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This month's theme might be loosely described as "Problems in Modern Medicine." Studies and commentary are discussed which challenge the clinical significance of cancer drug trials, the off-label use of experimental cancer drugs and the risk of harm upon hospitalization. In addition, this issue contains Part I of a review of alternatives to psychiatric drugs. This review is introduced by a rather lengthy and quite contrary view of the pharmaceutical approach to treating various real and not so real psychiatric problems. It appears that a growing number of psychiatrists are beginning to realize that all is not well with the evidence base for the standard of practice that the drug companies have with impressive skill persuaded them to adopt.

There are many significant issues associated with psychiatric drugs. Aside from the widespread use by the general public, these include psychiatric drug treatment of children including the very young, incarcerated youths and the institutionalized elderly. For these particular vulnerable groups, many prescriptions are for off-label disorders, that is, unapproved uses, especially in the case of antipsychotic drugs. A recent investigative report in the magazine Youth Today (October, 2010) details the extensive off-label use of antipsychotic drugs to deal with unruly and difficult to control incarcerated adolescents. While the extent this problem nationwide in the U.S. was hard to uncover, what was found suggests widespread use. To quote one psychologist-lawyer, "Fifty years ago, we were tying up kids with leather straps, but now that offends people, so instead we drug them…..We cover it up with some justification that there is some medical reason, which there is not."

But the crux of the matter with the whole field of psychiatric medication involves the issue of harm vs. benefit, and how and over what time period each is determined. The whole field is characterized by the almost total absence of long-term studies but long-term use is very common. There is fraud in trials, including those involving children. A psychiatrist working for a major drug company has recently been sentenced to 13 months in prison for fraud in trials of the pediatric use of a popular antipsychotic drug—she enrolled children who she knew did not have the disorder being treated and falsified records and diagnoses. The company is now also facing charges that for 15 years it concealed evidence that this drug increases the risk of suicide in children.

Psychiatric drugs are an area of such critical concern that the review devotes considerable space to introducing the evidence that, except in the most severe cases, the harms vastly outweigh the benefits and that the benefits may be in part simply fantasies. This point of view lends urgency and importance to alternative treatments and to adequate attention to the problem of differential diagnosis. It is obviously important that problems with a totally non-psychological root causes are not improperly and ineffectively treated with psychiatric drugs with net harm, when proper treatment would yield a complete cure, frequently over a short period.

That this subject merits the attention given in the Newsletter is justified by the almost unbelievable prevalence of the legal use of psychiatric drugs for all ages from 2 to over 90 years of age. The critics claim that these drugs do not, as advertised, treat pre-existing chemical imbalances in the brain and are safe, but rather these imbalances do not exist and the drugs operate by brain-disabling mechanisms and in many cases produce long-term permanent damage, in part severe and life-altering. If someone set about to collect case histories to justify this view, they could fill several large volumes with shocking, depressing and almost unbelievable stories. But even one popular volume

should be enough to convince anyone but the most ardent believers in the current standard of practice (see Medication Madness by Dr. Peter Breggin, M.D.)

Finally, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

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TARGETED CANCER DRUGS, CLINICAL TRIALS AND REALITY

Periodically in this newsletter the problem of the benefits, side effects and the huge expense of targeted cancer drugs have been discussed. We are now beginning to see calls for a realistic view of this therapeutic approach to metastatic and generally terminal cancer. Studies from Princess Margaret Hospital (the Toronto cancer treatment center) and the University of Toronto address two issues. One is the reporting of serious and fatal drug reactions of targeted therapy in the studies that form the basis of regulatory approval and acceptance by oncologists. The other involves the recurrent question concerning what should be accepted as a positive clinical trial,

Regarding the first question, Seruga, Tannock and colleagues searched the FDA web site for approved targeted anticancer drugs with updates to their labels that related to safety in 2008 and 2009 that had at least one randomized controlled trial (RCT) referenced in the updated drug label. They identified 12 eligible, targeted anticancer agents with 36 RCTs referenced in updated drug labels and looked at the prevalence of updated "labels" reflecting serious or fatal side effects not mentioned in the trials.[1] A label is medical jargon for the printed information drug companies are required to supply with the drug. The material in the label also gets into the *Physicians Desk Reference.* The label includes both approved indications for use and side effects. When side effects are particularly bad, adverse drug reactions (ADRs) are enclosed in a box, which is appropriately black.

In this study 76 serious ADRs were reported in updated labels and 50% of these were potentially fatal. For the ADRs identified, 39 % of the serious ADRs and 39% of the potentially fatal ADRs were not described in the published RCTs cited in the revised labels. In addition 49% of all serious ADRs and 58% of potentially fatal ADRs were not described in the initial drug labels. After a median of about 4 years, 42% of the eligible drugs acquired one or more black box warnings, which is the highest-level alert in the FDA system. Thus for a significant period after approval, oncologists do not have appropriate information to judge benefit vs. serious or fatal harm. Furthermore, the results show that the design of the RCTs used to gain approval is not very successful in uncovering these ADRs. The paper calling attention to this appeared in the *Journal of Clinical Oncology*, i.e. a mainstream peer-reviewed journal.

The second study questions one of the basic principles of drug evaluation and subsequent approval by either the FDA or the European equivalent.[2] The problem involves approval based on statistical significance, either for a comparison of a drug with a placebo or with another treatment or combined treatment. The judgement call is made on the basis that the probability of the outcome being simply due to chance is equal to or less than 5%. (a P value of ≤ 0.05). Tannock and Ocana take the position that this does not necessarily imply clinical significance and that statistical

significance for very small effects can generally achieved by studies involving a large number of participants. They illustrate their point with an interesting table giving the results of 14 randomized phase III clinical trials used since 2000 by the FDA for approval of new molecular-targeted anticancer drugs for advanced solid tumor disease. A number of drugs and cancer sites were involved and as well, endpoints involved both measures of progression and overall survival.

Out of 18 studies, 14 addressed the issue of overall survival, an important endpoint in metastatic or terminal cancer. Overall survival was measured in months, and the average was 2.5 with a standard deviation of ±1.35. Thus about 34% fell between 1.15 months and 2.5 months overall survival and the range was 10 days to 4.8 months. These survival statistics then must be weighed against ADRs and quality of life. The drugs with overall survival data were lapatinib, trastuzumab, bevacizurmab, cetuximab, erlotinib, sorafenib, and temsirolimus.
Because comparisons of endpoints are made between two groups, odds ratios or what is roughly equivalent, hazard ratios are also calculated. In one of the cited studies of a new, approved drug for pancreatic cancer cited by Ocana and Tannock, the relative risk reduction was 18% (hazard ratio of 0.82 with a 95% confidence interval of 0.69 to 0.99, a statistically significant results meeting the FDA rules of the game. However, this statistical significance did not seem to have much meaning with the median overall survival increased by only 10 days!

The authors take the position that a statistical significant P value or the equivalent expressed as confidence interval when used alone should not be considered evidence of a "positive" result that justifies the approval or use of the drug. They suggest a minimum of 3 months for increased overall survival as a realistic measure of clinical benefit. They also suggest 4 to 6 months increase in progression related endpoints, which translates into hazard ratios of approximately 0.5. In judging trials where there is an improvement in a measure of progression but no impact on overall survival, they point out that the toxic effects of the treatment now become paramount. It is disturbing that something that seems as obvious as this is still an issue in the oncology community. The same observation applies to what too many would appear to be trivial increases in life expectancy. Incidentally, the class of drug under discussion here is notorious for having a very high if not astronomical cost of treatment. These are not lifesaving drugs, as some patients claim when they voice their disappointment, frequently in the press or on local TV, over the failure of a government plan to pay the bill. The maximum increase in overall survival in the 12 studies cited by Tannock and Ocana was 4.8 months, and that one result approached the status of an outlier. This is not to say that there are no targeted cancer drugs that provide longer overall survival times, but these are very rare. This study was published in the *Journal of the National Cancer Institute*, another peer reviewed mainstream journal.

Based on mostly the same list of drugs, Sobrero *et al* arrive at the same conclusion with a median overall survival time of 2 months.[3] They also discuss the need to raise the bar of efficacy for drug approval. However, they point out that the targeted drug imatinib is an exception. It is used for gastrointestinal tumors and has much longer survival and progression-free times.

