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Research and Applications

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Understanding the research landscape of major depressive disorder via literature mining: an entity-level analysis of PubMed data from 1948 to 2017

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ABSTRACT

Objective: To analyze literature-based data from PubMed to identify diseases and medications that have frequently been studied with major depressive disorder (MDD).
Materials and methods: Abstracts of 23 799 research articles about MDD that have been published since 1948 till 2017 were analyzed using data and text mining approaches. Methods such as information extraction, frequent pattern mining, regression, and burst detection were used to explore diseases and medications that have been associated with MDD.
Results: In addition to many mental disorders and antidepressants, we identified several nonmental health diseases and nonpsychotropic medications that have frequently been studied with MDD. Our results suggest that: (1) MDD has been studied with disorders such as *Pain*, *Diabetes Mellitus*, *Wounds and Injuries*, *Hypertension*, and *Cardiovascular Diseases*; (2) medications such as *Hydrocortisone*, *Dexamethasone*, *Ketamine*, and *Lithium* have been studied in terms of their side effects and off-label uses; (3) the relationships between nonmental disorders and MDD have gained increased attention from the scientific community; and (4) the bursts of *Diabetes Mellitus* and *Cardiovascular Diseases* explain the psychiatric and/or depression screening recommended by authoritative associations during the periods of the bursts.
Discussion and conclusion: This study summarized and presented an overview of the previous MDD research in terms of diseases and medications that are highly relevant to MDD. The reported results can potentially facilitate hypothesis generation for future studies. The approaches proposed in the study can be used to better understand the progress and advance of the field.

Key words: literature mining, frequent pattern mining, temporal analysis, research landscape, major depressive disorder

BACKGROUND AND SIGNIFICANCE

According to the World Health Organization, depression affects the lives of more than 350 million people globally.[1] In the 2010 Global Burden of Disease study,[2] major depressive disorder (MDD) was ranked 11th among the 291 diseases and injuries, which was a 37% increase from being ranked 15th in the same study conducted in 1990. MDD is also known as a risk factor for suicide and ischemic heart disease.[3] Scientific publications have been a primary venue for researchers to discuss and report many important findings on MDD. However, with increasing rates of publication of scientific literature, it is almost impossible to inventory and understand all the articles relevant to the disease. This requires us to take a new approach in addition to the traditional way of reviewing scientific literature manually to better understand the disease.

Bibliometric analysis of scientific papers can be used as an effective complementary method to get a "bird's eye view" of previous studies. Analysis of biomedical entities such as diseases and medications[4] would give us a granular understanding of the MDD studies that have been conducted so far. For example, by investigating diseases and medications that have been frequently studied with MDD, we can understand their interactions with MDD. To fill the gap, in this study, we aim to analyze MDD research publications from the perspective of biomedical entities to better understand the research landscape of MDD.

In particular, the goal of this study is to identify important diseases and medications that have frequently been studied with MDD and understand how these diseases and medications have been studied over time. Specifically, we intend to investigate (1) the most frequently studied diseases and medications; (2) diseases and medications whose overall trends in the scientific literature during the explored period are increasing or decreasing; and (3) diseases and medications that have shown sharp increases in the frequency of mention and investigation in the scientific literature during a specific time period. Exploring these issues has vital importance, and the outcomes will allow us to gain insights in many aspects as follows. (1) Diseases (or medications) and disease (or medication) sets that have been frequently mentioned with MDD suggest their high relevance to MDD. If their relationships with MDD have not been clinically proven, these candidate relationships can serve as useful hypotheses for researchers to further investigate. (2) Trends tell us entities that have been gaining increasing or decreasing attention in the research community, which may suggest their increasing or decreasing importance to the study of MDD. These trends help investigators understand research streams and emerging research problems. (3) A sharp increase in the frequency of disease (or medication) discussion during a certain time period may suggest a series of new findings and warrant further systematic investigation. It can serve as a clue to pay attention to the disease (medication) that might have been overlooked previously. Overall, through a systematic analysis of MDD studies, we not only look back on previous studies to get an overview but are also able to gain insights for future research.

MATERIALS AND METHODS

In the following, we use an *entity* to denote either a disease or a medication and an *entity set* as a term for a group of diseases or medications. We use *entity-level analysis* to denote the analysis of publication data from the perspective of biomedical concepts such as diseases, medications, genes, etc. A *linear trend* and a *burst* of an entity are used to describe the entity's overall (the whole period) and partial (a specific period) trends of being studied in the literature.

