INTERNATIONAL SOCIETY OF DRUG BULLETINS

Newsletter

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CONTENTS

WELCOME TO THE THIRD ISDB NEWSLETTER OF 2024

This issue provides several items of news and food for thought from ISDB Members:

- An article from *Arzneiverordnung* in der Praxis (Germany), celebrating this year 50 years of independent drug information and challenges beyond.
- An article about *Australian Prescriber*'s recent history and experience, and how it was ultimately saved when its host organisation, NPS MedicineWise, went under.
- Two articles on prescribing cascades published in *Prescrire International* (France) and by *Therapeutics Initiative* (Canada)
- An article co-authored by David Healy (*RxISK*), providing food for thought on legal aspects of SSRI-induced violence

And last but not least, positive news from Ireland on disengagement from pharmaceutical industry funding.

Enjoy your reading!

THE NEXT NEWSLETTER IS PLANNED FOR DECEMBER 2024

We welcome comments, suggestions and articles. Please send them to rkessler@prescrire.org by mid November 2024.

Help save GeBu, the Dutch independent bulletin on medicines!

Geneesmiddelenbulletin (GeBu), the Dutch ISDB member, provides independent and objective information to healthcare professionals in the Netherlands to promote rational pharmacotherapy and the rational use of medical devices.

The Dutch Ministry of Health, Welfare and Sport has decided to discontinue funding for GeBu from January 2026.

Please sign the petition to help save GeBu!
https://chng.it/mgtfktMVZR

News from ISDB Members

50 years AVP, Arzneiverordnung in der Praxis (Germany), 50 years independent drug information

The independent, evidence-based drug bulletin of the Drug Commission of the German Medical Association (DCGMA), "Arzneiverordnung in der Praxis (AVP)" (English: Drug prescribing in clinical practice"), is celebrating its 50th anniversary in 2024. For an independent drug bulletin, 50 years is an outstanding achievement: 50 years of critical and evidence-based debate about drug advertising, about biased information, alleged experts´ opinions and convenient giveaways from the pharmaceutical industry such as pens, sticky notes, and gummy bears. As the pharmaceutical industry benefits from enormous resources and "invests" more in marketing and advertising than in research and development, we are more than proud to have been providing German physicians with independent, evidence-based information on medicines for so long without any advertising or funding by the pharmaceutical industry.

How did it start?

At the end of the 19th century, the industrial revolution led to the development of a large pharmaceutical industry. This replaced the individualized production of drugs by large-scale industrial production of drugs on stock. Drug advertising grew exponentially neglecting any risk by providing incomplete, misleading, or false information about efficacy and safety of new medicines. The resulting dangers in medical treatment led to the formation of the Drug Commission of the German Society of Internal Medicine by the pharmacologist Wolfgang Heubner and the physician Adolf Schmidt in 1911. They aimed to create an independent medical institution for the assessment of medicines. From 1925, the commission published the handbook "Arzneiverordnungen" (English: Drug Prescriptions), providing German physicians with the very first independent guidance on rational drug therapy. The handbook was issued every two to three years and included a selection of medicines proven to be effective and not harmful. The last version of the handbook was issued in 1938, before the 2nd World War (figure 1).

Figure 1: The 7th edition of the handbook "Arzneiverordnungen" (English: Drug Prescriptions), 1937, Berlin

The Drug Commission was re-established in 1952 as the Drug Commission of the German Medical Association. From then on, the commission functions as a scientific expert committee of the German Medical Association (GMA) on all questions of pharmaceutical policy.

To provide physicians with latest drug information between editions of the handbook "Arzneiverordnungen", a complementary format was developed in 1974: a drug bulletin "Arzneiverordnung in der Praxis (AVP)". The first issue consisted of four simple pages (figure 2) on one main theme: cardiac glycosides. The bulletin´s aim was to provide physicians with "concise and scientifically correct advice" in the format of short reports on current therapeutic topics. It also included overview price tables to increase the drug market transparency as well as reports on pharmaceutical regulation and drug safety.

