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ADR Focus

Atypical Antipsychotics and Diabetes Mellitus

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Editor's Note: Adverse drug reactions experienced by UWMC or HMC patients and reported to the pharmacy are reviewed quarterly by the Pharmacy & Therapeutics Committee. Following the Committee's review, a summary is published in this newsletter (see pages 45-46) along with a companion article regarding some aspect of adverse drug reactions. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, "No drug has only one action." By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you feel is experiencing an Adverse Drug Reaction, report it by calling the A.D.R. Phone Line, HMC: 731-3802; UWMC: 598-6837; SCCA: 288-6336.

Atypical antipsychotic medications (risperidone, clozapine, olanzapine, quetiapine, and ziprasidone) are replacing older typical antipsychotic agents due to superior tolerability and effectiveness, and a decreased incidence of extrapyramidal symptoms.[1,2] Although the atypical antipsychotics appear to have fewer side effects than their predecessors, some adverse "class effects" may be associated with their use.[1] In this Focus, atypical antipsychotic medication interference with blood glucose control and initiation and aggravation of diabetes mellitus will be discussed.

In 1997, the Centers for Disease Control (CDC) reported that 10.3 million people in the United States had diabetes mellitus and estimated that 5.4 million people were still undiagnosed.[1] Both the medical and economical consequences of diabetes are staggering. People with diabetes have increased mortality, and/or a high incidence of chronic comorbidities such as circulatory, ophthalmic, renal, and neurologic disorders.[1] Direct medical costs in 1992 for all people diagnosed with diabetes mellitus was estimated to be $45.2 billion.[1]

Studies indicate that diabetes mellitus may be more prevalent among people with schizophrenia than among the general population. A 1996 Italian retrospective study looked at the incidence of diabetes in 95 chronic schizophrenic patients between the ages of 45 and 74 years admitted to long-term care facilities.[3] The overall prevalence of diabetes mellitus in this group was 15.8%. This figure was significantly higher than the 3.2% figure reported in epidemiological studies in the general Italian population. In a previous study, these same researchers identified a 24.5% prevalence of diabetes mellitus in a group of schizophrenic outpatients in the United States.

The demographics of atypical antipsychotic-induced diabetes mellitus indicate that it is more prevalent in men and African-Americans.[4] Although people with schizophrenia in almost all age groups have the potential risk to develop new-onset diabetes associated with atypical antipsychotic drug therapy, three studies found the strongest effect in patients less than 40 years of age.[4,5,6] While there does not appear to be any established relationship between the dosage of these drugs and diabetes mellitus, this effect does appear to be related to onset of therapy.[7] In their analysis of 45 published

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cases of new-onset diabetes mellitus or diabetic ketoacidosis following atypical antipsychotic therapy, Jin, et al. reported that 84% of cases presented within 6 months of starting therapy and 59% within 3 months of therapy initiation.[4]

Several mechanisms have been proposed to explain the association between atypical antipsychotic use and serum glucose dyscontrol and/or the onset of diabetes. The phenomenon is most likely multifactorial. It is suggested that the central regulation of blood glucose is controlled by the hypothalamus; and it has been shown that dopamine agonists (i.e., bromocriptine) will decrease elevated blood glucose levels.[1] Because atypical antipsychotics are dopamine antagonists, they may potentially be a contributing factor to dysregulation of blood glucose control.[1] Altered glucose-insulin homeostasis may also be associated with the weight gain caused by atypical antipsychotics.[7,8] Weight gain can lead to an increase in adipose tissue that may result in diminished insulin sensitivity, glucose intolerance, and possibly diabetes mellitus.[7] Finally, one researcher proposes that clozapine-induced diabetes mellitus may result from primary damage to pancreatic islet cells.[9]

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There have been approximately 20 published case reports of diabetes exacerbated or induced by clozapine.[1] Diabetic ketoacidosis was the presenting symptom in 10 of the reported cases. Worldwide, at least 81 cases of diabetes following clozapine administration have been reported to the Clozapine Patient Monitoring Service.[10] A very limited number of studies exist that have attempted to make an association between atypical antipsychotic medication use and diabetes mellitus. A 1998 study by Hagg, et al. compared 63 patients treated with clozapine to 67 patients treated with conventional depot neuroleptic medications (haloperidol, etc.).[8] In this study, none of the patients had diabetes prior to the start of the study. Patients were screened with two random blood glucose tests. Those patients with an abnormal test were then given a more definitive 2-hour glucose tolerance test. In the clozapine group, 12% had diabetes and 10% had impaired glucose tolerance. Six percent had diabetes and 3% had impaired glucose tolerance in the conventional depot group. The difference between the two groups did not quite reach statistical significance (P value = .06). Results of a five-year follow-up study of 82 clinic outpatients taking clozapine showed 36.6% of patients were diagnosed with diabetes mellitus that was associated with weight gain and lipid abnormalities during the follow-up period.[11]

