

Pregabalin Addiction: A Bibliometric Analysis

Pregabalin Bağımlılığı: Bibliyometrik Bir Analiz

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Abstract

Objective: Bibliometric analyses allow determining the scientific research profile, revealing the current situation on the subject, and identifying new research areas. Pregabalin addiction is an addiction that has serious consequences for the individual, family and society. For this reason, taking photographs of studies related to this field can be a guide for researchers. In this regard, the aim of the research is to bibliometrically examine publications addressing the issue of pregabalin addiction.

Method: The study was conducted in the Web of Science database. The keywords “pregabalin addiction” were used during the screening without any time limit.

Results: 150 publications were reached. Their publication dates were between 2003 and 2023, the average age of publication was 4.83, and the annual increase rate was 5%. The most active country was the United States of America, and the journal with the highest number of publications was “Frontiers in Psychiatry.” In addition, “gabapentin, abuse” was the most frequently used, “opioid, drug abuse” were the motor, “withdrawal” was niche, and “pain, substance” were emerging or disappearing themes. Besides, “neuropathic pain” was a basic theme, and “benzodiazepine” showed consistent development.

Conclusion: This is the first bibliometric study addressing pregabalin addiction and provided a comprehensive overview of pregabalin addiction over 20 years. From the quantitative perspective, the mean age of the study and the annual growth rate were low, and the number of studies was limited. Qualitative data showed that research topics mostly clustered on pregabalin addiction, addiction potential, abuse and taking with other drugs, and demonstrated a need for studies in addiction prevention, treatment, and rehabilitation.

Keywords: Bibliometric, pregabalin, addiction

Öz

Amaç: Bibliyometrik analizler, bilimsel araştırma profilinin belirlenmesine, konu ile ilgili mevcut durumun ortaya konmasına ve yeni araştırma alanlarının tespit edilebilmesine olanak sağlamaktadır. Pregabalin bağımlılığı birey, aile ve toplum açısından ciddi sonuçları olan bir bağımlılıktır. Bu nedenle bu alana ilişkin çalışmaların fotoğrafının çekilmesi araştırmacılar için yol gösterici olabilir. Bu doğrultuda araştırmanın amacı pregabalin bağımlılığı konusunu ele alan yayınları bibliyometrik olarak incelemektir.

Yöntem: Çalışma Web of Science veri tabanında yürütülmüştür. Tarama sırasında, süre sınırı olmaksızın “pregabalin addiction” anahtar kelimeleri kullanılmıştır.

Bulgular: Çalışmada 150 yayına ulaşılmış, yayınların yayım tarihleri 2003-2023 tarihleri arasında, yayın ortalama yaşı 4.83, yıllık artış oranı ise %5'tir. En aktif ülke Amerika Birleşik Devletleri, en çok yayın yapan dergi “Frontiers in Psychiatry”dir. Ayrıca “gabapentin, abuse” en sık kullanılan, “opioid, drug abuse” alana yön veren, “withdrawal” gelişmiş ancak izole kalmış, “pain, substance” ise yeni ortaya çıkan ya da kaybolan temalardır. Yanı sıra “neuropathic pain” alan için önemli bir konu iken, “benzodiazepin” konusu ise tutarlı gelişim göstermektedir.

Sonuç: Bu çalışma pregabalin bağımlılığını konu alan ilk bibliyometrik çalışmadır ve 20 yılda pregabalin bağımlılığına ilişkin kapsamlı bir bakış sağlamıştır. Nicel veriler sonucunda; çalışmanın ortalama yaşı ve yıllık büyüme oranının düşük, çalışma sayısının sınırlı olduğu görülmüştür. Nitel veriler araştırma konuların çoğunlukla pregabalin bağımlılığının; bağımlılık potansiyeli, kötüye kullanımı, diğer ilaçlarla birlikte alınması üzerinde kümelenildiğini, bağımlılığı önleme, tedavi etme ve rehabilitasyonuna alanlarında da çalışmalara ihtiyaç olduğunu göstermiştir.