In 1981, AVP - now comprising 8-12 pages - reached over 60,000 general practitioners. Physicians in hospitals and medical students accessed AVP via special distribution sponsorships. In the 1990s, AVP was regularly enclosed within the German Medical Journal, taking the risk of being thrown away unread with the many promotional brochures that were also enclosed. Since 2014, AVP has been published exclusively online and is available free of charge on the DCGMA´s website. While AVP initially targeted general practitioners, today, the online bulletin offers a wide range of information on medicines, including cross-sectoral and interdisciplinary topics.

In 2005, AVP became a full member of the International Society of Drug Bulletins (ISDB). From then on, we are incredibly proud of this membership and also very appreciative for the inspiring exchange and communication with other independent bulletins from all over the world.

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Figure 2: The 1st edition of the drug bulletin "Arzneiverordnung in der Praxis (AVP)" (English: Drug prescribing in practice), 1974, Berlin

How do we work?

The DCGMA consists of up to 40 full members and approximately 135 associate members from all areas of medicine and pharmaceutical science. It is funded by the GMA and also by the National Association of Statutory Health Insurance Physicians. All members work voluntarily for the DCGMA. The main tasks of the commission are advising the GMA in fundamental questions of pharmaceutical policy and special requests of physicians as well as official institutions of health care. Furthermore, DCGMA provides physicians with independent, evidence-based information on rational drug therapy, drug safety and medication safety.

As an expert committee for pharmacological science DCGMA submits written and verbal statements on the benefit assessment of medicinal products in accordance with the German Social Code, Book Five (SGB V), section 35a ("early benefit assessment" within the first six months after market launch of novel drugs).

According to the professional code of conduct of German physicians all adverse drug reactions must be reported to the DCGMA. Therefore, DSGMA also acts as a national pharmacovigilance center, which processes physicians´ adverse drug reactions reports.

Carrying out these tasks, the independence of its members is of tremendous importance for the DCGMA. Since 2002 all full and associate members must declare their potential conflicts of interest to the chairman of the DCGMA.

AVP obtains content ideas from the DCGMA´s topics: therapy recommendations and guidelines, early benefit assessment of new medicines, reports on adverse drugs reactions and medication errors. Five DCGMA´s members are appointed by the board of DCGMA to build AVP´s editorial board. They decide on the topics and content of AVP, recruit independent, non-paid authors, and contribute themselves. They are actively supported in their work by scientific and office staff of the GMA, as the GMA is the publisher of AVP.

What´s next?

Today, we are facing a fast-moving flood of information and insidious marketing strategies of the pharmaceutical industry: pseudo-innovations through minor changes to medicines no longer under patent protection; extension of indications for ever smaller subpopulations with questionable benefits; novel medicines marked as safe because rare and very rare side effects do not occur in small pivotal studies.

It is almost impossible to stay on top of this when also facing the increasing challenges of daily medical practice. We are all in need of reliable information partners. This is crucial for physicians - but also for other healthcare professionals - because health or even human lives may depend on their actions. In the future, interpreting medical information correctly might become even more important in the light of the increasing use of artificial intelligence in this field.

Over the last 50 years, AVP has evolved from a humble four-page supplement to a modern, online drug bulletin and reliable information partner for German physicians. Today, AVP is one of the DCGMA´s most popular information products and has become a symbol of independent, evidence-based, and transparent drug information in Germany (figure 3). AVP is committed to carry on providing physicians with transparent, independent, and evidence-based information on rational drug therapy, drug safety and medication safety. We are looking forward to doing this hopefully for at least another 50 years.

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Figure 3: The anniversary edition of "50 Jahre Arzneiverordnung in der Praxis (AVP)" (English: 50 Years Drug prescribing in clinical practice), 2024, Berlin, available in German: www.avponline.de

More information available here

Australian Survivor
How Australian Prescriber was saved

John S Dowden, former Editor Australian Prescriber (no longer involved in Australian Prescriber or Therapeutic Guidelines)

Introduction

I am John Dowden the former editor of *Australian Prescriber* and a past member of the committee of the International Society of Drug Bulletins (ISDB).
Australian Prescriber has been reviewing drugs and therapeutics in Australia since 1975 and was one of the founder members of the ISDB. The journal was started by the Australian Department of Health, but in 2002 the publication was taken over by the National Prescribing Service (later known as NPS MedicineWise).
NPS MedicineWise was an independently managed organisation with an initial focus on activities to promote the quality use of medicines. As the quality use of medicines was part of the Australian National Medicines Policy, the funding for NPS MedicineWise came from the Australian government. There was a separate contract for NPS MedicineWise to publish *Australian Prescriber*. This ensured the continuity of publication and preserved the independence of the journal.
From 2018, problems emerged regarding the funding of NPS MedicineWise. These problems increased and eventually threatened the existence of *Australian Prescriber*.
This is my account of what happened, how *Australian Prescriber* survived and some lessons for other ISDB members.

