



## ISDB 2019 Update of activities and Newsletter

Welcome to the first ISDB newsletter of 2019. On 10-12 October 2019 the next General Assembly will take place in Paris and is organised by La revue Prescrire, details on page 2. As has been communicated many times already, the major topic to be discussed is the way ISDB bulletins have arranged their policy on Conflict of Interest (CoI) following agreement of the ISDB CoI statement in Leiden in 2016. As a reminder of this major issue, the items to be implemented by full members are printed on page 3. Those members who already fulfil to the new policy criteria are kindly asked to inform the president of this in detail.

We are very happy to announce that we have two new members. From Great Britain the organisation led by David Healy, RxISK.org, has joined us as an associate member. Healy is a well-known investigator of psycho-active drugs and is especially well informed on the side effects of drugs. From India Drug Action Forum - Karnataka (DAF-K) joined the Society as an associate member. Both new associated members introduce themselves on pages 4 and 7.

The Clinical Trials Working Group of Nuria Homedes from the United States, is working hard on their issues but no news is currently available. As the Cochrane Collaboration is facing tremendous trouble there is nothing new to mention on how to include Clinical Study Reports in their reviews.

Again we ask all members to check whether the contact details for their organisations on the website are correct. The expulsion of Peter Gøtzsche from the Cochrane Collaboration and the possible subsequent dismissal from the Rigshospitalet in Copenhagen gave rise to an enormous protest from many prestigious organisations and prominent researchers. ISDB wrote a letter to the Danish Minister of Health, see page 10.

Finally, on pages 11 to 18 of this Newsletter you will find 5 articles reprinted (with permission) from bulletins of full and associated members. These contributions come from La revue Prescrire (France), NoGracias (Spain), Therapeutics Initiative (Canada), MedCheck (Japan) and Arznei-telegramm (Germany).

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# ISDB General Assembly Paris 2019

La revue Prescrire is glad to host the next General Assembly in Paris (France). This will be a wonderful opportunity for Prescrire staff to meet colleagues from around the world, and for you to visit our office and the ISDB library, maintained by Minata Traoré at Prescrire since the creation of the society.

All members are kindly asked to sent proposals for the meeting to the Committee.



**Save the date:**

**Thursday to Saturday  
10<sup>th</sup> to 12<sup>th</sup> October 2019**

**Location:** Prescrire's meeting rooms, not far from Prescrire's offices in Paris.

**Address:** 68-70 Boulevard Richard Lenoir. The premises are located in the 11th district near Place de la Bastille, le Marais, Picasso museum.

More information about hotels and logistics will follow in due time.

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## ISDB Committee

The ISDB Committee currently consists of seven members. The last Committee meeting was held in Utrecht, the Netherlands, last year (reported in the previous issue of this Newsletter). The next meeting of the Committee is scheduled to take place in May 2019. The membership of the Committee for a new 3-year period (2019 - 2022) will be elected at the General Assembly in Paris in October 2019.

### ISDB Committee members:

- Christophe Kopp (France)
- Jörg Schaaber (Germany)
- Dick Bijl (President, Netherlands)
- Maria Font (Italy)
- Luis Carlos Saiz Fernández (Treasurer, Spain)
- Benoit Marchand (Ecuador)
- Ciprian Jauca (Secretary, Canada)

Rita Kessler (Prescrire's lobbyist for the European Parliament) is seated between Christophe and Jörg.



# Special attention to: Conflicts of interest

## Introduction

The new ISDB-policy on conflicts of interest (CoI) that has been approved in the Extraordinary General Meeting in Leiden 2016 and has been communicated already several times to you.

The new policy applies immediately for all new ISDB members.

Existing members have been given a three-year transition period, starting June 2016, to comply with the provisions of the new rules. So, during the General Assembly in Paris in October 2019 bulletins will be invited to show how they have implemented this policy.

We hope that all members will be represented there, but those who cannot attend the meeting are asked to submit their experience in writing and also make sure that their websites reflect how they implemented the new conflict of interest policy.

Here is a small recap of the main changes related to the definition of conflicts of interest: the independence of the editorial team and the organizational structure.

## Definition: Conflict of interest with the healthcare industry

Any financial or advisory relationship (paid or unpaid) with the pharmaceutical industry or related healthcare products industry (e.g. medical devices or diagnostics), including the conduct of industry funded clinical trials. Declarations of conflicts of interest must cover the last three calendar years. Members may use the CoI-forms provided by ISDB or their own forms as long as they cover a similar set of questions.

## Independent editorial team

Members of the editorial team must be free from conflicts of interest with the healthcare industry. Their conflicts of interest declarations should be updated annually and made publicly available.



## Organizational structure

### a. Institutional setup:

If the publication is part of a larger institution, safeguards must be in place to prevent any influence of the institution (or the governing board of a bulletin if applicable) on the editorial team, particularly regarding topic selection and article content.

### b. External authors:

If an editorial team makes use of external authors to write or draft articles:

- The editorial team must have the autonomy to change the content or reject articles.
- All authors who write articles which could influence therapeutic choices (e.g. drug and treatment reviews or guidelines) must be free from conflicts of interest as defined above.
- In exceptional circumstances a bulletin may publish an article (not influencing therapeutic choice) by an author who has a conflict of interest; in such a situation all potential conflicts of interest need to be declared at the end of the article.

### c. Reviewers of articles:

External reviewers of articles should declare their conflicts of interest.

## New Associate Member: RxISK

by David Healy



Data Based Medicine formally began in 2010 at a meeting involving Dee Mangin, Kal Applbaum and David Healy.



Dee Mangin

In 2010, Dee Mangin was an academic physician in the Department of Family Medicine and Public Health in Christchurch New Zealand. She was known for criticisms of Guideline based medicine and as a moving force behind Pegasus, a consortium of family medicine practices, that provided independent information about medicines, with an emphasis on safety rather than efficacy. She was also an author on a seminal article that kicked off deprescribing, which described how reducing the burden of medication in older subjects can reduce rates of hospitalization, extend life expectancy and in some instances lead to something close to a rebirth. She is now a Professor in the Department of Family Medicine at McMaster University in Canada, where her work on deprescribing has developed with a focus on new concepts like legacy prescribing and in particular the creation of TaperMD (see below).

Kal Applbaum was and is based in the Department of Anthropology in the University of Wisconsin Milwaukee. In 2004 his book *The Marketing Era* had been the first sophisticated mirror held up to the marketing practices of the pharmaceutical industry. A series of articles since have incisively characterized the interplay between industry and medicine. In 2010 it was becoming clear he had perhaps been too far ahead of his time. A few years later, aware that it may take decades for others to catch up, he turned to writing fiction, including something close to a *Gulliver's Travels* take on Pharma. Among the other takes on the interaction between medicine and meds that he has turned to has been cannabis farming.

