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The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) are science-based federal agencies that should promote medical research, not censor studies because their findings undermine Health and Human Services (HHS) Secretary Robert F. Kennedy Jr.'s anti-vaccine agenda.

In recent months, however, both the CDC and FDA have blocked publication of studies supporting widely used vaccines against COVID-19 and shingles (herpes zoster). Suppressing scientific research exposes the nonsense of Kennedy's frequently repeated claims that he would bring "gold standard" science and "radical transparency" to the nation's public health agencies.

In April 2026, the acting director of the CDC blocked publication of a COVID-19 vaccine effectiveness study in the Morbidity and Mortality Weekly Report (MMWR), the agency's leading scientific journal.

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Outrage of the Month: Censorship of CDC and FDA Vaccine Studies

Article published in the June 2026 edition of Public Citizen's Health Letter
By Robert Steinbrook, M.D., Director, Public Citizen's Health Research Group

The report, which had been scheduled for publication in March, showed that the 2025-2026 vaccines were about 50% effective during the first months after vaccination in preventing hospitalizations as well as emergency department and urgent care visits among adults who were not immunocompromised (September-December 2025).

Dr. Jay Bhattacharya, director of the National Institutes of Health and earlier this year the acting CDC Director, disputed the characterization of his actions as "blocking" publication in the MMWR, stating instead that he "raised specific concerns about the statistical methodology chosen for the study in question." In fact, the methodology has been widely used in peer-reviewed publications on COVID-19 vaccine effectiveness and was also used in a December 2025 report in the MMWR about COVID-19 vaccine effectiveness in children.

Ironically, the censored report is available online. By censoring the research, the CDC likely focused more attention on it than it would have otherwise received.

Separately, the FDA blocked publication of studies supporting widely used vaccines against COVID-19 and shingles. In October 2025, FDA scientists were told to withdraw two vaccine safety studies about the 2023-2024 COVID-19 vaccines that had already been accepted for publication in medical journals. One study, which looked at safety monitoring of vaccination among commercial health plan enrollees ages 6 months to 64 years and was presented at a medical meeting in August 2025, found “no new safety concerns.” The other, which examined vaccine safety among Medicare beneficiaries aged 65 years and older, is available online as a preprint, an earlier version that has not undergone peer review. The study found “no new safety signals” as well as “a potential, but rare, elevation in anaphylaxis” risk (a severe, potentially life-threatening allergic reaction) associated with one of the vaccines.

In defending the withdrawal of the COVID-19 vaccine safety studies, a HHS spokesperson told The New York Times: “The studies were withdrawn because the authors drew broad conclusions that were not supported by the underlying data.” The comment reflected a misunderstanding of how peer-reviewed medical journals

work.

From my work as an editor at the New England Journal of Medicine and JAMA Internal Medicine, I know that journal editors routinely work with authors to revise manuscripts and to ensure that the conclusions follow from the data. I did that all the time.

Abstracts of the shingles vaccine studies, one about the safety of the Shingrix vaccine and one about the effectiveness of the same vaccine, were scheduled for submission to a drug safety conference. The Shingrix vaccine, first approved by the FDA in 2017, is used for prevention of shingles in adults aged 50 years and older and in adults aged 18 years and older at increased risk due to immunodeficiency or immunosuppression.

The Senate will hold confirmation hearings for the vacant positions of FDA commissioner and CDC director. The nominees must commit to reversing the decisions to block the studies and to allowing their prompt publication. The nominees must assure the American people that, if confirmed, the agencies they will lead will no longer censor the publication of scientific research. Bona fide public health agencies do not censor bona fide vaccine research.



NSAIDs + oral anticoagulants: a combination with a high risk of bleeding?

Folia Pharmacotherapeutica October 2025

Full article available at: www.cbip.be



KEY MESSAGES

In a (nationwide) Danish cohort study of patients taking **oral anticoagulants** (DOACs, warfarin) for venous thromboembolism, the concurrent use of **non-steroidal anti-inflammatory** drugs (NSAIDs) was associated with a more than **doubled risk of bleeding**.

The risk of bleeding was not the same for all NSAIDs studied: the highest risk was associated with naproxen, followed by diclofenac and then ibuprofen.

The increased risk of bleeding associated with anticoagulants + NSAIDs applied to all oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban, warfarin). The risk of gastrointestinal as well as intracranial bleeding was also increased.

Caution is therefore advised when prescribing an NSAID and an oral anticoagulant, including warfarin, at the same time. In patients taking an anticoagulant who require a painkiller, it is therefore useful to reassess the risk-benefit balance and consider alternative options before prescribing an NSAID. Patients can obtain certain NSAIDs without a prescription (e.g. ibuprofen, naproxen) and particular care is required when dispensing them.

Why is this study important?

NSAIDs are commonly used to relieve pain, fever and inflammation – symptoms that are frequently seen in patients with venous thromboembolism (VTE). It is therefore not uncommon for these patients to take an oral anticoagulant alongside an NSAID.

Concerns remain regarding the risk of bleeding when oral anticoagulants and NSAIDs are used concurrently. As NSAIDs affect platelet function and the gastric mucosa, particular (though not exclusive) attention must be paid to the potential for gastrointestinal bleeding.

Previous studies on this topic are limited, either due to an insufficiently large sample size or because only one type of anticoagulant was included in the study. We therefore do not know whether the risk of bleeding depends on the type of anticoagulant and NSAID, and whether any increased risk of bleeding is limited to the gastrointestinal tract or also applies to other organ systems.

Study design

This is a (nationwide) Danish cohort study utilising all outpatient and hospital data for the entire Danish population between January 2012 and December 2022. The study is based on a population of patients aged ≥ 18 years with a first episode of venous thromboembolism who, between 1 January 2012 and 31 December 2022, started treatment with a direct oral anticoagulant (rivaroxaban, apixaban, dabigatran or edoxaban) or a vitamin K antagonist (warfarin).

The aim of the study was to assess the risk of bleeding associated with the concurrent use of oral anticoagulants and NSAIDs in patients with venous thromboembolism.

The primary endpoint was a composite endpoint of 'all types of bleeding': hospital-diagnosed gastrointestinal, intracranial, thoracic/respiratory or urinary bleeding, or anaemia caused by bleeding.

The secondary endpoint comprised the individual components of the primary endpoint.

Patients with a history of bleeding diagnoses were excluded.

Results in brief

The cohort study included 51,794 patients with a first episode of VTE who had started treatment with oral anticoagulants (48% women, with a mean age of 69 years).

The incidence of all types of bleeding, expressed per 100 person-years, was 3.5 (periods with anticoagulant alone) and 6.3 (periods with anticoagulant + NSAID), regardless of the anticoagulant used. This corresponds to a Number Needed to Harm (NNH) of 36 [95% CI 24 to 72], meaning that treating 36 patients with an anticoagulant + NSAID (compared with an anticoagulant alone) for one year resulted in one additional bleeding event.

Risk of all types of bleeding associated with the use of oral anticoagulant + NSAID versus oral anticoagulant alone:

1

Risk of bleeding by type of NSAID	
All NSAIDs	2.09 (1.67–2.62)
Ibuprofen	1.79 (1.36–2.36)
Diclofenac	3.30 (1.82–5.97)
Naproxen	4.10 (2.13–7.91)

2

Risk of bleeding by type of anticoagulant:

- ♦ direct oral anticoagulants (DOACs): adjusted hazard ratio = 2.27 (95% CI 1.73 to 3.00)
- ♦ warfarin: adjusted hazard ratio = 1.79 (95% CI 1.16 to 2.76)

3

Risk of bleeding associated with the use of oral anticoagulants + NSAIDs versus oral anticoagulants alone, by bleeding site	
Gastrointestinal bleeding	2.24 (1.61–3.11)
Intracranial bleeding	3.22 (1.69–6.14)
Respiratory/thoracic bleeding	1.36 (0.67–2.77) (not statistically significant)
Urinary bleeding	1.57 (0.98–2.51) (not statistically significant)
Anaemia due to bleeding	2.99 (1.45–6.18)

Limitations of the study

This is an observational cohort study, so residual bias and confounding cannot be ruled out. Nevertheless, the national scope of the study, which is based on the entire population (nationwide), is likely to enhance the generalisability of the results to other populations and healthcare systems similar to those in Denmark.