Problems with the publisher

The funding arrangements with NPS MedicineWise worked well for many years and *Australian Prescriber* was able to develop and expand its readership. While there was a growing online readership, many health professionals still preferred a printed journal, so the print circulation of each issue was over 50,000 copies. However, this changed in 2015 when the contract for publishing *Australian Prescriber* was combined with the main funding contract for NPS MedicineWise. The managers of NPS MedicineWise then decided that print publication of *Australian Prescriber* should stop. The last print issue rolled off the presses in June 2016.[1]

Australian Prescriber had been one of the first medical journals in the world to make its full text freely available online, having established its own website as early as 1996. However, under the new contract, the management of NPS MedicineWise also decided that the *Australian Prescriber* website should be incorporated into a new NPS MedicineWise website. That change did not go smoothly and the online readership fell. It took about three years to restore the number of readers to what it had been on the original *Australian Prescriber* website.

Around this time NPS MedicineWise was looking for new sources of funding. This decision included setting up a commercial subsidiary to generate revenue. Controversially, some of this commercial activity involved the pharmaceutical industry. Media reports in 2016 suggested that NPS MedicineWise had sold its soul to big pharma.[2]

The storm

In 2018 the contract between NPS MedicineWise and the Department of Health was renewed, however there was a substantial reduction in government funding. In turn, the management of NPS MedicineWise significantly reduced the budget of *Australian Prescriber*.

The effects of this budget cut included a reduced number of editorial meetings and, even though the journal was now only available online, the abolition of the position of the Digital Production Co-ordinator. There was also the loss of the *Australian Prescriber* library including its collection of ISDB publications. Some of the *Australian Prescriber* archives were saved by the University of South Australia, but many were destroyed. The *Australian Prescriber* office was also closed with the staff being relocated to an office shared with other businesses.

In addition to the new contract, the Department of Health ordered an inquiry into the activities of NPS MedicineWise. Although the submissions to this review were required by the end of January 2019, the 119-page report was not published until December 2019. The review made 37 recommendations.

Recommendation 19 was that *Australian Prescriber* should continue to be published.[3]

In April 2020 the government confirmed it supported all the recommendations of the review.4 In view of the outcomes of the review, the board and management of NPS MedicineWise decided to wind up its commercial subsidiary.[4] They also undertook to implement the other recommendations of the review.

One of these recommendations was to look at the efficiency of another NPS MedicineWise publication and whether it should be consolidated with *Australian Prescriber*. However, the management of NPS MedicineWise then proposed that *Australian Prescriber* should stop reviewing new drugs. I did not think that this was what the recommendation had intended. All ISDB members will know that reviewing new medicines is a very important role for drug bulletins. To have no reviews of new drugs in Australia's national journal of drugs and therapeutics made little sense. Thankfully, the proposal seemed to disappear after I had advised the Department of Health of the management's plan. To add to this turmoil in 2021 the Chief Executive Officer of NPS MedicineWise resigned and this key position then remained vacant for several months.

There seemed to be little remaining trust between the Department of Health and NPS MedicineWise. In March 2022, it was announced that ongoing funding for NPS MedicineWise was no longer certain. Some of its functions would be transferred to another agency and for other functions NPS MedicineWise would have to submit tenders to compete for government funding with other organisations wanting to provide services related to the quality use of medicines. There was no guarantee NPS MedicineWise would be successful in winning enough tenders to enable it to continue to support its activities, staff and infrastructure.

Complicating these developments in 2022 was a looming federal election. An approach was made to the then opposition party about the proposed changes to the funding of NPS MedicineWise. That political party agreed to review the decision, if it was elected.[5] The government did change in May 2022 and a review of the decision was announced in July. This review was conducted by the consulting company Deloitte.

