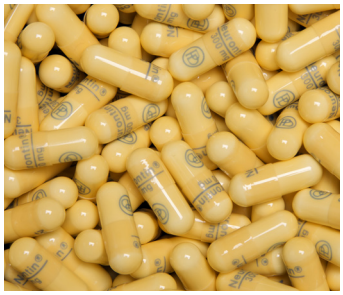
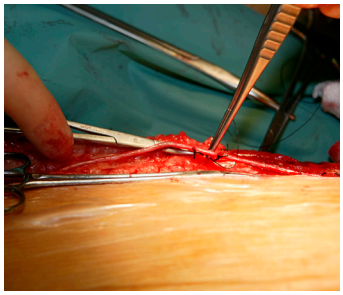
research



Gabapentinoids and risk of self-harm p133

Impact of retracted trials p136



Harvesting technique and risk of graft occlusion p138

Use of real world data to understand self-harm risk in people prescribed gabapentinoids

ORIGINAL RESEARCH Population based, self-controlled case series study

Use of gabapentinoid treatment and the risk of self-harm

Yuen ASC, Chen B, Chan AYL, et al

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Find this at doi: 10.1136/bmj-2024-081627

Study question Does the use of gabapentinoids increase the risk of self-harm?

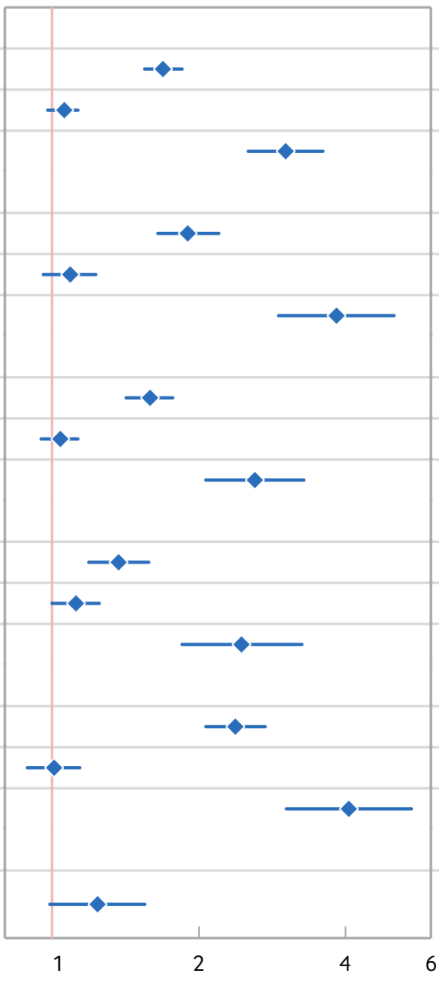
Methods Healthcare data were collected from the UK Clinical Practice Research Datalink Aurum, a database linked to the Hospital Episode Statistics and Office for National Statistics databases in England. 10 002 adults (age ≥18 years) were included who had received at least one prescription of gabapentinoids (gabapentin or pregabalin) between 1 January 2000 and 31 December 2020 and whose hospital records had an incident self-harm event. The research team defined treatment periods using prescription records and identified four risk windows: 90 days before treatment initiation, during treatment periods, 14 days after gabapentinoid treatments, and during reference periods. The analysis compared incidence rates of self-harm in different risk windows to the rate in the reference periods.

Study answer and limitations The association of gabapentinoids and risk of self-harm is multifaceted, but findings do not support a direct effect of gabapentinoid treatment on self-harm. The results yielded an increased risk of self-harm during the 90 day period before treatment, with an adjusted incidence rate ratio of 1.69 (95% confidence interval 1.55 to 1.85). Risk of self-harm increased before initiating gabapentinoid treatment (incidence of self-harm per 100 person years 16.79 (95% CI 16.65 to 16.92)), persisted during the initial phase of the treatment but returned to reference level during the treatment period (9.66 (9.62 to 9.70)), and rose again shortly after discontinuation (29.60 (29.09 to 30.11)). The findings remained consistent throughout a series of subgroups and sensitivity analyses. The study did not identify a cause of this trend.

What this study adds Healthcare providers should closely monitor patients receiving gabapentinoids for self-harm risk not only during gabapentinoid treatment but also before initiation and after discontinuation, considering underlying conditions that may contribute to this risk.

Funding, competing interests, data sharing Patient and public involvement activities were funded by the University College London Hospitals and National Institute for Health Research's Biomedical Research Centre. All authors declare no other competing interests. Data sharing requires approval from the UK Clinical Practice Research Datalink.

