Why do boys box? See p 782 and send us your thoughts at bmj.com

Rosiglitazone and the need for a new drug safety agency

PERSONAL VIEW **Silvio Garattini, Vittorio Bertele'**

The recent news about the suspension of rosiglitazone, a blockbuster antidiabetes drug, is not reassuring.[1] Once again a widely prescribed drug shows a degree of toxicity that should not have allowed it to remain on the market for so long. This is not an isolated case, because it follows in a short time similar concerns over cerivastatin, rofecoxib, rimonabant, and sibutramine, not forgetting the selective serotonin reuptake inhibitors. In addition, a further case is now on the table, concerning the relation between the use of bisphosphonates and cancer.[2]

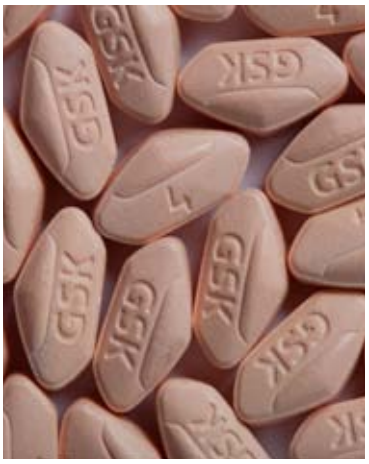
At least in the case of sibutramine and rosiglitazone, awareness of the risk of adverse events had been shown in the European Medicines Agency's request for large randomised trials to investigate possible cardiotoxicity. A trial of sibutramine was committed to in 2002 and the trial begun in January 2003, completed in November 2009, and published in September 2010,[3] well after the drug had been suspended, in January 2010. In the case of rosiglitazone the commitment was made in July 2000, the study published in June 2009,[4] and the drug suspended in September 2010.

Safety questions can be answered only by large, long term studies. Manufacturers have every interest in prolonging the time between beginning a trial and the final result, during which they carry on earning income. Certainly in the case of rofecoxib a meta-analysis showed the risk of cardiotoxicity four years before its withdrawal.[5]

No data are available for sibutramine, but in the case of rosiglitazone the first meta-analysis showing an increase in the risk of heart failure was available in 2007.[6] In the meantime many patients developed heart disease while seeing no significant improvement in their diabetes.

What can be done to improve the situation? Surely we must raise the bar, by adopting more stringent requirements before new drugs are allowed onto the market. However, obviously it will be hard for a regulatory agency that has authorised a drug to admit that it hadn't predicted its potential risk (or had underestimated or overlooked it). The usual regulatory reaction is to insert a warning or a contraindication in the summary of product characteristics or to issue a "Dear Doctor" letter. A regulatory agency seldom withdraws a drug from the market; it is more likely to be the manufacturer that takes the initiative.

Our proposal is to separate drug approval from post-marketing pharmacovigilance. Having both functions under a single body, as happens today, implies a sort of conflict of interest, quite apart from the enormous workload. Furthermore, while establishing the benefits of drugs is relatively straightforward, evaluating their safety is a much more complex and time consuming process that can hardly be expected to have resulted in any firm conclusions at the time of approval.



Manufacturers have every interest in prolonging the time between beginning a trial and the final result, during which they carry on earning income

The new safety evaluation agency could have several tasks, including auditing drug companies' commitments to and conduct of trials, promoting proactive pharmacovigilance, and making the appropriate regulatory decisions. It would first of all follow up drug companies' commitments to carry out trials required by the agency that had granted the marketing authorisation. It should verify that whatever is needed to fulfil the requirements is done properly, in the shortest possible time. The US Food and Drug Administration has admitted that only 30% of such requests for trials are fully adhered to by companies. (The EMA does not provide any such figures.)

The second task would be to act as a gathering point for all information on safety collected by national agencies, sustaining a true Europe-wide network such as the current European Centres of Pharmacoepidemiology and Pharmacovigilance promoted by the EMA itself. To promote proactive pharmacovigilance, the safety agency could commission and fund independent studies on critical issues of safety. In addition, it would maintain rigorous scrutiny of the literature, including meta-analyses, systematic reviews, and prospective studies on drug safety. Another useful task would be to promote a flow of information to all interested parties well ahead of publication.

