Demystifying A1AT Deficiency and COPD: A Practical Guidance for Clinicians

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- Chronic obstructive pulmonary disease (COPD) is a preventable and treatable chronic respiratory disease.
- COPD is characterized by persistent airflow limitation.
- An enhanced chronic inflammatory response in the airways and lungs is a key biological process in COPD.
- Acute exacerbations of COPD (AECOPD) are key events that are characterized by an acute worsening of respiratory symptoms and an enhanced inflammatory response.
- Diagnosis of COPD requires confirmation of chronic airflow limitation with spirometry; the presence of a post bronchodilator FEV1/FVC ratio < 0.70 confirms the presence of persistent airflow limitation.
- More patients with history of tobacco use and dyspnea should be offered spirometry.
- Spirometric disease severity is defined by the FEV1 value as a percent of predicted for the individual patient.
- 1-3% of all patients with COPD have Alpha-1 Antitrypsin Deficiency.
- It is impossible to distinguish Alpha-1 patients from average COPD patients, therefore all COPD patients need to be screened once.
- The American Thoracic Society released their guidelines in 2003, recommending screening for AAT in all COPD patients.
- Since more than 70% of COPD patients are cared for by primary care clinicians, screening for AATD needs to occur in both primary care and pulmonary settings.
- Screening can be in form of AAT levels alone, or better yet with phenotyping or genotyping so that counseling can be given to carriers.
- Therapeutic goals for COPD patients include:
  - Reducing symptoms, improving exercise tolerance, and improving health status
  - Reducing risk of future events including disease progression, AECOPD, and mortality
- Current paradigms for COPD management include assessing the burden of symptoms, documenting the degree of spirometric severity, and assessing the risk of future AECOPD.
- Symptom burden can be assessed with a variety of patient reported instruments including the mMRC (Modified Medical Research Council...
• COPD patients at risk for AECOPD include those with worse spirometric severity and/or a previous history of AECOPD (particularly two or more events in the previous year).
• Smoking cessation, influenza and pneumococcal vaccination and increased physical activity should be considered, as appropriate, for all COPD patients.
• First line, therapeutic options for COPD patients with increased symptoms include:
   Long acting bronchodilators (anti-muscarinics first line and/or beta agonists) alone
   Pulmonary rehabilitation
• First line, therapeutic options for COPD patients at risk for AECOPD include:
   Long acting anti-muscarinics or beta-agonists alone or in combination
   Inhaled corticosteroid combined with long acting beta agonist
• Roflumilast, a PDE4 inhibitor, can decrease AECOPD risk in COPD patients with chronic bronchitis, severe COPD, and a previous history of AECOPD.
• All pharmacotherapeutic strategies carry the potential of adverse events which vary by the individual drug class.
• COPD patients with Alpha-1 Antitrypsin Deficiency can be treated with augmentation therapy to increase the alpha-1 circulating levels in blood and lungs of these patients.
• Oxygen therapy is best established for COPD patients with resting hypoxemia (paO2 < 55 mmHg or SaO2 < 88%) while breathing room air in a stable clinical state.
• Alpha-1 Antitrypsin Deficiency Replacement Therapy can confer mortality benefits in the appropriate patients (FEV1<60%).
• Comorbid conditions can significantly impair outcomes and increase disease burden in COPD. These include:
   Cardiovascular disease
   Osteoporosis
   Anxiety/depression
   Lung cancer
   Serious infections
   Metabolic syndrome and manifest diabetes
• Therapy for these conditions in COPD patients or COPD therapy in the setting of these comorbid conditions should be considered as per usual guidelines.
Adult ADHD in Primary Care: Addressing the Unmet Need

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• ADHD is a highly genetic neurologic condition, which affects 4-5% of adults around the world.

• With a heritability of 75%, genetic factors that predispose towards ADHD are further modified by environmental influences such as in utero nicotine and alcohol exposure, childhood trauma and emotional neglect.

• Situational factors such as stress, cognitive load and both medical and psychiatric comorbidities may influence the severity of which ADHD symptoms are expressed.