Over-the-counter NSAIDs were not taken into account. Exposure to NSAIDs in the control group may therefore be underestimated.

Data on adherence to NSAID therapy are lacking; we do not know whether patients actually took their prescribed NSAIDs.

Comment from the BCFI

This study reminds us of the increased risk of bleeding – both gastrointestinal and intracranial – when combining an anticoagulant (DOAC, warfarin) with an NSAID.

Caution is therefore advised when prescribing an NSAID and an oral anticoagulant, including warfarin, at the same time. In patients taking an anticoagulant who require a painkiller, it is therefore advisable to reassess the risk-benefit ratio and consider alternative options before prescribing an NSAID. Patients can obtain certain NSAIDs without a prescription (e.g. ibuprofen, naproxen) and particular care is required when dispensing them.

As a reminder: The risk of bleeding is also increased when DOACs or vitamin K antagonists are combined with other medicines that can cause bleeding, such as SSRIs and SNRIs (see Folia December 2024).

Which medicines are affected?

Active substance	Brand names
Apixaban	Eliquis®
Dabigatran	Dabigatran(e), Pradaxa®
Edoxaban	Lixiana®
Rivaroxaban	Rivaroxaban(e), Xarelto®
Warfarin	Marevan®
Diclofenac	Cataflam®, Diclofenac(e), Motifene®, Voltaren®
Ibuprofen	Algidrin®, Brufen®, Ibuprofen(e), Nurofen®, Perdofemina®, Spidifen®
Naproxen	Aleve®, Apranax®, Naprosyne®, Naproxen

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Use of Independent Drug Information Sources by Clinical Pharmacologists and Clinical Pharmacists in CIS Countries: Results of a Survey Study

Natalia Cebotarenco, MD, PhD, editor in chief of MEDEX, Raikhan Tuleutayeva, MD. PhD, Semey Medical University.

Independent sources of drug information help physicians and pharmacists make evidence-based clinical decisions, ensure patient safety, resist promotional influence, and maintain a high level of professional competence. In the context of the continuous introduction of new medicines and the rapid expansion of clinical research evidence, the ability to identify, critically appraise, and effectively use reliable information has become one of the essential competencies of modern healthcare professionals.

In November 2025, CoRSUM (Coalition on Rational and Safe Use of Medicines) conducted a survey among clinical pharmacologists and clinical pharmacists from CIS countries to assess the information sources they use in their professional practice. Over a two-week period, 124 completed questionnaires were collected using Google Forms. Participants represented Kazakhstan, Belarus, Ukraine, Russia, Kyrgyzstan, and Moldova.

The findings revealed substantial differences in the use of professional information resources and highlighted important gaps in awareness and accessibility of several international drug information sources.

Most Frequently Used Information Sources

Respondents reported relying primarily on evidence-based medicine resources and national clinical guidelines. National clinical guidelines were the most frequently used source, with 65.8% of participants indicating regular use. Other highly utilized resources included PubMed (63.2%), Cochrane systematic reviews (55.3%), and the World Health Organization (WHO) Model Formulary (47.4%).

These findings suggest that healthcare professionals increasingly incorporate evidence-based resources and clinical practice guidelines into their therapeutic decision-making processes.

Underrecognized International Resources

Despite the widespread use of major evidence-based information sources, a considerable proportion of respondents reported being unfamiliar with several specialized international resources or not knowing how to access them.

The highest percentages of responses indicating "I do not know where to find this resource" were reported for Martindale: The Complete Drug Reference (36.8%), Briggs' Drugs in Pregnancy and Lactation (31.6%), international drug safety alerts (31.6%), British National Formulary for Children (BNFc) (31.6%), Therapeutic Guidelines Australia (30.3%), and the British National Formulary (BNF) (26.3%).

These results may reflect both limited access to specialized resources and insufficient awareness of internationally recognized tools that support evidence-based prescribing and medication management.

Use of International Clinical Guidelines

Analysis of open-ended responses demonstrated that many respondents actively consult guidance developed by international professional organizations and expert societies. Frequently mentioned resources included guidelines from the Infectious Diseases Society of America (IDSA), the European Society of Cardiology (ESC), Kidney Disease: Improving Global Outcomes (KDIGO), the European Alliance of Associations for Rheumatology (EULAR), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP Red Book). Respondents also reported using recommendations issued by the World Health Organization (WHO) and the European Medicines Agency (EMA).

These findings indicate a growing commitment among healthcare professionals to integrating international standards of diagnosis, treatment, and medication safety into routine clinical practice.

Emerging Digital Tools and Artificial Intelligence

Particular attention should be given to the emergence of digital decision-support tools among the information sources reported by respondents. Additional resources mentioned included GPT-based tools, specialized AI assistants for clinical pharmacologists, and the medical knowledge platform Empendium.

Although artificial intelligence cannot replace primary evidence sources, its increasing use reflects the development of a new model of information support in clinical practice. When used appropriately and combined with verification through authoritative references, AI tools may facilitate information retrieval, accelerate data analysis, and support clinical decision-making.

Conclusion

The survey demonstrated that clinical pharmacologists and clinical pharmacists across CIS countries widely use national clinical guidelines, PubMed, Cochrane systematic reviews, and the WHO Model Formulary. At the same time, significant gaps remain in awareness and utilization of specialized international drug information resources and medication safety references.

These findings highlight the need for continued development of medical and pharmaceutical education programs aimed at strengthening competencies in searching for, critically evaluating, and effectively using independent drug information sources. Particular emphasis should be placed on improving information literacy, expanding access to international evidence-based resources, and promoting the responsible use of modern digital technologies, including artificial intelligence, in healthcare practice.

Lecanemab (Leqembi®) in early Alzheimer's disease No tangible clinical efficacy, but established serious adverse effects



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 Full article available at: <https://english.prescrire.org/en>

In April 2026, Prescrire International published a critical assessment of lecanemab, the first anti-amyloid monoclonal antibody approved in the European Union for early-stage Alzheimer's disease, concluding that its risk-benefit profile remains unfavourable. The authors acknowledge that the Phase III CLARITY AD trial demonstrated a statistically significant slowing of cognitive decline compared with placebo. However, the magnitude of the observed benefit was deemed too small to be clinically significant, in the absence of convincing evidence of an improvement in quality of life, greater independence, a delay in admission to a care home or reduced caregivers burden.

The review also emphasises that, although lecanemab effectively reduces cerebral amyloid burden, no relationship has been established between amyloid clearance and clinically relevant outcomes, which limits the clinical significance of this biomarker.

Safety concerns represent the main limitation of the treatment. Lecanemab has been associated with an increased incidence of amyloid-related imaging abnormalities (ARIA), including cerebral oedema and haemorrhage, which can lead to serious neurological complications and have been fatal in some cases. Higher rates of infusion-related reactions, cardiac disorders, hypersensitivity reactions and treatment discontinuation have also been reported. Furthermore, the need for intravenous infusions every two weeks and repeated MRI monitoring further increases the complexity of treatment patients, caregivers, as well as the burden on the healthcare system.

Prescrire concludes that the modest efficacy observed with lecanemab does not outweigh its established safety risks. This position is consistent with the assessments of several independent organisations, including NICE and the French HAS, which have also questioned the drug's clinical value and its routine use in the management of early-stage Alzheimer's disease.

Antidepressant withdrawal

What patients and prescribers should know

Therapeutics Letter N. 156 - June 2025

Full article available at: <https://www.ti.ubc.ca/therapeutics-letter/>

PLAIN LANGUAGE SUMMARY

The Bottom line:

- ◆ Antidepressants can be helpful for some people; but starting or stopping requires care.
- ◆ Before starting, prescribers (doctors and nurse practitioners) should talk openly with patients about the risks of withdrawal, and make shared decisions about treatment and tapering.
- ◆ Knowing about the many types of possible withdrawal problems helps prescribers guide patients in stopping antidepressant drugs more safely.

