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Inside

EDITORIAL

Improving Physical Health: Role of Psychiatrists

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Aided by medical advances, the longevity of the general population has increased considerably over the last century. However, patients with severe and persistent psychiatric disorders continue to exhibit high mortality rates with a reduced life expectancy ranging from 13 to 30 years below that of the general population (1). Sixty percent of excess mortality is attributed to medical problems (2). Several individual and systemic factors play a role in poor physical health care access and uptake in patients with mental health problems. With the high prevalence of medical problems, psychiatrists commonly encounter these medical comorbidities in their patient population.

Traditional divide between mental health and physical health services impedes the care of mental health patients with medical comorbidities. The high rates of smoking, poor uptake of preventive care, and adverse metabolic profile of psychotropic medications, along with inherent psychopathology of psychiatric disorders, adversely affect the health of psychiatric patients. The concerning low uptake of metabolic monitoring in patients taking antipsychotics further emphasizes the gravity of the problem (3).

Among physician groups, psychiatrists have the most contact with this population. With engagement playing an important role in uptake and adherence with medical services, psychiatrists already having a well-established therapeutic relationship with this population are uniquely poised to have an impact on the physical health of these patients.

Familiarity with the primary care screening guidelines and metabolic adverse effect monitoring guidelines will aid psychiatrists in improving the physical health of their patients. Psychiatrists will benefit from acquaintance with the treatment guidelines of common but leading contributors of mortality like diabetes, hypertension, and hypercholesterolemia. It is equally important for psychiatrists to monitor the psychiatric impact of the medical treatments and potential drug interactions (4). Promoting adherence with medical screening and treatments, encouraging healthy lifestyles, and promoting smoking cessation can help reduce the high medical morbidity of psychiatric patients. Patients will benefit immensely when the philosophy of psychiatric care is "improving the overall health of patients."

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The integration of primary care into behavioral health settings shows promise in improving the physical health of psychiatric patients. A 2014 Milbank Memorial Fund report reviewed 12 randomized control trials with a total of 3,624 patients (5). The investigators found fully integrated care and case management to improve preventive medical services uptake in patients with bipolar disorder and severe mental illness. Another interesting finding is that mere co-locating primary care providers in chemical dependency settings did not improve outcomes, emphasizing the role of coordination and collaboration.

As we move on toward newer models of improving physical health, the leadership of psychiatrists is going to be vital for the success of these care delivery models. Training psychiatrists in understanding chronic medical conditions and their treatments and working in collaborative care models can go a long way in addressing the unmet medical needs of psychiatric patients.

Dr. Kolli was a child psychiatry fellow in the Department of Psychiatry, Creighton University, Omaha, Neb., while serving as Guest Section Editor for this issue of the Residents' Journal.

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ARTICLE

A Review of the Neurological Features and Diagnosis of Psychogenic Nonepileptic Seizures

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Psychogenic nonepileptic seizures (PNES), also known as pseudoseizures, psychogenic seizures, nonepileptic seizures, nonepileptic attack disorder, dissociative seizures, and hysterical seizures, are events that mimic epileptic seizures but do not have the physiological or electroencephalographic features that typify epileptic seizures (1–2). PNES are diagnosed as "conversion disorder (functional neurological symptom disorder) with attacks or seizures," a term that is part of a new category in the DSM-5 called "somatic symptom and related disorders" (3).

EPIDEMIOLOGY

The incidence of PNES ranges from 3.03/100,000 to 4.9/100,000, and the prevalence is 2/100,000 to 33/100,000 (4–6). The diagnosis of PNES is more often made in women than in men in the general population (4, 7). The highest age-specific incidence is between 25 and 44 years, with the incidence diminishing with age (5).

THE ROLE OF PSYCHIATRY

Although commonly managed by neurologists, psychiatrists can encounter PNES in a multitude of hospital settings either routinely or emergently through outpatient referrals, consult-liaison services, acute psychiatric services, and inpatient admissions (2, 4, 8). Psychiatric concerns associated with PNES include depression, anxiety disorders, posttraumatic stress disorder, dissociative disorder, substance use disorder, cluster B personality disorders, self-harm, and social issues such as relational problems, abuse or trauma, and unemployment (4, 7, 9). A significant challenge associated with PNES is that their diverse clinical features mimic a variety of epileptiform classes, which makes differentiation between the two difficult. Furthermore, delays in the diagnosis of PNES, co-occurrence of PNES and epileptic seizures, presence of organic intracranial pathologies, and treatment with multiple antiepileptic drugs are additional hurdles that impede the early identification and management of PNES (6–9).

CLINICAL FEATURES OF PNES

A description of the clinical features of PNES captured by video EEG recordings and a comparison of PNES and epileptic seizure semiologies is presented in Table 1. Common ictal features highly suggestive of PNES include thrashing/violent movements of the entire body, side-to-side head movements and side-to-side body turning, forward pelvic thrusting, fluctuating course with pauses in motor activity, eye closure, upper and lower extremity out of phase movements, memory recall, ictal crying, and long duration (10, 11). Based on the clinical features captured by video EEG, Hubsch et al. (12) have proposed a new classification system for PNES characterized by one or more of the features summarized below.

Class 1.
Dystonic attacks with primitive gestural activity: dystonic limb movements, generalization to the limbs, sparing the trunk, oro-alimentary movements, and primitive gestural phenomena such as hiding one's face, punching, and grasping, always lasting less than 5 minutes.

Class 2.
Pauci-kinetic attacks with preserved responsiveness: fine and focal tremors, preserved responsiveness, and sensory manifestations, having a gradual onset and end.

Class 3.
Pseudosyncopes: unresponsiveness, eye closure, and myoclonus, typically having an abrupt onset and end, and a motionless axis, always lasting less than 5 minutes.

Class 4.
Hyperkinetic prolonged attacks: auras, varied movements such as dystonias, head rotation or tremors, hyperventilation, and fluctuating intensity of symptoms, typically lasting more than 5 minutes.

Class 5.
Axial dystonic prolonged attacks: duration greater than 1 minute, gradual onset and end, dystonic movements of upper or lower limbs, axial extension including opisthotonus, vocalizations such as wailing, hyperventilation, and fluctuating intensity of symptoms.

DIFFERENTIAL DIAGNOSIS

The PNES classes described above are reminiscent of various categories of epileptic seizures. Class 1 PNES resemble temporal or frontal lobe seizures; class 4 PNES resemble partial seizures with secondary generalization; and class 5 PNES resemble generalized tonic-clonic seizures. Moreover, PNES can also mimic status epilepticus, which are seizures lasting more than 20 minutes or multiple episodes occurring in succession without return to baseline and are termed nonepileptic psychogenic status (8).

DIAGNOSIS

EEG

In order to diagnose PNES, health care providers commonly utilize variations of the EEG, such as video EEG with long-term inpatient monitoring or short-term

TABLE 1. Description of the Clinical Features of Psychogenic Nonepileptic Seizures (PNES) Captured by Video EEG Recordings and Comparison of PNES and Epileptic Seizure Semiologies

Seizure Type	
PNES	Epileptic Seizure
Gradual onset of event, during wakefulness or pseudosleep (a state that resembles normal sleep by behavioral criteria alone, with the presence of EEG features suggestive of wakefulness).	Abrupt onset of event.
Duration: variable, often greater than 2 minutes, ranging from 30 seconds to 31 minutes.	Duration: usually less than 2 minutes. Generalized tonic-clonic seizure: mean of 65–70 seconds (range: 35–122). Frontal lobe seizure: mean of 29–51 seconds.
Prolonged unresponsiveness without prominent motor features seen in 7%–76% of patients. Patients may have behaviors such as intermittent blinking, swallowing or mouthing movements during longer episodes, slumping forward, staring, avoidance behaviors, and very long duration (10–15 minutes).	Prolonged unresponsiveness without prominent motor features is seen in less than 5% of epileptic seizure patients.
Tongue biting: 0%–18% of patients, typically on the tip.	Tongue biting: 24% of patients with generalized tonic-clonic seizures, typically on the lateral or anterolateral side.
Eye closure: 55%–96% of patients, generally forceful with active opposition to opening.	Eye closure: <10% of all epileptic seizure patients and never complete or forceful when present in generalized tonic-clonic seizure. Eye opening: 92%–100% of patients with epileptic seizures, including frontal lobe seizures.
Incontinence: 6% of patients.	Incontinence: 23% of patients with all epilepsy.
Ictal heart rate is not significantly increased.	Ictal heart rate is significantly increased in generalized tonic-clonic seizure and complex partial seizure.
Motor phenomena: Asynchronous out-of-phase limb movements: 10%–96% of patients. In-phase limb clonic activity: 16%–20% of patients. Whole body rigidity: 44% of patients. Side-to-side head/body turning: 15%–63% of patients, head turning more common. Flexion and/or extension head movements: 29% of patients. Unilateral head turning: 0%–16% of patients. Pelvic thrusting: 8%–50% of patients (typically forward), more commonly in women. Thrashing behaviors: 18% of patients, most common motor manifestation in men, unpredictable, generalized in 18%, involving only the head and neck in 45.5%, and involving the lower limbs in 18%. Tonic posturing (abduction of upper extremities): absent. Opisthotonic posturing: 18%–40%. Pauses in motor activity with fluctuating course: common.	Motor phenomena: Asynchronous out-of-phase limb movements: 0%–9% of patients with generalized tonic-clonic seizures and 90% of those with frontal lobe hypermotor seizures. In-phase limb clonic activity: 88%–96% in generalized tonic-clonic seizures. Whole body rigidity: 100% of generalized tonic-clonic seizures. Side-to-side head/body turning: Generalized tonic-clonic seizures: 5%–8% of patients, less aggressive and slower frequency. Frontal lobe seizure: 45%–76% of patients, body turning more common. Flexion and/or extension head movements: 25% of patients with generalized tonic-clonic seizures and 9% of patients with frontal lobe seizure. Unilateral head turning: 64% of patients with generalized tonic-clonic seizures and 10% of patients with frontal lobe seizures. Pelvic thrusting: 0%–12% of patients with generalized tonic-clonic seizures (typically backward), and 5%–54% of patients with frontal lobe seizures. Thrashing behaviors: Very rare in generalized tonic-clonic seizures and seen on occasion in frontal lobe seizures. Supplementary motor seizures: stereotypic, generalized in 35%, never involving only the head and neck, and involving the lower extremities in 66%. Tonic posturing (abduction of upper extremities): 100% of patients with supplementary motor seizures. Opisthotonic posturing: absent. Pauses in motor activity with fluctuating course: very rare

