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ORIGINAL RESEARCH

Acupuncture for Major Depressive Disorder: A Data Mining-Based Literature Study

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Introduction: Acupuncture has a long history of treating major depressive disorder (MDD), yet the acupoint selection of acupuncture for MDD varies greatly. This study aimed to explore the characteristics and principles of acupuncture for MDD by analyzing clinical trials of acupuncture for MDD using data mining techniques.

Methods: In this study, clinical trials of acupuncture for MDD were retrieved and relevant data were extracted, and then the data were analyzed by data mining techniques. In addition, association rule mining, network analysis and hierarchical cluster analysis were used to determine the correlation between different acupoints.

Results: The results revealed that GV20, LR3, PC6, SP6 and GV29 were used most frequently; acupoints in the Yang meridian were used more often than those in the Yin meridian, with the most applied acupoints in the Governor Vessel; the percentage of specific acupoints applied was 69.39%, with the most applied being five-shu points; the frequency of acupoints used was highest in the lower limbs, while the head, face, and neck had the most acupoints used; GV29 combined with GV20 were the most used acupoint groups; the core acupoints used for MDD were GV20, PC6 and SP36; there were 5 acupoint groups according to the cluster analysis. The most used acupuncture method was manual acupuncture; the frequency of treatment was mostly 7 times per week and the duration of treatment was mostly 42 days.

Discussion: We discussed the current character of acupuncture treatment on MDD, including the frequency used of acupoints, the property of used acupoints, the acupoint combination, the acupuncture method, and the frequency and duration of treatment. These findings may provide new ideas for the clinical treatment of MDD. However, further clinical/experimental studies are needed to demonstrate the significance of this concept and approach.

Keywords: acupuncture treatment, data mining technology, association rule mining, network analysis, cluster analysis

Introduction

Major depressive disorder (MDD) is one of the most prevalent mental health disorders worldwide, affecting at least 3.8% of the population, and has a high relapse rate.[1–4] And the prevalence of MDD has increased significantly in the past decade, with higher rates in women than in men.[5–7] Mood disorders, cognitive dysfunction, and severe psychosocial impairment characterize MDD, which can last from weeks to years.[8] What is worse, MDD accounts for 10% of the worldwide burden of nonfatal disease production.6 Therefore, it is urgent to strengthen the research on the prevention and treatment of MDD.

The main clinical treatments for depression currently include antidepressant medication and other adjunctive treatments such as psychological therapy, cognitive therapy, transcranial magnetic stimulation, and light therapy.[9] Among

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them are mainly antidepressant treatment, which has varying degrees of side effects and risks limitations. A part of MDD patients prefers complementary therapies, as a survey shows.[10,11] Therefore, complementary therapies for MDD should be given attention. Acupuncture is increasingly used worldwide, and a meta-analysis study has shown that acupuncture combined with medication improves depressive symptoms and reduces the use of medication, and improves the quality of life of MDD patients.[12] Acupuncture has shown some potential and advantages in the treatment of MDD and is included in the clinical guidelines recommended by the American College of Physicians as a complementary and alternative therapy.[13]

Acupuncture therapy works by stimulating acupoints, so the selection and combination of acupoints are very important. In addition to acupoints, acupuncture stimulation methods and treatment courses are also important components of acupuncture prescription, which is a key step in acupuncture treatment. The acupuncture prescription is a combination of acupoints, stimulation methods, and treatment courses used in acupuncture to treat diseases. The acupuncturist's choice of acupuncture prescription depends on his or her ideas and experience. There have been many studies evaluating the efficacy of acupuncture in the treatment of MDD. However, because of the wide variation in acupuncture treatments in these studies, it is difficult to obtain from them the best acupoint selection and combination for MDD. Fortunately, the advent of data mining techniques has provided new methods for analyzing acupuncture information. Data mining techniques are the process of gathering potentially useful information and knowledge from a large amount of imperfect, noisy, imprecise, and random data in practical applications.[14] Therefore, this study aims to summarize the acupuncture prescription of acupuncture for MDD through association rule mining (ARM), network analysis and hierarchical cluster analysis to determine the characteristics and patterns of acupuncture for MDD, which is important for future research and clinical practice.

Methods

Search Strategy

The following eight electronic databases were searched by two dependent reviewers (SX and XW) from their inception to May 28th, 2022: PubMed, Excerpt Medical Database (Embase), Web of Science core collection (WOS), the Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Data and Chongqing VIP database (CQVIP). The search strategy combined the keywords (a) "acupuncture" or "electroacupuncture" or "electro-acupuncture" or "needle" or "needling"; and (b) "depress*" or "depression" or "depressive" or "depressed" or "despondent" or "antidepressant" or "depressive disorder" or "despondent" or "antidepressant*" (Supplementary Material 1).[15,16] In Chinese databases, Chinese characters with the same meaning were used for literature retrieval. References to the included literature were also screened to supplement the potential eligible trials.

Selection Criteria for Studies

Types of Studies

Clinical research on acupuncture for MDD, including randomized control trials (RCTs) and clinical control trials (CCTs). Reviews, systematic reviews, meta-analyses, case reports, commentaries, clinical protocols, and animal studies were excluded. The sample size was at least ten.

Participants

Patients with MDD were included in this study. Diagnostic criteria included one or more of the following: the Chinese Classification of Mental Disorders (CCMD-2/CCMD-3),[17,18] the International Classification of Diseases (ICD-9/ICD-10/ICD11),[19,20] or The Diagnostic and Statistical Manual of Mental Disorders (DSM-3/DSM-4/DSM-5).[21] Patients were not limited in duration or severity and without restrictions on age, sex, or race.

Intervention and Control Group

Interventions were acupuncture alone or acupuncture combined with basic treatment such as western medicine or psychotherapy. Studies that do not involve needle insertion should be excluded, such as Tuina and laser stimulating. And unconventional acupuncture types such as head acupuncture, ear acupuncture, wrist and ankle formation, and abdominal acupuncture were excluded. Control groups using medicine or Chinese medicine, sham acupuncture, or nothing at all were included. However, trials comparing the efficacy of different acupuncture treatments or different acupoint retrieval protocols were excluded.

Outcomes

As this study is focused on data mining of acupoints for the clinical treatment of MDD, we have only included studies featuring clinical efficacy indicators, such as Hamilton depression scale (HAMD), Montgomery and Asberg depression rating scale (MADRS) and self-rating depression scale (SDS). Studies reporting only physical and chemical examinations were excluded. In addition, only literature with positive results was included in the analysis.

