Decades On, SSRIs Remain Mired in Mystery and Debate

Experts worry MAHA could wage a war on antidepressants. But some researchers have long questioned the drugs' efficacy.

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In 2006, a new study on antidepressants was making headlines with its promising results: Two-thirds of participants who tried various antidepressants recovered from their depression symptoms within less than a year. The findings seemed to offer hope to the tens of millions of Americans who suffer from depression.

But Henry Edmund "Ed" Pigott, then a psychologist in private practice, wasn't buying it. After further exploring the study — a major National Institutes of Health trial that enrolled 4,000 patients — he was convinced that the researchers' methods greatly inflated their results, almost doubling them. In other words, the drugs may work, but not for as many people as the study suggested.

"Once I got started on it, it was like, 'Okay, this really needs to be exposed,'" said Pigott, who is now retired. His suspicion sparked a two-decade quest to correct the record and obtain a retraction from the authors of the NIH study, whose work had received $35 million of federal funding. In 2023, Pigott and colleagues published a reanalysis of the NIH data in BMJ Open, finding that the original study's remission rates were roughly half of what was reported.

Pigott isn't against antidepressants wholesale — he said he just wants patients to understand the complete risks and benefits. And many experts and clinicians stress that antidepressants are lifesaving medications. David Matuskey, a psychiatrist and associate professor at Yale University, described them as vital tools to help patients in desperate need: "Is it a perfect tool? No, but it's an important one."

The drugs are now widely prescribed in the United States. Around 13% of American adults regularly take an antidepressant, according to 2020 data, the most common of which are SSRIs — selective serotonin reuptake inhibitors — so called because they work to raise overall levels of serotonin, a neurotransmitter, in the brain.

Still, questions remain on how exactly antidepressants lift the symptoms of depression, which may include persistent feelings of hopelessness, low energy, and suicidal thoughts. In recent years, the

drugs have also been criticized for potential side effects, such as loss of libido and dizziness, while some patients experience withdrawal effects when they stop taking them.

Among the most vocals critics has been Robert F. Kennedy Jr., who has made numerous statements about the overprescription of antidepressants, particularly among children. Advocates now worry that Kennedy's influence as secretary of the U.S. Department of Health and Human Services could limit patients' access to SSRIs. In an executive order signed in February, President Donald J. Trump established the Make America Healthy Again Commission, which would, among other directives, "assess the prevalence of and threat posed by the prescription of selective serotonin reuptake inhibitors," alongside mood stabilizers and other drugs.

The American Psychiatric Association, National Network of Depression Centers, and other organizations shot back: The safety and efficacy of antidepressants had been clearly established through decades of rigorous study, they wrote. They further expressed concern that the MAHA Commission unfairly "casts doubt on this research."

But other researchers concede that some measure of doubt, or at least uncertainty, has dogged SSRIs for decades — not just in terms of their potential benefits and side effects, but even their basic mechanism of action. Rifaat El-Mallakh, who leads the Mood Disorders Research Program at the University of Louisville Depression Center, said that while many clinicians believe that antidepressants help their patients, "nobody has ever been satisfied with how effective they are."

To Pigott, that means more and better research is needed — at long last.

"These are not benign drugs. They have potential for benefit and harm," Pigott said. "You gotta weigh out those risks."

Until the 1950s, few pharmaceutical options were available to treat depression. At the time, the psychoanalytical theories of Freud and others emphasizing the role of the unconscious mind were dominant, but some clinicians were developing medical categorizations of mental conditions, and procedures like electroconvulsive therapy and lobotomy pointed towards somatic remedies — those focused on the physical body rather than psychology or emotions.

The early drugs were discovered somewhat by accident. One drug, iproniazid, was being used to treat tuberculosis when doctors realized that it helped improve patients' mood. It was prescribed off-label as an antidepressant for just a few years before researchers realized that it could severely damage the liver.

More pharmacological discoveries followed, including the first tricyclic antidepressants — drugs that reduce the absorption of neurotransmitters called catecholamines. But adverse effects ranged from blurred vision and dry mouth to more serious outcomes. Adults could fatally overdose if they took a two-week supply at once, said Siegfried Kasper, a professor emeritus of psychiatry at the Medical University of Vienna, Austria. If a child found their parents' medicine and took a single day's dose, they could die.