Hopefully these studies will encourage debate concerning what is obviously a very serious issue for patients who presumably have the right to give or withhold informed consent and who may be led to believe that a recommended therapy is solidly evidence based with a positive risk vs. reward. The patient or an insurer is agreeing to costs that can easily exceed $50,000, in some cases per year. Patients need to ask questions directed at these issues, but especially the issue of the magnitude of expected increase in overall survival and the associated evidence.

OFF-LABEL USE OF EXPERIMENTAL CANCER DRUGS

Cancer drug trials frequently involve drugs already approved for different doses or combinations or for different indications of the drug than being tested in the trials. A recent study by *Hamilton et al*[4] attempted to get a general picture of the potential or prevalence of the use of these drugs for the unapproved indications outside of studies i.e. off-label. They looked at the number of experimental drugs involved in trials published over the two-year period ending in April 2008 and then checked to see how many were already approved by the FDA for other indications, doses or combinations. The use of investigational cancer drug therapies outside trials for unapproved indications was termed "off-protocol therapy" (OPRx). In 172 randomized controlled trials, 63% were evaluating drugs available OPRx in the US at trial initiation and an additional 11% became available during the trials. An indication of OPRx use was seen in the abnormally slow accrual of study subjects when the drug was available for OPRx and in addition, the rate of accrual was almost two-thirds less efficient.

This study provides evidence that the use of experimental drugs for OPRx is not uncommon and that there are clearly issues with safety and efficacy. Reuters News Service ran an article on this study and interviewed several prominent cancer researchers (October 26, 2010). One pointed out that many women were treated for breast cancer with stem cells in the 1990s when the treatment was still in clinical trials and not approved for this use. This made enrolment difficult and it required about ten years accomplishing the trial. The results indicated that the treatment, which was very expensive, was not effective but was toxic. In the drugs included in the study by Hamilton *et al,* 66% reported at least one serious high-level example of toxicity in an experimental arm, only about half found any efficacy and only 27% reported an improvement in overall survival. No actual figures were given for days of extended overall survival. Obviously, the patients treated OPRx could not have been provided with information that would enable them to give informed consent since the studies concerning their indication were in progress! One interpretation of this whole picture is that of desperation on the part of the oncology community which is associated with the poor results obtained with most of the approved therapies. This would account for the interest in trying anything that might be better, even when the critical trials are not completed and by definition, the application has not been demonstrated to be effective or even safe, and when this class of drug is declared safe, it is obviously a very restricted and self-serving definition of the term. After all, the best hospitals are now taking almost heroic measures to protect oncology nurses and hospital pharmacists from even the slightest contact with drugs used for cancer therapy during the preparation of IV bags, an action based on evidence of a high level of potential harm.

U.S. INSTITUTE OF MEDICINE TAKES A POSITION ON VITAMIN D

In what some believe may be a historic consensus, the Institute of Medicine's Food and Nutrition Board (FNB) and its 2010 vitamin D panel recently handed down a recommendation concerning calcium and vitamin D deficiency and supplementation. When viewed in the context of hundreds of recent studies relating vitamin deficiency to a variety of chronic diseases and as well the widespread prevalence of vitamin D deficiency if not severe deficiency, it is interesting that the panel ended up recommending trivial increases in supplementation and promoting the view that most Americans were in general not deficient. The panel also dismissed studies of the association of this vitamin with chronic diseases. The report received widespread media attention with the message that most of us get all the vitamin D we need from food (actually a close to negligible source) and sunlight (also a negligible source in northern latitudes for half the year). This leads to great confusion and loss of confidence by the general public in so-called experts, a process that is ongoing. One high profile national cancer society has been recommending 2000

IU/day, vastly more than recommended by the FNB. Pregnant women have particularly high needs and yet they are being told by TV commentators or the press that expert, official, scientific opinion now regards 600 IU/day is more than enough for a pregnant woman when studies and vitamins D experts suggest up to 5000 IU.

The panel was made up of bone experts and was noteworthy for the extraordinary absence of any of the dozens of world-renowned vitamin D experts. To anyone who is familiar with the vitamin D literature, the panel consensus was absurd, but can be understood by a blind dedication to the proposition that all guidelines and officially sanctioned interventions must be based on randomized, double blind, placebo controlled clinical trials. The absence of trials translates to the absence of benefit. Interesting logic! The committee universally demonstrated its reluctance to recognize vitamin D as a precursor of a natural hormone, generated in the skin large amounts, especially in that part of the world where we are thought to have evolved. It rejected hundreds of studies indicating the importance of high levels of circulating 25-hydroxyvitamin D for optimum health simply because they did not meet their preconceived notion of what constitutes an acceptable study in this age of so-called evidence-based medicine. Yet there are vast areas of modern medicine where guideline-sanctioned interventions are approved be expert panels and the appropriate professional societies and yet are not really evidence-based. That they could not grasp the elementary fact that vitamin D is different from vitamin E or folic acid or beta-carotene (the poster child of allegedly dangerous supplements) suggests a mindset that is remarkably narrow.

The FNB committee consulted with 14 vitamin D experts but suppressed their reports. The individuals consulted included famous vitamin D researchers such as Robert Heaney and as well, Walter Willett from Harvard, one of the best-known nutritionists in the world. The Vitamin D Council is proceeding with legal action through the Freedom of Information Act to obtain the suppressed reports. In the usual scientific circles where the quest for truth is generally paramount and debate essential, requiring such action in order that interested scientists can get at this type of information is truly unthinkable and sends a highly uncomplimentary message as to how the system really works.

Hopefully, it will be eventually concluded that this consensus position was of no credit to the intelligent, educated individuals involved and that their mindset has done a huge disservice and will cause untold suffering. To the readers of this newsletter, it is a lesson in how modern medicine works when carefully selected thought moulders prefer the comfort and safety of being inside the narrow confines of a comfortable box (especially narrow in this case with the focus on bone health). Such behaviour has historically provided impediments to progress in medicine and has helped fill countless cemeteries.

The actual recommendations will not be reviewed since they represent trivial changes in what the critics term inadequate guidelines. Significant segments of mainstream medicine support the vitamin D researchers and their recommendations of 2000-5000 IU/day and understand the difficulties of financing a large number of randomized clinical trials when the supplement form of vitamin D costs pennies a day and the sun is free. Readers are referred to the commentary in a news release from Harvard by Willett and Bischoff-Ferrari.[5]

ANTIDOTE FOR THE IOM-FNB VITAMIN D REPORT

Recently the following reports concerning the benefits of elevated vitamin D levels have appeared:

- Two new studies found a positive link between low vitamin D blood levels and the risk of asthma symptoms.[6,7]
- Researchers have found a significantly lower risk of cancer progression and death in chronic lymphocytic leukemia patients who had sufficient vitamin D levels compared to those who did not.[8]
- In type 2 diabetics, a study revealed severe vitamin D deficiency predicts an

increase in risk of all cause and cardiovascular mortality.[9]

- School-age children with low vitamin D levels are found to be at higher risk of becoming overweight.[10]
- In older women, vitamin D therapy was found to in crease muscle function in those who were the weakest and slowest at baseline.[11]
- Vitamin D deficiency was linked to cognitive impairment in older women and another study found the same in elderly persons in general.[12-14]
- A recent French study found between 27% and 40% risk reduction for breast cancer for women with high levels of 25-hydroxyvitamin D.[15]

Presumably the reaction of the FNB to the above studies would be "so what, show me the large, multicenter, randomized, double blind, placebo controlled intervention trials." And by the way, these studies should be preceded by Phase I and Phase II trials to permit a design that will gain approval of the appropriate committees. Don't ask who is going to finance all of these trials – certainly not the pharmaceutical industry. It is unlikely that anyone is going to pay for a significant number of trials. In the context of chronic disease, we are being told just to forget about vitamin D. There is no evidence base for its benefit. The above is not a complete list, just a selection to make the point. If one puts "vitamin D" into PubMed (the National Library of Medicine search engine) and looks for publications containing this term in either title or abstract, there are over 4200 publications in the past 2 years.

So there you have it. One side, the bone experts, takes the position that all the vitamin D experts and many famous specialists in nutrition, some with PhDs in public health along with MDs, should simply be ignored. The other side points to thousands of studies that present compelling evidence that vitamin D is a truly unique and highly important hormone and one is incurring multiple health risks by being deficient, and being deficient is very common.