Anahtar kelimeler: Bibliyometrik, pregabalin, bağımlılık

Introduction

Pregabalin is a new-generation antiepileptic that reduces the emission of multiple stimulants by reducing the calcium flux induced by depolarization (1). It is indicated for use in epilepsy, peripheral neuropathic pain, fibromyalgia, generalized anxiety disorder, and post-herpetic neuralgia (2). Pregabalin is also used to treat chronic itching, restless legs syndrome, social anxiety disorder, insomnia, and bipolar disorder (3). Unfortunately, however, much evidence exists in the literature about pregabalin abuse (2, 4, 5). The Swedish national register of adverse drug reactions data indicates that pregabalin has the potential for abuse (6). Studies following this report have similarly shown that pregabalin abuse may lead to addiction (5), poisoning (4), and drug withdrawal syndromes (2).

Pregabalin addiction does not have a specific definition in the DSM-5 diagnostic criteria. Therefore, this issue is addressed within the scope of the criteria under the diagnosis of "Other Substance Use Disorder". In its 2018 report, the World Health Organization reported the prevalence of pregabalin addiction and abuse as 0.25-22% (7). Prior or current opioid use, male gender, young age (18-45 years), chronic diseases, history of addiction, psychiatric comorbidities, and low socioeconomic status are defined as risk factors for pregabalin addiction and abuse (8). Its use over the therapeutic dose causes euphoria, it may be used for recreational purposes, and gives energy, creates a relaxing effect, potentiates some substances (especially opioids), and is preferred to cope with substance withdrawal (1,9), which may be reasons for abuse.

Pregabalin addiction can occur, mainly when used in high doses and for a long time. (1). Signs of pregabalin addiction include tolerance development, withdrawal symptoms such as vomiting, restlessness, tachycardia, agitation, and sweating that occur when the drug is abruptly discontinued or the dose is reduced, the inability to control the habit of using the drug, adverse effects on professional, social and family life and a tendency to increase the dose or frequency taken (10,11).

Pregabalin addiction can have serious consequences. These include physical problems such as vomiting, tachycardia, agitation, and sweating; mental and emotional problems such as decreased attention and concentration, anxiety, mood disorder, and agitation; social and professional difficulties caused by disruptions in communication, relationships and roles, risky behaviours to obtain the drug and the risk of overdose to produce the desired effect, and death (10-12). Profiling the studies on this addiction with severe consequences for the individual, family, and society can guide researchers, and bibliometric analyses emerge as an opportunity in this context.

Bibliometric analysis is a new approach to presenting qualitative and quantitative data on a particular topic (13). It allows to determine the scientific research profile, reveal the current state for an issue, and identify new research areas (13,14). At this point, it is inevitable that a bibliometric analysis on pregabalin addiction, which has a high addiction rate, tends to increase the dose due to tolerance developing towards the drug, and as a result has the risk of overdose and death, will contribute to the field. Thus, the present study aimed to examine publications addressing pregabalin addiction bibliometrically.

Method

Study Design

This is a bibliometric study and used the guide developed by Donthu et al. (15). According to this guide, the bibliometric analysis procedure consists of four consecutive steps. These steps are as follows.

Step 1: Defining the purpose and scope of the bibliometric study,

Step 2: Selecting the most appropriate bibliometric analysis,

Step 3: Collecting data for bibliometric analysis,

Step 4: Performing bibliometric analysis and writing down the findings (15).

Data Collection

The research used secondary data from the Web of Science (WOS) database and included studies addressing pregabalin addiction (N=150). There was no restriction on the publication type, and all studies whose publication language was English were included. This is a bibliometric study addressing pregabalin addiction. Therefore, this study did not require ethics committee approval and an informed consent form.

The WOS database used during the study was searched in June 2023. The English keywords “pregabalin addiction” were used during the search without any time limit. The search yielded 161 publications. Of these, 11 non-English publications were excluded (German n=6, French n=2, Japanese n=1, Russian n=1, Spanish n=1). The research was completed with 150 publications (N=150). Included and excluded studies are indicated in the flowchart in Figure 1.