The Australian Prescriber campaign

The Editorial Executive Committee of *Australian Prescriber* was well aware of the problems of NPS MedicineWise. The members therefore agreed to campaign to save *Australian Prescriber*. This campaign had the support of the new Chief Executive Officer of NPS MedicineWise, but the organisation itself could not be involved. It was therefore down to the members of the Editorial Executive Committee, assisted by the editorial team, to lead the defence. With the stakes so high, several strategies were needed.

Rallying supporters

Every month over 300,000 people look at *Australian Prescriber* online. A digital petition was therefore an effective way to involve the readers.[6] The petition was organised through Change.org and within days several thousand people had given their support. Some even offered money to help save *Australian Prescriber*.

Since it began in 1975, *Australian Prescriber* has had a large Advisory Editorial Panel. This consisted of representatives of the major health professional colleges and societies. The Editorial Executive Committee wrote to all the representatives seeking their support and asking them to inform their organisations about what was happening with the journal. There was a great response with over 30 organisations pledging support for *Australian Prescriber* and some even writing directly to the Minister of Health. The Minister also received a letter from one of his constituents who happened to be a member of the Editorial Executive Committee!

Media

Australian Prescriber routinely provided a media release with each issue. The medical media and some of the general media were therefore interested in what was happening with NPS MedicineWise.[6] This gave the Editorial Executive Committee an opportunity to talk about *Australian Prescriber*.

Consulting the consultant

Although the Editorial Executive Committee was unable to have a meeting with the consultant from Deloitte, it was able to provide him with lots of information about *Australian Prescriber*. This included all the positive feedback from the readers and the health professional organisations, in addition to statistics from the latest readership survey.

Outcomes

The consultant reported to the Minister in August 2022. He upheld the previous decision to change the funding of NPS MedicineWise. However, the consultant had been impressed by the *Australian Prescriber* campaign. The report recognised that *Australian Prescriber* was 'considered an important resource that should be maintained as it is a reference relied upon by health professionals to remain up to date in the prescribing and use of new medications in Australia and optimal use of existing medications'. The consultant concluded that a transition plan would be needed to reallocate the NPS Me-

dicineWise functions, 'most notably the ongoing preparation and publication of *Australian Prescriber*.' [7]

The Board of NPS MedicineWise disagreed with some of the consultant's observations and decided not to enter into competitive tendering arrangements.[8] In September 2022 the Board announced that the company would be liquidated by the end of the year.[9] Its functions would either be transferred, put out to tender or discontinued.[10] All staff, including the *Australian Prescriber* team, would lose their jobs.

Three months to live

Although NPS MedicineWise was doomed, I had every confidence that *Australian Prescriber* would find a new publisher. Any publisher would be interested in having a readership of thousands of health professionals. In the three months before the December liquidation date, the editorial team had to make sure all our process and procedures were documented and the files updated so that they could be held by the Department of Health until they could be transferred to a new publisher.

In October 2022 the editorial team gave a presentation to the Department of Health. This explained the growth and success of *Australian Prescriber* as an independent source of trusted information about medicines. An important point was that it would appear odd if the actions of the Department of Health resulted in the destruction of a publication it had established to meet the needs of health professionals.

The work of the Editorial Executive Committee continued uninterrupted on the assumption that a new publisher would be appointed in early 2023. However, the Department of Health did request that no new authors be commissioned at the final meeting of the Editorial Executive Committee which was held in Sydney on 25 November 2022. The last issue of *Australian Prescriber* under the ownership of NPS MedicineWise was published in December 2022.[11] The final editorial reported on the demise of NPS MedicineWise after 24 years of supporting Australian health professionals.[12]

The ISDB intervention

Professor Barbara Mintzes alerted ISDB to what was happening in Australia at the ISDB General Assembly in November 2022. While this was after the decision to liquidate NPS MedicineWise had been made, the response of ISDB was important. The organisation wrote to the Minister of Health and several individual member bulletins wrote their own letters.[13] Although it was too late to save NPS MedicineWise, this international support added strength to the case for finding a new publisher for *Australian Prescriber*.

Limbo

The Editorial Executive Committee hoped that the tender to publish *Australian Prescriber* would be issued by the end of 2022 to ensure continuity of publication. Several articles had been drafted for the next issue. However, the tender was not released until mid-January 2023 and interested companies then had until 27 February to apply.