ALMONDS AND BLOOD SUGAR CONTROL

There is considerable evidence that dietary intake of nuts is beneficial, in particular as regards cardiovascular risks and glucose metabolism.[16,17] Nuts are an important component of the Mediterranean diet and turn up in dietary patterns identified as healthy. Recent studies have found that almonds consumed with meals reduce the height and magnitude of the post-meal glucose and insulin response, but in these studies the nuts were a major component at 15% of the caloric intake. While almonds contain about 50% fat by weight, they have beneficial rather than undesirable impact on blood lipids, in particular with regard to oxidative damage.[16] Almonds and nuts in general also qualify as an important component of diets designed to mimic that of the pre-agricultural era and the so-called Paleolithic or "Original" diets. Almonds share with other nuts the capacity to dull hunger even when eaten in small amounts and provide a low-calorie and low-carbohydrate option for between- meal snacks if eaten in moderation.

A new study by Choudhary *et al*[18] has examined an interesting question, does almond consumption have more than a transient impact on glucose metabolism in diabetics that occurs during digestion? Twenty locally residing female type 2 diabetics 40-60 years of age were recruited while excluding anyone who smoked, drank alcohol, or suffered from disorders other than diabetes. Most were on diabetic medication such as metformin. Subjects were first studied over three weeks to obtain baseline fasting and 2-hour post meal glucose values while maintaining their regular diets (about 1300 cal). Then they were told to eat 10 g of raw American almonds with their first meal every morning and the same measurements were repeated weekly for four weeks. It was observed that the mean fasting glucose levels continuously decreased from about 140 to 126 mg/dL and the 2-hour post meal levels decreased from about 217 to 171 mg/dL. The former result is of considerable interest since it is not associated with the digestion of a meal and may represent permanent changes in

insulin resistance. The mean fasting glucose at the end of week four of the intervention approaches one of the thresholds used to identify diabetes as do 2-hour post-meal glucose levels of < 200 mg/dL.

These results are surprising since the "dose" of almonds is low compared to earlier metabolic studies where meals were accompanied by up to 90 g of this nut and dose dependent response was observed. In the metabolic studies, the subjects did not have diabetes or impaired fasting glucose levels. Ten grams of almonds is equivalent to 10-12 nuts, fewer than many would casually nibble between meals or with a drink. Whether there is any special benefit associated with taking the almonds along with breakfast is unknown, as is the mechanism of action. It has been suggested that the beneficial effects seen in metabolic studies may arise from the high monosaturated fat content, vegetable protein, phytate and the high phenolic content of the nuts, the latter residing in particular in the skins. In the studies cited above the almonds were raw and in most cases unblanched.[18]

Another recent study examined the impact of almonds on cardiovascular and glucose metabolism markers in a pre-diabetic group. They followed an American Diabetes Association diet but 20% of the calories were derived from almonds (about ½ cup per day). After 16 weeks, significant changes were seen for fasting insulin and two markers of insulin sensitivity but fasting glucose was unchanged. The subjects had essentially normal baseline fasting glucose levels (about 105 mg/dL) and were on a typical mainstream diet for prediabetics of 50% energy from carbohydrates.[19]. By comparison, the study group in Choudhary's study experienced sharp drops in fasting glucose, consumed less than half the quantity of almonds, had elevated fasting glucose at baseline and were on glucose control medications.

The study by Choudhary *et al* clearly needs to be confirmed and additional studies should include men, non-diabetic individuals, pre-diabetics, diabetics not on medication, cover for a longer study period, and examine the dose dependence. While we wait for more studies, and it may be quite a while since almonds are not patentable, readers who monitor their blood sugar for one reason or another can obviously experiment with almonds. There is no doubt considerable human variability. Also, readers are warned that high dose oral vitamin C can interfere with the chemistry involved in the blood glucose meter strips and give false elevated values. Something else to experiment with!

LATEST ON STATINS IN PRIMARY PREVENTION

The Cochrane Database organization, a highly respected and trusted source of unbiased meta-analyses associated with the efficacy and risks of medical therapy, has just published an analysis of the use of statins in primary prevention.[20] According to the authors, this analysis differed from others done concerning primary prevention in that it looked just at those at low risk and limited the included studies to those with cohorts where < 10% had a previous history of cardiovascular disease. The study included 14 trials involving over 34,000 patients. Studies either compared treatment to placebos or to usual care. For the endpoints of overall mortality or coronary deaths, the results were consistent with either relative benefit (17% to 22% for mortality endpoints) or the "play of chance," but the important result involved the very small absolute benefits that translated into 1000 people needing to be treated (NNT) to prevent one death. The view is widely held that a NNT of this magnitude indicates that while a small relative benefit may be statistically significant as it was in this meta-analysis, it completely lacks any clinical significance. Those who worry about clinical significance like a NNT below 50, and although this is a bit arbitrary, it is a lot less than 1000! This point concerning small absolute benefit and large NNT has been made a number of times by those who regard statins as not having clinical significance in this context, but mainstream cardiology does not appear to be listening. The NNT is so large that it does not even suggest merit in looking for benefit outside lipid lowering for these drugs, as least for true primary prevention.

In the UK, the National Institute for Clinical Excellence (NICE) currently recommends that statins not be used with people with a risk of coronary heart disease below 20% over 10 years. This is the risk normally calculated by the Framingham risk calculators.

It is clear that this study stirred up controversy. *HeartWire* (theheart.org) carried comments from critics of the Cochrane study as well as quotes from the scientists involved in the study. Critics attempted to minimize the importance of the study and its conclusions and claimed the benefits were significant. This is easy if one focuses on relative risk reduction and considers small effects important if they reach statistical significance. As has been discussed on several occasions in this Newsletter, this is currently a topic of growing interest in epidemiology.

Critics of the Cochrane analysis also took the position that statins were safe except for the very small risk of muscle problems, and thus even if the benefits were not large, many healthy individuals would benefit from taking them. However, those actively involved in research in statin side effects or those attempting to collect adverse reactions independent of the notoriously inefficient government-based systems would no doubt strongly disagree. The Cochran authors also comment that in fact we don't know the extent of the harms of statin treatment, published primary prevention trials may include selective reporting and the inclusion of people with cardiovascular disease and they also point to the industry support of many of these studies. The best summaries of side effects with statins appear to be in the books by Dr. Duane Graveline, M.D. (see www.spacedoc.net). The bottom line seems to be that when one blocks a critical enzyme pathway, which then impacts a dozen or more other important pathways, watch out. Trouble can be expected and it may take a long time to show up and when it does, it may be in unexpected places.

CIRCULATING TUMOR CELLS

The media made a big deal out of the announcement that Johnson & Johnson (J & J) is teaming up with scientists from Massachusetts General Hospital (Mass General) to develop an inexpensive device that will make possible the identification and characterization of single or clumped circulating tumor cells (CTCs) obtained from a small blood sample. Finding and studying single circulating tumor cells is not new but rather an area of active research in a number of labs. In fact, the Mass General group first described the prototype of the device now under development and commercialization by J & J in 2007 in an article in *Nature.* This group has just published a paper in the *Proceedings of the National Academy of Science* which describes the second generation device and tests with blood from cancer patients and blood "spiked" with tumor cells.[21] The original device used a surface with 78,000 tiny nanoposts, which were coated with antibody that bound cancer cells. This design presented flow problems which the second-generation device solved by using a herringbone microchannel design. This greatly enhanced the contact between the circulating fluid and the coated walls. Circulating tumor cells were identified in 14 of 15 prostate cancer patients with metastatic disease (median 63 CTCs/mL). The occasional clump of cancer cells was also captured and to be able to do this may prove to be the gateway to some very interesting research on metastasis. They were able to image the cells using standard staining techniques and fluorescent labelling methods, and as well the cells could be isolated, cultured, and with on-plate lysis the researchers were able to isolate RNA of sufficient quality for assay. When blood was spiked with prostate cancer cells, the device captured
95% of the CTCs.

The inventors point out the obvious applications and the importance of this technique for quickly establishing the efficacy of treatment. The media hype was perhaps a bid overdone. The essential feature of the news was the partnership that may vastly speed up the availability of the second-generation device for use in the large number of studies required to move the technique from the research lab to clinical use. A news

release in November from the National Cancer Institute already described the merits and importance of the second-generation device.