• Studies both in the US and other countries have shown that individuals with ADHD have increased mortality and dramatically increased morbidity. ADHD leads to higher health risks and increased healthcare costs, higher divorce rates, lower levels of socioeconomic attainment and academic achievement, more motor vehicle accidents, and greater risk for co-morbid psychiatric disorders such as anxiety, depression, and substance use disorders.

• ADHD treatment has been associated with lower rates of substance abuse, decreased traumatic injury and lower rates of healthcare utilization.

• Diagnosing adults with ADHD is simplified by better understanding the adult manifestations of ADHD and how symptoms manifest throughout the lifespan.

• Assessment tools such as the Adult ADHD Self-Report Scale (ASRS), the ADHD-RS or other brief rating scales can be easily utilized in a busy primary care setting to more efficiently measure symptoms and monitor symptom improvement throughout treatment.

• Five once daily ADHD medications have been specifically studied
and approved for adult ADHD.

- Medications with FDA adult safety and efficacy data include include: Atomoxetine (Strattera®), oros-methylphenidate (Concerta®), dex-methylphenidate XR (Focalin XR®), mixed amphetamine salts XR (Adderall XR®), and lisdexamfetamine dimesylate (Vyvanse).

- Effect size for ADHD symptom improvement tends to be approximately 0.5 to 0.7 for atomoxetine, 0.8 to 0.9 for methylphenidate XR or OROS, 0.9 to 1.0 for mixed amphetamine salts XR and 1.1 to 1.7 for lisdexamfetamine.

- Short acting stimulants do not have specific indications or safety data for adults with ADHD and have increased potential for abuse and diversion.

- Common ADHD “Myths” include:
  1. Try a “test dose” to make the diagnosis
  2. ADHD occurs in boys not girls
  3. Hyperactivity is the outward marker to diagnose ADHD
  4. Children eventually grow out of it
  5. Only take your medication on school days

- Key ADHD Takeaways include:
  1. ADHD is a highly genetic neurologic condition
  2. 60 percent persist into adulthood
  3. Untreated ADHD has significant morbidity and increased mortality
  4. ADHD treatment has some of the highest effect sizes in all of medicine
  5. Short acting stimulants do not have specific indications or safety data for adult ADHD
  6. Long acting—once daily medications should be used to optimize symptom control
Atrial Fibrillation: Reducing Risk and Individualizing Therapeutic Choices

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- For patients with AF stroke risk assessment is key. Antithrombotic therapy can significantly reduce risk of cardioembolic stroke (~66% or more).

- 2014 ACC/AHA/HRS Guidelines define nonvalvular AF as that which occurs “in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral-valve repair.”

- Warfarin is the only FDA approved oral anticoagulant for patients with significant valvular heart disease.

- All DOAC’s are contra-indicated in the absence of adequate date demonstrating their efficacy.

- CHA2DS2VASc is the preferred risk stratification tool for nonvalvular AF patients.

- Document CHA2DS2-VASc score and shared decision process.

- For a CHA2DS2VASc of 2 or more, anticoagulation with warfarin or a DOAC (Direct Oral Anticoagulant) is recommended. For a CHA2DS2VASc of 1, current American Heart Association Guidelines support no anticoagulation, aspirin or anticoagulation (warfarin or DOAC). However the European Guidelines recommend anticoagulation.

- Patients at increased risk for stroke should receive anticoagulation indefinitely.

- Risk for intracranial bleeding with warfarin (when the INR is therapeutic 2-3) is very low (<1%). For most DOACs the risk of intracranial bleeding is even lower.

- Patient education and assessment of patients’ desires are important in
choice of anticoagulation. Continued assessment of patients’ understanding regarding risk of stroke and benefits of anticoagulants assists with continued adherence to therapy.

- Tools to assess bleeding risk such as the HASBLED score can help assess risk of bleeding when discussing anticoagulation with patients. In most cases the risk of cardioembolic stroke outweighs the risk of bleeding.

