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REVIEW

Research Trends and Hot Spots of Allopregnanolone Research in the Last 20 Years: A Bibliometric Analysis

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Background: Allopregnanolone is a kind of neuroactive steroid or neurosteroid in the central nervous system that acts as an endogenenous $GABA_A$ receptor positive modulator. However, at present, no comprehensive bibliometric analysis regarding allopregnanolone research is available. In our study, we intend to analyze the research trends and hot spots related to allopregnanolone in the past 20 years.

Methods: We searched for allopregnanolone related articles and reviews between 2004 and 2023 from the Web of Science Core Collection database. Then, the bibliometric analysis was conducted using VOSviewer, CiteSpace, Microsoft Excel 2019, as well as the online bibliometric analysis platform (http://bibliometric.com/).

Results: A total of 1841 eligible publications were identified. The number of annual publications and citations was generally on the rise. Among countries, the United States ranked first in overall publications, citations, international cooperation, and the number of research institutions. The University of North Carolina was the most active institution, conducting numerous preclinical and clinical work that focusing on allopregnanolone treatment for diverse psychiatric or neurologic disorders. As for authors, Dr. Frye CA, Morrow AL, and Pinna G were identified as the top three prolific scholars due to their great publications and citations. Based on the publication clusters and citation bursts analysis, the keyword co-occurrence network, the strongest citation bursts, and co-cited references analysis, the hot spots in recent years included "depression", "postpartum depression", "$GABA_A$ receptor", and so on.

Conclusion: Allopregnanolone is still a popular area of research, and the United States leads the way in this area. Dr. Frye CA, Morrow AL, Pinna G, and their teams contributed greatly to the mechanism study and translation study of allopregnanolone. The use of allopregnanolone for the treatment of psychiatric or neurologic disorders, especially postpartum depression, is the current hot spot. However, the underlying mechanisms of anti-depression are still not clear, deserving more in-depth research.

Keywords: allopregnanolone, VOSviewer, CiteSpace, bibliometric analysis, research trend

Introduction

As a kind of neuroactive steroid or neurosteroid, allopregnanolone is formed in the brain and peripheral nerves from its precursor, progesterone. Progesterone can be secreted from peripheral glands, sequestered and accumulated in the brain. Moreover, progesterone can be locally biosynthesized in the brain.[1] The essential factors for progesterone biosynthesis include the 18kDA translocator protein, which binds cholesterol and transports it into mitochondria.[2] Cholesterol is then oxidized to pregnenolone in the inner mitochondrial membrane by cytochrome P450 side-chain cleavage enzyme (P450scc) and then converted to progesterone by 3β-hydroxysteroid dehydrogenase. Finally, either derived from peripheral circulation or produced in the brain, the obtained progesterone is converted to allopregnanolone by the action of 5α-reductase type I and 3α-hydroxysteroid dehydrogenase.[3]

During the production of allopregnanolone, the requisite factors or enzymes, as described above, are widely expressed in the nervous system, including the spinal cord, cerebellum, hindbrain, midbrain, and forebrain. However, there are

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differences in expression levels depending on diverse factors such as age, sex, cell types, and stressors.[4,5] Nevertheless, the vast distribution of these factors and their conservation among species suggest the importance of allopregnanolone studies for brain function.[4]

Particularly, neurosteroids regulate the activity of the nervous system in an autocrine or paracrine manner via various membrane receptors or ion channels such as $GABA_A$ and glycine, as well as L-and T-type calcium channels.[6–9] Due to the wide distribution of these receptors or channels, allopregnanolone is reported to participate in diverse neurobiological processes, including pain and mood regulation, learning and memory, cognition, sleep, feeding, pregnancy, and response to stress.[10–12]

In recent years, there has been a great advance with regard to the molecular and cellular mechanisms studied for allopregnanolone in preclinical and clinical studies. For example, Antonoudiou et al proved that allopregnanolone modulated theta oscillations (6–12 Hz) in the basolateral amygdala through δ-containing GABA receptors, resulting in a long-lasting anti-depressive effect.[13] And in 2019, two groups showed that allopregnanolone and its precursors blocked pro-inflammatory signaling by promoting the degradation of the toll-like-receptor (TLR)-2/4 adaptor proteins TIRAP and TLR2, or inhibiting toll-like-4 receptor activation in macrophages and the brain.[14,15] However, at present, there is no bibliometric analysis with regard to allopregnanolone research available.

In this study, we collected the available literature related to allopregnanolone in the past 20 years from the Web of Science Core Collection (WoSCC) database, as well as analyzed the research trends and hot spots using the bibliometric analysis and visualization functions of VOSviewer and CiteSpace software.[16,17] Quantitative methods such as mathematics and statistics are used in the bibliometric analysis to conduct quantitative and qualitative analysis with regard to countries, authors, institutions, journals, and their relationship in existing publications in allopregnanolone research.[18,19] With the bibliometric analysis, we hope to provide a deep understanding of the academic framework so as to contribute to future research work.

Methods

Literature Research

We searched the WoSCC database for articles and reviews about allopregnanolone published in the past two decades. The data were retrieved and exported due on October 11, 2023. There was no language restriction. And the search strategy was as follows: TS = ("allopregnanolone" OR "3α,5α-tetrahydroprogesterone" OR "3 alpha,5 alpha-tetrahydroprogesterone" OR "3α-hydroxy-5α-pregnan-20-one" OR "3 alpha-hydroxy-5 alpha-pregnan-20-one" OR "(3 alpha, 5 alpha)-3- hydroxypregnan-20-one" OR "3 alpha,5 alpha-THP").

Data Collection

We identified and downloaded allopregnanolone-related bibliometric information, including title, publication year, citation, country or region, institution, author, journal, keywords, and references, from the WoSCC database. Export all records and references in "plain text file" format with the file name "download_***".

Data Analysis and Visualization

We analyzed the annual publication data using Microsoft Excel 2021. The collaboration data of different countries was processed and visualized using the online bibliometric analysis platform (https://bibliometric.com/). The co-authorship study of nations, institutions, and writers, as well as keyword co-occurrence analysis, were conducted using VOSviewer 1.6.19. The analysis of keywords and co-cited references was performed using CiteSpace 6.2.R4.