The third task for the agency would be to make decisions on the basis of its assessment of the information collected, with the priority aim of ensuring public health. When the risks of a drug exceed the benefits, the agency must decide on its temporary suspension or definitive withdrawal from the market. The agency should work swiftly and without secrecy and be open to external evaluation and input.

The continual problems of toxicity of drugs that have often been approved on the basis of surrogate end points need to be dealt with urgently so that the public's confidence can be regained and patients' safety assured.

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References are in the version on bmj.com

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- Feature: What went wrong? (*BMJ* 2010;341:c4848)
- Editorial: Drugs for diabetes (*BMJ* 2010;341:c4805)
- News: Europe wants suspension (*BMJ* 2010;341:c5291)
- News: FDA decision criticised (*BMJ* 2010;341:c5333)

GAVIN EVANS

REVIEW OF THE WEEK

Fight club

The beauty and allure of boxing are inescapable in this exciting piece of physical theatre, finds **Richard Hurley**, but so are its brutality and futility

Beautiful Burnout

A play by Bryony Lavery; directed by Scott Graham and Steven Hoggett

Presented by Frantic Assembly and the National Theatre of Scotland, in association with the Barbican, London www.franticassembly.com

13-16 October, Rothes Halls, Glenrothes, Fife; 3-13 November, Crucible Theatre, Sheffield; 16-27 November, Minerva Theatre, Chichester, West Sussex

Rating: ★★★★

What is it that makes young men want to be king, to put on a pair of gloves, to get in a boxing ring, to pummel the living daylights out of each other? *Beautiful Burnout* is a spectacular piece of theatre that explores this question.

It's perhaps as close to the rawness of a real match as you can get. The only difference is that these fighters don't spit blood. And this time, thank goodness, the heart wrenching conclusion is pure play.

These four boys and one girl actually hit each other; their fitness, dedication, and sweat are certainly for real. They dream of fame and fortune, as do their mentors. Whether these potential rewards are enough to compensate for the possible risk of damage to their health is left for you to decide.

The skilful performance is accompanied by an emotive story: a mother's hopes—and her fears; the boxers' intoxication with their sport; their trainer's paternalism and greed; and the trash to cash story of one boy done good and one who does rather less well.

Breathtakingly choreographed scenes show in detail the physical beauty in boxing and the fighters' coordination and control. When the actors pause the fighting mid-blow, a change in lighting allows the audience to admire the split second thought processes as each boxer contemplates his retort. This is stunning theatre.

I saw the show in a run at York Hall, Bethnal Green, London. This venue is world famous as a centre of boxing history. Lennox Lewis, Chris Eubank, and the current world heavyweight champion, David Haye, have all fought here—and it's still used as a venue for boxing today. We're on three sides of a revolving, boxing ring-like stage: we might as well be here for a real match. An array of screens behind, showing bodies, gloves, punches, and x ray films of broken bones, enhances the three dimensional performance.

The directors say that they wanted to make a show that feels, smells, and tastes like real boxing. And they have. Their motivation was a love for boxing and a desire to dramatise the extreme polarisation in the debate on its morality: a "noble art" and "sweet science" in the red corner; highly dangerous, even blood sport, in the blue.

And this pulsating fight plays out to strobe lighting and a pumping score by the UK electronic music group Underworld, of *Trainspotting*'s "Born Slippy" fame. "Burnout" refers to the point in a three minute bout when a boxer can't take any more.

The BMA gets a mention. Since the 1980s, because of evidence of cumulative damage to the brain from repeated blows to the head, it has called for a ban on amateur and professional boxing, especially for children (www.bma.org.uk/health_promotion_ethics/sports_exercise/BoxingPU.jsp).

But boxers still fight at York Hall each week, and children still attend boxing clubs. Boxing as a lifestyle is class entrenched. It's a working class dream of a better future; and it's an easy idea for everyone else that poor boys would be better off learning manners and discipline in the ring than fighting on the street.

Beautiful Burnout is the second play about boxing in London in 2010, after *Sucker Punch* at the Royal Court. Both explore the dangers of boxing, but they also glorify it. And what of the emerging interest in the spectacle of cage fighting or mixed martial arts, where the rules of combat are even weaker?

