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Hospitalist Update:

Monitoring and Metabolic Risks with Second Generation Antipsychotics

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As the armamentarium of antipsychotic medications continues to grow, so does data supporting expansion of their use for conditions beyond schizophrenia. For this reason, providers other than psychiatrists may see increasing numbers of patients on these medications and need to have an understanding of how to manage such patients. It is, therefore, important to take a moment to remind ourselves that while efficacious, these medications do not come without risk. The potential for extrapyramidal symptoms causes concern with first generation antipsychotics and has played a role in the shift toward increased use of second generation antipsychotics (SGAs), such as olanzapine, quetiapine, risperidone, ziprasidone, or paliperidone. This is due to the fact that SGAs are less likely to cause such movement disorders. The switch comes with a tradeoff, however. SGAs have been shown to increase patients' risk of developing metabolic syndrome.[1]

According to the Adult Treatment Panel III (ATP III) guidelines, diagnosis of metabolic syndrome involves evaluation of five main domains: abdominal

circumference, triglyceride (TG) levels, high-density lipoprotein (HDL) levels, blood pressure, and fasting glucose levels. Abnormalities in three or more of these areas are indicative of metabolic syndrome. Such abnormalities include:

- Waist circumference over 102cm for men or 88cm for women
- TGs greater than or equal to 150mg/dL
- HDL less than 40mg/dL for men and less than 50mg/dL for women
- Blood pressure greater than or equal to 130/85mmHg[2]
- Fasting glucose greater than or equal to 100mg/dL[2,3]

Changes in these parameters and the development of metabolic syndrome can have a large impact on a patient's health and lead to long term complications. If not addressed, patients may develop diabetes or cardiovascular disease.[1] Obesity alone is associated with multiple comorbidities such as hypertension, sleep apnea, and stroke, which may lead to increased mortality and morbidity.[4] These multitudes of potential complications may in turn lead to increased medication use or hospitalizations. It is, therefore, important to proactively seek opportunities to prevent them by identifying and monitoring patients at high risk for metabolic syndrome.

Certain populations have an increased risk of developing metabolic disorders. Among these are patients with mental health conditions such as schizophrenia or bipolar disorder.[5] When these patients are treated with SGAs, as is often the case, the potential for metabolic problems, including hypertriglyceridemia and insulin resistance, is amplified.[1,6] The mechanism by which SGAs pose this risk is not fully understood, but is likely multifactorial. Patients taking these medications may notice an increase in appetite or a craving for carbohydrate rich food, eventually leading to obesity and related complications. SGAs may also have a direct impact on patients' lipid profiles, increasing TGs and lowering HDL levels. Among other theories is the thought that activity at serotonin 2C ($5HT2_c$), histamine 1 (H1), and muscarinic 3 (M3) receptors leads to increased appetite, weight gain, and metabolic syndrome.[6]

Looking at the receptor profiles of many of the higher risk antipsychotics, this theory makes sense. The SGAs clozapine, olanzapine, and quetiapine all antagonize these three receptors, and all are highly associated with weight gain.[7] The receptor theory also helps to explain the risks associated with low doses of quetiapine, such as those used off-label for sleep. At low doses, quetiapine is more selective for H1 receptors and therefore poses as much of a metabolic risk as a dose used for treating psychosis.[6-8] For this reason, careful consideration should be made before starting someone on quetiapine simply to help with sleep.

Other SGAs, especially newer agents, are marketed as being less likely to cause weight gain or metabolic syndrome. Aripiprazole, ziprasidone, lurasidone, asenapine, and iloperidone are among such agents, and may be considered if metabolic complications are a concern or if a patient is unable to tolerate other SGAs. Risperidone and its metabolite, paliperidone, have moderate potential to cause weight gain, but evidence linking them to diabetes and hypertriglyceridemia is not as conclusive as with clozapine and olanzapine.[1,6,7,9]

While avoidance of the higher risk medications would help ameliorate the risk of metabolic complications, this is not always practical. Additionally, all SGAs increase the risk of metabolic

complications to varying degrees.[1] Therefore it is important to diligently monitor for adverse metabolic effects among patients on these medications. Doing so will help with early detection and management of the problem.