Results

Inclusion of Publications

We initially identified 2494 publications about allopregnanolone research after searching the WoSCC database. After excluding those not eligible for publication years or research types, we finally enrolled 1841 publications for bibliometric analysis. A detailed flowchart for screening is shown in Figure 1.

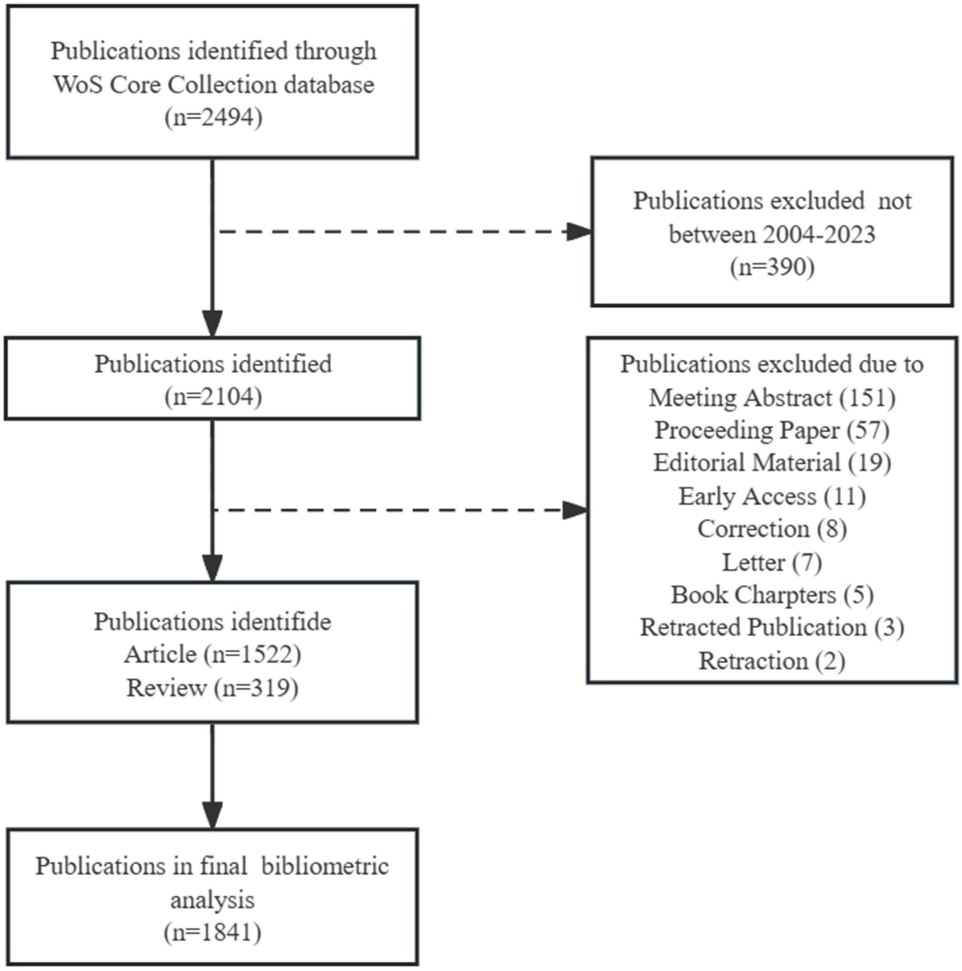

Figure 1 Flow chart of literature identification.

Annual Publications and Annual Citations

Ranging from January 1, 2004 to September 30, 2023, a total of 1841 publications were included in this bibliometric analysis. These publications received a total of 57,534 citations, had an average of 31.25 citations for each publication, and had an h-index of 105. As shown in Figure 2, there were more than 100 annual publications from 2019 to 2022 for allopregnanolone research. Moreover, the number of annual citations from 2004 to 2023 showed a gradual increase, with 2021 having the highest citations (n = 5291).

Contribution of Countries and Institutions

Figure 3A suggests that the 1841 publications involved 63 nations or regions, and the United States remains the center of global allopregnanolone research. Table 1 shows the United States led the way with 842 publications, followed by Italy (n = 220), China (n = 109), and France (n = 105). Meanwhile, as shown in Figure 3B, countries such as China, Australia, Brazil, and Switzerland are more active in recent years. Besides, the United States and Italy cooperate the most, followed by the United States and Canada, and then the United States and France.

With regard to institutions contributing to allopregnanolone research, a total of 1503 institutions were identified, of which 79 institutions published 10 or more. Figure 4A shows that 74 of the 79 institutions cooperated with each other. Table 2 provides the detailed information regarding the top 10 institutions, of which 7 are American universities, and the University of North Carolina contribute the most work (n = 82). Besides, the top three institutions for link strength are

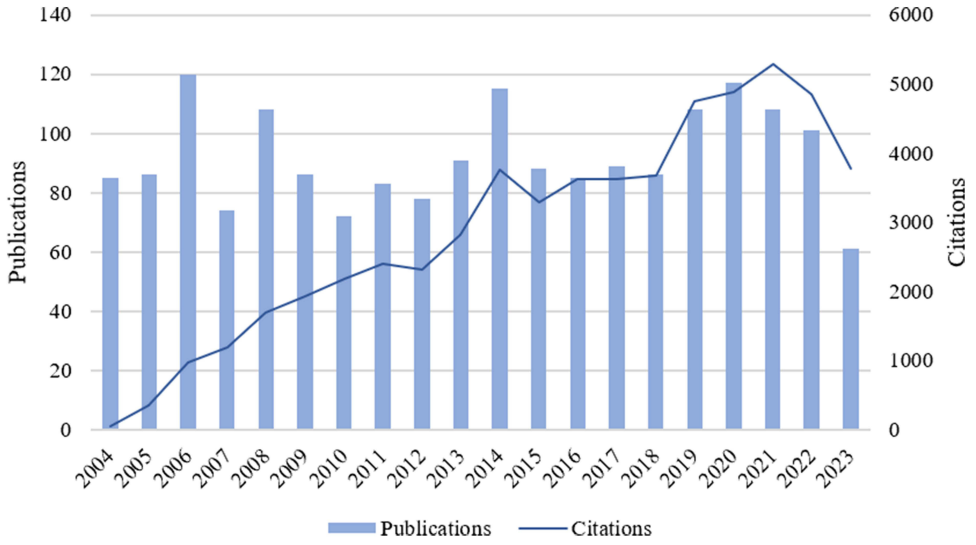

Figure 2 Annual publications and annual citations of allopregnanolone research.

