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ORIGINAL RESEARCH

Integrating Unified Medical Language System and Kleinberg's Burst Detection Algorithm into Research Topics of Medications for Post-Traumatic Stress Disorder

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Background: The treatment of post-traumatic stress disorder (PTSD) has long been a challenge because the symptoms of PTSD are multifaceted. PTSD is primarily treated with psychotherapy and medication, or a combination of psychotherapy and medication. The present study was designed to analyze the literature on medications for PTSD and explore high-frequency common drugs and low-frequency burst drugs by burst detection algorithm combined with Unified Medical Language System (UMLS) and provide references for developing new drugs for PTSD.

Methods: Publications related to medications for PTSD from 2010 to 2019 were identified through PubMed, Web of Science Core Collection, and BIOSIS Previews. SemRep and SemRep semantic result processing system were performed to extract the set of drug concepts with therapeutic relationship according to the semantic relationship of UMLS. Kleinberg's burst detection algorithm was applied to calculate the burst weight index of drug concepts by a Java-based program. These concepts were sorted according to the frequency and the burst weight index.

Results: Four hundred and fifty-nine treatment-related drug concepts were extracted. The drug with the highest burst weight index was "Psilocybine", a hallucinogen, which was more likely to be a hotspot for the pharmacotherapy of PTSD. The highest frequency concept was "prazosin", which was more likely to be the focus of research in the medications for PTSD.

Conclusion: The present study assessed the medication-related literature on PTSD treatment, providing a framework of burst words detection-based method, a baseline of information for future research and the new attempt for the discovery of textual knowledge. The bibliometric analysis based on the burst detection algorithm combined with UMLS has shown certain feasibility in amplifying the microscopic changes of a specific research direction in a field, it can also be used in other aspects of disease and to explore the trends of various disciplines.

Keywords: post-traumatic stress disorder, burst detection, Kleinberg's algorithm, burst word, Unified Medical Language System, SemRep

Introduction

Post-traumatic stress disorder (PTSD) is a mental disorder caused by sudden, threatening or catastrophic traumatic events.[1] Its clinical manifestations are characterized by re-experiencing the trauma, accompanied by emotional irritability and avoidance behavior.[2] It is often under chronic conditions that may lead to delayed onset and

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prolonged persistence of mental disorders.[3] About one-third of these patients do not heal throughout their lives,[4] PTSD affects blood pressure,[5] heart rate,[6] breathing, sleep[7] and many other physical indicators. PTSD is primarily treated with psychotherapy and medication, or a combination of psychotherapy and medication.[8] However, more than half of the patients had substance abuse and other mental disorders.[9] The clinical, social, and financial burden of ineffective or inadequate treatment is enormous.[10] It has been indicated that there was relatively little development of novel drug therapies in recent years.[3] A PTSD psychopharmacology working group has issued a consensus statement revealing the urgent need to address the crisis in the pharmacotherapy of PTSD.[10] However, to the best of our knowledge, there has been no bibliometric analysis to study the development trend of medication for PTSD.

One kind of the available methods to gain a comprehensive and extensive understanding of this field is the application of bibliometric analysis to PTSD-related literature. A substantial body of publications based on bibliometric analysis has accumulated to assess the volume and growth of PTSD-related publications, to explore the most frequent keywords, most active countries, institutions, journals, and to identify the pattern of the literature on PTSD.[11–14] However, due to the interdisciplinary nature of PTSD-related pharmacotherapy, some low-frequency new words which can indicate the emerging research topics have not yet attracted universal attention in those analyses that only focusing on high-frequency terms in this field.

Kleinberg proposed the "burst word detection algorithm" in 2002,[15] which is the way of detecting the frontiers of science by counting up the bursts of words that are low-frequency but more informative than high-frequency ones.[16] Here, "burst" refers to a phenomenon of one or more significant changes in the value of a variable in a short period of time,[17] and thus, if the frequency of one word in usage changes at a particular time, that is, the relative growth rate suddenly increases, then the word is called burst word.[18] Burst words can be divided into two categories according to the word frequency, one is the focus words with relatively high word frequency but not yet reached the threshold of high-frequency words and the other category is the low-frequency new words, which are the new research hotspots of this discipline and have not attracted general attention in this field.[19] It has been indicated that the density of a word's appearance determined its importance,[20] the intensity of the burst words is not restricted by time or the frequency of words, thus it is timely and more informative in revealing the dynamics of the frontiers of the disciplines from the density point of view.

In terms of detecting the emerging trend of the subject, the burst detection algorithm is more able to detect the dynamic development of the subject than the high-frequency word method. High-frequency words mainly record the static representation of the subject, they are not sensitive to the dynamic changes of time and frequency. In the real world, when the distribution of the burst words and related concepts in the field of PTSD treatment could be understood and considered by the researchers, the drug development could be accelerated correspondingly. With the increase of related publications, the convenience of literature databases and the popularity of burst word detection tool, detecting the burst words regularly will help the researchers grasp the research dynamics and adjust the research directions.[21–23]

The present study was designed to evaluate the current research status of medication for PTSD and predicted its development trend. Drug burst words involved in PTSD-related pharmacotherapy were extracted first, and then SemRep and SemRep semantic processing system were adopted to clean the dataset according to the Unified Medical Language System (UMLS) semantic relationship, finally, the terminology concept set was segmented, the burst weight index was calculated and the burst word frequency table of specific research direction in the target field was formed to judge the hot spots and focus. Aiming to provide decision support for the doctors to make personalized treatment plan and guide research strategies and funding decisions for drug development, we tried, for the first time, to Integrate UMLS and Kleinberg's burst detection algorithm into bibliometric analysis of medications for PTSD. This model can be applied to other clinical diseases or other aspects of the diseases, and can also be applied to explore the hotspots in various disciplines.

Materials and Methods

Literature and Dataset

The present study retrieved PubMed, Science Citation Index Expanded (SCI-Expanded) and Chemical Indexes integrated in Web of Science Core Collection (WoSCC), and BIOSIS Previews (BP) for the relevant literature. Data from January 1, 2010, to December 31, 2019, were retrieved from PubMed of the National Library of Medicine (NLM) on the website (http://www.ncbi.nlm.nih.gov/pubmed) with

"Stress Disorders, Post-Traumatic" as Medical Subject Heading (MeSH) terms and "drug therapy" as subheading. The retrieval strategy in PubMed was as follows: "Stress Disorders, Post-Traumatic/drug therapy" [Mesh] AND ("2010/01/01"[DP]:"2019/12/31"[DP]). In WoSCC, we used the "Topic (TS)" field to retrieve. The details were as follows: TS=(Post-Traumatic Stress Disorder* OR Posttraumatic Stress Disorder* OR PTSD) AND TS=(Drug Therap* OR Pharmacotherapy OR Medication*) AND PY=(2010–2019). For supplement proceedings, books, and patent records, we also searched BP database, a world-renowned abstracts database on life science research compiled and published by BIOSIS. We used the BP specific field "Disease Data (DS)" to retrieve the literature on the medication of PTSD. The retrieval strategy in BP was as follows: DS=(Post-Traumatic Stress Disorder* OR Posttraumatic Stress Disorder* OR PTSD) AND TS=(Drug Therap* OR Pharmacotherapy OR Medication*) AND PY=(2010–2019). All the literature types that could reflect the appearance of the original experimental data and reflect the frontier trends of the discipline directly were considered. While if an article belonged to only one publication type of "Review", it would be excluded. These publications were downloaded in May 2020 and removed duplicates. The retrieval results were independently screened and extracted by the study group of two investigators (SX and DX), and all the discrepancies were resolved by the principal investigator (PG). The overall workflow is shown in Figure 1.