What is antidepressant withdrawal and why is it important?

Antidepressant withdrawal is the problem some people have when they try to stop taking antidepressant medicines. It is now accepted that this can be much harder than many people and their prescribers realized. It is important for prescribers to help patients understand the withdrawal risks before patients decide if they want to start these medications.

What are antidepressant drugs?

Antidepressants are medications, supplied as pills or capsules. They are prescribed to help the patient manage strong feelings like being very sad for a long time (this is called depression) or feeling very worried and scared a lot without an obvious reason (this is called anxiety).

What happens when people take antidepressants?

The brain adapts itself to getting the medicine each day. This is called "tolerance". To feel normal, over time the person needs to take this drug that the brain has come to rely on. This is called "dependence". So, if the patient tries to stop the drug or take less of it, they can experience "withdrawal."

Can people have withdrawal symptoms when stopping antidepressants?

Yes. Stopping antidepressants - especially when people use them for a longer time - can lead to withdrawal symptoms (problems). These symptoms can be both mental (like panic attacks or depression) and physical (like feeling dizzy or having trouble with balance). For some people, these problems can be very hard to handle and can last a long time.

Why does this happen?

Antidepressants can change how the brain works. When

someone takes the drug for a longer time and then stops taking it suddenly or lowers the dose too quickly, the brain can struggle to adjust to not having the drug. This can cause withdrawal symptoms.

Are withdrawal symptoms the same as a return of depression or anxiety?

The symptoms may be different. Withdrawal symptoms can seem like a return of old problems, so it's important for prescribers and pharmacists to know the difference.

How common is this issue?

We don't know exactly how common. Using antidepressants for long periods of time, or years, makes withdrawal symptoms more likely. Some people can have withdrawal symptoms after much shorter periods, or even if they miss a dose. In the past, withdrawal risks were often downplayed. Now, we know better.

What should patients know before starting to take antidepressant drugs?

Patients should be informed clearly that:

- ◆ Their brain might get used to the medicine, making it hard to stop taking it later.
- ◆ Stopping can cause withdrawal problems that can be serious, last a long time, and sometimes be confused with relapse (return of the problems they were prescribed for).
- ◆ Prescribers should make sure that patients fully understand the risks and agree to the treatment before starting the medicine.

How should someone stop taking antidepressants safely?

Don't stop suddenly! Tapering the amount (slowly and carefully lowering how much of the drug is taken over time) is the safest way. Sometimes this is done using special customized smaller doses, prepared by a pharmacist.



Therapeutics Initiative

Better prescribing. Better health.

Antidepressant withdrawal syndrome - Update

ABSTRACT

► Background:

Antidepressants can cause tolerance, dependence, and withdrawal syndromes, often understated by the term “antidepressant discontinuation syndrome.” While they do not induce craving or compulsive use, brain adaptations to these drugs can make them hard to stop, especially after long-term use. Despite growing evidence of withdrawal risks, antidepressant prescriptions and long-term use continue to increase globally. The potential duration and severity of debilitating withdrawal symptoms, including akathisia, suicidality, and protracted withdrawal, have been minimized. This is partly due to commercially sponsored guidelines that relied on short-term clinical trial data.

► Aims:

Therapeutics Letter 156 updates evidence on antidepressant withdrawal syndrome, highlighting the potential for severe and prolonged symptoms. It encourages re-evaluation of prescribing practices, particularly in primary care, and suggests requirements for informed consent before patients start an antidepressant. Therapeutics Letter 156 also aims to distinguish withdrawal from relapse of an underlying mental illness. This topic will be explored further in Therapeutics Letter 157, which will examine deprescribing strategies in more detail, including “hyperbolic tapering.”



► Recommendations:

Prescribers should ensure patients provide fully informed consent before starting antidepressants, explicitly discussing the risks of tolerance, dependence, and potentially severe, prolonged, or even irreversible withdrawal symptoms. This includes warning about new-onset suicidality and chronic akathisia. Informed consent should be documented formally, ideally using consent forms tailored to the prescriber's practice. Patients should also be informed about the challenges of tapering, including the current lack of suitable drug formulations, and potential difficulties in finding experienced clinical support if withdrawal problems are severe.

Keywords: Antidepressive Agents; Deprescriptions; Drug Tolerance; Informed Consent; Patient Education; Primary Health Care; Risk Assessment; Substance- Related Disorders; Substance Withdrawal Syndrome.

Antidepressant withdrawal syndrome - Update

Vignette: A 53-year-old woman is new to your practice. Since the birth of her first child 19 years ago, she has taken extended release venlafaxine 75 mg/day for post-partum depression. At first she found the medication quite helpful. Now she wonders if her emotional blunting, sexual dysfunction, weight gain and mental fog could be due to the drug. She would like to stop venlafaxine, but is worried because of a difficult and ultimately unsuccessful attempt 5 years ago. After reducing the daily dose to the smallest capsule of 37.5 mg, she felt dizzy, experienced the first panic attacks of her life, and had trouble walking in a straight line. She says that when she started treatment after giving birth, she was not warned about the possible effects of withdrawal. A friend, who tried but failed to stop citalopram, urged her to consult you rather than trying to stop "cold turkey" on her own. How will you assist your new patient?



Summary and Conclusions

- Like other drugs that target the brain, antidepressants induce pharmacological tolerance and dependence. Not everyone finds it hard to stop an antidepressant, but for some the experience can be difficult and/or prolonged.
- Before they can provide informed consent to treatment, patients need to understand that withdrawal may be difficult. Formal documentation of consent could protect both patient and prescriber.
- Awareness of the range of withdrawal symptoms, and the possibility of protracted withdrawal, can facilitate safe deprescribing.

Introduction

Clinicians routinely alert patients to both the potential benefits and harms of drug therapy, especially for treatments that risk significant harms. Examples include insulins, steroid hormones, oral contraceptives, anticoagulants, cancer chemotherapy, and drugs with the potential to cause dependence or abuse.

Like benzodiazepines and opioids, antidepressants cause tolerance, dependence and withdrawal syndromes. The term "antidepressant discontinuation syndrome" is a euphemism that understates clinical problems patients can experience after dose reductions or deprescription.[1,2]

Antidepressants do not cause craving or compulsive drug-seeking, but the brain adapts to their pharmacological effects. Over a few weeks to months, this can make antidepressants difficult, or even impossible, to stop.[3,4]

In 2018, Therapeutics Letter 112 addressed the topic of

antidepressant withdrawal syndrome and its management.[5] The Letter emphasized that informed consent to treatment implies that patients should be alerted to this risk before starting drug treatment. It is also important to inform patients that most mild-to-moderate episodes of anxiety and depression will resolve on their own, and that non-drug treatments such as CBT and/or mindfulness or physical activity may be equally or more effective.

Since 2018, understanding of withdrawal has increased, yet prescriptions and long-term use of antidepressants continue to rise. In England, prescriptions doubled from 2010 to 2024, now including about 20% of the population, half of whom take antidepressants long-term.[6] According to United States (U.S.) national surveys, antidepressant use increased from less than 8% of people aged 12 years or older in 1999-2002 to nearly 13% by 2011-2014, and 19% in women over 60. More than two-thirds of Americans taking an antidepressant had done so for more than 2 years, and one-quarter for more than 10 years.[7] About 14% of Australians take antidepressants, half of them for longer than 12 months.[8] Figures 1 and 2 show similar trends in British Columbia, although the clinical indications could include anxiety and other diagnoses, as well as depression. During 2024, an antidepressant was dispensed to over 852,429 individual British Columbians, about 15% of BC's population of 5,722,318. Per capita dispensing increased by 50% from 2003, when 418,231 of 4,123,937 British Columbians, or 10%, received an antidepressant. These numbers do not include federally insured residents, nor beneficiaries of the First Nations Health Benefit Plan, who would increase the totals and percentages.

Dispensing of antidepressants for at least 6 months grew even faster than total dispensing, from 235,691 people during 2003 to 620,831 during 2024.