Outcome	Incidence rate ratio (95% CI)	Incidence rate ratio (95% CI)
Gabapentinoids		
90 days before treatment		1.69 (1.55 to 1.85)
Treatment period		1.06 (0.98 to 1.13)
14 days after treatment period		3.02 (2.53 to 3.60)
Males		
90 days before treatment		1.90 (1.65 to 2.20)
Treatment period		1.09 (0.96 to 1.23)
14 days after treatment period		3.84 (2.92 to 5.04)
Females		
90 days before treatment		1.59 (1.42 to 1.77)
Treatment period		1.04 (0.95 to 1.13)
14 days after treatment period		2.61 (2.07 to 3.29)
Gabapentin only		
90 days before treatment		1.37 (1.19 to 1.58)
Treatment period		1.12 (1.00 to 1.25)
14 days after treatment period		2.45 (1.85 to 3.26)
Pregabalin only		
90 days before treatment		2.38 (2.07 to 2.74)
Treatment period		1.01 (0.89 to 1.14)
14 days after treatment period		4.07 (3.03 to 5.47)
Took both gabapentin and pregabalin		
Pregabalin only period compared with gabapentin only period		1.24 (0.99 to 1.55)



Forest plot summarising the adjusted incidence rate ratios (IRRs) for self-harm associated with gabapentinoid use, stratified by sex, types of gabapentinoids, and patients who took both gabapentin and pregabalin. CI=confidence interval

An interactive version of this graphic is available at https://public.flourish.studio/visualisation/22458780/

Gabapentinoids, including gabapentin and pregabalin, are a class of drugs that have anticonvulsant, analgesic, and anxiolytic properties and are broadly approved for treating epilepsy and neuropathic pain disorders. However, in recent years, off-label use has been increasing for a wide range of related conditions,[1] including psychiatric disorders (eg, major depression and bipolar disorder), sleep disorders (including insomnia), and postoperative acute pain management, for which the evidence of treatment efficacy and tolerability remains limited.[2]

Randomised controlled trials are considered gold standard evidence for the assessment of treatment efficacy because the design allows for the balancing of confounding factors between treatment groups, given sufficient statistical power. However, randomised controlled trials are both costly and time consuming and studies often struggle to recruit a sufficient number of participants to meaningfully estimate treatment effects.[3] Additionally, randomised controlled trials often have short follow-up periods, making assessment of long term treatment effects challenging, particularly in the case of relatively rare outcomes, such as self-harm and mortality. These limitations were apparent in a 2008 US Food and Drug Administration (FDA) report that concluded, after reviewing randomised controlled trials of 11 antiepileptic drugs, including gabapentin and pregabalin, that the medications were collectively associated with an 80% increased risk of suicidal behaviours over an average of around three months follow-up.[4] However, specific estimates linked with suicidal behaviours for gabapentin (odds ratio 1.57; 95% confidence interval (CI) 0.12 to 47.66) and pregabalin (1.88; 0.41 to 13.58) lacked precision and were not informative owing to a small number of outcome events across drug and control groups.

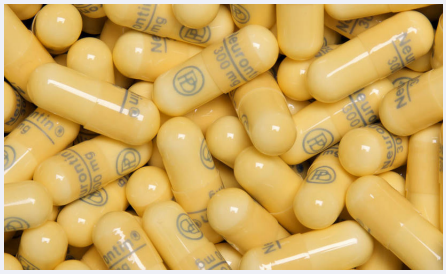
Yuen and colleagues address many of these limitations by examining the associations between prescriptions of gabapentoids and subsequent risks of self-harm in the UK between 2000 and 2020. They used data from the Clinical Practice Research Datalink (CPRD), which covers around 1500 GP practices in the UK and is broadly representative of the wider population.[5] The authors examined four distinct follow-up periods for each individual: 90 days before the treatment period; the treatment period; the 14 days following the end of treatment; and any other period (which acted as the reference category).

Clinical implications

The main findings indicated that the incidence rate of self-harm increased by 69% (adjusted incidence rate ratio 1.69; 95% CI 1.55 to 1.85) during the 90 day period before the initiation of treatment compared with the reference period. This increase was fully attenuated during the treatment period (showing no association with self-harm), but was elevated threefold in the 14 day period after treatment had ended. This finding suggests that gabapentinoids are unlikely to be linked to self-harm risk. These results are potentially important in allowing clinicians and their patients to weigh up risks and benefits of these medications, particularly in people with co-occurring mental health problems and background risk factors for suicide.