Data Selection and Extraction

The collected studies were input into Endnote X9 by two reviewers (SX and XW), who then eliminated duplicates both automatically and manually. The eligible trials were identified by carefully examining the titles, abstracts, and full texts of the retrieved papers in light of the inclusion and exclusion criteria. The two reviewers separately extracted comprehensive data from the final eligible trials using a preset data-extraction form. Any discrepancies were arbitrated by the third reviewer (XS). Characteristics of the included studies encompassed acupoints, meridians, acupuncture methods, outcomes, and adverse effects. In addition, missing data were obtained by contacting the corresponding or relevant authors. The nomenclature and location of acupoints served as the basis for the names of acupoints and meridians (GB/T 12346–2021).[22]

Data Processing

Firstly, we summarized the frequency of acupoints and meridians in the prescription of acupuncture for MDD and further counted the distribution of these acupoints in different body parts and the details of the specific acupoints. Secondly, to identify the most often utilized acupoint group (two or three acupoint combinations), we employed ARM and network analysis to identify the correlation of different acupoints. Finally, We extracted as much data as possible from the eligible studies, including outcomes, acupuncture methods, and adverse effects of patients with MDD, and reanalyzed them to obtain more information about acupuncture for MDD. This part of the study was implemented by two reviewers (MT and SL).

ARM

The Apriori algorithm in Python 3.8 (https://python.org) was used for ARM analysis. Each acupoint association item has support, confidence, and lift. Support and confidence can be used to measure the strength of association rules. Support is a metric that describes the probability of events A and B occurring simultaneously under certain conditions, which is used to measure the statistical significance of the association rule across the entire data set. Confidence was the conditional likelihood that the subsequent event would occur given the antecedent, demonstrating how credible the connection rules were. Briefly, the support (A→B) indicates the prescriptions containing both acupoint A and acupoint B as a percentage of the total; the confidence (A→B) shows the prescriptions containing both acupoints A and acupoint B as a percentage of the prescriptions containing acupoint A. Lift shows the relationship between the rule's confidence and the prior probability that the consequent will occur. Rules with lifts that are distinct from 1 are typically more intriguing than rules with lifts that are close to 1. In addition, we used Gephi 0.9.7 (https://gephi.org) to investigate the co-occurrence matrix of acupoints, presented as a heat map.

Network Analysis

We preprocessed the data to obtain the relevant node acupoints and their weight values. Then we imported the results into Gephi 0.9.7 (https://gephi.org/) to get the results such as core nodes as well as correlation and visualize the network

images. The central aggregation distribution model was created using the "Fruchterman Reingold" algorithm, and the core acupoints were examined using the "k-core" method.

Hierarchical Cluster Analysis

The literature that would select acupoints based on pattern identification was first screened, and a matrix text was created with the pattern identification and its associated acupoints. The frequency of occurrence of an acupoint in a given pattern and the sum of the frequencies of all acupoints in that text were counted, and the former divided by the latter to yield a globally corrected weight for an acupoint in each pattern identification. A hierarchical clustering analysis of the acupoints for MDD treatment was performed using the "dendrogram" package with scipy software (version 1.8.0), and the resulting figures were plotted using matplotlib software (version 3.5.1). Ward's minimum variance method was employed for clustering.

Results

Search Results and Profile of Acupuncture Prescriptions

In total, 10,738 records were identified. After screening and evaluation, 664 prescriptions of acupoints from 311 records were analyzed. 292 of the eligible records were in Chinese and 19 were in English. The research flow is shown in Figure 1.

Application of Acupoints

Of the 664 prescriptions, 138 meridian acupoints and 9 extraordinary acupoints were recorded 2949 times in MDD acupuncture treatments. Table 1 lists the 20 most frequently applied acupoints, with GV20, LR3, PC6, SP6, and GV29 being the top 5.

Application of Meridians and Acupoints

After analysis, we found 147 acupoints used for the treatment of MDD, 138 of which were distributed in the fourteen meridians (the twelve regular meridians, Governor Vessel, and Conception Vessel) and 9 were extraordinary acupoints. Table 2 shows the frequency and proportion of meridians and the number and proportion of acupoints used in each meridian. From the results of the meridian application, the acupoints of GV, BL, LR, SP, and ST were the top 5 most frequently applied. Of the fourteen meridian acupoints, 59.42% (82/138) were Yang meridian acupoints and 40.58% (56/138) were Yin meridian acupoints.

Application of Specific Acupoints

The results showed the use of specific acupoints in the acupuncture prescription, including frequency, proportion, amount of acupoints, selected acupoints, and their frequency. Of the 147 acupoints, 102 were specific acupoints, accounting for 69.39% of the total number of acupoints. Overall, a total of 10 specific acupoints were involved. The most used specific acupoints were five-shu points (23.13%), and crossing points, yuan-primary points, and back-shu points were also frequently used to treat MDD (Table 3).

Application of Acupoints on Different Body Parts

We analyzed the distribution of acupoints in acupuncture prescriptions. Table 4 demonstrates the frequency and percentage of acupoint distribution, as well as the names and frequencies of acupoints. The frequency of acupoints used was highest in the lower limbs (30.36%), with 33 acupoints used a total of 896 times, while the head, face, and neck had the most acupoints used (28.57%), with 42 acupoints used a total of 867 times.

Association Rules of Acupoints for MDD

Table 5 summarizes the 10 pairs of acupoint combinations with the highest support values in MDD acupuncture prescriptions. The top 3 supported pairs were GV29 with GV20, GV20 with PC6, and LR3 with GV20. In these 10 pairs of acupoint association rules also included LR3, SP6, and HT7. These results were consistent with the results in the