continued

outpatient monitoring, ambulatory EEG with or without video, and routine EEG (2). Video EEG is considered the gold standard and provides the highest level of diagnostic certainty because it enables the simultaneous visualization of seizure semiologies and documentation of brain waves (2, 10–12). However, video EEG may not be present at the disposal of every clinician, while some clinicians may choose not to use it (2, 11). Moreover, clinicians may utilize a combination of diagnostic techniques (e.g., video EEG and clinical history, or routine EEG, the Minnesota Multiphasic Personality Inventory-2, and clinical history) in establishing the diagnosis, rather than relying on any one method (11, 13).

TABLE 1. Description of the Clinical Features of Psychogenic Nonepileptic Seizures (PNES) Captured by Video EEG Recordings and Comparison of PNES and Epileptic Seizure Semiologies (*continued*)

Seizure Type	
PNES	Epileptic Seizure
Vocal features: Vocalization reported in 9%–44% of patients. Epileptic cry always occurs at the beginning, but some studies report a cry at the beginning as well as mid-episode. Type of vocalization: Highly variable, frequently nonverbal with moans, grunts, gasps, snorts, or shouting and screaming. Speaking understandable verbal statements, discontinuous vocalization, vocalization with an emotional flair, and responding appropriately to questions have also been recorded. Ictal stuttering: 8.5% of patients.	Vocal features: Vocalization reported in 60%–86% of patients with generalized tonic-clonic seizures and 39%–73% of patients with frontal lobe seizures. Epileptic cry occurs in 71% of generalized tonic-clonic seizures when seizure is well established rather than at the beginning. Type of vocalization: In frontal lobe seizure vocalization is continuous, often monotonous with moaning or grunting, sometimes similar to animal sounds, with utterances of words and rarely loud. Ictal stuttering: Never seen in epileptic seizures.
Postictal state: Postictal agitation: 13%. Postictal confusion: 13%. Breathing pattern is rapid, shallow (87%), and soft, irregular (79%), and associated with pauses. Snoring is always absent. Stertorous breathing absent. Duration of altered breathing is 94 seconds.	Postictal state: Postictal agitation: 39% after generalized tonic-clonic seizures; 61% after frontal lobe hypermotor seizure. Postictal confusion: 100% after generalized tonic-clonic seizures; 61% after frontal lobe hypermotor seizure. Breathing pattern after generalized tonic-clonic seizures is deep (100%) with prolonged inspiratory and expiratory phases, regular (96%), and loud (91%), usually with snoring (61%). Stertorous breathing seen in 91% of cases. Duration of altered breathing is 357 seconds. Breathing pattern after frontal lobe hypermotor seizure is shallow (81%), regular (100%), and quiet (90%). Duration of altered breathing is 64 seconds.

Clinical History

The clinical history elicited from patients and caregivers is often used in isolation or in combination with other methods to diagnose PNES (2). Syed et al. (14) found that of the diverse signs that accompany PNES, only three signs (eye flutter, preserved awareness, and ability of bystanders to influence epileptic activity) are the most reliable indicators of PNES; however, eyewitnesses and caregivers may not be able to accurately report them. Hence, the clinical history is important in establishing a diagnosis, but diagnostic accuracy is dependent upon the capacity of eyewitnesses to recall these signs. Thus, the International League Against Epilepsy Nonepileptic Seizures Task Force recommends that in the absence of video evidence or observation by a clinician and epileptiform EEG patterns, a clinical history can only support a diagnosis of possible PNES (11).

Psychological Testing

Psychological testing profiles, such as the Minnesota Multiphasic Personality Inventory-2, can also provide clues toward the classification of seizure typologies. Schramke et al. (13) inferred that in the presence of a normal routine EEG, greater elevations in the scores of scale 3 (hysteria) were more predictive of PNES than epileptic seizures. Patients with PNES also showed evidence of the following additional psychopathologies: 1) greater number of scores above 65, 2) greater and more frequent elevations on scales 1 (hypochondriasis), 2 (depression), 3 (hysteria), and 8 (schizophrenia), and 3) more likely to show the "conversion valley" profile wherein scores for scales 1 and 3 were elevated and the score for scale 2 was at least 5 points lower than scores on scales 1 and 3 (13).

Serum Markers

In the acute setting, serum markers, particularly prolactin, have been studied for their ability to distinguish between PNES and epileptic seizures (15). The American Academy of Neurology's guidelines state that a prolactin level measured 10–20 minutes after an event is probably a useful adjunct to differentiate a complex partial seizure and generalized tonic-clonic seizure from PNES among adults and older children (15). An elevated prolactin level is specific for generalized tonic-clonic seizure and complex partial seizure; however, the negative predictive power and sensitivity are low. Hence neither can PNES be predicted nor can generalized tonic-clonic seizure and complex partial seizure be excluded based on a normal prolactin level (15, 16). Certainly, there is a significant postictal elevation of median prolactin levels, in comparison to the median baseline preictal values, among patients with epileptic seizures for 6 hours, but patients with PNES may also demonstrate this finding for up to 12 hours (16). Additionally, prolactin levels may also be influenced by psychotropic medications such as dopamine antagonists (11). Therefore, caution is required when relying solely on prolactin levels for the diagnosis of PNES. Prolactin levels may be a useful alternative in situations where EEG facilities are unavailable.

Neuroimaging

There has been a growing interest regarding the role of neuroimaging studies in diagnosing PNES. For example, subtraction ictal single-photon emission computed tomography (SPECT) coreg-

istered to MRI (SISCOM) may be useful in differentiating between PNES and epileptic seizures (17). In patients with PNES, SISCOM can demonstrate the absence of localizing or lateralizing hypo- or hyperperfusing areas, which are characteristic of epileptic seizures. Thus, SISCOM may be useful in predicting PNES in cases of ambiguity, especially when video EEG is not able to do so. Arthuis et al. (18) evaluated patients with positron emission tomography and found that patients with PNES exhibited hypometabolism within the right inferior parietal and central region and the bilateral anterior cingulate cortex. These findings may point to the underlying neuropathological mechanisms in PNES, since these areas are responsible for emotional regulation (cingulate area) and consciousness of the self and environment (right parietal area), both of which are abnormal in patients with PNES.

MANAGEMENT

Recognizing PNES semiologies and differentiating them from epileptic seizures is essential for instituting appropriate management protocols and avoidance of unnecessary treatments. Unlike epileptic seizures, where antiepileptic drugs constitute the mainstay of treatment, behavioral therapies, particularly cognitive-behavioral therapy, figure prominently in the management of PNES (1). However, randomized and nonrandomized trials demonstrating their effectiveness are lacking, as well as a dearth of high-quality evidence supporting the use of behavioral therapies in the treatment of PNES (1). Withdrawal of antiepileptic drugs is a safe option in the absence of coexisting epileptic seizures and if patients are monitored for any adverse events (19). Pharmacological interventions are important primarily for the management of any associated psychopathologies rather than PNES itself (2).

Once the diagnosis of PNES is established, patients may have varied reactions, including relief, anger, aggression, disappointment, fear, and shame, as well as differing levels of acceptance (20). Thus, it is important to educate and communicate with patients in an empathetic and nonpaternalistic manner, taking into account their understanding of this condition (2, 20). It is essential to continue engaging with the patient in a multidisciplinary manner that involves both the neurology and behavioral health teams, even if epileptic seizures are excluded.

KEY POINTS/CLINICAL PEARLS

- The similarities between the clinical manifestations of psychogenic nonepileptic seizures (PNES) and different classes of epileptic seizures make it difficult to differentiate between the two.
- Ictal features highly suggestive of PNES are: thrashing/violent movements of entire body, side-to-side head movements and side-to-side body turning, forward pelvic thrusting, fluctuating course with pauses in motor activity, eye closure, upper and lower extremity out of phase movements, memory recall, ictal crying, and long duration.
- Video EEG is considered the gold standard for diagnosing PNES and differentiating between PNES and epileptic seizure, but not all clinicians may use video EEG.
- Although behavioral therapies figure prominently in the management of PNES, there is a lack of randomized and non-randomized trials demonstrating their effectiveness and a dearth of high-quality evidence supporting their use in the treatment of PNES.