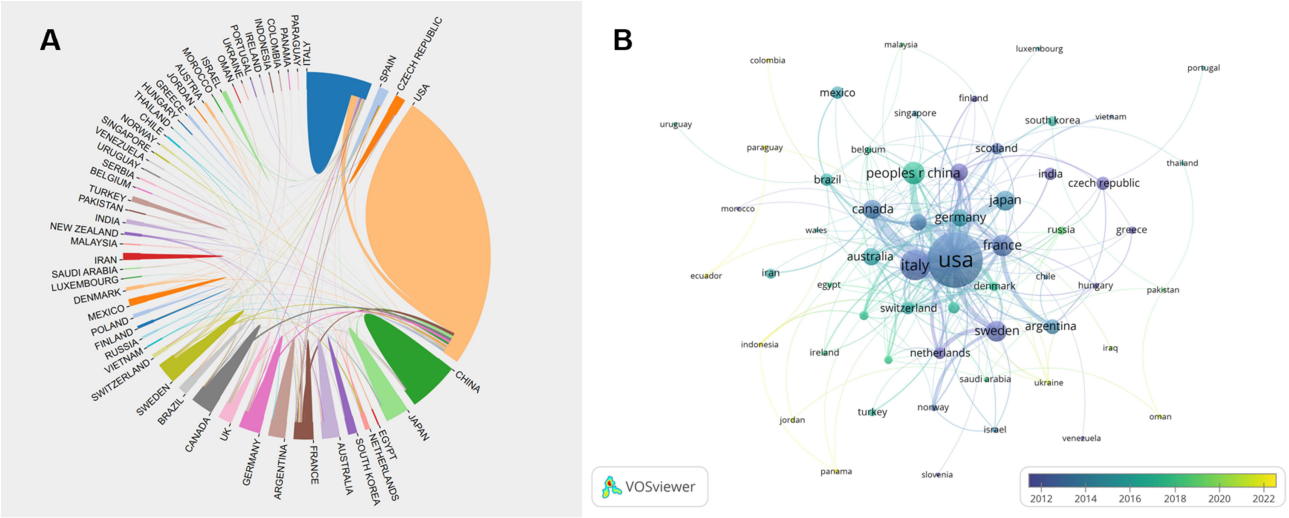

Figure 3 Contributions of countries and institutions in allopregnanolone research. (**A**) Distribution and cooperation among countries for allopregnanolone research. (**B**) Country cooperation map related to allopregnanolone research (threshold = 1). The nodes color and line thickness indicate the average year of publication and the frequency of cooperation between countries, respectively.

Harvard Medical School (n = 60), the University of Cagliari (n = 59), and the University of Illinois (n = 57). And link strength is an indicator of cooperation strength.

Contribution of Authors

With regard to authors contributing to allopregnanolone research, a total of 6228 authors are identified, of which 84 authors contribute 10 or more publications. Table 3 shows us the top 10 authors with the highest citations and publications. Dr. Frye CA, Morrow AL, and Pinna G are the top 3 influential authors due to their great publications and citations.

Figure 4B presents the co-authorship network map, with 54 out of the top 84 authors having collaborative relationships. Additionally, it shows there are several core research groups in this field, such as Dr. Frye CA's group and Dr. Morrow AL's group. Dr. Caruso D, Giatti S, Meltzer-Brody S, and their respective teams are emerging research groups in recent years.

Table 1 The Top 10 Countries or Regions Contributing to Allopregnanolone Research

Rank	Country/Region	Publications	Citations	Total Link Strength
1	USA	842	32,199	255
2	Italy	220	5803	142
3	China	109	2340	37
4	France	105	4607	75
5	Sweden	93	3119	55
6	Japan	89	2074	35
7	Canada	82	2408	53
8	Germany	69	1792	59
9	Spain	63	1643	33
10	Australia	63	1380	25

Journal Analysis

A total of 449 journals are identified to have publications about allopregnanolone. Table 4 shows the top 10 productive journals. The 2023 impact factor (IF) for the top 10 journals ranged from 2.7 to 5.0. Among them, Psychopharmacology has the largest number of publications (n = 85, IF 3.4), followed by Psychoneuroendocrinology (n = 63, IF 3.7), and Neuroscience (n = 48, IF 3.3).

Keywords Analysis

We identified 7012 keywords with regard to allopregnanolone research. As shown in Table 5, we displays the top 20 keywords with the highest occurrences and the total link strength of each keyword. Then, we mapped the keyword co-occurrence network on 186 keywords with occurrences not lower than 20. Descriptive and repetitive keywords such as "allopregnanolone", "neuroactive steroids", "neurosteroids", "progesterone", "gaba (a) receptors", and "neurosteroid" were excluded. In Figure 5A, the similar colored nodes mean these keywords are within the same cluster. In this study, cluster 1 (red) relates to animal experiments. Cluster 2 (green) is mainly associated with anxiety and stress. Cluster 3 (blue) is mainly related to depression and postpartum depression. Cluster 4 (yellow) is associated with the gaba (a) receptor. Figure 5B shows a visualization of the evolution of keywords over time to help understand the hotspots in the field. Node colors represent the average year in which keywords appear.

