HeFH, history of coronary revascularization [outside of a major ASCVD event], diabetes mellitus [DM], chronic kidney disease, hypertension, smoking, congestive heart failure, or LDL-C ≥100 mg/dL despite maximally-tolerated statin therapy). These patients warrant maximally-tolerated statin therapy followed by ezetimibe and then a PCSK9i mAb for LDL-C ≥70 mg/dL.

Patients with a prior event who do not meet these criteria are termed "not very high-risk ASCVD" and are divided by age ≤75 or >75 years. In the former group, treatment is similar to that for very high-risk but PCSK9i are not indicated. For the former group, high- or moderate-intensity statins are warranted, whereas for patients age >75 years, statin continuation may be considered, but initiation of statin therapy is not said to be warranted. That said, a CVOT with ezetimibe in patients age >75 years (EWTOPIA, see below) was first reported at the time of the presentation of the 2018 Multi-Society guidelines. The results of EWTOPIA showed convincing ASCVD benefit with ezetimibe monotherapy, which should, therefore, be considered in these patients.

The 2018 guidelines also state that, for patients without a prior ASCVD event, those with DM and age 40-75 years should receive at least moderate-intensity statin therapy regardless of calculated ASCVD risk. High-intensity statins are warranted in patients with DM in the setting of multiple additional risk factors, independent of age. Treatment of patients age 40-75 years without prior ASCVD, DM, or FH may be guided by the estimated 10-year ASCVD risk score. For risk <5%, lifestyle is sufficient. For risk 5% to 20%, moderate-intensity statins are usually recommended, depending on the presence and number of ASCVD "risk enhancers" [eg, family history of premature ASCVD, South Asian ancestry, metabolic syndrome, Lp(a) or triglycerides, renal insufficiency and/or inflammatory conditions/markers]. For a 10-year ASCVD risk ≥20%, statins are always warranted, with a goal to reduce LDL-C by ≥50%.[14]

BEYOND STATINS

A key question for clinicians is: *What is the overarching strategy for LDL-C lowering?* In contrast to treatment of hypertension or type 2 DM, where overtreatment is always a practical concern, there is good evidence for additional benefit and no harm from treatment to very low LDL-C levels. Patient cost and inconvenience, and side effects of LDL-lowering medications, as well as limitations to prescriber time and effort constitute practical limits, however, to the degree of LDL-C lowering that is reasonable in a given patient.[16]

The concept of LDL-C goal, although not stated in the 2018 Multi-Society Guidelines, was presented in the 2017 AACE Lipid Guidelines, was upheld in the 2019 ESC/EAS Guidelines, and remains the most widely used approach to LDL-lowering worldwide. An LDL-C goal <100 mg/dL is used for high-risk primary prevention, a goal <70 mg/dL for secondary prevention, and a goal <55 mg/dL or even <50 mg/dL is to be considered for patients with very high-risk secondary prevention, or "extreme risk." Because on-treatment LDL-C is an excellent predictor of ASCVD risk, it is standard-of-care to optimize the intensity of the statin regimen (to match ASCVD risk but also to manage side-effects, if any, and to acknowledge diabetes risk). If the LDL-C remains above threshold or goal, then statin adjuncts are needed.[16]

ESTABLISHED STATIN ADJUNCTS

Well-established statin "adjuncts" (add-on therapies) include ezetimibe, niacin, bile acid sequestrants (BAS), and PCSK-9i, the first 3 providing much less LDL-C lowering than statins or the PCSK9i class. While ezetimibe is well-tolerated and well-established as the first-line statin adjunct, niacin and the BAS have limited use because of common adverse effects (AEs) and cumbersome administration.[14,15]

Surprisingly, ezetimibe is commonly underutilized, likely due to the modest degree of its LDL-C-lowering effect, as well as a history of poor insurance coverage (as a branded product) and questionable risk-benefit ratio suggested by early trials following its approval.[17] Ezetimibe is frequently prescribed, however, by lipidologists due to 1) good LDL-lowering relative to statin up-titration, (2) low rates of AEs, (3) generic availability, (4) positive CVOT data, and (5) ease of administration as a small tablet given once daily without regard to meals. For these same reasons, ezetimibe can and should be used widely by family practitioners and other generalists.

The large CVOT of ezetimibe, IMPROVE-IT, demonstrated that ezetimibe added to simvastatin 40 mg daily among patients with recent acute coronary syndrome and well-controlled LDL-C, further reduced CV events by 6%.[18] The mean LDL-C level of 54 mg/dL achieved with ezetimibe (added to simvastatin) was unprecedented at the time and provided strong support for the LDL-C hypothesis that "lower is better." Importantly, IMPROVE-IT resolved any safety concerns with ezetimibe, as major AEs were no different than placebo during the 6-year study. Further, there was no increase in new-onset diabetes, in contrast to statins, and CVD benefits tended to be better in patients with diabetes at baseline. Further, EWTOPIA, a recent CVOT of ezetimibe monotherapy in adults age ≥75 years with elevated LDL-C showed ezetimibe to be quite effective for primary prevention,[19] which is consistent with a sub-analysis of IMPROVE-IT.[20] These findings support ezetimibe as the preferred therapy after a statin, as reflected in the various clinical guidelines.[14-16,21]

NEWER STATIN ADJUNCTS

The recent Food and Drug Administration (FDA) approval of 2 new LDL-C-lowering classes provides the ability to achieve unprecedented LDL-C reduction in high-risk patients.[22]

Bempedoic acid

Bempedoic acid (BA) inhibits the cholesterol synthesis pathway a few steps above HMG CoA reductase (inhibited by statins), thus reducing LDL-C in the same way as statins, to which its effect is additive. An advantage of BA is that it is given as a pro-drug which is converted into the active form only in the liver and not in the muscle, thus limiting muscle-related AEs.[22]

The LDL-C reduction with BA is only moderate and similar to that of ezetimibe, to which it is fully additive. Together, they decrease LDL-C comparable to monotherapy with low- to moderate-intensity statins.[22] BA is indicated as an adjunct to diet and exercise and maximally tolerated statin therapy in patients with HeFH or established ASCVD who require additional LDL-C lowering. Although this indication does not mention ezetimibe use, ezetimibe should always be used before, or concomitantly with BA. BA may be taken any time, once daily, without regard to meals.

