Clinical Messages

Ask The Expert

This part of EJP has a goal of presenting and discussing the best and latest findings of an important topic with a distinguished Egyptian and/or International scientist with vast clinical experience, acknowledged high level scientific research work, in addition to a unique panoramic knowledge that covers the various aspects of brain disorders and closely related disciplines. To promote further exchange of facts and results, please visit EJP web site as well as that of the invited expert.

Every day people are taking their medicines prescribed by doctors to treat their sufferings. Improvement might take place using the medicine, however, undesirable events still bother patients and doctors and might be a direct cause for them to discontinue taking their medicines and subsequently have less chances for improvement and more chances to attain longer illness with more possibility of disruption of their social and academic lives, loss of career, and economic country loss. The hot topic of this issue of EJP is the association of hyperglycemia and hypercholesterolemia with the use of atypical antipsychotics that has been documented in uncontrolled studies and case reports.

Many people are caring of the others welfare and happiness, spending a lot of time and work with facts and results to reach their goals. Among these scientists is Prof. A. Sadek, Chairman of Neurology & Psychiatry Department of Ain Shams Univ. and Head Psychiatrist of AS center of Psychological Medicine. Honouring his latest findings is a real reward that was brought on papers of the EJP of this issue, produced from his talk on "The great safety depat" given in a symposium on (The mountain of evidences in management of schizophrenia and mood disorders) during the last Annual Congress of Psychiatry 19-22 March, 2003, Cairo, as well as the illustrations used in teaching his students at AS psychiatric center, kindly made available to us by him. All these pieces of his scientific and clinical excellence are put together especially for the EJP, as we were able to meet him during a scientific café for 30 minutes and ask him;

QUESTION

Are there disadvantages to taking atypical antipsychotics that placed the patients in a dangerous situation of developing diabetes?

RESPONSE

I assume that the suggested association represents a "déjà vu" experience for more senior clinicians as several conventional antipsychotics, particularly low potency agents such as chlorpromazine, were through to impair glucose metabolism following their introduction more than 50 years ago. Further to this, DM appeared to occur at higher rates in patients with schizophrenia even before the introduction of antipsychotics, being more common when considering factors like age (over 50 ys.) and gender. Prof. Sadek has emphasized that earlier studies reported that association with chlorpromazine, thiorridazine, haloperidol, sulpiride, pimozide, fluphenazine, loxapinme, and amoxapine. However, many of those studies had major flaws, in the diagnosis of schizophrenia and diabetes, and attention to other factors impacting on glucose metabolism.

Prof. Sadek added that the role of polypharmacy must not be ignored in this respect, where in clinical practice, schizophrenics are commonly receiving two or more medications for their illness or illnesses. In fact, this trend has significantly confused the picture (e.g.) valproic acid that is frequently prescribed to schizophrenics, particularly those with mood symptoms, has been shown to impair glucose metabolism, cause body weight gain, and induce polycystic ovary syndrome.

Prof. Sadek coined out risk factors for diabetes in patients with mental illnesses, which are psychiatric diagnosis (schizophrenia, depression, bipolar disorder, and Alzheimer's disease), obesity (high BMI > 27 kg/m^2 or > 20% over appropriate body wt), age (> 45 ys.), hypertension (BP > 140/90 mmHg), abnormal lipid level (low HDL or high triglycerides), genetic predisposition (1^{st} degree relatives with DM, family history), diet (poor food choices), inactivity (sedation, fatigue), and ethnic proness.

Accessing the main point of the question, Prof. Sadek noted that while there have been numerous reports of atypical antipsychotic-associated hyperglycemia, type 2 diabetes and diabetic ketoacidosis, there have been no well-controlled, randomized trials examining the impact of these drugs on glucose metabolism. However, mounting CLINICAL evidence suggests that DM occurs at higher than expected rates in schizophrenics treated with atypical antipsychotics. The MOST EVIDENCE exists for clozapine, followed by olanzapine. Ziprasidone appears to cause minimal body weight gain or changes of fasting serum insulin, and lipid levels Quetiapine is reported to reduce body weight and improve glucose metabolism if combined with clozapine. Risperidone

