PROCEEDINGS FROM *ADVERSE REACTIONS TO DRUGS: WHAT IS OUR RESPONSIBILITY?* (November 2008, UK)

By Sara Bostock

Last week, on November 6, 2008, I was afforded the wonderful opportunity to attend a conference on "Adverse Psychiatric Reactions to Drugs: What is Our Responsibility?" I say "wonderful," not because the news that came out of this conference was particularly good. Far from it, it is quite clear that there is a crisis in medication prescribing and monitoring that is costing health care systems around the world enormous sums of money and many patients their lives or well being. No, what was "wonderful" about this conference were the many different walks of life from which the presenters came and their very high level of intelligence and commitment to improving prescribing practices and adverse event monitoring, not just in England where the conference was held, but around the world. Continuing Medication Education credits were offered for this conference, but unlike typical events that offer such credit, in this case, the presenters received no fees, and the conference was organized and paid for by a non-profit organization started by a mother who lost her adult daughter to adverse effects of medication. The only drug company presence there, if any, were by reps in disguise as patients, taking notes on what was being said, reputedly what happened at the last two APRIL conferences. No posters, handouts, or any brand insignia on Power Point presentations were ever on display as they so often are at Continuing Medical Education events.

Appropriately the conference took place at Friends' House, a Quaker run facility, that hosts many events determined to be in the public welfare. The speakers ranged from a medical expert on pharmacogenetics, to a mother who lost a son to a psychotic reaction to anesthesia, to a policy wonk who runs a public watchdog website, to a coroner troubled by superficial investigations of possible drug induced deaths. The conference came at adverse drug reactions from every possible point of view and highlighted the very broad scope of the problem from how prescribing is taught in medical schools to the influence of the pharmaceutical industry on the quality of clinical research as well as society's view of health. The take home message was really that patients' experiences must be used as a force for change and not dismissed as they so often are now.

The first speaker was Dr. Munir Pirmohamed, Professor of Pharmacogenetics at Liverpool University. He described the need for pharmacogenetics as "pressing." Reactions to drugs can differ dramatically between patients depending on a variety of factors. The sources for variability include *pharamcogenetics*, the genetic basis for different ways patients respond; *pharmacokinetics*, what the body does to the drug including the rate of metabolism and the ability to excrete from the kidneys; and *pharmacodynamics*, what the drug does to the body in terms of action on receptors, enzymes, and in systemic channels. He was careful to reiterate that variable reactions may be genetic ***or*** environmental. The patient may forget to take the meds, the prescribing decision or dosage may have been a poor one or there may be a drug interaction. Relying on genetics exclusively is not the answer. We cannot predict how

patients are going to respond or who will be adversely affected by side effects. A much better evidence base is required to stop what he pointed out are at least a quarter of a million people each year being admitted to hospital in the U.K. (6.5% of the total) following adverse reactions to a range of commonly prescribed drugs and even some over the counter drugs. It is estimated that this is costing the National Health Service in Great Britain close to half a billion pounds per year and blocks over 5000 beds at any given time which would otherwise be available to other patients. Much better evidence and tracking is crucial to ensuring the health services benefit rather than harm the patient. Genetics is a powerful tool but it is not the only one required.

Dr. Pirmohamed's statistics only referred, however, to people who survived their adverse reactions at least long enough to be admitted to hospital. Next up on the roster of speakers was someone touching on the possible numbers of *deaths* from adverse reactions – the coroner from Manchester, Nigel Meadows. Mr. Meadows was a solicitor and partner in a firm specializing in serious crime, mental health work and medical negligence work before being appointed a coroner. He has investigated over 25,000 deaths in ten years and conducted some 4000 inquests including complex and controversial jury and non-jury cases. He is a member of the steering group for the National Confidential Inquiry into Suicides and Homicides by people with mental illness. His talk focused on how imperfect coroner investigations often are. Deaths are often much more complex than meets the eye. In his last year as a coroner he said there were at least 25-30 deaths that he alone witnessed that had a link to drugs and in some of which SSRIs might have been a contributory cause. In his estimation close to half the certifications of death by doctors could be wrong. The yellow card reporting system in Britain for adverse effects (similar to Medwatch in the States) is imperfect. His talk was a plea for greater and more thorough investigation. He personally tells the pathologist to do whatever is necessary to determine a cause of death but often this is not typically done by other coroners and even at that the knowledge they can bring to the analysis is limited.