The safety and efficacy of BA have been tested in several relatively small, short-term randomized controlled trials.[22-24] When administered with moderate- or high-intensity statin therapy, BA lowers LDL-C by about 18% and the fixed-dose combination with ezetimibe provides LDL-C reductions of 28% to 36%.[22,23] Importantly, in statin-intolerant patients, BA provides an additional 5% to 10% LDL-C-lowering. BA appears to have anti-inflammatory effects, significantly reducing levels of high-sensitivity C-reactive protein by about 25% to 30%, similar and additive to the effects of statins and ezetimibe.[22]

Overall, BA is well tolerated with reports of most AEs, including myalgias, not differing between BA and placebo, likely due to a lack of pro-drug activation in skeletal muscle.[22,23,25] Importantly, however, BA is associated with small but significantly higher rates of gout (1.5% vs 0.4%) and tendon rupture (0.5% vs 0%) compared to placebo,[25] primarily in those with predisposing or underlying conditions (eg, hyperuricemia, gout, prior tendon rupture). Due to the strength and consistency of ASCVD benefit with all LDL-lowering agents, BA was approved by the FDA even while awaiting results from CLEAR Outcomes, the large CVOT of BA, which are expected in 2022.[24]

BA should clearly be used only in patients who require further LDL-lowering despite optimal use of statins then ezetimibe. BA will likely be of particular benefit in patients with statin intolerance, since they will have greater need for LDL-C lowering and BA will provide somewhat greater LDL-C decreases in such patients. Except in the rare case of ezetimibe intolerance, the fixed-dose combination of BA and ezetimibe will likely be preferred over BA alone since the combination simplifies the use of 2 needed medications. Interestingly, despite a lack of CVOT data, BA is likely best used before a PCSK9i, due to the strong evidence for the LDL hypothesis. This is due to greater ease of use of a tablet vs an injection, as well as easier payer approval and generally lower patient out-of-pocket expenses with BA than with a PCSK9i. An important potential exception to this sequence would be in patients with LDL-C >30% above goal, in whom BA would be unlikely to provide sufficient LDL-lowering. Additional considerations are the presence of anti-inflammatory effects vs their absence with PCSK9i, contrasting with the ability of PCSK9i to lower Lp(a), lacking with BA.[14,15]

Proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i)

The liver secretes PCSK9 into plasma, where it binds to the LDL-receptor. Although formation of this complex does not impair binding of LDL to its receptor, when that receptor is internalized into the hepatocyte, the PCSK9/LDL-receptor complex is degraded. This prevents the usually robust recycling of LDL-receptors, greatly lowering LDL-receptor number and function, thus increasing LDL-C levels.[26]

Two fully human monoclonal antibodies to PCSK9, alirocumab and evolocumab, were developed and received FDA approval in 2015 for use in patients needing additional LDL-C lowering after diet, lifestyle and maximally tolerated statin therapy.[26,27] Despite the lack of mention of ezetimibe in their label, a PCSK9i should almost always be tried after adding ezetimibe (and BA). PCSK9is are administered via subcutaneous (SC) injection, typically every 2 weeks, although once-monthly dosing is also available.[26,27] They cause a dramatic 50% to 65% LDL-C decrease, depending on regimen details. The PCSK9i mAbs, being fully human proteins, evoke minimal to no production of blocking antibodies and only rare allergic reactions. Further, other AEs are minimal, beyond an occasional mild injection site reaction.[27] Importantly, since their approval, CVOTs of both agents have demonstrated a 15% reduction in major CV events when added to maximally tolerated statin therapy.[28,29] Both CVOTs showed unprecedented very low LDL-C levels roughly in the range of 7 to 40 mg/dL, well beyond that achievable with statin monotherapy. The fact that CV event rates continued to decline (albeit gradually) within this ultralow LDL-C range has served to further prove the LDL hypothesis and to reinforce the clinical impetus for aggressive LDL-C reduction in patients at extremely high ASCVD risk.

The use of PCSK9is has been less widespread than initially expected due to high annual cost (both alirocumab and evolocumab $5850), payer requirements, which have eased somewhat, and the patient education needed to regularly self-administer a subcutaneous injection.[30]

LDL apheresis and the MTP inhibitor

Two other treatments are used only by a small number of highly sub-specialized lipidologists, but it is useful for family physicians to be aware of them so that they can refer their patients when other treatments are inadequate to bring LDL-C levels down to goal.

LDL-apheresis is a procedure in which a patient's plasma is run over columns to remove most of the LDL, very low-density lipoprotein and Lp(a) from the circulation. Other pro-atherogenic factors, such as fibrinogen and inflammatory factors are also removed. This procedure is offered only in a handful of centers across the United States and is indicated only for patients with prior ASCVD and an LDL-C remaining above 100 mg/dL (or higher, in the absence of a prior event), despite maximally tolerated medical therapy. It is also newly approved for lowering elevated Lp(a), an important ASCVD risk factor, for which it is the only FDA-approved treatment.[13] Apheresis lowers the LDL-C level by about 70%-80%. Although levels quickly rebound, when the treatments are repeated on a regular basis, usually every 2 weeks, there is a cumulative time-averaged decrease of roughly 60%, while CV events are reduced by roughly three-quarters.[2,31,32] The 2- to 4-hour treatment session is safe and generally well tolerated.

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor approved by the FDA for HoFH[33]; it is occasionally used off-label for severe HeFH. Lomitapide blocks synthesis of both apo B-48 in the intestine and apo B-100 in the liver. High-dose lomitapide can reduce LDL-C up to 50%, even in the absence of LDL-receptor function. Unfortunately, it usually can be tolerated only at lower doses, due to severe gastrointestinal AEs (eg, bloating, steatorrhea) which occur even with fairly low fat intake. Further, concerns regarding hepatoxicity restrict the use of lomitapide under a Risk Evaluation and Mitigation Strategy (REMS) program.[13,33]

EMERGING LIPID-LOWERING THERAPIES

Inclisiran

Inclisiran is a PCSK9i agent in late clinical development, which employs a novel mechanism for inhibiting production

of the PCSK9 protein in hepatocytes.[34] Inclisiran consists of a small interfering RNA (siRNA) segment that blocks synthesis of PCSK9 for a prolonged period of time and reduces[22,34-36] LDL-C by about 50%.[36] Due to the long intracellular persistence of the siRNA molecule, after the initial 2 doses (generally given at a 2-month interval), efficacy is maintained with a dosing interval of just twice annually, making this treatment dramatically easier than the once- to twice-monthly injections required for the PCSK9i mAbs. In light of the novel mechanism and prolonged half-life of action of inclisiran, evaluation of its safety will require special FDA scrutiny. Extensive testing to date has shown similar AEs with inclisiran and placebo (except for a low rate of injection site reactions).[22,36] A decision by the FDA is expected late in 2020. Meanwhile, a large CVOT with inclisiran is expected to complete in 2023.