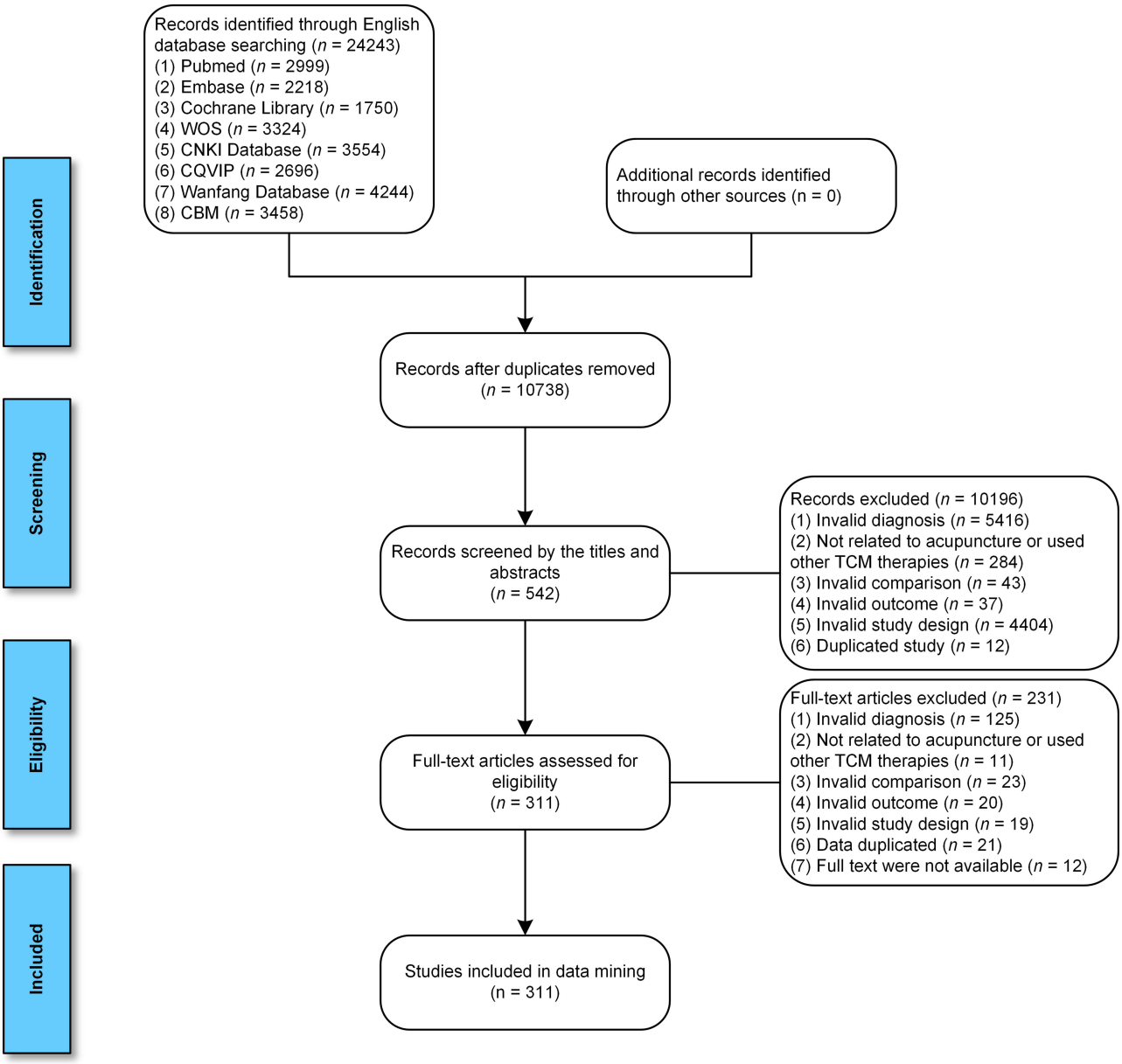

Figure 1 Study flow diagram.
Abbreviations: WOS, web of science; CNKI, China national knowledge infrastructure; CQVIP, Chongqing VIP database; CBM, Chinese biomedical database; TCM, traditional Chinese medicine.

co-occurrence matrix of acupoints (Figure 2). The most predominant paired acupoints were GV29 with GV20, which had the highest support rate of 56.41% and a co-occurrence frequency of 97.78%.

Network of Acupoints for MDD

Finally, we output 207 edge weights and 30 node acupoints through ARM to build the complicated network (Figure 3). The network model's average degree was 13.8, meaning that on average, each acupoint can coexist with 13.8 other acupoints. Only 3 acupoints had degrees of 25 or above (GV20, PC6, and SP36). PC6 was the most frequently used of these. The network diameter was 2 and the average path length was 1.524. When K-core ≥14, the top 3 core acupoints were GV20, PC6 and SP36, as shown in Figure 4.

Table 1 The Top Twenty Acupoints for MDD Treatment

Number	Acupoints	Frequency	Proportion (%)*
1	Baihui (GV20)	260	8.81
2	Taichong (LR3)	213	7.22
3	Neiguan (PC6)	200	6.78
4	Sanyinjiao (SP6)	194	6.57
5	Yintang (GV29)	183	6.20
6	Shenmen (HT7)	174	5.90
7	Zusanli (ST36)	141	4.78
8	Hegu (LI4)	90	3.05
9	Sishencong (EX-HN1)	82	2.78
10	Taixi (KI3)	80	2.71
11	Xinshu (BL15)	79	2.68
12	Ganshu (BL18)	65	2.20
13	Pishu (BL20)	60	2.03
14	Shenshu (BL23)	60	2.03
15	Shenting (GV24)	59	2.00
16	Fengchi (GB20)	55	1.86
17	Danzhong (CV17)	54	1.83
18	Fenglong (ST40)	52	1.76
19	Shuigou (GV26)	50	1.69
20	Qimen (LR14)	46	1.56

Note: *Proportion, the frequency of an acupoint as a percentage of the total frequency of all acupoints.

Table 2 Association Analysis of Meridians and Acupoints Used in MDD Treatment

Number	Meridian	Frequency	Proportion (%)*	Acupoints in Each Meridian		
				Number	Proportion (%)#	Acupoints (Frequency)
1	GV	677	22.94	20	13.61	GV20 (260), GV29 (183), GV24 (59), GV26 (50), GV14 (35), GV16 (24), GV23 (16), GV11 (12), GV17 (7), GV9 (6), GV15 (5), GV4 (4), GV18 (4), GV21 (4), GV19 (2), GV12 (2), GV6 (1), GV22 (1), GV25 (1), GV3 (1)
2	BL	330	11.18	22	14.97	BL15 (79), BL18 (65), BL20 (60), BL23 (60), BL17 (18), BL13 (10), BL19 (8), BL62 (8), BL21 (3), BL1 (3), BL52 (2), BL10 (2), BL14 (2), BL4 (2), BL22 (1), BL25 (1), BL7 (1), BL42 (1), BL44 (1), BL47 (1), BL49 (1), BL43 (1)
3	LR	313	10.61	9	6.12	LR3 (213), LR14 (46), LR2 (40), LR8 (6), LR5 (2), LR6 (2), LR13 (2), LR7 (1), LR1 (1)
4	SP	250	8.47	9	6.12	SP6 (194), SP9 (16), SP4 (12), SP10 (9), SP1 (9), SP3 (6), SP5 (2), SP21 (1), SP2 (1)
5	ST	247	8.37	12	8.16	ST36 (141), ST40 (52), ST25 (21), ST44 (13), ST37 (7), ST8 (5), ST6 (3), ST34 (1), ST24 (1), ST32 (1), ST41 (1), ST2 (1)
6	PC	244	8.27	7	4.76	PC6 (200), PC7 (18), PC8 (15), PC5 (8), PC9 (1), PC4 (1), PC3 (1)
7	HT	191	6.47	6	4.08	HT7 (174), HT5 (12), HT4 (2), HT6 (1), HT3 (1), HT9 (1)

(*Continued*)

Table 2 (Continued).