My favorite presentation of the day was by Charles Medawar, co-author of *Medicines Out of Control? Antidepressants and the Conspiracy of Goodwill* and co-founder of Social Audit Ltd (www.socialaudit.org.uk) that sought to develop and apply methodologies for social accounting. He is now a specialist on medicines policy and drug safety issues and on matters of corporate, governmental and professional accountability relating to these topics. His talk was entitled "Pharmageddon and Beyond" and the main theme was that adverse drug reactions are only the tip of an iceberg of other much more global and far reaching problems in health care, namely that we live in a world in which medicines and the practice of medicine now almost certainly produce ironically more sickness than health and medical progress is doing more harm than good.

Each presenter was to prepare "ten golden rules for survival" and Charles, a professorial and intellectual fellow, son of a Nobel prize winner, who thinks profoundly and articulately about these problems, presented rules that stretched one's thinking in new and challenging directions. The first rule for instance is " to take for granted at one's peril that health (i.e. healing) is the natural output of medical and pharmaceutical endeavor." Medical and pharmaceutical endeavor clearly has produced great health gains but it has

now passed the point of diminishing returns according to Charles. Health output increasingly fails to realize its potential. We all proceed largely in ignorance of health output's *destructive* effects. Feeble drug regulation sustains the illusion that all is well enough with our medication use and dishonest and irrelevant scientific inquiry abets the neglect of adverse effects. Globalization has magnified the dominant influence of commercial and financial interests on the character of medicine and the role of medicines in medical intervention. Innovation used to be the mainstay of these endeavors; now it is marketing. He went on from here with nine more tenets, all of which are thought provoking.

Second: Your health and well-being depend ultimately on the health of the community. No one escapes when others feel ill or are impoverished, desperate, miserable or insecure. One cannot exist sanely in a sea of madness. Your own health depends overwhelmingly on the health and well being of people around you. America has led the trend to ill health from malign dependence on "health" products and purveyors. The CDC (in the U.S,) estimates that only 3% of the population leads a healthy lifestyle; the rest smoke, take insufficient exercise, eat a nutritionally deficient diet and/or gain excessive weight.

Third: Excessive demand for medicine by some populations means deprivations for others. Pharma depends for its survival on the ability to stimulate mass demand and is slavishly supported by professional and government agencies. True innovation and fair competition plays second fiddle to market acumen and exploitation. In richer countries demand for medicines and medical intervention perpetuates the growth of a global prescription drug production system that over-medicates us and under-medicates the third world. The overall health loss is catastrophic as is the equilibrium between the two.

Fourth: The treatment one gets is the product of a "system" in which the doctor plays an increasingly marginal part. The Hippocratic Oath says, "And I will use treatments for the benefit of the ill in accordance with my ability and my judgment, but from what is to their harm and injustice I will keep them." But in recent times professional understanding of drug treatment modalities and outcomes is overwhelmingly guided by market forces that are tempered only to some minimum standard of safety by political and regulatory intervention. The quality, quantity and thrust of "health" messages tends to leave the average health practitioner out of touch with honest expert opinion and apparently oblivious to the influence of commercial and political influence. He is dependent for treatment modalities and outcomes on information from commercial courses. More and more false measures of safety and efficacy are relied upon but actual outcomes are not evaluated.

Fifth: There is a 'paradox of progress' in the sense that initially medicine produced great benefit from technological advances (and still does) but now catastrophe looms on the horizon because of over-medication and over-treatment. In addition there is a 'conspiracy of goodwill,' that is the fervent wish by health professionals, government, manufacturers and users that drugs and treatment should be safe and effective and never anything less." At the heart of medicine is a delicate but powerful interdependency based on fear of ill health, trust in a healer, and hope and dreams of well being. The result of these trends is

growth of unsustainable demand, unmet needs, disappointed expectations, destructive dependencies on doctors and medication, corrupt practices in clinical and scientific work and far fetched official denials of failure.

Sixth: Counting and classifying adverse drug reactions is only the first step in responding to the issues of medicine-induced harm. Even more necessary is recognition of the risks that are now being incurred by our health care system to healthy responses to suffering, impairment and even death. If, for instance, antidepressants really were completely efficacious with no side effects then clearly the 3% of people who are truly very badly depressed would benefit enormously but if the pills were so perfect almost everyone would take them and society would deprive itself of the feedback mechanism that depression provides. There would be a paralysis of healthy responses to suffering. Responsibility for health has been *expropriated* from the individual to a vast construct of society. The fault lies not so much with doctors but with the system on which doctors increasingly depend.