The five proud and pumped kids in *Beautiful Burnout* give themselves stage names: Fists of Fury, the Puncher from Paisley, the Asian Invasion, Fists of Steel, Tits of Terror. In 100 minutes we're treated to their very highs and their very lows. Bandaged hands, sparring, skipping, punching bags: these underdogs are put through their paces in the gym by their trainer, Bobby Burgess.

Amid all this testosterone, what of women? Carlotta, one boxer's mother, embodies the love-hate that accompanies her pride at her son becoming a man: she encourages, she cheers, but she has to wash his bloody clothes, and ultimately it's she who has to pick up the pieces. Dana, the girl boxer, is adamant that she never wanted to do drama or dancing or community work in her spare time—but the boys don't have to give excuses for wanting to break jaws.

The directors' motivation was a love for boxing and a desire to dramatise the extreme polarisation in the debate on its morality

Bobby chooses two boys to go professional—and now big money's involved. As *Beautiful Breakout* concludes we're the crowd watching a big match between two former friends. The frenzy builds in crescendo, with devastating consequences, and our once proud mother has no choice but to swallow that pride as her son swallows blood.

"Raise your guard . . . Stay outside the distance . . . Watch your man." I've never been to a boxing match, and I'm pretty sure that I wouldn't like it, but *Beautiful Burnout* has tempted me. Carlotta says, "It's as good as sex, only less complicated." Seconds out. I saw stars. This show's a knockout.

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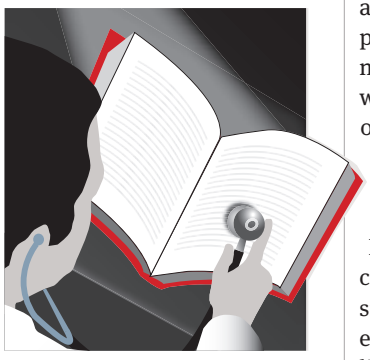
- Editorial: Boxing and the risk of chronic brain injury (*BMJ* 2007;335:781-2)
- Seconds out: boxing medicine (*Student BMJ* 2009;17:b1767)
- Boxing doctor: get involved (*BMJ Careers* 2009 Dec 2)

The beauty in browsing

BETWEEN THE LINES
Theodore Dalrymple



Through indecision, cowardice, grief, and concern over whether his father will be able to bear the truth, he misses opportunities to break [the cancer] to him gently, only to blurt it out in an abrupt fashion later on

Sometimes in a bookshop one is gripped by the first few pages of a novel of whose existence one was previously unaware. That is why I should very much regret the passing of bookshops, if it ever happens, as seems quite likely. Web browsing and book browsing are not the same thing at all.

It was in a bookshop that I picked up *The Sickness* by the Venezuelan author Alberto Barrera Tyszka. First published in Spain in 2006 and winner there of a prestigious literary prize, it seemed to me a small masterpiece.

The protagonist of the novel is Andres Miranda, a doctor who diagnoses his father's cancer. He agonises over what, if anything, to tell him. Through indecision, cowardice, grief, and concern over whether his father will be able to bear the truth, he misses opportunities to break it to him gently, only to blurt it out in an abrupt fashion later on.

The terrible silence and lack of communication between son and father in the face of death that develops after the breaking of the news is beautifully, if painfully, delineated; it is all the more painful because father and son are normally on good terms, unlike so many fathers and sons.

At the same time Dr Miranda is pursued by a hypochondriac man who was once briefly his patient. This man, who has a variety of psychosomatic symptoms brought on by a general or existential angst, believes that Dr Miranda is the only doctor who can help him. He bombards him with emails, not knowing that he does not use email; unknown to Dr Miranda, his secretary replies in his place and in his name. When the fraud is revealed the patient continues to write to Dr Miranda as if no fraud had taken place: he prefers his illusion to the truth and cannot bear to part with it. We do not laugh, because we all live most of our lives with the necessary illusion that death will not come for us. Indeed, it is almost a condition of the possibility of our existence that we should live in illusion.

Many things are beautifully observed in this book, including the propensity of poor people to give their children unconventional first names: a small phenomenon, no doubt, but a significant one. The father's maid is called Merny, and she names her son Willmer and her daughter Yurber.

"Merny will probably have no control over anything . . . Perhaps the only personal private thing Merny could offer her children in that first moment was a name . . . a different name, a name so different that only she could have thought of it . . . It is not only in the barrios of Caracas that such a thing happens."