As doctors were beginning to prescribe these drugs to patients in the 1960s, two views on brain biochemistry came together to offer new models for depression. One was the brainchild of Joseph J. Schildkraut, a researcher from Brooklyn who spent most of his career at Harvard University and the Massachusetts Mental Health Center. Schildkraut had initially planned to become a psychoanalyst but completed training just as tricyclic antidepressants came into use. He began to explore the role of pharmacology in treating depression, and in 1965 published a seminal paper positing that depression arose due to low levels of certain neurochemicals, highlighting the role of one, norepinephrine. According to a psychiatrist and historian of the field, David Healy, Schildkraut's paper "defined the psychopharmacological era."

Around the same time, a psychiatrist called Alec Coppen was working in the United Kingdom. He was a less charismatic figure, according to Kasper, who was a young researcher at the time. "Alec Coppen did not communicate that well," he said. "He was a smart guy, but Schildkraut was an excellent communicator."

Coppen was interested in mood disorders and studied the effect of lithium on major depression and bipolar disorder, and the role of serotonin imbalance as a cause of depression. His 1967 paper, titled "The Biochemistry of Affective Disorders," reviewed studies of reserpine, iproniazid, and other recently discovered drugs, and proposed that low levels of a different neurotransmitter, serotonin, could underlie depressive illness.

That idea took hold in the pharmaceutical industry, which set out to find a pill that could address the chemical imbalance.

It took another 20 years for one to be brought to the U.S. market: the first SSRI, Prozac. Psychiatrists were enthusiastic. Patients could tolerate higher doses than earlier drugs; a fatal overdose was a much smaller risk. SSRIs had other more minor side effects, but at the time, Kasper said, their arrival was "a big revolution." (Other SSRIs have since become available, including Zoloft, Paxil, Celexa, and Lexapro.)

David T. Wong, who helped develop Prozac at the drug company Eli Lilly, described the profound effect of that development in a co-authored account published in Nature Reviews: "Numerous lives have been saved from suicide by the widespread use of these drugs, as well as many relationships restored and careers saved."

Wong and his colleagues explained that the idea of needing to boost serotonin helped reduce the stigma surrounding depression. "Having an underlying biological rationale for a treatment — that is, the modulation of serotonergic function — also helped to improve the public understanding of the role of mental-health professionals," they wrote, "as it provided a clear basis for discussing the biology of a psychiatric disorder."

And these medications really helped people, said El-Mallakh, who witnessed their introduction first-hand while working in the field in the 1990s and still values their role today. SSRIs were not more effective than tricyclics, but they "had fewer side effects and were generally safer," he told Undark.

People who take antidepressants frequently testify to their efficacy. Maura Kelly, a writer who has described her experience with antidepressants in The Atlantic, told Undark by email that the drugs helped her feel less despair and rebuild many aspects of her life. But it took almost two decades to receive an accurate diagnosis and care, and to find the right medication. Depression "really upended my life and if I hadn't gotten treatment, it would have killed me — I thought a lot about suicide," she wrote. "I can only imagine how hard it is for people who don't have a strong education, who don't have the confidence or assurance or language to push doctors to help them."

Hannah Gurholt, a 26-year-old graduate student, wrote an essay in Science magazine describing how antidepressants had quieted her anxiety. "Not having racing thoughts, and being able to sleep through the night is a huge win for me," she told Undark.

And psychiatrists stress that research backs up these experiences. Among the array of scientific studies that have shown that SSRIs improve people's mental health in both real-world and lab settings is the NIH-funded project Pigott came across in his morning newspaper. Nicknamed STAR*D — for the "Sequenced Treatment Alternatives to Relieve Depression" — it has been described by the NIH as the "largest and longest study ever conducted to evaluate depression treatment." In developing its protocol, the researchers aimed to mimic real-world conditions, and included patients who had other illnesses beyond depression. In a summary for clinicians, they also offered guidance that doctors could follow if a patient did not initially recover.

The project laid out a four-stage approach, summarized in a 2006 paper giving an overview of the findings. At level one, patients received citalopram, an SSRI also known under the brand name Celexa; about 37% of patients recovered after six and a half weeks.