- Direct Oral Anticoagulants, which are currently available, include Dabigatran (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis), and Edoxaban (Savaysa).

- Management of major bleeding with DOACS or warfarin includes standard hemodynamic support with fluid resuscitation and transfusion therapy. For warfarin, use of fresh frozen plasma, 4-factor prothrombin complex concentrate (PCC) and recombinant factor VIIa may be used to reverse its anticoagulation effects. Dabigatran has an approved reversal agent called idarucizumab. PCC may be useful off-label for reversal of factor Xa inhibitors.

- The higher the stroke risk, the greater the relative benefit of OAC, despite the risks of bleeding.

- Each of the antithrombotic agents used to treat AF has specific instructions for management in the perioperative period.

- Surgical procedures for which there is low risk of major bleeding (eg, dermatologic, dental) can generally be managed without discontinuation of antithrombotic treatment.

- AF ablation is not an alternative to anticoagulation in high-risk patients and LAAC devices are limited to patients who are truly intolerant to or incapable of taking OAC’s.
GLP-1 Receptor Agonists: New Insights and New Strategies for Successful Long-Term Diabetes Management

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- Postprandial hyperglycemia is often under diagnosed, unmonitored, and under treated component of diabetes management.
- In pre-diabetes, postprandial hyperglycemia can occur up to a decade prior to the development of elevated fasting glucose.
- Over 2/3 of diabetic patient have diabetic postprandial glucose levels, but non-diabetic fasting glucose levels at disease onset, though not necessarily at clinical diagnosis.
- Consider dual therapy for patients with A1C > 7.5 %.
  Monotherapy with agents such as sulfonylureas, metformin are less efficacious over time.
- Treatment should target postprandial glucose excursions in patients with A1C < 8 %. Patients with A1Cs > 8.5 % should have their fasting hyperglycemia addressed.
- Postprandial hyperglycemia is associated with greater incidence of complications of diabetes, both micro- and macrovascular.
- Incretin based strategies for treating diabetes are a safe and effective means of improving postprandial hyperglycemia without risk of significant hypoglycemia. The “pharmacologic” advantages of GLP-1 analog therapy is a much more potent means of achieving this than the “physiologic” effect of oral DPP-4 inhibitors.
- GLP-1 analogs may be used prior to initiation of bolus insulin with similar, to superior A1c, lowering with less hypoglycemia
and no weight gain, and different effects on beta cell function.

- Use of basal insulin at bedtime is an effective means of lowering fasting and diurnal glycemia but does not address postprandial needs.

- The combination of basal insulin and GLP-1 analogs are very effective means of controlling fasting and postprandial hyperglycemia, utilizing both endogenous and exogenous insulin.

- Recent clinical trials with liraglutide and semaglutide have shown favorable impact on CV outcomes, and ADA guidance recommends use of these agents or empagliflozin in patients with CVD or high CVD risk.
Challenges in Hypertension: Incorporating Evolving Clinical Data into Practice

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• Hispanic Americans are less likely to be aware, less likely to be treated, and less likely to have their BP controlled to < 140/90 mm Hg compared to White and African-Americans with hypertension.

• Recent BP control rates suggest that 80% or more of those with hypertension have their BP reduced to < 140/90 mm Hg.

• Out-of-Office elevations in systolic BP are a better predictor of cardiovascular risk than office BP elevations yet we base everything we do on office BP values.

• Out-of-office BP measurements by patients, at a minimum, and 24-hr ambulatory BP measurement by clinicians should be performed to ensure the diagnosis of hypertension before the diagnosis of hypertension is made.

• The use of effective lifestyle interventions (low salt diet, weight loss, exercise) and pharmacotherapy including a thiazide-type diuretic, calcium channel blocker, and ACEI or ARB [RAS blocker] should be utilized as the initial three antihypertensive drug classes in the treatment of hypertension unless there is a compelling reason to use a different antihypertensive class.

• Chlorthalidone, when given 12.5-25 mg once a day, is evidence-based for CV outcome improvement in the SHEP and ALLHAT trials.