Seventh: Great doctors are always well aware of their limitations. We are ignoring sane strictures about the limits of medical intervention to create “perfect health.” The quest for health has become shrill. We are becoming health anxious and succumbing to selfish demand that threatens to destroy common sense about health and community driven public policy and initiative. We are after all a reasonably healthy people. Far from being ineptly put together as one might think from all the fear mongering about sickness, we are amazingly tough durable organisms, ready for most contingencies. The new danger to our well-being is in becoming a nation of healthy hypochondriacs, living gingerly and worrying ourselves half to death. We are being taken in by propaganda (such as DTCA) and it is bad not only for the spirit of society but also it will make any health care system no matter how large and efficient, unworkable.

Eighth: Consider the root causes and the nature of other world crises, such as climate change and the financial crisis before dismissing the threat of *Pharmageddon*, which is a notional end point in our current health climate. The main causes of *all* these crises are these “systemic trends:” complacency, the triumph of mediocrity over excellence, weak imagination and leadership, grotesque lack of transparency, labyrinthine organizational complexities, tick-box accountability, dishonest communication, manipulative behavior, suppression of dissent, manifold conflicts of interest, rampant personal ambition and hope of advantage and gain, institutional greed, market and global pressures, unthinking commitment to growth and choice, preoccupation with present rather than future imperatives, and a grinding focus on minutiae rather than the larger picture. The common denominator is the illusion of rectitude sustained by flimsy, self-serving and self-satisfied systems of control and regulation.

Ninth: Celebrate and utilize with the utmost discrimination the best of medicine, medicines, and medical intervention. The best is superb and indispensable if still essentially an adjunct to “health.” The best, however, is not representative of the whole and uncritical acceptance of “health” endeavor is bad for my health and yours and bad for the future of medial and pharmaceutical endeavor.

Tenth: Trust and rely on your own judgment, notwithstanding your own levels of ignorance and the professed wisdom of the media and the drug establishment. If we were individually capable of knowing, synthesizing, digesting and processing all available and obtainable information on drug benefits and harm, we would undoubtedly radically revise our views on the relationship between the two and on where health value is really to be found.

Medicine, he concluded, is a "dreadful disappointment." For too long we have assumed that good intent produces good results. Because of this we have failed to be thoroughly critical of how medicine works and what its effects are. Good intent does ***not*** necessarily produce good results. We desperately need to investigate health outcomes; we are not doing this. And medical accidents are not being investigated. This is gravely bad for the progress of medical endeavor.

As if to add insult to injury after Charles' disturbing points on the sorry state of medical endeavor, the next presenter, Dr. Ben Goldacre, a doctor/journalist/whistleblower and author of *Bad Science*, brought us back to some of the nitty gritty of where things are going wrong by setting out specific examples of "How drug trials are rigged." Having read a lot on this topic from other sources I decided to take the opportunity of his talk to leave the main hall and attend one of the breakout sessions on medication withdrawal. In separate rooms smaller groups were meeting to discuss antidepressant, benzo and antipsychotic withdrawal. In fact, discussion of withdrawal protocols turned out to be disappointingly vague. Most of the sessions veered towards anger at the poor disclosure at the commencement of treatment about long-term dependence as well as a discussion of alternative ways of coping with mental illness. Many participants described very great difficulty in trying to stop medications as well as being tripped into more serious mood problems by the medications themselves, the worsening or creation of "bipolar disorder" in particular. Peer support was mentioned several times as an effective tool for helping with problems.

Back in the main hall, perhaps the star presenter of the day, Dr. David Healy, professor of psychiatry at Cardiff University, who is well known for drawing attention to the suicidal and homicidal side effects of antidepressants as well as the drugs' dependency issues, was on after two mothers touched on their experiences losing their adult children after inexplicable changes in personality following medical interventions. The first mother, Clare Milford-Haven, was strikingly attractive and I learned later that she is one of Fergie's best friends and her deceased son moved in royal circles. He died from a self-inflicted gunshot wound ten days after a routine operation to a varicose vein on his testicle. This suicide was almost certainly brought on by an adverse psychiatric reaction to anesthesia, warnings for which are woefully inadequate. The second was Mille Kieve, the founder of APRIL and organizer of the conference, whose 30 year old daughter died after more than one episode of adverse reactions to a variety of drugs that in turn led to additional prescriptions to treat the side effects. In addition she was the victim of a prescribing error and was taking a dose of an anti-Parkinson drug that was three times the recommended intended dose for two years just before her death that was ruled an

accident but could have been a suicide. She fell from an upper story window of a holiday flat with her mother in the adjoining room.