For Healy the route to RxISK began in 1991 when Lilly published their meta-analysis of the fluoxetine clinical trial data claiming it showed that fluoxetine did not make anyone suicidal. As someone with a doctoral degree on serotonin reuptake in depression, he was well placed to liaise closely with pharmaceutical companies and was among the first to use SSRIs in Britain when they became available. While using fluoxetine in early 1990,



David Healy

two of his patients became suicidal with the problem clearing when treatment stopped and re-emerging with another serotonin reuptake inhibitor. So when Lilly's analysis appeared it was either a case that something was wrong with their clinical trials or with his patients' compelling accounts. This was the start of a journey that led to a recognition that we have no access to the data from company trials, that almost everything to do with pharmaceuticals in even the best medical journals is ghostwritten, and that RCTs even if done by angels are a poor method for establishing what drugs do and a gold-standard way for hiding adverse effects.

All three founders who linked up in 2010, therefore, were committed in one way or the other to the idea that what people said was happening to them on a drug usually was happening. All three distrusted the standard "evidence" especially when it conflicted with what seemed evident to people - the data. This led to the name for the new group – Data Based Medicine, which was the title of some early articles. All three were comfortable with the idea of using the word cause when someone on treatment gave a compelling account of something happening to them on a drug, despite an awareness that many others regarded any use of "cause" as indicative of a certain immaturity.

In 2011, we fortunately met Peter and Julie Wood. Peter had just retired as a partner in a global accountancy firm having had set up websites as part of his brief. A family experience of adverse events

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## New Associate Member: RxISK (continued)



Peter Wood

made both Julie and Peter receptive to helping get RxISK off the ground. Peter took control of setting up the RxISK.org website, along with SSRI Stories.org which Julie curated, and then later Study329.org and the healy blog. This involved huge amounts of programming, along with sorting out multiple privacy related issues, while plotting a course toward sustainability. The RxISK.org name came from Nancy Olivieri.

For RxISK to survive, some other organization needed to figure as we did that there must be some value in the 99% of things that happen to people on drugs that health systems discard, from effects on sexual functioning or hair through to suicidality or effects that might be beneficial in other circumstances – as when the discovery that certain eye-drops led to hair growth resulted in a method to lengthen eye-lashes.

### Trajectory

In 2010, our sense was that there was a problem with the culture of medicine and that this was getting worse rather than better. The question was how to turn things around.

One early idea was to introduce Quality Marks. It was clear doctors were on their way to being replaced as prescribers by psychologists,

pharmacists and nurses. This opened up the possibility of introducing competition to be good prescribers, where a good prescriber was someone who reported on adverse events when they happened. Could prescribers be incentivized through reports to us (which could be relayed to regulators), which would lead to a Quality Mark. This hasn't taken off yet.

Another idea was the use of a RxISK report to level the power imbalance between doctors and patients. Armed with an expert report on their problem, we thought patients would feel more comfortable mentioning the issue to their doctor. Having a physician endorse a link between treatment and an adverse effect would offer a potent testimony as to cause and effect. But even with a RxISK report patients don't appear to feel comfortable mentioning adverse events and we have had almost no reports from doctors.

One of the hopes was that reports from doctors would help build a RxISK map of doctors who listen and are prepared to entertain the possibility that some of a patient's difficulties might link to their treatment. We get regular requests from all over North America and Europe as to whether we know doctors willing to engage with adverse effects but so far we cannot offer any names.

In terms of finding someone who might value what RxISK does sufficiently to support its operation both financially and by embedding it in a clinical service, we turned to insurers. Given that the earliest possible intervention when something is going wrong on treatment should minimize the harms done and the costs incurred, there seemed to be good fit. But despite access to the highest echelons of some insurers, it seems that the incentives are less compelling to them than we initially thought.

Another pitch was to generic phar-

maceutical companies. RxISK could enable them to offer not just cheaper but better medicines on the basis that a medicine is a chemical allied to information and RxISK could enhance the quality of that information. This message has had no traction so far.

Safety is not the selling point that efficacy is. In a risky world efficacy appears to offer a management of risks. In contrast, talking about adverse events, ghost-writing and lack of access to trial data takes people beyond their comfort zone. Some resolve the conflict created by rejecting the medical model and turning to non-orthodox approaches or paramedical approaches as in the case of psychotherapy within the mental health field. But within mental health, this turn to "anti-psychiatry" doesn't enable anyone to engage with the adverse events medical treatments cause or to support people who may be suffering from them.

### Recent developments

The RxISK approach turns traditional pharmacovigilance on its head. At present, most people endorse the idea that RCTs deliver the best information on a drug's effects but that RCTs need to be supplemented by signal detection methods to detect effects that are rare or that emerge outside the timeframe of an RCT. For RxISK the most common effects of a treatment are often not detected in RCTs, such as for instance the sexual effects of antidepressants which are more common than the effects on mood, and the most pressing task for pharmacovigilance now is to restore confidence in the ability of patients and clinicians to decide a treatment is causing a problem without thinking an RCT is needed before this claim can be made.

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# New Associate Member: RxISK (continued)

There is a further aspect to current pharmacovigilance that RxISK brings into view. In the case of both medicines and weapons, efficacy has been a trump card – the armies with the most potent weapons win. But with the nuclear bomb it is now clear that efficacy has a limit – these weapons cannot be used. Another way to frame this lies in the concerns about school shootings in the USA, where one proposal has been to have a “good guy” with a gun in every school. Clearly this works in the case of guards posted outside the White House, but most of us know at some level that multiplying efficacy up too far and deploying potentially efficacious elements too widely risks causing more problems than it solves.

What applies to guns applies to medicines also. There is growing consensus that having people on 5 or more medicines risks losing efficacy; reducing medication burden can, in contrast, increase life expectancy, reduce hospitalization and sometimes dramatically improve the quality of a life.

Over 4 decades of extreme hyping of efficacy and hiding of harms, along with a move to chronic treatment of risk factors, medication burdens have increased dramatically. Where the average person was on one medicine and only then for a limited period in 1980, 50% of those over 45 are now on 3 or more meds and 45% of those over 65 are on 5 or more medicines every single day of the year, and this burden increases with every further year of life. Allied to this, there are recent indications that life expectancy may be falling or at least stalling.