Publication data

We used "(humans [MeSH Terms]) AND depressive disorder, major [MeSH Terms]" as the query to search and download relevant PubMed citations. The use of MeSH terms guarantees the retrieval of only highly relevant studies by effectively filtering studies that are not about MDD but mention the term in the text. As of August 10, 2017, we retrieved and downloaded 23 799 PubMed citations with publication years ranging from 1948 to 2017.

Entity annotation and extraction

PubTator[5] developed by the National Center for Biotechnology Information (NCBI) was used to annotate the 23 799 PubMed citations. The tool annotates species, diseases, chemicals, genes, and mutations described in titles and abstracts of the PubMed citations. The tool also normalizes different names that denote the same concept to unified ID systems (eg MeSH IDs for diseases). We extract annotated entities from the free text and replace their names with MeSH terms. For each citation, MeSH terms are stored in a set to remove any duplicates. For example, if a set includes either "Depressive Disorder" or "Depressive Disorder, Major," which are MeSH terms, we consider the citation as relevant and include it in our analysis. This 2-step filtering (MeSH terms-based search and Named Entity Recognition-based filtering) guarantees that the resulting citation set that we analyze is highly relevant to MDD. In the study, we focus on co-occurrence of diseases and medications with MDD at the citation-level. For example, if a medication co-occurs with MDD in the abstract of an article, we assume that there is a direct or indirect relationship between the two. This assumption is reasonable because entities are studied in the context of MDD.

Top entities

Entities that frequently co-occur with MDD imply their higher relevance to MDD than other entities that do not. By exploring entities based on the frequency of co-occurrence with MDD, we can identify important entities that have been actively studied with MDD in the past 70 years. The number of articles that discuss an entity together with MDD is used to represent the entity's frequency. The frequency is a simple, yet meaningful indicator that shows entities' overall relatedness with MDD in the scientific literature.

Frequent entity sets

Some entities co-occur frequently with MDD as a set. This implies that there may be associations among the entities and the co-occurring patterns may signify important research contexts that should be examined in greater detail. For example, if diabetes mellitus, cardiovascular diseases, and MDD frequently co-occur together, it may suggest that the 2 diseases interact with each other within the context of MDD. In our study, we applied a commonly used frequent pattern mining algorithm called FP-growth[6] to generate a list of frequent disease sets (ie sets of diseases that co-occur frequently with MDD) and another list of frequent medication sets, respectively. A second-step was applied to the frequent disease sets, where for each set, for a given disease, we remove it from the set if the set also includes another disease that is a subconcept of the given disease. We use MeSH Tree Structures to determine whether a given disease is a subconcept of another or not. For example, if a frequent disease set includes *Mental Disorders* (MeSH Tree: F03), *Anxiety Disorder* (MeSH Tree: F03.080), and *Personality Disorders* (MeSH Tree: F03.675), we remove *Mental Disorders* from the set because there are 2 subconcepts of it within the same set. We perform this operation iteratively to ensure that every set includes only the most granular concepts within a branch of the MeSH Tree. This approach enables each frequent set to remain as specific as possible.

Linear trends of entities

Throughout the explored time span, entities have trends of frequencies of having been discussed in the literature. Overall, we can identify entity trends, whether increasing or decreasing, by using the linear trend model (with least squares fitting).[7] Because the number of publications varies from year to year, in each year, for each entity,