Those who did not moved to level two, where they faced seven treatment options, including staying on Celexa and adding one of a range of antidepressants, switching to another drug, or switching to cognitive therapy (although only a small number chose the psychotherapy option); here, about 30% of those patients improved. Those who did not moved to level three. These patients would switch to other types of antidepressants, including tricyclics, or could augment the treatment with either lithium or the thyroid hormone Cytomel; close to 14% experienced remission of their depression symptoms.

Patients who continued to experience depressive symptoms were deemed highly treatment-resistant and progressed to level four, in which the researchers offered more aggressive treatments. Just 13% of those patients experienced improvements in the final stage.

There was no placebo arm because the treatments under scrutiny were already known to work, said Michael Thase, one of the researchers involved in STAR*D. The research question was to study the relative effectiveness of different regimens after a first treatment failed.

But cumulatively, the remission rate was 67%.

This finding has been regularly cited by scientists and the media ever since. Pigott noted that in

2009, the then-director of the National Institute of Mental Health, Thomas Insel, wrote that at the end of the 12-month study "with up to four treatment steps, roughly 70% of participants were in remission." Last year, The New York Times stated that "nearly 70% of people had become symptom free by the fourth antidepressant. As of this May, the study's flagship article has been cited over 1,800 times according to PubMed.

The investigators, led by Augustus Rush, now an emeritus professor at Duke University, wrote in 2008 that the drug used was not as important as the approach: giving patients adequate doses of medication, monitoring symptoms and side effects, adjusting the regimen, and switching drugs if needed after allowing adequate time to pass. In a summary article providing practical advice for doctors, the researchers wrote that "depression can be treated successfully by primary care physicians under 'real-world' conditions." (Rush declined an interview with Undark, and instead provided by email two previously published responses to the STAR*D criticisms.)

The project formed the basis of dozens of publications, and has remained a touchstone for psychiatrists ever since. A recent paper by U.S. clinicians looking at depression in children and teens described STAR*D as a "landmark" trial of adults with depression. A 2021 European analysis that looked at treatment-resistant depression referred to the U.S. project as "the largest multistep treatment study of patients with depression to date," which "provided key insights into treatment failure in the clinical setting."

STAR*D still features in lectures and educational material on depression, said John J. Miller, a psychiatrist and editor-in-chief of the Psychiatric Times, an industry journal. "It was such an expensive study, and involved so many different algorithms," he told Undark via email. "In today's climate it does not seem we will have another 'STAR*D' anytime soon."

From the outset, critics of antidepressants have pointed to an array of potential side effects, ranging from the very rare possibility of brain damage and an increased risk of suicide, to more common ones like loss of libido.

Others question the drugs' efficacy. As early as 1999, Irving Kirsch, a lecturer at Harvard, began to explore the role of the placebo effect in antidepressant studies, asserting that the placebo response to medication was greater than any pharmacological effect. Kirsch, who is a co-author on Pigott's 2023 paper, later published "The Emperor's New Drugs," an article and then book based on data obtained from the U.S. Food and Drug Administration, which found that the impact of antidepressants was not much greater than the placebo effect.

In 2017, a team of researchers from Denmark (who had also collaborated with Kirsch) concluded that, compared with a placebo, the side effects of SSRIs seemed to outweigh "any potentially small beneficial effects." More recently, a small group of researchers have called attention to the fact that the hypothesis on which understanding of these medications is based have never been proven.

Before Pigott embarked on his project to reassess the STAR*D data, he knew little about antidepressants and had no bias against them, he said. (As a psychologist, he doesn't prescribe medications.) In the 1980s and 1990s, he often dealt with suicidal patients at a crisis intervention service he had set up, where he worked with two psychiatrists who regularly prescribed the medications. "I do have psychiatrist friends, I really do," he said with a laugh. "I'm not against

psychiatry."

But after spotting what he considered to be major flaws in how the STAR*D authors reported their results, and after what he described as "much obsessing," he crafted his re-analysis. Over the next two years, he worked with other researchers, and published a review of research on antidepressants. In 2011, he connected with Kirsch, and in 2023 the group published their reanalysis in BMJ Open, a peer-reviewed general medicine publication.

Pigott and his colleagues pointed out a long a long list of methodological issues with the study. Among the problems, the researchers noted that the STAR*D's own protocol proposed the use of one scale to assess symptoms, the Hamilton Rating Scale for Depression (HRSD or HAM-D) as a primary measure of outcome, but in the main summary article deployed a secondary measure, the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR), to report remission rates.