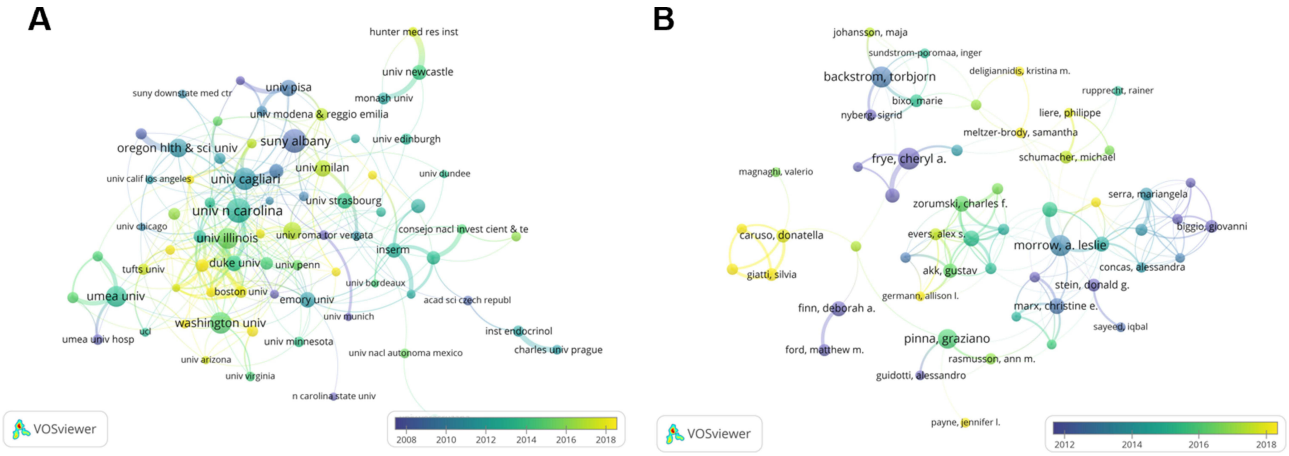

Figure 4 Institutions and authors co-authorship network maps. (**A**) A network map of cooperation among 79 institutions that have at least 10 publications. The nodes color and line thickness indicate the average year of publication and the frequency of cooperation between institutions, respectively. (**B**) A network map of cooperation among authors that have collaborative relationships. The nodes color and line thickness indicate the average year of publication and the frequency of cooperation between authors, respectively.

Table 2 The Top 10 Institutions Contributing to Allopregnanolone Research

Rank	Institution	Country	Publications	Citations	Total Link Strength
1	University of North Carolina	USA	82	3499	44
2	University at Albany	USA	76	2800	10
3	University of Cagliari	Italy	68	1898	59
4	Washington University	USA	62	1664	18
5	University of Illinois	USA	58	2702	57
6	Umea University	Sweden	58	1653	29
7	Oregon Health and Science University	USA	48	1223	27
8	University of California, Davis	USA	44	1200	18
9	University of Pisa	Italy	37	727	28
10	University of Milan	USA	36	1133	21

Table 3 The Top 10 Influential Authors in Allopregnanolone Research

Rank	Author	Citations	Rank	Author	Articles
1	Pinna G	2149	1	Frye CA	49
2	Frye CA	1714	2	Morrow AL	46
3	Backstrom T	1408	3	Backstrom T	45
4	Guidotti A	1270	4	Pinna G	41
5	Morrow AL	1206	5	Covey DF	28
6	Stein DG	1144	6	Marx CE	26
7	Marx CE	1042	7	Zorumski CF	26
8	Walf A	946	8	Finn DA	25
9	Meltzer-Brody S	940	9	Porcu P	25
10	Reddy DS	902	10	O'buckley TK	24

Table 4 The Top 10 Most Productive Journals in Allopregnanolone Research

Rank	Journal	Documents	Quartile in category	IF (2023)
1	Psychopharmacology	85	Q2	3.4
2	Psychoneuroendocrinology	63	Q2	3.7
3	Neuroscience	48	Q3	3.3
4	Behavioural Brain Research	40	Q2	2.7
5	Brain Research	40	Q3	2.9
6	Neuropharmacology	38	Q1	4.7
7	Pharmacology Biochemistry and Behavior	36	Q1	3.6
8	Journal of Neuroendocrinology	35	Q3	3.2
9	Journal of Steroid Biochemistry and Molecular Biology	28	Q2	4.1
10	European Journal of Pharmacology/	27	Q1	5.0
	Hormones and Behavior	27	Q1	3.5

Notes: Q1: JCR divides the journals into 176 different discipline categories, each of which is classified into Q1-4 according to the impact factor of the journal in the current year. The journal with the top 25% (including 25%) impact factors is Q1. Journals with impact factors ranging from 25% to 50%, 50%-75%, and after 75% are Q2, Q3, and Q4, respectively.

Figure 6 displays the top 25 keywords with the strongest citation bursts, which means a sudden increase in citation frequency within a short period and is used to reflect research trends and hotspots at different times. From the perspective of burst strength, the top five keywords with the greatest outbreak intensity are "postpartum depression", "symptoms", "women", "pregnancy", and "rat brain". From the point of burst duration, the longest-lasting keywords are "depression", followed by "central nervous system" and "spinal cord". Meanwhile, the recent outbreak keywords are "postpartum

Table 5 The Top 20 Keywords in Allopregnanolone Research

Rank	Keyword	Occurrences	Total Link Strength	Rank	Keyword	Occurrences	Total Link Strength
1	Allopregnanolone	1077	5444	11	Gamma-aminobutyric-acid	135	737
2	Neuroactive steroids	545	2982	12	Expression	134	621
3	Neurosteroids	516	2712	13	Depression	133	791
4	Progesterone	482	2589	14	Rat-brain	127	713
5	Brain	242	1239	15	Women	125	701
6	Neurosteroid	204	1107	16	Modulation	122	616
7	Gaba(a) receptor	203	1142	17	Gaba	118	672
8	Stress	185	1087	18	Rat	118	643
9	Gaba(a) receptors	185	1000	19	Hippocampus	117	689
10	Anxiety	146	855	20	Menstrual-cycle	107	631

depression", "symptoms", "women", "prevalence" "corticotropin releasing hormone" and "perinatal depression." These results gave us clues about the hot spots for allopregnanolone research.

Co-Cited References Analysis

If two references cited by a third publication, these two references will form a co-citation relationship. Table 6 shows the top 10 co-cited publications in allopregnanolone research. All ten publications are within the JCR Q1 division. The publication "Neurosteroids: endogenous regulators of the $GABA_A$ receptor" published by Belelli D on Nature Reviews Neuroscience in 2005 ranked first with a total of 344 citations.[20] Then, "Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor" published by Majewska MD on Science in 1986, with 339 citations, ranked second.[21] These two reviews suggested the GABA mechanism of allopregnanolone action.