Routine and periodic follow-up of people prescribed gabapentinoids should be considered

However, a number of important limitations should be considered when interpreting the findings. Firstly, the self-controlled design is only informative for individuals who have at least one self-harm episode in the follow-up period (n=10 002), which implies that the findings may not generalise to the large majority of patients who did not have such events (n=864 273). Individuals with no mental health diagnoses but with a history of self-harm (n=760) had higher incidence rates of self-harm occurring during their treatment periods compared with reference periods (adjusted incidence rate ratio 1.82; 95% CI 1.40 to 2.37), as shown in the appendix. Secondly, the authors conducted more than 20 sensitivity analyses, which are interpreted as being consistent with the main findings. However, some important differences are of note, such as in young adults (aged 24-44 years, n=4214), who were shown



to have significantly elevated incidence rates of self-harm occurring during their treatment periods compared with reference periods (adjusted incidence rate ratio range 1.19 to 1.40), which was not consistent with the main findings. Additionally, one limitation that is shared with other studies using healthcare registers and electronic health records is that treatments were measured using prescription drug records, and therefore, whether the medication was only collected and not taken is not clear. This approach introduces misclassification bias, as some individuals who did not take the medicine are incorrectly classified as having taken the drug. Future research may benefit from pooling analyses across multiple large scale databases using a common analytical pipeline to determine whether differences in findings stem from methodological variations or reflect true effects.[8]

This research can also be viewed in the wider context of observational studies on gabapentinoids. Another population based self-controlled study,[9] which included 10 026 people in Sweden but based in secondary care, reported consistently increased risks of suicidal behaviours occurring during treatment periods across all age groups. The investigation by Yuen and colleagues shows the importance of testing associations in primary and secondary care, and their novel approach of considering periods before and after treatment is an important contribution. Clinically, their results suggest that routine and periodic follow-up of people prescribed gabapentinoids should be considered, particularly in the weeks after medication has been discontinued. Whether young adults and people with no psychiatric diagnoses need more supervision while taking gabapentinoids requires further research to clarify.

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Retracted studies in systematic reviews and guidelines

ORIGINAL RESEARCH Retrospective cohort study

Investigating the impact of trial retractions on the healthcare evidence ecosystem (VITALITY Study I)

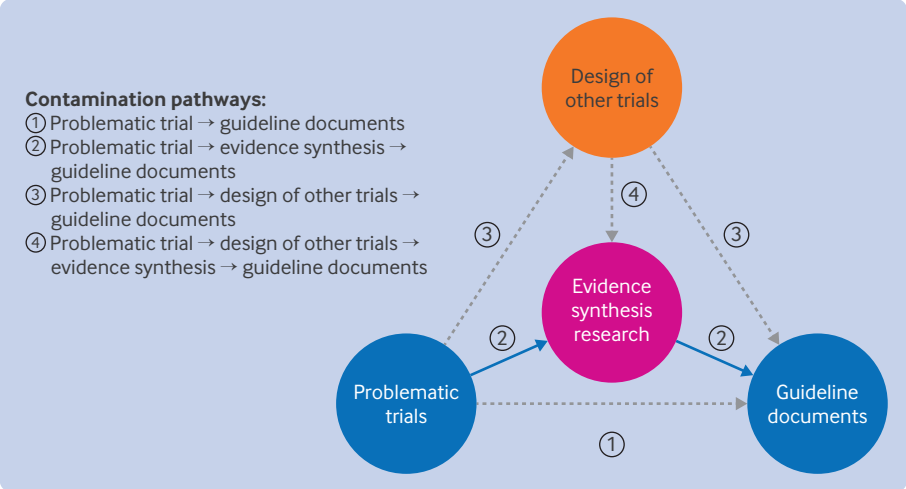
Xu C, Fan S, Tian Y, et al; on behalf of the VITALITY Collaborative Research Network

Cite this as: *BMJ* 2025;389:e082068
Find this at doi: 10.1136/bmj-2024-082068

Study question How frequently are retracted trials found in evidence syntheses and what is the impact of these retracted trials on the evidence ecosystem?

