Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Clinical Guideline (CANMAT 2016) Discordance of Medications for Patients with Major Depressive Disorder in China

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Objective: This survey aims to explore the current medical treatment of major depressive disorder (MDD) in China and match its degree with Canadian Network for Mood and Anxiety Treatments (CANMAT).

Methods: A total of 3275 patients were recruited from 16 mental health centers and 16 general hospitals in China. Descriptive statistics presented the total number and percentage of drugs, as well as all kinds of treatments.

Results: Selective serotonin reuptake inhibitors (SSRIs) accounted for the largest proportion (57.2%), followed by serotonin-noradrenaline reuptake inhibitors (SNRIs) (22.8%) and mirtazapine (7.0%) in the first therapy, while that of SNRIs (53.9%) followed by SSRIs (39.2%) and mirtazapine (9.8%) in the follow-up therapy. An average of 1.85 medications was administered to each MDD patient.

Conclusion: SSRIs were the first choice in the first therapy, while the proportion of those drugs decreased during the follow-up therapy and were replaced by SNRIs. Plenty of combined pharmacotherapies were directly selected as the first trial of patients, which was inconsistent with guideline recommendations.

Keywords: major depressive disorder, Chinese, guideline, antidepressants

A successful treatment for major depressive disorder (MDD) depends on early diagnosis, proper treatment in time, and relieving symptoms. Antidepressants are acknowledged as the main treatment method for moderate to major depression during outpatient treatment. It is advocated that the second-generation antidepressants (SSRIs, SNRIs, NaSSA, and so on) are the first-line recommendations with high safety and promising efficacy.[1] With a high failure rate of initial therapy, switching to another antidepressant is one of the alternative treatment strategies.[2]

With growing attention to evidence-based medicine in psychiatry, a number of clinical guidelines have been published. These guidelines were well-designed to help clinicians make the right clinical decisions. It is worth noticing that the CANMAT attracts compelling attention in China.[3–5] Compared to the 2015 Guidelines for Prevention and Treatment of Depressive Disorder in China (PTDDC), second edition,[6] the CANMAT guideline has been more widespread and updated. Furthermore, patients' adherences to the CANMAT guideline recommendations are related to a greater remission in symptoms and improvement in outcomes of MDD.[7] Moreover, PTDDC and CANMAT are highly consistent in the description of medications except for quetiapine or traditional Chinese medicine (TCM). Therefore, we compared both guidelines to the present medications of MDD for the convenience of domestic and foreign readers.

Received: 13 December 2022
Accepted: 23 March 2023
Published: 12 April 2023

From a more macroscopic perspective, we need to know that the purpose of the guidelines initially informed mental healthcare provision in China.[8] It should be more applicable to basic medical institutions such as community mental health services. Evidence-based graded recommendations for quality assurance in mental health were developed, which should next be implemented and evaluated for feasibility and validity in China. It would lead to the necessary investigation of the current status of medications in China since the feedback system has not been established yet.

The CANMAT guideline has three levels of recommendations. A first-line treatment recommendation indicates good-quality evidence (Meta-analysis with randomized controlled trials) as well as clinical utility. However, treatments with good-quality evidence may be downgraded to second- or third-line recommendations because of safety or side effect profiles.[9]

The National Survey on Symptomatology of Depression (NSSD) involved the commonly used antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), mirtazapine and bupropion, which were recommended as the first-line treatment strategy, as well as tricyclic antidepressants (TCAs), trazodone and quetiapine as the second-line recommendations, and monoamine oxidase inhibitors (MAOIs) as the third. Furthermore, antipsychotic and antidepressant cotreatment for MDD with psychotic features (Level 1) and benzodiazepines for clinical specifiers and dimensions of MDD with catatonic features (Level 3) are also recommended.[9] Nowadays, the third-line treatment is rarely used in China because of some potential side effects and drug–drug interactions.[10]