CONCLUSIONS

PNES are among the most challenging neuropsychiatric conditions that psychiatrists may encounter in their clinical practices. Their association with numerous biopsychosocial issues makes them highly relevant to the field of psychiatry. Therefore, psychiatrists should be aware of the clinical manifestations of PNES and the modalities useful in diagnosing them. Early and accurate diagnosis of PNES is helpful in instituting appropriate treatment protocols and avoiding unnecessary treatments.

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ARTICLE

A Review of the American Cancer Society Screening Guidelines

Matthew Fadus

Early detection of cancer provides opportunities for interventions to diagnose and treat malignancies before they become too aggressive to manage. However, those affected by psychiatric disorders do not appear to be benefiting as much as the rest of the population from early screening and treatment of malignancies. Consequently, a major discrepancy exists in the morbidity and mortality due to malignancies between patients with psychiatric disorders and the general population.

All-cause mortality is higher in those who suffer from psychiatric disorders, translating into an estimated 10–20 year reduction in life expectancy compared to the general population (1). Cancer mortality is particularly staggering among those with psychiatric disorders. A 2013 study found that cancer mortality rates were 30% higher among those with psychiatric disorders compared to rates in the general population (2). In a comparison of patients who were matched for sex and age, it was found that psychiatric patients were more likely to present with metastases than the general population, implying that these cancers which were detected later and at less manageable stages were the result of delayed screening and treatment (2).

The purpose of this article is 1) to review the latest recommendations for cancer screening and 2) to provide a brief overview of the barriers to cancer screening and treatment in individuals with psychiatric disorders.

COLORECTAL CANCER

Colonoscopy screening has led to a decrease in incidence of colorectal cancer by an average of 3% every year over the last decade (3). However, patients with psychiatric disorders have higher rates of non-treatment and lower colon cancer-specific survival rates, even after adjustments are made for sociodemographic characteristics, comorbid disease, and stage at diagnosis (4).

The American Cancer Society recommends that all men and women be screened for colon cancer after the age of 50 (Table 1). Individuals may undergo one of the screening assessment measures described below (5):

- Annual guaiac-based fecal occult blood test (with at least 50% test sensitivity) or fecal immunochemical test (with at least 50% test sensitivity);
- Stool DNA test every 3 years;
- Flexible sigmoidoscopy, double-barium enema or CT colonoscopy every 5 years; or
- Colonoscopy every 10 years

If there is family history of colorectal cancer in a first-degree relative, screening should start at age 40 or 10 years prior to the age of the affected family member at diagnosis. For example, if a patient's mother was diagnosed with colorectal cancer at 48 years old, screening should begin at 38 years old (5).

LUNG CANCER

In 2015 it is estimated that lung cancer, commonly linked to smoking, will account for 26.8% of all cancer deaths, the most among any malignancy (3). The Centers for Disease Control and Prevention estimates that 21% of the adult American population smokes cigarettes, defined as smoking either "every day" or "some days" (6). It is estimated that the 36% of the population with psychiatric disorders smokes cigarettes. This rate rises even further with declining socioeconomic status. It has been found that 48% of those with psychiatric disorders below the poverty line smoke cigarettes (6).

Per the American Cancer Society guidelines (Table 1), clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about lung cancer screening with patients aged 55 to 74 years who meet the criteria described below (5).

- Have at least a 30-pack-year smoking history;
- Are current smokers or have quit within the past 15 years; and
- Are in relatively good health

The discussion should include the benefits, uncertainties, and harms associated with screening for lung cancer with low-dose CT. Adults who consent to be screened should undergo annual low-dose CT screening until age 74 years. Chest x-ray is not recommended for cancer screening.

BREAST CANCER

Breast cancer is the most common cancer in women, affecting 12.3% of all women at some point in their lifetime (3). A 2014 meta-analysis of more than 700,000 women found that women with psychiatric disorders had significantly reduced rates of mammography screening compared to those without psychiatric disorders (7).

The American Cancer Society recommends women with an average risk of breast cancer undergo regular screening mammography starting at age 45

years old. Women aged 45–54 years should be screened annually (Table 1) (5). Women 55 years or older should transition to biennial screening or have the opportunity to continue screening annually. Women should also have the opportunity to begin annual screening between the ages of 40 and 44 years old. The American Cancer Society no longer recommends clinical breast exams for women at average risk for breast cancer (5). An annual screening mammography and MRI starting at age 30 is recommended for women with one or more of the risk factors described below (8).

- Known *BRCA* mutation;
- First-degree relative with a *BRCA* mutation;
- Other high-risk genetic syndrome with known penetrance; or
- 20%–25% or greater lifetime risk of breast cancer based on specialized breast cancer risk-estimation models

While breast self-exam is not specifically recommended, the guidelines do not recommend against breast self-exam. If a woman chooses to perform regular breast self-examination or occasional self-exam, she should receive instructions in the technique and periodically have her technique reviewed (8).

There is no specific upper age limit at which mammography screening should be discontinued. Rather, the decision to discontinue regular mammography screening based on the American Cancer Society guidelines recommends that mammography screening should be continued in states of overall good health, as well as a life expectancy of 10 years or greater (5).

CERVICAL CANCER

Cervical cancer has decreased significantly over the last few decades as the result of screening with Pap smears. However, a 2013 meta-analysis of 19 studies found considerable disparities in cervical cancer screening among those with psychiatric disorders compared to the general population, leading to decreased detection and later presentations of cervical cancer (9).

TABLE 1. American Cancer Society Screening Guidelines

Colorectal cancer
- Begin screening after the age of 50.
- If there is family history of colorectal cancer in a first-degree relative, screening should start at age 40 or 10 years prior to the age of the affected family member at diagnosis.
- Patients may undergo one of the following for screening:
  - Annual guaiac-based fecal occult blood test (with at least 50% test sensitivity) or fecal immunochemical test (with at least 50% test sensitivity)
  - Stool DNA test every 3 years
  - Flexible sigmoidoscopy, double-barium enema or CT colonoscopy, every 5 years
  - Colonoscopy every 10 years

Lung cancer
- Consider annual low-dose CT scan in patients aged 55 to 74 years who meet the following criteria:
  - Have at least 30 pack-year smoking history
  - Are current smokers or have quit within the past 15 years
  - Are in relatively good health

Breast cancer
- Clinical breast exam no longer recommended for any age.
- Breast self-exam is not specifically recommended nor recommended against.
- Annual mammography screening for women 45-54 years old.
- Women 55 years and older should transition to biennial screening, or have the opportunity to continue annual screening.
- Women 40-45 years old should also have the opportunity to screen annually at 40 years old.
- Continue mammography screening based on overall state of good health and a life expectancy of 10 years or greater.
- Annual screening mammography and MRI starting at age 30 years old is recommended for women with one or more of the following:
  - Known BRCA mutation
  - First-degree relative with a BRCA mutation
  - Other high risk genetic syndrome with known penetrance
  - 20% to 25% or greater lifetime risk of breast cancer based on specialized breast cancer risk-estimation models

Cervical cancer
- Cervical cancer screening with a Pap smear should begin at age 21 regardless of sexual activity, and continue every three years until the age of 29.
- HPV testing before age 29 is not recommended.
- Women ages 30-65 can be screened with either:
  - Pap test in addition to an HPV test every five years (preferred)
  - Pap test alone every three years.
- Cervical cancer screening can be discontinued for all women over 65 who have had either:
  - ≥3 consecutive negative Pap tests
  - ≥2 consecutive negative HPV and Pap tests within the last 10 years, with the most recent test occurring in the last 5 years
- Women who have had a total hysterectomy (for a benign condition) can stop cervical cancer screening.
- Women with a history of serious pre-cervical cancer should be tested for 20 years after the result, even if testing continues beyond age 65.
- HPV vaccination for females ages 11-18.

Prostate cancer
- Screening should be initiated only after informed decision-making regarding potential benefits, risks, and uncertainties associated with prostate cancer screening in patients over 50 years old who have at least a 10-year life expectancy.
- Screening is recommended with the Prostate Screening Antigen (PSA) test with or without digital rectal examination (DRE).
- PSA <2.5 ng/mL: screening intervals can be extended to every 2 years.
- PSA >2.5 ng/mL: screen annually.
- PSA > 4.0 ng/mL: should be referred for further evaluation or biopsy.

Cervical cancer screening with a Pap smear should begin at age 21, regardless of sexual activity, and continue every 3 years until the age of 29 (Table 1) (5). Human papillomavirus (HPV) testing before age 29 is not recommended.