Analysis of Semantic Relations

Semantic Representation (SemRep) and SemRep Semantic Processing System

Semantic representation (SemRep), a program developed by the US National Library of Medicine, was adopted to extract the related concepts and identify the semantic relations in natural language which was based on UMLS.[24] SemRep extracts three-part propositions from biomedical text sentences in MEDLINE format, called semantic predicates.[25] The subject and object of each semantic predicate are derived from the UMLS metathesaurus.[26] The relationship between them is the mutual relation structure provided by UMLS semantic network through 135 semantic types.[27]

SemRep semantic processing system developed by Lei Yan and Chunhe Liu was adopted to clean the SemRep output data,[28] the system can extract relevant concepts according to the semantic relations specified in SemRep semantic results, and calculate the frequency of valid concepts with such relations. It can sort all relationships extracted from SemRep by PMID number or by the concept. After importing the data into the system, it queries out the target concept of a semantic relationship as 'TREATS'. Then, two concepts are extracted for each semantic relationship. Suppose we extracted a set of concepts as follows: concept "A" 'TREATS' concept "B"; in this case, we only counted the frequency of concept "A". Since concept "A" was the subject, and its role was to treat concept "B", then the extracted concept "A" sum constituted the burst word set.

Detection of Burst Words

Kleinberg's burst detection algorithm was adopted to analyze the word burst by means of dynamic monitoring of the word burst.[29] We assume that there are n batches of data, t batches of data have d_t publications, and γ_t publications contain burst words. R represents the total number of references containing burst words in n batches of data and is defined as

$$\mathrm{R} = \sum_{t=1}^{n} \gamma_t$$

D represents the total number of references in n batches of data and is defined as

$$\mathrm{D} = \sum_{t=1}^{n} d_t$$

Let the finite-state probability automaton be, where k is the number of burst states and s is the scale parameter controlling the significance of state differences of the probability automaton. The larger s is, the more significant the difference between the two states, and the more intense the burst. γ is the cost parameter that controls the state change of the probabilistic automaton and defaults to 1. We assume that under the state q_i (i≥0), the proportion of literature containing burst words in the literature set is p_i. The base state is

$$p_0 = R/D$$

$$p_i = p_0 s^i (s>1, i=0,1,\ldots, k),$$

p_i is the proportion of the literature containing burst words in the literature set under the i state, $p_i \leq 1$. We assume that the sequence of probabilistic automaton states is $\mathrm{q} = (q_{i1}, \ldots, q_{it}, \ldots, q_{in})$, where q_{in} means the state of burst words in the data of batch n is q_i. In the state q_i, the probability of the burst words is p_i which obeys the following quadratic polynomial

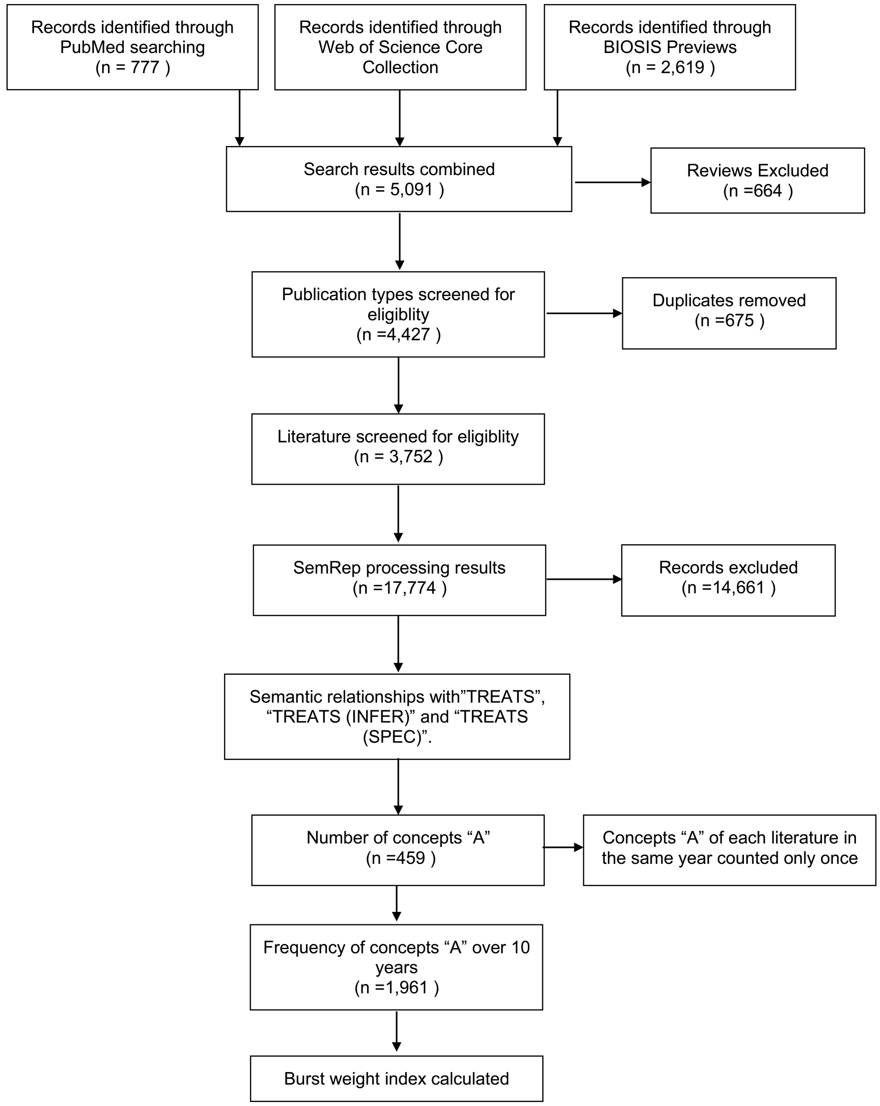

Figure 1 Flowchart of PTSD pharmacotherapy research.

$$\binom{d_t}{\gamma_t} p_i^{\gamma_t}(1-p_i)^{d_t-\gamma_t}$$

According to the bayesian formula for q_i, the probabilistic automaton is still at the cost of q^i at batch t of data is

$$\sigma(\mathrm{i},\gamma_t,d_t) = -\ln\left[\binom{d_t}{\gamma_t} p_i^{\gamma_t}(1-p_i)^{d_t-\gamma_t}\right]$$