Do falling life expectancies indicate that we have reached the limits of medical efficacy? If we have, we will need to think about trimming medication burdens and in this case the

values of patients are likely to come into play in any consideration of how to reduce the medical burden.

While it has always been the case that in order to achieve effectiveness, safety has had to be a consideration, this has been rather side-lined in recent decades. A link to falling life expectancy changes the conversation about safety. In this new world, in order to get the best possible efficacy, both patients and clinicians will have to embrace safety and the values of patients.

In order to facilitate this, the primary focus of RxISK in the last two years has lain in developing TaperMD, a cloud based system, that allows doctors, pharmacists and patients working together to perm a patient’s medication in a direction that best suits them. TaperMD is currently in clinical trials in Canada and Australia and will launch soon, with an initial focus on older adults in both ambulatory and long-term care including assisted living facilities, retirement homes, and home care.

Deprescribing offers another take on pharmacovigilance also. The traditional focus has lain on observing effects after exposure to a drug. But equally on stopping treatment a patient or clinician may become aware of effects that drug had been having.

Aside from the input from the key players noted above, RxISK has had a number of achievements that have hinged on the input from people reporting on adverse effects. These have led to compelling reports on SSRI triggered alcoholism, and the identification of common enduring sexual effects common to retinoids, 5 alpha reductase inhibitors, and serotonin reuptake inhibiting drugs.

All the input to RxISK to date from all involved has been voluntary. The input from those who have been har-

med by treatment has been the driving force that has sustained everything else. The key input has not however come from specific discoveries but from an appreciation that motivation and trust are worth more than expertise – the motivation of individuals who have no background in healthcare but who because of a problem on treatment have the motivation to research and assess what is happening. In this endeavour the key support a clinician can bring lies in their trustworthiness rather than their expertise.

Finally, one other breaking development has been a recognition that reports from individuals that carry their names have a legal and scientific weight that anonymous reports and even RCT data do not have.

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## New Associate Member: Drug Action Forum - Karnataka (DAF-K), India

Drug Action Forum - Karnataka (DAF-K) is an Indian registered, independent, not-for-profit, non-government organization campaigning for rational drug treatment and policy. It is a part of All India Drug Action Network, AIDAN - <https://aidanindia.wordpress.com/>, Health Action International Asia-Pacific <http://www.haiasiapacific.org/> and No Free Lunch India <http://nofree-lunchindia.org>

DAF-K campaigns for medicines and vaccines that can meet the health requirements, are only essential, are safe and of which the costs are within the reach of the people.

The bulletin of DAF-K is titled "SANJEEVINI" and is its official publication since the last three years and is financially supported by DAF-K members. It is our policy not to accept any sort of support from any drug manufacturer or profit making corporate body. See: [http://nofree-lunchindia.org/index.php/daf\\_k\\_kannada\\_bulletin](http://nofree-lunchindia.org/index.php/daf_k_kannada_bulletin)

### Objectives of DAF-K:

- To bring out publications and conduct training on rational drug use and policies.
- To promote the concept of "Health for All", as stated in the Alma Ata Declaration by World Health Organizations.
- To support and actively participate in People's Health Movements by joining hands with like minded national and international organizations.
- To take legal course of action for public cause as and when necessary.

### Some activities of DAF-K :

DAF-K along with others filed a Public Interest Litigation (693/1993) in Supreme-Court of India, New Delhi to screen and weed out irrational and hazardous medicines in the Indian market. As a consequence to this court intervention several categories of irrational medicines have been weeded out. For example the fixed dose combination of Vitamin B1, B6



and B12 and fixed dose combination of cough syrup containing codeine and anti-histamine.

DAF-K challenged the policy of iodization of salt by the central government through a Public Interest Litigation in the High Court of Karnataka, Bangalore.

DAF-K along with other like-minded organizations such as the Human Rights Law Network (HRLN) is currently filing a case in the Supreme Court of India, New Delhi with regard to the closure of public sector vaccine manufacturing units.

'Walk for Affordable Medicines' on 2nd October 2015. DAF-K along with other like-minded local organizations of Dharwad, walked through the streets of the city and created awareness about affordable medicines. DAF-K and other NGO based in Dharwad have initiated an outlet where consumers can buy generic medicines at affordable price. To promote the Generic Drug Outlet, several like minded organizations joined hands for a walk on the streets of Dharwad to promote the Affordable Medicine Outlet. See the link at <https://www.youtube.com/watch?v=xrngXS5cW4c>

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Walk for affordable medicines

## New Associate Member: DAF-K, India (continued)

DAF-K has been at the forefront for the campaign on Drug Price Control by supporting the Public Interest Litigation of AIDAN. Though India is known as the “Pharmacy of the Developing Countries” because it exports generic drugs to around 200 developing countries but still many people cannot afford because of its high cost. To address this problem the government of India has set up “Drug Price Regulation Ordinance”. There are lacunas in this Ordinance and towards this AIDAN has filed a case in the Supreme Court of India and DAF-K is supporting the case by educating consumers. See: NGO wants drug prices regulated, Business Standard, 2nd November, 2012, [https://www.business-standard.com/article/economy-policy/ngo-wants-drug-prices-regulated-112110202014\\_1.html](https://www.business-standard.com/article/economy-policy/ngo-wants-drug-prices-regulated-112110202014_1.html)

Novartis Boycott campaign: DAF-K along with other Karnataka state and Indian’s national campaign

groups launched the campaign for boycott as Novartis had challenged Section 3d of Indian Patent Act in the Indian Courts, even though it was within the TRIPS (Trade Related Aspects of Intellectual Property Rights) World Trade Organization’s agreement. Section 3d of the Indian Patent Act prevents ever greening of patents and based on this act the Indian Patent Office had rejected granting patent to its drug Gleevac (drug for blood cancer). This particular rejection of grant for patent had irked Novartis and so they had challenged the same in the Indian court. It was in this context that DAF-K had launched a campaign urging doctors to boycott Novartis products by not prescribing the medicines manufactured by Novartis. The campaign had huge impact as several doctors refused to prescribe Novartis medicines. Six local Indian Medical Associations joined the Novartis Boycott campaign and DAF-K also launched an online signature campaign. The

boycott campaign certainly had an impact on the company, but it is not possible to sales loss to Novartis. But the Mumbai sales manager of Novartis came to discuss the issue with DAF-K members. See: <https://www.livemint.com/Companies/ApCAc88e6fGy22tIaYgNuO/Activists-to-boycott-Novartis-drugs-plan-nationwide-campaig.html> and <https://www.thehindu.com/todays-paper/tp-national/tp-karnataka/Call-to-boycott-Novartis-products/article14887616.ece>

