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Hospitalist Update:

Monitoring and Metabolic Risks with Second Generation Antipsychotics

Rebecca Reiss, PharmD.
PGY-1 Pharmacy Practice Resident
University of Missouri Health Care

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.

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Diagnostic Dilemma

Sudharshan Balla, MD
Fellow, Division of Cardiovascular Diseases, University of Missouri Health Care

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