• Chlorthalidone is a true once-a-day thiazide-like diuretic and is more effective than hydrochlorothiazide for BP reduction when given once-a-day for 24-hour BP control.

• In most adults – regardless of age and diabetes status – reducing SBP to 130-139 mmHg (if tolerated) appears to offer the best overall organ protection (the “sweet spot for BP control”).
Recognition and Management of Idiopathic Pulmonary Fibrosis:
The Role of Primary Care

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• Be attuned to the patient with shortness of breath and/or chronic cough where idiopathic pulmonary fibrosis (IPF) may be present: Get a Chest X-ray and pulmonary function testing (PFT).

• When the PFT suggests restriction (decreased forced vital capacity with normal FEV1/FVC ratio), or the CXR suggests a diffuse parenchymal process (AKA, interstitial lung disease), multiple questions need to be asked:
  ❖ Is there a systemic connective tissue process?
  ❖ Are there inhalational exposures?
  ❖ Are there drug exposures?
  ❖ Is there a family history of lung disease?

• All patients with a potential diffuse parenchymal lung disease should have a high resolution computed tomograph (HRCT) of the chest.

• IPF is the diffuse parenchymal lung disease with a particularly poor prognosis and should be aggressively sought out and treated.

• A diagnosis of IPF is based on:
  ❖ A pattern of usual interstitial pneumonia (UIP) on HRCT (lower lobe predominant, honeycomb changes) or surgical lung biopsy, and
  ❖ Exclusion of a secondary causative process

• Disease severity associated with particularly poor short term prognosis is based on:
  ❖ Male gender
  ❖ Age greater than 60 years
  ❖ Greater baseline pulmonary function abnormality
  ❖ Short term change in simple pulmonary function testing

• Therapy is best started at Specialized Centers.
- No trials of immunosuppressive therapy or anticoagulation are indicated in confirmed IPF.

- Two new therapeutic agents have been approved to treat IPF as they decrease lung function decline: Pirfenidone and Nintedanib.

- Multiple promising pharmacotherapeutic agents are under active study.

- Lung transplantation evaluation should be considered early.

- Patients need close follow-up, especially with advancing disease.
Leaning in to LARCs: Long Acting Reversible Contraception Options

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- LARCs are Long Acting Reversible Contraceptive methods that prevent pregnancy for between 3-10 years, depending upon the option used, with an immediate return to fertility when removed.

- Of the 6 million pregnancies that occur in the United States each year, over 2.5 million are unintended, with over approximately 1 million occurring in women who are using some form of contraception sporadically or inconsistently.

- Contraceptive options are stratified into Tiers based on effectiveness. With > 99% effectiveness in preventing pregnancy, LARCs and Sterilization are the only options in Tier 1. Pills, patches, injections and rings are in Tier 2.

- According to the CDC, the use of LARCs has increased 5 fold since 2002, with women aged 25-34 being the highest users.

- All currently available LARCs are radiopaque and MRI safe.

- The mechanism of action for the subdermal implant is based on the progestin thinning out the endometrial lining of the uterus, inhibiting ovulation and increasing the viscosity and thickness of the cervical mucus, which interferes with sperm transport.

- Approximately 20% of women using the subdermal implant can expect to have amenorrhea, while half of those experiencing an unfavorable bleeding pattern will see an improvement over 6 months.

- While 81% of women using the subdermal implant will see an overall reduction on menstrual bleeding, the discontinuation rate for unfavorable bleeding patterns, that is frequent and/or prolonged is 11.1%.

- According to ACOG, the American Congress of Obstetrics and
Gynecology, many women may benefit from using a subdermal implant, including women with hypertension, liver disease, CVD, BMI >35, HIV, PID, cervical cancer, smokers >35, contraindication to the use of estrogen and those with current purulent cervicitis.

- ACOG recommends all forms of Intrauterine LARCS including both Copper containing IUDs and progestin containing IUDs for teens and women regardless of whether they’ve had a pregnancy or birth.