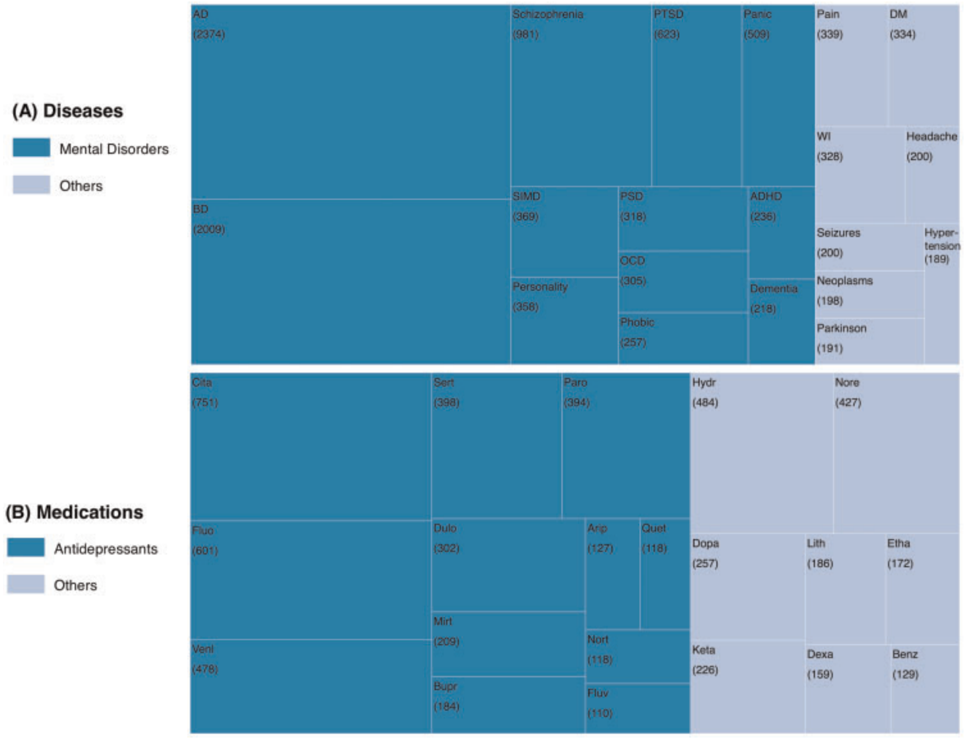

Figure 1. Top 20 diseases (A) and medications (B). AD: anxiety disorders; BD: bipolar disorder; PTSD: stress disorders, post-traumatic; Panic: panic disorder; SIMD: sleep initiation and maintenance disorders; Personality: personality disorders; DM: diabetes mellitus; WI: wounds and injuries; PSD: sexual dysfunctions, psychological; OCD: obsessive-compulsive disorder; Phobic: phobic disorders; ADHD: attention deficit disorder with hyperactivity; Parkinson: Parkinson Disease. Medications are abbreviated with the first 4 characters.

we use the percentage of articles within each year that discussed the entity to represent the entity's frequency in the year. The purpose of this analysis is to identify entities that have been continuously gaining or losing mentions in the literature but not to estimate the correct trends. An entity's increasing trend may suggest its increasing importance within the research community, whereas a decreasing trend may suggest that research interest has declined over time. In addition, the slopes of linear trend lines indicate intensities of the trends, allowing us to compare them among entities.

Bursting entities

Not every entity has an overall increasing or decreasing trend and a more common trend among entities is its "rise" and "fall." In this paradigm, "burst" is a phenomenon that explains how an entity rises sharply in frequency at a certain point of time and grows in intensity for a period.[8] This is an important indicator that highlights a time span during which an entity has received increased, unusual spotlight (represented as mentions in the literature). Yearly percentages of articles that discuss an entity are represented as time series data and used to detect bursts for the entity if any.

RESULTS

Top entities

Top 20 diseases and medications were selected based on frequency (Figure 1). Frequency of an entity was defined as the number of articles that mention both the entity and *MDD*. The medications were manually extracted from the list of chemicals because PubTator does not differentiate medications from other chemicals.

In the treemap (Figure 1), entities are visualized such that the size of the rectangle represents how each entity is proportional to the frequency of the entity. A 2-color scheme was used to differentiate mental health disorders from nonmental health conditions (in the case of diseases) and antidepressants from nonpsychotropic drugs (in the case of medications).

As shown in the figure, among the top 20 diseases that co-occurred frequently with *MDD*, 12 diseases are mental disorders (based on MeSH Tree Structures) and their frequencies are greater than that of other diseases. These 12 diseases with decreasing frequencies are *Anxiety Disorders* (2374), *Bipolar Disorder* (2009), *Schizophrenia* (981), *Stress Disorders, Post-Traumatic* (623), *Panic Disorder* (509), *Sleep Initiation and Maintenance Disorders* (369), *Personality Disorders* (358), *Sexual Dysfunctions, Psychological* (318), *Obsessive-Compulsive Disorder* (305), *Phobic Disorders* (257), *Attention Deficit Disorder with Hyperactivity* (236), and *Dementia* (218). Among the 12 diseases, *Panic Disorder*, *Obsessive-Compulsive Disorder*, and *Phobic Disorders* are subconcepts of *Anxiety Disorders* in the MeSH Tree Structures. We can see that researchers have studied *Anxiety Disorders* as a whole as well as specific types of *Anxiety Disorders*. A possible reason that *MDD* has been studied with many other mental disorders is that a large portion of *MDD* patients have comorbid mental illness. For example, a nationally representative epidemiologic study reported that more than 70% of *MDD* patients have comorbid mental disorders.[9] The limitations of the current psychiatric diagnostic system can also partly explain the results. The International Classification of Diseases (ICD) system and the Diagnostic and Statistical Manual of Mental Disorders (DSM) system for mental disorders are primarily based on symptoms, and therefore, a patient can be diagnosed with