The likelihood for the development of drug-induced diabetes mellitus in this patient population may be of great concern due to other medical conditions such as obesity, cardiovascular disease, and elevated serum lipids frequently associated with schizophrenia and its treatment.

In another study, Sernyak et al. looked at the incidence of diabetes mellitus in outpatients with schizophrenia treated with both atypical and conventional antipsychotics in the Veterans Health Administration of the Department of Veterans Affairs over a 4-month period in 1999.[6] A total of 38,632 patients were included in the study: 58.6% received an atypical antipsychotic and 41.4% received a conventional antipsychotic. Results of the study showed that patients that received an atypical antipsychotic were 9% more likely to have diabetes than those patients who received conventional antipsychotics. The incidence of diabetes was significantly increased in patients who received olanzapine, clozapine, and quetiapine, but not risperidone. However, in the subset of patients less than 40 years old, all of the atypical antipsychotics were associated with a significantly increased incidence of diabetes mellitus.

Although people with schizophrenia in almost all age groups have the potential risk to develop new-onset diabetes associated with atypical antipsychotic drug therapy, three studies found the strongest effect in patients <40 years of age.

Koller and Doraiswamy examined 237 cases of olanzapine-associated diabetes mellitus that they identified either from the FDA MedWatch Drug Surveillance System or from the published literature.[5] Their analysis showed that 188 cases consisted of new-onset diabetes, 44 cases were exacerbations in patients with preexisting diabetes mellitus, and 5 cases could not be categorized. Hyperglycemia appeared within 6 months of the start of olanzapine therapy in 73% of all cases. Forty-one patients had glucose

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levels of 1000 mg/dL or greater, 80 patients had developed metabolic acidosis or ketosis, and 15 patients died. With discontinuation or dose reduction of olanzapine, 78% of patients experienced improved glycemic control.

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Finally, there have been three cases of quetiapine-induced diabetes mellitus, three cases of risperidone-associated diabetes mellitus, and one case of ziprasidone-associated hyperglycemia reported in the literature.[4,12] Although risperidone has been widely used since its approval in 1993, it has been associated with relatively few cases of diabetes mellitus or serum glucose dysregulation. Two mechanisms possibly explain this phenomenon. The first theorizes that risperidone may interact with fewer receptors associated with the development of glucose dysregulation than the other atypical antipsychotics.[1] Secondly, risperidone has been associated with less weight gain liability than the other atypical antipsychotics.[1] Quetiapine is a dibenzothiazepine, structurally similar to clozapine (a dibenzodiazepine) and olanzapine (a thienbenzodiazepine), but it is much less widely prescribed.[4,13]

Although risperidone has been widely used since its approval in 1993, it has been associated with relatively few cases of diabetes mellitus or serum glucose dysregulation.

A 1999 retrospective study conducted by Reinstein, et al. assessed changes in weight and diabetes status for 65 patients originally treated with clozapine who developed diabetes mellitus and were then switched to therapy with a clozapine-quetiapine combination.[14] The study authors reported that this combination therapy resulted in weight loss and improved glycemic control in patients that gained weight and developed diabetes mellitus after the institution of clozapine therapy. It is noted that this data should be interpreted with caution, due to study limitations such as the lack of a control group.[1]

Health care practitioners who provide medical care for psychiatric patients need to be vigilant in monitoring for potential diabetogenic effects of atypical antipsychotics on their patients.