- The Copper IUD is effective immediately, can be used for up to 10 years and is the most effective form of emergency contraceptive if inserted within 5 days of unprotected intercourse.

- The Copper IUD prevents pregnancy by inducing a very mild inflammatory response that inhibits sperm migration, mobility and viability. Any effect on tubal mobility or ovum transport speed occurs before implantation.

- Women who have light periods with minimal cramping and those who desire more than 5 years of contraception are good candidates for the Copper IUD as well as those who have any hormone contraindication or sensitivity. Women who are breastfeeding and those who don’t want to suppress ovulation or their periods are also good candidates.

- With the Copper containing IUD bleeding patterns, women should be counseled to expect more bleeding, especially in the first 6 months.

- With the Copper containing IUD, after 6 months of use, 40% of women report more bleeding with the device than what they experienced prior to insertion, while only 10% of women report less bleeding.

- When considering menstrual pain in women with the Copper containing IUD, 40% see no difference, 25% have less and about 35% have more.

- The main difference between Progestin containing IUDs is how long they’re effective and can remain in place, and the total amount of hormone that’s present in each device, which impacts menstrual flow.

- Progestin containing IUDs with 52 mg of progestin result in lighter - or even absent – periods in approximately 40-50% of women.

- Progestin containing IUDs act by creating progestin dominant, thickened cervical mucus that interferes with sperm transport, thinning the endometrial lining, which further inhibits sperm mobility and
motility. These do not inhibit ovulation.

- Progestin containing IUDs are good contraceptive options for women who have heavy periods, adenomyosis, Von Willebrands factor, have anovulatory bleeding, are in perimenopause, are breastfeeding, or have a copper allergy.

- Women who use the lower dose Progestin containing IUDs have 12-20% rates of amenorrhea, less amenorrhea than what's seen with the higher doses, however the irregular bleeding patterns reduce over time and discontinuation rates are reported as less than 2% for bleeding.

- Expulsion rates with all IUDs are slightly higher in nulliparous vs. parous women with the 1st year having the highest incidence: 5.7% for the Copper containing IUD, 4.5% for the 52 mg Progestin containing IUD and 3.2% for the 13.5 mg Progestin containing IUD.

- The overall risk of an ectopic pregnancy is reduced in women who use LARCS because the likelihood of pregnancy is <1%. However any contraceptive failure that leads to pregnancy, has an increased risk that it will be ectopic and must be evaluated.

- The risk of PID is similar for women with and without the IUD, in a study of 20,000 women rates of PID per 1,000 women at least 21 days after insertion were 1.5%.
New Agents, New Options, and Expanded Potential In Lipid Management: Integrating The Data Into Practice

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According to the Statin therapy is a cornerstone of primary and secondary prevention of cardiovascular events

2013 ACC/AHA Cholesterol guidelines, statin therapy is beneficial for the 4 statin benefit groups
- Clinical ASCVD
- LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes: ≥7.5% 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

Even in well-treated patients on maximum statin dose, up to 75% of patients will still have another cardiovascular event. This is termed “residual risk.” Non-adherence to statin therapy is an important deterrent to lipoprotein goal attainment

Furthermore, even though statins are robust LDL-C lowering drugs, there is significant inter-patient variability in statin response

Consider Familial Hypercholesterolemia (FH) whenever the LDL-C is >190 mg/dL

Familial hypercholesterolemia is an inheritable, autosomal dominant disorder due to mutations that result in decreased clearance of LDL particles from plasma

The genetic defect in familial hypercholesterolemia is usually an LDL receptor gene mutation, however other mutations include Apo B and PCSK9 genes

Familial hypercholesterolemia greatly increases the risk for coronary heart disease

Familial hypercholesterolemia is among the most widely prevalent metabolic disorders and is associated with dramatic elevations in risk
for all forms of atherosclerotic disease

- In the heterozygous form, FH occurs in approximately 1:500 individuals making it 4X as common as sickle cell disease and 5X as common as cystic fibrosis.