has been reported in the literature to be used without complications in schizophrenics who have comorbid diabetes.
Similar linkage to abnormalities in lipid profiles (serum triglycerides and cholesterol levels) was reported to the forementioned drugs associated with body weight changes and increased risk of cardiovascular diseases.
Recent findings also demonstrate that even mild hyperglycemia or prediabetic hyperglycemia (i.e. impaired fasting glucose) may increase comorbidities as retinopathy, nephropathy, neuropathy, coronary artery disease, myocardial infarction, and stroke.
The majority of hyperglycemic cases reported have occurred in the first 6 months of treatment. Partial of complete remission when the drug was decreased or discontinued and to have hyperglycemia return upon reinstitution of the drugs forementioned were also recorded. When asked on the accussed metabolic errors, Prof. Sadek showed that efforts to detect abnormalities at any step in the entire insulin action sequence to point at possible mechanism of impaired glucose metabolism in those cases, broadly identified receptor or post-receptor defects in insulin action, with a decrease of insulin-sensitive glucose transporters (GLUT) or an inability to stimulate recruitment of GLUT transporter from microsomes to plasma membrane that may be caused by atypical antipsychotics, through antagonism of 5HT 1A receptors that decreases pancreatic cells response to blood glucose levels, which is not yet documented.
Prof. Sadek have stressed that mental illness puts patients at even greater risk for diabetes related problems as they may lack the insight to recognize diabetic symptoms, and may have limited access to medical care, if they are suffering from weight loss or polydipsia, the lab. evaluation could be delayed when treated with atypicals associated with weight gain, dry mouth, and sedation. The changes in mental status of these patients due to hyperglycemia or hypoglycemia could be mistaken for psychotic behavior and result in improper management or incarceration. Insulin availability can magnify the lethality of suicidal attempts in these patients and moreover, concomitant treatment with anti-diabetics could result in hypoglycemia if they are switched to another anti-psychotic or are noncompliant with the diabetic-inducing agent.

At The End, Prof. Sadek recommended that schizophrenic patients, in general, be regularly screened for DM and lipid level abnormalities, while also monitoring body weight changes and blood pressure. Relying on clinical symptoms of DM in these patients may not be adequate as they frequently underreport or ignore symptoms and the adverse effects of atypicals and other medications may mask symptoms of DM. Additionally, the patients with higher risk factors should be examined more closely. Patients treated with atypical anti-psychotics particularly those noted above, should be screened more frequently. However, Prof. Sadek said "I see it is too early to rule out a class effect at this stage of published papers and clinical experience". He advised baseline measures (FBS, plasma lipid levels, body weight, BP) for all patients, to be repeated if it can be obtained every 6 months, with body weight and BP be monitored more frequently in the office. Glyco-haemoglobin monitoring may be useful in this population where FBS is difficult to obtain or OGTT if available. Education and referral to body weight reduction and exercise programs may play a vital preventive role.
While consideration should be given to switching to another atypical agent if a patient develops DM during a treatment course with an atypical antipsychotic, it remains for clozapine-treated patients, who have failed to respond to several other antipsychotics, to reduce the risk factors as body weight loss programs, encouraging exercise, and lowering clozapine dose and combining with other atypical with less diabetogenic effects.
Finally, diabetic patients who are placed on atypical antipsychotics must be monitored more closely to prevent a worsening in the control of their serum glucose levels.
... The editors would like to thank Prof. Sadek for his valuable contribution and help.

For more information, please visit his web site (http:// www.adelsadek.com)

Commentaries

This part of the EJP is considered as a supplement to provide information in a problem-oriented format from our practice. It is designed in a case-study approach to create a sense of excitement, challenge, and pleasure of our field, and to stimulate a perfect exercise of your flexibility, creativity, and humanity, and to bridge the gap between texts and clinics.
Despite that case descriptions do not represent the whole story, read it, enjoy it, and finally let us know if you have proved to reach a decision. You, the reader, is urged to review your package information data and please send the answer to the editors.

The Case

A 29-year-old man arrived 50 minutes late for his psychiatric appointment, having gotten lost trying to find the office. His request evaluation represented just one in a long series of attempts to get help; he had seen (by rough count) 15 psychiatrists, neurologists and psychologists over the preceding 12 years and had undergone two courses of "intensive psychotherapy", each lasting longer than one year. He had received many diagnoses including generalized anxiety disorder, dysthymic disorder, borderline personality, impulse control disorder (explosive subtype), and atypical psychotic disorder, he had been treated with different types of psychotherapy, and had received trials of several medications (primarily traditional and novel antipsychotics, tricyclic and SSRIS, benzodiazepines, and antiepileptics), all without significant benefit. His expectations for successful treatment was low.
By his report, he has had "just about every symptom in the book". He has been depressed on and off for as long as he can