Function $\tau(i_t, i_{t+1})$ returns state-transition cost from state q_i to state q_j,[30] and is defined as

$$\tau(i_t, i_{t+1}) = (\mathrm{j}-\mathrm{i})\gamma \ln n$$

The burst weight index represents the transition cost from non-burst state to burst state. In other words, the greater the burst weight index, the higher the burst credibility.[31]

$$\begin{aligned}\text{weight} &= \sum_{t=t_1}^{t_2} d_t((s(0,r_t,d_t)-s(1,r_t,d_t))) \\ &= \ln\binom{\mathrm{d}}{r} + \ln p_1^r + (d-r)\ln(1-p_1) \\ &\quad - \mathrm{Ln}\left[\ln\binom{\mathrm{d}}{r} + \ln p_0^r + (d-r)\ln(1-p_0)\right] \\ &= \mathrm{r}\ln p_1 - \mathrm{r}\ln p_0 \\ &\quad + (d-r)[\ln(1-p_1) - \ln(1-p_0)]\end{aligned}$$

$$= \mathrm{r}\ln(p_1/p_0) + (d-r)\ln[(1-p_1)/(1-p_0)]$$

In this simplification formula, r is the frequency of the word in the current year, d is the amount of literature in the current year, and p_0 is the occurrence of the word in 10 years (total frequency/amount of literature). p_i=$p_0 s^i$, s is the burst threshold, and it is appropriate to take 8–16.[2] The larger it is, the larger the distance between the two burst states is. In order to make the burst state more obvious, the value of eight was assigned to s in the present study. Therefore, the burst weight index was as follows.

$$\text{weight} = r\ln(8) + (d - r)\ln[(1 - p_1)/(1 - p_0)].$$

In the present study, we used Java language programming to access the Access database,[32] and calculated the burst weight index according to the word frequency and the amount of literature.

Results

Characteristics of Included Publications

Based on the search strategy, a total of 5091 relevant publications were retrieved in PubMed, WoSCC and BP on the topic of PTSD-related pharmacotherapy from 2010 to 2019 (Figure 1). After excluding 664 reviews, the annual number of publications is shown in Figure 2 and there is an increasing trend of the annual number of publications. After removing 675 duplicates in the three databases, there were 3752 publications screened for eligibility (Figure 1).

SemRep Processing results

SemRep outputted the concepts and relationships according to UMLS in the following format.

20108200.ab.1|relation|C0162758|Serotonin Uptake Inhibitors

|phsu|phsu|||TREATS|C0038436|Stress Disorders, Post-Traumatic

|mobd|mobd||

'20108200.ab.1′ represented the position of the extracted concepts and relations of SemRep, which was the first sentence in the document abstract with the PubMed Unique Identifier (PMID) 20108200. "Serotonin Uptake Inhibitors" and "Stress Disorders, Post-Traumatic" were the two meaningful co-occurrence concepts extracted from this sentence by SemRep. 'C0162758′ and 'C0038436′ were the concept unique identifiers (CUI) assigned to these two concepts by the UMLS. "Phsu" and "mobd" were the semantic types that UMLS provided for these two concepts. "Phsu" stands for "Pharmacologic Substance", and "Mobd" stands for "Mental or Behavioral Dysfunction", indicating that "Serotonin Uptake Inhibitors" was a "Pharmacologic Substance" and "Stress Disorders, Post-Traumatic" was "Mental or Behavioral Dysfunction". "Relation" meant there was a relationship between "Serotonin Uptake Inhibitors" and "Stress Disorders, Post-Traumatic". The semantic relationship between the two concepts was "TREATS", suggesting that "Serotonin Uptake Inhibitors" could treat "Stress Disorders, Post-Traumatic".

Frequency of Concepts Extracted by SemRep Semantic Processing System

There were 17,774 records extracted by SemRep. According to the results provided by the SemRep Semantic Processing System, there were 3,113 records of "TREATS" relationship, including "TREATS (INFER)" and "TREATS (SPEC)" (Figure 1). The distribution of concepts "B" was as follows, post-traumatic stress disorders 29.23%, patients 8.29%, symptoms 4.02%, anxiety disorders 2.63%, nightmares 2.60%, depressive disorder 2.41%, Veterans 2.41%, disease 2.12%, mental disorders 2.06%, and 55.77% in total. Other concepts "B" accounted for less than 2% (Figure 3). Here, we identified

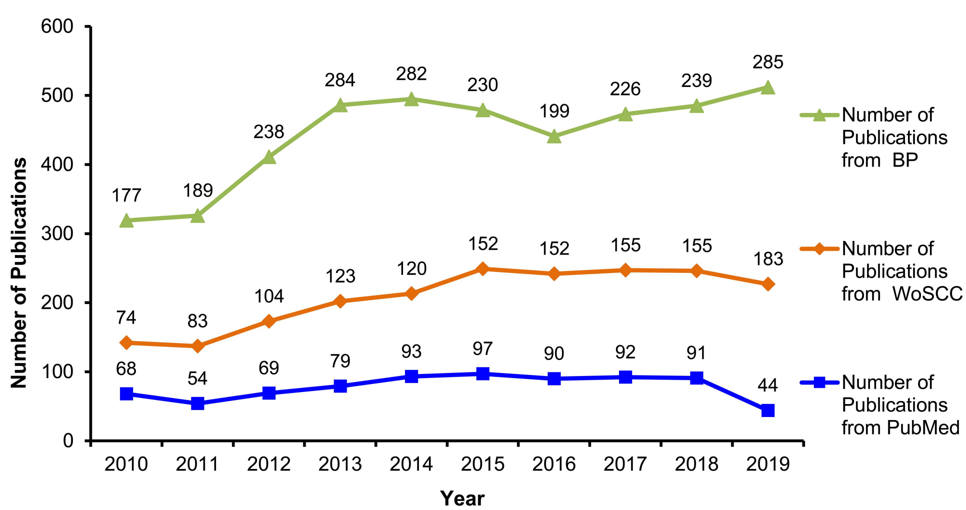

Figure 2 Number of the publications indexed in PubMed, Web of Science Core Collection, and BIOSIS Previews on the topic of PTSD pharmacotherapy (2010–2019).