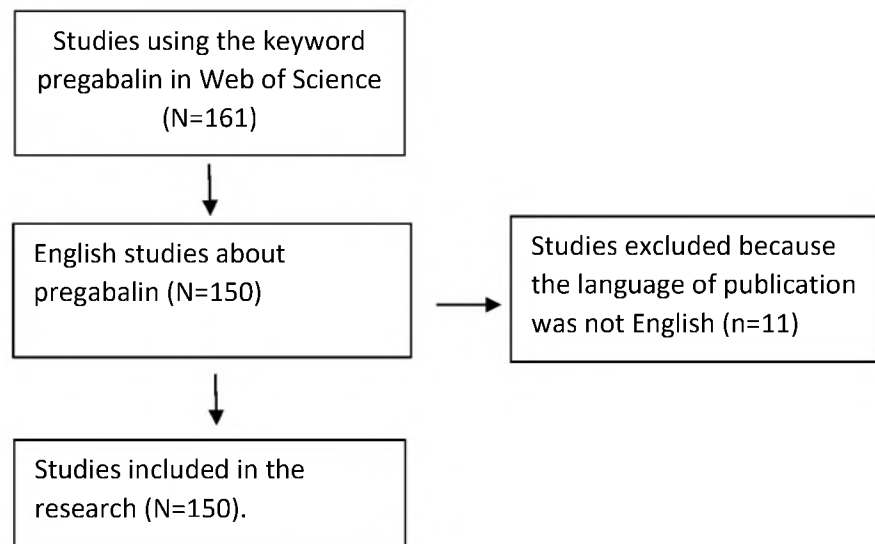


Figure 1. Flowchart indicating included and excluded studies

For data analysis, all the data obtained from the WOS database were first downloaded in BibTeX format and uploaded to the biblioshiny program, an extension of the R program. The studies were then examined for publication language. Random publications were selected from the data set to evaluate their fit for the purpose of the study. Those not meeting the inclusion criteria were excluded. Synonyms were combined (abuse: misuse, opioids: opioid, drug abuse: drug misuse, addiction: dependence, gabapentinoids: gabapentinoid), after which the analysis process was started.

Statistical Analysis

The biblioshiny interface of the open access R program (R 4.2.2.) in the bibliometrix tool was used for data analysis. R package and bibliometrix tool are recommended for comprehensive scientific mapping analyses (16). “Author’s keywords” were used in the entire data analysis process, and the details were presented under four main headings.

1. Essential information: Key information about related publications is presented in this context. Data analyses are presented as numbers, percentages, or proportional values (Table 1).
2. Treemap: It is an analysis technique that reduces a data set to the most frequently seen words and offers an idea about the boundaries of the subject. With this analysis, the words in the data set are sorted by their frequency of occurrence (17). The first 25 most frequently used keywords were included in the treemap analysis in this study (Figure 2).
3. Trend topics: It reveals the distribution of themes specific to a subject by years. The size of the lines indicates the time interval in the publications of the relevant theme, the location of the circles

indicates the median dates, and the size indicates the word's frequency of use (17). In this study, the minimum word frequency was five, and the number of words per year was three (Figure 3).

4. Thematic map: This analysis reveals information about the conceptual and intellectual structure of the field (18). Each node in the map represents a network cluster, and node names represent words that belong to the cluster and have a higher occurrence network. Node sizes are determined by the number of publications the keyword occurs. Node location is based on cluster centrality and density (17). Two hundred fifty keywords and the fast greedy algorithm were used for thematic analysis. The minimum cluster frequency was determined as five, and the number of levels for each cluster as one (Figure 4).

The concepts that should be considered when interpreting the analysis are as follows: (14,15,17)

1. Centrality: It is represented by a horizontal line. It is a measure of the theme's relevance and external pertinence to other studies. The stronger the centrality, the more critical it is to the subject area.
2. Density: It is represented by a vertical line. It is a measure of the theme's development and internal cohesion. The stronger the intensity, the more coherent and integrated the subject.
3. Motor themes: They are located in the upper right quadrant and are characterized by high centrality and high density. They are the developed and vital themes of the research area.
4. Basic themes: They are located in the lower right quadrant and are characterized by high centrality and low density. They indicate the themes that are still developing for the research area.
5. Niche themes: They are located in the upper left quadrant and are characterized by low centrality and high density. They indicate that the research area contains developed but isolated themes.
6. Emerging or declining themes: They are located in the lower left quadrant and are characterized by low centrality and low density. They are considered emerging or disappearing themes for the research field.