As shown in Figure 7A, we obtained the visualized network of the cited references using the CiteSpace software. The nodes that appear in different colors show the reference's publication date. The purple circle around the node denotes the centrality of references, indicating the importance of references in this field. And the size of the node represents the frequency of references' citations. Figure 7B depicts the top 25 references with the strongest citation bursts, suggesting these publications were suddenly cited frequently in a short period of time. As shown, the publication "Belelli D, 2005, Nat Rev Neurosci, V6, P565"[20] had the highest burst value of 45.35, followed by "Meltzer-Brody S, 2018, Lancet, V392,

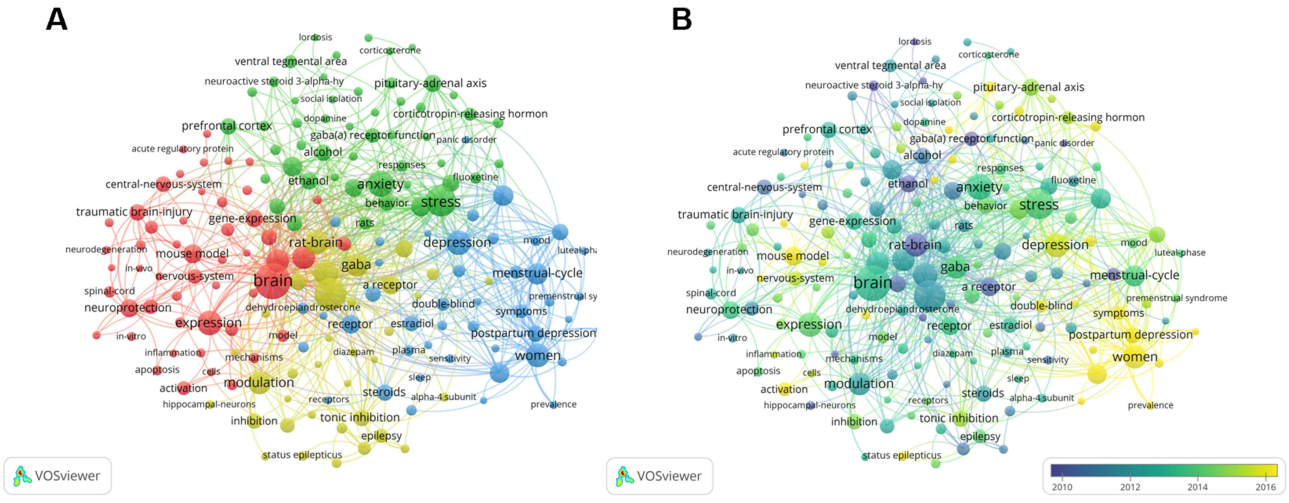

Figure 5 The visualization network map for keywords analysis by VOSviewer. (**A**) Cluster analysis of the top 186 keywords with an occurrence frequency ≥ 20 for the allopregnanolone research. (**B**) Keywords timeline view. The nodes size and color indicate the citation counts and average publication year, respectively. The closer the distance between nodes, the stronger the co-occurrence of keywords.

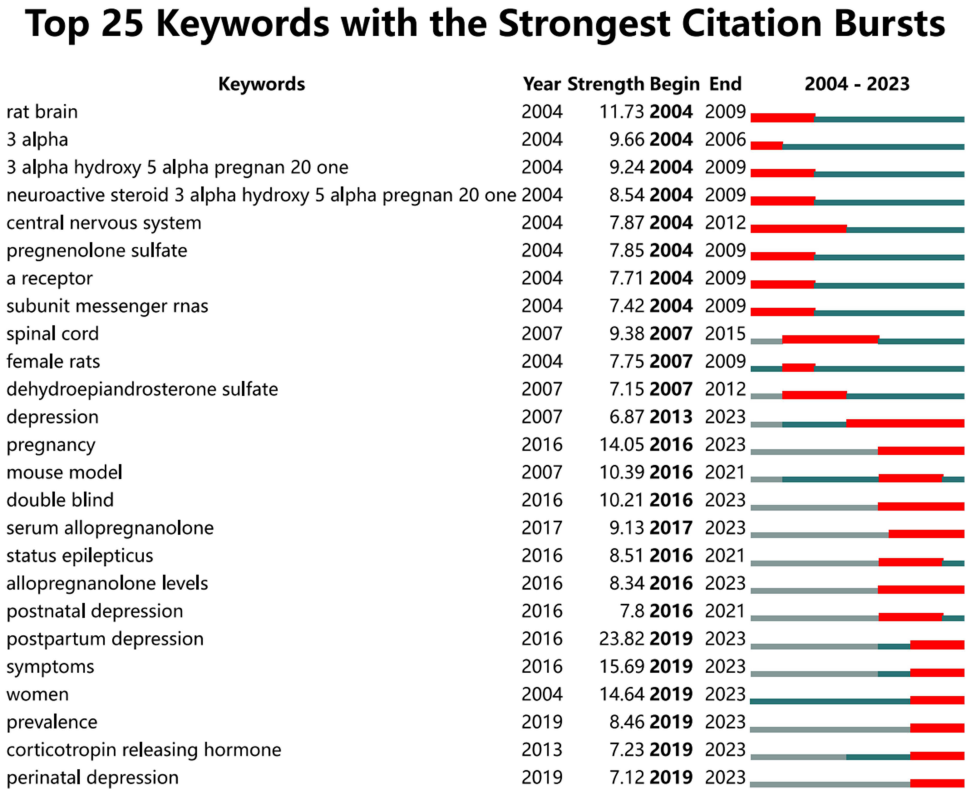

Figure 6 The top 25 keywords for allopregnanolone research with the highest citation bursts.

P1058"[22] with a burst value of 39.95, ranking second, and "Kanes S, 2017, Lancet, V390, P480"[23] with a burst value of 28.94, ranking third. These publications provide us clues for the hot spots in allopregnanolone research.

Discussion

In this study, we identified all the publications in allopregnanolone research over the past two decades and performed a bibliometric analysis for these publications. The results helped us understand the trends and hot spots in allopregnanolone research.

Firstly, we observed steady annual publications and citations on allopregnanolone research, suggesting that allopregnanolone is still a popular area of research. Then, among countries, the United States contributed significantly. It leads in overall publications, citations, international cooperation, and the number of research institutions. The University of North Carolina published the most work and conducted numerous preclinical and clinical studies focusing on allopregnanolone treatment for diverse psychiatric or neurologic disorders such as postpartum depression,[22,23] alcohol use disorder,[24] premenstrual dysphoric symptom,[25] reproductive mood disorder,[26,27] schizophrenia,[28] stress-related disease,[29] and pain hypersensitivity.[30]

As for authors, Dr. Frye CA, Morrow AL, and Pinna G were identified as the top three prolific scholars due to their great publications and citations. Dr. Frye CA led or participated in a lot of work with regard to allopregnanolone. In one of his most cited publications, available in 2016 and titled "Neurosteroidogenesis today: novel targets for neuroactive steroid synthesis and action and their relevance for translational research",[31] the authors suggested that modulation of neurosteroidogenesis rather than administration of foreign neuroactive steroids might restore endogenous neuroactive steroid levels and provide a better translational potential for certain neurodegenerative or neuropsychiatric diseases such as Alzheimer's disease or alcohol use disorder. They also summarized recent approaches that target the factors or enzymes involved in neurosteroidogenesis, including the 18kDA translocator protein, the pregnane xenobiotic receptor, and P450scc.