Study titled “Hepatitis B vaccine – misleading policy and promotion” by DAF-K the study critically appraises the policies of the government of India on the issue of vaccinating every new born with hepatitis B vaccine. The Policy of the government of India is that every new born child should be vaccinated against Hep B, but DAF-K thinks that it is really not necessary. Does India have enough resources for this? Is it a priority disease in India? What are the alternatives? The alternative is that all pregnant women can be tested for Hep B and if found positive then the newborn can be vaccinated immediately after birth. By this simple method we can also get an idea of the exact number of women with Hep B and in addition save the vaccine cost by immunizing only those who need it. Additionally the booklet informs the reader about the correspondence between DAF-K and the vaccine manufacturer and the Drug Controller of India. See: [http://www.mediafire.com/file/zzw4tlzwhvy/Hepatitis\\_B\\_vaccination\\_in\\_India.pdf](http://www.mediafire.com/file/zzw4tlzwhvy/Hepatitis_B_vaccination_in_India.pdf)



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## New Associate Member: DAF-K, India (continued)



**Testing for tuberculosis in animals by injecting tuberculin by veterinary doctor with assistant.**

“A Study on Drugs for Treating Anaemia” by DAF-K examines the sorry plight of the poor people in India with regard to access to medicines for treating anaemia. On the one hand drug companies are marketing irrational formulations while essential and cheap medicines to treat anaemia are not available in the Indian market. Doctors are compelled to prescribe such irrational medicines because of the absence of useful medicines in the Indian market. There are preparations of iron with vitamin C, with vitamin B12, with Magnesium – all of them heavily promoted by drug companies. The most popular brand is FEFOL, which is in capsule form and standard text books mention that it is wrong to administer iron in capsule as iron gets absorbed in duodenum (the first part of small in-

testine). The entire nation is facing a severe shortage of medicines to treat anaemia – even at the government outlets. A big scandal indeed. See: [http://www.mediafire.com/file/itymt-gumngw/A\\_Study\\_On\\_Drugs\\_for\\_Treating\\_Anaemia.pdf](http://www.mediafire.com/file/itymt-gumngw/A_Study_On_Drugs_for_Treating_Anaemia.pdf)

DAF-K had started a affordable medicines outlet in Dharwad town, which got closed after two years. But subsequently after four years Jagruti (an NGO [www.jagruti.org](http://www.jagruti.org) – campaigning for rights of the girl child ), another affordable medicine outlet has been started since last six months. The main aim of this outlet is to make generic medicines at affordable price, for the common man. Even though India exports large amount of generics to Europe and the US, but medicines are unaffordable to majority in India.

DAF-K along with Jagruti, an NGO did a field based study on zoonotic tuberculosis, demonstrating as to how tuberculosis can be transmitted from animals to humans and vice versa. The study has been presented at national and international conferences. The study was presented at People Health Movement – India chapter People’s Health Assembly-3 held at Raipur in Chattisgarh state held during 22nd and 23rd October. The study was also presented at Dhaka in Bangladesh at People’s Health Assembly 4, held during November 2018. In addition it was presented at National Bioethical Conference held at Bangalore during 7th to 8th December 2018.

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## Actions and Campaigns

# Letter of support for Peter Gøtzsche to the Danish Minister of Health

To Miss Ellen Trane Norby  
Minister of Health Denmark

Dear Minister Norby,

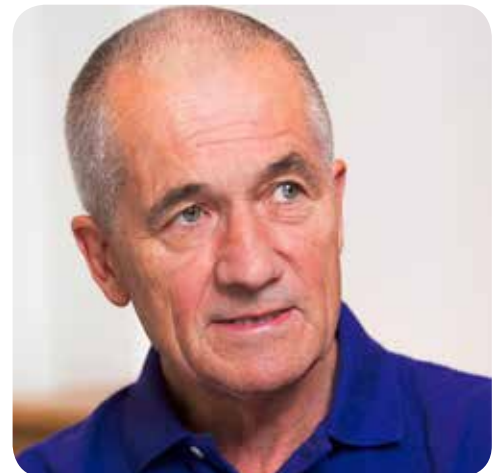
The International Society of Drug Bulletins\* writes to you to express our deep concern with the way professor Peter Gøtzsche is dealt with in Denmark and his upcoming dismissal from the Rigshospitalet. Peter Gøtzsche is one of the leading scientists in medicine. He has contributed through many articles, books, lectures and interviews to the awareness of sound methodological rigor in medical science. This achievement is acknowledged worldwide also by his opponents.

Science and medicine have evolved and changed enormously in the past decades as the result of ongoing scientific debate in which advocates and opponents 'struggle' and try to convince each other. It is necessary that scientific debate evolves in freedom and that there is sufficient space for all to contribute to the discussions.

Drugs play a major role in medicine and the revolution that has taken place in the past century has given us quite a few life-saving drugs. Yet, there is a growing gap between doing science and doing business. It is well known that researchers with conflicts of interest judge more positively about drug therapies than researchers without such ties. Peter Gøtzsche has shown in his work that there are many flaws in the way scientific drug studies are presented in the medical literature and in the media. This knowledge saved many lives as well as it reduced costs in health care.

The Portuguese-Dutch philosopher Baruch de Spinoza finished his Ethics with the words: 'All excellence is difficult just like it is rare'. We believe as well as many others that we should be proud of the excellent achievements of Peter Gøtzsche. We urgently request you to reconsider the expulsion of Peter Gøtzsche from the Rigshospitalet.

On behalf of the Committee,  
Dr Dick Bijl, President  
International Society of Drug Bulletins



Prof. Peter Gøtzsche



# Drugs for hepatitis C: it's time to slash prices!

When so-called direct-acting antiviral drugs against hepatitis C came onto the market around 2015, some stakeholders hailed them as a means of eradicating this disease (1). Where do we stand a few years later?

**Prices designed for shareholders.** *Sofosbuvir* (Sovaldi®) was marketed in the United States at the exorbitant price of 1000 dollars per day, reflecting the stock market speculation to which this drug gave rise (2). In 2015, stock markets applauded the performance of Gilead whose share price increased by 157% in two years thanks to Sovaldi® and Harvoni® (*sofosbuvir* and *ledipasvir*) (3). This company's real strategy was to seek maximum profits in the richest countries and not disease eradication, which would require very low prices to allow access to treatment by the largest number of people.