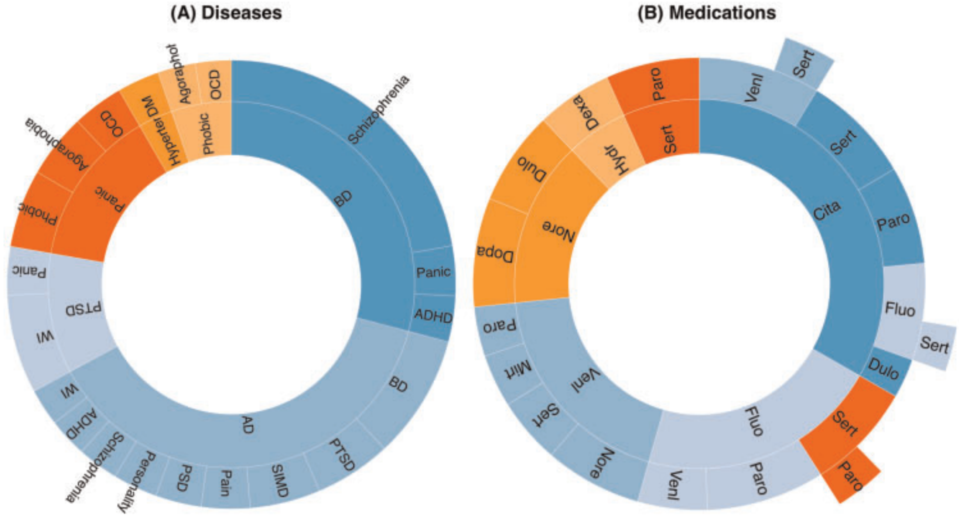

Figure 2. Top 20 frequent disease (A) and medications (B) sets. AD: anxiety disorders; BD: bipolar disorder; PTSD: stress disorders; post-traumatic; Panic: panic disorder; SIMD: sleep initiation and maintenance disorders; Personality: personality disorders; DM: diabetes mellitus; WI: wounds and injuries; PSD: sexual dysfunctions; psychological; OCD: obsessive-compulsive disorder; Phobic: phobic disorders; ADHD: attention deficit disorder with hyperactivity; Parkinson: Parkinson disease. Medications are abbreviated with the first 4 characters.

multiple mental disorders that share the same symptoms. To address this, there are on-going efforts to improve the classification and diagnostic systems to convey the heterogeneous pathophysiology.[10] Eight nonmental disorders with decreasing frequencies are *Pain* (339), *Diabetes Mellitus* (334), *Wounds and Injuries* (328), *Headache* (200), *Seizures* (200), *Neoplasms* (198), *Parkinson Disease* (191), and *Hypertension* (189). Here, we briefly explain the relationships between some of the above diseases with *MDD*. *Chronic Pain* is known to be common among *MDD* patients,[11] and it has been shown that caring for patients with both physical pain and psychiatric illness can be challenging.[12] Depression is also associated with the prevalence of *Diabetes Mellitus*,[13] and patients' treatment adherence.[14] In terms of *Wounds and Injuries*, we found that many studies have explored associations between depression and traumatic brain injury,[15] war,[16] sexual violence,[17] childhood abuse,[18] and early life parental loss.[19]

Among the top 20 medications that co-occurred frequently with MDD, 12 medications are antidepressants, and include (in decreasing order of frequency) *Citalopram* (751), *Fluoxetine* (601), *Venlafaxine* (478), *Sertraline* (398), *Paroxetine* (394), *Duloxetine* (302), *Mirtazapine* (209), *Bupropion* (184), *Aripiprazole* (127), *Quetiapine* (118), *Nortriptyline* (118), and *Fluvoxamine* (110). Among the other 8 nonantidepressants, *Norepinephrine* (427) and *Dopamine* (257) were extracted by the tool, likely because these 2 terms are parts of classes of antidepressants (ie Norepinephrine reuptake inhibitors, Serotonin-norepinephrine reuptake inhibitors, and Norepinephrine-dopamine reuptake inhibitors). *Hydrocortisone* (484), *Dexamethasone* (159), and *Benzodiazepines* (129) are known to have depression as one of their side effects.[20,21] *Ketamine* (226) and *Lithium* (186) are off-label uses, and they have not been officially approved for treating depression.[22,23] Increasing involvement with *Ethanol* (172) is known to increase the risk of depression. [24]