Number	Meridian	Frequency	Proportion (%)*	Acupoints in Each Meridian		
				Number	Proportion (%)#	Acupoints (Frequency)
8	CV	147	4.98	13	8.84	CV17 (54), CV12 (32), CV4 (23), CV6 (14), CV15 (7), CV10 (3), CV14 (3), CV24 (3), CV22 (3), CV23 (2), CV11 (1), CV1 (1), CV21 (1)
9	EX	143	4.85	9	6.12	EX-HN1 (82), EX-HN5 (29), JLSXX-QX (19), EX-UE11 (5), EX-B2 (4), EX-HN12 (1), EX-HN13 (1), EX-HN11 (1), EX-B8 (1)
10	GB	137	4.64	16	10.88	GB20 (55), GB34 (26), GB43 (14), GB8 (12), GB13 (5), GB11 (5), GB12 (5), GB40 (3), GB41 (2), GB39 (2), GB6 (2), GB15 (2), GB5 (1), GB14 (1), GB7 (1), GB37 (1)
11	KI	115	3.90	6	4.08	KI3 (80), KI6 (17), KI1 (12), KI14 (3), KI17 (2), KI4 (1)
12	LI	102	3.46	4	2.72	LI4 (90), LI11 (10), LI6 (1), LI10 (1)
13	SJ	28	0.95	6	4.08	SJ6 (12), SJ5 (8), SJ3 (4), SJ17 (2), SJ4 (1), SJ20 (1)
14	LU	22	0.75	6	4.08	LU11 (10), LU7 (5), LU9 (3), LU10 (2), LU1 (1), LU5 (1)
15	SI	5	0.17	2	1.36	SI3 (4), SI17 (1)

Notes: *Proportion, the percentage that a specific meridian frequency accounts for the total frequency of all meridians. #Proportion, the percentage that the number of acupoints in a meridian accounts for the total number of meridian acupoints.

Abbreviations: GV, the Governor Vessel; BL, the Bladder Meridian of Foot Taiyang; LR, the Liver Meridian of Foot Jueyin; SP, the Spleen Meridian of Foot Taiyin; ST, the Stomach Meridian of Foot Yangming; PC, the Pericardium Meridian of Hand Jueyin; HT, the Heart Meridian of Hand Shaoyin; CV, the Conception Vessel; EX, the Extraordinary acupoints; GB, the Gallbladder Meridian of Foot Shaoyang; KI, the Kidney Meridian of Foot Shaoyin; LI, the Large Intestine Meridian of Hand Yangming; SJ, the San Jiao Meridian of Hand Shaoyang; LU, the Lung Meridian of Hand Taiyin; SI, the Small Intestine Meridian of Hand Taiyang.

Table 3 Association Analysis of Specific Acupoints Used in MDD Treatment

Number	Specific Acupoints	Frequency	Proportion (%)*	Acupoints in Each Specific Acupoints		
				Amount of Acupoints	Proportion (%)#	Acupoints (Frequency)
1	Five-shu points	850	24.55	34	23.13	LR3 (213), HT7 (174), ST36 (141), KI3 (80), LR2 (40), GB34 (26), PC7 (18), SP9 (16), PC8 (15), GB43 (14), ST44 (13), SJ6 (12), KI1 (12), LU11 (10), LI11 (10), SP1 (9), PC5 (8), LR8 (6), SP3 (6), SI3 (4), SJ3 (4), LU9 (3), GB41 (2), SP5 (2), LU10 (2), HT4 (2), ST41 (1), PC9 (1), HT3 (1), LR1 (1), PC3 (1), SP2 (1), LU5 (1), HT9 (1)
2	Crossing points	803	23.19	29	19.73	GV20 (260), SP6 (194), GV24 (59), GB20 (55), GV26 (50), GV14 (35), CV12 (32), GV16 (24), CV4 (23), GB8 (12), GV17 (7), GV15 (5), GB12 (5), GB11 (5), ST8 (5), GB13 (5), CV10 (3), CV24 (3), CV22 (3), KI14 (3), BL1 (3), KI17 (2), GB6 (2), GB15 (2), CV23 (2), LU1 (1), GB14 (1), GB7 (1), CV1 (1)
3	Yuan-primary points	588	16.98	9	6.12	LR3 (213), HT7 (174), LI4 (90), KI3 (80), PC7 (18), SP3 (6), GB40 (3), LU9 (3), SJ4 (1)
4	Back-shu points	307	8.87	11	7.48	BL15 (79), BL18 (65), BL20 (60), BL23 (60), BL17 (18), BL13 (10), BL19 (8), BL21 (3), BL14 (2), BL22 (1), BL25 (1)
5	Luo-connecting points	302	8.72	12	8.16	PC6 (200), ST40 (52), SP4 (12), HT5 (12), SJ5 (8), CV15 (7), LU7 (5), LR5 (2), KI4 (1), LI6 (1), GB37 (1), SP21 (1)
6	Eight-confluent points	256	7.39	8	5.44	PC6 (200), KI6 (17), SP4 (12), SJ5 (8), BL62 (8), LU7 (5), SI3 (4), GB41 (2)

(*Continued*)

Table 3 (Continued).

Number	Specific Acupoints	Frequency	Proportion (%)*	Acupoints in Each Specific Acupoints		
				Amount of Acupoints	Proportion (%)#	Acupoints (Frequency)
7	Front-mu points	182	5.26	8	5.44	CV17 (54), LR14 (46), CV12 (32), CV4 (23), ST25 (21), CV14 (3), LR13 (2), LU1 (1)
8	Eight-influential points	137	3.96	7	4.76	CV17 (54), CV12 (32), GB34 (26), BL17 (18), LU9 (3), LR13 (2), GB39 (2)
9	Lower he-sea points	33	0.95	2	1.36	GB34 (26), ST37 (7)
10	Xi-cleft points	5	0.14	4	2.72	LR6 (2), ST34 (1), HT6 (1), PC4 (1)

Notes: *Proportion, the percentage of the frequency of a specific acupoint to the total frequency of all specific acupoints. #Proportion, The amount of a specific acupoint as a percentage of the total amount of specific acupoints.

Abbreviations: GV, the Governor Vessel; BL, the Bladder Meridian of Foot Taiyang; LR, the Liver Meridian of Foot Jueyin; SP, the Spleen Meridian of Foot Taiyin; ST, the Stomach Meridian of Foot Yangming; PC, the Pericardium Meridian of Hand Jueyin; HT, the Heart Meridian of Hand Shaoyin; CV, the Conception Vessel; GB, the Gallbladder Meridian of Foot Shaoyang; KI, the Kidney Meridian of Foot Shaoyin; LI, the Large Intestine Meridian of Hand Yangming; SJ, the San Jiao Meridian of Hand Shaoyang; LU, the Lung Meridian of Hand Taiyin; SI, the Small Intestine Meridian of Hand Taiyang.