Table 6 The Top 10 Co-Cited Publications in Allopregnanolone Research

Rank	Title	Journal (IF)	First Author	Publication Time	Country	Co-Citation	Quartile in Category
1	Neurosteroids: endogenous regulators of the $GABA_A$ receptor	Nature Reviews Neuroscience (34.7)	Belelli D	Jun, 2005	UK	344	Q1
2	Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor	Science (56.9)	Majewska MD	May, 1986	USA	339	Q1
3	Neuroactive steroids	The FASEB Journal (4.8)	Paul SM	Mar, 1992	USA	304	Q1
4	Stress-induced elevations of y-aminobutyric acid type A receptor-active steroids in the rat brain	Proceedings of the National Academy of Sciences of the United States of America (11.1)	Purdy RH	May, 1991	USA	283	Q1
5	Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine	Proceedings of the National Academy of Sciences of the United States of America (11.1)	Uzunova V	Mar, 1998	USA	222	Q1
6	Endogenous neurosteroids regulate $GABA_A$ receptors through two discrete transmembrane sites	Nature (64.8)	Hosie AM	Nov, 2006	UK	182	Q1
7	Role of brain allopregnanolone in the plasticity of gamma-aminobutyric acid type A receptor in rat brain during pregnancy and after delivery	Proceedings of the National Academy of Sciences of the United States of America (11.1)	Concas A	Oct, 1998	Italy	166	Q1
8	Effects of antidepressant treatment on neuroactive steroids in major depression	The American Journal of Psychiatry (17.7)	Romeo E	Jul, 1998	Italy	150	Q1
9	Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences	The Journal of Clinical Endocrinology and Metabolism (5.8)	Genazzani AR	Jun, 1998	Italy	150	Q1
10	Neurosteroid modulation of $GABA_A$ receptors	Progress in Neurobiology (6.7)	Lambert JJ	Sep, 2003	UK	143	Q1

Morrow AL ranked second in publications, with one of the most cited papers being available in the Journal of Neuropsychopharmacology in 2009 and titled "Proof-of-Concept Trial with the Neurosteroid Pregnenolone Targeting Cognitive and Negative Symptoms in Schizophrenia".[32] In this randomized, double-blind, placebo-controlled trial, baseline allopregnanolone levels were proved to be inversely correlated with the improvement of negative symptoms in patients with schizophrenia.

Besides, a publication titled "Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis",[6] that was available in 2006, was the most frequently cited finding by Dr. Pinna G. In this work, the authors proved that neurosteroidogenesis happens not in glial cells but mainly in the principal output neurons of several

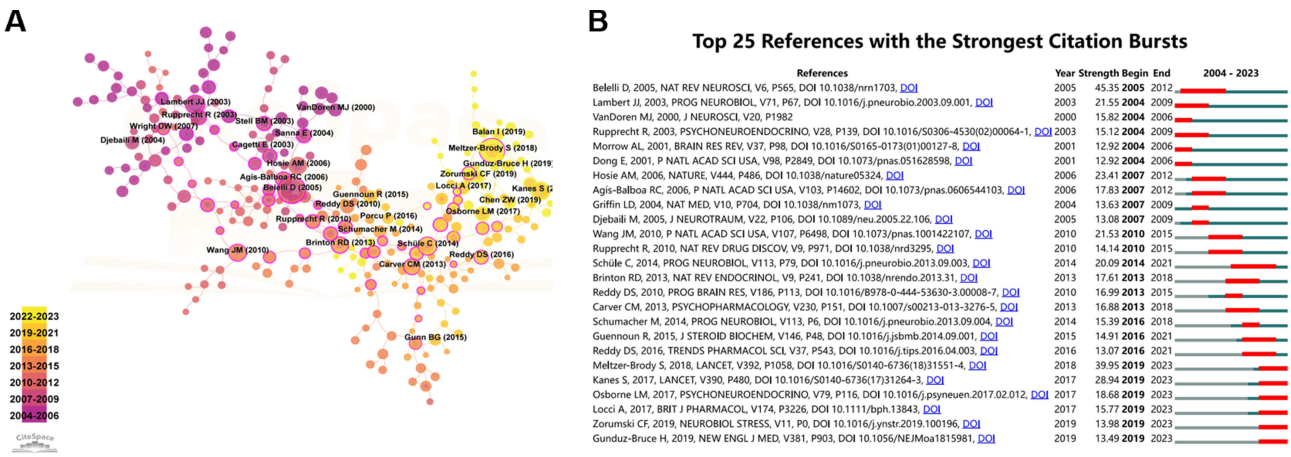

Figure 7 References analysis in allopregnanolone field by CiteSpace. (**A**) The visualized network of cited references related to allopregnanolone research. CiteSpace parameters were set as follows: time slicing (2004–2023), years per slice (3), node types (reference), selection criteria (Top N = 40), and select Pathfinder. According to the set parameters, a network with 281 nodes and 321links was obtained. (**B**) The top 25 references in the allopregnanolone field with the highest citation bursts.

brain areas that possess the necessary enzymes to convert cholesterol into allopregnanolone. And in another high-cited work, Dr. Pinna G and his team suggested a reduction of cerebrospinal fluid allopregnanolone might lead to depressive symptoms in premenopausal women with posttraumatic stress disorder (PTSD).[33] These findings advanced our understanding of the mechanism of PTSD and spurred the development of its prevention and treatment.

Of note, as shown in Figure 5A, a bibliometric analysis for keywords identified several publication clusters, for instance, "animal experiments", "anxiety and stress", "depression and postpartum depression", as well as "gaba(a) receptor". Further, the results in Figure 5B suggest that "woman", "depression", "postpartum depression", and "mouse model" are emerging keywords in recent years. Furthermore, "postpartum depression", "symptoms", "women", "pregnancy", and "rat brain" showed the strongest citation bursts during 2004 to 2023 as shown in Figure 6. Taken together, these results attracted great attention to the correlation between allopregnanolone and depression, especially postnatal or postpartum depression (PPD).