LIB003

LIB003 is an investigational agent in early phase III trials that offers another approach to inhibiting PCSK9. The novel agent is a recombinant fusion protein that combines the PCSK9-binding domain, adnectin, with human albumin to extend the half-life to 15 days.[37] Phase II dose-ranging studies demonstrated that LIB003 once-monthly reduced LDL-C by 77% after 12 weeks and by 60% after 36 weeks.[37] Treatment was well tolerated with overall AEs being similar to placebo in early studies.

Evinacumab

Evinacumab is another agent in development for hypercholesterolemia that consists of fully human mAbs which inhibit angiopoietin-like protein 3 (ANGPTL3), reducing LDL-C levels independently of the LDL-receptor.[22,38] Given this mechanism of action, evinacumab has reduced LDL-C by 49% in patients with HoFH, and the FDA has granted it "breakthrough therapy" designation for this disorder.[38] Interestingly, evinacumab also increases lipoprotein lipase activity and has shown a 75% reduction in triglyceride levels.[39] The FDA accepted the biologics license application for evinacumab for priority review in August 2020.

SUMMARY

Elevated LDL-C levels are the primary treatable cause of ASCVD. Decades of CVOTs involving multiple therapies for lowering LDL-C demonstrate remarkably consistent reductions in ASCVD events, proportional to LDL-C reductions. Statins remain the foundation for LDL-C-lowering treatment; however, their efficacy at doses tolerated by the patient is not always sufficient to achieve goal levels. Existing statin adjuncts can efficiently and safely provide further LDL-C-lowering. Further, with the likely advent of additional LDL-lowering agents in the near future, even better LDL-C control should become easier and more universally achievable. ●

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Strategies for Preventing COPD Exacerbations

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LEARNING OBJECTIVES

After participating in this activity on chronic obstructive pulmonary disease (COPD), family physicians will be better able to:

- **Identify** symptomatic patients at increased risk of COPD to prompt early diagnostic evaluation
- **Individualize** evidence-based therapy with the goal of reducing COPD exacerbations and improving patient outcomes
- **Identify** the role of fixed triple-combination inhalers as part of individualized therapy

It's natural to think about the burden of chronic obstructive pulmonary disease (COPD) in terms of the prevalence (6% of US adults),[1,2] mortality (fourth leading cause of death at a rate of 44 deaths per 100,000 US population),[3,4] and total cost of care ($49 billion/year).[5] Although sobering, these statistics don't adequately capture the patient perspective, where the burden of COPD generally is characterized as daily symptoms, limited activity, poor quality of life, and contributing to fear of acute worsening of respiratory symptoms (previously called exacerbations), often leading to hospitalization and early death.[6,7] In fact, COPD is a leading cause of disability, accounting for 1.2 million years lived with disability in the United States in 2016.[8]

A survey of patients with COPD who were hospitalized for acute worsening of respiratory symptoms identified 6 major unmet needs: (1) understanding of disease: most correctly identified their diagnosis and recognized their symptoms worsening over time, but only one-half understood their disease severity and prognosis; (2) symptoms: breathlessness was universal and severe; (3) physical limitations: COPD prevented participation in activities; (4) emotional distress: depressive symptoms and/or anxiety were present in most participants; (5) social isolation: most identified social limitations and felt confined to their homes; and (6) concerns about the future: one-half expressed fear about their future.[9]

To improve the health outcomes of these patients by reducing COPD-related hospital readmissions, the American Thoracic Society identified barriers to optimal care[10]:

- Poor communication
- Ineffective discharge guidance
- Lack of effective follow-up
- Limited efforts to engage patients and family
- Patient not being placed at the center of care
- Fragmentation of system/differences in where individual seeks care.

More recently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has provided several key recommendations[11]:

1. The management strategy for stable COPD patients should be based on assessment of symptoms and risk of exacerbations.
2. The assessment should determine the level of airflow limitation, its impact on the patient's health status, and the risk of future events (eg, exacerbation, hospitalization, or death).
3. All individuals who smoke should be strongly encouraged and supported to quit.
4. The main treatment goals are reduction of symptoms and future risk of exacerbations.
5. The goal for treating COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent a future event.
6. Following an exacerbation, appropriate measures for preventing a future event should be initiated.

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CONFLICT OF INTEREST
Dr. Yawn discloses that she has served on advisory boards for GlaxoSmithKline, AstraZeneca, Novartis and Boehringer Ingelheim. She is a consultant for GlaxoSmithKline on epidemiology studies of COPD and herpes zoster and has an investigator initiated grant to study patient and clinician awareness of risk of HZ in people with COPD.

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FIGURE 1. **COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk questionnaire**[21]

For each question, place an X in the box with the answer that is best for you. There are no right or wrong answers, only answers which are right for you.

Please answer each question	No		Yes
1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?	☐		☐
2. Does your breathing change with seasons, weather, or air quality?	☐		☐
3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis, or swim?	☐		☐
4. Compared to others your age, do you tire easily?	☐		☐
	0	1	2 or more
5. In the past 12 months, how many times did you miss work, school, or other activities, due to a cold, bronchitis, or pneumonia?	☐	☐	☐

For questions 1-4, no = 0; yes = 1. Maximum total = 6.

Abbreviation: COPD, chronic obstructive pulmonary disease.

SCREENING/CASE FINDING

A key objective identified by GOLD is early detection of COPD.[11] One approach is to identify persons at increased risk of COPD before signs and symptoms of the disease develop. This approach has been systematically investigated by the United States Preventive Services Task Force, which found a lack of evidence of benefit for screening on quality of life, morbidity, or mortality in asymptomatic patients.[12,13]

Another approach for the early detection of COPD is to identify patients with symptoms and signs of COPD that the patient and family physician have not recognized.[14] GOLD advocates case finding in this population.[11] Patients who fit into this population include smokers in their 30s who don't have asthma, but have had a lower respiratory tract infection treated with antibiotics or oral corticosteroids. Some patients with COPD attribute the slow decline in lung function and compensatory activity limitation as consequences of aging, obesity, poor conditioning, or smoker's cough.[15] Such changes often become their new normal. Family physicians might not ask patients about chronic respiratory symptoms or fail to note the importance of recurrent respiratory events.[15,16] The use of validated tools to identify chronic or recurrent respiratory symptoms in the primary care setting has demonstrated up to a 4-fold increase in COPD diagnoses, indicating under recognition of patients with symptomatic COPD.[17-20]

The COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) questionnaire was developed to identify patients with undiagnosed, yet symptomatic COPD who would benefit from treatment with available therapies if the COPD diagnosis is confirmed.[21] The 5-item self-administered questionnaire asks patients about symptoms, impact, and acute respiratory illness (**FIGURE 1**).[21] Patients with a CAPTURE score of 0 or 1 are not considered at risk of an exacerbation or to have moderate-to-severe airflow obstruction (ie, forced expiratory volume over 1 second [FEV_1] <60% of predicted); therefore, further evaluation is not warranted. Patients with a CAPTURE score of 5 or 6 are considered to have a high likelihood of symptomatic respiratory disease and/or exacerbation risk and should undergo further evaluation, including spirometry. Patients with a CAPTURE score of 2, 3, or 4 should undergo peak expiratory flow testing. It is important to note that the CAPTURE questionnaire is not intended to identify patients with mild COPD (ie, FEV_1 >60% predicted and no exacerbation in the prior 12 months).

