**Doctors and medicines**

*A problematic* *and dangerous combination*

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Although we have many good and life-saving drugs, medicines are increasingly seen as a major cause of death in western countries. We have seen many examples of drugs that have killed thousands of patients, like rofecoxib, rosiglitazone and benfluorex. Most of the indications were for non-life-threatening or everyday complaints. A major problem related to this is that medical doctors hardly learn anything about epidemiology, methodology and statistics. Therefore, they are vulnerable for the marketing influences of the pharmaceutical industry. Doctors are not taught that there is not much difference between a drug and a poison. Furthermore, medicines are released into the market when they work statistically significant better than placebo. What we need are medicines that give a clinical relevant effect so that patients feel and get better.

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**Introduction**

The advance of neoliberalism in Western countries has been accompanied by the government's resignation from various social sections. The consequences are particularly noticeable in health care and medicine. In academic medicine, most departments and professors have established links with the pharmaceutical industry. As a result, the importance of patients no longer prevails, but that of shareholders. This has also led to an unbridled belief in medication, there is a pill for every ailment and doctors prescribe a lot of medicines. However, drugs are increasingly cited as a third cause of death after cardiovascular disease and cancer and global excessive drug use is increasingly related to declining life expectancy in the United States and a stagnant one in the European Union.1 Tis is despite the fact that we also have very good and important drugs that can be life-saving, like antibiotics.

**Efficacy and safety guaranteed by regulating authorities?**

In the 1960s, the West-German manufacturer Grünenthal brought *thalidomide* (Softenon®) to the market, intended for the treatment of nausea and sleep disorders in pregnancy. Softenon was found to cause severe birth defects, the most prominent of which are missing or heavily shortened arms and legs (phocomelia). The Softenon affair accelerated actions initiated in Western countries to strengthen drug supervision. Regulating authorities were set up. In the Netherlands, the Medicines Evaluation Board (CBG-MEB) was established. In the United States the Food and Drug Administration (FDA) and later in the European Union the European Medicines Agency (EMA). Agreements were made on the research data that manufacturers had to provide to show that their drugs were working and are not too dangerous. For example, they had to show how their medicine works in the body (pharmaco-dynamics), how it is absorbed, distributed, processed and excreted (pharmacokinetics), and had to conduct animal research into side effects. Then phase I to IV research had to be carried out. Phase I is done in a small number of healthy volunteers to examine toxicity in particular, Phase II in a limited number of patients with the condition for which the drug is intended, Phase III in large numbers of patients comparing efficacy and side effects with placebo, and phase IV after the market introduction to investigate how the drug is used in practice. This quickly inclines you to think that the control and safety of medicines are in good hands. Politicians, doctors, pharmacists and patients could be reassured. But is that justified?

**Insufficient education in epidemiology, statistics and** **pharmacotherapy**

Doctors have received virtually no education in epidemiology, methodology, statistics and pharmacotherapy and therefore they are sensitive to marketing and advertising by the industry. That translates into non-rational prescribing, and in recent decades we have seen what this can lead to. The anti-inflammatory *rofecoxib* marketed as a safer alternative to medicines such as *ibuprofen*, *diclofenac* and *naproxen*, was taken off the market after four years because it caused heart attacks. It killed about 120,000 people.2 The drug was intended for the treatment of symptoms of osteoarthritis but was quickly prescribed off-label as a painkiller for all sorts of other symptoms. At the beginning of this century, the antidiabetic *rosiglitazone* was promoted with the slogan that it would reduce the complications of diabetes, such as heart attacks. Ten years later it was taken off the market because it achieved the exact opposite, namely heart attacks. The drug killed more than 47,000 people.3

Medicines with unproven efficacy and unknown side effects continued to enter the market. *Daclizumab* (Zenapax®) was marketed in 1999 to prevent rejection reactions after kidney transplants but was taken off the market by the manufacturer in 2009 for commercial reasons. There would be no safety concerns, the manufacturer communicated. The drug was introduced again as Zinbryta® in 2016 to treat multiple sclerosis.4 Registration studies already showed that the drug had serious and sometimes fatal side effects. In 2018 it was taken out of the market due to serious side effects and deaths of multiple patients.4 In France, a legal process is currently being pursued against manufacturer Servier, producer of *benfluorex*, a weight-losing drug for patients with diabetes. It was estimated that this drug killed several thousands of people and destroyed the lives of nearly 10,000 people due to serious heart and lung problems.5

**Medicine or poison?**

In the education for medical doctor, students are no longer taught that there is little difference between a drug and a poison. Many medications have a narrow therapeutic width and if one doses too high, serious side effects can occur. Also, many medications in overdose are deadly. Basic knowledge of poisons is lacking in doctors. In the consulting room there is hardly time to properly consider the balance of efficacy and side effects of an intended drug treatment. A recipe is written quickly at the end of a consultation. Doctors miss the notion that drugs can be deadly. As a result, this is not reflected in the death statistics because doctors do not consider a relationship with the use of medicines when filling them out.