I assumed at first that the book was written by a doctor, that Alberto Barrera Tyszka was "one of us," the highest compliment I could pay him. A little web browsing disabused me of the false notion that he was a doctor, however. Luckily I did discover by further web browsing that, aged 18, he had served for a time as a nurse on an oncology ward, and I therefore felt vindicated, at least in large part. I had been almost right all along. Incidentally, I found the information at www.letralia.com/156/entrevistas01.htm. How much time would it have taken me to discover it in a bookshop?

Theodore Dalrymple is a writer and retired doctor

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MEDICAL CLASSICS

The Poisonwood Bible
A novel by Barbara Kingsolver

First published 1998

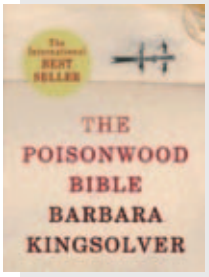
The Poisonwood Bible might be considered Southern Baptist preacher Nathan Price's journey into his own heart of darkness. Barbara Kingsolver, who trained as a biologist, is the offspring of two medical and public health workers who worked in what was then the Belgian Congo.

Her story, of the Price family's mission to the Congo, is told from the perspective of Nathan's wife, Orleanna, and his four daughters, one of whom, Adah, is mute and hemiplegic but who overcomes her disability to train as an infectious disease doctor. At the book's conclusion, in the 1990s, she is a distinguished virologist at the Centers for Disease Control and Prevention in Atlanta, researching HIV and Ebola virus.

The novel features all the public health problems you'd expect in sub-Saharan Africa in the late 1950s: sanitation, schistosomiasis, tuberculosis, filariasis, trypanosomiasis, malaria, all manner of parasites, guinea worm, and raging epidemics of infection, such as typhus, cholera, and kakakaka, the local word for a lethal diarrhoeal disease that intermittently kills babies.

The youngest Price daughter, Ruth May, contracts malaria, having hidden her chloroquine tablets, but ultimately dies from a snake bite. Orleanna, Adah, and her twin Leah return to the United States. Years later Orleanna "still suffers from the effects of several diseases she contracted in the Congo, including schistosomiasis, Guinea worms, and probably tuberculosis."

For some of the characters disease even assumes a quasi-metaphorical dimension. Orleanna reflects, "I was afflicted with Africa like a bout of a rare disease, from which I have not managed a full recovery." And later Leah observes, "When I'm nervous or sad I fall prey to the awful itch from filaires, tiny parasites that crawl into your pores and cause a flare-up every so often. Africa has a thousand ways of getting under your skin." One of Nathan's first activities involves him getting covered in the toxic sap of the poisonwood tree, which provides a clue to the title of the book: his incorrect pronunciation of the local language while preaching actually makes him say "poisonwood" rather than "dearly beloved."



Adah, reflecting on the magnitude of the task that Albert Schweitzer faced when trying to eradicate epidemics, claims, "Out of sympathy for the Devil and Africa, I left the healing profession. I became a witch doctor." It is mainly her observations that add a medical and scientific perspective to the novel's many themes and its exploration of how human beings fit into nature's complexity. "Africa has a thousand ways of cleansing itself. Driver ants, Ebola virus, acquired immune deficiency syndrome, all these are brooms devised by nature to sweep a small clearing very well . . . A parasite of humans that extinguished us altogether, you see, would quickly be laid to rest in human graves. So the race between predator and prey remains exquisitely neck and neck."

Birte Twisselmann web editor, *BMJ* btwisselmann@bmj.com

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We welcome submissions for Medical Classics. These should be no more than 450 words and should focus on a book, film, play, artwork, or piece of music that considers the practice of medicine or the role of doctors in society. The work should be older than 10 years. Please email ideas to Richard Hurley (rhurley@bmj.com).

Peddling consumption over health

FROM THE FRONTLINE
Des Spence

The last time I watched much television, Kylie Minogue had a frizzy perm and was married to Jason Donavon, who sported a dreadful mullet, as I did, and we all drank Castlemaine XXXX. But recently I have been watching *The Biggest Loser USA*.