Healy's topic following on from these two tragic stories was aptly entitled "When Treatments Go Wrong." Meetings like the one organized by Millie, he said, should be run ***in*** medicine. What has medicine come to when stories like Clare's and Millie's are labeled "case reports" or "anecdotes?" Doctors turn the other way and say they are sorry but ***no*** signal to that effect has been seen in clinical trials. Science points the other way. 14 years ago a two-fold increase in the risk of suicidal behavior was noted in a clinical trial but this was not considered statistically significant. No significant difference in risk, however, morphed into something more expedient for drug manufacturers – no significant risk at all. Well the two are ***not*** the same. Little evidence of risk is not the same as evidence of ***no*** risk, yet this is how it is treated. It represents a dreadful mix of science and politics. We should assume drugs are harmful until they are proven beneficial. It's the other way around in the current system.

Science is good, he said, when anecdotes are actually consistent with the scientific evidence, not at odds with it. Experiential and scientific evidence should converge. We must break that barrier between them. Medicine should be evidence based but because so much raw data from clinical trials is concealed and then misrepresented in the write-up, including the placing of adverse placebo events that actually occur in the wash-out period and after the actual trial back into the active comparison period. This serves to increase negative placebo events thus lowering the hurdle for a favorable comparison with adverse events on antidepressants. In addition some of the adverse "placebo" events may actually be withdrawal events from prior treatment or from the active treatment in the trial that may conclude at the end of the active comparison period. He quoted another mother who said her "daughter was the victim of a commercial enterprise."

Companies market the drugs under the guise of science. They ought to make the data available. The subjects in a clinical trial deserve to have the information disclosed. Patients signing informed consent forms for a trial should be able to insist on data disclosure as a condition for being in the trial. According to Healy the current focus on conflict of interests is almost a distraction. The real issue is that the quality of clinical trials is very poor. In fact, he said 95% of them are rubbish. The MHRA should require audits of good clinical practice and compliance currently is only 40% at most.

The last presenter was Dr. Simon Maxwell, a Senior Lecturer in Clinical Pharmacology at the University of Edinburgh, who spoke on "Educating a new generation for safe prescribing." What was shocking about his presentation was the admission that very little attention is paid to teaching safe prescribing in medical school at all. Nearly 80% of medical students feel that they get far too little education in prescribing. Nurses get 35 hours of prescribing instruction while medical students are expected to "pick it up." At some medical schools clinical pharmacology courses have been eliminated and there is no official hurdle or assessment that has to be passed before young doctors can start prescribing. The NHS has recently become interested in the problems this leads to and actually withdrew prescribing rights from some doctors because errors were so bad.

Finally there has been a call for strengthened prescribing education after a move away from it for the past 15 years. In 1993 a document was published entitled “Tomorrow’s Doctors” that urged an interdisciplinary approach and a move to avoid all reference to traditional subjects of which clinical pharmacology was one. There was a move to system-based learning, the circulatory system, the reproductive system etc. and a reduction of the factual burden. But the problem is that drugs do not respect system boundaries; they affect multiple systems in the body at once.

At the same time he said it is difficult to accumulate evidence about exactly what improves and affects prescribing practices. What should the standards for safe prescribing be? The NHS has formed a safe prescribing working group. A new version of “Tomorrow’s Doctors” is due to be published in 2009 and is expected to address these issues. E-learning for health is underway.

The take home message from the conference and one that was agreed upon by a surprising number of speakers there and for a variety of different reasons is that there needs to be new and far better methods of analyzing adverse effects of medication and poor prescribing. And health outcomes need to be critically evaluated. All manner of individuals can and do see that this is a fundamental problem in health care today and causing untold problems. It’s costing individuals their lives or well being and it’s costing health care systems millions of dollars. It doesn’t have to be this way. And one of the ways it might get better is through patient empowerment and everyone listening and respecting what patients can tell us about the treatments they are receiving.