Editorial

Every rose has it's thorn!

Ambika Gopalakrishnan Unnikrishnan, Sanjay Kalra[1], Ganapathi Bantwal[2]

Department of Endocrinology, Amrita Institute of Medical Sciences, Kochi, [1]Department of Endocrinology, Bharti Hospital and B.R.I.D.E, Karnal, [2]Department of Endocrinology, St. John's Medical College and Hospital, Bangalore, India

In our fight against the epidemic of metabolic disease, researchers have provided us with an array of compounds. Drugs belonging to various classes, such as endocannabinoid receptor antagonists, serotonin–norepinephrine reuptake inhibitors, and PPAR-γ receptor antagonists, have been in use for the management of various aspects of metabolic syndrome.[1,2] All had been through rigorous preclinical and clinical trials, and were proposed to be answers to the global epidemic of metabolic disease.

Drugs such as fenfluramine, phentermine, and pioglitazone were a success, as they tried to meet a significant therapeutic gap. Many reviews quoted extensive research, which established the utility of these drugs in management and prevention of disease. At about the same time, suggestions were put forward by the scientific community, and later implemented; we refer to proposals for reducing the lower limits for diagnosis of hypertension, diabetes, dyslipidemia, and obesity. While this approach was driven by an increased understanding of the risks and morbidity associated with high blood pressure, hyperglycemia, deranged lipids, and overweight/obesity, it did lead to an increase in the number of patients being offered pharmacological therapy.

Aggressive management of all constituents of the metabolic syndrome, using these, and other, drugs, was hypothesized to be a means of preventing morbidity and mortality.[2]

Physicians and endocrinologists welcomed these drugs as helpful tools in the fight against disease. Many patients benefited from good glycemic control, blood pressure control, healthy lipid levels, and weight loss.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.83048

The list of beneficial pleiotropic effects expanded with new publications. Biochemical markers, physiological parameters, imaging techniques, and other surrogate investigations were used to assess and define the mechanism of action of these drugs. This helped complement the clinical effects of these molecules.

Various publications explored the effect of these drugs not only as management tools, but also as preventive pharmaco-therapeutic strategies in the prophylaxis of metabolic syndrome and diabetes.

Minor adverse events were reported. A few patients did not tolerate the drugs. Some developed unacceptable symptoms which led them to withdraw the drug.

Yet, all was rosy. A bright future was predicted for the management of metabolic syndrome.

And then, the bubble burst. At amazing regularity, reports of major adverse events began pouring in. Meta-analysis and reviews were published regarding the lack of safety of the newer drugs. This led regulatory authorities to withdraw or refuse approval to sibutramine and rosiglitazone.[3,4]

Although the methodology of these meta-analyses has been criticized in many quarters, regulatory authorities eventually ruled against these drugs, and these rulings often followed and were followed by an onslaught of media attention.

The latest target in the series of 'drugs non grata' is pioglitazone. The glucose-lowering utility of pioglitazone has been well documented as monotherapy, as well as in combination. The drug has been used in combination with sulfonylureas, metformin, and insulin. Its efficacy has been demonstrated in various ethnic groups.

While the efficacy of pioglitazone is undoubted, its safety and tolerability have been studied carefully. The adverse effect on cardiovascular outcomes is well known. The drug survived the post-rosiglitazone era when its cardiovascular

Corresponding Author: Dr. Sanjay Kalra, Department of Endocrinology, Bharti Hospital and B.R.I.D.E, Karnal, India. E-mail: brideknl@gmail.com

effects were analyzed in depth. The review article in this issue of IJEM discusses this issue in detail.

It is important to retain a practical approach to pharmacological treatment. The links between Pioglitazone and bladder cancer were highlighted in a recent study by Piccinni *et al*., from Bologna. The authors concluded that there is an association and called for urgent epidemiological surveillance.[5]

In another large, recent study from the USA, the authors studied 30173 users of pioglitazone and concluded that a longer duration of use of Pioglitazone was weakly associated with increased risk.[6] The FDA has suggested that pioglitazone not be used in patients with a present or past history of bladder cancer, but has informed that patients and health care providers continue medications as per their labeling.[7] France has suspended the use of pioglitazone, while Germany has recommended not to start it in new patients.[7]

What should India do? Clearly, it is important to weigh the risks and benefits of therapy, and discuss findings with our patients, and make the right decision. It is important that the link between bladder cancer and pioglitazone be studied in India based on scientific evidence of the association in people of our country. Till such evidence is made available, we will continue to rely on the international evidence. We must continue to recognize the benefits of pioglitazone, and use it judiciously, but with caution. A difficult task, but isn't the combination of knowledge (read: science) and wisdom (read: experience) familiar to every practicing physician?

The famous proverb "Every rose has its thorn" originated as a French or Italian saying (Pas de rose sans epine; Non i.e rosa senza spine). Closer to home, is a Persian saying "He who wants a rose, must respect the thorn."

Similarly, pioglitazone, too, may have its thorn. Respect the rose, but be cautious about the thorn.

References

1. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *et al*. Management of hyperglycemia in type 2 diabetes mellitus: A consensus algorithm for the initiation and adjustment of therapy. Update regarding the thiazolidine-diones. Diabetologia 2008;51:8-11.
2. Bray GA. Pharmacological treatment of the overweight patient. In: Bray GA, editor. The Metabolic syndrome and Obesity. Tatowa, New Jersey: Humana; 2007. p. 203-56.
3. Nissen SE, Kathy W. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
4. James WP, Caterson ID, Countinho W, Finer N, Van Gaal LF, Maggioni AP, *et al*. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010;363:905-17.
5. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care 2011;34:1369-71.
6. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, *et al*. Risk of bladder cancer among diabetic patients treated with pioglitazone: Interim report of a longitudinal cohort study. Diabetes Care 2011;34:916-22.
7. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226257.htm. [Last accessed on 2011 Jun 24].