DIAGNOSIS

The most characteristic symptom of COPD is chronic, progressive dyspnea, while cough with sputum production is found in <30% of patients. These symptoms might vary from day to day and could occur before development of airflow limitation by many years. Chronic respiratory symptoms or an acute exacerbation are the common reasons patients seek medical care. The presence of one or more of these respiratory symptoms should prompt further evaluation to identify the underlying cause(s). Disorders to be considered in the differential diagnosis include asthma, heart failure, and bronchiectasis. Differentiating asthma from COPD

TABLE 1. **Differentiating COPD vs asthma**

Feature	COPD	Asthma
History of tobacco smoking or exposure to other types of smoke	Most	Possibly
Symptoms first occur before age 35	Rare	Often
Family history	Uncommon	Common
History of atopic disease	Uncommon	Common
Chronic productive sputum	Common	Uncommon
Breathlessness	Persistent, progressive	Variable
Nighttime awakening with breathlessness and/or wheeze	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common
Lung function between symptoms	Abnormal	Normal/near normal

Abbreviation: COPD, chronic obstructive pulmonary disease.

often is challenging (**TABLE 1**)[11,22]; COPD and asthma often are comorbid.[23]

The history and spirometry form the basis of the COPD diagnosis.[11] Key aspects of the history include exposure to risk factors (tobacco and other smoke, occupational dusts, vapors, fumes, gases, biomass fuels, and chemicals), personal history (eg, childhood respiratory infections, low birthweight, genetic factors, congenital/developmental abnormalities), family history of chronic respiratory disease, pattern of symptom development, history of acute respiratory events, comorbidities, and impact on activities of daily living and quality of life. It is important to consider that one-quarter of patients who develop COPD do not have a smoking history. Spirometry is essential for the diagnosis because it is more specific for COPD than peak expiratory flow measurement.[11] Patients with COPD typically show a decrease in both FEV_1 and forced vital capacity (FVC).[11] A post-bronchodilator FEV_1/FVC ratio <0.70 confirms the presence of airflow limitation.[11]

To assess for the presence of symptoms, the COPD Assessment Test (CAT) is preferred over the Modified British Medical Research Council (mMRC) Questionnaire[11] because CAT assesses symptoms beyond breathlessness, such as chest tightness, sleeping soundly, and confidence to leave home.[24] A CAT score ≥10 (maximum 40) indicates the need to consider symptomatic treatment.[11,25] A limitation of CAT is that it does not categorize patients into symptom severity groups for treatment purposes.

The CAT score has been combined with the FEV_1 and history of moderate or severe exacerbations to form the ABCD assessment tool which is used for the diagnosis, prognosis, and development of an individualized treatment plan. The refined ABCD assessment tool includes a number and letter (**FIGURE 2**).[11] The number relates to the GOLD grade of severity of airflow limitation, which is based on the FEV_1, while the letter relates to the symptom burden, which is based on the CAT (or mMRC) score and history of exacerbations. The refined ABCD tool facilitates greater treatment individualization based on parameters that are driving the patient's symptoms at any given time.

PREVENTING FUTURE ACUTE EVENTS

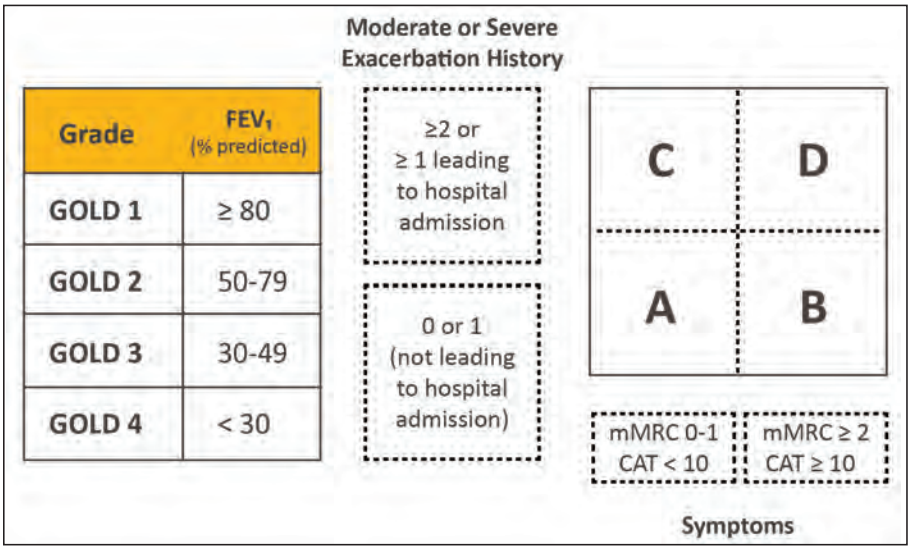
A key shift in treatment in recent years has been away from focusing on acute treatment of exacerbations to an emphasis on chronic treatment to maintain stable disease and prevent exacerbations and other events, such as hospitalization and death. This approach is analogous to the treat-to-target approach used for patients with type 2 diabetes mellitus.

In addition to eliminating or minimizing risk factors, this shift to preventive treatment requires early initiation of individualized, comprehensive therapy consisting of nonpharmacologic therapy, often including pulmonary rehabilitation, as well as combination pharmacologic therapy, with treatment escalation as needed based on symptoms and history of exacerbations. The importance of pulmonary rehabilitation should not be overlooked because of its benefits in improving symptoms, quality of life, and physical and emotional participation in everyday activities.[11] Holistic management directed at comorbidities and risk factors, as well as psychosocial support, is essential. As a chronic, debilitating, often fatal disease, it is important to provide team-based care that nurtures hope and supports patients to acquire knowledge, skills, and attitudes needed to self-manage their COPD.