The 263% increase over 21 years means that almost 11% of British Columbians now take antidepressants long-term.

Figure 1: Number of British Columbians dispensed an antidepressant 2003-2024

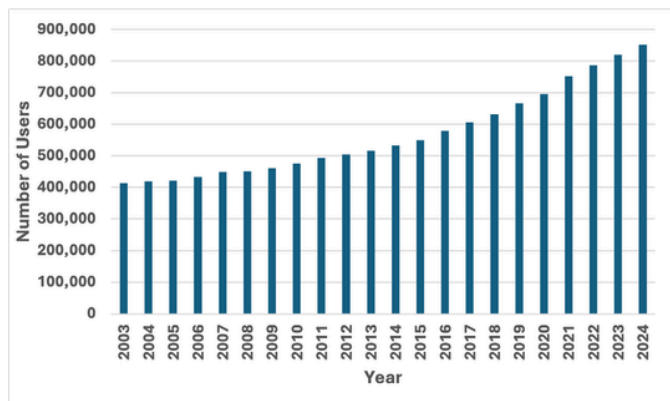
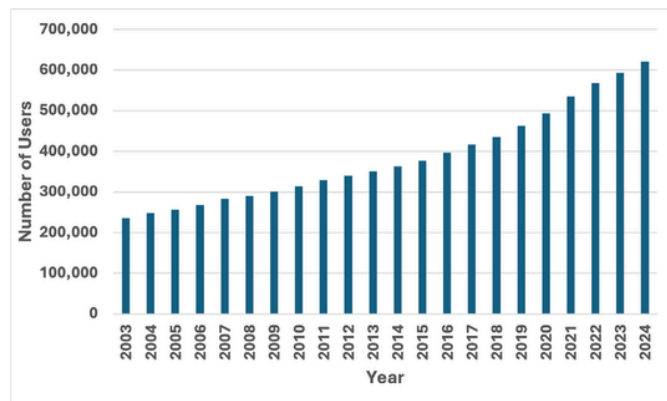


Figure 2: British Columbians dispensed an antidepressant for ≥6 months 2003-2024



Notes:

1. Source data exclude federally insured residents and beneficiaries of the First Nations Health Benefit Plan.
2. Antidepressant users had active Medical Service Plan coverage during the relevant calendar year.
3. Figure 2 includes antidepressant users who received at least 180 days supply of any antidepressant (switching allowed) during the relevant calendar year.
4. Antidepressants included: tricyclics/tetracyclic (amitriptyline, doxepin, nortriptyline, trimipramine, maprotiline), selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other antidepressants (bupropion, mirtazapine, trazodone, vilazodone, vortioxetine). Excluded: low dose doxepin (3mg, 6mg), esketamine, MAO inhibitors, nefazodone, tryptophan.

Because most antidepressant prescriptions are initiated in primary care - and not always after thorough diagnosis and documentation - there is growing recognition of the need to re-evaluate how primary care clinicians prescribe.[9]

This Letter updates evidence about antidepressant withdrawal, and proposes requirements for informed consent to antidepressant treatment. Some clinicians who are trying to help their patients may find the information upsetting - because it reflects a paradigm shift in understanding of antidepressants. Therapeutics Letter 157 will focus on how to avoid or manage the clinical problem of antidepressant withdrawal.

Withdrawal: a corollary of tolerance and dependence

Soon after discovery of the first antidepressant drugs, psychiatrists recognized withdrawal symptoms in patients who reduced or stopped treatment. By 1959, a Canadian report described withdrawal from imipramine, the first tricyclic antidepressant.[10] The chief symptoms were nausea, vomiting, dizziness, chills, and great anxiety. U.S. pioneers of imipramine therapy reported in 1961: "The intensity of physiological symptoms is directly proportional to the duration of drug administration and the abruptness of withdrawal." Over half of their first patients experienced withdrawal symptoms, including nausea, vomiting, dizziness, coryza (runny nose), muscular pains, and malaise.[11]

Fluoxetine, the first SSRI antidepressant, was not long on the market before a 1991 case report documented distressing symptoms that occurred 2 days after cessation of a 6-month

drug treatment.[12] The term "withdrawal syndrome" was used in 1996 by Pfizer Inc., the manufacturer of sertraline; however Pfizer was reluctant to disclose this to Norwegian regulators.[13] Eli Lilly & Company (the inventor of fluoxetine) was also alert to the issue, but preferred to popularize the more benign language "discontinuation syndrome" in the non-peer-reviewed proceedings of a "closed symposium" it sponsored for influential psychiatrists in 1996.[14] The Introduction to these proceedings (published as a 1997 Supplement to the Journal of Clinical Psychiatry) acknowledged that withdrawal occurred with many antidepressants - and that the syndrome could be prolonged and severe. It emphasized that withdrawal was often misdiagnosed - or recognized only after expensive consultations and investigations.[15] Today, antidepressant withdrawal syndrome is acknowledged as possible after even brief exposure to any antidepressant.[2,3,4] The World Health Organization's database of spontaneous adverse drug reaction reports includes records of withdrawal from at least 28 different antidepressants.

Paroxetine, duloxetine, venlafaxine/desvenlafaxine, and sertraline are represented disproportionately in the database; and all but sertraline are reported to have an odds ratio exceeding that of the opioid buprenorphine. [16,17]

Characteristics of withdrawal

Physical and psychological symptoms can manifest after stopping or reducing a dose, or even after missing doses. [18,19]

Although various explanations are proposed [20-22], withdrawal mechanisms are no better elucidated than the actions of antidepressants. Changes in the availability or effects of neurotransmitters have diverse physiological consequences.[21-24] During daily drug treatment, homeostatic adaptations of the brain and body gradually minimise these effects; but when drug treatment is reduced or stopped, brain re-adaptation is not immediate, and may take months or years.[21,25] Neurotransmission modulated by antidepressants affects myriad biological processes: more than 80 different withdrawal symptoms are recorded.[26]

These are often categorized into emotional symptoms or physical symptoms and signs.

Acute and persistent symptoms include low mood, anxiety, panic attacks, obsessive thinking, crying, emotional lability, "dizziness," headache, increased dreaming or nightmares, insomnia, irritability, myoclonus, nausea, electric shocks ("zaps"), tremor, flu-like symptoms, imbalance, sensory disturbances, akathisia, and suicidal feelings.[3,26-29]

Three clinically important withdrawal syndromes typically arise after rapid discontinuation of antidepressants (Table 1).

Table 1: Clinically important antidepressant withdrawal syndromes

Withdrawal syndrome	Characteristics	Comments
Akathisia ^{3,28}	- Restlessness, terror, agitation; - Patients may report their "nervous system is on fire"; - Substantial risk of suicide.	Resembles akathisia from antagonism of dopamine receptors by antipsychotics and antiemetics. Clinicians may mistake this as "agitated depression," anxiety, mania, or even psychosis.
Suicidality ^{25,29}	Suicidal feelings during withdrawal, even in people without such feelings before drug treatment.	A 2021-2022 survey of online support group members who had experienced antidepressant withdrawal (N=1,148) found that twice as many reported feeling suicidal after stopping an antidepressant as before treatment.
Protracted withdrawal ³	Often defined as lasting >6 weeks after a dose reduction but can last for months or years.	Long-lasting neurological, psychological, and somatic symptoms that do not respond well to resuming antidepressant may reflect a " <i>withdrawal injury</i> " - more akin to other brain injuries than to conventional acute withdrawal states. ^{29,30}

Neuropsychiatric and somatic symptoms most characteristic of withdrawal include "electric shocks/brain zaps," akathisia, dizziness or lightheadedness, nausea/vomiting, vertigo, gait and coordination problems, or increased sensitivity to light and noise.[29] Protracted antidepressant withdrawal can be misdiagnosed as the return of a patient's underlying mental illness [29], or a new mental or physical health condition.[31] Derived from patient self-reported experiences, the Discriminatory Antidepressant Withdrawal Symptom Scale ("DAWSS"), proposed in 2024 [29], may help to distinguish protracted withdrawal from relapse. This syndrome can be so debilitating that people lose jobs, relationships, or die by suicide.[31,32]