In past Newsletters, the utility of the enzyme CYP1B1 as a tumor cell specific marker was discussed in connection with the commercially available therapeutic agents called Salvestrols which use this enzyme to generate cytotoxins.[22] Exploiting the properties of this tumor specific enzyme also has the potential for identifying and sorting circulating tumor cells.[23]

NEWS BRIEFS

PREVENTING HARM IN HOSPITALS—A STILL UNSOLVED PROBLEM

A study just reported in the *New England Journal of Medicine* examined the question of the prevalence and trend in medical errors and harms in U.S. hospitals. The study found 25 harms per 100 admissions and 63% were considered preventable. A key finding was that the rates of overall and preventable harms did not change significantly between 2002 and 2007.[24] In a comment in *Journal Watch* (December 16, 2010), it was pointed out that this is not surprising since medical harms often result from errors in clinical reasoning and suboptimal diagnostic and therapeutic decision making, types of errors not addressed by new electronic technology to prevent prescribing mistakes or attempts to decrease hospital acquired infections. This comment implies that if the new approaches are having an impact, then the other problems are increasing in frequency.

WHAT IF ONE AIRBUS 380 CRASHED EVERY DAY?

Directly related to the above study is a report from U.S. government investigators reported by Reuters (November 16, 1010). Based on data in the Medicare database, it was found that in any given month, more than 13% of hospitalized, elderly patients, or about 134,000 individuals, have some sort of adverse reaction and 15,000 die from mistakes such as surgical errors and problems such as hospital acquired infections or severe hypoglycaemia. That is 180,000 deaths per year or about 500 per day, equivalent to one new double-decker Airbus 380 going down with all lost each day. The latter would for sure stimulate activity in the corridors of power. And this data just applies to elderly patients.

FLUORIDE IN WATER LINKED TO LOWER IQ IN CHILDREN

In a study just published in *Environmental Health Perspectives,*[25] evidence is presented that water fluoridation impacts childhood intellectual development. The study is significant because the investigators controlled for key confounding variables and also found lower IQ correlated both with fluoride levels in drinking water and fluoride levels found in children's blood. Two essentially equivalent villages were compared. About 28% of the children in the low-fluoride village scored as bright, or of higher intelligence whereas the figure was 8% in the high fluoride village. Mental retardation rates also differed with 6% in the low-fluoride village, 15% in the high fluoride area.

The director of the Fluoride Action Network commented in a press release (*PR Newswire*, December 21) that this is the 24th study that found this association and it is scientifically the strongest yet and is most suggestive of a cause and effect relationship. He also points to a report in 2005 from the National Research Council of the National Academies (US) that found the link between fluoride exposure and lowered IQ both consistent and plausible.

Since public health authorities appear to ignore this problem, the only simple solution is an in-home reverse osmosis system for drinking and cooking water. They are not that expensive, fit under many kitchen counters, and remove a vast number of other undesirable or dangerous substances commonly found in municipal drinking water. Fluoride-free toothpaste is also available in some drug stores and almost all health food stores.

MORE GOOD NEWS REGARDING CHOCOLATE

Frequent chocolate consumption has been found to dramatically reduce the risk of hospitalization or death from atherosclerotic vascular disease in older women.[26] For mortality or hospitalization due to

ischemic heart disease the risk reduction was 35%, heart failure, 59% and for finding carotid artery atherosclerotic plaques, 23%. Frequent consumers had more than seven servings per week. A "serving" contained approximately 1-5 g of cocoa. The authors comment that this study is consistent with one finding a 50% lower risk for cardiovascular mortality associated with consuming more than about 2 g/day of cocoa (average 4.2 g/day) and stratifies the benefits according to the various aspects of cardiovascular disease. Some special dark chocolate bars contain up to 50-70% cocoa, frequently termed cacao. Chocolate experts refer to the beans as cacao and the powder made from them as cocoa. It is very easy to get 1-5 g of cocoa per day and calories do not appear to be an issue. One popular American "special dark" chocolate bar has 230 calories per 50 g of chocolate with 50% cacao. The typical large bar weighs 100 g.

AIRWAY "TASTEBUDS"—AN ANSWER TO ASTHMA AND COPD?

Recent research from the University of Maryland School of Medicine has fond bitter taste receptors on airway smooth muscle tissue which can be targeted to open constricted airways such as experienced in asthma or chronic obstructive pulmonary disease (COPD).[27] In lay terms, these receptors can be called taste buds. Inhaled bitter tastants were shown to produce airway dilation in a mouse model of asthma that were much more dramatic than asthma or COPD medications currently in use. The authors comment that this newly discovered pathway can be exploited for therapy with thousands of known synthetic and naturally occurring bitter tastants. Unfortunately, natural bitter inhalants are of no interest to Big Pharma, and this may strongly hinder the development and especially marketing of natural inhalants which might have the advantage of harmless metabolites when absorbed after inhalation.

IT IS JUST THE COST OF DOING BUSINESS

According to Reuters and the Associated Press, the pharmaceutical giant GlaxoSmithKline announced in mid January that they will take a 4th quarter $3.4 (US) billion charge arising mainly from costs related to the investigation sales and promotional practices by the U.S. Attorney for Colorado. This after a $2.4 billion charge in July. At issue is the drug Avandia (see the November Newsletter) and charges include settlement of claims related to this drug. The 4th quarter charge effectively wiped out profits for that quarter.

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BRAVE NEW WORLD OF THE PSYCHO-PHARMACY AND THE ALTERNATIVES

William R. Ware, Ph.D.

PART I
THE MOTIVATION FOR SEEKING AN ALTERNATIVE

"If we wish to base psychiatry on evidence-based medicine, we run a genuine risk in taking a closer look at what has long been considered fact."
Emmanuel Stip, *European Psychiatry* (2002)[1]

INTRODUCTION

Based on what one is told by the media, the drug industry and many proponents of its psychiatric drug products, disorders of the brain are now well enough understood to permit successful, targeted drug therapy tailored to specific pathology and related symptoms associated with the diagnostic labels of depression, anxiety or the so-called bipolar disorders, and one must not forget attention deficit, hyperactivity, fear of social interaction, etc., etc. The list is long. But this ignores the unfathomable complexity of the human brain-mind system which is vastly greater than the most sophisticated computers it has helped develop. It ignores the views of many experts that most of what science and in particular medical science would like to know about how the brain develops or functions is still unknown. It ignores what appears to be the fact that any particular psychological disorder may have a number of causes, almost all currently unknown or poorly understood, and that some are addressed by the brain itself in the form of self-healing or a placebo effect that is probably stronger in this case than in many other disorders that afflict humans. It ignores the well-established fact that in a significant number of cases these disorders resolve over time with no intervention whatsoever. The above state of affairs has given rise to what critics point to as a large mythological structure with its well-defined dogmas, intense resistance to scrutiny or alternative views and wildly successful commercialization and marketing of psychiatric drugs. Modern drug-based psychiatry has even been described as possessing many features of a religion[2] and research in this area as exhibiting an "intellectual crisis."[3] The most serious and worrisome criticism is based on strong evidence that psychiatric drugs in fact act *only* by disabling the brain with the attendant potential for both transient and permanent harm.[4]

Before pharmaceutical drugs became the standard of care for patients with any of a large number of psychological complaints, psychiatrists hardly needed a prescription pad. Psychotherapy and behavior modification were the norm. Evidence of benefits from natural remedies, mainly based on vitamins such as high-dose niacin and vitamin C for schizophrenia, were ignored or actively opposed. As drugs targeting schizophrenia, depression, anxiety, attention deficit /hyperactivity disorder (ADHD) or the need to be "tranquilized" or get a good night's sleep or to enjoy social gatherings appeared in rapidly increasing numbers and variety, the psychiatry community suddenly became like real doctors—they now could treat their patients with patent medicines. The prescription pad replaced the much more complex and time-intensive process of psychotherapy, behaviour modification or simply helping milder disorders take their course, which could ultimately result in remission. These drugs also proved useful to the internist, general practitioner and even the pediatrician. The advent of powerful drugs targeted at brain chemical imbalances *never proven to be root causes or even initially present* was the beginning of a new era which can be seen today in full bloom in all its glory.