INITIAL PHARMACOLOGIC TREATMENT

The choice of initial pharmacologic therapy in a patient with stable COPD is based on which 1 of the 4 ABCD groups the patient fits as determined by symptoms and exacerbation risk (**FIGURE 3**).[11] The choice within each class of medication depends on availability and the patient's responses and preferences. Patients in group A can be offered a short- or long-acting bronchodilator to reduce breathlessness, while patients in group B are best treated with a long-acting bron-

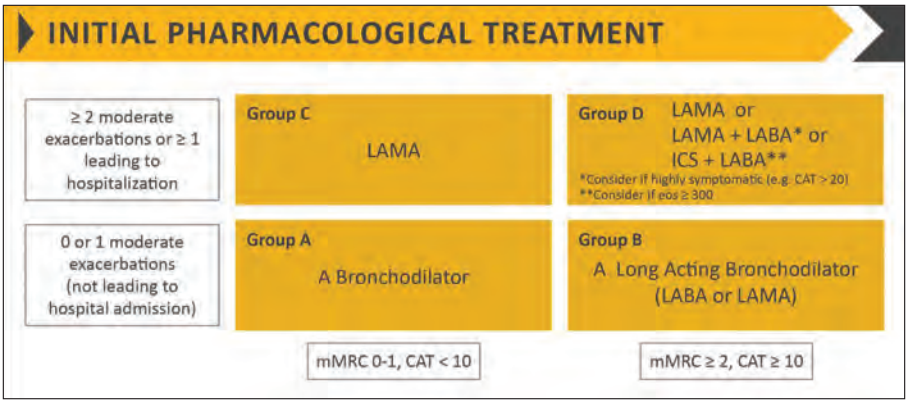
FIGURE 2. **GOLD refined ABCD assessment tool**[11]



Example: Consider 2 patients – both patients with FEV_1 <30% of predicted, CAT scores of 18 and one with no exacerbations in the past year and the other with 3 moderate exacerbations in the past year. Both would have been labeled GOLD D in the prior classification scheme. However, with the new proposed scheme, the patient with 3 moderate exacerbations in the past year would be labeled GOLD grade 4, group D.

Abbreviations: CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council dyspnea questionnaire.

FIGURE 3. **Initial pharmacological treatment**[11]



Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive lung disease; eos, eosinophils; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council dyspnea questionnaire.

chodilator, or, in the case of severe breathlessness, 2 bronchodilators. Treating patients in group C should consist of a single long-acting bronchodilator, preferably a long-acting muscarinic antagonist (LAMA).

A LAMA generally is appropriate as initial therapy for patients in group D. However, for patients with more severe symptoms such as those with a CAT score ≥20, the combination of a LAMA plus a long-acting $beta_2$ agonist (LABA) is recommended. In patients with a history of asthma or blood eosinophil count ≥300 cells/μL, initial therapy with a LABA plus inhaled corticosteroid (ICS) is recommended. If breathlessness or exercise limitations persists or the patient develops exacerbations, escalation to inhaled triple therapy (ICS + LABA + LAMA) is recommended.[11]

Inhaled medications

Localization of the COPD disease processes within the respiratory system lends itself to orally inhaled medication administration. Numerous orally inhaled medications for COPD are available, including nebulizers, pressurized metered-dose inhalers with/without spacers, soft-mist inhalers, breath-actuated metered-dose inhalers, and single- and multi-dose dry powder inhalers. Selection of an inhaler should be based on availability and storage requirements, as well as efficacy and safety.[11,26] Patient factors include affordability, preference, and ability and understanding about proper use.[11,26,27] For patients who require ≥2 inhaled controller medications, consider the same type of device for all inhaled medications prescribed for the patient.[28] Ideally, all inhaled controller medications should be available as dual or triple therapy in a single device. Advantages of combination inhalers is improved adherence and lower medication cost.[29]

Two recent systematic reviews and meta-analyses assessed the safety and efficacy of single inhaler triple therapy with other inhaled medications for COPD, as well as separate inhalers of the 3 medications. The single inhaler triple therapies included ICS + LAMA + LABA. Two products are approved by the US Food and Drug Administration: fluticasone furoate/umeclidinium/vilanterol and budesonide/glyco-

TABLE 2. **Checklist for the COPD follow-up office visit**

• Repeat the CAT
○ Have patient complete in the waiting room or examination room[a]
• Ask about:
○ Respiratory problems or events since last visit, particularly if they required an urgent care/emergency department visit
○ Changes in comorbidities
○ Changes in activity level (be specific)
○ Difficulties with prescription refills
○ Difficulties following the treatment plan
○ Satisfaction with treatment
• Observe inhaler technique
○ Can be done by trained staff
• Review medications the patient is taking to be sure they are the ones prescribed
○ Requires patient to bring in actual medications instead of a list
○ Brand might have been changed by pharmacist because of insurance
• Review patient's goals and action plan[a]

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease.

[a]Can be facilitated by using the COPD Foundation application (https://www.copdfoundation.org/Learn-More/The-COPD-Pocket-Consultant-Guide/Healthcare-Provider-Track.aspx?gclid=CjwKCAjwnIr1BRAWEiwA6GpwNZxd9C7jZuLRF55ltEdWb-gVSLyVEc_YaNAi8puwJ_8nymlXeBVrlhoC31wQAvD_BwE)

pyrronium bromide/formoterol fumarate. A third product, beclomethasone dipropionate/glycopyrronium bromide/formoterol fumarate, is investigational. The recent approval of budesonide/glycopyrronium bromide/formoterol fumarate is based on the results of the phase 3 ETHOS trial. The ETHOS trial showed that at both the standard budesonide dose of 320 mcg and half-dose of 160 mcg demonstrated significant reductions in exacerbations compared with single inhaler dual therapy of glycopyrronium/formoterol fumarate and budesonide/formoterol fumarate, respectively, in patients with moderate to very severe COPD.[30] At the standard budesonide dose, the observed reductions in rate of moderate and severe exacerbations were 24% and 13% with the single inhaler triple therapy vs the single inhaler dual therapies, respectively. In addition, the single inhaler triple therapy showed a 46% reduction in the risk of all-cause mortality compared with glycopyrronium/formoterol fumarate.

The meta-analyses showed that the rate ratios for moderate-to-severe exacerbations with a single inhaler triple therapy were 0.69 (95% confidence interval [CI], 0.55 to 0.87) and 0.80 (95% CI, 0.71 to 0.90) vs LABA + LAMA and ICS + LABA dual therapy, respectively. Improvements in lung function and quality of life were greater with single inhaler triple therapy compared with single inhaler dual therapy (LABA + LAMA or ICS + LABA).[31,32] Meta-analyses found no significant differences in several clinical endpoints, including exacerbations or FEV_1, between single inhaler triple therapy and triple therapy using 3 separate inhalers. In both analyses, the risk of pneumonia was significantly higher with single triple inhaler therapy compared with LABA + LAMA (relative risk 1.38; 95% CI, 1.14 to 1.67[31] and 1.53; 95% CI, 1.25 to 1.87[32]) but not ICS + LABA dual therapy.