Figure 2. Prominent keywords in the treemap

Results

The publication dates of 150 (N=150) studies included in the study were between 2003 and 2023, and the mean publication age was 4.83. The studies were written by 675 authors, and the average citation for each

publication was 20.51. The country with the most publications was the United States of America (USA), and the journal with the most publications on the topic was Frontiers in Psychiatry (Table 1).

Table 1. Essential information on the publications

Key information	Results
Data	
Sources	91
Documents	150
Time range of publications	2003-2023
The average age of publication	4.83
Annual growth rate of publications	% 12.2
Authors	
Number of authors	675
Publication content	
Number of keywords used in publications	418
Number of sources used in publications	5628
Publication type (n)	
Research paper	107
Review	22
Editorial material	18
Meeting abstract	3
Citations	
The average number of citations in each publication	20.51
Country of the first three corresponding authors with the most publications (n)	
USA	28
Germany	17
United Kingdom	14
Top three journals with the most publications (n)	
Frontiers in Psychiatry	9
CNS Drugs /Journal of Psychoactive Drugs/Journal of Substance Use	5
Addiction/Expert Opinion on Investigational Drugs	4

The prominent keywords in the treemap were pregabalin (n=71, 24%), addiction (n=40, 13%), abuse (n=39, 13%) and gabapentin (n=29, 10%). These were followed by opioids (n=14, 5%), gabapentinoids (n=10, 3%), drug abuse (n=10, 3%), and withdrawal (n=10, 3%) (Figure 2).

Among the trend topics of the study, “pregabalin” was studied the most frequently, while “neuropathic pain” and “pharmacovigilance” were studied the longest. The themes of “opioids, gabapentin, gabapentinoids” have been in trend in the last three years (Figure 3).

According to the thematic map, the “pregabalin” theme, which was the most centrally located, the most studied and continues to develop, was a basic theme. “Neuropathic pain,” situated on the centrality line, was the second most central subject. The motor themes were in two clusters: the “drug abuse” cluster with higher centrality and “opioids” with the highest density. While “benzodiazepines” was on the density line, “withdrawal” has a niche theme. Emerging or declining themes were “substance” and “pain” (Figure 4).