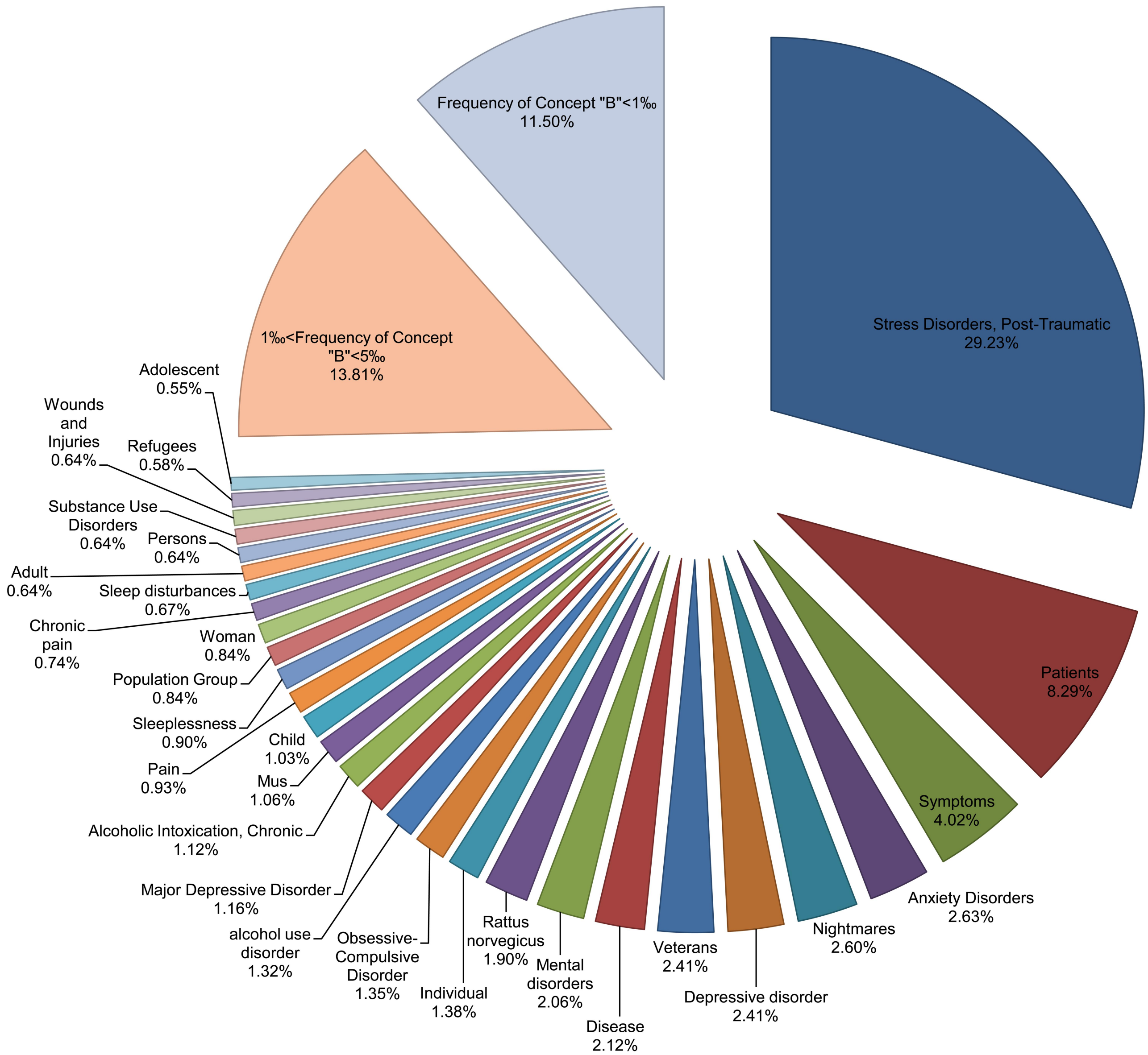

Figure 3 Distribution of concepts “B”.

concepts “B” as disorders, symptoms, patients and other related aspects of PTSD. Therefore, we only counted the frequency of concepts “A”. We supposed concepts “A” as a concept that could “TREAT” PTSD, patients of PTSD, PTSD-related symptoms or disorders. Four hundred and fifty-nine concepts “A” related to drug therapy were extracted. The frequency trends of these concepts “A” over the target ten years are presented in Figure 4.

Distribution of Burst Weight Index

According to the formula of burst weight index, the burst weight index calculated by Java programming language is presented in Figure 5. The concepts were sorted by the burst weight index and the top 50 burst concepts are listed in Table 1. The drug with the highest burst weight index is “Psilocybine”. We traced the dataset back to the source literature that extracted “Psilocybine”. Four relevant articles appeared in 2019, whereas there were few studies in the previous nine years. These studies include clinical trials and effect of psilocybin for the treatment of PTSD,[33,34] and the production of psilocybin in *E. coli*.[35,36] “Psilocybin” and “PTSD” were used as keywords to retrieve a total of 17 articles in PubMed database. Nine relevant articles appeared in 2019 and 2020, and

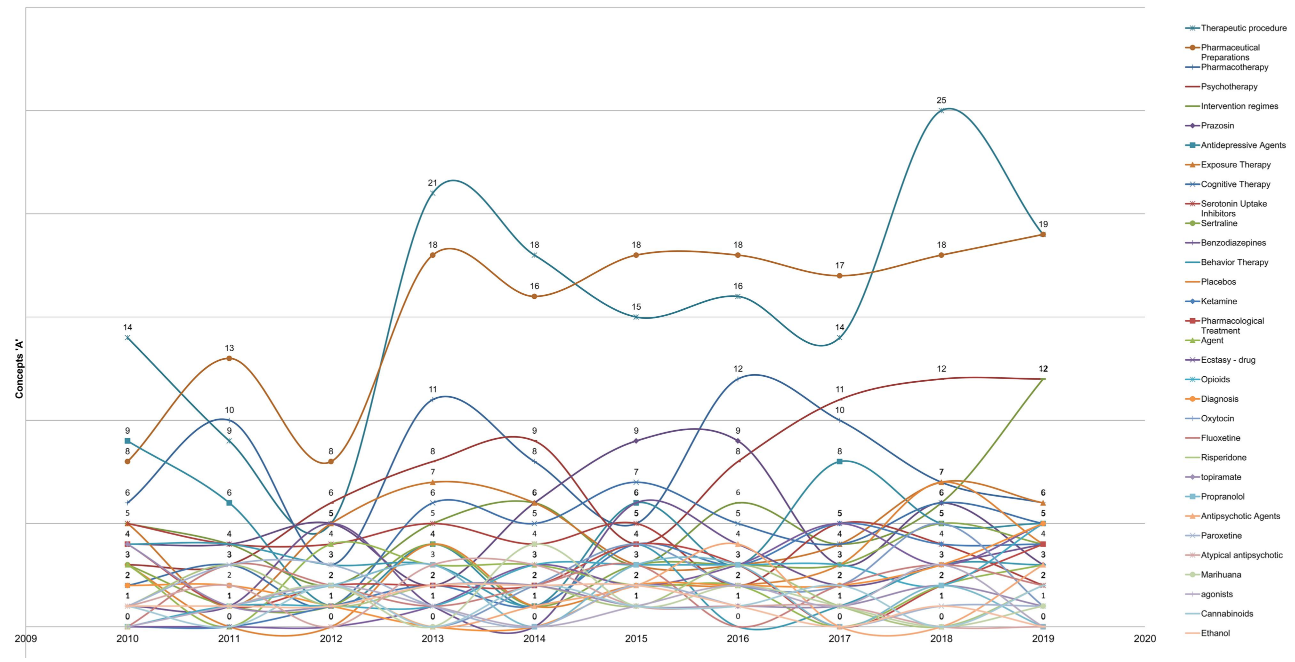

Figure 4 Frequency of the concepts "A" (n=32, frequency>10).