Frequent entity sets

The frequent disease and medication sets were computed and the top 20 sets in each category are shown in Figure 2. In Figure 2, the length of an arc is proportional to the frequency of the entity in the arc co-occur with entities in its inner arcs and *MDD*. For example, among the frequent disease sets, *Schizophrenia* (top-right) co-occurred with *Bipolar Disorder* and *MDD* more frequently than *Diabetes Mellitus* (top-left) with *Hypertension* and *MDD*.

As shown in Figure 2, many mental disorders co-occurred frequently with each other, which is consistent with previous findings.[9] The 4 frequent disease sets that include both mental disorders and other diseases are: *MDD*, *Stress Disorders, Post-Traumatic*, and *Wounds and Injuries* (157); *MDD*, *Anxiety Disorders*, and *Pain* (77); *MDD*, *Hypertension*, and *Diabetes Mellitus* (67); and *MDD*, *Anxiety Disorders*, and *Wounds and Injuries* (59). The co-occurrence of *MDD* and *Wounds and Injuries* with *Stress Disorders, Post-Traumatic* and *Anxiety Disorders* is explained by the fact that trauma experience caused by *Wounds and Injuries* can lead to mental disorders such as *MDD*, *Anxiety Disorders*, and *Stress Disorders, Post-Traumatic*.[25] The frequent disease set of *MDD*, *Anxiety Disorders*, and *Pain* has been discussed as a challenging psychiatric comorbid condition because of the "complex interplay of affective, behavioral, cognitive and physical aspects of pain."[12] The co-occurrence pattern of *MDD*, *Hypertension*, and *Diabetes* Mellitus can be explained by the fact that *Hypertension* and *Diabetes Mellitus* may co-occur as a metabolic syndrome.[26] Studies also reported that MDD is related with both *Diabetes Mellitus*[27] and *Hypertension*[28] independently.

In the top 20 frequent medication sets, most are sets of antidepressants. The only set that includes nonantidepressant medications is *Hydrocortisone* and *Dexamethasone*, which co-occurred 119 times with *MDD*. As mentioned previously, both *Hydrocortisone* and *Dexamethasone* are known to have depression as one of their side effects.[20]

Linear trends of entities

The linear trends of diseases (from 2000 to 2016) are shown in Table 1 with nonmental disorders boldfaced. The year 2000 was chosen because the volume of the publications available electronically via PubMed each year prior to 2000 is small with the average number of 23. In most years, the size of MDD publications is

Table 1. Linear trends of diseases (2000–2016)

Name	Frequency	Slope	*P*-value
Bipolar disorder	1885	0.00159	.00933
Diabetes mellitus	353	0.00102	.00031
Stress disorders, post-traumatic	606	0.00010	.00073
Wounds and injuries	345	0.00087	.00004
Cardiovascular diseases	291	0.00046	.01059
Sleep initiation, and maintenance disorders	360	−0.00038	.01485
Obsessive-compulsive disorder	292	−0.00076	.00025
Personality disorders	389	−0.00077	.00085
Phobic disorders	225	−0.00078	.00053
Dementia	299	−0.00080	.00276
Panic disorder	485	−0.00113	.00027

Table 2. Linear trends of medications (2000–2016)

Name	Frequency	Slope	*P*-value
Citalopram	735	0.00155605	.005598284
Ketamine	185	0.001131715	1.09E−06
Ethanol	164	0.001026535	.013549743
Aripiprazole	121	0.000560246	3.11E−05
Quetiapine	114	0.000400164	.003401941
Nortriptyline	109	−0.000465342	.004795913
Imipramine	87	−0.000551417	.004298498
Lithium	175	−0.000592834	.00034675
Dexamethasone	150	−0.000636098	.000637746
Fluvoxamine	106	−0.000742118	.63E−06
Hydrocortisone	465	−0.001293984	.000232898
Paroxetine	379	−0.001306111	2.23E−05
Fluoxetine	581	−0.001360485	.004872951