Women ages 30–65 can be screened with either a Pap test in addition to an HPV test every 5 years (preferred) or a Pap test alone every 3 years. Cervical cancer screening can be discontinued for all women over 65 years old who have had ≥3 consecutive negative Pap tests or ≥2 consecutive negative HPV and Pap tests within the last 10 years, with the most recent test occurring in the last 5 years. Women who have had a total hysterectomy (for a benign condition) can discontinue cervical cancer screening. Women with a history of serious pre-cervical cancer should be tested for 20 years after the result, even if testing continues beyond age 65 (5).

American Cancer Society Guidelines recommend routine HPV vaccination for females aged 11–18 years and state that there is insufficient data to recommend for or against universal vaccination of females ages 19 to 26 years (5).

PROSTATE CANCER

Prostate cancer is the leading cause of cancer in men, and it is estimated that there are approximately three million men in the United States living with prostate cancer (3). As prostate cancer has favorable prognoses, extensive screening and biopsies can cause unnecessary morbidity. Prostate cancer screening should be initiated only after informed decision making regarding potential benefits, risks, and uncertainties associated with prostate cancer screening in patients over 50 years old who have at least a 10-year life expectancy (Table 1). Screening is recommended with the prostate screening antigen (PSA) test with or without digital rectal examination. If PSA is less than 2.5 ng/mL, screening intervals can be extended to every 2 years. Screening should be conducted annually for men whose PSA level is 2.5 ng/mL or higher. Patients with a PSA level of 4.0 ng/mL or higher should be referred for further evaluation or biopsy (5).

BARRIERS TO CARE

Access to screening and therapeutic interventions is a critical issue for treatment of malignancies. Those affected by psychiatric disorders and those who are lower income are often less likely to receive specialist procedures such as adjuvant or palliative radiotherapy (10). Psychiatric patients also present later and with more advanced stages of cancer than the general population (11). This is because there is often a reduced recognition or misinterpretation of early cancer symptoms, affecting the stage at diagnosis (2 ,12, 13).

Other complicating factors of psychiatric disorders include impaired abilities to follow medical recommendations, ensure proper follow-up, and adhere to complex treatment regimens, especially those with the altered cognition and disorganized thinking that is associated with psychiatric disorders (4). Other manifestations of psychiatric disorders such as delusions or paranoia may lead patients to perceive cancer treatments such as radiation therapy or chemotherapy to be invasive, harmful, and threatening (4). Treatment for cancer can be overwhelming for any patient. The psychopathology of certain psychiatric disorders can predispose patients to mistrust and fear physicians at baseline. This may interfere with a patient's ability to trust physicians administering aggressive treatments such as chemotherapy and radiation. Some practitioners also believe that patients with psychiatric disorders have a compromised ability to obtain informed consent. This can result in psychiatric patients receiving less aggressive treatment measures for cancer and becoming less likely to enroll in clinical cancer trials (4).

Socioeconomic factors that lead to health discrepancies in treating cancer include decreased education levels, downward social drift of certain psychiatric disorders, and unemployment, all of which limit access to health insurance, screening, and primary care interventions (4).

CONCLUSIONS

The role of the psychiatrist is integral in decreasing morbidity and mortality from malignancies. It is hoped that recognition of the discrepancies and barriers among those affected with psychiatric disorders can improve the quality of care in this vulnerable population. Questioning patients about screening and providing psychoeducation are important roles of the psychiatrists in helping patients not only with mental health but physical health as well.

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KEY POINTS/CLINICAL PEARLS

- Cancer mortality rate is 30% higher among those with mental health illness, despite incidence remaining similar to the general population.
- Psychiatric patients are more likely to present with metastases and cancers that are detected at later and less manageable stages.
- Manifestations of mental health illness such as delusions or paranoia may lead patients to perceive cancer treatments such as radiation therapy or chemotherapy to be invasive, harmful, and threatening.
- The altered cognition and disorganized thinking that is associated with mental illness makes it very difficult to follow medical recommendations, ensure proper follow-up, and adhere to complex treatment regimens.

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ARTICLE

The Pharmacological Treatment of Obesity: A Literature Review

Connie L. Thomas, M.D.

Obesity, defined as a body mass index of 30 kg/m^2, has become an epidemic. The management of obesity necessitates lifestyle modifications through dietary changes and physical activity. However, the frequency of relapse is high and often requires a multidisciplinary approach. Although pharmacological agents for weight management have existed for years, they have had many setbacks because of serious adverse effects. There are currently five agents that have been approved by the U.S. Food and Drug Administration (FDA) for weight management: orlistat, lorcaserin, phentermine/topiramate extended-release formulation, bupropion/naltrexone extended release formulation, and liraglutide injection.

NEUROBIOLOGY OF OBESITY AND TREATMENT TARGETS

Energy balance regulation dysfunction results in excessive adipose disposition and is mediated by the brain and neuroendocrine hormones. The brain controls both food intake and energy expenditure, primarily through the hypothalamus, the dorsal vagal complex, and the mesolimbic dopamine reward system (1).

Overeating has been compared to other addictive behaviors, such as compulsive drug use, due to involvement of the reward system, which also contributes to addiction regulation. Food triggers brain reward circuitry via several hormones involved in the neural hormone gut-brain axis. For example, palatability is mediated by endogenous opioids and cannabinoids and agents that alter dopamine activity, such as insulin, ghrelin, and leptin (1). These hormones target the hypothalamus and brainstem, which directly or indirectly affect the midbrain dopamine pathways and modulate eating patterns (2).

Although there are some antiobesity medications that interfere with the breakdown or absorption of foods, many agents alter some component of the reward system in order to affect food consumption. They also often overlap with medications used to treat drug abuse, such as cannabinoid antagonists, stimulants, or GABA agonists (3).

PHARMACOLOGIC AGENTS

The FDA sets several benchmarks for the safety and efficacy of antiobesity agents: 1) the difference in mean weight loss between the drug and placebo groups is at least 5% over at least 1 year and statistically significant, and 2) the proportion of subjects who lose at least 5% of baseline body weight in the drug group is at least 35% and is double the proportion in the placebo group (4) (see Table 1).

Orlistat

Orlistat was approved by the FDA in 1999 for prescription sale for adults at 120 mg and in 2007 for over-the-counter sale at a lower dose of 60 mg. It is the only agent licensed for use in the management of obesity in the United Kingdom.

In a metanalysis of 16 double-blind placebo-controlled randomized trials in which 10,631 patients were followed for 1–4 years with a combination of orlistat and weight loss diet, a 2.9-kg (95% confidence interval [CI]=2.5 kg–3.2 kg) or 2.9% (95% CI=2.5%–3.4%) greater weight loss was found when compared with placebo (5).

Orlistat is a synthetic hydrogenated derivative of the endogenous lipase inhibitor lipstatin, which interferes with lipase catalyzed breakdown and systemic absorption of about 30% of dietary ingested fats (6). Therefore, orlistat's most common side effect is steatorrhea. In a pooled analysis of studies, 5% of patients discontinued due to gastrointestinal-related disturbance, 2% greater than placebo (7). Other more serious side effects that were identified in postmarketing reviews included hepatotoxicity, nephrotoxicity, pancreatitis, and kidney stones (4).

Lorcaserin

Lorcaserin, usually dosed at 10 mg twice daily, is a highly selective and potent 5-HT$_{2C}$ agonist with 15-fold and 100-fold higher affinities for the serotonin 2$_C$ receptors, compared to the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors, respectively (8). Unlike earlier serotonergic drugs, which were withdrawn due to hallucinations and cardiovascular adverse effects, lorcaserin's receptor selectivity is what has led to further investigation of the drug (9). There are three randomized double-blind placebo-controlled phase 3 clinical trials conducted by the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) study group: BLOOM, BLOSSOM, and BLOOM-DM (10–12).

Pooled analysis of the BLOOM and BLOSSOM trials found that at week 52, more than twice as many lorcaserin-treated patients achieved weight loss ≥5% from baseline compared with placebo (lorcaserin, 47.1%; placebo, 22.6%); a significantly greater proportion of lorcaserin-treated patients achieved weight loss ≥10% (lorcaserin, 22.4%; placebo, 8.7%); and overall, lorcaserin-

TABLE 1. Food and Drug Administration Benchmarks for the Safety and Efficacy of Antiobesity Agents

Drug	Dosage	Side Effects	Contraindications	Drug Interactions
Orlistat	60 mg or 120 mg three times daily	Steatorrhea, fecal urgency and incontinence, hepatotoxicity, nephrotoxicity, pancreatitis, cholelithiasis, increased urinary oxalate	Pregnancy	Vitamins (fat soluble), vitamin D analogs, levothyroxine, warfarin
Lorcaserin	10 mg daily or twice daily	Headache, dizziness, nausea, fatigue, diarrhea, constipation, dry mouth, priapism	Pregnancy	Serotonergic agents, agents that impair metabolism of serotonin, or antidopaminergic agents; potent 5-HT2B receptor agonists; metoprolol; tamoxifen; ergot derivatives; bupropion
Phentermine/topiramate extended-release formulation	3.75 mg/23 mg, 7.5 mg/46 mg, 15 mg/92 mg	Paresthesias, dry mouth, constipation, dysgeusia, insomnia, tachycardia, memory or cognitive changes, nephrolithiasis, and teratogenic effects (orofacial clefts), hypokalemia, suicidal ideation, angle closure glaucoma	Hyperthyroidism; glaucoma; pregnancy	Monoamine oxidase (MAO) inhibitors; hydrochlorothiazide or furosemide; sedative agents
Bupropion/naltrexone extended release formulation	8 mg/ 90 mg, 16 mg/180 mg; 32 mg/360 mg	Neuropsychiatric events (changes in mood and behavior, suicidal behavior and ideation), seizures, hepatotoxicity, hypertension, nausea, constipation, vomiting, dry mouth, diarrhea, headache, dizziness	Acute opioid withdrawal or intoxication; uncontrolled hypertension; current or history of seizure disorder; eating disorders; recent discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; pregnancy	Opioid, opiate agonist or partial agonist; MAO inhibitors; linezolid; or intravenous methylene blue
Liraglutide injection	6 mg/mL (3 mL)	Nausea, vomiting, tachycardia, exacerbations of renal disease, injection-site disorders (pain/extravasation; hematoma; irritation; and discomfort); psychiatric effects (suicidality, depression), pancreatitis	Personal or a family history of medullary thyroid cancer and in patients with multiple endocrine neoplasia syndrome type 2 (MEN2); pregnancy	Sulfonylureas, insulin

treated patients lost significantly more body weight (lorcaserin, –5.8%; placebo, –2.5%) (13).