- According to the 2013 ACC/AHA Cholesterol guidelines, addition of nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

- PCSK9 is a secreted protein that targets the LDL receptor for degradation.

- PCSK9 Inhibitors are a new class of drugs in development to treat hypercholesterolemia. PCSK9 inhibitors allow for the upregulation of LDL receptors on the surface of hepatocytes, resulting in greatly augmented clearance of LDL-C from the circulation. At least 8 different PCSK9 inhibitors are currently in development.

- The first outcome study evaluating the effect of a PCSK9 inhibitor (evolocumab) was published in March 2017. In this trial, 27,564 patients with cardiovascular disease and on a moderate- to high-intensity statin were randomized to receive subcutaneous injections of evolocumab (either 140 mg every two weeks or 420 mg every month based on patient preference) or matching placebo. Evolocumab reduced LDL-C by 59% from a median of 92 to 30 mg/dL. Patients on evolocumab had a 15% reduction in the primary endpoint – a composite of heart attack, stroke, and hospitalization for angina, revascularization or cardiovascular death. There was also a 20% reduction in the secondary endpoint of the composite of cardiovascular death, heart attack or stroke. In addition, the therapy was safe and well tolerated.1

- The other FDA approved PCSK9 inhibitor, alirocumab, is currently being tested in the ODYSSEY OUTCOMES trial. More than 18,000 post acute coronary syndrome patients are being randomized to receive either alirocumab 75 milligrams (mg) every two weeks or placebo. Although the outcome study is currently ongoing, prior studies of alirocumab revealed LDL-C reduction of approximately 60% on top of statin therapy. In a post hoc analysis, the rate of adverse cardiovascular events was lower with alirocumab than placebo.2

- The 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the

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1 Sabarine et al. March 17, 2017 10.1056/NEJMoa1615664
Management of Atherosclerotic Cardiovascular Disease Risk was recently released

- This document states that use of non-statins may be considered in selected high-risk patients, such as those with existing ASCVD or LDL-C ≥190 mg/dl, if maximally tolerated statin therapy has not achieved >50% reduction in LDL-C from baseline

- Ezetimibe is the first non-statin medication that should be considered in most of the patient scenarios, given its safety and tolerability, as well as demonstrated, though modest, efficacy when added to moderate-dose statin in one trial of patients with acute coronary syndrome

- PCSK-9 inhibitors may be considered if the goals of therapy have not been achieved on maximally tolerated statin and ezetimibe in higher-risk patients with clinical ASCVD or familial hypercholesterolemia

- Despite improvements in cardiovascular care, coronary heart disease (CHD) rates remain unacceptably high

- In patients treated with statins, residual cardiovascular risk remains

- Response to statins is variable and influenced by many factors including genetic factors

- Patient populations at highest CHD risk may potentially benefit greatly from novel lipid lowering therapies

- CMS Quality Measures for the use of statin therapy:
  - % high-risk patients prescribed statin therapy:
    - adults aged ≥21 years with ASCVD
    - adults aged ≥21 years with LDL-C ≥190 mg/dL or with familial or pure hypercholesterolemia; and
    - adults aged 40-75 years with diabetes and LDL-C 70-189 mg/dL
Pseudobulbar Affect: A Call to Action

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- PBA is an acquired neurologic condition, which affects nearly one third of individuals with an underlying neurological condition.

- Under normal conditions, cerebrospinal-ponto-cerebellar circuitry is intact and works in concert to coordinate appropriate emotional expression, however neurologic conditions or injuries may disrupt this circuitry, affecting the normal control of emotional expression.

- PBA occurs secondary to a variety of otherwise unrelated neurologic conditions or injuries and is characterized by episodes of crying and/or laughing.
  - PBA may be mischaracterized as depression or symptoms associated with the patient’s primary neurologic condition.

- The estimated PBA symptom prevalence in Alzheimer’s Dementia appears to be 29% with approximately 473,000 new cases of AD estimated in 2015 in people over 65 y/o. Neuropsychiatric symptoms often occur in patients with AD and depression can co-occur.