The HRSD was blinded and conducted by phone, whereas QIDS-SR was reported by the patient at the clinician's office, making the report more vulnerable to overstatement or bias. And the differences between the two were stark: When Pigott applied the Hamilton scale to the data, the cumulative remission rate of patients fell from 67% to 35%. The STAR*D researchers, Pigott pointed out, also included 125 patients in steps two through four who were already considered recovered prior to starting their next level of treatment.

"It could have been an honest mistake on their part," Pigott said of those patients' inclusion. He said he could not imagine the investigators sitting around a table and choosing to fudge the data. But they should have corrected it once the error was pointed out, he added, and "now they're complicit."

Of the downswing from 67% to 35%, Thase, one of the researchers on the STAR*D project, and a professor of psychiatry at the University of Pennsylvania, said: "This is the accusation, that we violated the protocol to fluff up the rates." (Thase, like some other researchers who spoke in support of antidepressants for this story, has consulted for pharmaceutical companies that manufacture antidepressants. El-Mallakh has disclosed in publications that he is a speaker for various pharmaceutical companies.)

He told Undark there was a simple reason why the team had used the QIDS rather than HRSD measure in the 2006 paper: The researchers took HRSD measures at the start and end of the project, but QIDS was taken more frequently. And although the HRSD was meant to be the primary measure of outcome, Thase said, some patients were unavailable for the final HRSD when their QIDS data pointed towards remission. In their 2006 summary paper, the researchers wanted to use all available participants and evaluate long-term outcomes. The QIDS measure allowed them to feature the outcomes of more patients, including those who missed a HRSD measure, he said. "Those self-reports actually reflect how the patient was doing," he added. "They're not false data, they're the same data, just from a different vantage point."

Thase said the calls for retraction had an accusing tone. It was, he said, “the only time in my 40-something-year career this has happened.”

In 2023 and 2024, Miller, the editor-in-chief of the Psychiatric Times, published a series of articles about the controversy. In a cover story titled “STAR*D Dethroned?” he called on the field to probe the gap between the 2006 analysis and that of Pigott in 2023, and he subsequently published a response by Thase and his colleagues. In an editorial that March, Miller wrote that he did not think the STAR*D team intended to inflate their results, but did think that using the original measure would have been “a more clinically relevant choice.” And in an email to Undark, he added that Pigott’s analysis was very important: “Because the STAR*D data is used so ubiquitously in lectures and articles on the treatment of major depression, the misrepresentation of the outcomes in each of the four steps of STAR*D are reinforcing percentages of response to antidepressant treatment that psychiatric providers are continuing to be told are accurate.”

Still, Miller suggested that many psychiatrists have probably not read either paper. The burden of electronic health records and increased productivity requirements take time away from self-education. “Psychiatric practitioners are so overbooked and stressed these days that it is likely they do not spend as much time as years ago reading complete articles in a wide range of journals,” he wrote in an email to Undark. “There has been no notable change in the field of psychiatry.”

Meanwhile, criticism of the study’s methods has featured in alternative publications, Substacks, and blogs. A slew of articles appeared on the website Mad in America with headlines like “STAR*D: The Harms of Orchestrated Psychiatric Fraud.” Apart from his publication, Miller said he was not aware of other platforms trying to engage the psychiatric profession to revisit the STAR*D data.

But the controversy did not go entirely unnoticed. Pigott’s 2023 co-authored piece was one of the most read BMJ Open articles for July that year. And commenting on the study, an editorial in Nature Mental Health stated that antidepressants have underpinned psychiatric care since the 1950s. Now, the authors wrote, “some of the bedrock of clinical wisdom in psychiatry has begun to erode.”

The STAR*D trial has not been the only pillar of antidepressant research to face critique: Around the same time that Pigott was questioning the effectiveness of antidepressants, the serotonin hypothesis — which posits that a chemical imbalance in the brain causes depression — was undergoing scrutiny.

In 2022, Joanna Moncrieff, a professor of critical and social psychiatry at University College London, published a review in Molecular Psychiatry, a prestigious Nature publication, in which she wrote that there is “no consistent evidence of there being an association between serotonin and depression.”