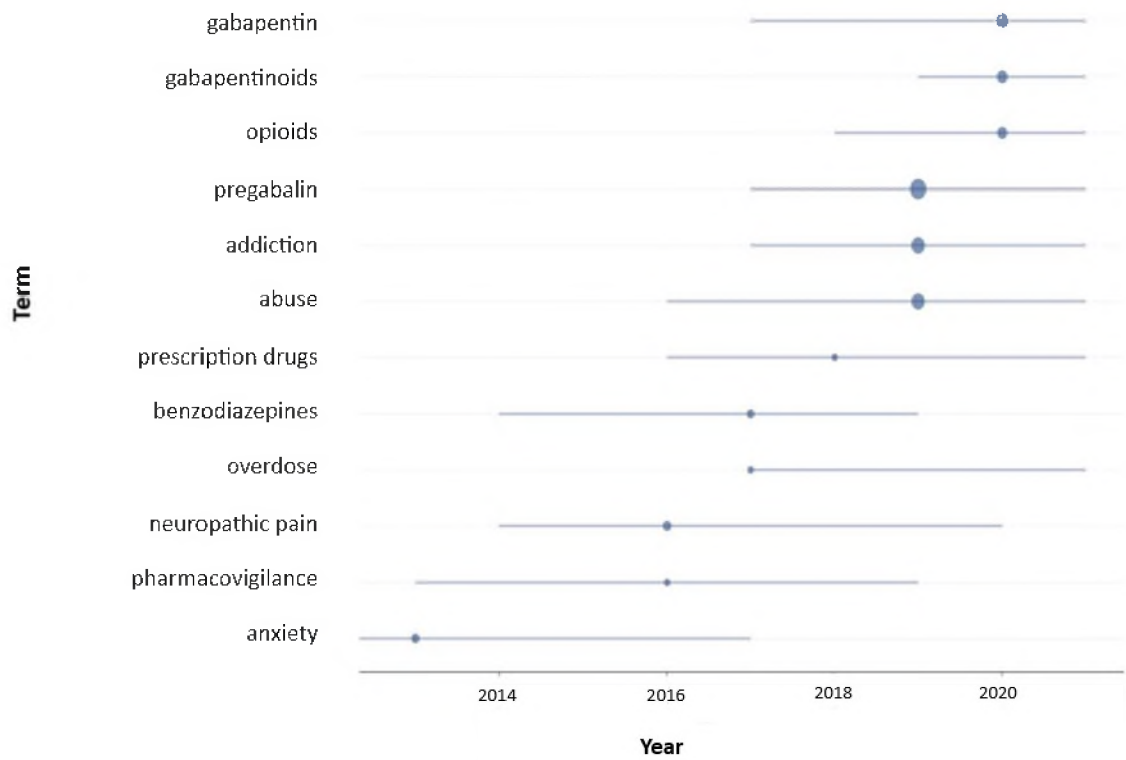


Figure 3. Authors' keywords trend topics

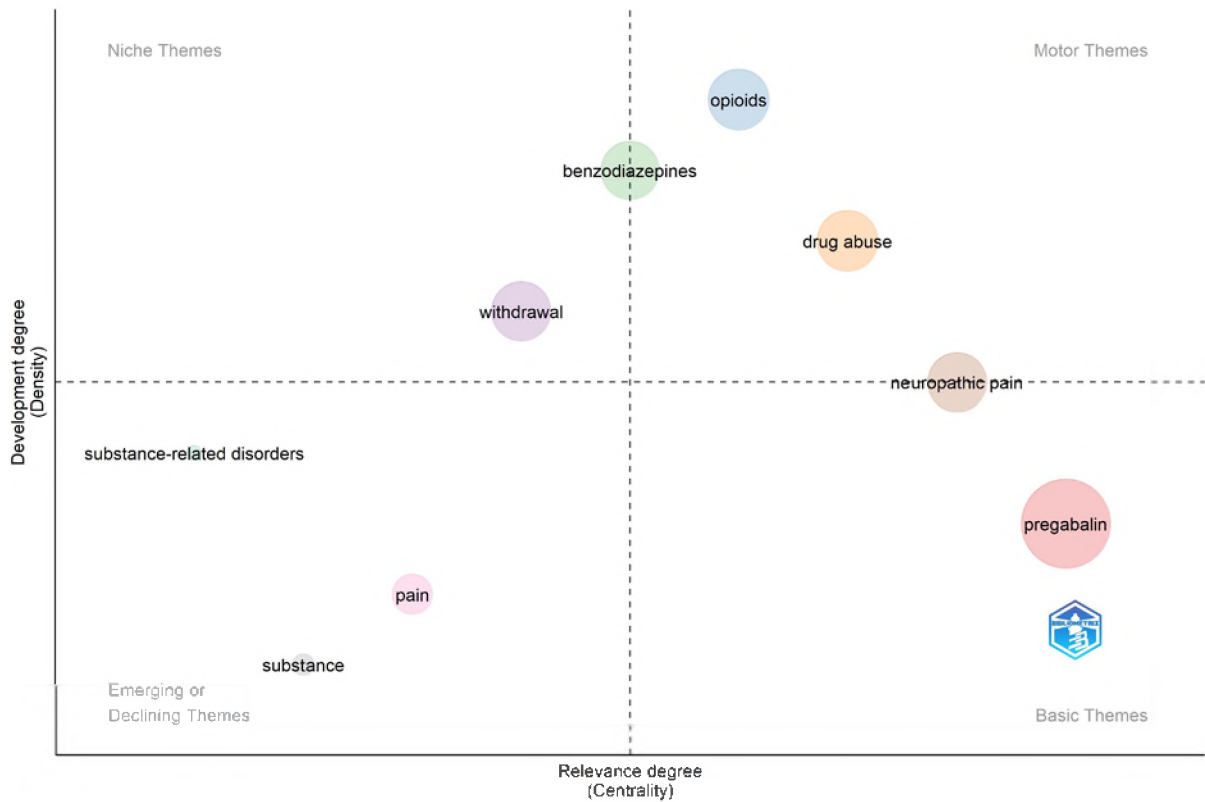


Figure 4. Authors' keywords thematic map

Discussion

The risk of addiction and serious consequences can occur if drugs such as pregabalin are misused, used outside its prescribing information, or overdosed (9, 19). Quantitative and qualitative bibliometric evaluations of studies addressing pregabalin addiction were made with this study. To our knowledge, this is the first bibliometric study on pregabalin addiction.