ISSUES WITH PSYCHIATRIC DRUG THERAPY

"The great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact."
Thomas Huxley (1870)

After the Second World War the phrase "better things for better living through chemistry" not only referred to synthetic plastics and synthetic fibers, insecticides etc., but also to synthetic chemicals designed for human consumption including as a major component, pharmaceuticals. In all of this the chemist was indispensable and served his or her masters very well indeed. Motivated by patent protection, the pharmaceutical industry aggressively addressed the drug discovery problem with synthetic chemicals, and there is probably no other area in this industry that has seen as many chemicals make it from the bench to the bedside than the psychopharmaceuticals. Along with this evolution came great "advances" in diagnosis of psychological problems and as a consequence their prevalence, with ever broadening definitions which came to include a number of mild behaviour patterns traditionally considered within the broad bounds of normal but now named disorders with the implication of cerebral pathology. Once fully developed, the new field of psychopharmatherapy had a pill, and frequently several, for almost every officially recognized mental disorder. The skill in marketing, the flexibility and cooperation of the regulatory agencies and the growth in sales have been utterly phenomenal.

Within the profession, views regarding the widespread use of psychiatric drugs by everyone from toddlers to elderly nursing home residents have become more and more polarized. At one extreme there is the mainstream view that these are wonder drugs developed to target what were believed to be chemical imbalances in the brain which cause such disorders as inattention, compulsive behaviour, anxiety, depression and more serious psychoses. The drugs are described as mainly correcting chemical imbalances related to serotonin and dopamine. This is the traditional view projected by the industry, in TV ads, in guidelines and in the positions of professional organizations associated with the practice of psychiatry. The benefits are promoted as evidence based and used to justify the widespread use both for approved indications and "off label" which refers to prescriptions for unapproved indications. What some describe as an extraordinarily cosy relationship has developed between many members of the profession and the companies in the business of making psychopharmaceuticals. This has had a profound impact on the success of marketing.

At the other extreme some members of the psychiatry profession as well as other observers hold diametrically opposing views. This view is not as well known to the general public. It is not a view the industry wants publicized and if taken seriously would threaten the very foundations of modern psychiatric drug therapy and an industry with demonstrated capability to generate billions in revenue. One of the most vocal members of this group of critics is Dr. Peter R. Breggin, M.D., a practicing psychiatrist who has written numerous scientific papers and in addition a number of books for the lay as well as for the medical audience. Some call him the conscience of modern psychiatry. Incidentally, he does not use psychiatric drugs in his practice except on rare occasions. His goal has been to promote a realistic view of psychopharmacotherapy and raise awareness of what he and others perceive as very great dangers associated with these drugs. His views are neatly summarized in his book *Medication Madness* by the following list of what he calls "marketing myths and the truth about psychiatric medication." Seven of the ten he presents are directly relevant to this review.

Myth: Biochemical imbalances are corrected by psychiatric drugs.
Breggin's position. These drugs do not correct biochemical imbalances, they cause them. He points to the mainstream *Textbook of Psychiatry* which admits that antidepressant-induced biochemical imbalances may cause increased suicidality. These drugs are developed precisely with the aim of causing chemical imbalances in the normal brain. No pre-existing biochemical imbalances have been identified in the brains of patients diagnosed with anxiety disorders, depressive disorders, bipolar disorders (depression and mania or the oscillation either between them or a normal state) or schizophrenia. Even the *Textbook of Psychiatry* admits that biochemical imbalances remain entirely unproven. These drugs force the brain to adapt and the changes, which are by and large harmful, can last long after treatment is terminated and lead to long-term disability. The severe reactions

associated with withdrawal confirm that these drugs cause significant biochemical imbalances and malfunction.

Myth: Psychiatric drugs do not cause permanent harm to the brain.
Example: Antipsychotic drugs cause what is called tardive dyskinesia (involuntary repetitive body movements that slowly develop), a disorder most have witnessed in individuals with Parkinson's disease. This indicates brain damage as do a number of studies that show these drugs kill or maim brain cells. There is growing evidence that stimulants given for ADHD and selective serotonin reuptake inhibitors (SSRIs) used to treat depression can permanently damage the brain's physical structure including shrinkage or boosting brain tissue growth and cellular damage, and can "rewire" areas of the brain that are important for thinking and feeling and controlling the autonomic nervous system. He quotes a 2005 press release from Johns Hopkins School of Medicine saying "It required a mere four weeks for Prozac to accomplish this "rewiring." Only the naïve and uninformed view the brain as fairly simple and reasonably well understood. Breggin concludes this section with "A principle to remember: Tampering with the human brain to influence human emotions and actions is not a good idea."

Myth: Small doses of psychiatric drugs are relatively harmless.
Breggin suggests that if a drug dose is large enough to affect the brain and mind, it is also large enough to cause serious dysfunction, including compulsive violence and suicide. He also points out something that quite probably is not widely appreciated. Up to 10% of the population have a genetic defect such that they lack fully functional liver enzymes necessary for the effective breakdown of many medications including the newer antidepressant drugs. This can result in a dangerous build-up. Taking multiple drugs simply aggravates the situation. Are all patients tested for this prior to being advised to take psychiatric drugs? Probably not.

Myth: In order to prevent suicide and violence, psychiatric drugs are necessary.
Breggin points to the extensive evidence in the literature and from case studies that indicate antidepressants cause rather than prevent suicide. Furthermore, no compelling evidence has been produced that these drugs reduce the suicide rate and the FDA, as of 2008, had not approved any drug for treating suicidal feelings or behaviour. As regards controlling violence, any drug that temporarily immobilizes or heavily tranquilizes an individual can prevent violence, but so does physical restraint.

Myth: Psychiatric disorders are diseases just like diabetes is a disease.
Breggin points out that comparing anxiety, depression, and mania to diabetes is often done and is false and misleading. In contrast to ordinary diseases, psychiatric disorders have no biological markers, no known physical causes and no rational physical [drug] treatments. Thus treatments are not actually for a real disease but they end up causing them.

Myth: Psychiatric drugs unmask underlying psychiatric disorders.
This is the argument used by the pro-drug advocates against the assertion that these drugs cause psychiatric disturbances. It is part of the justification for multiple drug use. Breggin argues against the unmasking hypothesis, mainly based on his extensive clinical experience where he has found no evidence of predisposition in cases with which he is familiar of what he calls medical madness.

Myth: Life-long psychiatric drug medication is necessary.
There are no life-long studies to back up this assertion. Most studies are very short-term (few weeks) with a large drop-out rate, and there are also very few studies on children. There is growing evidence that long-term use results in permanent, harmful effects. Children can be afflicted with tardive dyskinesia just as can adults.

The documentation for the above is extensive. The reader is referred to following sources, which are comprehensive and include extensive references to the peer-reviewed literature.

- *Brain-Disabling Treatments in Psychiatry. Drugs, Electroshock, and the Psychopharmaceutical Complex*. Peter R. Breggin, M.D. Second Edition. Springer Publishing Co., New York, 2008. An expensive book intended mainly for the medical profession but accessible for the most part to the educated layman. A definitive, modern treatment of the potential for harm.
- *Medication Madness. The Role of Psychiatric Drugs in Cases of Violence, Suicide and Crime.* Peter R. Breggin, M.D. St. Martin's Griffin, New York, 2008. Breggin's recent book for the lay audience. This book contains many fascinating case histories.
- *Anatomy of an Epidemic*. *Magic Bullets, Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America.* Robert Whitaker. Crown Publishers, New York, 2010. A just-published, comprehensive and scholarly book for the layman. Whitaker has an interesting chapter on "The Hunt for Chemical Imbalances" which reviews and supports the position that people with psychiatric disorders do not suffer from any known neurochemical imbalance.