Pigott and Moncrieff’s papers looked at different things — Pigott’s cast doubt on a landmark trial in

the medication's effectiveness; Moncrieff's probed whether evidence exists to prove the serotonin hypothesis — but both poked at core beliefs underpinning why antidepressants are appropriate treatments for depression. Going even further, Moncrieff told Undark that the full implications of her paper are that "We don't know whether there is a link — whether there is a biological mechanism that underpins depression."

Moncrieff is a leading player in critical psychiatry, a movement that challenges psychiatric norms. A polarizing figure, Moncrieff is not new to criticism, but the response to her 2022 paper, she said, was "extraordinary." A profile in Rolling Stone described her as "the psychiatrist behind the antidepressant study taking over right-wing media," and stated that her views "align with the right on other matters." Moncrieff, who has said publicly she has always been to the left in politics, told Undark that she did she not agree with all of the statements made by Secretary Kennedy. But, she said, "It's good that he's raising questions about antidepressants."

Her 2022 paper was not the first time the serotonin hypothesis had been questioned, but Moncrieff and her colleagues had presented a bank of data to back up a provocative conclusion: "This review suggests that the huge research effort based on the serotonin hypothesis has not produced convincing evidence of a biochemical basis to depression," they wrote, and added, "We suggest it is time to acknowledge that the serotonin theory of depression is not empirically substantiated."

The paper triggered a cascade of reactions: first a slew of letters to the editor, and then a formal counter-argument, co-authored by 35 academics and psychiatrists, charging that Moncrieff had excluded relevant studies and showed "an underappreciation of the complexities of neuroscience and neuropsychopharmacology."

One of the authors of that critique was David Matuskey, who said some of his co-authors were shocked that Moncrieff's article had made it through peer review into Nature's distinguished pages. Some colleagues wanted the piece to be retracted, he said. "I think the scientific review process is good," he told Undark, but added, "I think it's not perfect." Another co-author, David Erritzoe, a researcher at Imperial College London, said Moncrieff's team would have benefitted from involving researchers with expertise in areas relevant to the review, like biological neuroimaging.

Earlier this year, Moncrieff published a book titled, "Chemically Imbalanced: The Making and Unmaking of the Serotonin Myth," which articulated a more explicit position. The book outlined how, as she painted it, a quest for money and professional status, scientific hubris, and patient desperation had led to "one of the most widespread and harmful delusions of recent times: the idea that emotional problems can be resolved with a pill."

It received favorable reviews, including in The Sunday Times Magazine — an event that moved Awais Aftab, a psychiatrist and blogger, to write a post in response to the coverage. As he saw it, public understanding of depression as a chemical imbalance is vague, a "mishmash of buzzwords," he wrote, and Moncrieff had used that misperception to attack the validity of antidepressants themselves. And while he acknowledged that the serotonin hypothesis is still, well, a hypothesis,

the scientific literature strongly suggests serotonin plays some kind of role in mood regulation.

Aftab's depiction sketched a faithful picture of critical psychiatry, according to Philip Cowen, a professor of psychopharmacology at the University of Oxford and another co-author on the response to Moncrieff who has spent decades examining the role of serotonin in depression. He said that Moncrieff and her colleagues fundamentally oppose pharmacological interventions in treating depression. "I have to say that this is a coherent and not uncommon point of view," Cowen wrote in an email. "However, no evidence one could produce of relevant neurobiological changes in depression or the fact that antidepressants help some depressed people would ever change Moncrieff's mind."

When Undark spoke to Moncrieff by phone, she said she first became interested in the topic after working in a psychiatric institution. This was the '90s, and many patients seemed "zombified," she said. These days, Moncrieff said she would not rule out prescribing the drugs to a patient who really wanted them, but she would make sure they were aware of possible side effects and withdrawal symptoms, and that they understood "that antidepressants are not treating a chemical imbalance or any other underlying mechanism, that there's little evidence that they're different from placebo."

Even some researchers wary of Moncrieff's broader stance towards antidepressants agreed with her point. Cowen, for example, said that Moncrieff is correct in stating that no evidence exists for a serotonin deficit causing depression.