Individualizing inhaler selection and teaching and reinforcing proper administration technique have a direct impact on patient adherence and health outcomes.[33] Unfortunately, adherence often is poor and administration errors are common with inhaled medications; clinicians might not be familiar with proper administration technique.[26,34-37] Moreover, clinicians do not routinely assess a patient's ability to use their prescribed inhaler.[38] Common errors in the use of an inhaler device relate to difficulties with inspiratory flow, inhalation duration, coordination, dose preparation, exhalation maneuver before inhalation, and breath-holding following dose inhalation.[39] In patients with a low peak inspiratory flow, for example, which is common after a severe exacerbation, it might be best to avoid using a higher resistance inhaler. When used properly, there appear to be no clinically important differences among the devices, including hand-held devices vs nebulized therapy.[11,40]

FOLLOW-UP VISITS

The shift to preventing exacerbations and other acute events as a primary treatment goal makes frequent follow-up visits critical so that the treatment plan can be adjusted as needed based on patient symptoms, as well as difficulties he or she might be experiencing (**TABLE 2**).[11] The written treatment plan, which is indispensable to promote effective patient self-management,[41,42] should be updated to reflect any changes.

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Stemming the Progression of Diabetic Kidney Disease: The Role of the Primary Care Clinician

George Bakris, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Identify the risks of kidney disease and their consequences in patients with T2DM.
- Initiate evidence-based therapy to slow the progression of kidney disease in patients with T2DM and CKD.
- Become familiar with the mineralocorticoid receptor antagonist and endothelin receptor antagonist under late-phase investigation.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes mellitus and kidney disease.

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Dr. Bakris discloses that he is a principal investigator for Bayer's FIDELIO diabetic nephropathy outcome trial, a steering committee member for the Novo Nordisk FLOW trial, and on the CALM-2 steering committee for Vascular Dynamic.

Gregory Scott, PharmD, RPh, editorial support, discloses he has no real or apparent conflicts of interests to report. Additional PCEC staff report no conflicts of interest.

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DEFINITION

Chronic kidney disease (CKD) is defined as ≥1 abnormalities of kidney structure or function that have been present for >3 months and have health implications.[1] Markers of kidney damage include albuminuria (urine albumin excretion rate ≥30 mg/24 hours or urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), urine sediment abnormalities, electrolyte and other abnormalities caused by tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation. Decreased kidney function is indicated by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

EPIDEMIOLOGY

CKD is a common disease that affects 37 million U.S. adults, more than 1 in 7, with the highest prevalence among those age 20 to 54.[2] Nearly one-half (48%) of individuals with severely reduced kidney function, but not on dialysis, are not aware of having CKD.[2] CKD is especially common among persons with diabetes or hypertension, their combination representing approximately 3 out of 4 new cases of CKD.[3] Other risk factors for CKD include heart disease, obesity, family history of CKD, certain ethnicities (ie, African Americans, Hispanic Americans, Asians, Pacific Islanders, and Native Americans), older age, low birth weight, smoking, and acute kidney injury, as well as exposure to heavy metals and excessive alcohol use, recreational drugs, or analgesic medications.[2,4]

There is a bi-directional relationship between CKD and cardiovascular disease because CKD is an independent risk factor for coronary heart disease, heart failure, and stroke. CKD also increases the risk of pulmonary failure, anemia, immune failure, metabolic bone disease, anorexia, and edema.[2] Cognition also is affected as CKD progresses, independent of age-related changes, affecting both lower-order and higher-order cognitive abilities.[5]

The natural history of CKD in persons with diabetic kidney disease (DKD) progresses from glomerular hyperfiltration to rising albuminuria, declining eGFR, and finally end-stage kidney disease.[6-8] It is important to recognize that albuminuria can precede a decline in the eGFR by more than a decade.[6,9] Analysis of data from the ACCORD trial showed that among persons with type 2 diabetes mellitus (T2DM), those with non-albuminuric CKD showed a slower rate of decline in eGFR than those with albuminuric non-CKD or albuminuric CKD.[10] Further data supporting the importance of recognizing and managing albuminuria is the finding that higher UACR is associated with a greater risk of cardiovascular death, independent of eGFR.[1]

CARDIOVASCULAR OUTCOME TRIALS

The contribution of hyperglycemia to kidney disease and the microvascular benefits of reducing blood glucose are the basis of the goal for achieving glycemic control in persons with T2DM. There was, however, little evidence demonstrating cardiovascular benefit with glucose-lowering medication. In fact, a 2007 systematic review and meta-analysis showed a significantly increased risk of myocardial infarction and suggested a higher risk of cardiovascular death in patients with T2DM treated with rosiglitazone.[11] Although the finding related to cardiovascular death subsequently was proven inaccurate,[12,13] the FDA issued guidance in 2008 requiring pharmaceutical manufacturers to evaluate the cardiovascular risk of new glucose-lowering medications for T2DM in a cardiovascular outcome trial (CVOT).[14]

Since 2008, more than 20 CVOTs have demonstrated that the cardiovascular safety of each of the dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and sodium glucose cotransporter-2 inhibitors (SGLT-2i) investigated is non-inferior to placebo as part of standard therapy. Moreover, linagliptin,[15] saxagliptin,[16] dulaglutide,[17] liraglutide,[18] semaglutide (injectable),[19] canagliflozin,[20] dapagliflozin,[21,22] and empagliflozin[23] have been shown to significantly reduce the occurrence of one or more kidney endpoints compared with placebo. Endpoints included change in UACR, serum creatinine, and/or eGFR, as well as time to dialysis and renal death. Among these medications shown to reduce kidney endpoints, only linagliptin and canagliflozin have been investigated in a clinical trial specifically powered to assess kidney outcomes in high-risk patients with T2DM.

The CARMELINA trial included adults with T2DM, a history of vascular disease, UACR >200 mg/g, and reduced eGFR and micro- or macroalbuminuria; patients with end-stage kidney disease (ESKD) were excluded.[15] Participants were randomized to linagliptin, 5 mg/d, or placebo in addition to standard care. After a median follow up of 2.2 years, the renal-specific composite outcome (time to first occurrence of adjudicated death because of renal failure, ESKD, or sustained ≥40% decrease in eGFR) did not differ between the linagliptin and placebo groups (9.4% and 8.8%, respectively; $P = .62$).

In the CREDENCE trial, participants were treated with renin-angiotensin-aldosterone inhibitor therapy at baseline and had a mean eGFR of 56 mL/min/1.73 m^2 and UACR of 927 mg/g.[24] This trial showed that canagliflozin significantly reduced a renal-specific composite outcome (ESKD, doubling of serum creatinine, or renal death) over the median follow up of 2.62 years in patients with an eGFR as low as 30 mL/min/1.73 m^2. In addition, the risk of ESKD was 32% lower in the canagliflozin group compared with placebo (hazard ratio: 0.68; 95% confidence interval 0.54 to 0.86; $P < .001$).