**A tiny minority of people have received treatment.** According to the World Health Organization (WHO), 71 million people around the world were infected with the hepatitis C virus in 2015, and as a result, 400 000 persons died that year, mainly from cirrhosis or liver cancer (4). Three out of four infected persons live in low- or middle-income countries: 10 million in China, 7.2 million in Pakistan, 6.2 million in India and 5.6 million in Egypt (4).

In part to escape criticism of their prices, Gilead and other companies producing these direct-acting antivirals offered lower prices for the poorest countries or sometimes accepted the manufacture of generics. In some countries, generics are also being marketed without the agreement of the companies concerned (4).

According to the WHO, only 1.5 million people started treatment for hepatitis C in 2016. The pricing of these drugs means that essentially only the richest countries and the poorest countries have implemented large-scale access to treatment for this disease. In middle-income countries (China, Mexico, Turkey, etc.) where about 40% of infected

people live, access to the drugs is virtually non-existent due to their unaffordable price (4).

**Slash the prices.** Against the background of this very unsatisfactory situation, the WHO applauds the counterexample provided by Egypt, which has adopted a vigorous policy for combating this disease, and where 1.5 million people received treatment between 2014 and 2017 (a). In this country, local generic manufacturers offer *daclatasvir* at 7.5 dollars for a 28-day supply (as opposed to 165 dollars which is the discounted price from Bristol-Myers-Squibb) and *sofosbuvir* at 50 dollars (compared to Gilead's discounted price of 275 dollars). Thanks to generics, Egypt should be in a position to eradicate hepatitis C by 2030, according to the WHO (4).

As in the case with AIDS since the beginning of the 21st century, the best means for most of the world to combat hepatitis C will be through companies which rely on high-volume sales, such as generic manufacturers, including the use of flexibilities in intellectual property rights.

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**a- In Egypt, millions of people were infected iatrogenically during the years 1960-1970 following injections aimed at eradicating schistosomiasis (ref 5).**

### Selected references from Prescrire's literature search

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# My dismissal is scientific judicial murder

By Peter C. Gøtzsche

Translation of text “*Min fyring er et videnskabeligt justitsmord*”. *Politiken* 11 Dec 2018



You would not believe that this could happen in a country like Denmark. That Rigshospitalet fires an official without prior service warning who co-founded the Cochrane Collaboration 25 years ago, created the Nordic Cochrane Centre out of nothing and made it a world-class research centre.

Deputy director of Rigshospitalet, Per Jørgensen’s official reason for firing me is that he has lost confidence in my ability to lead the centre. This is not an objective reason and it is contradicted by my results.

The firing was brutal. It took place on October 29, during my first official call ever. I was suspended and treated as if I had committed serious crime. I was not even allowed to go back to my office and my staff were banned from contacting me, which in particular my 5 PhD students cannot understand the reasoning behind, and they have written to the hospital and the minister and pointed out that they cannot do their work without me as supervisor. Jørgensen and Personal Manager Mette Risak preferred to avoid a firing and therefore invited me to enter into a “mutual agreement on resignation”, as it is misleadingly called, with a few months extra salary beyond the three months I would receive in any case.

My union was proud that they had negotiated 10 months’ extra pay, which had never happened before, while I took it as an indication that the hospital had an immensely bad case that would not withstand public spotlight. The agreement mentioned that:

“There is agreement between

the parties that the content of the agreement is not communicated to third parties. Announcement to employees and relevant internal and external partners will be agreed with the Executive Board. The agreement is the complete and final decision about any claim between the parties without prejudice.”

Total gagging. I reported back a week later, copying the Ministry, that my freedom of speech is not for sale and that what was going on should come to light. In my letter, I wrote that politicians and patients are very happy about my efforts; that in 2015, psychiatric patients voted for me to become Dane of the Year and I ended up in top 10; that in 2016 I became Protector of the Hearing Voices Network; that everyone has attached great importance to the independence of the Centre; and that I have saved the community billions of Danish kroner by just three of my reviews.

I also wrote that I thought my impending firing was about silencing an important voice in the debate, just like my expulsion from the Cochrane Collaboration on September 13th. Cochrane’s leadership was very annoyed that I had published a well-founded criticism of the Cochrane review of the HPV vaccines, and I was told that it is bad behaviour to criticize colleagues’ science when you are a Governing Board member or a Cochrane Director. Obviously, this is scientific censorship.

By reviewing the randomized trials we received from the European Medicines Agency, we have shown that the HPV vaccines may cause serious neurological harms, which the authorities otherwise claim do not

exist. We are publishing this, also in a PhD thesis, and we presented the results at our 25th anniversary symposium at Rigshospitalet on October 12th.

Instead of silencing an important voice, Rigshospitalet and the Ministry should protect me. Firing me sends the unfortunate signal that if your research results are inconvenient and cause public turmoil, or threaten the pharmaceutical industry’s earnings, which we are very concerned about in Denmark, we will fire you. Strikingly many of the documents my lawyer has obtained from the Ministry through the Freedom of Information Act are articles where healthcare stakeholders – e.g. psychiatrists, doctors with conflicts of interest, the Health and Medicines Agencies, and editors of journals financed by the pharmaceutical industry – try to depict me as untrustworthy to promote their own interests.

It led to massive resentment, with several articles in, for example, *Science*, *Nature*, *BMJ* and *Lancet*, that I was expelled from the Cochrane Collaboration after a process where new accusations were invented on the spot after Cochrane’s own lawyer’s investigation had exonerated me from all charges. I believe I have unequivocal evidence that the process is invalid. The next day, four members resigned from the board in protest.

The case is not about my person, but about important principles that the leadership of Cochrane trampled underfoot. Cochrane’s credibility plummeted because I am known for high quality research, integrity and incorruptibility.

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## My dismissal is scientific judicial murder (continued)

The 31 Centre Directors in Spain and Latin America demanded an independent investigation of the Cochrane process against me, which the Board rejected because such an investigation would lead to its demise. I have complained to the Charity Commission in England about serious mismanagement committed by Cochrane's CEO Mark Wilson and the Governing Board who have violated all the key rules for charities and for Cochrane. Why does Rigshospitalet want to fire me? It is extremely rare that Rigshospitalet fires a chief physician. I have taken care of the interests of the Nordic Cochrane Centre, the Cochrane Collaboration, the patients and Denmark, and believe I have served my country in an exemplary manner during my 25-years senior role as an official.

Others share my view. More than 8000 signatures have been sent to the minister with a request to overturn my sacking, with such prominent names as Cochrane co-founder, Sir Iain Chalmers, BMJ's editor-in-chief, Fiona Godlee, Member of the European Parliament Margrete Auken who has done a lot to make data available to researchers, psychiatrist David Healy, highly respected as one of the world's leading experts on psychiatric drugs, and the world's most cited health researcher, John Ioannidis from Stanford University.