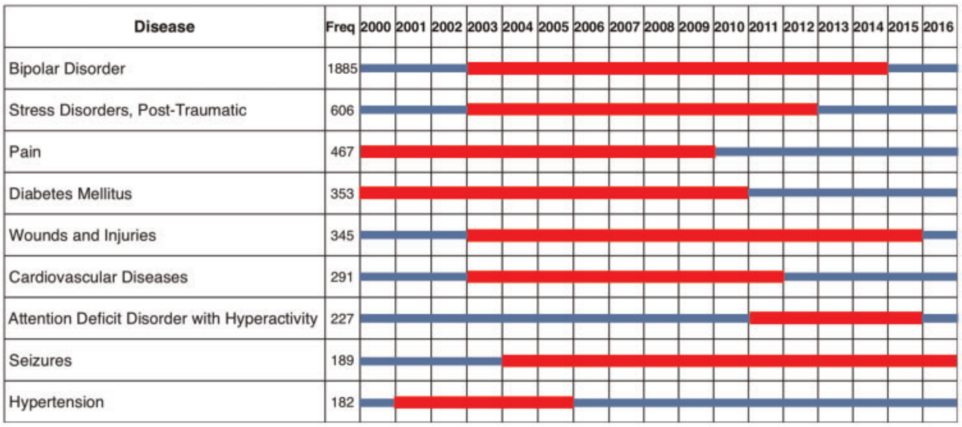

Figure 3. Bursting diseases (2000–2016). Bursting diseases and the time periods (red bars) during which the bursts occurred and continued are plotted.

smaller than 100. The year 2017 was excluded because the publication records for the year are not complete. Table 1 shows diseases whose linear trends are significant (*P*-value <.05). Slopes represent intensities of trends with positive values indicating increasing trends and negative values indicating decreasing trends. For example, in Table 1, *Bipolar Disorder* has a stronger increasing trend than *Diabetes Mellitus*. Diseases that have been mentioned less than 10 times each year on average are not included. We set the constraint to focus on diseases that have been frequently or moderately mentioned and show significant trend lines. Among the 11 diseases shown in Table 1, 5 diseases have been increasingly mentioned in the literature and 3 of them (*Diabetes Mellitus*, *Wounds and Injuries*, and *Cardiovascular Diseases*) are not mental disorders. On the other hand, all the other 6 diseases, which are mental disorders, have been gaining decreasing interests among researchers with respect to their relationships with *MDD* are mental disorders. It shows that, in recent years, researchers are more actively involved in understanding relationships between mental disorders and other diseases.

Table 2 shows the linear trends of medications (from 2000 to 2016) with nonantidepressants boldfaced. Table 2 includes medications that have been mentioned more than 5 times each year on average. Because medications have not been mentioned as frequently as diseases in the literature, we set the minimum frequency value of 5 in order to be included. Among antidepressants, *Citalopram*, *Aripiprazole*, and *Quetiapine* have been studied increasingly whereas *Nortriptyline*, *Imipramine*, *Fluvoxamine*, *Paroxetine*, and *Fluoxetine* have not been studied as frequently as before. Among nonantidepressants, *Ketamine*, which has been reported to have antidepressant effect has been gaining increasing interests among researchers along with *Ethanol*. Another off-label use, *Lithium* with 2 medications (*Dexamethasone* and *Hydrocortisone*) have decreasing trends.

Bursting entities

Bursts were only identified in diseases, as no bursts were detected in medications. Figure 3 shows bursting diseases and the time periods (red bars) during which the bursts occurred and continued. Among the 9 bursting diseases, 6 diseases such as *Pain*, *Diabetes Mellitus*, *Wounds and Injuries*, *Cardiovascular Diseases*, *Seizures*, and *Hypertension* are nonmental disorders.