As I had predicted, there were many companies interested in publishing *Australian Prescriber*. There may have been others, but the publishers who contacted me for information ranged from small start-up businesses to large international companies. One major publisher offered to pay me to assist with its bid, but I declined because I wanted to be able to provide information to any of the bidders. In particular, I wanted to make sure they were all aware of the importance of editorial independence in drug bulletins. It was a concern, but probably not surprising, that one of the commercial publishers was looking at changing the editorial process in ways I think would have reduced the quality of *Australian Prescriber*.

Survival

I suspect the Department of Health underestimated the interest there would be in taking over *Australian Prescriber*. It took until May 2023 to announce the winner of the tender process. The successful bid was by Therapeutic Guidelines.[14,15] This not-for-profit organisation was a good choice and will be familiar to many members of ISDB. The staff of Therapeutic Guidelines worked hard to quickly absorb *Australian Prescriber* and the first issue published by Therapeutic Guidelines appeared online in June 2023.[16] With *Australian Prescriber* in safe hands it was time for me to retire!

Lessons for ISDB members

All bulletins need funding to operate. For those bulletins that rely on grants there is always the risk of that funding being removed. This happened to *Australian Prescriber* in 1982 with the journal going out of publication until it was refunded in 1983.[17] Forty years after that event, there was a danger history was repeating itself. What can be done if your bulletin is under threat?

Maintain good relationships with the funders

It is important for the funders to know that they are getting good value for their money. Bulletins should be able to explain what they are doing and provide statistics to support their claims. Readership surveys can be a useful source of data.

Editorial board support

Most bulletins have an editorial board or committee. The members may include prominent people who can promote the cause of the journal. All members should be willing to lobby to keep the bulletin in publication. This could include writing letters, making phone calls seeking support and giving media interviews.

Rally the readers

The readers of your bulletin are your best supporters. If they value the information you publish, they will want it to continue. Keep them informed about what is happening and invite them to support you. The response to the *Australian Prescriber* petition was tremendous. Many voices are likely to be heard.

Support from the professions

Professional organisations such as medical colleges and societies want to promote best practice. As this is also an aim of drug bulletins, the professional organisations are likely to be willing to give their assistance. This may take time to arrange, but it is worth asking for their support.

Media

Drug bulletins have a good story to tell. Even if your bulletin does not usually deal with the media, it can be worthwhile to find a journalist who is interested in a story about why your bulletin is under threat.

Political lobbying

For some bulletins in difficulty, it may be appropriate to talk to politicians if they can influence the funding of the bulletin. However, there can be risks, so any approach must be considered carefully. The defunding of NPS MedicineWise was raised in the Australian Parliament but this did not change the outcome. [18]

Conclusion

The demise of NPS MedicineWise resulted in the fragmentation of activities related to the quality use of medicines. [19] *Australian Prescriber* is one of the activities that survived. Its survival was due to a multifaced campaign which involved the readers and the support of key organisations including ISDB.

Acknowledgement

Thanks to Barbara Mintzes for commenting on an earlier version of this article.

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Legal aspects of SSRI-induced violence

By Andre Marx (GP, Stockholm) and Dr. David Healy, RxISK

Forty-eight hours after being prescribed paroxetine for insomnia in 1998, Donald Schell shot his wife, his daughter, his grand-daughter and himself. Tobin v SmithKline Beecham in 2001 returned a verdict that «Paxil (paroxetine) can cause certain individuals to commit murder and/or suicide» and that SmithKline Beecham «knew, or should have known, that Paxil (...) can cause certain individuals to commit murder and/or suicide".

At trial, GlaxoSmithKline (GSK) argued their clinical studies ruled out the possibility that paroxetine could cause any behavioural problems. Many prior cases had been settled, notably Fentress v Eli Lilly in 1994, following a 1989 killing of 8 people along with the shooter who had injured 11 others. The shooter had been taking fluoxetine (Prozac).

In the 1980s, prior to marketing the selective serotonin reuptake inhibitors (SSRI), fluoxetine, sertraline and paroxetine, company healthy volunteer studies showed these drugs could trigger suicidality and homicidality. The studies, however, are not in the public domain. The first published articles outlining cases of SSRI-triggered violent impulses, primarily suicidal, appeared in 1990 with approximately 20 further reports in the following months. Compulsive and violent thoughts appeared within weeks of starting treatment. In several cases, challenge with the medicine caused the problem, which cleared on discontinuation, and reappeared on rechallenge. In terms of medical causation, this sequence is viewed as offering strong evidence for cause and effect.