- The estimated prevalence of PBA in stroke is 38%, with an annual incidence of approximately 795,000. Neuropsychiatric symptoms often occur in patients with stoke, and comorbidities can include depression and anxiety.

- The estimated prevalence of PBA in traumatic brain injury is 52%; in 2010 TBI accounted for approximately 2.5 million emergency department visits, hospitalizations and deaths in the US. Neuropsychiatric symptoms often occur in TBI and comorbidities can include PTSD, depression and mania.
  - You can assess for TBI by asking: Have you ever had your bell rung?

- Episodes of PBA may not occur during a medical visit. To make a diagnosis, HCP’s need to ask their patients if they are experiencing uncontrollable/exaggerated episodic crying or laughing incongruent
with the circumstances at play.

- Symptoms of PBA may be mischaracterized as other behavioral disturbances. Sometimes patients may be unable to accurately recall or report their symptoms or have difficulty communicating physical symptoms; inappropriate outburst of laughter or crying may suggest PBA.

**Common PBA “Myths” include:**
1. If a patient cries its depression
2. PBA is a made up condition (This is a condition that’s been described in literature since 1872)
3. PBA will go away if it’s ignored (it won’t; furthermore it will cause embarrassment, isolation and withdrawal)
4. Cough syrup will do the same thing as dextromethorphan/quinidine in treating PBA (there’s a reason there’s only one medicine FDA approved for this condition)
5. PBA happens in the absence of a neurologic condition (No, a neurologic condition/injury will always precede PBA)

**Key PBA takeaways include:**
1. PBA is an acquired neurologic condition
2. One third of patients with a neurologic condition will develop PBA
3. Untreated PBA causes embarrassment, withdrawal and isolation
4. Dextromethorphan/quinidine, the only FDA approved PBA treatment, has a significant effect size in reducing episodes.
5. Asking the following questions: *Have you ever had your bell rung?* and *Have you experienced involuntary episodes of crying and/or laughing that were exaggerated or even contrary to how you felt at the time?* can make a significant difference.
6. The CNS-LS is helpful to initiate a dialogue of PBA but is not a diagnostic tool. PBA diagnosis is clinical.
The kidney plays an essential role in maintaining blood glucose homeostasis. Roughly 180 grams of glucose are filtered by the glomerulus daily.

The obligate glucose needs of brain, CNS and renal medulla are exactly 180 g a day, and the body has a meticulously balanced reabsorption of all filtered glucose to match obligate demands.

The kidney plays an important role in fasting gluconeogenesis, contributing 25% of all fasting glucose production.

The SGLT transporters regulate reabsorption of filtered glucose, with SGLT-2 responsible for 90% of glucose reabsorption and are paradoxically upregulated in diabetes.

The expected reduction in A1c with SGLT-2 inhibitors is 0.6-1.0%, both as monotherapy or as add-on to other agents. The reduction is greatest in treatment naïve patients as well as those with baseline A1Cs > 9%.

SGLT-2 inhibitors are an effective means of address postprandial hyperglycemia in patients with type-2 diabetes because on their postprandial glucoretic effect.

Recent trials have suggested a CV mortality and all cause mortality and renal benefit with empagliflozin, but other agents are still under study. Recent ADA guidance recommends use of this agent or GLP-1 agents in patients with CVD or high CVD risk.

Each of the drugs in this class has eGFR guidance for use, with dapagliflozin not indicated for GFR below 60mg/min, and the other agents contraindicated when GFR is below 45. This is not due to
safety concerns but reduced efficacy as GFR declines.
• Rare but important side effects of the class are euglycemic ketoacidosis, acute kidney injury, orthostatic hypotension, and increased fracture risk, likely due to increased falls from orthostasis.
  — SGLT2 inhibitors may be less effective and pose more adverse effects in patients > age 65 years.
  — The most common side effects for SGLT2 inhibitors include orthostatic hypotension, lower urinary tract infections, and genital mycotic infections.