To interpret this data, we reviewed literature to get insights on bursts of articles related to very common chronic conditions in the adult US population: *Diabetes Mellitus* and *Cardiovascular Diseases*. *Diabetes Mellitus* burst between 2000 and 2010. The number of relevant articles increased from <5 in early years (2010, 2001, and 2002) to more than 40 in 2010. The scope of the study on *Diabetes Mellitus* and *MDD* during the period was broad including studies on association,[27] test,[29] treatment adherence,[14] prognosis,[30] quality of care,[31] and medical cost.[32] In 2005, Standards of Medical Care in Diabetes published by the American Diabetes Association included the recommendation for "screening for psychosocial problems in diabetes patients with poor adherence."[33] Many relevant articles published between 2000 and 2005 might have contributed to the recommendation. In addition, the recommendation might also have drawn researchers' attention to further study the relationship between *Diabetes Mellitus* and *MDD*. The publications related to *Cardiovascular Diseases* burst between 2003 and 2011. The number of relevant articles increased from 3 in 2003 to 25 in 2011. Many laboratory studies[34–36] on the association between *Cardiovascular Diseases* and *MDD* have contributed to the burst as well as to the publication of clinical recommendation for "depression screening in patients with coronary heart disease" by the American Heart Association Prevention Committee in 2008.[37] From the aforementioned 2 examples, we can see that, the bursts identified in the entities correctly represent temporal characteristics of research and can serve as an effective signal for later findings and clinical decisions.

DISCUSSION

In the study, we broadly explored diseases and medications that have frequently been studied with *MDD* by analyzing abstracts of approximately 24 000 *MDD* research articles that have been published since 1948. Results of the study provided a research overview and landscape of *MDD* from 4 perspectives: top entities, frequent entity sets, linear trends of entities, and bursting entities.

Many mental disorders have frequently been studied with MDD, which is consistent with a previous finding that 70% MDD patients have comorbid mental disorders. Nonmental disorders such as *Pain*, *Diabetes Mellitus*, and *Hypertension* have also been studied. MDD has also been studied in terms of its relationships with traumatic brain injury,[15] war,[16] sexual violence,[17] childhood abuse,[18] and early life parental loss.[19]

In addition to common antidepressants, medications that cause depression as a side effect (*Hydrocortisone*, *Dexamethasone*, and *Benzodiazepines*)[20,21] and off-label uses of medications that may act as or supplement antidepressants (*Ketamine* and *Lithium*)[22,23] have also been widely studied. Top entities and frequent entity sets are a simple, yet a very useful way to identify a core set of entities that play an important role in MDD research.

Through the temporal analyzes, we found that relationships between MDD and nonmental health disorders such as *Diabetes Mellitus*, *Wounds and Injuries*, and *Cardiovascular Diseases* have gained increasing attention in the scientific community in recent years. Among nonpsychotropic drugs, *Ketamine* has been studied significantly in the recent past. Bursts were identified in several diseases, and our results suggest that that they can correctly represent temporal characteristics of trends in research interests and direction. We found bursts of *Diabetes Mellitus* and *Cardiovascular Diseases* that may help to explain the psychiatric and/or depression screening recommendations by authoritative associations during the periods of the bursts.

The study has a few limitations. First, publication data used in the analyzes were only from PubMed and scientific literature that is not indexed in PubMed was not considered. In future work, we plan to incorporate additional databases which might lead to different findings. Second, due to the limited data access, diseases and medications were only extracted from abstracts rather than full-texts of research articles. This may have resulted in limited sets of diseases and medications. In turn, the focus of the study was precision rather than recall because abstracts only report central, important, and highly relevant entities whereas full-texts have broader coverage with possibly irrelevant entities. Third, our analyzes were based on co-occurrence of entities. Co-occurrence is a useful method to identify relationships between entities. However, co-occurrence does not always imply relationships. Therefore, it is possible that entities co-occur together with MDD in an abstract do not necessary mean they have clear relationships with MDD.

CONCLUSION

Scientific literature is a valuable repository of knowledge. Researchers have been continuously contributing to that repository by publishing research articles. Because we cannot keep up with the rapid pace of knowledge production, a bibliometric systematic analysis of research publications is of great help to both researchers and practitioners to have a general understanding of a research domain. The study achieved this by exploring diseases and medications that have important relationships with *MDD* based on the entity-level analysis of a comprehensive set of *MDD* research articles published from 1948 to 2017. We presented the research landscape of *MDD* from various perspectives by considering both static (top entities and frequent entity sets) and dynamic (linear trends and bursts) characteristics of entities.

With the rapid growth and accumulation of MDD research publications, there is a continuous need to systematically analyze them to get overall and up-to-date research landscapes. The approaches proposed in the study can be used to better understand the progress and advance of the field. The study not only provides researchers and practitioners a clear understanding of previous work, but results reported in this study can serve as useful hypotheses and help researchers formulate meaningful research questions.

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