Table 4 Association Analysis of Body Parts and Acupoints Used in MDD Treatment

Body Part	Frequency	Proportion (%)*	Acupoints in Each Body Part		
			Amount of Acupoints	Proportion (%)#	Acupoints (Frequency)
Lower limbs	896	30.36	33	22.45	LR3 (213), SP6 (194), ST36 (141), KI3 (80), ST40 (52), LR2 (40), GB34 (26), KI6 (17), SP9 (16), GB43 (14), ST44 (13), KI1 (12), SP4 (12), SP10 (9), SP1 (9), BL62 (8), ST37 (7), SP3 (6), LR8 (6), GB40 (3), GB41 (2), SP5 (2), LR5 (2), LR6 (2), GB39 (2), ST34 (1), LR7 (1), ST32 (1), ST41 (1), KI4 (1), LR1 (1), GB37 (1), SP2 (1)
Head, face, and neck	867	29.38	42	28.57	GV20 (260), GV29 (183), EX-HN1 (82), GV24 (59), GB20 (55), GV26 (50), EX-HN5 (29), GV16 (24), JLSXX-QX (19), GV23 (16), GB8 (12), GV17 (7), GB13 (5), ST8 (5), GV15 (5), GB11 (5), GB12 (5), GV18 (4), GV21 (4), BL1 (3), CV22 (3), CV24 (3), ST6 (3), BL4 (2), GB6 (2), GB15 (2), GV19 (2), SJ17 (2), BL10 (2), CV23 (2), SI17 (1), SJ20 (1), EX-HN11 (1), ST2 (1), BL7 (1), GB5 (1), EX-HN13 (1), EX-HN12 (1), GB7 (1), GB14 (1), GV22 (1), GV25 (1)
Upper limbs	592	20.06	28	19.05	PC6 (200), HT7 (174), LI4 (90), PC7 (18), PC8 (15), SJ6 (12), HT5 (12), LU11 (10), LI11 (10), SJ5 (8), PC5 (8), LU7 (5), EX-UE11 (5), SJ3 (4), SI3 (4), LU9 (3), LU10 (2), HT4 (2), PC9 (1), HT6 (1), LI6 (1), PC4 (1), LI10 (1), SJ4 (1), HT3 (1), PC3 (1), LU5 (1), HT9 (1)
Back and lumbar	380	12.88	26	17.69	BL15 (79), BL18 (65), BL20 (60), BL23 (60), GV14 (35), BL17 (18), GV11 (12), BL13 (10), BL19 (8), GV9 (6), GV4 (4), EX-B2 (4), BL21 (3), BL52 (2), BL14 (2), GV12 (2), GV6 (1), BL22 (1), BL25 (1), EX-B8 (1), BL42 (1), BL44 (1), BL47 (1), BL49 (1), BL43 (1), GV3 (1)
Chest and abdomen	215	7.29	17	11.56	CV17 (54), LR14 (46), CV12 (32), CV4 (23), ST25 (21), CV6 (14), CV15 (7), KI14 (3), CV14 (3), CV10 (3), KI17 (2), LR13 (2), LU1 (1), ST24 (1), CV11 (1), CV21 (1), SP21 (1)

Notes: *Proportion, the frequency of acupoints in a specific body part as a percentage of the total frequency of acupoints in all body parts. #Proportion, the amount of acupoints in a specific body part as a percentage of the total amount of acupoints in the body part.

Abbreviations: GV, the Governor Vessel; BL, the Bladder Meridian of Foot Taiyang; LR, the Liver Meridian of Foot Jueyin; SP, the Spleen Meridian of Foot Taiyin; ST, the Stomach Meridian of Foot Yangming; PC, the Pericardium Meridian of Hand Jueyin; HT, the Heart Meridian of Hand Shaoyin; CV, the Conception Vessel; EX, the Extraordinary acupoints; GB, the Gallbladder Meridian of Foot Shaoyang; KI, the Kidney Meridian of Foot Shaoyin; LI, the Large Intestine Meridian of Hand Yangming; SJ, the San Jiao Meridian of Hand Shaoyang; LU, the Lung Meridian of Hand Taiyin; SI, the Small Intestine Meridian of Hand Taiyang.

Table 5 The Top ten Acupoint Combinations in MDD Treatment

Number	Combination of Acupoints	Support (%)	Confidence (%)	Lift
1	GV29 → GV20	56.41	97.78	1.20
2	GV20 → PC6	52.24	64.17	1.12
3	LR3 → GV20	51.60	85.64	1.05
4	SP6 → GV20	46.15	91.14	1.12
5	HT7 → GV20	43.91	86.16	1.06
6	SP6 → PC6	40.38	79.75	1.40
7	LR3 → PC6	39.74	65.96	1.16
8	HT7 → LR3	39.74	77.99	1.29
9	HT7 → PC6	39.10	76.73	1.34
10	SP6 → GV20, PC6	37.50	74.05	1.42

Notes: Support of A → B indicated that the prescriptions containing both acupoint A and acupoint B account for the total ones; confidence of A → B displayed that the prescriptions containing both acupoint A and acupoint B account for the ones containing acupoint A.
Abbreviations: GV, the Governor Vessel; PC, the Pericardium Meridian of Hand Jueyin; LR, the Liver Meridian of Foot Jueyin; SP, the Spleen Meridian of Foot Taiyin; HT, the Heart Meridian of Hand Shaoyin.

Hierarchical Cluster Analysis of Acupoints for MDD

A total of 289 literature were selected for acupoint selection based on pattern identification, involving a total of 33 pattern identifications (Supplementary Material 2). By hierarchical cluster analysis, the acupoints were clustered into 5 clusters based on distances less than 0.04: Cluster 1 included ST36, BL15, SP6 and BL20; Cluster 2 included LR3 and LR14; Cluster 3 included KI3, BL18 and BL23; Cluster 4 included LR2, HT7, PC6, LI4, CV17, GB34, GV20, GV29 and SJ6; the other acupoints were clustered into Cluster 5 (Figure 5).

Adverse Effects of Acupuncture for MDD

84 publications mentioned adverse effects (AEs) of the trial. There were 33 types of AEs in the intervention group and 27 types of AEs in the control group (Table 6). Although more types of AEs occurred in the intervention group than in the control group, the rate of AEs was higher in the control group than in the intervention group for the same type of AEs. The more AEs that occurred in the intervention group were mainly from acupuncture, such as acupuncture pain, acupuncture dizziness, mild burns, and subcutaneous hematoma.

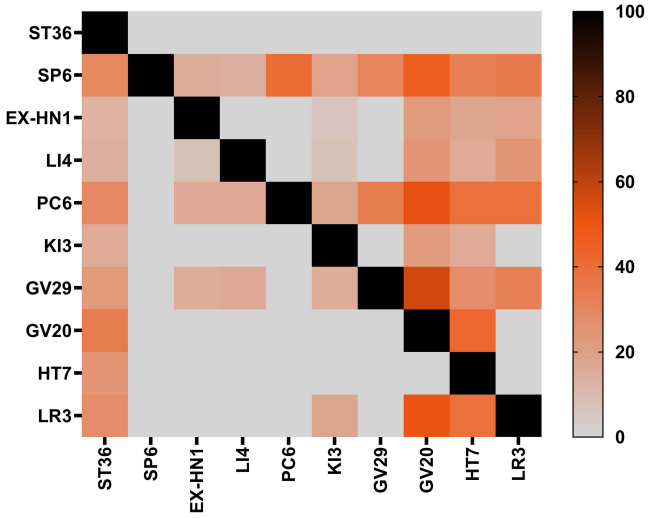

Figure 2 Cooccurrence matrix of acupoints.