To properly monitor these patients, guidelines recommend taking a thorough medical and family history and obtaining a baseline body mass index (BMI), waist circumference, blood pressure, fasting glucose, and fasting lipid profile. Thereafter, the following monitoring schedule is recommended:

- Weeks 4 and 8: BMI
- Week 12: BMI, blood pressure, fasting glucose, and fasting lipids
- Quarterly after week 12: BMI
- Annually: medical and family history update, waist circumference, blood pressure, and fasting glucose
- Every 5 years: fasting lipids[1]

Patients who have abnormal results within these time frames should be monitored more closely until they stabilize. Additionally, monitoring for patients switched to a new SGA should restart according to the recommended schedule.[1]

If metabolic profiles are found to be out of range or consistently worsening for a patient, lifestyle modifications should be implemented. It is also likely they could benefit from being switched to a different SGA. An agent with lower metabolic risks would be preferred in such cases, although other medication and patient specific characteristics should not be overlooked. For patients in whom switching is not an appropriate option, medical management of their lipids, weight, and blood pressure may be needed to prevent long term complications.[1]

Management of these problems, however, can become complex as multiple providers may be involved in a patient's care. This issue of a psychiatric medication causing problems typically managed in a primary care setting highlights the need for collaboration among multiple disciplines.[5] In order to ensure that patients on these medications adhere to a proper monitoring regimen, all providers should perform recommended monitoring. Results and treatment plans should then be shared to allow for better interdisciplinary collaboration and to prevent repetitive testing.

Close follow-up and monitoring of patients on SGAs is paramount. Apart from clinical efficacy, providers should also continually evaluate the metabolic effects of these drugs.[1,6] While the risks associated with these medications cannot always be avoided, close follow-up can decrease the rates of untoward effects and play a role in the successful long-term use of these medications.

REFERENCES

1. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care.2004; 27(2): 569-601.
2. National Institutes of Health. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). NIH Publication No. 02-5215. 2002 Sept.

3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013; 36: S67-S74.
4. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. NIH Publication No. 98-4083. 1998 Sept.
5. Balf G, Stewart TD, Whitehead R, Baker R. Metabolic adverse events in patients treated with antipsychotics: A primary care perspective. Prim Care Companion J Clin Psychiatry. 2008; 10(1): 15-24.
6. Stahl SM, Mignon L, Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? Acta Psychiatr Scand. 2009; 119: 171-179.
7. Stahl SM. Antipsychotic agents. In: Stahl's essential psychopharmacology: neuroscientific basis and practical applications. 3rd ed. New York: Cambridge University Press; 2008.
8. Gugger JJ, Cassagnol M. Low-dose quetiapine is not a benign sedative-hypnotic agent. Am J Addict. 2008; 17: 454-455.
9. Lexi Drugs™ [Internet]. Hudson (OH); Lexi-Comp, Inc. [cited 2013 May 28]. Available from: http://online.lexi.com/lco/action/home.

Diagnostic Dilemma

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Questions:

1) A 37 year old female is admitted with increasing dyspnea and orthopnea of 1 week duration. She had received chemotherapy and radiation for breast cancer 1 year ago. On exam she has elevated JVP and diminished breath sounds at bases. Bilateral lower extremities have 2+ pitting edema. Which of the following conditions could be the potential culprits leading to this presentation?

    A) Cardiac Tamponade
    B) Dilated Cardiomyopathy
    C) Constrictive Pericarditis
    D) Restrictive Cardiomyopathy
    E) All the above

2) A 68 year old male with history of hypertension was admitted with a blood pressure of 220/120 mm/Hg. He has been on treatment for hypertension and has a known history of paroxysmal atrial fibrillation and coronary artery disease. His home medications include amiodarone, amlodipine, aspirin, losartan and hydrochlorothiazide. He was diagnosed with hypertensive urgency and treated with labetalol. Which of the following is the least likely cause of hypertensive urgency in this patient?