To those unfamiliar with it, it features a group of morbidly obese Americans who attend a health ranch for several weeks. Of course, this seems like standard voyeuristic, cheap, exploitive reality television, used to sell cat food, horrible hot chocolate, and rotating leather effect sofas—and you would be right. It's loaded with the usual sugary Americana, crying men, soft focus shots, and whooping so loud it can heard in Scotland. But I find myself drawn to the show because obesity and its mental pain plagues the United Kingdom.

I often meet young adults afflicted by obesity who see no way to change their lives. Powerless, gastric surgery is their only hope. And we have seen a steady rise in these operations. Whether this is a good idea and effective in the long term, only time will tell. But why are we seeing a rise in the prevalence of obesity and its associated misery? There is a fundamental flaw in our cultural thinking: we believe that happiness comes with an easy life, one of convenience, which comes from the gift of wealth. Happiness is cars, walk-in wardrobes, eating out, and entertainment centres, and if we don't get what we want we complain aggressively till we do. It is a culture of excesses and excuses.

Medicine is complicit in this, offering the easy options: pills to lower the risk of cardiovascular illness and diabetes, pills to control mood and conduct, and all the rest. Huge international drug companies are now drilling for new markets in the developing world, peddling consumption not health. Obesity is the defining example: we offer drugs and surgery, interventions of passivity and convenience, which are the root of the problem in the first place. The drug industry's holy grail is an obesity pill. And we are compounding the problem by offering palatable but essentially junk medicine. Specialist obesity services, research institutions, nutritionists, and dietitians should have no role in obesity, as there is only one physiological certainty: the imbalance between input and output.

The Biggest Loser USA literally lays bare the cure. Through diet but above all through exercise contestants have lost up to 200 pounds (91 kg) in six months. Firstly, therefore, we must confront the comfort of our disposable, calorie loaded food culture and promote home cooking. But above all we need to be honest about exercise and insist that our children engage in an hour of vigorous aerobic exercise a day and adults likewise. The contestants on this show have not merely lost weight and learnt how to maintain their weight but have earned self respect and regained control. Respect.

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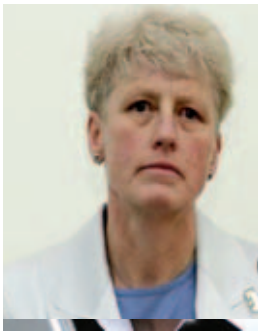
None may sleep

OUTSIDE THE BOX
Trisha Greenhalgh



I signed the consent form, confirmed that I did not have a pacemaker fitted, and took my position on the rack. The technician fitted me with headphones and ascertained my taste in music: rock, pop, jazz, or opera? Opera, please. She warned me to stay very still and pressed the button, which moved the rack into the tube. I clutched the panic button gratefully.

There was plastic in all directions, 3 inches from my face. Most people lying in this position, I mused, have probably got headaches, dizzy spells, or progressive neurological symptoms and are wondering whether they have a brain tumour. Claustrophobic reactions abort a substantial proportion of magnetic resonance imaging investigations to the head.

My head was only in this machine because it was joined to my neck and thence to my shoulder, where an old sports injury had flared up. Even so, it was hard to fight off the vertigo.

After three bars of Chuck Berry (sorry, wrong tape) the aria began. I tried to imagine myself in Covent Garden (or, better, Verona). Someone clearly had a sense of irony: the tape was "Nessun Dorma" ("None May Sleep"), from the final act of Puccini's *Turandot*.

The suitor of a disdainful but beautiful princess has correctly answered the three questions needed to win her as his bride, but she recoils at the thought of marrying him. He gallantly offers her a get out: if she guesses his name before dawn next day, she may behead him. If she does not, she must marry him. The princess decrees that every one of her subjects must stay awake to try to find out the suitor's name.

"Nessun Dorma" is the suitor's song of hope: no one will sleep tonight, but tomorrow the lovely princess will be his. It was chosen as the theme tune for the 1990 World Cup in Rome, where Luciano Pavarotti performed it live along with José Carreras and Plácido Domingo to an estimated audience of 800 million people, which explains why it became the best selling classical album in history.

I wonder whether the three tenors imagined that their rich, soothing voices singing "None May Sleep" would subsequently emerge as one of the auditory stimuli of choice to distract clients from 45 minutes of AK-AK-AK-AK-AK at about the same decibel level as a pneumatic drill?

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