Role of Serotonin from Thought and Anxiety to Weight Gain and Metabolic Syndrome

Gollapudi Shankar

Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, USA

Recently, there has also been lot of research on serotonin and its correlation with schizophrenia. In a study called "Decreased Serotonin 2A Receptor Densities in Neuroleptic-Naive Studies showed significantly small serotonin receptor densities before the exposure to antipsychotics in the frontal cortex index when compared schizophrenia postmortem patients with healthy subjects at the onset of illness. Patients With Schizophrenia: A PET Study Using [18F] Setoperone", serotonin receptor binding capacity was measured in both schizophrenic as well as healthy individuals. It was demonstrated in the article that there was a significant decrease of serotonin binding index in the prefrontal cortex in patients with schizophrenia. The results also concluded that this reduction occurs in the early stage of the illness before the use of any neuroleptics despite previous belief that the decline progressively increased with age. Atypical antipsychotics act on the brain's serotonin (5-HT). These sites have been implicated in the control of appetite. Research has shown that either the increased 5-HT2C availability or the direct activation of 5-HT2C receptor sites has caused reduced food consumption in both animals and humans.

Studies indicated that targeting localized serotonin 5-HT2C receptors can treat obesity which is consistent with the role in regulating pathways of food intake and body weight that could lead to obesity. The association of diminished serotonergic activity with metabolic syndrome may have implications for the prevention and treatment of the metabolic syndrome. Antipsychotics are 5-HT2C receptors antagonists that can knock down the satiety centers located in ventromedial nucleus in hypothalamus leading to increased weight gain. The potential for weight gain differs among atypical antipsychotics. While ziprasidone and aripiprazole care thought to be weight neutral, dibenzodiazepines like clozapine and olanzapine are implicated in lot of weight gain that can cause obesity and metabolic syndrome. The amount of body weight gain varies with each drug. The difference in weight gains between quetiapine and each of the other atypical medication was significant in our studies (Mean weight gain was least with quetiapine 9.31b and greatest for olanzapine 20.89 lb). Weight gain was also greater with olanzapine than with clozapine. In the literature survey we observed clozapine has been associated with some of the largest bodyweight gains of olanzapine in the long term use and higher weight gain with clozapine seems to be on shorter duration. For many of the metabolic disorders related to weight gain and obesity, scientists have implicated abdominal visceral fat. An increase in visceral fat, in turn, leads to an increased concentration of free fatty acids in the portal vein. An increased free fatty acid concentration may lead to a decrease in hepatic insulin clearance, insulin resistance, hyperinsulinemia, and hypertension. This sequence of events may lead to diabetes, assorted dyslipidemia, and ultimately to coronary artery disease.

The purpose of the study was to evaluate the impact of intervention on improving overall cardiovascular adverse effects of antipsychotic therapy. Long-term metabolic complications such as obesity, diabetes, dyslipidemia, hypertension, and ECG changes were of particular interest but the results from our study has not shown any significant change in clinical practice that lead to reduction in cardiovascular risk. During the study period (8/2009 – 11/2009), 118 treatment recommendations were made by pharmacy students and clinical pharmacist preceptor and most were for new lipid and FBG/HgA1C panel for missing lab values or more accurate assessment of patient's recent status and 82 recommendations were accepted.

As appreciated by the result from this study period, the key limiting factor in accurately assessing effectiveness of consultant intervention is that the treatment decision is ultimately made by the patient's psychiatrist who reviews the recommendation. However the clinical recommendation from the psychopharmacy consultant may still help to increase overall awareness on part of psychiatrists regarding patients' current cardiovascular risk. Whether it will lead to active intervention will be dependent on other factors. For example, most of the psychopharmacy recommendations are for lipid and A1C/FBG labs as seen during this study period, but even when the recommendation is accepted, the patient may not necessarily require therapeutic intervention as the lab values often do not show any significant changes or are stable-normal. Or in case the recommendation is not accepted, it may be influenced by the therapy/lab cost or availability of other non-pharmacological interventions (e.g. diet/lifestyle modification) more so than the clinical competency of the recommending pharmacist. Other limiting factors of the study include lack of control group for comparison and need for objective monitoring tool for evaluating overall cardiovascular risk of the patients. For this study period, there was significant cardiovascular reduction seen through clinical pharmacy intervention in high-risk patients receiving antipsychotic. More studies are needed to support clinical pharmacist's role in improving overall cardiovascular risk associated with antipsychotic therapy but in the meanwhile, interdisciplinary monitoring and care-plan in regards to high-risk patients should be continued and American diabetic association recommends serum glucose and serum lipids on quarterly basis for the patients who receive atypical antipsychotics (dibenzoazepine more so) and that is the standard of care.

In the future, there may be several changes that can be made to the study protocol for better assessment of effectiveness of clinical pharmacy intervention. First, one may consider increasing the sample size by increasing the duration and thus more patients to increase the power of the study. Second, recommending pharmacist should leave a written progress note for which other psychiatrist/physicians may be able to refer back to rather than verbal recommendations to one attending psychiatrist as done so far. And lastly, one may consider

*Corresponding author: Gollapudi Shankar, Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, USA, Tel: 909-469-5259; Fax: 909-469-5539; E-mail: GShankar@westernu.edu

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using Framingham Risk Assessment as another monitoring tool. In a recent APhA review by Ried et al., Framingham Risk Score has been used to note the changes in CHD risks from atypical antipsychotics and although this is not a tool specifically designed for such purpose, it would be one way to objectively assess overall cardiovascular risk in a single number along with any other clinical monitoring that we may do. One goal of evidence-based medicine is to promote the individual practitioner’s conscientious, explicit, and judicious use of the up-to-date scientific literature in making patient care decisions. Limiting the use of drug treatment to prevent weight gain may present a serious therapeutic dilemma to clinicians who may practice in total-care institutional settings. Nevertheless, the appropriate monitoring of atypical antipsychotic use needs to happen. This is because many of the schizophrenic patients can have trouble adhering to a weight loss or exercise program, and to lose any added weight, may be difficult for these patients. Weight gain is a major concern because it has been associated with greater morbidity and mortality and often, weight gain leads to reduced quality of life, and societal expectations make obesity a social stigma. These adverse responses may lead to poor compliance as patients are afraid of becoming obese, resulting in poor clinical outcome. Also, weight gain can particularly manifest cardiovascular disease, diabetes mellitus, osteoarthritis, and some types of cancer. Also, our studies showing antipsychotics as low to moderate risk for developing QT prolongation is the main concern of the cardiovascular disease. Our studies also showed patients receiving antipsychotics with the clinical pharmacy intervention found to have no significant cardiovascular reduction in high risk patients. Thus, treatment with antipsychotics and its action on the serotonin receptors leading to weight gain is a serious concern and more studies are needed to research for the alternate strategies.