An analogous syndrome of protracted withdrawal from

benzodiazepines was recognized by the 1980s, and explored by U.S. psychiatrists in a 2018-2019 internet survey (N=1,207). [33] In 2023 the investigators characterized a constellation of new but enduring symptoms that appeared to have arisen de novo from benzodiazepine use, sometimes persisting for at least a year after benzodiazepines had been stopped. To distinguish this from acute withdrawal, they proposed the term "benzodiazepine-induced neurological dysfunction." [34] Studies of antidepressant drugs usually do not follow patients for long periods, or after drug discontinuation. Thus, the proportion of people who experience protracted withdrawal is unknown. A 2021-2022 survey of patients in London, England provides a clue. The patients surveyed were receiving primary care "Talking Therapies", and had tried to stop an antidepressant (N=310). About 25% of the respondents who had taken an antidepressant for more than 2 years reported "severe" withdrawal effects after stopping [35]

Withdrawal differs from relapse

In primary care, most people for whom antidepressants are prescribed do not have a long-term or recurrent underlying condition that can be expected to relapse. More often, a drug is first prescribed after a life crisis such as stress related to education, divorce, job loss, or death of a loved one. Therefore, when an antidepressant is stopped, or the dose is reduced, distinguishing withdrawal from a relapse of the original clinical problem is essential to avoid unnecessarily prolonged drug treatment [35], as well as to prevent long-term harms (Table 2).

Table 2: Distinguishing antidepressant withdrawal from relapse of underlying condition

Characteristic	Withdrawal	Relapse
Timing ^{27,36}	- May begin within days of dose reduction or even between doses of short half-life drugs (e.g., venlafaxine, paroxetine, [es]citalopram) - But may also be delayed for weeks to months	Begins weeks or months after discontinuation of successful treatment
Symptoms ^{27,29}	- Symptoms may be distinct from those of depression or anxiety (e.g., dizziness, brain zaps, depersonalization—a dream-like sense that the world around one is unreal or distant) - Emotional symptoms can differ qualitatively, or be far more severe than the original complaints	Symptoms consistent with original complaints
Response to medication ³⁷	- Symptoms resolve quickly after prompt diagnosis and resumption of medication - If resumption delayed, response is unpredictable - symptoms sometimes worsen	Typically slower, and may be consistent with spontaneous improvement.

Conflicted early guidelines minimized withdrawal problems

At the 1996 "closed symposium" sponsored by Eli Lilly & Company, psychiatric key opinion leaders described withdrawal effects as "generally mild, short lived, and self-limiting." [38]

They did acknowledge serious outcomes such as hospitalization for suspected myocardial infarction during withdrawal from venlafaxine, and suggested that patients be asked routinely if there are medications they have stopped taking in the past few days.

Wyeth Pharmaceuticals (maker of venlafaxine) sponsored a similar meeting in 2004. In proceedings published in 2006 (as a non-peer-reviewed journal supplement), Wyeth's "Consensus Panel" better acknowledged the frequency and potential severity of "discontinuation," noting that withdrawal symptoms from paroxetine, sertraline, and venlafaxine had been observed within 12 to 24 hours after a missed dose. However, while the authors recommended routine tapering of antidepressants instead of abrupt cessation, they advocated that *"clinicians should reassure their patients that this syndrome is easily manageable."*[39]

In the United Kingdom (U.K.) guidelines, this benign characterization of withdrawal as "usually mild and self-limiting over about one week" persisted until 2019.[40] The 2024 update of Canadian depression guidelines (CANMAT) recognized that "up to 50% of patients may experience discontinuation symptoms when stopping long-term use of antidepressants, especially with abrupt stopping." [41] However, like their U.S. predecessors, the authors characterized withdrawal symptoms as likely to occur within a few days of decreasing or stopping a drug, as "mild or moderate in severity," and as expected to resolve "within a few weeks."

Has the 'evidence' changed?

Our review of evidence found that commercially sponsored "consensus recommendations" related to antidepressant withdrawal (like many guidelines in psychiatry), were affected by conflicts of interest. They also rely on withdrawal effects observed after only 8-12 weeks of antidepressant exposure during randomized controlled trials (RCTs).[42] Yet most patients take antidepressants for much longer. The BBC found that from 2015/16 to 2019/20, over one-quarter of the more than 8 million people in England taking antidepressants had done so for 5 years.[13] And an ongoing Australian deprescribing cluster RCT (RELEASE) found, by screening more than 12,000 patients from 26 general practice clinics, that 50% had used an antidepressant for at least 12 months. [9]

Longer duration of antidepressant use greatly increases the likelihood, severity, and potential duration of withdrawal effects.[21,43] For example, of respondents reporting withdrawal effects in a 2013 online survey in New Zealand (N=1,367), 28% of those who had used antidepressants for less than 3 to 6 months reported withdrawal effects, of which 18% were "moderate/severe." [44]

The 2021-2022 survey of Londoners who had ever tried to stop an antidepressant (N=310, 79% female) found that 64% of those who had taken drug therapy for at least 2 years reported "moderate or severe withdrawal." One in eight said the effects lasted for over a year.[35]

An early double-blind RCT in the U.S. examined SSRI discontinuation over 5 to 8 days, after a mean of 11 months of use (N=192). It identified withdrawal effects in 60% and 66% of patients taking sertraline or paroxetine, versus 14% of those taking fluoxetine – a much longer acting drug.[45] In contrast, a 2024 systematic review of shorter RCTs estimated an absolute risk increase of about 15% for withdrawal symptoms after stopping active drug therapy. The number needed to harm (NNH) was estimated at 6 to 7 patients. For severe withdrawal symptoms, the NNH was estimated at 35. [46] A 2025 systematic review published after we first posted Letter 156 concluded that "on average, those who discontinue antidepressants experience 1 more discontinuation symptom compared to placebo or continuation of antidepressants, which is below the threshold for clinically important discontinuation syndrome." However, it relies on 11 short RCTs (10 of 8-12 weeks and 1 of 26 weeks using agomelatine, a drug not known to have a withdrawal syndrome), and analysis of withdrawal symptoms at 1 week after study drugs were stopped. [47] But evaluations of longer RCTs indicated that about 50% of patients experienced withdrawal effects, of which about half were reported as severe.[43,48]

Finally, an influential RCT in the U.K. examined antidepressant deprescribing in patients who had taken citalopram, fluoxetine, sertraline, or mirtazapine for more than 2 years (N=150 general practices, 478 patients).[49] Participants randomized to stop the drugs experienced significantly more withdrawal symptoms for at least 9 months of the 12-month trial.[50]

What constitutes informed consent to treatment?

For any proposed therapy, a patient's ability to provide informed consent requires access to information about potential harms as well as benefits. For antidepressants, as when starting a benzodiazepine, an opioid, or a corticosteroid, this includes understanding that it may be very difficult to stop, and that long-lasting withdrawal symptoms are possible. Potentially these can be as severe as new-onset suicidality, and persistent akathisia. For some people, withdrawal symptoms are irreversible or so debilitating that an antidepressant cannot be stopped.[3]

This issue has unique implications for women of reproductive age, because antidepressant use during a planned or unexpected pregnancy also has implications for the fetus and neonate. Stopping an antidepressant during pregnancy may be especially challenging.

Stopping an antidepressant during pregnancy may be especially challenging.

Canadian and other prescribers and patients should also appreciate that drug formulations to facilitate tapering and safe discontinuation of antidepressants are not currently available. To reduce dose slowly and gradually, patients may have to crush tablets, or dissolve them in water and use syringes. They should be informed that it may be challenging to identify a clinician with expertise and experience in stopping psychotropic drugs. Dedicated deprescribing services may not be available to assist [51], although BC's Primary Care Network pharmacists may be helpful.

The Appendix is a modifiable Informed Consent to Start an Antidepressant form, adapted from opioid and benzodiazepine treatment agreements recommended by the College of Physicians and Surgeons of British Columbia. [52,53]

Data References and Disclaimer

The BC Ministry of Health approved access to and use of BC data. The following data sets were used: PharmaNet (ClaimsHist), Client Roster. All inferences, opinions and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the data stewards.