The BLOOM-DM clinical trial examined the use of lorcaserin for weight loss among patients with type 2 diabetes. They found that more patients lost ≥5% of their body weight with lorcaserin twice daily (37.5%; $p<0.001$) or lorcaserin daily (44.7%; $p<0.001$) compared with placebo (16.1%; modified intent to treat/last observation carried forward) (12).

Adverse effects of lorcaserin in these studies included headache, dizziness, nausea, fatigue, diarrhea, constipation, and dry mouth. Some initial findings suggested that locaserin resulted in serotonin-associated valvulopathy, similar to other weight loss drugs. However, further research found that the rate of echocardiographic valvulopathy was similar to placebo (14).

Phentermine/Topiramate

Phentermine/topiramate extended-release formulation (PHEN/TPM) was approved by the FDA in July 2012 for short-term (less than 12 weeks) obesity treatment. Phentermine, which is chemically related to amphetamines, acts by increasing adrenergic tone and thereby induces appetite suppression and increases resting energy expenditure (15). Topiramate appears to increase satiety through the inhibitory activity of GABA, which results in alteration of taste via the modulation of voltage-gated calcium and sodium channels, inhibition of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainite glutamate receptors, and inhibition of carbonic anhydrase (16).

Efficacy and safety of the PHEN/TPM is supported by three phase 3 trials: CONQUER, EQUIP, and SEQUEL (17–19). All were randomized double-blind placebo-controlled trials comprising three study groups: low-dose PHEN/TPM (7.5 mg/46 mg), high-dose PHEN/TPM (15/92), and placebo.

In the 56-week EQUIP study, a significantly greater proportion of patients on PHEN/TPM achieved ≥5% weight loss compared to placebo: 44.9% on the low dose, 66.7% on the high dose, and 17.3% taking placebo ($p<0.0001$) (17). The largest trial, the CONQUER study, found that after 56 weeks, significantly more participants on PHEN/TPM achieved

≥5% and ≥10% weight loss compared to placebo: 62% and 37% taking the low dose and 70% and 48% taking the high dose compared with 21% and 7% for placebo, respectively (18). As an extension study, the SEQUEL trial enrolled participants from CONQUER for an additional 52 weeks. Significantly more patients ($p<0.001$) at both dose levels of PHEN/TPM demonstrated ≥5%, ≥10%, ≥15%, and ≥20% weight loss compared to placebo (19).

Adverse effects noted in these trials included paresthesias, dry mouth, constipation, dysgeusia, insomnia, memory or cognitive changes, and teratogenic effects such as orofacial clefts. Although no short-term cardiovascular effects were confirmed, postapproval requirements included a long-term trial to assess its effects on the risk for cardiovascular events in subjects with confirmed cardiovascular disease, drug utilization, and pregnancy exposure, as well as other animal and in vitro studies (6).

Bupropion/Naltrexone

The extended-release combination of naltrexone and bupropion was approved by the FDA in September 2014 but is also undergoing evaluation through mandatory postmarketing studies. Due to concerns about its cardiovascular safety profile, the FDA did not approve naltrexone HCI/bupropion HCI in February 2011 after initial approval in 2010. In 2014, FDA approval was contingent on postmarketing studies focused on cardiovascular outcomes (20).

In animal models, bupropion has been shown to stimulate hypothalamic proopiomelanocortin neurons (21). Proopiomelanocortin releases alpha-melanocyte stimulating hormone (α-MSH) that binds to MC3 and MC4 receptors, resulting in propagation of the anorexigenic signal. Naltrexone antagonizes the effects of β-endorphins, which are also released in response to bupropion action, and complete a negative feedback loop. Thus, the combination leads to synergistic effects on energy balance by causing a more potent and prolonged stimulation of proopiomelanocortin.

The phase 3 program, CONTRAVE Obesity Research, consisted of four multicenter, randomized double-blind and placebo-controlled studies. Over 56 weeks, the proportion of patients who achieved ≥5% weight loss from baseline values for patients treated with naltrexone HCI/bupropion HCI ranged from 44.5% to 66.4% (for placebo, 18.9% and 42.5%, respectively). The mean total weight loss across all studies was 6.8% (95% CI=6.6%–7.1%) or 7.3 kg (95% CI=7.0 kg–7.6 kg) (22).

Other adverse effects noted in studies included the black box warning of increased risk of suicidal behavior and ideation, nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea.

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (4). Although previously approved under another formulation for obese individuals with diabetes, the FDA approved the injection formulation of liraglutide in December 2014 for long-term weight management.

The Satiety and Clinical Adiposity-Liraglutide Evidence in Non-diabetic and Diabetic Adults (SCALE) phase 3 clinical trial program encompassed three clinical trials with approximately 4,800 obese patients (23). The first trial examined specifically obese or overweight individuals with one comorbid condition other than diabetes. The investigators found that 62% of liraglutide-treated patients lost ≥5% of their body weight (34% in the placebo group), with an average weight loss at 1 year of 4.5% compared to placebo (24).

The liraglutide brand name drug has a black box warning stating that thyroid C-cell tumors have been observed in rodent studies. The FDA approved the drug contingent on postmarketing studies and a risk evaluation and mitigation strategy, which consists of a communication plan to inform health care professionals about the drug's serious risks.

KEY POINTS/CLINICAL PEARLS

- Management of obesity necessitates lifestyle modifications through dietary changes, physical activity, and behavior modification.
- Due to the growing obesity rates and high rates of relapse through lifestyle changes alone, medications can be helpful for short- and long-term weight loss strategies.
- Currently, five agents have been approved by the Food and Drug Administration for weight management: orlistat, lorcaserin, phentermine/topiramate extended-release formulation, bupropion/naltrexone extended release formulation, and liraglutide injection.

CONCLUSIONS

The projected growth rate of the obesity epidemic in upcoming years has driven the development of several promising weight-loss strategies. Conventional therapies for obesity treatment, such as behavioral modification, can be labor intensive, requiring a multidisciplinary approach to achieve effect. Medications approved by the FDA for obesity treatment have been shown to be efficacious in combination with lifestyle changes, and several new drugs are currently under investigation due to the substantial need (4).

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ARTICLE

Understanding Type 2 Diabetes Management: A Review of the American Diabetes Association 2015 Guidelines

Eric T. Wilkerson, B.S.

In 2011, an estimated 26 million people, 11.3% of the U.S. population, greater than 20 years of age were diagnosed with diabetes mellitus (1). As such, diabetes is frequently encountered by psychiatrists. The two types of diabetes are type 1 and type 2. Type 1 diabetes is characterized by a lack of insulin production in the beta cells of the pancreas. Type 2 diabetes is characterized by insulin insensitivity in the periphery and variable insulin deficiency. Type 2 diabetes is more common in the United States and is more frequently encountered by psychiatrists (2); therefore, type 2 diabetes is the focus of the present review.

DIAGNOSIS

Type 2 diabetes classically presents as polyuria, polydipsia, weight loss, blurred vision, nocturia, obesity, acanthosis nigricans, and metabolic syndrome. Type 2 diabetes is the predominant form of diabetes and accounts for greater than 90% of cases. It may remain asymptomatic, making screening tests fundamental for diagnosis. The 2015 American Diabetes Association (ADA) diagnostic criteria for symptomatic patients is a random blood glucose ≥200 mg/dL with classic symptoms of diabetes, as mentioned above. If asymptomatic, the criteria are a fasting blood glucose ≥126 mg/dL, 2-hour post oral glucose challenge ≥200 mg/dL, or HgA1C ≥6.5% (Table 1). A second positive test of the previous tests is diagnostic for diabetes mellitus if the first test is unequivocal. HgbA1C level provides an average blood glucose level from the past 3 months (3).

The 2015 ADA recommends screening every 3 years for adults with a body mass index (BMI) ≥23 kg/m2 and one of the following risk factors: a sedentary lifestyle, first-degree relative with type 2 diabetes, delivery of a baby >4.1 kg, dyslipidemia, polycystic ovarian syndrome, vascular disease, or a high-risk racial group (African American, Hispanic, Native American, Pacific Islander, and Asian American). All patients over the age of 45 should be screened every 3 years regardless of risk factors or BMI (3).