Although there are no large-scale epidemiological studies and few randomized controlled trials proving a definitive relationship between the use of atypical antipsychotics and the induction of diabetes mellitus, there is accumulating evidence from the literature suggesting that a significant association exists. Health care practitioners who provide medical care for psychiatric patients need to be vigilant in monitoring for potential diabetogenic effects of atypical antipsychotics on their patients. Additionally, the likelihood for the development of drug-induced diabetes mellitus in this patient population may be of great concern due to other medical conditions such as obesity, cardiovascular disease, and elevated serum lipids frequently associated with schizophrenia and its treatment.[1] Henderson, et al. recommended that patients taking clozapine be screened for diabetes every 6 months.[11] Other authors recommend periodic serum glucose monitoring of patients receiving treatment with atypical antipsychotics who have additional risk factors for diabetes.[9,15] This approach would seem prudent in a patient population which traditionally has required heightened medication monitoring, to prevent a possible lifelong requirement for diabetic care and/or to prevent potentially fatal adverse events.

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UWMC/HMC ADVERSE DRUG REACTION SUMMARY
Fiscal Year 2001/2002
2nd Quarter (October 2001-December 2001)

University of Washington Medical Center

- A total of 100 adverse drug reactions were reported at UWMC in the 2nd quarter of FY 01/02.
- These ADRs were reported by physicians, nurses, and pharmacists.
- Eighty-three inpatients and 17 outpatients experienced an ADR this quarter.
- The drug class for which the largest number of ADR reports was filed was antibiotics- 32.
- The ADR reaction types[†] reported were: augmented- 39, hypersensitivity- 32, false alarm- 6, idiosyncratic- 28, and unknown- 1.
- Adverse drug reaction severity ratings[‡] included: unknown- 2, insignificant- 3, mild- 59, moderate- 29, and severe- 7.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "unknown" in 2 reports, "possible" in 44 reports, "probable" in 46 reports, and "highly probable" in 8 reports.
- One ADR report was submitted to the FDA this quarter.

Harborview Medical Center

- A total of 65 adverse drug reactions were reported at HMC in the 2nd quarter of FY 01/02.
- These ADRs were reported by pharmacists, nurses, physicians, and CT technicians.
- Fifty-nine inpatients and six outpatients experienced an ADR this quarter.
- The drug class for which the largest number of ADR reports was filed was antibiotics- 14.
- The ADR reaction types[†] reported were: augmented- 30, hypersensitivity- 25, and idiosyncratic- 8.
- Adverse drug reaction severity ratings[‡] included: mild- 35, moderate- 22, and severe- 6.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "definite" in 1 report, "probable" in 36 reports, and "possible" in 28 reports.
- Seven ADR reports were submitted to the FDA this quarter.

[†] ADR reaction type definitions- **Augmented**: reactions consistent with the pharmacology of the drug; **Idiosyncratic**: unusual reaction independent of the pharmacology of the drug; **Hypersensitivity**: newly identified allergy or one previously identified; **False Alarm**: reaction deemed not related to drug therapy.

[‡] ADR reaction severity rating definitions- **Insignificant**: requires no change in therapy; **Mild**: requires therapeutic intervention but no change in length of hospital stay; **Moderate**: requires intervention and increased length of hospital stay by at least one day; **Severe**: life threatening contributes to death or permanent disability, or recovery takes greater than 2 weeks.

UWMC/HMC ADVERSE DRUG REACTION SUMMARY (continued)
Fiscal Year 2001/2002

3rd Quarter (January 2002-March 2002)

University of Washington Medical Center

- A total of 84 adverse drug reactions were reported at UWMC in the 3rd quarter of FY 01/02.
- These ADRs were reported by physicians, nurses, and pharmacists.
- Seventy-four inpatients and 10 outpatients experienced an ADR this quarter.
- The drug classes for which the largest numbers of ADR reports were filed were antibiotics-16 and antineoplastics-16.
- The ADR reaction types† reported were: augmented- 40, hypersensitivity- 15, and idiosyncratic- 29.
- Adverse drug reaction severity ratings‡ included: unknown- 1, insignificant- 3, mild- 50, moderate- 24, and severe- 6.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "unknown" in 1 report, "possible" in 34 reports, "probable" in 45 reports, and "highly probable" in 3 reports.
- Four ADR reports were submitted to the FDA this quarter.

Harborview Medical Center

- A total of 66 adverse drug reactions were reported at HMC in the 3rd quarter of FY 01/02.
- These ADRs were reported by pharmacists and physicians.
- Forty-four inpatients and 22 outpatients experienced an ADR this quarter.
- The drug class for which the largest number of ADR reports was filed was antibiotics- 16.
- The ADR reaction types† reported were: augmented- 40, hypersensitivity- 6, and idiosyncratic- 20.
- Adverse drug reaction severity ratings‡ included: mild- 38, moderate- 20, and severe- 8.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "definite" in 3 reports, "probable" in 31 reports, and "possible" in 32 reports.
- Eleven ADR reports were submitted to the FDA this quarter.