It is apparent from the correspondence that we have got access to that the Ministry and Rigshospitalet have worked closely together and with Wilson, whereas I have not been heard, although it is well documented that Wilson does not always provide a complete and correct picture, which I had warned Rigshospitalet about, and provided

examples of in my hearing letter to the hospital. Wilson has required that I shall no longer be allowed to work at the Cochrane Centre, and the Ministry and Rigshospitalet have pleased him, although, according to Cochrane rules, I can continue working as head of department or as chief physician. It is outrageous that a person in this way interferes with internal affairs in another country, on top of this contrary to the rules.

The Ministry is, to a considerable extent, jointly responsible for the fact that it has come this far because the Ministry announced to Rigshospitalet on 12 October that the payment of the fiscal grant to the five Danish Cochrane groups was detained until Rigshospitalet complied with the prerequisites in the Finance Act, including ensuring that the Centre is part of the international Cochrane Collaboration.

Through our access to documents, we have recently learned that the Ministry and Rigshospitalet, since October 1 via Wilson's emails have been fully aware that the Centre has always been part of Cochrane. However, the Ministry and the hospital have kept this knowledge to themselves. At a meeting with my staff on November 5, when Jørgensen tried to explain why I would be fired, reasons of which the staff did not understand, he continued to give the impression that the Centre was not part of Cochrane.

On September 28, I tried to withdraw the Centre from the Cochrane Collaboration because I discovered via a journalist that Wilson's staff had changed our website behind our backs; had deprived us of our administrative rights without informing us; had deleted me among the employees, even though I was still employed; and had uploaded an in-

correct and deeply defamatory statement from the board about me on the front page.

I acted in good faith when I tried to withdraw the Centre because the hospital has always emphasized that it was only our host and would not interfere with my dispositions, and I could not see in the remarks to the Finance Act that it was a requirement that we should participate in the Cochrane Collaboration. Later, it dawned on me that the withdrawal was never enforced because Wilson did not approve of it.

My staff has been very afraid of losing their jobs and still are because the Finance grant is being withheld. The Ministry and Rigshospitalet has caused great and unnecessary insecurity among about 50 employees through two months by giving, contrary to the facts, the outside world the impression that the conditions for payment of the grant were not met. This has nothing to do with whether I'm still working at the Centre because its Deputy Director will handle Cochrane related tasks if I cannot or must not do it. It seems that the Ministry and the hospital have used all means at their disposal needed to accommodate Wilson's unusual requirement that I must be fired, even though 50 employees suffered as a result.

My situation is the result of a power struggle between two wings. One wing is led by Wilson who advocates that everyone in Cochrane should speak with the same voice; he opposes open scientific debates about the quality and reliability of concrete Cochrane reviews; he puts more emphasis on "brand", "our product" and "business" than getting the science right; and he allows economic conflicts of interest in relation to the pharmaceutical

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# My dismissal is scientific judicial murder (continued)

industry. The other wing wants to bring Cochrane back to its original values: Free scientific debates; no financial conflicts of interest for the researchers making Cochrane reviews in relation to the companies whose products they evaluate; and openness, transparency, democracy and cooperation.

As a member of the Cochrane Governing Board (with the largest number of personal votes of all 11 candidates, despite the fact that I was the only one who criticized Cochrane's management in my election statement), I did my best to change the situation.

Despite great support, I lost the power struggle. If that's why the health service wants to fire me, then Denmark supports Cochrane's new line of "one voice", lack of scientific debates and relationships that are too close to the pharmaceutical industry, which basically will make Cochrane superfluous.

I have suggested that the Centre changes status to a Centre for Evidence-Based Medicine, as well as several other Cochrane Centres are currently doing, because it would be of greater benefit to Denmark than to be a member of a Cochrane organization that does not live up to its declared values.

It takes many years to build a successful research centre, but only a moment to destroy it by an unwise administrative decision. Every researcher's nightmare is lack of understanding and appreciation from those who have the formal power. It has hit me totally in Cochrane and is now also hitting me in Denmark.

The case is one of principles because it is about one of the heaviest areas in healthcare: beneficial and harmful effects of medicines and other medical technologies. If

you can easily get rid of inconvenient people and thus their research and participation in the academic debate, it can have serious consequences both for community health and economics. If Denmark supports Cochrane's fundamental principles of free scientific debate and independence of the pharmaceutical industry, then Denmark should provide me with all possible support instead of firing me.

Denmark should also consider if it is acceptable that someone in London, to an increasing degree, has the ability to decide what the Danish Ministry's appropriation is to be used for, and even wants to decide whether people employed with someone else's money, who have done nothing wrong, should be fired. All Cochrane Centres in the world, except the British one, are opposed to the strong central control of the freedom of action over the funds the centres themselves have acquired.

If Rigshospitalet fires me, it will result in the following:

1. Everyone loses, incl. Rigshospitalet, the Ministry, Denmark and Cochrane. Psychiatrist David Healy told in a lecture in 2000 at the University of Toronto that the world's best-selling drug, a depression pill from Eli Lilly, could lead to suicide. Eli Lilly was a major donor for the department, and Healy was fired. This scandal is still being talked about even though it is 18 years ago. Rigshospitalet should think about this.
2. The turmoil that already exists is going to increase considerably. Many are angry with the treatment Cochrane exposed me to and they know it comes from Wilson who controls everything, including the Cochrane Board,

which I have experienced myself. If Wilson also succeeds in getting me fired, it will have unimaginable consequences. People in Cochrane are already nervous about what they may be exposed to, and many will withdraw their centres or groups when they see that Wilson's power is virtually unlimited.

3. My lawyer and I will carefully assess the basis for my sacking with the purpose of filing lawsuits for damages against Rigshospitalet for my unjustified firing, and against Cochrane for the propagation of seriously defamatory statements, with financial consequences for me. This would further harm Cochrane.
4. The Ministry, Denmark and Rigshospitalet will get an unattractive key role in the documentaries and books on scientific freedom and the fate of whistleblowers, which are being prepared. It has gained attention abroad that Denmark will not re-employ a person if he wins a case of unjustified firing.

Since the matter is of paramount importance, I have today sent a copy of my hearing to Rigshospitalet to the Minister and to the Association of Specialist Doctors. I have also sent a copy of a letter from my lawyer, which is included in my response. This is not just a case between Rigshospitalet and me.

The Ministry has a significant co-responsibility for the situation. The world's most cited health researcher has written to the Minister saying that he is confident that she does not want to be on the wrong side of history.