Recently, the DAPA-CKD trial was stopped early after a routine assessment of efficacy and safety showed earlier than anticipated benefits with dapagliflozin for the primary endpoint of a composite of renal function or death in patients with CKD regardless of the presence of T2DM.[25,26]

The 1 DPP-4i, 3 GLP-1RA, and 3 SGLT-2i medications with a demonstrated kidney benefit—with preference given to the SGLT-2is—are recommended by the American Diabetes Association for patients with T2DM and established CKD who do not achieve adequate glycemic control with lifestyle management combined with metformin.[27] Although this rec-

ommendation is for secondary prevention, that is, in patients with established CKD, evolving evidence suggests there might be a role for these medications for primary prevention, meaning patients who do not have established CKD.[28,29]

The kidney benefits of selected glucose-lowering medications and their rapidly evolving role in treating patients with T2DM and CKD is a reminder of the importance of identifying patients with DKD and early use of comprehensive evidence-based treatment that includes SGLT-2is as recommended.

CASE SCENARIO

Louise, age 69, was diagnosed with T2DM 4 years ago. Her glycated hemoglobin (A1c) was 8.8% at diagnosis. Her A1c has remained above her target of <7%, rising to 7.8% over the past 9 months. Louise complains of puffiness in her hands and feet.

Vital signs: within normal limits

Labs: eGFR 56 mL/min/1.73 m^2 (60 mL/min/1.73 m^2 17 months ago); UACR 35 mg/g

Current medications: metformin, DPP-4i, atorvastatin, ramipril, and low-dose aspirin

How would you modify her therapy?

RISK FACTOR MANAGEMENT

Goals of therapy

Evaluation of the management plan requires reviewing the treatment goals. In the case of patients with DKD, the overarching goal is to reduce the risks of kidney disease progression and cardiovascular disease.[30] To achieve this, comprehensive treatment is needed to address/include the following[9,30]:

- Glycemic control
- Blood pressure control
- Renin-angiotensin-aldosterone system (RAAS) blockade
- Lipid management
- Lifestyle/physical activity
- Smoking cessation
- Nutrition
- Aspirin (low-dose)

Glycemic control

The American Diabetes Association recommends an A1c <8% for patients with advanced microvascular or macrovascular complications, extensive comorbidities, limited life expectancy, or history of severe hypoglycemia.[31] By comparison, the National Kidney Foundation (NKF) recommends a target A1c of <6.5% to <8% in patients with T2DM and non-dialysis dependent CKD to prevent or delay progression of microvascular complications.[30,32] The NKF recommendation advises that safe achievement of lower A1c targets, such as A1c <6.5% or <7%, could be facilitated by blood glucose self-monitoring or combined continuous glucose monitoring and glucose-lowering medications that are not associated with hypoglycemia.[30] Moreover, the NKF recommends treatment consisting of lifestyle management in combination with metformin and SGLT-2i therapy, with additional drug therapy as needed for glycemic control. The use of both metformin and SGLT-2i therapy is contingent on an eGFR ≥30 mL/min/1.73 m^2.[30] A GLP-1RA shown to offer a cardiovascular benefit may be used as an alternative to metformin or SGLT-2i.

Blood pressure control

Blood pressure is also a key target and should be ≤140/90 mm Hg in patients with DKD and urine albumin excretion <30 mg/24 hours or those with a 10-year atherosclerotic cardiovascular disease (ASCVD) risk <15%.[32,33] [The American College of Cardiology ASCVD Risk Estimator Plus may be found here: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/.] Target blood pressure is ≤130/80 mm Hg in patients with DKD and urine albumin excretion ≥30 mg/24 hours or 10-year ASCVD risk >15%.[32,33] RAAS blockade with an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) is recommended in patients with albuminuric CKD and hypertension.

Other comorbidities

Other comorbidities, such as obesity,[34] dyslipidemia,[35] smoking,[36] etc., should be treated as recommended by existing guidelines.[9]

RAAS inhibitor therapy

The ACE-I and ARB medication classes have been shown to effectively reduce albuminuria, and even reverse moderately increased albuminuria, thereby avoiding or delaying the progression of CKD to ESKD in patients with DKD.[30] There appears to be no difference between ACE-I and ARB in renal outcomes or side effects.[37] Because the albuminuria-lowering effect, as well as side effects, are dose-related, it is important to optimize ACE-I or ARB therapy by starting at a low dosage and increasing to the highest tolerated recommended dosage.

Blocking aldosterone with a steroid-based mineralocorticoid receptor antagonist (MRA), such as spironolactone or eplerenone, might be beneficial in patients with resistant hypertension who have eGFR >45 mL/min/1.73 m^2 and no history of hyperkalemia.[30] Additive benefits are observed with the addition of a steroid-based MRA to an ACE-I or ARB.[38-40] The use of steroid-based MRA therapy is limited by adverse events, such as hyperkalemia in patients with stage ≥3 CKD.[41,42]

Management of RAAS inhibitor complications with approved therapies, eg, patiromer or sodium zirconium cyclosilicate for chronic hyperkalemia, is recommended by KDIGO rather than decreasing the dose of RAAS inhibitor therapy.[30]

The kidney and medications

In patients with CKD, it is important to be mindful of how medications are cleared so as to appropriately dose those that are primary cleared by the kidneys. These include metformin, many of the DPP-4is, GLP-1RAs, and SGLT-2is, as well as ACE-Is and ARBs, and several statins. The nephrotoxic potential of medications also must be considered because inappropriate use could cause acute kidney injury. Examples include ACE-Is and ARBs, diuretics, and nonsteroidal anti-inflammatory drugs. The most up-to-date source for information about use in kidney disease remains the FDA-approved product label.

CASE SCENARIO (CONTINUED)

To address the patient's worsening glycemic control, the addition of a SGLT-2 inhibitor is appropriate. Consideration should also be given to intensifying RAAS inhibitor therapy by increasing the dose of ramipril, if possible, with close monitoring of the serum potassium.

CONSIDERATIONS FOR NEPHROLOGIST REFERRAL

Many patients with kidney disease can be managed successfully in the primary care setting, depending on the provider's comfort. However, patients for whom nephrology referral might be considered include[43]:

- uncertain etiology of kidney disease
- eGFR <30 mL/min/1.73 m^2
- rapidly progressing kidney disease
- difficult management issues, such as anemia, metabolic bone disease, secondary hyperparathyroidism, resistant hypertension, and electrolyte disturbances.

When seeking a nephrology referral, it might be helpful to begin the referral request with: "Per KDIGO guidelines, I am referring this patient because of uncontrolled hypertension, stage 4 CKD, serum creatinine increased 25% in 6 months, (or similar reason)."