Our results showed that previously published studies on pregabalin addiction are limited in number and, as remarkable findings, previous studies had a history of only 20 years and a low annual growth rate, at about 5%. Thus, planning longitudinal studies, especially focusing on long-term effects seems essential. On the other hand, the fact that there were more research articles than other types of publications was a positive finding, as more new information will be obtained with more research.

Within the scope of the study, the countries and journals of the corresponding authors who made the most publications on the subject were also examined. The USA ranked first among the nations. Pregabalin ranked 30th on the list of most prescribed drugs in the USA in 2011. The fact that deaths due to synthetic opioids in the USA are almost twice as high as those in armed assaults and car accidents, and the widespread intake of pregabalin with these synthetic opioids (20) may be effective in bringing the USA to the first place in publications related to pregabalin addiction. The finding that "Frontiers in Psychiatry" was the journal with the most publications on the subject can be explained by addiction being treated within the scope of psychiatric disorders. However, it should be noted when interpreting these results that there were no noteworthy differences between the number of publications between countries and journals. But it is possible to say that there is limited research on pregabalin addiction.

Keywords are one of the most important elements that represent the essence of research. They provide an idea about the boundaries of the topic and the main issue that the article intends to present (21). The treemap analysis made within the scope of the study used the keywords that the authors used to describe their work. The keywords "pregabalin, addiction, gabapentin, abuse" were prominent in the studies on pregabalin addiction. The phrase "pregabalin addiction" was expected to rank first since it was the keyword used during the search. Gabapentin, like pregabalin, is an antiepileptic drug with similar indications and addictive properties (22). Both drugs are widely used for similar reasons (19), which may explain why pregabalin and gabapentin, called gabapentinoids (1), were among the prominent keywords in pregabalin addiction. Studies addressing these topics are likely to offer insights into the addiction potential of pregabalin, its mechanisms of action, risk factors for abuse, and treatment modalities. Therefore, these studies can guide healthcare professionals in the safe and effective use of the drug. Another prominent keyword was "abuse." When taken in high doses, pregabalin produces euphoria, energy and relaxation, potentiates the effect of some substances (especially opioids), and is a preferred agent in coping with substance withdrawal (1,9) which contribute to its abuse, making abuse a dominant word. It is essential for the consistency of the data that similar topics come to the fore within the scope of trend topics. Although research on pregabalin addiction provides some findings to examine the potential risk of addiction, it seems that more research is needed on problems caused by addiction, prevention and intervention. By researching this subject, health professionals can be better equipped to combat pregabalin addiction.

Thematic map analysis showed that the subject of "opioids" was a motor theme in research on pregabalin addiction. The emergence of opioids as a motor theme, one of the trend topics of the last three years, may be due to the effect of pregabalin on reducing opioid withdrawal syndrome (1). According to the results of a study, 39 of 440 individuals using opioids were found to use pregabalin (23). In another study, most individuals with pregabalin addiction were opioid users, supporting our result (5). Another motor theme was "drug abuse." The fact that the abuse rate of pregabalin varies in a wide range of 3-68% (24) may explain this. In addition, pregabalin is abused due to factors such as energizing, euphoric and relaxing effects and its recreational use (1, 9). This may explain why abuse was a motor theme. Considering the consequences of pregabalin abuse and addiction, it is encouraging that these topics are discussed in the publications.

Identifying situations that may pose a risk in abuse and planning studies that address individual and social containment methods to prevent these risks can provide guidance in managing pregabalin addiction.