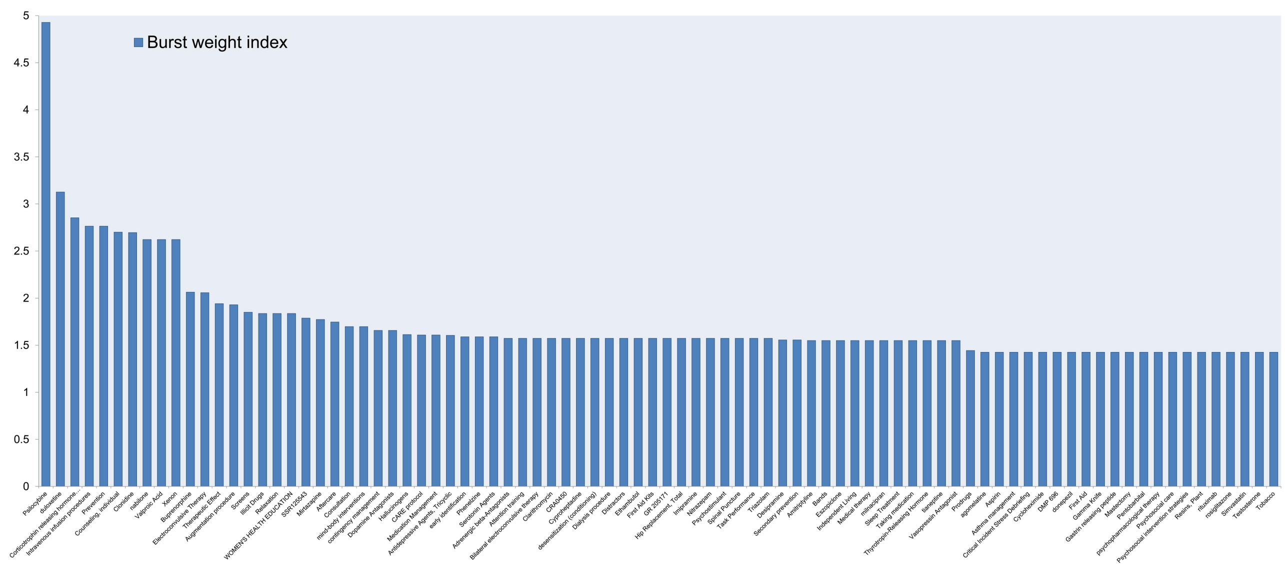

Figure 5 Burst weight index of the concepts "A" (n=86, burst weight index>1.4).

eight articles before 2019. It can be seen from this, psilocybin is a burst drug of the last two years. "Duloxetine" also has a high burst weight (Table 1), it is an antidepressant in a class of medications called selective serotonin and norepinephrine reuptake inhibitors (SNRIs). Duloxetine was proved to be an effective and well-tolerated drug for patients with PTSD.[37,38] The medications in Table 1 reflected the burst characteristics in the last 10 years, indicating the hot research field in the treatment of PTSD.

High-Frequency Concepts

The top 50 high-frequency concepts are presented in Table 2. The top 5 most frequent concepts are "Therapeutic procedure", "Pharmaceutical Preparations", "Pharmacotherapy", "Psychotherapy", and "Intervention regimes". This kind of

Table 1 Burst Weight of the Top 50 PTSD Pharmacotherapy Related Concepts Extracted by SemRep Semantic Processing System

Rank	Concepts	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Burst Weight
1	Psilocybine	−2.04	−2.14	−2.63	−3.13	−3.10	−2.94	−2.81	−2.94	−2.99	4.93	4.93
2	duloxetine	2.64	0.48	−1.97	−2.34	−2.32	−2.20	−2.11	−2.20	−2.24	−2.56	3.13
3	Corticotrophin releasing hormone test	−1.02	−1.07	2.85	−1.56	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	2.85
4	Intravenous infusion procedures	−1.02	−1.07	−1.31	−1.56	−1.54	−1.47	2.76	−1.47	−1.49	−1.71	2.76
4	Prevention	−1.02	−1.07	−1.31	−1.56	−1.54	−1.47	2.76	−1.47	−1.49	−1.71	2.76
6	Counseling, individual	−1.02	−1.07	−1.31	−1.56	−1.54	2.70	−1.40	−1.47	−1.49	−1.71	2.70
6	Clonidine	2.70	−3.75	−0.44	−5.49	−5.44	−5.16	−2.85	−3.07	−5.26	−6.01	2.70
8	nabilone	−1.02	−1.07	−1.31	−1.56	2.62	−1.47	−1.40	−1.47	−1.49	−1.71	2.62
8	Valproic Acid	−1.02	−1.07	−1.31	−1.56	2.62	−1.47	−1.40	−1.47	−1.49	−1.71	2.62
10	Xenon	−1.02	−1.07	−1.31	−1.56	2.62	−1.47	−1.40	−1.47	−1.49	−1.71	2.62
10	Buprenorphine	−1.53	−1.60	−1.97	−2.34	−2.32	−2.20	2.06	−2.20	−2.24	−0.48	2.06
12	Electroconvulsive Therapy	1.63	−2.67	−3.29	−3.91	−3.88	−3.68	−3.52	−3.68	0.43	−2.19	2.06
13	Therapeutic Effect	−1.53	−1.60	0.11	1.83	−2.32	−2.20	−2.11	−2.20	−2.24	−2.56	1.94
14	Augmentation procedure	−1.53	−1.60	−1.97	−2.34	−2.32	−2.20	−2.11	−2.20	1.93	−0.48	1.93
15	Screens	−1.53	−1.60	−1.97	−2.34	1.85	−0.12	−2.11	−2.20	−2.24	−2.56	1.85
16	Illicit Drugs	1.07	−1.07	0.77	−1.56	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.84
16	Relaxation	1.07	−1.07	0.77	−1.56	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.84
16	WOMEN'S HEALTH EDUCATION	1.07	−1.07	0.77	−1.56	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.84
19	SSR125543	−1.02	1.02	0.77	−1.56	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.79
20	Mirtazapine	−3.07	−3.21	−3.96	−2.61	−4.66	−2.33	−2.14	−4.42	1.77	−5.14	1.77
21	Aftercare	1.07	−1.07	−1.31	−1.56	−1.54	−1.47	0.68	−1.47	−1.49	−1.71	1.75
22	Consultation	−1.02	1.02	−1.31	−1.56	−1.54	−1.47	0.68	−1.47	−1.49	−1.71	1.70
22	mind-body interventions	−1.02	1.02	−1.31	−1.56	−1.54	−1.47	0.68	−1.47	−1.49	−1.71	1.70
24	contingency management	1.07	−1.07	−1.31	−1.56	−1.54	−1.47	−1.40	−1.47	0.59	−1.71	1.66
24	Dopamine Antagonists	1.07	−1.07	−1.31	−1.56	−1.54	−1.47	−1.40	−1.47	0.59	−1.71	1.66
26	Hallucinogens	−4.62	−4.84	−5.96	−4.98	−4.91	−6.65	−4.27	−4.56	1.61	−5.64	1.61
26	CARE protocol	−1.02	1.02	−1.31	−1.56	−1.54	−1.47	−1.40	−1.47	0.59	−1.71	1.61
26	Medication Management	−1.02	1.02	−1.31	−1.56	−1.54	−1.47	−1.40	−1.47	0.59	−1.71	1.61
29	Antidepressive Agents, Tricyclic	1.07	−1.07	−1.31	−1.56	0.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.60
30	early identification	1.07	−1.07	−1.31	0.52	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.59
30	Phenelzine	1.07	−1.07	−1.31	0.52	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.59
30	Serotonin Agents	1.07	−1.07	−1.31	0.52	−1.54	−1.47	−1.40	−1.47	−1.49	−1.71	1.59
33	Adrenergic beta-Antagonists	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Attention training	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Bilateral electroconvulsive therapy	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Clarithromycin	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	CRA0450	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Cyproheptadine	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	desensitization (conditioning)	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Dialysis procedure	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Distractors	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Ethambutol	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	First Aid Kits	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	GR 205171	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Hip Replacement, Total	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Imipramine	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Nitrazepam	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57