TABLE 1. Criteria for Diagnosis of Diabetes

Criteria
HgbA1C ≥6.5%
Fasting blood glucose ≥126 mg/dL
2-hour plasma glucose ≥200 during oral glucose tolerance test
≥200 mg/dL when patient has classic symptoms of hyperglycemia or hyperglycemic crisis
Two positive if first test is unequivocal

SECOND-GENERATION ANTIPSYCHOTICS AND DIABETES

Second-generation antipsychotics are fundamentally important in treating schizophrenia, dementia, and depressive disorder with psychotic features, but they are also associated with increased obesity, dyslipidemia, and type 2 diabetes (4). Patients taking olanzapine and clozapine have a 34%–41% increased risk of developing diabetes compared to patients not taking a second-generation antipsychotics (5). Therefore, the ADA and the American Psychiatric Association recommend checking fasting blood glucose/HgbA1C, BMI, waist circumference, blood pressure, and fasting lipid profile as outlined in Table 2 (4). Olanzapine and clozapine have been shown to have the greatest risk of weight gain, risperidone and quetiapine were associated with intermediate risk of weight gain, and aripiprazole and ziprasidone were associated with the lowest risk of weight gain. It is important to consider switching antipsychotics if there is a body weight increase ≥5% from baseline or if there is an increase in hyperglycemia (4). Furthermore, patients taking antidepressants are also at an increased risk of developing diabetes. Patients taking selective serotonin reuptake inhibitors and tricyclic antidepressants are at the greatest risk of developing diabetes, with an odds ratio of 1.50 (6).

COMPLICATIONS

Complications due to uncontrolled diabetes include microvascular and macrovascular events. The microvascular complications are diabetic retinopathy, diabetic nephropathy leading to chronic kidney disease, and diabetic neuropathy. Macrovascular complications include hyperlipidemia causing atherosclerosis, leading to hypertension, hypercoagulability, cardiovascular disease with increase risk of myocardial infarction, and cerebrovascular accident with resulting dementia. Common comorbid conditions that occur are depression, obstructive sleep apnea, fractures, low testosterone, and a variety of cancers (3).

MANAGEMENT

Treatment options for type 2 diabetes include lifestyle management, oral medications, injectable medications, and in-

TABLE 2. Monitoring for Patients on Second-Generation Antipsychotics

Variable	Baseline	4 Weeks	8 Weeks	12 Weeks	Annually
Individual and family history	X				X
Physical examination	X				X
Body mass index	X	X	X	X	X
Waist circumference	X				X
Blood pressure	X			X	X
Fasting plasma glucose or HgbA1C	X			X	X
Fasting lipid profile	X			X	X

sulin. Tight glycemic control along with non-diabetic pharmacologic treatments are important for management of type 2 diabetes. Decreasing HgbA1C from 7.9% to 7.0% lowers all-cause mortality by 6%. Furthermore, tight glycemic control decreases microvascular complications by 25% when HgbA1C is 7.0% compared to 7.9% (7). Unlike tight glycemic control in younger patients, higher HgbA1C may be necessary for patients over age 60, those with decreased functional status, and those with a life expectancy of less than 5 years due to the risk of hypoglycemia and related complications (8). Macrovascular complications from type 2 diabetes are not corrected by tight glycemic control. Therefore, treatment with daily aspirin, aggressive hypertension control, angiotensin-converting enzyme inhibitor treatment regardless of blood pressure, dyslipidemia treatment, and smoking cessation are recommended. This therapy was shown to reduce all macrovascular complications in 18% of patients compared with 38% of patients among those not receiving this multidrug therapy over the course of 9.8 years (3).

Prediabetes (HgbA1C of 5.7%–6.4%) treatment is lifestyle management and close follow up by a primary care physician (3) (Table 3). Lifestyle changes are important for both prediabetes and diabetes management. Exercise therapy of aerobic exercise, 150 minutes per week of moderate intensity, and anaerobic exercise of resistance therapy, 2 times per week, is recommended. Diet changes aiming for 7% weight loss by calorie reduction, reduced dietary fat, and increased dietary fiber to 14 g/1,000 kcal helps control HgbA1C levels. Working with a registered dietician is recommended. Lifestyle changes are an effective means of improving glycemic control, lowering low-density lipoprotein, and reducing microalbuminuria. Lifestyle modifications should be offered to all patients with diabetes and prediabetes as the initial therapy (3).

Pharmacologic treatment of hyperglycemia in type 2 diabetes has a wide variety of oral and injectable options. Patients unable to control blood glucose after 6 months of lifestyle changes should be started on metformin. Metformin is preferred as initial therapy due to low cost, propensity to promote weight, glycemic control, lack of hypoglycemia, and its tolerability (9). If metformin is not able to control HgbA1C to less than 7% after 3 months at maximum dose, then a second medication should be added (3). When HgbA1C is greater than 8.5% on metformin monotherapy, then metformin and insulin is preferred (3).

Patients whose levels do not respond to metformin monotherapy due to lack of HgbA1C control should be started on dual therapy utilizing metformin and sulfonylureas to decrease HgbA1C by an additional 1.6% from original metformin monotherapy alone (8). Patients can be initiated on a different hypoglycemic agent (Figure 1) based on side-effect profile and HgbA1C control (9).

TABLE 3. Criteria for Diagnoses of Prediabetes

Criteria
Fasting plasma glucose of 100 mg/dL–125 mg/dL
2-hour plasma glucose after the oral glucose tolerance test of 140 mg/dL–199 mg/dL
HgbA1C 5.7%–6.4%

Furthermore, if metformin is contraindicated or is intolerable due to side effects, sulfonylureas are an appropriate initial agent. Hypoglycemia is an important consideration in elderly patients. If a patient on a maximum dose of sulfonylurea has a HgbA1C <8.5 and is in need of greater glycemic control, additional therapy with a different hypoglycemic agent can be added (Figure 1) (10). If a patient cannot take metformin and has a HgbA1C >8.5% on sulfonylurea monotherapy, the patient should be switched to insulin therapy for treatment. Sulfonylurea and insulin combination is not the preferred double therapy because both increase blood-insulin levels (11).

Patients who do not achieve glycemic control with dual oral therapy but are close to glycemic control (<1.5% HgbA1C from the goal) can begin a third

KEY POINTS/CLINICAL PEARLS

- Test all patients with a random blood glucose level with a body mass index >23 kg/m2 every 3 years when they have one other risk factor (see diagnosis in Table 1); test all patients over 45 years of age every 3 years.
- Test patients on a second-generation antipsychotic annually for diabetes.
- A patient should initially try lifestyle management for treatment; if this is not effective and the patient has adequate renal function, initiate metformin therapy.

FIGURE 1. Overview of Hypoglycemic Agents[a]

Intervention	Names	Mechanism	Decrease in A1C with monotherapy, %	Weight Changes	Side Effects
Lifestyle management of exercise and diet			1.0 to 2.0	Weight Loss	
Metformin	Metformin	Decreases hepatic glucose output and lowers fasting glucose levels	1.0 to 2.0	Weight Loss	GI upset, lactic acidosis in renal failure, B12 deficiency
Insulin			1.5 to 3.5	Weight Gain	Hypoglycemia, Poor long term glycemic control
Sulfonylurea	Glipizide and glyburide	Increase insulin secretion in the pancreas	1.0 to 2.0	Weight Gain	Hypoglycemia
Thiazolidinedione	Pioglitazone and Rosiglitazone	Increase sensitivity of muscle, fat, and liver to insulin	0.5 to 1.4	Weight Gain	Fluid Retention causing CHF, Potential increase risk of MI with rosiglitazone
GLP-1 agonist	Exenatide, liraglutide, and albiglutide	Increases glucose stimulated insulin production in the pancreas	0.5 to 1.0	Weight Loss	Slows gastric motility, GI disturbances
Alpha- glucosidase inhibitor	Alpha- glucosidase inhibitor	Decreases the digestion of polysaccharides in the small intestines	0.5 to 0.8	Weight Neutral	Flatulence and GI disturbances
Glinide	Glinide	Stimulate insulin secretion in the pancreas	0.5 to 1.5	Weight Gain	Hypoglycemia
Amylin	Pramlintide and amylin	Prevents glucagon production by the liver causing a decrease in postprandial glucose levels	0.5 to 1.0	Weight Loss	GI disturbances
DPP-4 inhibitor	Sitagliptin, linagliptin, saxagliptin, and alogliptin	Increases glucose-mediated secretion and inhibit glucagon secretion	0.5 to 0.8	Weight Neutral	Immune disturbance
SGLT-2 inhibitor	canagliflozin, dapagliflozin, empagliflozin	Decrease glucose reabsorption in the kidney causing glucose excretion in urine	0.5-1.0	Weight Loss	Frequent Urination, Discomfort with urination, Vaginal or penile mycotic infections

[a] GLP-1 agonist=glucagon-like peptide-1; DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor; SGLT-2=sodium-glucose co-transporter 2.

oral therapy (DPP-4, SGLT-2, or thiazolidinediones), for patients who do not want to begin insulin therapy (Figure 2). However, if patients are not achieving appropriate glycemic control with two oral drugs (>9.5% HgbA1C), or the patient is interested in initiating insulin therapy, then insulin should be started. Insulin therapy is found to have better glycemic control without increased hypoglycemic events, equivocal quality of life, treatment satisfaction, and compliance compared to triple oral therapy (12). Furthermore, treatment with three oral therapies carries greater side effects than one oral agent, typically metformin, and insulin therapy (13).