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[Clinic or Office letterhead]
[name of prescriber]

INFORMED CONSENT TO START AN ANTIDEPRESSANT

Name: _____ Date: _____ Medication/dose: _____

Today we discussed the possibility of treating your symptoms with an antidepressant. Please be sure you understand the intent of today's prescription, and feel free to ask more questions.

Clinical reason(s) to start an antidepressant (diagnosis: e.g. depression, anxiety, other):

Your reason(s) (what you hope will change): _____

How will we know if I'm better? (e.g.: happier overall, more energy, sleeping better, back to work, doing well again in school, relationships better):

Before you start to take a new prescription on an antidepressant:

1. ☐ Did we cover the likelihood of effectiveness, and non-drug alternative evidence-based treatments including a "wait and see" approach, exercise, or psychological treatments?
2. ☐ Did we cover the most common or important side effects?
3. ☐ Do you have questions about side effects, or how to cope with them if they affect you?
4. ☐ If you have thought about harming yourself, do you know what to do if you feel worse? BC's mental health crisis line is [1-800-784-2433](tel:1-800-784-2433) or [9-8-8](tel:9-8-8)
5. ☐ Do you know for how long the treatment is planned? Do you understand that if you take the medication for more than a few weeks, it could be difficult to stop?
6. ☐ Have you planned follow-up with your prescriber to monitor how you're doing?

Signature acknowledging receipt (if desired): _____

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Stopping antidepressants safely

Therapeutics Letter N. 157 - July 2025

Full article available at: <https://www.ti.ubc.ca/therapeutics-letter/>

PLAIN LANGUAGE SUMMARY

What is this Therapeutics Letter about?

This Therapeutics Letter looks at the problems people may have when they stop taking antidepressant drugs. It talks about how to stop safely, and avoid withdrawal problems.

What are antidepressants used for?

They are medicines (drugs) used to treat depression and other mental health conditions.

Do people always need to keep taking antidepressants?

Not always. Many people start antidepressants during a stressful time but may find that they've learned other ways to cope and now feel better, or no longer feel the medication is helping. For many, the negative side effects of the medication might start to outweigh any benefits.

What is antidepressant withdrawal?

Antidepressant withdrawal can happen when someone stops taking antidepressant medication. The body has adjusted to having the drug, and reacts in a negative way while it rebalances and gets used to not having it. It's a common problem, but many people don't realize it can happen.

What happens when people stop taking antidepressants?

At least half of the people who stop taking antidepressants will notice some withdrawal symptoms. This can include trouble sleeping, unusual physical sensations, and mood changes. For those taking larger amounts over a long time, symptoms can be quite severe. Some are described as feeling like electric pulses in the head ("brain zaps") and feelings of extreme physical and emotional restlessness (akathisia).



What does the research recommend for stopping antidepressants?

Experiments are ongoing in Australia to determine the best way to stop. Meanwhile, doctors, nurse practitioners, and pharmacists can help patients stop gradually, sometimes over months or even years, if needed. Stopping slowly can reduce the chance of having severe withdrawal problems. Sometimes, the drug dose is lowered in very small steps, using liquid versions or smaller doses specially made by pharmacists.

How should patients be supported during the stopping process?

Patients should:

- Be part of the decision to stop.
- Understand the risks and steps to lower the dose.
- Be checked every 2-4 weeks after lowering a dose.
- Feel free to pause or go back a step at their own comfort level

Why is this important?

Stopping antidepressants the wrong way can cause serious problems. But with careful planning and support, most people can stop safely and feel better in the long run.

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PATIENT HANDOUT



ANTIDEPRESSANT TAPERING

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THE UNIVERSITY OF BRITISH COLUMBIA

Stopping Antidepressants

WILL I ALWAYS NEED THEM?



Maybe not. Many people start antidepressants during stressful times or for milder conditions. Over time, some may find they've learned other ways to cope, or they no longer feel the medication helps.

WITHDRAWAL IS COMMON



At least half of the people who stop taking antidepressants will notice some withdrawal symptoms, especially if they've been taking larger amounts of the drug or taking it for a longer time.

TAPER SLOWLY



To reduce the likelihood or severity of withdrawal symptoms, avoid sudden stopping and consider very gradual tapering over months, or even longer if the withdrawal is severe.



It's important for your prescriber to monitor you every 2 to 4 weeks after each dose reduction, with the option to pause or reverse a dose taper at your comfort level.



CHECK WITH YOUR DOCTOR

Therapeutics Initiative

Better prescribing. Better health.

How to stop antidepressants

ABSTRACT

► Background:

Most people treated with antidepressant drugs for mild-to-moderate depression may not benefit from ongoing pharmacotherapy. Over time, adverse effects often outweigh benefits. Yet many, especially women, take antidepressants for much longer than clinical guidelines recommend. Therefore, when prescribers recommend starting an antidepressant, they also need to know how to stop it. Antidepressant withdrawal is a common but under-recognized clinical issue. At least half of people who stop antidepressants experience significant withdrawal symptoms, particularly from higher doses or after long-term treatment.

► Aims:

Therapeutics Letter 157 discusses the rationale for stopping antidepressants, and provides guidance on safe and effective deprescribing. It recommends dose tapering tailored to a patient's individual risk, and adjusting an individualized care plan to the clinical response. Successful deprescribing also includes distinguishing withdrawal symptoms from possible relapse of a mental health condition. This Letter offers suggestions from physicians experienced in stopping antidepressants to manage challenging cases such as antidepressant withdrawal-induced akathisia or protracted withdrawal.



► Recommendations:

To reduce the likelihood or severity of withdrawal symptoms, avoid abrupt discontinuation. For high-risk patients, consider very gradual tapering over months or even years. Hyperbolic dose tapering can be facilitated by liquid formulations or compounding pharmacies. Monitor patients every two to four weeks after each dose reduction, with the option to pause or reverse a dose taper as needed. Patient education, shared decision-making, and informed consent to deprescribing should minimize harms and improve outcomes.

Keywords: Antidepressive Agents; Depressive Disorder; Deprescriptions; Drug Tapering; Drug Tolerance; Patient Education; Primary Health Care; Risk Assessment; Substance-Related Disorders; Substance Withdrawal Syndrome.

How to stop antidepressants

Vignette: Your new patient is a 53-year-old woman who started venlafaxine 75 mg/day for post-partum depression 19 years ago. Withdrawal symptoms ended a prior attempt to reduce to 37.5 mg/day, suggesting potential problems if she tries again. (See *Therapeutics Letter* 156, June 2025) But she is now determined to stop the antidepressant. You agree to help her plan an approach more likely to succeed. During a 30-minute follow-up appointment tomorrow, how will you advise her?

Summary and Conclusions

- At least half of people experience significant withdrawal symptoms when stopping an antidepressant.
- Prolonged antidepressant treatment and high doses increase the risk of a significant withdrawal syndrome.
- Some people require months or even years of gentle, supervised dose tapering to minimize disturbing or dangerous symptoms.
- A compounding pharmacy or use of a liquid formulation or pill/capsule fragments may be necessary for very gradual dose tapers.

Therapeutics Letter 156 (June 2025) updated our understanding of the characteristics and frequency of antidepressant withdrawal syndrome. This Letter focuses on how to avoid or manage what can become a serious clinical problem. It includes a modifiable form to document Informed Consent to Taper an Antidepressant.

Why stop an antidepressant?

Patients and prescribers have a variety of reasons for wanting to stop an antidepressant. Many people start drug therapy at a stressful period in life, but adjust over time to a loss, or develop non-drug coping skills. Medication may become superfluous.¹ For up to 30-50% of people taking antidepressants, no evidence-based reason is found to continue [2-6]. Without compelling clinical reasons to continue an antidepressant, it may simply be time to attempt a return to life without medication.

Women are especially likely to receive long-term prescriptions. For example, an Australian longitudinal study on younger women's health from mid-2012 through 2019 found a mean duration of drug treatment of 2.4 years in women who refilled an initial prescription (N=4,416 born after 1945).^[7] In contrast, most guidelines recommend 6-12 months of treatment for an episode of anxiety or depression, reserving longer-term treatment for severe and recurrent cases.