MEDICATIONS IN LATE-STAGE INVESTIGATION FOR CKD

Beyond the medications previously discussed, numerous agents are undergoing clinical investigation for CKD and are not yet approved for use in the United States. Three of these are the non-steroidal MRAs esaxerenone and finerenone and the endothelin-1 (ET-1) receptor antagonist atrasentan. Esaxerenone has not entered phase 3 clinical trials in the United States and will not be discussed further.[44]

Finerenone

The importance of aldosterone in causing cardiovascular and kidney injury beyond the effects of renin and angiotensin II increasingly is being recognized.[45] Patients with DKD show increased activity of the mineralocorticoid receptor, which might be driven by increased levels of circulating aldosterone, altered cortisol activity, or increased local expression of the mineralocorticoid receptor itself.[46] Whereas the steroid-based MRAs bind to the ligand domain of the mineralocorticoid receptor, finerenone induces a conformational change within the mineralocorticoid receptor. This change is thought to result in less potassium retention compared with steroid-based MRAs.[37]

ARTS-DN Trial

The safety and efficacy of finerenone were investigated in the Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) in patients with diabetes and high or very high albuminuria; most received concomitant treatment with an ACE-I or ARB.[47] Patients (N = 823) were randomized to 1 of 7 finerenone dosage levels or placebo for 90 days. Dosage levels of finerenone were 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg/d. At baseline, 37% of patients had very high albuminuria (UACR ≥300 mg/g) and 40% had an eGFR ≤60 mL/min/1.73 m^2. Finerenone demonstrated a dose-dependent reduction in UACR compared with placebo at 90 days, with significant reductions achieved at daily dosages ≥7.5 mg (7.5 mg, 0.79, $P = .004$; 10 mg, 0.76, $P = .001$; 15 mg, 0.67, $P < .001$; 20 mg, 0.62, $P < .001$).

In the ARTS-DN trial, there was no difference in the overall incidence of adverse events and serious adverse events between the finerenone groups and the placebo group. Treatment was discontinued because of an adverse event in 4.3% and 3.2% of finerenone- and placebo-treated patients, respectively. An increase in serum potassium to ≥5.6 mEq/L, leading to treatment discontinuation, occurred in 1.7% and 0% of finerenone- and placebo-treated patients, respectively. The occurrences of a decrease ≥40% in the eGFR at any time post-baseline through 120 days generally were similar in the placebo and finerenone groups.

FIDELIO-DKD and FIGARO-DKD Trials

Finerenone is being evaluated in 2 randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical tri-

als: Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD)[48] and Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD)[49] trial. Both trials examine adults with T2DM and albuminuria concomitantly treated with an ACE-I or ARB. Patients are randomized to finerenone, 10 or 20 mg/d, or placebo with dosages titrated based on serum potassium level and change in eGFR. The primary endpoints are a composite of time to first occurrence of kidney failure, sustained decrease of eGFR ≥40% for ≥4 weeks, or renal death (FIDELIO-DKD) or time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure hospitalization (FIGARO-DKD). FIDELIO-DKD was completed in April 2020, with preliminary analysis indicating that a significant benefit in the primary endpoint was achieved with finerenone vs placebo; full results have not been published yet. FIGARO-DKD is expected to be completed in July 2021.

Atrasentan

Atrasentan is an endothelin-1 (ET-1) receptor antagonist. ET-1 exerts potent vasoconstrictive effects on the efferent renal vasculature resulting in reduced renal blood flow and glomerular hyperfiltration.[50,51] In addition, ET-1 is thought to promote kidney injury by activating pro-inflammatory and profibrotic pathways.[52,53] Increased production of ET-1 results from hyperglycemia, insulin resistance, obesity, dyslipidemia, RAAS activation, endothelial dysfunction, and increased oxidative stress.[52] A limitation of blocking endothelin receptors is sodium and water retention.[37]

The safety and efficacy of atrasentan were demonstrated in the RADAR trial, which examined patients with T2DM, albuminuria, and decreased kidney function.[54] After 12 weeks of treatment, atrasentan, 0.75 and 1.25 mg/d, significantly reduced albuminuria vs placebo by 35% and 38%, respectively, with no significant change in eGFR.

SONAR Trial

Based on the results of the RADAR trial, the phase 3 Study of Diabetic Nephropathy with Atrasentan (SONAR) trial was conducted in adults with T2DM, UACR of 300 to 5000 mg/g, eGFR of 25 to 75 mL/min/1.73 m^2, and brain natriuretic peptide ≤200 pg/mL.[55] Patients underwent a run-in phase (N=5630) to optimize ACE-I/ARB and/or diuretic therapy followed by a 6-week enrichment phase (N=5117) to identify those treated with atrasentan, 0.75 mg/d, who had a ≥30% reduction in UACR without substantial fluid retention (responders). Responders (N=2648) and non-responders (N=1020) were separately randomized to atrasentan, 0.75 mg/d, or placebo.

The trial was terminated early after a median follow up of 2.2 years because of a lower-than-planned event rate. Significantly fewer patients in the atrasentan "responder" group experienced the primary endpoint (composite of time to first occurrence of doubling of serum creatinine, onset of ESKD, or kidney death) compared with placebo (6% vs 7.9%; $P = .0047$).[56] Similarly, among "responders" and "non-responders" combined, significantly fewer patients treated with atrasentan experienced the primary endpoint (8.3% vs 10.5%; $P = .0023$). Significant reductions in individual kidney endpoints were observed as well. Significantly more patients treated with atrasentan experienced hypervolemia/fluid retention (36.6% vs 32.3%) or anemia (18.5% vs 10.3%), as well as a serious adverse event (36.3% vs 32.6%). There was no difference between the 2 groups on serious heart failure events (1.7% vs 1.1%). Overall, the results of SONAR showed that patients with T2DM and CKD who initially experience a substantial reduction of UACR without significant sodium and fluid retention achieve a reduction of kidney events.

SUMMARY

Among patients with T2DM, CKD is common, resulting in an increased risk of cardiovascular, lung, bone, and other events. The UACR and eGFR are independent predictors of cardiovascular events. Achieving target glycemic and blood pressure goals is important for reducing the risk and progression of CKD. RAAS inhibitor therapy is well-established for reducing adverse kidney events. Based upon evolving evidence, SGLT-2 inhibitors are recommended to reduce kidney events in patients with T2DM and established CKD. To overcome limitations with currently available MRAs, the non-steroidal MRA finerenone is in late-stage development and has demonstrated significant reductions in key kidney endpoints. Atrasentan, an ET-1 receptor antagonist, provides a new approach to treating CKD and has demonstrated significant reductions in kidney endpoints.

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