Diabetes control with insulin carries side effects of hypoglycemia and weight gain. Hypoglycemia is more common in patients who are attempting to return HgbA1C to near normal levels. Patients who are most at risk for developing hypoglycemia are those with a history of severe hypoglycemia, males, and adolescents (3).

CONCLUSIONS

Tight glycemic control and control of other complicating factors of type 2 diabetes is important to prevent future complications of the disease process. Oral hypoglycemics (metformin or sulfonylureas) are preferred methods to control HgbA1C levels. Initial therapy for all type 2 diabetes patients should include daily aspirin, aggressive hypertension control, angiotensin-converting enzyme inhibitor treatment regardless of blood pressure, dyslipidemia treatment, and smoking cessation. Psychiatrists should encourage adherence to diabetes management to reduce morbidity and mortality. Additionally, psychiatrists should monitor patients closely for

FIGURE 2. Antihyperglycemic Medications Recommendations[a]

Monotherapy		
Metformin		
Dual Therapy		
Metformin	+	Sulfonylurea
	or	Thiazolidinedione
	or	DPP-4 Inhibitor
	or	SGLT-2 Inhibitor
	or	GLP-1 Receptor Antagonist
	or	Insulin
Triple Therapy		
Metformin +1 of the following groups		
Sulfonylurea	+	TZD
	or	DPP-4 inhibitor
	or	SGLT-2 Inhibitor
	or	GLP-4 Receptor Antagonist
	or	Insulin
Thiazolidinedione	+	Sulfonylurea
	or	DPP-4 inhibitor
	or	SGLT-2 Inhibitor
	or	GLP-4 Receptor Antagonist
	or	Insulin
DPP-4 inhibitor	+	Sulfonylurea
	or	TZD
	or	SGLT-2 Inhibitor
	or	Insulin
SGLT-2 Inhibitor	+	Sulfonylurea
	or	TZD
	or	DPP-4 inhibitor
	or	Insulin
GLP-4 Receptor Antagonist	+	Sulfonylurea
	or	TZD
	or	Insulin
Insulin	+	TZD
	or	DPP-4 inhibitor
	or	SGLT-2 Inhibitor
	or	GLP-4 Receptor Antagonist

[a] TZD=thiazolidinedione; DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor; SGLT-2=sodium-glucose co-transporter 2; GLP-1 agonist=glucagon-like peptide-1.

diabetes, especially those taking antipsychotic medications.

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CASE REPORT

Grasping for Words: A Case Series and Comparison of Language Loss in Frontotemporal Dementia vs. Early-Onset Alzheimer's Disease

Philip M. Yam, M.D., Marc A. Bouchard, D.O., Ryan P. Schwer, D.O.

Dementias are neurodegenerative diseases with chronic disturbances in functioning, thinking, and ability to communicate. With 13.9% prevalence in individuals over 70 years old (1), cost of management amounts to $215 billion yearly (2). Psychiatrists are among the multidisciplinary providers that evaluate, diagnose, and treat patients with dementia.

Neurocognitive disorders have considerable overlap in symptoms and etiologies. The present cases explore patients in their early 50s with different forms of dementia, with emphasis on aphasia.

CASE 1

"Mr. J" is a 53-year-old man with no past psychiatric history. Over 2 years, he developed difficulty finding words and later had gradual changes in his personality from being meticulous and well organized to gullible, unkempt, and lackadaisical. He exhibited phonemic errors, paucity, impaired word retrieval, and poor sentence repetition. Positron emission topography (PET) via GE Discovery 690/64 Slice with administration of F18-Fluorodeoxyglucose using iterative reconstruction revealed right-sided frontal and temporal lobe atrophy and hypometabolism. He was diagnosed with logopenic aphasia, a subtype of the primary progressive aphasias, which are considered forms of major neurocognitive disorder due to frontotemporal lobar degeneration. He met criteria of this diagnosis given his family's description of his cognitive decline, substantial impairment on assessed cognition, and decreased functionality.

CASE 2

"Mr. O" is a 54-year-old man with no past psychiatric history who presented with severe anxiety. Over 1 year, he developed impaired long-term memory, language difficulties, and loss of executive function. His mini-mental status examination rating was 25/30 with deficits in delayed recall and serial subtraction. His speech was notable for decreased word retrieval and semantic errors. His condition progressed to profound forgetfulness, personality changes, and decreased independence. PET imaging with amyloid-beta binding compound 18F-Florbetapir revealed frontal and parietal plaques. These data, along with meeting criteria including decline of previous performance in language, memory, and executive function based on knowledge of his wife, his neuropsychiatric assessment, and interference with activities, were supportive of an early-onset diagnosis of major neurocognitive disorder due to Alzheimer's disease.

DISCUSSION

Language disturbances cause significant morbidity and loss of function. For providers, such clinical pictures create diagnostic challenges and obstacles to treatment.

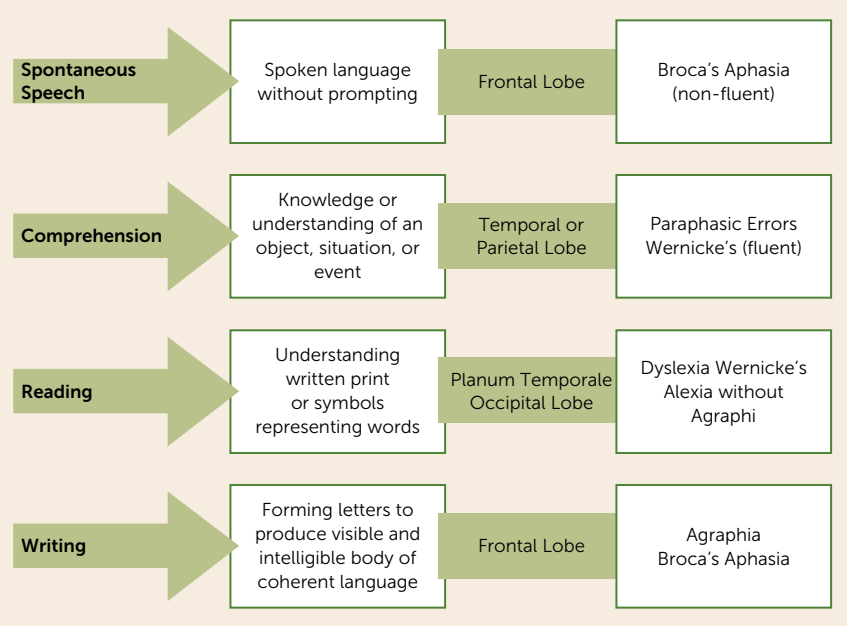
Clinicians first must distinguish aphasias (cortical damage) from dysarthrias (subcortical, nerve, or muscle damage). Dysarthrias may be caused by insult to the thalamus, basal ganglia, or brainstem nuclei without disturbing higher brain regions (3), displaying motor dysfunctions of speech and pronunciation errors.

Language assessment also includes tests such as naming, sentence repetition, comprehension (following instructions), reading, and writing. Specific deficits in these functions guide clinicians in locating lesions, as well as track disease progression (4).

The key to understanding differential diagnoses of aphasias is examining language fluency or the smoothness of speaking. In neurocognitive disorder due to Alzheimer's disease, there is impaired word retrieval and loss of complex words, but language fluency is maintained until late in the illness (5). "Mr. O" (case 2) was diagnosed with the frontal-variant form of Alzheimer's disease (FvAD), which includes, in addition to memory loss, behavioral problems, personality changes, and executive function deficits. FvAD presents earlier in life as demonstrated in our patient. He initially experienced memory loss and anxiety that developed rapidly into impaired functionality and significant change of character. Compared to typical Alzheimer's disease, autopsies of FvAD patients demonstrate increased neurofibrillary tangle burden in the frontal and medial temporal lobes; however, there are similarities in the distribution of amyloid plaques (6). FvAD may be difficult to differentiate from frontotemporal lobar degeneration, and conclusive diagnosis may be delayed until an autopsy demonstrates presence of amyloid deposits.

Other dementias that cause aphasia include subtypes of neurocognitive disorder due to frontotemporal lobar degeneration, which is an umbrella term for related dementias, including Pick's disease, primary progressive aphasias, and motor-related syndromes such as

FIGURE 1. Neuroanatomy and Function of Language Domains



progressive supranuclear palsy and corticobasilar syndrome (7). The primary progressive aphasias include three types: progressive nonfluent aphasia, logopenic aphasia, and semantic dementia. The most debilitating of these, progressive nonfluent aphasia, exhibits limited to zero spontaneous speech (see Figure 1), broken and spaced-out words, and slowed speech rate at one-third the normal rate. Similarly, logopenic aphasia is slowed but still retains spontaneous speech. Deficits include impaired word retrieval, phonemic errors, and poor sentence repetition. Lastly, semantic dementia retains speech fluency but includes loss of word meanings (8). Beyond the name of primary progressive aphasias, these syndromes develop further into severe cognitive decline and ultimately death. Our patient in case 1 was diagnosed with logopenic aphasia given that he retained spontaneous speech (ruling out progressive nonfluent aphasia), but he exhibited labored speech, phonemic errors, and poor sentence repetition. He displayed a typical disease course of mild language symptoms that later developed into severe cognitive, personality, and functional decline, eventually requiring full-time observational care.