However, most people who are prescribed antidepressants have mild conditions.^[8,9] When patients treated with antidepressant drugs improve, it is natural human psychology - but faulty logic - to attribute this with certainty to a pharmacological effect. Most people improve with time alone.^[10] What appears to be obvious clinical logic should be tempered by understanding that in randomized clinical trials (RCTs), the average difference between antidepressants and placebo is about 2 points on the 52-point Hamilton Depression Rating Scale. And the proportion of participants in randomized controlled trials (RCTs) who achieve clinically meaningful improvement - compared with placebo - varies from a high of about 15% to a low of about 10%.^[11] This translates to a number needed to treat for clinical benefit (NNT) of about 7-10.^[12] The large majority would do equally well without an active drug. Even when drug therapy at first seems clearly beneficial, pharmacological tolerance may reduce the effect over time, an inevitable consequence of the brain's adaptation.^[13]

For many people, adverse effects of antidepressants outweigh benefits. For example, 50% experience treatment-emergent sexual problems with arousal, erectile dysfunction and orgasm.^[14] Emotional numbing, cognitive and memory impairment, and sleep disturbance are also common.^[15] Evidence of analogous effects in healthy volunteers taking antidepressants indicates that such adverse effects do not arise from a mental illness alone.^[16,17]

Other harms are not clinically obvious. Antidepressant RCTs are typically small, brief, and enrol relatively healthy participants; longer-term harms in the real world are detectable only from pharmacoepidemiologic studies.

While epidemiological associations must account for confounding factors and do not prove causation [18], antidepressants (including SSRIs and venlafaxine) have been found increase falls, fractures, osteoporosis, bleeding risk, strokes, dementia, cardiovascular disease, weight gain,

cataracts and premature mortality, especially in older people.[19-23] An increased risk of withdrawal after long-term use may be another unanticipated harm.[24]

Is there an optimal way to deprescribe?

Few RCTs have studied how best to stop antidepressants, mostly in people treated for recurrent depression by specialists (total N=4,995 people).[25] At least 2 deprescribing trials are now underway in Australia.[26,27] Several cohort studies have compared traditional linear tapers and gradual hyperbolic tapers.[28]

Current recommendations, guidelines, and algorithms are based on the clinical experiences of clinicians and patients - not experimental results. Just as people differ in their tolerance for drugs and dose increases, their experiences of dose reductions vary. This is similar to other drugs that induce pharmacological tolerance and dependence (e.g. nicotine, alcohol, benzodiazepines, and opioids). After antidepressant treatment for more than a few weeks or months, many patients may require a relatively cautious approach to deprescribing.

Speed of tapering

Unsurprisingly, the more slowly antidepressants are stopped, the lower the risk of withdrawal effects or apparent relapse of depression.[29] A meta-regression analysis of antidepressant discontinuation RCTs found no increase in depression relapse when doses were tapered over 6 months compared with continuing drug treatment.[30] But fast tapering over 1 or 2 months was associated with significantly increased relapse in the largest RCT of deprescribing.[31] The meta-regression authors emphasize that antidepressant withdrawal can easily be mistaken for relapse of depression.[30]

Tapering pattern

The pattern of tapering is also thought to be important. The relationship between the dose and blood concentration of a drug and its effects on receptors in the brain is believed to be hyperbolic. Drug effects rise steeply at doses near the lower end of the approved dose range. But at higher doses and concentrations, many drug effects plateau.[29] Hyperbolic dose tapering attempts to mimic this relationship inversely. As the daily dose declines, reductions become progressively smaller. This can be approximated by reducing at an arbitrary percentage, such as 10% per month of the most recent daily dose.

Pragmatic alternatives recommended by many guidelines include stepwise dose reductions over a few weeks, a “slow slide,” or substitution of the very long-lived SSRI fluoxetine for related antidepressants.[32] However, even the long elimination half-life of the active metabolite norfluoxetine

(mean 9 days, range 4-16 days) [33] does not avoid withdrawal in about half of people who take fluoxetine – in whom withdrawal may be delayed for 4-6 weeks after stopping.[34] Some people need a very gentle approach. In the United Kingdom (U.K.), a cluster RCT of general practices found that traditional stepwise tapering (e.g. sertraline 200 mg/day, 150 mg/day, 100 mg/day, 50 mg/day, 25 mg/day, stop) was unsuccessful for 58% of patients who had taken at least 9 months of antidepressant therapy for depression or anxiety (N=274 assessable at 6 months).[35] For people unable to stop antidepressants in a traditional taper, Dutch researchers have reported success with a much more gradual hyperbolic taper, facilitated with specialized dose “tapering strips.” For example, 608 people mostly taking venlafaxine and paroxetine used 28-day tapering strips to reduce drug doses hyperbolically over schedules of 4 to 20 weeks.[28]

To reduce withdrawal symptoms markedly, a cautious approach to tapering antidepressants (including hyperbolic dose reductions) is now recommended by the UK National Institute for Health and Care Excellence (NICE) and a number of UK specialty organizations.[36,37]

Safe and effective deprescribing in practice

The rate and pattern of tapering are clinical decisions specific to the circumstances and needs of individual patients. The Canadian Medication Appropriateness and Deprescribing Network provides a convenient, concise, and lucid guide for patients, their family or friends, and clinicians (also available in French).[32] As a general rule, people who have taken an antidepressant for more than 4 weeks should preferably not stop abruptly. A practical approach to avoid or minimize withdrawal is a test dose reduction, using the patient's response to determine further steps. Barring an urgent need to stop the antidepressant, slow decrements are reasonable. One can accelerate the pace as tolerated. A very slow taper implies a few weeks or months of unnecessary drug exposure. On the other hand, excessively rapid dose reduction potentially risks akathisia, suicide, or possible years of disability. Poor outcomes are not always reversible.[1]

Patients can be risk stratified based on duration of use, type of antidepressant, past experience of stopping and dose. [38,39] People who have taken an antidepressant for only several weeks are at low risk of serious withdrawal, compared with those with years of exposure. Past experience of withdrawal, and high doses, also predict future risk. But the smallest doses used clinically affect amine transporters and brain receptors almost as much as maximum doses. Therefore, even a “low” dose of an antidepressant often confers a substantial risk of withdrawal upon discontinuation. Without direct comparisons between antidepressants after long-term use, withdrawal risk categories are inherently arbitrary.

Table 1, adapted from a review of data available in 2022 [34], shows categorical risk estimates for frequent or severe withdrawal, and published incidence estimates for antidepressants commonly used in Canada.

Two analyses of the World Health Organization's adverse drug reaction (ADR) database also identified paroxetine, venlafaxine/desvenlafaxine, duloxetine, sertraline, and citalopram/escitalopram as the highest risk for withdrawal. [40,41] However, this could reflect ADR reporting biases for newer antidepressants. A 2023 Canadian guideline on treatment of depression provides different ratings, but does not cite sources. [42] And a 2024 systematic review of short RCTs and observational studies also identified imipramine (the original tricyclic antidepressant) as especially problematic. [43]

Table 1: Comparative risks for withdrawal after stopping antidepressants

Drug (alphabetical)	Categorical risk for severe or frequent withdrawal	Reported incidence of withdrawal
Duloxetine	Higher	not available
Fluvoxamine	Higher	not available
Levomilnacipran	Higher	not available
Mirtazapine	Higher	not available
Paroxetine	Higher	66-100%
Venlafaxine/desvenlafaxine	Higher	44%
Citalopram/escitalopram	Moderate	27-70%
Fluoxetine	Moderate	14-77%
Sertraline	Moderate	59-60%
Vortioxetine	Moderate	not available
Trazodone	Low	not available
Bupropion	Unknown	not available

Starting an antidepressant taper

For low-risk patients (weeks of use, low risk antidepressant), a rule of thumb is to start with a 25% dose reduction. For patients deemed at moderate risk (months of use, moderate risk antidepressant), reducing by 10% may be more appropriate. For patients expected to be at high risk for withdrawal (years of use, high risk antidepressant, significant prior problems with withdrawal), a 5% initial reduction is unlikely to cause serious problems.