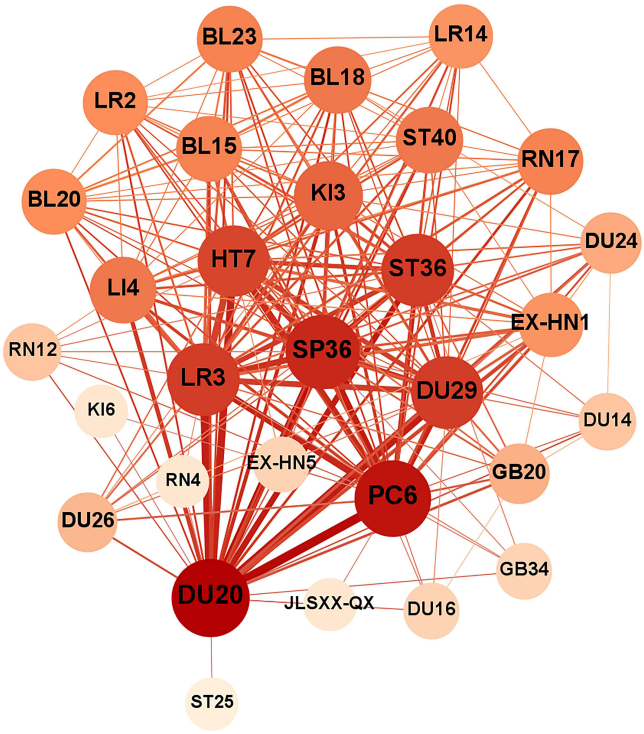

Figure 3 Acupoints association network of acupuncture for MDD.

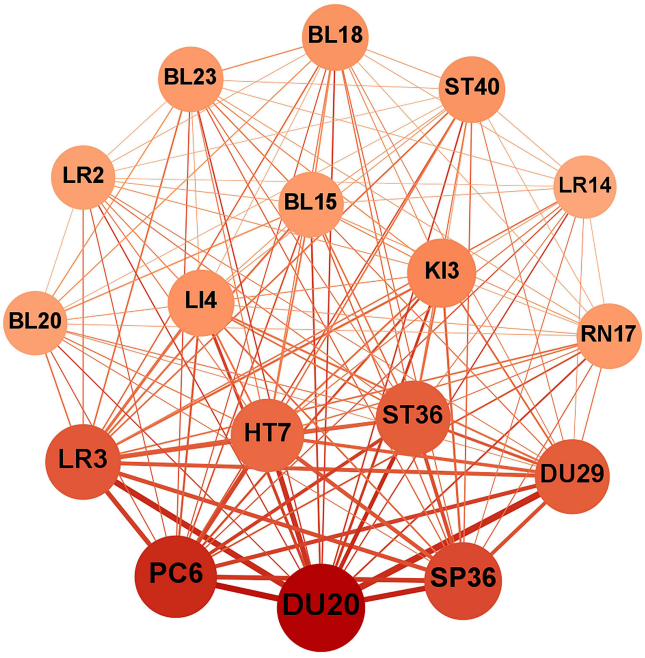

Figure 4 Core acupoints network of acupuncture for MDD.

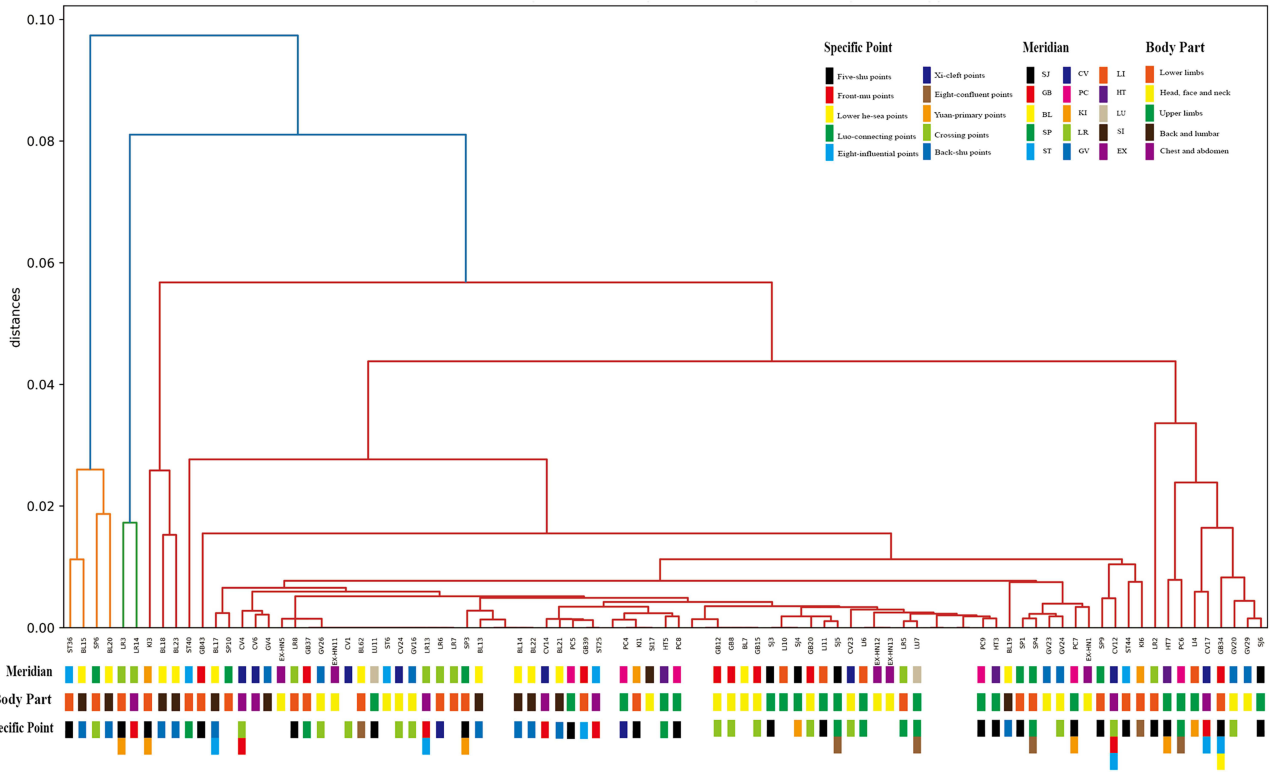

Figure 5 Hierarchical clustering dendrogram of acupoints for MDD.

Abbreviations: SJ, the San Jiao Meridian of Hand Shaoyang; GB, the Gallbladder Meridian of Foot Shaoyang; BL, the Bladder Meridian of Foot Taiyang; SP, the Spleen Meridian of Foot Taiyin; ST, the Stomach Meridian of Foot Yangming; CV, the Conception Vessel; PC, the Pericardium Meridian of Hand Jueyin; KI, the Kidney Meridian of Foot Shaoyin; LR, the Liver Meridian of Foot Jueyin; GV, the Governor Vessel; LI, the Large Intestine Meridian of Hand Yangming; HT, the Heart Meridian of Hand Shaoyin; LU, the Lung Meridian of Hand Taiyin; SI, the Small Intestine Meridian of Hand Taiyang; EX, the Extraordinary acupoints.