Company responses to publications on violence claimed randomized clinical trials (RCTs) provide a science of cause and effect and analyses of company RCTs showed no evidence their drugs caused suicide or homicide. Dismissing apparently compelling clinical cases as anecdotal, companies claimed depression rather than SSRIs caused the problems.

In line with this response, from the mid-1990s in both criminal and civil cases, companies distinguished between general and specific causation. They argued that if RCTs did not in general show their drug caused violence, specific cases in which there was apparently strong causal evidence should be dismissed.

Company RCTs test for a benefit companies hope to make money from; they are not designed to investigate whether their drug causes violence or other problems. The fact that on average husbands do not murder wives does not mean that where the evidence strongly indicates this husband did murder his wife juries are wrong to find him guilty.

In a recent ruling, the Southern District of California sidestepped the issue of the average beneficial effects companies claim for their drug, ruling that [1]:

Courts define general causation to mean "whether the substance at issue had the capacity to cause the harm alleged."

We now know about pertinent features of company trials not apparent in the 1990s. First company claims are not based on publicly available evidence. Suicidal events commonly disappeared behind coding rubrics. Some of the articles reporting trial results are ghostwritten - written by medical writers with added academic names chosen by company marketing departments. Studies in which drugs were ineffective and unsafe have been published as safe and effective. Rather than meeting legal or scientific standards for evidence, company studies are effectively hearsay.

There are three other areas to note. First, the status of the serotonin system on which these drugs act. Second, a distinction between treatment effects and mental illness. Third, these treatments are available on prescription-only.

SSRI drugs originated in Sweden with Arvid Carlsson. He expected that acting on a normal serotonin system, SSRIs would produce a serenic (anxiolytic) effect. In line with regulatory statements that prescription drugs are unavoidably hazardous, acting on a normal system risks throwing it out of joint and causing problems, as LSD can. Compared with an action on a normal serotonin system with potentially unpredictable consequences, company claims that treatment corrects an abnormality makes serious behavioural disturbances seem less likely. There is no evidence for a serotonergic abnormality in any mental disorder.

Assigning responsibility for violence induced by treatments acting on behaviour interfaces with the assignment of responsibility in cases where the perpetrator is mentally ill. In general legal systems have been reluctant to entertain claims that mental illness excuses criminal behaviour. There are, however, two exceptions. Brain damaged patients unable to conform their behaviour to social norms are not held responsible. Cases of delirium, which compromise the formation of intent, also offer an absolute defense against a guilty verdict.

Antidepressants tap into both these mechanisms. Their action on sensory systems can generate restlessness and irritability, commonly called akathisia. Genital akathisia can trigger persistent involuntary orgasms that are so distressing women resort to clitoridectomy to relieve the problem.

When thinking about responsibility for a behaviour legal systems have in general dealt with the motor behaviour implicit in a voluntary action. The effects of SSRIs to generate emotional numbing or akathisia have more in common with the effects of LSD on sensation or perception which judicial thinking has not specifically addressed to date. These drug-induced effects drugs produce involuntary, ego-alien impulses for which drastic remedies can appear to offer the only relief. These are delirious states that can be expected to resolve when the treating agent is removed, rather than features of an enduring mental illness.

SSRIs can also produce versions of their target serenic state that leave takers profoundly emotionally numb and not inhibited by anxiety about the consequences of their actions. Although rare, these events are extremely troubling. A society hostess may be unaware of the impropriety of greeting her guests topless. Takers can watch videos of ISIS beheadings 'in order to be able to 'feel'. These drugs require more than normal monitoring of behaviour to ensure it conforms with social norms, but few if any doctors check for this.

These mechanisms make unintentional and deviant behaviour more likely. An additional factor adds to the legal dilemmas these drugs pose. When behaviours of this kind are triggered by illicit drugs, we hold the taker responsible for the consumption of the illicit agent. When the causative agent is a prescription drug, the consumer is the doctor rather than the patient who takes 'as ordered'. Doctors consume without experiential consequences, and often in the face of efforts by the patient to alert them to impending problems. In a de facto Stockholm syndrome, patients taken hostage in this manner are commonly reluctant to go against their medical captor who can appear the best means of escape from an increasingly dangerous situation.