(*Continued*)

Table 1 (Continued).

Rank	Concepts	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Burst Weight
33	Psychostimulant	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Spinal Puncture	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Task Performance	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57
33	Triazolam	1.57	−0.53	−0.66	−0.78	−0.77	−0.73	−0.70	−0.73	−0.75	−0.85	1.57

concepts are the hypernyms of the medications,[39–41] not specific kind of drugs. They usually appear in the title or abstract of a literature to illustrate the properties of the drug being studied. In terms of frequency of the concepts, the most common treatments for PTSD are pharmacotherapy and psychotherapy (Table 2). Besides these words, the specific drug with the highest frequency is "Prazosin". Prazosin is indicated for the treatment of hypertension, to lower blood pressure. The articles on the treatment of PTSD with prazosin were published every year. The number of publications ranged from two in 2012 to nine in 2014 and 2015, with the average of 5.1 per year. The drugs in Table 2 mainly include antihypertensive agents, antidepressants, antianxiety agents, antipsychotic agents, anticonvulsants, sedatives, hypnotics, analgesics, hormones, etc. These medications are commonly used in the treatment of PTSD. The treatment of these symptoms is the key and difficult to treat PTSD. These medications have always been the focus of research on the drug treatment of PTSD.

The concepts of the top 20 burst weight index with frequency greater than 3 and the concepts of the top 20 high-frequency with burst weight index greater than 1 are presented in Figures 6 and 7, respectively. These concepts include "Psilocybine", "duloxetine", "Clonidine", "Buprenorphine", "Electroconvulsive Therapy", "Therapeutic Effect", "Augmentation procedure", "Screens", "Mirtazapine", "Hallucinogens", "Glucocorticoids", "inhibitors", "Norepinephrine", "pregabalin", "Eye Movement Desensitization Therapy", "Transcranial magnetic stimulation", "Deep Brain Stimulation", "lamotrigine", "Residential Treatment", and "Screening procedure". They are both bursty and highly frequent, they will be both the focus of research in the field of PTSD medication and the future trend of research.

Discussion

The present study presented a framework that based on burst word detection algorithm to assess the medication-related literature on PTSD treatment and reveal the research trend and topics in the field. The burst word detection was a new attempt for the discovery of textual knowledge and could serve as a reliable complement to the traditional bibliometric analysis and scoping review. Importantly, to the author's knowledge, this is the first bibliometric analysis model combined with burst detection algorithm to study the development trend of medication for PTSD.

An interesting discovery in the present study was that "Psilocybine" and "Hallucinogens" were top in Figures 4 and 5, respectively. They are all MeSH (Medical Subject Headings) terms in PubMed. Psilocybine's interpretation in MeSH is that "it is the major of two hallucinogenic components of Teonanacatl, the sacred mushroom of Mexico, the other component being psilocin". Its pharmacologic action is to hallucinate, indicating that "Psilocybin" is a kind of "Hallucinogens". Recently, Krediet et al reviewed the potential of four types of psychedelic compounds that acted on PTSD, including psilocybin.[42] Psilocybin was one of the classic hallucinogens, which could induce neurobiological changes associated with psychotherapy.[42] Psilocybin had been shown to promote neural plasticity in vivo and vitro[43] and these effects were beneficial in dispelling the fear.[44] Classic hallucinogens had been shown to reduce amygdala reactivity,[45] which was often elevated during emotional processing in PTSD patients.[46] There are also studies on the setting and administration of hallucinogens in treating PTSD. These evidences suggest 'Hallucinogens' (including but not limited to 'Psilocybine') as potential new drugs for PTSD treatment.

As can be seen from Figures 6 and 7, the concept with the highest frequency may not have the highest burst weight index. On the contrary, the concept with the highest burst weight index may not have the highest frequency. Therefore, the high-frequency words and the burst words are inconsistent in judging the development trend of a discipline. High-frequency words focus on the current routine research in the field, while burst words focus on

Table 2 Frequency of the Top 50 PTSD Pharmacotherapy Related Concepts Extracted by SemRep Semantic Processing System