Treatment of aphasia involves therapeutic modalities to improve speech and communication. This includes picture-word matching, naming exercises, and face-to-face repetitions (9). New treatments for aphasia have been introduced in recent years, such as transcranial magnetic stimulation (TMS), which targets cortical networks modulating language. TMS suppression of right hemisphere areas has positive effects on language performance (10). Larger clinical studies are indicated for this treatment modality.

KEY POINTS/CLINICAL PEARLS

- Dementias affect approximately 14% of persons above 70 years of age.
- Although they are not life-threatening, aphasias do provide a subtle avenue for exploration of etiologies, functional loss, and prognosis of dementias.
- A multidisciplinary and family-based treatment approach leads to best outcomes.

CONCLUSIONS

Evaluating dementia requires extensive history taking, physical examination, and diagnostics testing. Early identification of disease decreases morbidity and mortality. Clinicians should have a high index of suspicion for neurologic findings in the context of language loss and poor functioning in home and occupational settings, even in the face of having normal or minimal impairment on mental status examinations. Language disturbances may be common between neurocognitive disorder due to Alzheimer's disease and neurocognitive disorder due to frontotemporal lobar degeneration, with the latter displaying worse deterioration and prognosis. Interdisciplinary approach and family involvement delineate best approach to care and hence improved patient outcomes.

Dr. Yam and Dr. Bouchard are fourth-year residents and Dr. Schwer is a second-year resident at the Department of Psychiatry, Walter Reed National Military Medical Center, Bethesda, Md.

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Call for Applications to Join the 2016 Editorial Board

The *American Journal of Psychiatry—Residents' Journal* is now accepting applications to join the 2016-2017 Editorial Board for the following positions:

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- Frequent correspondence with AJP-Residents' Journal Editorial Board and AJP professional editorial staff.
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- Collaborate with the Editor-in-Chief in selecting the 2017 Senior Deputy Editor, Deputy Editor, and Associate Editors.
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Requirements

- Must be an APA resident-fellow member.
- Must be a PGY-3 in July 2016, or a PGY-4 in July 2016 with plans to enter an ACGME fellowship in July 2017.
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Selected candidate will be considered for a 2-year position, including advancement to Editor-in-Chief.

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- Collaborate with others as necessary to develop innovative ideas.
- Prepare a monthly Residents' Resources section for the Journal that highlights upcoming national opportunities for medical students and trainees.
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- Attend and present at the APA Annual Meeting.
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This is a 1-year position only, with no automatic advancement to the Senior Deputy Editor position in 2017. If the selected candidate is interested in serving as Senior Deputy Editor in 2017, he or she would need to formally apply for the position at that time.

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- Collaborate with the Senior Deputy Editor, Deputy Editor, and Editor-in-Chief to develop innovative ideas for the Journal.
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- Attend and present at the APA Annual Meeting.
- Commitment averages 5 hours per week.

Requirements

- Must be an APA resident-fellow member
- Must be a PGY-2, PGY-3, or PGY-4 resident in July 2016, or a fellow in an ACGME fellowship in July 2016
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***

For all positions, applicants should e-mail a CV and personal statement of up to 750 words describing their a bit about who they, their reasons for applying, as well as any ideas for journal development to Katherine.Pier@mssm.edu . The deadline for applications is 3/2/2016.

Residents' Resources

Here we highlight upcoming national opportunities for medical students and trainees to be recognized for their hard work, dedication, and scholarship.

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JANUARY DEADLINES

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
Jeanne Spurlock Congressional Fellowship **Deadline: January 15, 2016**	APA	The purpose of this fellowship is to provide an educational opportunity for all psychiatry residents, fellows, and early-career psychiatrists in the areas of child and minority mental health advocacy through a work experience in a congressional office.	• APA Resident-Fellow or early-career psychiatrist members • U.S. citizen or a permanent resident	Thomas Smoak for updated application procedures: 703-907-7324	http://www.psychiatry.org/residents-medical-students/residents/awards-and-competitions//jeanne-spurlock-congressional-fellowship
Psychiatric Research Fellowship **Deadline: January 30, 2016**	APA	The fellowship provides funding for a post-graduate psychiatry trainee, under the supervision and guidance of his/her mentor, to design and conduct a research study on a major research topic.	M.D. or D.O. APA member who completed residency training prior to the time the fellowship commences	psychresearch@psych.org	http://www.psychiatry.org/residents-medical-students/residents/awards-and-competitions//psychiatric-research-fellowship
Resident Psychiatric Research Scholars **Deadline: January 30, 2016**	APA	The purpose of the program is to identify promising psychiatric residents and encourage them to enter the field of psychiatric research. Emphasis is placed on mentoring whereby the recipient chooses a research preceptor for advice and encouragement throughout the project. Funds are awarded to develop a pilot project and for travel reimbursement to attend the APA Annual Meeting.	• M.D. or D.O. APA member • PGY 1, PGY 2, or PGY 3 resident in an accredited U.S. or Canadian psychiatry residency program	scholars@psych.org	http://www.psychiatry.org/residents-medical-students/residents/awards-and-competitions//resident-psychiatric-research-scholars
American Psychiatric Leadership Fellowship **Deadline: January 30, 2016**	APA	Fellows will have the opportunity to network with residents from around the country and serve alongside psychiatrists who are considered leaders in their area of expertise. Fellows are immersed in the governance structure of the APA through service on a Council and receive supplemental training on topics such as leadership development, mentorship, media interaction, and advocacy. Fellows will be funded to attend the APA Annual Meeting.	• APA Resident member • Enrolled as PGY 2 at an accredited psychiatric residency training program	psychleadership@psych.org	http://www.americanpsychiatricfoundation.org/get-involved/fellowships/american-psychiatric-leadership-fellowship
Child & Adolescent Psychiatry Fellowship **Deadline: January 30, 2016**	APA	This 2-year fellowship is designed to promote interest and a career in child and adolescent psychiatry. Gain an understanding of APA Governance through participation in an assigned APA Council. Offers travel support for two APA Annual Meetings and two APA September Components Meetings.	• APA membership • At least PGY 2	kids@psych.org 703-907-8639	http://www.psychiatry.org/residents-medical-students/residents/awards-and-competitions//child-and-adolescent-psychiatry-fellowship
Public Psychiatry Fellowship **Deadline: January 30, 2016**	APA	This is a 2-year fellowship that provides experiences that will contribute to the professional development of residents who will play future leadership roles within the public sector psychiatry and heighten awareness of the public psychiatry activities and career opportunities. Travel support will be offered to the APA's Components Meeting and Institute of Psychiatric Services.	• APA membership • Enrolled as a PGY 2 or PGY 3 in an accredited U.S. or Canadian residency program • Must be in training during the two-year fellowship	spatel@psych.org	http://www.psychiatry.org/residents-medical-students/residents/awards-and-competitions//public-psychiatry-fellowship
APA/Substance Abuse and Mental Health Services Administration (SAMHSA) Minority Fellowship **Deadline: January 30, 2016**	APA and SAMHSA	Section Criteria: Commitment to serve ethnic minority populations; awareness of the importance of culture in mental health; interest in the interrelationship between mental health/illness and transcultural factors; and demonstrated leadership abilities.	• APA Resident-Fellow Member • At least PGY 2 • U.S. citizen or a permanent resident	Tatiana Claridad: tclaridad@psych.org	http://www.psychiatry.org/residents-medical-students/residents/awards-and-competitions//minority-fellowships

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To submit a manuscript, please visit http://mc.manuscriptcentral.com/appi-ajp, and select "Residents" in the manuscript type field.

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2. **History of Psychiatry:** Provides a historical perspective on a topic relevant to psychiatry. Limited to 500 words and five references.
3. **Treatment in Psychiatry:** This article type begins with a brief, common clinical vignette and involves a description of the evaluation and management of a clinical scenario that house officers frequently encounter. This article type should also include 2-4 multiple choice questions based on the article's content. Limited to 1,500 words, 15 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
4. **Clinical Case Conference:** A presentation and discussion of an unusual clinical event. Limited to 1,250 words, 10 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
5. **Original Research:** Reports of novel observations and research. Limited to 1,250 words, 10 references, and two figures. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
6. **Review Article:** A clinically relevant review focused on educating the resident physician. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
7. **Drug Review:** A review of a pharmacological agent that highlights mechanism of action, efficacy, side-effects and drug-interactions. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
8. **Letters to the Editor:** Limited to 250 words (including 3 references) and three authors. Comments on articles published in *The Residents' Journal* will be considered for publication if received within 1 month of publication of the original article.
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