The problems outlined here arise from the action of drugs on normal physiological systems. They may be idiosyncratic but are not unexpected nor recently discovered. These factors combined have produced legal scenarios that require judicial input. How best to assign responsibility? Are there ways to reduce the risks?

Other interesting articles:

- Healy D, Herxheimer A, Menkes DB (2006) Antidepressants and violence : problems at the Interface of Medicine and Law. PLoS Med 3(9):e372. Article available here
- Andre Marx (GP, Stockholm) is author of Loved, Hated antidepressants

On October 5, David Healy will participate in a panel discussion on "Antidepressants and homicide - Understanding automatism spectrum disorders". More information is available here ; see MIA events here

1- 524 F.Supp.3d 1007, United States District Court, S.D. California. IN RE INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION, Case No.: 13-md-2452-AJB-MDD, Signed 03/09/2021

Prescribing cascades: recognise them and take corrective action

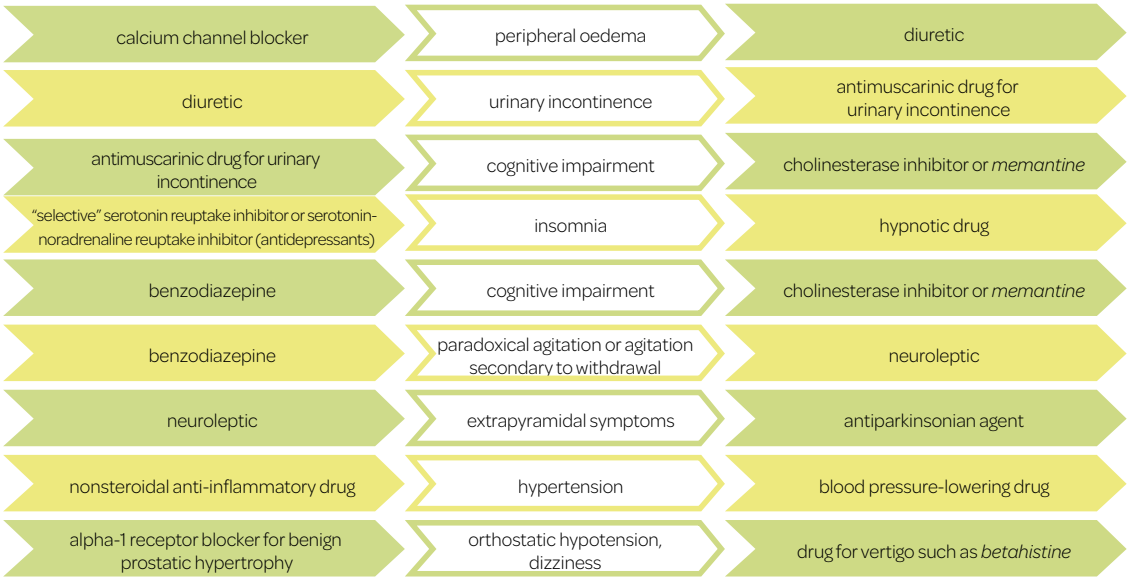
● Using a systematic literature review, a team identified situations in which a drug was prescribed to treat a disorder caused by another drug. Around ten prescribing cascades turned out to be particularly problematic in older patients, due to their clinical consequences, the frequency with which the drugs involved were prescribed, or the severity of potential adverse effects, whereas alternatives were available.

A prescribing cascade starts when a drug is added in order to treat a disorder that is, in fact, an adverse effect of ongoing drug therapy, but which has not been recognised as such (1).

A large number of prescribing cascades, sometimes at multiple levels, can be uncovered by analysing the drugs patients are taking, including dietary supplements and other self-medication products (2). For example, in 2022, one study showed that patients taking *pregabalin* or *gabapentin* were more likely to be prescribed diuretics than those not taking these drugs, whereas peripheral oedema is a known adverse effect of these gabapentinoids (3).