Acupuncture Methods and Treatment Course for MDD

A total of 330 intervention groups were included in the study, including 210 groups for manual acupuncture (MA) and 112 groups for electroacupuncture (EA), and 8 groups for warm acupuncture (WA). Treatment was administered most frequently 7 times per week (30.55%) and for 42 days (36.53%) on average (Table 7).

Table 6 Adverse Effects of Acupuncture for MDD in the Intervention Group Compared to the Control Group

Adverse Effects		Intervention Group		Control Group	
		Frequency	Proportion (%)	Frequency	Proportion (%)
Behavioral Toxicity	Excitement or arousal	1	0.15	5	0.73
	Decreased activity	2	0.29	4	0.58
	Insomnia	21	3.07	38	5.55
	Sleepiness	9	1.31	21	3.07
Nervous System	Tremor	3	0.44	11	1.61
	Restlessness	0	0.00	3	0.44
	Dizziness and headache	38	5.55	55	8.03
	Dry mouth	34	4.96	49	7.15
Vegetative Nervous System	Blurred vision	4	0.58	11	1.61
	Constipation	23	3.36	39	5.69
	Sweating	1	0.15	7	1.02
	Nausea and vomiting	29	4.23	52	7.59
	Diarrhea	9	1.31	12	1.75

(*Continued*)

Table 6 (Continued).

Adverse Effects		Intervention Group		Control Group	
		Frequency	Proportion (%)	Frequency	Proportion (%)
Cardiovascular System	Lower blood pressure	4	0.58	9	1.31
	Heartburn and palpitations	6	0.88	22	3.21
	High blood pressure	2	0.29	1	0.15
	Electrocardiogram abnormalities	4	0.58	5	0.73
	Heart attack	1	0.15	0	0.00
Other	Itchy skin or rash	3	0.44	10	1.46
	Weight gain	5	0.73	5	0.73
	Loss of appetite or anorexia	22	3.21	37	5.40
	Abnormal liver function	2	0.29	3	0.44
	Difficulty in urination	5	0.73	7	1.02
	Anxiety	2	0.29	5	0.73
	Fatigue	6	0.88	8	1.17
	Sexual dysfunction	2	0.29	8	1.17
	Chest tightness	1	0.15	2	0.29
	Menstrual disorders	1	0.15	1	0.15
	Mild burns	2	0.29	0	0.00
	Acupuncture pain	3	0.44	0	0.00
	Subcutaneous hematoma	3	0.44	0	0.00
	Acupuncture dizziness	6	0.88	0	0.00
	Hospitalization after external stimulation	1	0.15	0	0.00

Table 7 The Top Seven Treatment Frequency and Duration of Treatment for MDD

Number	Treatment Frequency (Times / Week)	Frequency	Proportion (%)	Duration of Treatment (Days)	Frequency	Proportion (%)
1	7	95	30.55	42	118	36.53
2	5	81	26.05	56	70	21.67
3	3	72	23.15	28	47	14.55
4	6	41	13.18	30	14	4.33
5	2	17	5.47	60	11	3.41
6	14	4	1.29	84	11	3.41
7	4	1	0.32	90	9	2.79

Acupoints Used in Various Outcomes

We counted the various outcomes using efficiency with the acupoints they used. The most frequently used medications to reduce the severity of depression as measured by HAMD were GV20, LR3, and PC6; PC6, GV20, and GV29 were used most often to improve the degree of depression evaluated with SDS; CV6, CV12, CV4 and CV10 are several Ren meridian acupoints that have been utilized to reduce depression as measured by MADRS. To decrease the use of antidepressants, ST36, SP6, LR3, HT7, GV20, PC6, and etc. were employed. See Supplementary Material 3 for details.

Discussion

Currently, there are various acupoint prescriptions for the treatment of MDD with no uniform standard. From the perspective of RCT, the development of a standard effective MDD prescription may not only be beneficial in reducing confounding factors in the study but also necessary for optimizing the treatment protocol. Our study used data mining to

perform a secondary analysis of literary studies to explore the characteristics of acupoint prescriptions for acupuncture for MDD, which may help to develop a standard effective MDD acupoint prescription.

Our study found that acupoints for MDD involve the 14 meridian acupoints and extraordinary acupoints, indicating that MDD is not a single meridian lesion, but is related to multiple internal organs and meridians. The result of the study was consistent with the theory of traditional Chinese medicine (TCM). TCM believes that "the heart is the master of the mind" and "the five organs hide the mind", MDD is an emotional disorder and its disease location is in the mind. In addition, we found that a higher percentage of acupoints were applied to the Governor Vessel and the Bladder Meridian of Foot-Taiyang, suggesting that acupoints located in the Yang meridian may play an important role in the treatment of MDD. According to TCM theory, MDD is a yin disease and the pathogenesis is an imbalance of yin and yang due to the impairment of yang energy, so the treatment should focus on regulating yang energy, so the yang meridian is selected to treat MDD. In our study, we found that most amount of acupoints are located on the head, face, and neck. According to TCM, "the brain is the capital of the mind" and the head is the confluence of the Yang meridians, so the intervention of head acupoints can be used to treat MDD.

The results of the study showed that the most central acupoint was GV20, which could theoretically be used as a key acupoint for the treatment of MDD, based on the local therapeutic properties of the acupoint. It has been found that electroacupuncture stimulation of GV20 can down-regulate functional connectivity (FC) between important brain areas mainly involving the affective network, default mode network, and pain matrix in MDD patients with abnormal intrinsic. This suggests that GV20 electroacupuncture has a positive effect on eliminating formatted negative emotions and mediating memories associated with depression.[23,24] In our study, GV29 combined with GV20 is proved to be the most common combination of acupoints for the treatment of MDD. A study found that electroacupuncture interventions GV20 and GV29 can improve the behavioral responses in an animal model of chronic unpredictable mild stress (CUMS)-induced depression, including reduced exercise, reduced sucrose intake, and weight loss.[25] The above mechanism may be the reason for the combination of GV29 and GV20 in the treatment of MDD. In addition, we found that GV20 is also often combined with PC6 or LR3 for MDD. In this study, GV20, LR3, and PC6 were found to be the top 3 most used acupoints. A preclinical study found antidepressant effects of electroacupuncture LR3 on behavioral effects by increasing expression of the glial glutamate transporter protein excitatory amino acid glutamate transporter 2 (EAAT2) in the hippocampus and prefrontal cortex.[26] Acupuncture stimulation of PC6 significantly reduced depression-like behavior and increased neuropeptide Y expression in the hypothalamus in a rat model of chronic corticosterone-induced depression.[27] We were pleasantly surprised to find that both PC6 and LR3 are both Jueyin meridian acupoints. Jueyin is the final stage of Yin development and begins to transform into the Yang aspect. It happens that MDD is a yin disease, so MDD can be treated by stimulating the Jueyin meridian acupoints to regulate the yin and yang. Therefore, the local acupoint GV20 on the head was combined with the distal acupoints PC6 or LR3 on the extremities to treat MDD by regulating the Qi of the Pericardium meridian of hand-Jueyin and liver meridian of foot-Jueyin while regulating the mind.