4th Quarter (April 2002-June 2002)

University of Washington Medical Center

- A total of 73 adverse drug reactions were reported at UWMC in the 4th quarter of FY 01/02.
- These ADRs were reported by physicians, nurses, and pharmacists.
- Sixty-four inpatients and nine outpatients experienced an ADR this quarter.
- The drug class for which the largest number of ADR reports was filed was antineoplastics- 19.
- The ADR reaction types† reported were: augmented- 40, hypersensitivity- 18, and idiosyncratic- 15.
- Adverse drug reaction severity ratings‡ included: insignificant- 2, mild- 49, moderate- 13, and severe- 9.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "doubtful" in 1 report, "possible" in 37 reports, "probable" in 29 reports, and "highly probable" in 6 reports.
- Fifteen ADR reports were submitted to the FDA this quarter.

Harborview Medical Center

- A total of 80 adverse drug reactions were reported at HMC in the 4th quarter of FY 01/02.
- These ADRs were reported by pharmacists and nurses.
- Fifty-eight inpatients and 22 outpatients experienced an ADR this quarter.
- The drug class for which the largest number of ADR reports was filed was antibiotics- 25.
- The ADR reaction types† reported were: augmented- 37, hypersensitivity- 28, and idiosyncratic- 15.
- Adverse drug reaction severity ratings‡ included: mild- 47, moderate- 25, and severe- 8.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "definite" in 2 reports, "probable" in 43 reports, and "possible" in 25 reports.
- Sixteen ADR reports were submitted to the FDA this quarter.

† ADR reaction type definitions- **Augmented**: reactions consistent with the pharmacology of the drug; **Idiosyncratic**: unusual reaction independent of the pharmacology of the drug; **Hypersensitivity**: newly identified allergy or one previously identified; **False Alarm**: reaction deemed not related to drug therapy.

‡ ADR reaction severity rating definitions- **Insignificant**: requires no change in therapy; **Mild**: requires therapeutic intervention but no change in length of hospital stay; **Moderate**: requires intervention and increased length of hospital stay by at least one day; **Severe**: life threatening contributes to death or permanent disability, or recovery takes greater than 2 weeks.

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost‡	Therapeutic Classification	Use	Usual Adult Starting Dose*
Insulin Aspart (NovoLog)	Injection: 100 units/mL (10 mL)-$17.75	Insulin	Management of diabetes mellitus	Individualized
Pegfilgrastim (Neulasta)	Injection: 6 mg/0.6mL-$1,916.08	Colony Stimulating Factor	Decrease the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy	6 mg SubQ once per chemotherapy cycle

* Refer to product labeling for full prescribing information. ‡ Costs represent UWMC/HMC outpatient acquisition costs and do not include pharmacy dispensing fees.

Prescription Drug Costs: Some Key Statistics

Source: Maximizing value: what every practitioner should know about drug costs. *Drug Therapy Topics* 2002 Vol 31 Special Edition (available electronically at http://uw.prnrx.org/therapyTopics.asp or by request from the Drug Information Center).

Did you know that:

- **Spending on prescription drugs** increased 18.8% to $131.9 billion (not including mail-order sales) in 2000. The 50 most frequently prescribed drugs rose 18.6% to $866.6 million (up from $730 million in the preceding year).
- According to the Health Care Financing Administration, **national spending for drugs tripled** in the last decade and is expected to more than double again before 2010, from an estimated $177 billion to $366 billion.
- Since 1992, of the **39 prescription drugs** most commonly used by seniors, prices of 19 have increased more than two times the rate of inflation, with some increasing as much as 26 times. Prescription drug expenditures per senior have increased by 115.6% since 1992 due to increases in the price per prescription and the number of prescriptions per senior.
- **Prescription drug costs** are the most rapidly increasing expense for employer-based insurance, representing 40% of the premium increases between 1998 and 2000. Between 1993 and 1998, retail prescription costs increased 84% or $42.7 billion.
- **Generic drugs** account for 46% of all prescription drugs, but only 8% of total prescription costs.

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