Methods Retraction Watch was searched to identify retracted trials up to 5 November 2024. Forward citation searching via Google Scholar and Scopus was then used to identify evidence synthesis research that included the retracted trials. The pooled effects of the meta-analyses were updated by excluding the retracted trials. The proportion with changes in effect size magnitude, direction, and P values was estimated. Further forward citation searching was used to find guideline documents that used evidence from the "contaminated" systematic reviews.

Study answer and limitations The searches identified 1330 retracted trials and 3902 meta-analyses for replication. Exclusion of the retracted trials led to a change in the direction of the pooled effect in 8.4% (95% confidence interval 6.8% to 10.1%), in its statistical significance in 16.0% (14.2% to 17.9%), and in both direction and significance in 3.9% (2.5% to 5.2%), and the magnitude of the effect changed by more than 50% in 15.7% (13.5% to 17.9%) of trials, after account was taken for potential clustering effects. Evidence from 68 systematic reviews with conclusions distorted by retracted trials was used in 157 guideline documents. Identifying all problematic studies as well as related evidence synthesis research was not possible, so the impact could be underestimated.



Contamination chain of retracted trials on evidence ecosystem

COMMENTARY Flawed evidence risks harming patients

Scientific integrity is fundamental not only for the development of science but also to allow society to trust the scientific community and research. However, the number of retractions has skyrocketed in recent years.[1 2] Pressure to publish, combined with negligent editorial practices by journals or publishers, paves the way for bad science. This situation is compounded by the rise of relatively new types of scientific misconduct, such as paper mills—organisations that mass produce scientific manuscripts, often with fabricated or duplicated data, and then sell them to researchers.[3]

Retractions can have real consequences in healthcare, as Xu and colleagues have clearly demonstrated in a linked study (doi:10.1136/bmj-2024-082068).[4] The results of retracted papers in healthcare may lead to decisions that do harm, claim false benefits, or in any case lack the desired effect. Xu and colleagues have quantified how retracted clinical trials affect the results of systematic reviews and meta-analyses, and the effect is not negligible. Following the exclusion of retracted clinical trials, the results of 8% of the meta-analyses changed direction and the results of one in six meta-analyses changed statistical significance. Although these results are impactful on their own, they have even stronger implications if data from retracted clinical trials have been introduced in clinical practice guidelines published by scientific societies and their recommendations applied directly to patients. Clinical practice guidelines are regarded as the standard of evidence based medicine, but this paper shows that some clinical practice guidelines might have flawed recommendations, identifying 157 guidelines that relied on evidence from 69 systematic reviews that were significantly influenced by meta-analyses containing retracted data.[4]

The results from Xu and colleagues build on previous evidence,[5-7] emphasising the need to exclude retracted articles when conducting systematic reviews and meta-analyses. The problematic situation highlighted by this research requires strong and immediate action from health professionals, editors, publishers, and others. That retractions alone are not sufficient to prevent the onward citation of retracted studies seems clear, especially considering that previous research has found that retractions have no effect on citations.[8-10] But what can we do?

Action is needed

Firstly, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines for systematic reviews,[11] which are globally used and are even mandatory for some journals, could include a new checklist item that mandates

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What this study adds The findings suggest that retracted trials had a substantial impact on the evidence ecosystem, including evidence synthesis, clinical practice guidelines, and evidence based clinical practice.

Funding, competing interests, and data sharing This study was funded by four grants from the Natural Science Foundation of China and one grant from Shanghai Eastern Hepatobiliary Surgery Hospital of Navy Medical University. The authors have no competing interests to declare. The dataset is accessible at Open Science Framework (https://osf.io/ukg3j).

Study registration Open Science Framework (https://osf.io/7eazq/).

the exclusion of retracted publications from systematic reviews. This would require authors to declare whether retracted papers were identified and excluded during the screening process. Secondly, journals should include in their instructions to authors that systematic reviews and meta-analyses will be thoroughly scrutinised by editors or administrative staff to avoid the inclusion of retracted research.

A significant problem arises when one or more of the included studies are retracted after the publication of a systematic review. According to the study by Xu and colleagues,[4] approximately 60% of meta-analyses are published before any of their included studies are retracted; this is similar to the results of previous studies.[5] In this scenario, no standard mechanism exists to alert authors, journals, or readers.[12] To tackle this, an automated alert to the publishing journals and authors should be issued when a cited paper has been retracted, specifying the reason for retraction. An automated alert system could link retraction databases, such as Retraction Watch via Crossref, with citation indexes, such as Scopus or Web of Science, to identify affected systematic reviews. The corresponding author of the affected systematic review and the publication journal could be automatically notified via email.