To the above can be added the recent meta-analyses and studies concerning the efficacy and risk/benefit of antidepressants and antipsychotics, which yielded negative results. These include analyses of study sets which included unpublished and suppressed negative studies. The forced unearthing and use of unpublished studies is not new. Already in 2004 a meta-analysis which included unpublished or suppressed studies cast great doubt on the benefits of psychiatric drugs when compared to a placebo.[5] Further evidence of selective publication was presented in 2008 where when all studies submitted to the FDA concerning the efficacy of antidepressants were considered, 49% were negative.[6] A meta-analysis published in 2008 found that antidepressants were no better than a placebo in treating anything but the most severe cases and even in these cases, the efficacy was modest.[7] Other recent studies reinforce this doubt.[8-11] There is clearly a disconnect between trials and clinical practice.[12]

The obvious question then arises. Why is there a perception of benefit among the treated and those who are prescribing the therapy? The explanation Breggin offers is based on his belief that medication used in psychiatry actually disables the brain. The primary therapeutic effect is causing malfunctions of the brain and the mind which are then, among other things, misidentified as an improvement or benefit. Based on this, he evokes what he calls the *spellbinding* effect (*Intoxication anosognosia*). For example, the apathy or euphoria created by antidepressants is misinterpreted as an improvement in depression. In the case of antipsychotic drugs, the blunting of self-awareness and all emotions is seen as an improvement in the psychosis and the generalized sedation and suppression of brain function by the antianxiety drugs is seen a positive impact on anxiety. In fact, no specific improvements have taken place with regard to the underlying problem, but rather the brain has been partially disabled, which has resulted in an artificial change in the individual's mood, and at the same time rendering the patient less able to feel, perceive or express their underlying mental condition. These drugs impair both the ability to perceive the adverse effects of treatment and also the ability to appreciate psychological problems. Thus spellbinding is the natural result of treatment since drug therapy always impairs the activities of the patient's brain and thus the mind. Spellbinding also complicates if not invalidates the interpretation of studies since the patient is unable to provide a true evaluation of the results. Spellbinding may also account for the variation in study results and provide undesirable flexibility in interpretation. Breggin's book for the medical profession, *Brain-Disabling Treatments in Psychiatry,* contains a detailed, documented discussion of spellbinding and its consequences, as does his book *Medical Madness.* Finally, the perception of benefit may in some cases be based on a recovery or improvement that would have happened without treatment.[13]

While Bergin's view of the adverse impact of psychopharmaceutical therapy is to a large extent evidence based, this does not appear to be the case with the therapy itself as currently used, in spite of the fact that it is promoted as just that. Selective publication of trial results and its impact on the validity of meta-analyses is one of the problems.[6] Fraudulent trials are another issue. Also, subjects in pharmacological treatment trials of depression may not be generally representative of patients encountered in routine clinical practice.[14] Robert Whitaker also carefully develops and documents many of these problems in the 360 pages of his new book cited above. The book is hard to put down—spellbinding in the literary sense!

One age group of great concern is the elderly, especially those confined to nursing homes. Just the events over a number of years leading up to this transition from free living to nursing home care can produce psychological problems that may trigger the use of psychiatric drugs. The occurrence of spellbinding in this context is especially disturbing given these patients may be quite fragile. If this treatment causes tardive dyskinesia it may be ascribed to the development of Parkinson's disease. If it causes what passes for cognitive problems, it may simply be ascribed to aging. In the arsenal of psychiatric drugs are a number with a high level of utility for making life easier for those providing care, but the end result is not pretty.

CHILDREN—A SPECIAL CASE FOR CONCERN

You wonder all the time: are you helping or harming your child?"
A mother quoted by Robert Whitaker[15]

Children and adolescents are a special concern in this context. They are not able give informed consent. Psychiatric drugs are being used over a wide spectrum of ages, frequently off-label, while all the young patients are still undergoing active and critical mental development. Even toddlers are being medicated. Parents tempted or advised to put a child on a stimulant (e.g. Adderall, Desoxyn, Dexedrine, Focalin, Ritalin, Concerta, Daytrana, Vyvanse—note the zoo) should pay the high price and purchase Dr. Peter Breggin's book *Brain-Disabling Treatments in Psychiatry.* Then read chapter 11 titled *Stimulant-Induced Brain Damage, Brain Dysfunction and Psychiatric Adverse Reactions*. Breggin is particularly well qualified to comment on this subject. He has published papers on childhood stimulation for ADHD and its problems and has been involved in FDA panels debating the extent to which the public and physicians should be warned about what he views as frightening dangers associated with these drugs. The magnitude of the problem is clear. As of 2006, 4.5 million children aged 5-17 have been diagnosed with ADHD and over 56% were treated with medication.[16] Even higher estimates of the treatment prevalence can be found.

Parents confronted with pressure to medicate their children with psychiatric drugs should also read the appropriate chapters in Peter Breggin's book *Medical Madness. The Role of Psychiatric Drugs in Cases of Violence, Suicide and Crime.* This is basically a case history book and a number of chapters relate to experiences of children and adolescents. Many of these histories are both powerful and quite disturbing, but it is this reality that parents must face when called upon to exercise their responsibility as surrogate informed consent providers for underage children. Parents with children on stimulants, antidepressants or antipsychotic drugs will find this book especially unsettling, as the subtitle suggests. ***If prompted by reading or non-professional advice to withdraw a psychiatric drug from a child, do it only under careful supervision from a trusted physician. Sudden withdrawal can precipitate a disaster.***

There appears to be a serious issue with overdiagnosis of ADHD. Diagnosis is strongly influenced by classroom observations that lead ultimately to labelling and treatment. These observations are based in part on subjective comparisons across children in the same grade of school. Two papers recently addressed the problem of the greater likelihood of being labelled with ADHD if a child is young for their grade rather than old for their grade, a problem that arises because of the use of an age cut-off for admission. Many of these children do not have ADHD, they are merely acting their age![17,18] This is a serious issue because the label sticks and many are then medicated long-term.

Almost all studies involving either adults or children are very short term. Commenting on this in an article posed November 5 in the *Huffington Post*, Dr. Ronald Ricker, a psychiatrist and founder and director of the Linden Center, points to an ad in *Clinical Psychiatry News*, which concerned the new drug Intuniv for ADHD. The ad indicated that two clinical trials were run prior to FDA approval. One lasted six weeks, the other nine. He comments, "I think our children deserve a vastly more through evaluation by the FDA prior to approval of this or any drug. How one determines the actual usefulness and safety of a new drug in 6 to 9 weeks of clinical trials completely escapes me."

The only long-term randomized trial of stimulants focused on children looked at outcomes of short-term (14 weeks) intensive stimulant therapy against a placebo or behavior therapy or both and then conducted long-term follow-up. The study found that the end of 8 years there was no evidence of benefit for the use of stimulants in this age group as compared to non-drug interventions.[19] In addition, the short-term benefit seen in the classroom, which is a significant part of the basis for regulatory approval and popularity among prescribers, parents and teachers, is based on the capacity of stimulants to suppress all spontaneous behaviour and to enforce obsessive behaviour. While this may solve a classroom problem, critics regard this as a highly undesirable result if it continues for any length of time. Also, there was no evidence of improvement in learning or educational performance associated with stimulant therapy[4,19]

Some studies directed at children may have been designed in a manner akin to fraud and produce meaningless results. A psychiatrist employed by a major drug company has pleaded guilty to committing research fraud in trials of an antidepressant where the subjects were children. She was accused by the FDA of enrolling children in a clinical trial even though she knew they did not have a major depressive or obsessive-compulsive disorder, the condition under study, and is serving a 13 month sentence in prison. She simply falsified records and psychiatric diagnosis. According to media reports, she was paid $5000 for each child enrolled.

Parents probably not generally appreciate it, but all but one ADHD medication is a U.S. Drug Enforcement Agency Schedule II drug which translates to being a category considered to have strong potential for abuse or addiction. Included in Schedule II are opium, morphine and cocaine. The one exception, Strattera, is marketed as a non-stimulant, but Breggin considers it more deadly than the Schedule II drugs.

The most serious questions involve the impact of stimulants on brain development and adverse side effects that seriously alter personality and attitudes. The common belief is that very little if anything is known regarding the impact on the developing brain.[16] However, Breggin deals at length with this aspect and provides a number of examples strongly suggesting the potential for long-term brain damage and even cancer. Animal studies provide overwhelming evidence of profound risk. Furthermore, the adverse effects he lists and documents, some of which appear shortly after starting on medication, are shocking, given that stimulant drugs are so widely prescribed. He classifies them as impacting brain and mind function, cardiovascular function, gastrointestinal function, endocrine and metabolic function, and withdrawal and rebound. Over forty specific harmful effects are listed[4] (Table 11.2). If in the first place the diagnosis was by and large nonsense, then the situation is even more shocking. In addition to Breggin's book, the book by Robert Whitaker mentioned above is highly recommended for a comprehensive and well documented view of the special case of children (see chapters 11 and 12).