A group of specialists in geriatric pharmacotherapy carried out a systematic literature search and identified 139 prescribing cascades. They then organised a critical analysis of this list of cascades by 40 healthcare professionals involved in geriatrics (geriatricians, general practitioners, pharmacists and nurses) from several countries. The 139 cascades identified were analysed according to their clinical consequences, the frequency with which the drugs involved were prescribed, the severity of the potential adverse effects, the availability of alternatives, etc.

Figure. **Prescribing cascades that are particularly problematic in older patients** (based on ref. 1)



ADVERSE EFFECTS

At the end of this process, 9 cascades were considered to be particularly problematic in older patients (1). They are illustrated in the table below.

Some drugs used in these cascades for treating a disorder which is in fact an adverse effect of a drug, such as cholinesterase inhibitors or *memantine* to treat drug-induced cognitive impairment, are furthermore on Prescrire's list of drugs to avoid because they are more dangerous than beneficial (4).

IN PRACTICE The adverse effects of drugs sometimes lead to adding another drug to ongoing treatment, in the hope of alleviating such adverse effects, or because the drug-related origin of the disorder has not been identified. The additional drug then itself carries a risk of further adverse effects. The combined treatments become more and more hazardous, which is even more of an issue when the efficacy of the drug triggering the cascade has not been demonstrated.

When faced with a scenario of multiple prescriptions linked to adverse effects, it is helpful to regularly re-assess the situation as a whole, to review treatment goals with the patient, and to look for a treatment that is both simpler and more suitable (5,6).

More generally, when faced with any disorder, one should ask oneself: "Could a drug be responsible?". When a new disorder is observed, considering the possibility that it is a drug-induced adverse effect can benefit patients, and may spare them from exposure to additional, unnecessary drugs.

► Translated from *Rev Prescrire* September 2023
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Selected references from Prescrire's literature search

1- McCarthy LM et al. "ThinkCascades: A tool for identifying clinically important prescribing cascades affecting older people" *Drugs Aging* 2022; **39**: 829-840.
2- Therapeutics Initiative "Reducing prescribing cascades" *Therapeutics Letter* 2022; **138**: 4 pages.
3- Prescrire Editorial Staff "Gabapentin and pregabalin result in the prescription of diuretics" *Prescrire Int* 2022; **31** (239): 190.
4- Prescrire Editorial Staff "Towards better patient care: drugs to avoid in 2023" *Prescrire Int* 2023; **32** (245): 50-53 (full version: 11 pages), free to download at english.prescrire.org.
5- Prescrire Rédaction "7 principes pour une bonne pratique face aux risques d'interactions médicamenteuses" Interactions Médicamenteuses Prescrire 2023.
6- Prescrire Editorial Staff "Treatment goals: discuss them with the patient" *Prescrire Int* 2012; **21** (132): 276-278.

Reducing prescribing cascades, Therapeutics Initiative, Canada

In September 2022, Therapeutics Initiative, published Therapeutics Letter 138 on "Reducing prescribing cascades".

The focus is on common examples that commonly lead to prescribing cascades. This includes anticholinergic drugs such as specific antidepressants, antipsychotics and drugs for urinary incontinence that can cause cognitive dysfunction, leading to prescribing for dementia. On the other hand, drugs for dementia can lead to urinary incontinence, and prescribing of anticholinergics. Anticholinergics lead to reflux and heartburn, leading to prescribing of proton pump inhibitors (PPIs). And the list goes on...

Conclusions:

– Prescribing cascades cause avoidable polypharmacy and harms.

– Prevent them by careful indication-based prescribing and screening for cascades during medication reviews. Use expert pharmacist or medical consultation when available.

– Start by familiarization with cascades involving drugs common in primary care; reduce doses if deprescribing seems too radical.

– Identifying a prescribing cascade is a teachable moment: use it.

Full article available here

Other news

No free lunch: disengagement from pharmaceutical Industry funding

ICGP, the Irish College of General Practitioners, decided to stop accepting pharmaceutical industry funding at their Annual General Meeting in May 2024. They will gradually reduce the amount of industry funding they accept by 10% each year and stop accepting this funding altogether in 2034. This is an enormously important step towards independence from industry of a professional society that represents over 5000 Irish GPs. It took leadership, willingness to challenge the status quo, a strategic alliance, and rigorous evidence to support the need for independence. More information is available on a new guest blog (published on the HAI- Health Action International - website).