    A) Drug induced hypertension
    B) Primary Hyperaldosteronism
    C) Renal artery atherosclerosis
    D) Fibromuscular dysplasia

3) A 32 year old female presented to ER with progressively increasing shortness of breath. She also reported orthopnea, paroxysmal nocturnal dyspnea and increased swelling in her legs. She is 30 weeks pregnant and has not received any prenatal care so far. She recently immigrated from Southeast Asia. An emergent chest x-ray done in ER showed pulmonary edema and normal heart size. She received intravenous furosemide in the ER with good relief of her symptoms. Which of the following findings is not likely to be present on physical examination?

A) Loud first heart sound
B) Mid diastolic murmur at the apex
C) Holo-systolic murmur at left lower sternal border
D) Ejection systolic murmur at right upper sternal border

Answers on page: 7

ASK A PATHOLOGIST

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QUESTION: I have heard about the recent increase in *Paragonimus kellicotti* infections in Missouri. If I am suspicious of this diagnosis in one of my patients, how can I test for it?

ANSWER: *Paragonimus kellicotti*, also known as the North American lung fluke, is a parasitic trematode which uses snails and crustaceans as intermediate hosts. Human infections have previously been rare, with only 7 cases reported between 1968-2008. Recently, the number of reported cases in Missouri has increased: three cases were reported in 2009, and an additional six cases from the St. Louis area were reported during 2009-2010. All nine of these patients had been involved in recreational activities on various Missouri rivers prior to their infection and had consumed raw or undercooked crayfish.

The symptoms of Paragonimiasis infection are nonspecific and onset of symptoms occurs 2-12 weeks after crayfish ingestion, so a high level of suspicion is required to make an accurate diagnosis. The median time to correct diagnosis in this series of nine patients was 12 weeks. The most common signs and symptoms included cough (100%), fever (88.9%), and eosinophilia (100%). Additional symptoms included fatigue, headache, shortness of breath, chest pain, and weight loss. All nine patients had a pleural effusion on chest x-ray. Initial diagnoses included pneumonia, bronchitis, influenza, gastroenteritis, acute cholecystitis, and pulmonary embolism. Malignancy and tuberculosis may also be considered in the initial differential diagnosis.

To confirm the diagnosis of *Paragonimus kellicotti* in a patient with suspected infection, several testing options are available. Sputum for ova and parasite testing is very specific when characteristic operculate ova are present; unfortunately, the ova may only be present intermittently so sensitivity

is low at 30-40%. Tuberculosis may also be in your differential diagnosis, but unfortunately the acid-fast stains used for diagnosing tuberculosis will destroy *Paragonimus* eggs so the pathologist should be notified if you have a suspicion for Paragonimiasis. Ova in the stool (from eggs that are coughed up and then swallowed) are also specific but are found even less frequently, with a sensitivity of 11-15%.

Eggs, adult organisms and/or eosinophilia can be seen in needle core and other types of tissue biopsies; this diagnostic method also has the potential advantage of looking for malignancy or other conditions on your differential diagnosis at the same time. If a less invasive approach is needed, a blood sample from the patient can be sent to the CDC for an immunoblot assay against a crude extract from *Paragominus westermani,* a related lung fluke found in Asia. The immunoblot test is highly sensitive for diagnosing *P. westermani*, but cross-reactivity also occurs in some patients with *P. kellicotti* infection. In patients with no history of travel to areas endemic for *P. westermani*, a positive immunoblot test can be used to confirm the diagnosis of *P. kellicotti* infection. An IgG Western blot test using specific *P. kellicotti* antigen has been developed and has been found to be both sensitive and specific for *P. kellicotti* infection, but this test is not yet commercially available.