## New evidence of severe abnormal behaviors/psychiatric reactions to oseltamivir(Tamiflu)

Translated from Med Check-TIP (in Japanese) Nov 2018 : 18 (80):138

MedCheck-TIP Editorial team

### Serious abnormal behaviors occurred 29 times more frequently

From a prospective cohort study by Fujita et al. [1], Fukushima et al. (Hirota team) [2] extracted "abnormal behavior A", serious cases that could lead to accidents (24 persons in Tamiflu group and 4 persons in non-Tamiflu group) to examine the risk of Tamiflu use by self-controlled case series method.

The risk ratios for Tamiflu use compared to non-use were determined by adjusting various factors. They were between 1.9-fold and 29-fold (95%CI: 4.21-201) depending on the duration of Tamiflu use and non-use that was utilized in their analysis. The greatest risk ratio was yielded when the duration of about six hours after taking Tamiflu was utilized in the analysis. Fukushima et al. concluded that they could not deny the possibility that abnormal behavior was induced by influenza itself, since the duration overlapped with the early period of influenza where high fever was observed.

On the contrary, according to the data by Fujita et al. [1], the incidence rate of delirium per 1000 person-days during high fever phase (until about 24 hours after start of fever) was about 5 persons before Tamiflu use while exceeding 30 persons at most after Tamiflu use. Therefore, it should be considered that Tamiflu causes "abnormal behavior A".

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[https://www.jstage.jst.go.jp/article/jjpe/15/2/15\\_2\\_73/\\_pdf/\\_char/ja](https://www.jstage.jst.go.jp/article/jjpe/15/2/15_2_73/_pdf/_char/ja)
- 2) Fukushima W et al. Oseltamivir use and severe abnormal behavior in Japanese children and adolescents with influenza: Is a self-controlled case series study applicable? *Vaccine* 2017; 35: 4817-24

### Severe psychiatric reactions occurred 35 times more frequently

In Cochrane's systematic review [1], the risk of psychiatric symptoms increased dose-dependently in treatment trials of oseltamivir (Tamiflu), and in the prophylaxis trials it was significantly higher in the Tamiflu group than in the placebo group. The review reported that psychiatric symptoms were induced in about 1 person per 100 persons. However, the risk ratio was 1.8 and not so high.

Jones et al. used logistic regression method and analyzed psychiatric symptoms taking duration and intensity of symptoms into account. The odds ratio was 3.46 (95% CI: 1.28 - 9.32) for overall intensities. Analysing the intensity of the symptoms showed little difference between groups for mild ones (OR 1.23, 95% CI: 0.30 - 5.04), but a statistically nonsignificant increase for moderate symptoms (OR 4.34, 95% CI: 0.79 - 24.0), and a large, significant increase for severe psychiatric events (OR 34.5, 95% CI: 3.66 - 325).

Based on these results, Jones et al. stated that their analysis shows evidence of a causal effect of oseltamivir on psychiatric symptoms.

There was little difference between both groups for mild cases, even when symptom duration was taken into account. However, Tamiflu induced moderate and severe psychiatric symptoms 1 per 210 persons and 1 per 230 persons, respectively which show that Tamiflu induces moderate or severe psychiatric symptoms rather frequently.

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# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Antidepressant Withdrawal Syndrome

**A**ntidepressant drugs are associated with drug tolerance, dependence and a discontinuation syndrome similar to other drug classes such as the opiates and benzodiazepines. **The effects of stopping any antidepressant should be more precisely termed “withdrawal syndrome” instead of “antidepressant discontinuation syndrome.”**

### What is it?

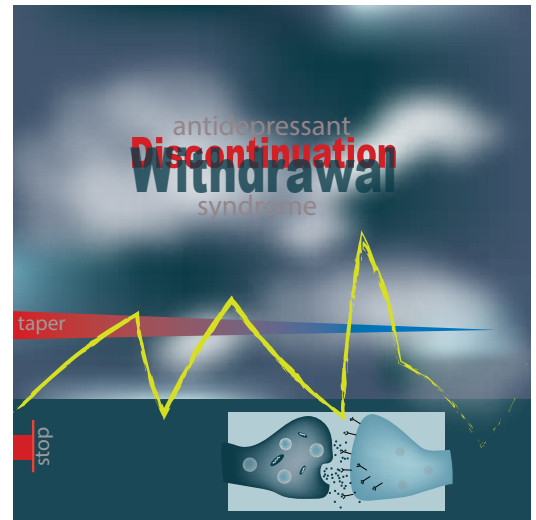
Antidepressant withdrawal syndrome refers to physical and psychological symptoms that occur when stopping, missing doses or reducing doses of any antidepressant.<sup>1,2</sup> The mechanism has not been determined but various explanations have been proposed.<sup>3,4</sup> Daily drug treatment can affect the availability of several neurotransmitters that can lead to many downstream physiological consequences. When drug treatment stops, the body's adaptive changes take time to recalibrate, resulting in a period of possible symptoms.<sup>5</sup>

### Clinical Features

- Symptoms usually appear within a few days of stopping, or dose reduction.
- Symptoms include anxiety, crying, dizziness, headache, increased dreaming, insomnia, irritability, myoclonus, nausea, electric shocks (zaps), tremor, flu-like symptoms, imbalance, and sensory disturbances.<sup>1</sup>
- Most antidepressant withdrawal symptoms resolve within 2 weeks.<sup>1</sup>
- Severe and prolonged withdrawal symptoms have been reported lasting weeks to months.<sup>5</sup> Numerous cases are reported anecdotally in great detail online.<sup>1,2</sup>

### Systematic Reviews

Two systematic reviews studied withdrawal reactions with selective serotonin reuptake inhibitors (SSRIs). The first review asked whether withdrawal reactions were different between benzodiazepines and SSRIs, and authors concluded the two were “very similar.” They strongly assert that SSRIs fulfill the criteria for tolerance and dependence in addition to a withdrawal syndrome.<sup>6</sup> The second review



studied withdrawal symptoms associated with SSRIs. That review found 15 RCTs, 4 open trials, 4 retrospective investigations and 38 case reports. It concluded that SSRIs should be added to the list of drugs where stopping can induce withdrawal symptoms. This list includes benzodiazepines, barbiturates and other psychotropic drugs.

