



DAKOTA DIABETES  
COALITION



Dr. Johnson is a family practice doctor in Grand Forks with a special interest in diabetes -- and a special knack for writing. As a member of the Dakota Diabetes Coalition, he has generously made himself available to answer questions through our listserv. ***If you have comments about the column, or questions for Dr. Johnson to address in future columns, please contact [gailhand@qwest.net](mailto:gailhand@qwest.net)***

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## TZDs in the news

### The jury may be out -- but the black box is in

**Q. Has a definitive view emerged on the controversy raised over Avandia and cardiac issues last spring?**

**A.** No, the jury is still out. But just last night the U.S. Senate unanimously passed a measure that will result in more FDA oversight after drugs have been released to the public. The president is expected to sign the bill.

Back to your question on Thiazolidinediones, or TZDs, which are common in the treatment of type 2 diabetes and are also used in people with pre-diabetes.

Their primary mode of action involves p-par receptors, which increase insulin sensitivity and reduce blood glucose levels. TZDs are indicated for monotherapy or combination therapy with sulfonylureas and/or metformin. These agents are sometimes used with insulin as well.

TZDs are thought to have some positive effects on triglycerides and HDL levels, which are notoriously hard to improve. Although cardiac concerns

have been a recent focus, TZDs may turn out to have some cardiac effects that are beneficial. This leaves clinicians in a quandary.

Few areas in medicine have stirred as much controversy or uncertainty as a recent report in the New England Journal of Medicine regarding possible increases in risk of cardiac death in patients using the TZD medication rosiglitazone, Avandia.

This finding has been called into question in recent weeks, leaving clinicians in the difficult position of deciding how to manage patients on Avandia and perhaps those on Actos or pioglitazone, also a member of the TZD family.

In May of 2007, Dr. Stephen Nissen and colleagues published a meta-analysis of 42 clinical trials involving more than 15,000 patients on rosiglitazone, in the NEJM. An odds ratio of myocardial infarction was noted to be 1.43 in the patients treated with rosiglitazone, but overall cardiovascular death was not increased (odds ratio .98).

Subsequently, there has been considerable debate regarding this analysis -- because of the possible flaws inherent in a retrospective study. A counter analysis performed by Dr. George Diamond and colleagues, to be published in the Annals of Internal Medicine in October, did not show statistical differences.

The prospective trial RECORD, which stands for Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes, was recently the subject of an interim analysis. To date, no trend toward increased cardiovascular death was noted. This trial is due to be published in 2009.

In the case of pioglitazone, no trends have emerged that point to worse cardiovascular outcomes. In fact, pioglitazone has been studied in patients receiving cardiac intra-luminal stenting. A related condition, congestive heart failure and/or edema, is an established potential side effect of TZD's.

These medications have always carried precautions but recently an FDA advisory panel recommended elevating the precautions to its strictest "black box" warning.

So, what are clinicians to do in terms of prescribing these agents and dealing with patient concerns? As always, the risks and benefits for the individual should be considered. Fortunately, if the concern is great enough to stop the TZD, other efficacious agents are available, including old standbys such as sulfonylureas or metformin.

Patients should always be discouraged from discontinuing medications on their own, unless they note a problem or suspect one is emerging. It's good to emphasize with patients that they should always check with their providers with any such concerns. That attitude reassures patients that they -- and their questions -- will never be dismissed as silly.

TZDs are probably better used earlier in the course of an individual patient's diabetes. Consideration of different medications depends many factors, including the stage of the patient's condition, so individual consultation is best.

Remember, insulin is always an excellent choice for any diabetes patient. And with more modern insulins available in better delivery systems such as pens, patients can use them quite easily.

Newer agents such as exenatide (Byetta) or sitagliptin (Januvia) may be good alternatives for appropriate patients, especially given their novel mechanisms of action. The controversy surrounding TZDs remains an interesting story and data available in the next few years may help settle the debate.

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[TZDs, Dr. Johnson's Column #7, Sept. 21, 2007](#)

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**Make sure you are up to date and following guidelines. The ADA Standards of Care for diabetes are updated each January and can be found at this site:**

**[http://care.diabetesjournals.org/cgi/reprint/30/suppl\\_1/S4](http://care.diabetesjournals.org/cgi/reprint/30/suppl_1/S4)**

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