Some clinical practice guidelines might have flawed recommendations

In cases in which a journal, a scientific society, or coauthors are aware of a retracted publication in their already published meta-analysis, a reanalysis should be done. If the effect is modified but the conclusions remain unaffected, a correction should be issued by the publishing journal of the affected meta-analysis. If a change occurs in the direction and/or magnitude of the effect that affects the conclusions, the original review would need to be retracted and rewritten and the corrected version published as soon as possible.

Correcting guidelines

The organisations and scientific societies that publish clinical practice guidelines should play a role in correcting any guidelines affected by retractions, as they have the obligation to publish the best evidence based recommendations. If such recommendations are flawed owing to the inclusion of synthesis documents affected by retracted research, they must be modified, and it is the responsibility of the publisher of the guideline (that is, scientific society, journal) to make these amendments. In general, these guidelines are published in scientific journals.

Retractions are often said to be the mechanism for correcting science. Yet, simply indicating in a journal that a certain paper has been retracted falls short. Flawed science, once included in systematic reviews and meta-analyses, continues to influence clinical decisions through clinical practice guidelines. We all agree that having flawed science guide decision making is not acceptable. Are we prepared and committed to move forward?

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r724

No-touch versus conventional vein in coronary artery bypass grafting

Tian M, Wang X, Feng W, et al

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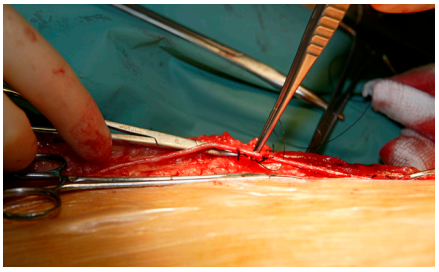
Find this at doi: 10.1136/bmj-2024-082883

Study question Does the no-touch vein harvesting technique reduce vein graft occlusion compared with the conventional approach in coronary artery bypass grafting (CABG) surgery over a three year period?

Methods This multicentre, randomised controlled trial was conducted across seven cardiac surgery centres in China, with enrolment between April 2017 and June 2019. A total of 2655 adult patients undergoing isolated CABG surgery were randomly assigned 1:1 to the no-touch vein harvesting technique or the conventional approach. The primary outcome was vein graft occlusion at three years assessed by computed tomography angiography. Secondary outcomes included all cause death, rates of myocardial infarction, stroke, repeat revascularisation, recurrence of angina, and readmission to hospital for cardiac reasons. The primary analysis was performed using an intention-to-treat approach.



ANTONIA REEVE/SPL

Computed tomography follow-up results of vein grafts at three years

Three year outcome	No-touch	Conventional	Odds ratio (95% CI)	Absolute risk difference, % (95% CI)	P value
Primary outcomes (per graft)					
Three year vein graft occlusion	114/1988 (5.7)	175/1953 (9.0)	0.62 (0.48 to 0.80)	−3.15 (−4.96 to −1.41)	<0.001
Other graft outcomes					
Vein graft failure (per graft)	176/1988 (8.9)	245/1953 (12.5)	0.67 (0.54 to 0.84)	−3.59 (−5.72 to −1.68)	<0.001
Vein graft occlusion (per patient)	105/1140 (9.2)	152/1141 (13.3)	0.66 (0.51 to 0.86)	−4.11 (−6.70 to −1.52)	0.002
Vein graft failure (per patient)	158/1140 (13.9)	210/1141 (18.4)	0.72 (0.57 to 0.90)	−4.54 (−7.56 to −1.53)	0.003

Study answer and limitations At three years, vein graft occlusion occurred in 5.7% (114/1988) of grafts in the no-touch group compared with 9.0% (175/1953) in the conventional group (odds ratio 0.62, 95% confidence interval 0.48 to 0.80; P<0.001). The no-touch group also had lower incidences of myocardial infarction (1.2% *v* 2.7%, P=0.01), repeat revascularisation (1.1% *v* 2.2%, P=0.03), and recurrent angina (6.2% *v* 8.4%, P=0.03). Leg wound complications were more frequent in the no-touch group, though they diminished over time. Limitations include the geographical restriction to China and a follow-up rate of 86.5% for computed tomography angiography.

What this study adds The no-touch vein harvesting technique significantly reduces vein graft occlusion and adverse cardiac events at three years after CABG surgery.

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Trial registration ClinicalTrials.gov NCT03126409.