### What proportion of patients have withdrawal symptoms?

Antidepressant withdrawal symptoms have typically been identified by post-marketing adverse drug reports. They are more frequent than suggested from early drug approval trials.<sup>7</sup> The drug monograph for duloxetine (Cymbalta), for example, reports each discontinuation-related symptom experienced by 1% or more patients at a higher rate than placebo in controlled trials<sup>8</sup>, but doesn't provide the overall proportion of patients experiencing symptoms. A manufacturer-funded uncontrolled observational study reported that 51% of patients discontinuing duloxetine experienced one or more symptoms.<sup>9</sup> In general, one to two-thirds of patients have at least one new symptom when abruptly discontinuing an antidepressant.<sup>10</sup> When stopping is investigated in clinical trials, the Discontinuation Emergent Signs and Symptoms (DESS) checklist is often used.<sup>11</sup> The incidence of withdrawal symptoms appears higher with short half-life antidepressants (e.g. paroxetine, venlafaxine) than from long half-life antidepressants (fluoxetine and its long-lived metabolite norfluoxetine).<sup>10</sup> A major gap in the literature surrounding the DESS checklist is that improvement in symptoms after stopping is not captured.



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### Is there evidence for an optimal method of stopping antidepressants?

There are few controlled trials reporting methods for antidepressant discontinuation and resulting symptoms.<sup>11,13-30</sup> Only one controlled trial directly compared a taper to an abrupt stop.<sup>22,23</sup> In this, tapering reduced the rate of emerging withdrawal symptoms, but did not eliminate symptoms. One trial compared taper lengths and found a short taper may be no different than a longer taper.<sup>24</sup> The studies relied upon un-validated means to quantify symptoms, primarily focused on new or worsening symptoms, and may be biased due to loss of blinding. Populations tended to be patients with moderate depression whose depression was somewhat reduced before the antidepressants were stopped. Despite the lack of evidence most antidepressant monographs and guidelines recommend a slow taper approach.<sup>1,31</sup>

### When to taper or abruptly stop?

The optimal method of stopping antidepressants is currently unknown and withdrawal symptoms can happen unpredictably, despite tapering. Some considerations favouring abrupt stopping or tapering are shown in Table 1.

### Other considerations

It is essential that patients are informed of the potential for antidepressant withdrawal symptoms before starting an antidepressant. For patients treated for depression, it is important they are aware of and monitored for a recurrence of depressive symptoms, or increased suicidality.<sup>24</sup>

### Conclusions

- Antidepressants should be added to the list of drugs associated with tolerance, dependence and a withdrawal syndrome.
- Withdrawal symptoms occur in at least one-third of patients who stop.
- Before starting an antidepressant, patients must be informed of the possibility of withdrawal symptoms. The requirements for informed consent are analogous to recommendations before initiating long-term opioid therapy.
- Some symptoms may improve upon stopping but this is not captured in the studies of antidepressant withdrawal.
- Any decision to abruptly stop or taper an antidepressant must consider the potential that recurrent depressive symptoms or increased suicidality may represent withdrawal or re-emergence of the original condition.

**Table 1: Considerations for choosing a method of stopping antidepressants**

Favours Taper	Favours Abrupt Stopping
<ul style="list-style-type: none"> <li>• No toxicity from ongoing antidepressant therapy.</li> <li>• Short half-life of drug and metabolites (&lt;24 hrs).</li> <li>• Previous antidepressant withdrawal symptoms.</li> <li>• Patient prefers autonomy of self-regulated taper.</li> </ul>	<ul style="list-style-type: none"> <li>• Pregnancy and the safety of the antidepressant has not been established.</li> <li>• Important new drug may interact significantly with antidepressant.</li> <li>• Patient is experiencing troubling toxicity related to their antidepressant.</li> <li>• Treatment duration &lt;6-8 weeks.<sup>32, 33</sup></li> <li>• Trial of tapering is prolonging the discomfort of withdrawal symptoms.</li> <li>• Long half-life of drug and metabolites.</li> </ul>

**EXAMPLE:** Long-term paroxetine 40 mg daily is no longer indicated in a patient. A reasonable approach to discontinuation might be:

- Reduce to paroxetine 30 mg daily x 1 week, then 20 mg daily x 1 week, then 10 mg daily x 1 week, then 5 mg daily x 1 week, then stop.
- If intolerable symptoms occur, increasing back to the previously tolerated dose and reducing more slowly (e.g. every 2-4 weeks) may help.

**USEFUL RESOURCES:**

- [medicationinfoshare.com](http://medicationinfoshare.com)
- [rxisk.org](http://rxisk.org)
- [switchrx.ca](http://switchrx.ca)
- [iipdw.com](http://iipdw.com)
- [withdrawal.theinnercompass.org](http://withdrawal.theinnercompass.org)
- [wiki.psychiatrienet.nl/index.php/SwitchAntidepressants](http://wiki.psychiatrienet.nl/index.php/SwitchAntidepressants)

For the complete list of references and links to useful resources go to: [www.ti.ubc.ca/letter112](http://www.ti.ubc.ca/letter112)

## CURRENT ADR NETWORK REPORT

### Impulse control disorders with combinations of aripiprazole (ABILIFY, generic drug) with other neuroleptics

During a manic phase a 60-year-old man with severe bipolar disorder received aripiprazole (ABILIFY, generics) in addition to existing neuroleptic medication, a combination which he then remained on. A year later he mentioned that he had been playing on gambling machines for a long time. Looking back he was no longer able to determine the precise date on which he started, but the urge to play disappeared following discontinuation of aripiprazole and did not return after a year (NETZWERK report 17.344). Impulse control disorders such as gambling addiction or excessive sexuality that initially appeared in patients receiving dopaminergic drugs to treat PARKINSON's disease such as pramipexole (SIFROL, generics) (a-t 2004; 35: 36 and 2005; 36: 84) have also been

documented in combination with atypical neuroleptics, particularly aripiprazole (a-t 2014; 45: 32 and 2016; 47: 68). In contrast to other antipsychotics, the partially agonistic effect of aripiprazole on dopamine receptors is currently under discussion as a possible cause. Prior treatment with other neuroleptics appears to increase this effect, possibly because the dopamine antagonistic drugs cause increased dopamine sensitivity (1). A worsening of psychoses with aripiprazole was therefore feared already on introduction of aripiprazole to the market, particularly when patients who had received previous treatment were switched to it (a-t 2004; 35: 81-2). References to the possible interaction can also be found in two overview articles in which 43 and 22 reports of psychiatric adverse effects including impulse control disorders

with concomitant use or when switched from or to aripiprazole were evaluated (2, 3). Doctors should inform patients and their close relatives and friends of the possible development or worsening of impulse control disorders or other psychiatric adverse effects when taking aripiprazole and should avoid combining it with other neuroleptics.

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