We found that acupoints in the lower limbs were used much more frequently than those in other parts of the body, suggesting that distal acupoints have an important role in the treatment of MDD. Distal healing is characteristic of the acupoints on the fourteen meridians. These meridian acupoints can be used to treat not only diseases of regional tissues, but also the internal organs, tissues, and organs associated with the meridians in which they are located.

By analyzing the properties of the acupoints, we found that the most used specific points are the five-shu points. The results of the study found that the use of specific acupoints in the treatment of MDD exceeded the use of non-specific acupoints in both number and frequency. In addition to five-shu points, crossing points, yuan-primary points, and back-shu points are often used to treat MDD. Crossing points are acupoints located at the intersection of two or more meridians. MDD involves problems with multiple meridians, so multiple meridians can be adjusted at the same time by stimulating the crossing points. Besides, the yuan-primary points are the site where the Qi of the internal organs is injected through the Sanjiao and is closely related to the internal organs. Therefore, diseases of the zang-fu organs can be treated by acupuncture at the yuan-primary points.

In the clinical practice of acupuncture treatment, the selection and combination of acupoints based on pattern identification is crucial to the therapeutic effect. This study used hierarchical cluster analysis to analyze the similarity of acupoints selected based on pattern recognition for MDD treatment. TCM theory suggests that MDD initially presents

as an "excess" pattern, mainly caused by liver Qi stagnation, and over time becomes a "deficiency" pattern, caused by deficiency of Qi and Blood and imbalance of Yin and Yang. Under the principle of "treating both the symptoms and the root causes", TCM treatment of MDD emphasizes draining the liver Qi to treat the symptoms, and tonifying Qi and blood and regulating Yin and Yang to treat the root cause. This study identified several acupoints clusters for the treatment of MDD, each with a distinct therapeutic focus. In Cluster 4, HT7, PC6, GV20 and GV29 focus on tonifying the Shen; LI4, CV17, LR2, GB34 and SJ6 have the effect of tonifying Qi. LR3 and LR14 in Cluster 2 located on the liver meridian, were found to have the effect of draining the liver and regulating Qi. Cluster 1, comprising ST36, BL15, SP6 and BL20, was found to have good effects in strengthening the heart and spleen. KI3, BL18 and BL23 in Cluster 3 performed well in the treatment of MDD in the Yin deficiency of liver and kidney pattern. While acupoints in Cluster 5 were found to be subdivided into several subcategories with high similarity and low frequency, probably due to the small number of literature involving fewer witnessed types of selected acupoints, such as SP10 and BL17 can be used to treat blood stasis pattern of MDD; CV4, CV6, and GV4 have the effect of cultivating the vital energy, etc. The study findings suggest that acupoints can be selected and combined based on their therapeutic focus and specific pattern identification, in line with the principles of Traditional Chinese Medicine.

In terms of safety, although more types of AEs occurred in the intervention group than in the control group, the AEs that occurred more in the intervention group were mainly from acupuncture, such as acupuncture prick pain, fainting, mild burns, and hematomas. These side effects were not serious and would resolve with appropriate intervention or rest. In addition, we found that for the same type of AEs, the incidence of AEs was higher in the control group than in the intervention group, which to some extent suggests that acupuncture may reduce the incidence of AEs caused by drugs. Some clinical studies and meta-analyses have found acupuncture is effective in reducing antidepressant side effects and reducing the dose of antidepressants.[28–31]

This study found that acupuncture for MDD used MA more than EA, and a few studies utilized WA. Results from a clinical trial showed that either MA or EA combined with selective serotonin reuptake inhibitors (SSRIs) were effective in improving depressive symptoms in patients with moderate to severe depression. The difference was that MA combined with SSRIs showed an advantage in improving sluggishness, while EA combined with SSRIs showed an advantage in improving anxiety, somatization, and sleep disorders.[32] The study showed that WA significantly improved anxiety and depression-like behaviors in rats with chronic restraint stress, and increased the level of monoamine transmitters in the brain, whose mechanism of action may be related to the regulation of the BDNF/TrkB pathway.[33]

However, this study still has the following limitations and our results should be interpreted with caution. First, the non-uniform outcome measures and acupuncture stimulation methods included in the studies may affect the assessment of the therapeutic effect contributed by the acupoints. Second, in terms of literature inclusion, the quality of some non-RCT studies included in the analysis was difficult to assess and may affect the objectivity of the results. In addition, this study only included literature reporting positive results, as it focused exclusively on identifying effective acupoints for MDD treatment. Third, although this study investigated the TCM theory of clustering acupoints according to pattern identification, this analysis was performed on the basis of existing databases. The specificity of acupoints for MDD syndrome was not studied in depth in this study, and future research could be conducted to address the specificity of pattern identification/syndrome and acupoints for MDD.

Conclusion

Through data mining, we determined the frequency and characteristics of the use of acupoints in MDD treatment. GV20, LR3, PC6, SP6, and GV29 were the most frequently used. Acupoints of the Yang meridian were used more frequently than those of the Yin meridian, with the most frequent applications being those of the Governor meridian. The most used specific acupoints were five-shu points. In addition, GV29 combined with GV20 was the most frequently used acupoint group. The core acupoints used for MDD were GV20, PC,6 and SP36. The different acupoint clusters for the treatment of MDD were identified by hierarchical cluster analysis, each with a specific therapeutic focus. The most used method of acupuncture was MA. The frequency of treatment was mostly 7 times a week and the duration of treatment was mostly 42 days. However, further clinical/experimental studies are needed to demonstrate the significance of this concept and approach.

Abbreviations

MDD, major depressive disorder; Embase, Excerpt Medical Database; WOS, Web of Science; CBM, Chinese Biomedical Database; CNKI, China National Knowledge Infrastructure; CQVIP, Chongqing VIP database; RCTs, randomized control trials; CCTs, clinical control trials; CCMD, the Chinese Classification of Mental Disorders; ICD, the International Classification of Diseases; DSM, The Diagnostic and Statistical Manual of Mental Disorders; ARM, association rule mining; AEs, adverse effects; MA, manual acupuncture; EA, electroacupuncture; WA, warm acupuncture; HAMD, the Hamilton Depression Scale; SDS, the Self-Rating Depression Scale; MADRS, the Montgomery and Asberg Depression Rating Scale; TCM, traditional Chinese medicine; CUMS, chronic unpredictable mild stress; EAAT2, excitatory amino acid glutamate transporter 2; SSRIs, selective serotonin reuptake inhibitors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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