Children are not only being given stimulants for ADHD, many of which are actually amphetamines, they are prescribed antidepressants and antipsychotics. Antipsychotic treatment of children ages 2 to 5 (not a misprint!) doubled between 1999-2000 and 2007. The disorders treated by this class of powerful drugs were pervasive developmental disorder or mental retardation, attention deficit/hypertension disorder (ADHD), the disruptive behaviour disorder and bipolar disorder.[13,20] David Healy points out that new generation antipsychotics, which are as dangerous or more so than the original drugs are being given to preschoolers in North America to treat bipolar disorder while most of the rest of the world does not even believe this disorder really happens in children. For fifty years antipsychotic drugs were historically viewed as too dangerous to use outside secondary care and were largely restricted to those with chronic psychotic disorders where the benefits justified the hazards of treatment.[13] A systematic review in 2004 which included published and unpublished (suppressed) studies found that risks of SSRIs outweigh benefits for children diagnosed with depression.[5] A meta-analysis published in 2008 found no benefit associated with psychiatric drugs measured in terms of response for children under 12 years of age.[9]. While some evidence exists of benefit from fluoxetine in the treatment of major depression in children, the benefit vs. a placebo was "modest" and not seen in all efficacy variables nor within all types of statistical analysis.[21] Studies of long-term effects were not done. But as discussed above, benefit appears to be an illusion, in part

caused by spellbinding.[4] The simple fact is that pediatric therapy with antidepressants or antipsychotics is not evidence based but rather, to quote David Healey, "eminence-based medicine."[13] Healy and Le Noury, in their scathing critique of the treatment of pediatric bipolar disorder, which they describe as an object of study in the creation of an illness, comment "…a number of forces appear to have swept aside traditional academic scepticism with the result that an increasing number of children and infants are being put on cocktails of potent drugs without any evidence of benefit."[22]

Another serious issue on the horizon that impacts children involves schizophrenia, a disorder that most frequently presents in the adolescent years or the 20-30 age group. There is currently considerable research and interest in identifying the early markers, either genetic, biochemical or psychological, that predict this disorder. The motivation is that this will lead to therapy, including a drug intervention protocol that would prevent progression.[23] However, psychiatric drug therapy could be a prescription for disaster. As mentioned above, brain development is still occurring during adolescence. The neurological and physiological aspects of schizophrenia are poorly understood at best. In fact, partly for this reason some major companies have recently decided to pull out of psychiatric pharmacology altogether.[24] Long-term (10-20 years minimum) studies of adverse effects are out of the question for any company in business to make money. The short-term nature studies that lead to drug approval in this context should be sufficient cause for parents to reject drug therapy or advise their older children that this is unwise. Consider Breggin's position. Tinkering with cerebral biochemistry with drugs appears to produce only damaged brains.

Finally, it is interesting to consider a private institution in California that among other things provides a home of last resort for severely damaged children. When they arrive, they are typically on several psychiatric drugs, firmly believe they can't live without them, and in many cases have been reduced to the zombie state. The approach taken by this institution is by Robert Whitaker.[15] It involves gradual withdrawal from all drugs, a process that initially is difficult and challenging but when successful reclaims the individual.

RISK OF ADDICTION AND SUICIDE

Modern terminology seems to prefer dependence to addiction. Whichever term is used, psychiatric drugs that become addictive present a very serious problem, since there is frequently the need to continuously increase the dose level, which in turn increases the severity of side effects. Attempts to withdraw are accompanied by many of the same problems experienced by narcotic drug addicts. The problem of addiction arises principally with the stimulants such as Ritalin used to treat ADHD. The scenario plays out as one would expect from narcotic addiction. Consider the addicted adolescent. Parents and the doctor become alarmed and attempt to withdraw the drug. This drives the addict to stealing, forging prescriptions, finding illegal sources, etc. The prescription drug has become like a typical street drug, which is not surprising given that most ADHD drugs are amphetamines or behave biologically in the same way as this type of drug. As the patient spirals down into the depths of addiction, suicide becomes a real possibility. By then neither the doctor nor the parents have any control or way of dealing with the problem aside from temporary and perhaps forced confinement to a rehab center. In his book *Medication Madness*, Peter Breggin provides case histories that end in suicide. The patients were teenagers. In all fairness, it is true that many children and adolescents take stimulants without having to deal with addiction. However, judging the risk prior to the first prescription is probably impossible.

The risk of suicide is not restricted to stimulants used to treat ADHD. Both antidepressants and tranquilizers also have this unfortunate side effect and for antidepressants it is a major issue which requires black box warnings, the highest level of concern, mandated by the FDA. Incidentally, it is not uncommon for treatment with stimulant drugs to lead to antidepressant therapy. *Medical Madness* contains three case histories where antidepressants were associated with suicide, in either an adolescent or adult. Suicide is simply one manifestation of the potential for worsening mental conditions associated with this class of drug.

Breggin also points out in *Medical Madness* that it is impossible to diagnose underlying psychiatric disorders when a patient is abusing street drugs. Drug abuse or addiction mimics every possible psychiatric problem from ADHD to bipolar disorder and brief psychosis to anxiety disorder and sociopathic personality disorders. If the drug abuse or addiction is resolved, then it is frequently observed that the patient no longer fits into any psychiatric diagnostic category except substance abuse in remission. The point would appear to be that one does not treat addiction to or abuse of street drugs with psychiatric drugs and to do so may only make matters worse. Breggin also makes readers aware of the research indicating that a long-term study of children treated with Ritalin found that they have a seven-fold increased risk of using cocaine as a young adult. This strengthens the argument that stimulants are implicated in long-lasting abnormalities in the brains of children. Also he mentions cases where young patients who had their Ritalin stopped turned to cocaine which turns out physiologically to be the best substitute.

VIOLENCE

Medical Madness contains case reports of serious violence associated with psychiatric drugs but only very recently has this phenomenon been systematically studied. In a paper published in *PLoS One* (December 2010), Moore *et al*[25] appear to be the first to subject government adverse event reporting databases to an analysis with this in mind. Their method identified drugs which were strongly disproportionally reported. Their method corrected for extent of clinical use, reporting rate, size of the patient population treated, and the magnitude of international sales. Violence was defined for the study as homicide, physical assault, physical abuse, homicidal ideation or a violence related symptom. Suicide and spousal abuse were excluded, as were aggression, belligerence and hostility. The results were impressive. The overwhelming majority of drugs do not stand above the crowd in terms of this approach to measurement of the prevalence of violence. But based on their data, the psychiatric drugs look like weeds standing almost alone above a field of grass and some of them are very large and impressive.

While varenicline (Chantix or Champix), a very heavily advertised aid for smoking cessation had the strongest association with violence by every measure, 11 antidepressant drugs, 6 sedative/hypnotics and three ADHD drugs were identified as having important or very strong associations with violence. The evidence was weaker or mixed for antipsychotic drugs and absent for all but one anticonvulsant/mood stabiliser. Psychiatric drugs that increase the availability of serotonin and dopamine dominated the list. This is also how varenicline works. Widely used mood stabilizers, which gave no indication for concern, do not function through this mechanism. It is interesting that many of the drugs implicated in violent behaviour also carry warnings regarding suicide, especially antidepressants. Among the ADHD drugs, amphetamines and atomoxetine ranked with the worst antidepressants but methylphenidate (Ritalin) was only about half as dangerous. This study did not look at multiple drug use, which might make the picture more alarming.

These results illustrate the large human variability in reactions to the brain altering actions of psychiatric drugs since millions are on these drugs but the incidence of violence is small. But it is obviously really bad when it happens. However, it is widely appreciated that the vast majority of adverse reactions go unreported. Some estimates are as high as 98-99%. However, this probably would not change the picture—higher grass, much higher weeds. These drugs will continue in use for the foreseeable future, and the only hope is that clinicians will become more aware of the problem, look for early signs and encourage those close to the patient to do likewise. This paper is in the public domain. Google T. J. Moore and PLoS One.