And El-Mallakh, the director of the Mood Disorders Research Program at the University of Louisville School of Medicine, noted that determining the brain physiology behind depression wasn't necessarily important so long as patient symptoms improve. "We don't know what is wrong with their brain, but that's okay," he said. "We have a tool that makes them feel better."

Research about the side effects and adverse impacts of antidepressants side effects has led to some changes in guidance. Scientists have begun to look at the possible long-term impact on sexual function, referred to as post-SSRI sexual dysfunction. The difficulty some people may have coming off antidepressants has led to the publication of formal guidelines in the U.K. And there is widespread agreement even within the psychiatric community that the medications have been overprescribed.

But these shifts don't always trickle down swiftly to individual patients. Hannah Gurholt, the graduate student who has had some success with the drugs, wishes that her psychiatrists had explained the potential side effects more clearly. She has found herself with acne or clammy hands, only to realize they are potential side effects when people are on some antidepressants. Often, now, she said, when she experiences side effects she ends up Googling them herself.

And Maura Kelly, the writer who has taken antidepressants for many years, said that because depression is so complex, the prescription of antidepressants should be done by psychiatrists

alone: “I don’t think primary care docs should be allowed to prescribe antidepressants.”

Even as the MAHA Commission probes prescription rates, the ways in which antidepressants are prescribed make them vulnerable to scrutiny. “I think the reason that a lot of people, including people like Kennedy, are against antidepressants, is because they are overused by physicians, at least in the United States,” El-Mallakh said. He ascribed this to the incompetence of physicians who think they are benign. “They’re used in people who aren’t depressed,” he said. “They’re used in people who just feel bad. They’re used to help people deal with life.”

Thase, the co-investigator of the STAR*D study, agreed. There are different ways of tackling depression, including exercising and spending time in the sun outside, he suggested, and medication should be part of a comprehensive approach. “These are natural and healthy ways to minimize your level of depression,” he said, later adding, “I think medication should be used, not at the drop of the hat.”

But, referring to the MAHA Commission, he noted there is a tension in trying to avoid overuse. In the early 2000s, the FDA cited a potential link between suicidality in young people taking antidepressants on its labeling. In the years that followed, doctors were more careful about prescribing the medication, and the teen suicide rate rose visibly. “When you try to do good and minimize the overuse of something, you can actually inadvertently put more people at risk,” Thase said.

Nineteen years since he first came across STAR*D in the newspaper, Pigott and his colleagues are still subjecting the study’s data to investigation. They have an article in development probing the changes in suicidality after a switch in medications in the study’s step 2. In contrast to the original analysis, they say they found a 30% increase in suicidality among patients. As a result of this finding, he said, “People will be changing what they do.”

In terms of mechanism, the focus of research on depression has largely moved on from trying to verify the serotonin hypothesis. But Erritzoe, the Imperial College London researcher who did his doctoral thesis on serotonin markers in patients, recently published a study that gave weight to the hypothesis, which appeared after Moncrieff’s article. He did PET scans of the brains of 17 depressed patients not receiving medication and detected reduced serotonin release. The study offered the most direct assessment of the serotonin hypothesis, but needs to be replicated, ideally in greater numbers — the basis for a major project Erritzoe is now embarking on with funding from the U.K.’s Medical Research Council.

Erritzoe hopes his next study will help inform which patients are likely to respond to an SSRI. Most of his work now is on psychedelics, but he said that the classic psychedelics, like psilocybin and LSD, are “absolutely serotonergic drugs,” he noted. “The serotonergic system is an absolute focus, it’s just other aspects of the neurotransmission in the serotonin system that is gaining traction.”

To Erritzoe, the debate about the serotonin hypothesis remains a useful one because that’s what

science is — agreeing and disagreeing about different kinds of evidence.

Thase made a similar point. “No one study answers all questions and is the definitive study,” he said. “All studies are estimates of some truths.”

UPDATE: An earlier version of this piece incorrectly stated that Pigott sought to obtain a review or retraction of the STAR*D study. He sought a correction and retraction of the study. The piece also did not make clear that Pigott and colleagues identified multiple methodological errors in the STAR*D study. Additionally, the piece mischaracterized a quote from Pigott. When he said “It could have been an honest mistake on their part,” he was referring to the inclusion of 125 patients in steps two through four, not the drop from 67% to 35%. The piece has also been updated to clarify the accusation Thase was referring to.

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