After starting a dose taper, experts in deprescribing antidepressants recommend monitoring patients clinically for 2-4 weeks per step, to assess the response. In "slow slide" or "hyperbolic" tapering, milligram reductions in daily dose become smaller and smaller as the dose declines. Table 2 shows a hyperbolic tapering schedule that would last well over 1 year for the Vignette patient who took venlafaxine 75 mg/day for 19 years.[1] Schedules recommended by the Canadian Medication Appropriateness and Deprescribing Network are somewhat faster.[32] The ongoing Australian RELEASE deprescribing RCT also provides a series of possible "slow" and "slower" schedules for 15 antidepressants.[44]

Expert advice - in the absence of evidence from trials

English and Dutch physicians with substantial deprescribing experience indicate that people at low risk can generally stop in 6-9 months, and people at moderate risk in 9-18 months. But high-risk patients may require 2 years or longer. Other experienced clinicians indicate that people treated only briefly with an antidepressant may be able to stop within 2-4 weeks without problematic withdrawal.[32] As with other habituating drugs like nicotine, alcohol, and caffeine, some patients may simply prefer to stop "cold turkey," after short-term use of antidepressants. Difficult withdrawal symptoms often improve by pausing dose reductions, or retreating a step or two in dose reduction, and slowing the taper. Profound suffering can necessitate reinstating the original dose. Prescribing other drugs to suppress withdrawal substitutes another potential problem, so it is clinically more sensible to interpret withdrawal symptoms as a useful signal to slow the tapering process.

Table 2: Hyperbolic dose tapering: example of venlafaxine 75 mg/day

Step	Dose mg/day	Step	Dose mg/day	Step	Dose mg/day
1	75	16	8.6	31	2.1
2	55	17	7.8	32	1.9
3	45	18	7.2	33	1.6
4	37.5	19	6.6	34	1.4
5	30.4	20	6	35	1.2
6	26	21	5.5	36	1.1
7	22.6	22	5	37	0.89
8	19.8	23	4.6	38	0.72
9	17.5	24	4.2	39	0.56
10	15.6	25	3.8	40	0.41
11	14	26	3.5	41	0.27
12	12.6	27	3.2	42	0.13
13	11.4	28	2.9	43	0
14	10.4	29	2.6		
15	9.4	30	2.3		

Source: Horowitz M, Taylor D. The Maudsley Deprescribing Guidelines in Psychiatry: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs. 2024. [1]

Practical aspects for clinical practice

1. Explain the process: inform patients about risks of tapering too rapidly, and that gradual tapering appears to minimize withdrawal problems. Balance the rate of taper against harms of long-term antidepressant use, and adjust to the experience of individual patients.

2. Facilitate tapering with appropriate drug formulations, when necessary: available tablets and capsules are not suited to very slow tapering. Even fragments of the lowest dose tablets or part of a capsule produce high neuronal receptor occupancy and end organ effects. Hyperbolic tapering requires provision of much smaller doses. In Canada, fluoxetine oral solution is one option – including for "cross-tapering" from another antidepressant.[45] It is covered by Pharmacare in BC.

But, it too should be tapered carefully. Compounding pharmacies can produce small doses as liquids, capsules or tablets, equivalent to the tapering strips popular in the Netherlands.[28] This service is not covered by Pharmacare, and could be expensive. Some patients use techniques devised by pharmacists to overcome swallowing difficulties. [46,47] This can include subdividing tablets with a pill splitter, crushing tablets, using the powdered contents of capsules to make suspensions, opening capsules to count or weigh beads, or even weighing tablet fragments.[1] Pharmacists can provide guidance on technical issues such as tablet splitting.

3. Alternate day dosing often not appropriate: Because the elimination half-life of many antidepressants is <1 day, every-second-day dosing can produce wide fluctuations in drug concentrations, and precipitate severe withdrawal effects. [48] If inter-dose withdrawal symptoms arise, divided daily doses can be helpful. Fluoxetine is an exception, because both the parent drug and its active metabolite have very long half-lives.[33]

4. Evidence for switching to fluoxetine is equivocal: Although its long elimination half-life and availability as a liquid formulation are obvious advantages for tapering, fluoxetine is not a panacea. Withdrawal is not unusual, even if it is often misdiagnosed because of delayed onset.^{34,41} Diverse antidepressant effects on neurotransmission and other brain processes may not be replaced adequately by a substitute drug.¹ This differs from the typical interchangeability of benzodiazepines, opioids, or beta-blockers. Tapering the antidepressant already familiar to the patient can simplify clinical assessments.

Vignette resolution: *Your new patient has taken venlafaxine 75 mg/day for 19 years. Given her prior experience trying to reduce the dose to 37.5 mg/day, she is at high risk for a withdrawal syndrome if she stops precipitately. But you agree that stopping venlafaxine is reasonable, and propose a cautious approach. After thorough discussion, you provide her with written information,³² and plan to request preparation of progressively smaller doses by a compounding pharmacist. You inform the patient that she may have to pay for this service. At the next visit, you and your patient can agree on a supervised taper and a first follow-up in 2 weeks.*

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5. Managing withdrawal-induced akathisia: Reinstating or increasing the dose of the antidepressant may improve symptoms, especially soon after symptom onset. [1,49] Akathisia normally resolves spontaneously; but when symptoms persist for months or longer, they can be unbearable. Using other drugs to suppress akathisia yields mixed results; patients can be exquisitely sensitive to psychotropic drugs, sometimes with negative responses.[1] If a short trial of another drug is ineffective, continuing it is irrational.

6. Managing protracted withdrawal: Although this affects only a small minority of patients, it can be very difficult to treat if it occurs. The term “protracted withdrawal” is misleading because it implies that resuming the drug will resolve the syndrome, which is not always the case.[1,48,49] A conservative approach is to wait for improvement to occur – generally over months or even years. Non-pharmacological techniques to manage ongoing psychological symptoms are sometimes helpful. Resuming the withdrawn drug at a low dose, months after stopping it, can have unpredictable effects, including paradoxical worsening of symptoms. [1,48,50] To mitigate these risks, clinicians experienced with antidepressant deprescribing recommend a very smallest dose (e.g. 2 mg of venlafaxine, or 1 mg of citalopram), with further steps determined by the patient’s response.[1] This helps determine whether to increase the tiny dose cautiously, or to abandon the approach. As with treating withdrawal-induced akathisia, prescribing other psychotropic drugs as sedatives or to numb symptoms, should be a last resort. [1,42,43] The U.K. government has called for specialist services to help manage such patients.[51,52] In British Columbia, Primary Care Network (PCN) pharmacists may be able to assist.

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[Clinic or Office le-erhead]
[name of prescriber]

INFORMED CONSENT TO TAPER AN ANTIDEPRESSANT

Name: _____ Date: _____ Medica<on/dose: _____

Today we discussed tapering and poten3ally stopping your an3depressant medica3on. Please be sure you understand the intent of today's prescrip3on for a reduced dose, and feel free to ask more ques3ons.

Clinical reason(s) to reduce dose or stop (e.g. depression/anxiety resolved, side effects):

Your reason(s) (what you hope will change): _____

How will we know if I'm be-er? (e.g.: side effects gone, more complete emo3ons, sexual func3on improved):

Before you start to taper your an;depressant:

1. ☐ Did we cover possible withdrawal symptoms, and how to dis3nguish them from a return of your original condi3on?
2. ☐ Did we cover what could go wrong and how to respond?
3. ☐ Are you comfortable with the planned tapering schedule and how to modify it?
4. ☐ Is there a plan to provide very small drug doses, if needed?
5. ☐ Is a follow-up appointment or series of appointments arranged?
6. ☐ If you think about harming yourself, do you know what to do?
BC's mental health crisis line is [1-800-784-2433](tel:1-800-784-2433) or [9-8-8](tel:9-8-8)

Signature acknowledging receipt (if desired): _____