A CHALLENGED INDUSTRY

In a commentary in the journal *Nature*, Allison Abbott presented interesting insight into the challenges faced by the psychiatric drug designers.[24] The development of psychiatric pharmaceuticals started over 50 years ago. A popular antipsychotic at that time was perphenazine, but its use was accompanied by horrible side effects. Later a new class of antipsychotic drugs, called second-generation, was introduced and presented as causing fewer side effects, especially associated with

uncontrollable body movements. But some questioned that this new generation was really superior and a large government sponsored trial (CATIE) was carried out in the U.S. and reported in 2005. The results came as a shock to the profession and the industry. The trial made it clear that the new therapies barely differed from the old, as represented by perphenazine. The new drugs were just as effective in controlling delusions and hallucinations, but patients taking the new drugs remained confused, socially withdrawn and lacked drive, just as they did on perphenazine. Side effects associated with the new drugs were so bad that three-quarters of the trial patients dropped out of the CATIE trial during the 18 months of treatment, regardless of which drug they took.

The results of CATIE made it clear that it was time to go back to the drawing board. Several giant pharmaceutical companies declined to accept the challenge and have left the field altogether.[24] Among other problems, the real challenge was in understanding the system with which they were dealing. As Thomas Laughren, the FDA's director of psychiatric drugs, pointed out, "we don't even understand schizophrenia at the biological level."[24] Attempts to regain momentum and achieve real success have been mainly based on enhanced cooperation and information exchange between interested parties including academic groups, Big Pharma, and small biotech firms. For example, one consortium has developed a nose operated rodent touch-screen technology to facilitate animal studies. This is not an attempt to be funny. Some might say that this does not represent much progress in solving the fundamental problem that the brain—mind system is so complex and the networks so intertwined that one needs to be pathologically optimistic to see any light at the end of the drug discovery tunnel.

We are talking about an industry that had sales just for schizophrenia drugs in 2007 of $10 billion on the basis of 55 million prescriptions. By 2007 essentially the entire market was in the second generation antipsychotics. It is estimated that the disease affects about 1% of the world's population. That statistic in itself is food for thought. In 2009 the U.S. spent about $170 billion on mental health services with the tax payer picking up about 60% of the tab.[15] A major component is medication.

THE BOTTOM LINE

Life circumstances can produce depression, anxiety, insomnia or some other reaction to the external circumstances. Children may exhibit behavioral problem, as they always have. These are normal human reactions or behaviours in many but of course, not all cases. Also, there are those exhibiting serious psychological disorders, some presenting crisis situations. Traditionally, a variety of non-drug approaches was used and many individuals returned to normal, or the individual simply dealt with the problem in their own way and most recovered. But in the modern era, the symptoms are viewed as suggesting brain pathology, and a disorder diagnosed with the aid of the current bible, the *Diagnostic and Statistical Manual of Mental Disorders,* called the DSM—IV. Disorders are then frequently "treated," mostly by medication but much less frequently with non-drug approaches. In some cases the patient self-diagnoses a problem and convinces the family physician to prescribe some pills. The medication produces psychiatric effects, in some cases almost instantly, in other cases after longer use. These may be initially viewed as an improvement, but as time passes, this view may change and the patient's condition may appear to worsen. In spite of no justification, this is viewed as uncovering disorders already present at the initial diagnosis rather than the result of the action of the drug. The medication is seen as not working adequately, or not up to the real challenge, or not being given at an adequate dose, so the dose is increased and new drugs may be added. Problems may become more severe and are interpreted as indicating the need for additional drugs. Antidepressants may replace or supplement stimulants used for ADHD. The choice available within each class of drug is impressive. In this field, so-called polypharmacy appears to be the rule rather than the exception. But there is ample anecdotal evidence that just increasing the dose of the original single drug can for some patients rapidly bring about disaster, including violence and suicide, and this is in individuals with no prior indication of violent or suicidal tendencies or thoughts. When changes in medication make the patient worse, the answer is to play with dose and try more drug switching. At this point, the typical patient is on 3 to 5 drugs, which confirms the reality of a downward spiral.

The real problem, which started with the first prescription, perhaps for symptoms that were relatively mild, is not addressed but amplified. The patient has gone from being mildly symptomatic to disabled. Few following the mainstream standard of practice apparently ever stop to consider that this downward spiral is caused by the drugs prescribed or that side effects are a misnomer and really reflect the principal drug action.

The end result is apparently highly variable but the minimum long-term impact generally results in an individual who is significantly mentally, socially and emotionally altered *without in many cases being aware of what has really happened*. In some cases the individual becomes violent, commits crimes without even being aware of doing something wrong, tries or succeeds in committing suicide, injures or kills family members, co-workers or even strangers, and ends up either institutionalized, incarcerated, under the control of the courts or on disability assistance. Repeatedly it has been pointed out that most individuals involved in mass shooting episodes were taking psychiatric drugs. Nevertheless, what ever happens, frequently medications are continued if not increased in number or dose, or both. In many cases, the notion is not even entertained that the problems were started and caused by the initial drug treatment and that everything done subsequently simply exacerbated the problem.

It is the brave institution or physician, when confronted by patients "at the end of the road," that steps outside the mainstream and tests the drug elimination hypothesis by gradual drug withdrawal of all psychiatric medication. Some might view this as malpractice—a radical departure from the standard of care. Yet this may well be the only approach offering hope of recovery and a return to normal. The brain damage at this late stage in the therapy may be so extensive that recovery can only be partially achieved even if all drugs are removed. For case histories supporting the above picture in vivid detail, read Peter Breggin's book *Medication Madness.* The reader is warned than most cases he describes do not have happy endings and in each case history, generally more than one life is forever altered. As Breggin puts it, "Medication madness cuts a wide, deep swath of misery through the lives of family and friends." However, a balanced view is necessary. Obviously not everyone on psychiatric drugs by any means suffers from gross side effects described in the above scenario. It is not even clear that anyone knows the real numbers, and there are many degrees of seriousness and disability involved. Those going through life spellbound by drugs do not even know what has happened or why.

The view presented in the books cited above is very far removed from the mainstream. The big picture, which is one of significant long-term failure and harm for a significant number of those "treated" with drugs is in a blind spot and ignored aside from the occasional editorial and commentary in the peer-reviewed literature. There seems to be a problem with denial, of missing the big picture. The campaign to convince both the profession and the general public that a wide variety of psychological symptoms, many common to everyday life, in fact have a pathological (biological) origin in the brain, has been extraordinarily successful. As well, the notion that modern pharmaceutical science has the answer in safe and effective pills is now widely accepted.

This may seem like a long prelude to a review on alternative approaches, but the above perspective is essential to provide an incentive for individuals who have psychological problems to consider the contrarian evidence. The risk that psychiatric drugs may only make matters worse and result in permanent harm should be of paramount concern. The importance of seriously considering alternatives extends from individuals to parents under pressure from schools or physicians to medicate children with psychiatric drugs and to children watching their elderly parents becoming excessively medicated zombies through the use of psychiatric drugs.

If the standard of practice changed to employ mostly one or more of the various forms of psychotherapy, this would overwhelm the psychiatric community, might find many uncomfortable with providing such treatment and would be an admission of operating for several decades with a false paradigm. However, some psychologists also engage in non-drug therapy. Another very important issue involves looking for common medical disorders that trigger psychological problems. The most prominent are diabetes and thyroid gland dysfunction. Finally, there is diet which can induce psychological problems through allergies to certain proteins, reactions to neurotoxins commonly

masquerading as food additives, excessive sugar intake, or last but far from least, through micronutrient (vitamin and mineral) deficiencies. The documented benefits of micronutrient or thyroid intervention in this context suggest that while biochemical imbalances of the sort that modern psychiatry postulates, e.g. involving serotonin or dopamine, have never been demonstrated prior to psychiatric drug treatment, there can be important imbalances associated with hormones and as well the micronutrients which supply essential cofactors for the myriad of enzyme controlled reactions that are essential for a healthy brain.

Next month in Part II we will explore the alternatives open to those who say no to psychiatric drugs, either for themselves or for their children or others under their care.

DISCLAIMER

The information presented in this review is not intended to be medical advice nor should it be regarded as such. The reader is also advised that stopping taking psychiatric drugs is associated with significant risk and that withdrawal can be very dangerous and should be carried out only under the close supervision of a medical professional. Please consult your healthcare provider if you are interested in following up on the information presented in this review.

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