Rank	Concepts	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Cumulative Frequency
1	Therapeutic procedure	14	9	5	21	18	15	16	14	25	19	156
2	Pharmaceutical Preparations	8	13	8	18	16	18	18	17	18	19	153
3	Pharmacotherapy	6	10	3	11	8	5	12	10	7	6	78
4	Psychotherapy	3	3	6	8	9	4	8	11	12	12	76
5	Intervention regimes	5	4	2	5	6	3	6	4	6	12	53
6	Prazosin	4	4	5	2	6	9	9	3	6	3	51
7	Antidepressive Agents	9	6	1	4	1	6	3	8	5	5	48
8	Exposure Therapy	5	1	5	7	6	3	3	4	7	6	47
9	Cognitive Therapy	2	3	1	6	5	7	5	4	6	5	44
10	Serotonin Uptake Inhibitors	5	4	4	5	4	5	2	5	4	2	40
11	Sertraline	3	1	1	4	1	3	3	3	5	4	28
12	Benzodiazepines	1	1	5	1	0	6	4	2	3	4	27
13	Behavior Therapy	4	4	3	3	1	4	0	1	3	3	26
13	Placebos	3	0	0	4	1	2	2	3	7	4	26
15	Ketamine	0	0	1	2	1	4	3	5	4	4	24
15	Pharmacological Treatment	4	1	2	2	2	4	3	0	2	4	24
17	Agent	3	0	4	3	3	2	2	0	2	3	22
17	Ecstasy - drug	0	0	0	1	3	2	3	5	3	5	22
17	Opioids	0	1	1	1	3	3	3	3	2	5	22
20	Diagnosis	2	2	1	0	0	2	2	2	3	5	19
20	Oxytocin	1	0	2	0	2	4	2	2	5	1	19
22	Fluoxetine	0	3	2	1	2	3	0	2	3	2	18
23	Risperidone	1	3	1	2	2	1	3	1	0	2	16
23	Topiramate	4	1	1	2	2	1	1	1	2	1	16
25	Propranolol	0	1	2	3	0	3	3	0	2	0	14
26	Antipsychotic Agents	0	1	2	0	1	2	4	0	0	3	13
26	Paroxetine	1	3	3	1	0	2	1	0	1	1	13
28	Atypical antipsychotic	1	2	0	3	3	1	1	1	0	0	12
28	Marihuana	0	1	2	0	4	1	2	1	0	1	12
30	Agonists	0	1	2	1	0	1	2	1	3	0	11
30	Cannabinoids	1	0	2	0	2	1	1	2	0	2	11
30	Ethanol	1	1	1	2	2	2	1	0	1	0	11
33	Hydrocortisone	2	0	0	3	0	1	0	2	1	1	10
34	Follow-up	0	0	2	1	0	2	0	2	1	1	9
34	Hallucinogens	0	0	0	1	1	0	1	1	4	1	9
34	Quetiapine	2	1	0	1	0	0	1	0	3	1	9
37	Anticonvulsants	2	0	1	0	1	1	1	1	1	0	8
37	Aripiprazole	0	1	1	1	0	1	1	1	0	2	8
37	Cannabidiol	0	1	2	0	0	0	0	1	2	2	8
37	Mental health care	2	1	0	2	0	0	1	1	1	0	8
37	Naltrexone	0	1	0	3	1	2	0	0	0	1	8
37	Olanzapine	1	1	1	1	1	0	2	0	1	0	8
37	Pain management	1	0	2	0	0	2	0	2	0	1	8
37	Psychotropic Drugs	1	0	1	1	0	0	1	0	2	2	8
45	Clonidine	3	0	2	0	0	0	1	1	0	0	7
45	Gabapentin	2	0	1	0	2	1	0	0	0	1	7
45	Hospitalization	1	0	0	1	0	0	2	0	0	3	7
45	Screening procedure	1	0	0	1	0	0	1	1	3	0	7

(*Continued*)

Table 2 (Continued).

Rank	Concepts	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Cumulative Frequency
49	Antagonists	0	0	0	0	2	1	0	2	1	0	6
50	Mental health treatment	0	0	0	0	1	2	0	2	0	1	6
50	Mirtazapine	0	0	0	1	0	1	1	0	3	0	6
50	Pregabalin	0	2	2	0	0	1	0	1	0	0	6
50	Psychiatric therapeutic procedure	0	1	0	1	0	0	1	1	1	1	6
50	Trazodone	1	0	0	0	0	1	0	2	0	2	6
50	Venlafaxine	0	1	0	1	0	1	1	1	1	0	6

the potential research trends in the field. When a new disease or epidemic emerges, drugs for similar diseases may be considered as an emergency response to the outbreak. Burst drugs may be considered as a follow-up research direction of the disease after the epidemic is over.

Figure 6 contains the same words as Figure 7 but in a different order. These words are both the focus and trend in the treatment of PTSD, but the emphasis is in a different direction. The clinicians can refer to the high-frequency drugs (Table 2) for routine treatment. These drugs or treatments have gradually matured and are widely used in clinical practice. New drug developers can refer to burst drugs (Table 1). For these drugs, there is still a lot of research and development space; and these drugs' clinical application is not yet mature.

When presenting the results, we found that in addition to the medication itself, there were three kinds of concepts easily extracted by SemRep in the present study, the hypernyms of medications such as "Antidepressive Agents", the therapies such as 'Psychotherapy', and a kind of concepts that has no specific therapeutic meaning such as "Screens". One of these articles that extracted "Screens" was about screening for patients who might benefit from the treatment.[47] Thus, it is necessary to go back to the original literature to understand the specific meanings of these words. In addition to pharmacotherapy, the concepts of therapy that we extracted are also valuable in the treatment of PTSD. These concepts of frequency greater than 3 include 'Psychotherapy', 'Intervention regimes', 'Exposure Therapy', 'Cognitive Therapy', "Behavior Therapy", "Mental health care", "Pain management", 'Hospitalization', 'Screening procedure', 'Mental health treatment', 'Psychiatric therapeutic procedure', "Assessment procedure", 'Electroconvulsive Therapy', "Transcranial Magnetic Stimulation, Repetitive", "Treatment Guidelines", "brief intervention", "Deep Brain Stimulation", "Eye Movement Desensitization Therapy", "Prophylactic treatment", "Residential Treatment", "Stellate ganglion block", and 'Transcranial magnetic stimulation'. Doctors may consider these therapies as they plan their medication.

What calls for special attention is that SemRep cannot recognize or eliminate those semantics with negative relationships, this means that there may be negative or false positive data in concept "A" extracted by SemRep. For example, "Benzodiazepines" as the most commonly

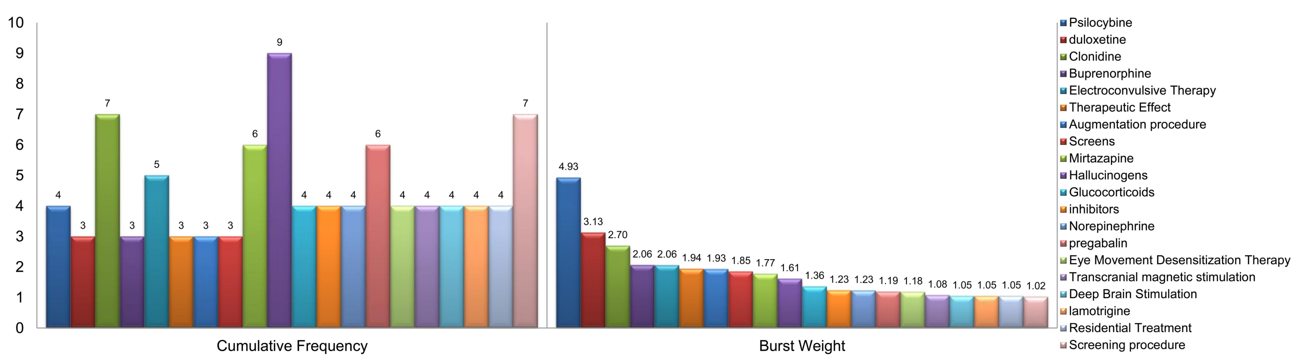

Figure 6 Bursty concepts with high frequency (top 20).