**Medications work statistically significantly better than placebo**

An important point that receives far too little attention in the training for medical doctor and also after that is the fact what it actually means that a drug works. Pharmacology describes mechanisms of action, presents theoretical models and describes receptors, underpinning their effect. However, the studies comparing a drug to placebo refer to something else. In this, the manufacturer must demonstrate that its agent has an arithmetically better effect than placebo, a statistically significant effect. These are the well-known asterisks in scientific publications: \*P<0.05, \*\*P<0.01, \*\*\*P<0.001. The theory about this was developed by Ronald Fisher.6 Fisher was engaged in crop breeding a century ago and faced the question of when the yield of a new crop was actually better than the previous one. He reasoned that an additional yield of 5% is statistically significant.

A drug thus works statistically significantly better than a placebo if it has an arithmetically better effect. And if a manufacturer can demonstrate such an effect in two studies and the drug does not have too serious side effects, then the manufacturer gets a commercial license and can market its drug. With this, we have advanced from a pharmacological explanation of the action of a drug to a statistical explanation for its mode of action.

**Statistically significant or clinically relevant**

So far, nowhere has been asked what the patient is experiencing. For Fisher, it was enough to establish that a new crop had better yield, he didn't have to ask what the crops felt. But this is important in medicine and for patients. It will not bother a patient if he knows that a drug has an arithmetic effect on a particular complaint or condition, he wants to know if he is going to feel better.

I'm giving an example of antidepressants. A manufacturer must show for registration that its new antidepressant works better than placebo in reducing the severity of depression. That severity is measured with a questionnaire, such as the Hamilton Depression Rating Scale.7 The scale ranges from 0 (no complaints) to 52 (very serious). On average, in studies, patients with severe depression have a score of 20, both in the placebo-group and the antidepressant-group. During the study, usually six to eight weeks, due to the favorable natural course of depression, the severity in the placebo-group will decrease to 13 and in the antidepressant-group to 12. If there are enough patients in such a study, several hundreds, then a difference of 1 point on the Hamilton scale is sufficient to demonstrate an arithmetic effect. But there is no doctor or patient who can perceive such a difference of one point. If a patient really wants to experience an effect, at least a difference of 3 points must be made, as British guidelinemakers8 have devised but independent researchers believe it should be 7 or 8 points9. We speak of a clinically relevant effect, because the patient really indicates that he feels better. But a clinically relevant effect is not an requirement for getting a marketing-authorisation for antidepressants.

One would like that doctors are able to distill the effects of medicines from scientific articles discussed above and to adequately inform their patients about this. But they are not taught that during their education. As a result, they are sensitive to marketing and advertising and they are at the mercy of guidelines. The latter are increasingly co-drafted by doctors with financial conflicts of interest with manufacturers and it is well known what that means for the independence of the opinions contained in those directives.

**Reflection**

The developments mentioned have led to a shift to the background of important principles in medicine like *In dubio abstine* (in doubt refrain from treatment) and *Primum non nocere* (first do not harm). Some have seduced this into statements such as "Trust your doctor but don't trust his medications." 10 Because doctors have far too little knowledge of medicines, the prescribing policy, i.e. writing prescriptions, should be drastically revised. It is unacceptable for people to die from the use of medications, especially for everyday and non-life-threatening symptoms, and doctors do not realize that this may be linked to the use of those drugs.

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**References**

**1.** [https://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality\_and\_life\_ expectancy\_statistics#Life\_expectancy\_at\_birth\_increased\_in\_2017\_only\_for\_men](https://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality_and_life_%20expectancy_statistics#Life_expectancy_at_birth_increased_in_2017_only_for_men)

**2.** <https://www.drugwatch.com/vioxx/>

**3.** Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010;304:411-8.

**4.** Anonymous. Daclizumab: deaths due to unjustified marketing authorization [editor’s opinion]. Prescrire Internat. 2018;27:175.

**5.** Anonymous. The Mediator disaster: So much time wasted, so many lives destroyed. Prescrire Internat. 2019;29:303-5.

**6.**<https://www.britannica.com/biography/Ronald-Aylmer-Fisher>

**7.** Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.

**8.** [www.nice.org.uk](http://www.nice.org.uk)

**9.** Moncrieff J, Kirsch I. Empirically derived criteria cast doubt on the clinical significance of antidepressant-placebo differences. Contemp Clin Trials. 2015;43:60-2.

**10.** Gøtzsche P. Deadly Medicines and organized crime. London: Radcliffe Publishing, 2013.