Pregnancy related increase in pregnanolone elevated allopregnanolone level in the brain, which quickly declined postpartum. This neurosteroid withdrawal is one accepted etiology of PPD. Accordingly, maintaining a stable allopregnanolone concentration is important for postpartum women, which promotes the development of neurosteroid replacement therapy. In 2014, several clinical trials evaluated the potential use of Brexanolone for adult women with PPD.[34] Brexanolone was a mixture of allopregnanolone and sulfobutylether-beta-cyclodextrin, a solubilizing agent. It is developed by Sage Therapeutics under the license of the University of California and administered intravenously.[35] These clinical trials showed a single dose of Brexanolone could effectively relieve depressive symptoms as early as hours after injection, with an effect lasting up to one week. In 2019, the Food and Drug Administration approved Brexanolone for the treatment of adult women with PPD, which is a milestone event for the treatment of PPD.[35]

Thereafter, as shown by meta-analysis, more clinical trials further validated the efficacy of brexanolone for the improvement of the core symptoms of depression in patients with PPD.[36] It is well recognized that pregnancy alters $GABA_A$ receptor subunit expression and function, the major inhibitory signaling of the central nervous system. Besides, as shown by the top two co-cited publications, "Neurosteroids: endogenous regulators of the $GABA_A$ receptor"[20] by Belelli D on Nature Reviews Neuroscience in 2005 and "Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor"[21] published by Majewska MD on Science in 1986, allopregnanolone is a potent endogenenous $GABA_A$ receptor positive modulator, acting on both synaptic and extrasynaptic $GABA_A$ receptors. Mechanically, allopregnanolone prolongs the activation time of $GABA_A$-activated chloride channels and enhances the inhibitory tone of neurons to exert an anti-depressive effect.[37] Besides the $GABA_A$ mechanism, recent work from Dr. Morrow's group showed the anti-inflammatory action of allopregnanolone on various Toll-like receptors in mouse and human macrophages and the brain.[38,39] Then, in 2023, this group showed that allopregnanolone inhibition of proinflammatory cytokines as well as activation of TLR pathways predicted the anti-depressive response in humans treated for PPD.[40]

Finally, from the visualized network of the cited references, we paid attention to the work by Dr. Meltze-Brody that was published in the Lancet in 2018.[22] This is a randomized, double-blind, placebo-controlled trial, and the authors proved the clinical advantage of Brexanolone for PPD treatment. Besides, the keyword citation bursts indicate modulation of neurosteroidogenesis may be a preferred alternative for the treatment of stress-induced psychiatric disorders, including depression and post-traumatic stress disorder.[41] Beyond GABA, the other involved mechanisms of pregnanolone for depression treatment were discussed, such as increased autophagy or neurogenesis.[42] However, the underlying mechanisms of allopregnanolone for neuropsychiatric or neurologic disorders are still unclear.

Other than the obtained picture of allopregnanolone research in recent years from this bibliometric analysis, we also need to admit that there were certain limitations in our study. Firstly and importantly, we obtained few clues with regard to mechanism advances for allopregnanolone research with this bibliometric analysis. Secondly, we only obtained data from the WoSCC database, which means we might ignore publications from other databases. However, the more than 1800 publications in this study suggest such omission might be negligible.

Conclusion

Allopregnanolone is still a popular area of research, and the United States leads the way in this area. Dr. Frye CA, Morrow AL, Pinna G, and their teams contributed greatly to the mechanism study and translation study of