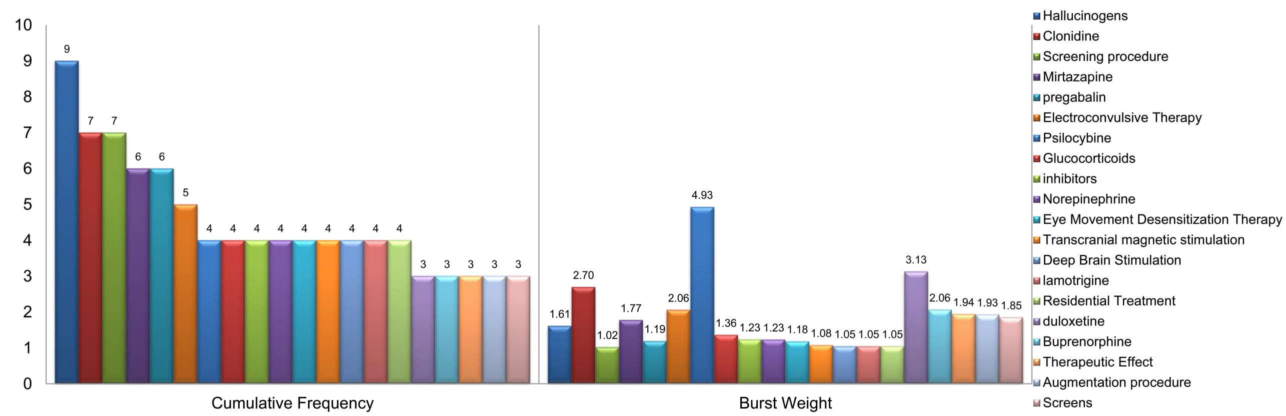

Figure 7 High-frequency concepts with burstiness (top 20).

prescribed psychotropic drugs for PTSD with a high frequency in Table 2, while growing evidence suggests a contraindication to their use in the PTSD treatment, it has been discussed that it could not prevent PTSD in trauma survivors[48] and might even increase the incidence of PTSD.[49] Even though the efficacy and contraindications of conventional drugs in Table 2 may have been well realized by the clinicians, the latest research trends on burst drugs may not have received much attention. For this reason, some potentially new relations were independently reviewed by two neurologists (LW and CZ) in different hospitals. After independent annotations for 108 original literatures of burst drugs, all the discrepancies were resolved by the principal investigator (PG). Most of the burst drugs had definite curable effect on PTSD, only two burst drugs showed negative or false positive effect, 'Illicit Drugs' and 'GR 205171′. Using illicit drugs or misusing prescription medications to control PTSD because of patients' own motivations were misidentified by SemRep as the positive treatment findings.[50] The other false positive burst drug was NK_1R antagonist GR205171 which had fewer adverse effects but was not significantly superior to placebo in the treatment of PTSD.[51] There was another category of burst words that must be understood in the original literatures to express therapeutic approaches, such as "Therapeutic Effect", "Augmentation procedure", "Screens", 'Consultation', "Medication Management", and "Distractors". There were six meeting abstracts and two non-English papers (one in Russian and the other in Italian) that we could not get the full texts. The two neurologists annotated the burst words through the titles or abstracts of eight articles, the rest of the 100 full texts had been sent to them for annotation. The reason why few burst drugs had negative or false positive effects on PTSD might be that the research on burst drugs was still on the rise and people tended to consider or report the positive effect first when developing new drugs. However, with further research, when the frequency of burst words reaches the threshold of high-frequency words, the negative effect may be gradually discovered and reported. Therefore, the next step is to integrate other models[52] to mine some plausible, false positive or negative semantic relations.

In the present study, the drug concept and its hypernym can be extracted simultaneously by the SemRep Semantic Processing System. There are also some concepts that are not classified into their hypernyms, but they represent the same class of drugs. For instance, increasing attention has been devoted to the use of atypical antipsychotics as a new possible treatment for PTSD,[53] risperidone and olanzapine are two types of atypical antipsychotics. The most studied antipsychotic agent in PTSD is risperidone, olanzapine has been proved effective in the treatment of PTSD as monotherapy.[53,54] However, "Risperidone", "olanzapine" and "Atypical antipsychotic" appear together in Table 2. This may result in scattered statistics of concepts in the same research direction. As a result, high-frequency concepts become medium or even low frequent, which may lead to some limitations in this study.

The setting of some parameters in Kleinberg's algorithm was subjective. In particular, the value range of burst threshold s was large; thus, the choice of the value could only be estimated according to the results of previous studies. The parameters k and γ were also determined subjectively, these parameters might ultimately have an impact on the selection of the optimal sequence. At present, the burst detection algorithm still requires high professional quality of the operators' expertise in terms of parameter selection, word screening and the elimination of interference word. As the results provided by SemRep need further manual review, the present study failed to assign a positive/negative score for each keyword. The results of this dimension need to be improved in future research to help quickly summarize the pharmacotherapy's impact for the medical researchers interested in PTSD. The present study has several other limitations that are inherent in the bibliometric methodology. The retrieved publications indexed in the three databases are skewed towards those articles and documents in English and hence the literature in other languages was underestimated. Additionally, the quality of literature in the three databases is not uniform. This dataset may be incomplete due to the limitations of intelligence in the databases.

Conclusion

The present study assessed the medication-related literature on PTSD treatment, providing a framework of burst words detection-based method, a baseline of information for future research and the new attempt for the discovery of textual knowledge. According to the semantic relationship of UMLS, SemRep extracted 459 drug concepts from the retrieved publications of PubMed, WoSCC, and BP. Among the concepts of PTSD medications, the highest frequency concept was "Prazosin", with 51 in 10 years. The burst weight indices of these concepts were calculated by burst detection algorithm and the highest burst index concept was "Psilocybine". And we also obtained some relevant therapies that were available for combination with pharmacotherapy. Additional investigation is needed to optimize the pharmacologic treatment for different severities of PTSD symptoms.

The burst word detection is a method to detect the frontier of the subject by observing the development and change of the words with a sharp increase in the growth rate, and the Java code used in the present study is available from the author upon request. This method can observe the change trend of low-frequency words, which provides a useful reference for the detection of the frontier. There are many research directions in a field, and the sensitivity of word frequency statistics in the whole field is inconspicuous in the microscopic changes of local hot spots, so it is difficult to track the frontier dynamics of specific research directions. The bibliometric analysis based on the burst detection algorithm shows certain feasibility in amplifying the microscopic changes of a specific research direction in a certain field. This method can also be used in other aspects of disease and to explore the trends of various disciplines.

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Disclosure

The authors declare no conflicts of interest in this work.

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