Although pregabalin and benzodiazepines are different drug classes, they can be considered agents with similar effects. Pregabalin can be used as an adjunct to the withdrawal therapy of benzodiazepines (1,22,25). Since both classes of drugs have sedative actions, their simultaneous use can potentiate their effects (25). One study reported that the most common drug taken with pregabalin was benzodiazepines, and taking these two drugs together caused serious problems, even death (26). Prescribing pregabalin for benzodiazepine withdrawal and addiction is associated with the risk of drug abuse. In this study, “benzodiazepines” were located above the density line on the thematic map. Considering that the studies related to pregabalin addiction are still young in age and the number of studies is limited, it seems that this topic may become a motor theme over time.

Withdrawal symptoms may occur if pregabalin is discontinued or its dose is reduced (5). Individuals tend to retake this drug to avoid withdrawal symptoms (24). After a while, finding and using the medicine may become the most important focus of their lives (27). In this study, “withdrawal” emerged as a niche theme. It is crucial that drugs such as pregabalin are used as prescribed and following healthcare professionals’ recommendations. However, when withdrawal occurs, it is essential to develop a treatment protocol for withdrawal to control the symptoms (24). Case report outcomes can aid in developing the protocol.

Pregabalin is in the group of drugs used in the first-line treatment of neuropathic pain (22). Neuropathic pain can occur due to multiple sclerosis, diabetic neuropathy, traumatic nerve injury, and spinal cord injuries (28). Potential for addiction may thus arise with misuse or improper use of pregabalin for several patient groups. In this study, the subject of “neuropathic pain” was both among the trending topics and was on the line of centrality with a high rate of centrality in studies in the field of pregabalin addiction, consistent with the literature. This means that it is a very basic theme for the area. The fact that neuropathic pain is a symptom of many diseases and the effective use of pregabalin in its treatment suggests that this may become a motor theme as further studies will be performed in the future.

Author’s keywords were used in analysing the data in this study. “Pain” and “substance,” which are among the emerging or disappearing themes, may be components of another term due to the keyword preference of the authors. For example, “pain” can be a descriptor of neuropathic or chronic pain, and “substance” can be a descriptor of the term substance abuse. Although the size of the clusters indicates very few studies on the subject, the topics included in this theme should be interpreted with care. However, since pregabalin addiction is a young theme with few studies, “pain” and “substance” may be emerging rather than disappearing themes.

An interesting result obtained from this study is that no theme for the prevention, treatment and rehabilitation of addiction to a potentially addictive drug was not included in the analysis results. In addition, the fact that topics addressing the family and society were not included in the themes indicates some gaps regarding these subjects. Conducting studies on these topics can be instrumental in increasing knowledge and awareness, preventing addiction, preventing off-label use of drugs, and producing new policies.

This study has some limitations. First, the results are limited to the time covered by the literature search. Second, the literature search was done in the “Web of Science Core Collection” database. The last limitation of the study is that because the selected keywords were in English, only articles with English as the publication language were included in the analysis. Searches made in different time periods, databases, and languages may yield different research results.

In this study, a bibliometric publication map, including quantitative and qualitative evaluations, was created in line with the studies in the field of pregabalin addiction. The quantitative evaluation demonstrated that the publications on pregabalin addiction had a history of 20 years, the average age of publication was small, the number of publications was limited, the annual growth rate was low, the USA was the country with the most publications, and the journal “Frontiers in Psychiatry” was the journal with the highest number of published work. Qualitative evaluation showed that the studies focused on “gabapentin” and “abuse” and also revealed

that studies on “opioid” and “drug abuse” were motor themes, “neuropathic pain” was a basic theme, while “benzodiazepine” showed consistent development, and studies on “withdrawal” were niche. The results also showed that the research topics mainly were clustered on pregabalin addiction, addiction potential, abuse and taking with other drugs, and demonstrated a need for studies in addiction prevention, treatment, and rehabilitation. Based on these results, it is recommended that further, in-depth, and especially longitudinal research on pregabalin addiction should be conducted, and the study area be broadened to encompass the issue of combating addiction.

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Etik Onay: Bu çalışma için ilgili Etik Kuruldan etik onay alınmasına gerek yoktur.
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Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
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Conflict of Interest: The authors have declared that there is no conflict of interest.
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