REFERENCES:

1. Fischer PU, Curtis KC, Folk SM, Wilkins PP, Marcos LA, Weil GJ. Serological Diagnosis of North American Paragonimiasis by Western Blot Using Paragonimus kellicotti Adult Worm Antigen. The American Journal of Tropical Medicine and Hygiene. Published online April 15, 2013.
2. Lane MA, Marcos LA, Onen NF, Demertzis LM, Hayes EV, Davila SZ, Nurutdinova DR, Bailey TC, Weil GJ. Paragonimus kellicotti Flukes in Missouri, USA. Emerging Infectious Diseases. 18(8) August 2012.
3. Centers for Disease Control and Prevention. January 10, 2013. http://www.cdc.gov/parasites/paragonimus/health_professionals/index.html#dx

Send your questions to coberlye@health.missouri.edu to be published in future editions of the Missouri Hospitalist.

ID Corner

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Endocarditis

A recent basic clinical review of Infective Endocarditis in NEJM-Clinical practice:

Hoen B, X Duval . Infective endocarditis. N Engl J Med 2013;368:1425-33.

http://www.nejm.org/doi/pdf/10.1056/NEJMcp1206782

Diagnostic Dilemma

Answers:

1) **E**

- The patient has symptoms and signs suggestive of congestive heart failure. The patient in the vignette is at risk for all the mentioned conditions due to breast cancer and its treatment.
- Cardiac tamponade can develop from metastasis of breast cancer to pericardium. Most common malignancies to metastasize to the pericardium are lung and breast cancer.
- Dilated cardiomyopathy is a known complication of treatment with anthracycline derivatives (Doxorubicin) or trastuzumab, which are often used to treat breast cancer.
- Radiation therapy to chest is associated with constrictive pericarditis, which often presents with symptoms of heart failure.
- Mediastinal irradiation is associated with restrictive cardiomyopathy which often stems from myocardial fibrosis.

2) **D**

- Fibro-muscular dysplasia is a common cause of secondary hypertension in young adults, but not in the elderly. So it is unlikely to be the cause of secondary and resistant hypertension in this 60 year old gentleman.
- Amiodarone use has been linked to hyperthyroidism, and patients, especially the elderly, can present with cardiovascular manifestations like resistant hypertension, atrial fibrillation with poor rate control and unexplained tachycardia.
- Presence of atherosclerotic vascular disease in other vascular territories is a risk factor for atherosclerotic renal artery stenosis, which can lead to secondary hypertension.
- According to the recent data, primary hyper-aldosteronism may be present in up to 10% of patients with resistant hypertension.

3) **D**

- This patient has presented with symptoms of heart failure in the third trimester of her pregnancy. In a young patient of Southeast Asian origin, who has recently migrated to USA, a serious consideration should be given to rheumatic heart disease, even though it is seen less frequently now. Patients with rheumatic heart disease sustain chronic damage to heart valves and often develop mitral stenosis. Some of these patients present with symptoms of overt heart failure in the third trimester of pregnancy when there is a physiological increase in plasma volume. Classic physical exam findings in mitral stenosis include loud first heart sound and a mid-diastolic rumble at the apex.
- A holo-systolic murmur at the left lower sternal border denotes a functional tricuspid regurgitation that results from increased pulmonary pressures related to mitral stenosis.
- An ejection systolic murmur at right upper sternal border is seen in aortic valve stenosis and is unexpected in this young patient.

MISSOURI HOSPITALIST SOCIETY

CONFERENCE CALENDAR

Click on Conference Title to View Webpage

41st Annual Update in Family Practice and Primary Care
Dates: September 9 - 13, 2013
Venue: University of Washington Health Sciences Building, Seattle, Washington

Hospitalist and Emergency Procedures Course 2013
Dates: September 14 - 15, 2013
Venue: Crowne Plaza Hotel, Seattle, Washington

Missouri ACP 2013 CME Meeting
Updates in Internal Medicine
Dates: September 26 - 29, 2013
Venue: Tan-Tar-A, Osage Beach, Missouri

Mayo Clinic Hospital Medicine: Managing Complex Patients
Dates: November 6 - 9, 2013
Venue: Loews Ventana Canyon Resort, Tucson, Arizona

14th Annual Southern Hospital Medicine Conference
Dates: November 7 - 9, 2013
Venue: Hyatt Regency New Orleans, New Orleans, Louisiana

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