allopregnanolone. The use of allopregnanolone for the treatment of psychiatric or neurologic disorders, especially postpartum depression, is the hot spot. However, other than the $GABA_A$ mechanism, the underlying mechanisms of antidepression are still not clear, deserving more in-depth research.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Frye CA, Koonce CJ, Walf AA. Novel receptor targets for production and action of allopregnanolone in the central nervous system: a focus on pregnane xenobiotic receptor. *Front Cell Neurosci*. 2014;8:106. doi:10.3389/fncel.2014.00106
2. Papadopoulos V, Baraldi M, Guilarte TR, et al. Translocator protein (18kda): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. *Trends Pharmacol Sci*. 2006;27(8):402–409. doi:10.1016/j.tips.2006.06.005
3. Liang JJ, Rasmusson AM. Overview of the molecular steps in steroidogenesis of the gabaergic neurosteroids allopregnanolone and pregnanolone. *Chronic Stress*. 2018;2:1–7.
4. Mellon SH. Neurosteroid regulation of central nervous system development. *Pharmacol Ther*. 2007;116(1):107–124.
5. Frye CA. Neurosteroids' effects and mechanisms for social, cognitive, emotional, and physical functions. *Psychoneuroendocrinology*. 2009;34 Suppl (Suppl 1):S143–161.
6. Agís-Balboa RC, Pinna G, Zhubi A, et al. Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis. *Proc Natl Acad Sci U S A*. 2006;103(39):14602–14607.
7. Cauli O, González-Usano A, Agustí A, Felipo V. Differential modulation of the glutamate-nitric oxide-cyclic gmp pathway by distinct neurosteroids in cerebellum in vivo. *Neuroscience*. 2011;190:27–36.
8. Hu AQ, Wang ZM, Lan DM, et al. Inhibition of evoked glutamate release by neurosteroid allopregnanolone via inhibition of l-type calcium channels in rat medial prefrontal cortex. *Neuropsychopharmacology*. 2007;32(7):1477–1489.
9. Pathirathna S, Brimelow BC, Jagodic MM, et al. New evidence that both t-type calcium channels and gabaa channels are responsible for the potent peripheral analgesic effects of 5 alpha-reduced neuroactive steroids. *Pain*. 2005;114(3):429–443.
10. Patte-Mensah C, Meyer L, Taleb O, Mensah-Nyagan AG. Potential role of allopregnanolone for a safe and effective therapy of neuropathic pain. *Prog Neurobiol*. 2014;113:70–78. doi:10.1016/j.pneurobio.2013.07.004
11. Chen S, Gao L, Li X, Ye Y. Allopregnanolone in mood disorders: mechanism and therapeutic development. *Pharmacol Res*. 2021;169:105682. doi:10.1016/j.phrs.2021.105682
12. Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog Neurobiol*. 2014;113:79–87. doi:10.1016/j.pneurobio.2013.09.003
13. Antonoudiou P, Colmers PLW, Walton NL, et al. Allopregnanolone mediates affective switching through modulation of oscillatory states in the basolateral amygdala. *Biol Psychiatry*. 2022;91(3):283–293. doi:10.1016/j.biopsych.2021.07.017
14. Murugan S, Jakka P, Namani S, Mujumdar V, Radhakrishnan G. The neurosteroid pregnenolone promotes degradation of key proteins in the innate immune signaling to suppress inflammation. *J Biol Chem*. 2019;294(12):4596–4607. doi:10.1074/jbc.RA118.005543
15. Balan I, Beattie MC, O'Buckley TK, Aurelian L, Morrow AL. Endogenous neurosteroid (3α,5α)3-hydroxypregnan-20-one inhibits toll-like-4 receptor activation and pro-inflammatory signaling in macrophages and brain. *Sci Rep*. 2019;9:14.
16. van Eck NJ, Waltman L. Software survey: vosviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. doi:10.1007/s11192-009-0146-3
17. Chen C, Chen Y, Hou J, Liang Y. Citespace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. *J China Soc Sci Tech Infor*. 2009;28(3):401–421.
18. Ninkov A, Frank JR, Maggio LA. Bibliometrics: methods for studying academic publishing. *Perspect Med Educ*. 2022;11(3):173–176. doi:10.1007/S40037-021-00695-4
19. Hicks D, Wouters P, Waltman L, de Rijcke S, Rafols I. Bibliometrics: the Leiden manifesto for research metrics. *Nature*. 2015;520(7548):429–431. doi:10.1038/520429a
20. Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the gaba(a) receptor. *Nat Rev Neurosci*. 2005;6(7):565–575. doi:10.1038/nrn1703
21. Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the gaba receptor. *Science*. 1986;232(4753):1004–1007. doi:10.1126/science.2422758
22. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, Phase 3 trials. *Lancet*. 2018;392(10152):1058–1070.
23. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (sage-547 injection) in post-partum depression: a randomised controlled trial. *Lancet*. 2017;390(10093):480–489.
24. Pierucci-Lagha A, Covault J, Feinn R, et al. Gabra2 alleles moderate the subjective effects of alcohol, which are attenuated by finasteride. *Neuropsychopharmacology*. 2005;30(6):1193–1203.
25. Martinez PE, Rubinow DR, Nieman LK, et al. 5α-reductase inhibition prevents the luteal phase increase in plasma allopregnanolone levels and mitigates symptoms in women with premenstrual dysphoric disorder. *Neuropsychopharmacology*. 2016;41(4):1093–1102.

26. Schiller CE, Schmidt PJ, Rubinow DR. Allopregnanolone as a mediator of affective switching in reproductive mood disorders. *Psychopharmacol*. 2014;231(17):3557–3567.
27. Schweizer-Schubert S, Gordon JL, Eisenlohr-Moul TA, et al. Steroid hormone sensitivity in reproductive mood disorders: on the role of the gaba(a) receptor complex and stress during hormonal transitions. *Front Med*. 2020;7:479646.
28. Marx CE, Bradford DW, Hamer RM, et al. Pregnenolone as a novel therapeutic candidate in schizophrenia: emerging preclinical and clinical evidence. *Neuroscience*. 2011;191:78–90.
29. Boero G, Porcu P, Morrow AL. Pleiotropic actions of allopregnanolone underlie therapeutic benefits in stress-related disease. *Neurobio Stress*. 2020;12:100203.
30. Mechlin B, Morrow AL, Maixner W, Girdler SS. The relationship of allopregnanolone immunoreactivity and hpa-axis measures to experimental pain sensitivity: evidence for ethnic differences. *Pain*. 2007;131(1–2):142–152.
31. Porcu P, Barron AM, Frye CA, et al. Neurosteroidogenesis today: novel targets for neuroactive steroid synthesis and action and their relevance for translational research. *J Neuroendocrinol*. 2016;28(2):12351.
32. Marx CE, Keefe RS, Buchanan RW, et al. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. *Neuropsychopharmacology*. 2009;34(8):1885–1903.
33. Rasmusson AM, Pinna G, Paliwal P, et al. Decreased cerebrospinal fluid allopregnanolone levels in women with posttraumatic stress disorder. *Biol Psychiatry*. 2006;60(7):704–713.
34. Zheng W, Cai DB, Zheng W, et al. Brexanolone for postpartum depression: a meta-analysis of randomized controlled studies. *Psychiatry Res*. 2019;279:83–89.
35. Scott LJ. Brexanolone: first global approval. *Drugs*. 2019;79(7):779–783.
36. Zou J, Yang L, Yang G, Gao J. The efficacy and safety of some new gabakines for treatment of depression: a systematic review and meta-analysis from randomized controlled trials. *Psychiatry Res*. 2023;328:115450.
37. Akk G, Shu HJ, Wang C, et al. Neurosteroid access to the gabaa receptor. *J Neurosci*. 2005;25(50):11605–11613.
38. Balan I, Aurelian L, Schleicher R, Boero G, O'Buckley T, Morrow AL. Neurosteroid allopregnanolone (3α,5α-thp) inhibits inflammatory signals induced by activated myd88-dependent toll-like receptors. *Transl Psychiatry*. 2021;11(1):145.
39. Balan I, Aurelian L, Williams KS, Campbell B, Meeker RB, Morrow AL. Inhibition of human macrophage activation via pregnane neurosteroid interactions with toll-like receptors: sex differences and structural requirements. *Front Immunol*. 2022;13:940095.
40. Balan I, Patterson R, Boero G, et al. Brexanolone therapeutics in post-partum depression involves inhibition of systemic inflammatory pathways. *EBioMedicine*. 2023;89:104473.
41. Locci A, Pinna G. Neurosteroid biosynthesis down-regulation and changes in gaba(a) receptor subunit composition: a biomarker axis in stress-induced cognitive and emotional impairment. *Br J Pharmacol*. 2017;174(19):3226–3241.
42. Zorumski CF, Paul SM, Covey DF, Mennerick S. Neurosteroids as novel antidepressants and anxiolytics: gaba-A receptors and beyond. *Neurobio Stress*. 2019;11:100196.