There is evidence that greater provider adherence to guideline recommendations was associated with greater treatment effectiveness[11] toward improving the outcome of the disease. However, China is a developing country with an expansive land, a large population, and an extremely uneven distribution of mental health resources or services.[12] In particular, the development of psychiatry is relatively lagging behind. Therefore, this survey aims to explore the current status of MDD treatment in China to inform the decision-making and resource allocation policy in the future. Antidepressant treatment is supposed to be consistent with the guidelines. We already have two editions of the guidelines[13] that are significantly influenced by the CANMAT. In this study, we tried to focus on the CANMAT concordance for the treatment of MDD in China.

Methods

Study Design

The *NSSD* was blueprinted to investigate the magnitude of symptoms across a widespread symptomatology[14] within and outside the DSM framework and medical treatment of MDD with guidelines concordance. The data were constructed based on the following materials for decades (Chinese version).

(1) The diagnostic criteria derived from three diagnostic systems [DSM-IV /DSM-5, ICD-10, and the Chinese Classification of Mental Disorders, 3rd version (CCMD-3)].[15] The DSM system has been widely accepted in clinical research fields in China for decades, while to some extent a formal psychiatric diagnosis cannot be made based on the ICD system. The ICD-10 is currently accepted in routine clinics in China according to insurance policies and medical regulations. The CCMD system had been abolished nearly a decade ago, and there was no major discrepancy in the diagnostic requirements of depression from the ICD system.[16,17]

(2) A variety of literatures examining the classic description of depression from Chinese textbooks and the clinical presentation of MDD represent Chinese psychiatric experts' opinions about the important signs and symptoms of depression, as well as diagnosis and treatment guidelines with Chinese characteristics. We list commonly used medications recommended by the clinical guidelines. See Table 1.

The study protocol was designed by team experts and a discussion group composed of 10 senior psychiatrists who have sophisticated expertise in psychiatric clinics and research on depression in China. Then the consensus was reached.

Settings and Participants

Participants' data were consecutively collected from 16 mental health centers and psychiatric departments of 16 general hospitals within 22 cities of 15 provinces, across all 7 administrative regions (ie, East, Southwest, South, Northwest, North and Northeast China) of mainland China from 07/2014 to 02/2015. They are Beijing Anding Hospital, Peking University Sixth Hospital, Beijing Huilongguan Hospital, Beijing Chaoyang Hospital, Shanghai Mental Health Center, Shanghai Jinshan Health Center,

Table 1 Comparison of Recommendation Level Between CANMAT 2016 and PTDDC 2015

	CANMAT 2016	PTDDC 2015
SSRIs	First line	First line
SNRIs	First line	First line
Mirtazapine	First line	First line
Bupropion	First line	First line
TCAs	Second line	Second line
Trazodone	Second line	Second line
Quetiapine	Second line	/
Benzodiazepines	Second line	/
Shuganjieyu capsule	/	Second line
St John's Wort	/	Second line

Abbreviations: CANMAT 2016, Canadian Network for Mood and Anxiety Treatments 2016 Clinical Guidelines; PTDDC 2015, 2015 Guidelines for Prevention and Treatment of Depressive Disorder in China, second edition.

Shanghai Ruijin Hospital, Shanghai Tenth People's Hospital, Zhejiang Provincial Tongde Hospital, Changshu Third People's Hospital, No. 102 Hospital of People's Liberation Army, the Seventh People's Hospital of Dalian, Guangzhou Brain Hospital, the Third People's Hospital of Huzhou, Nanjing Brain Hospital, Mental Health Center of Shantou University, Shenzhen Kangning Hospital, Suzhou Guangji Hospital, the Third People's Hospital of Taicang, Jiangsu Provincial People's Hospital, West China Hospital of Sichuan University, Guangdong Provincial People's Hospital, Tianjin Medical University General Hospital, the First Affiliated Hospital of Harbin Medical University, Hubei Provincial People's Hospital, the First Affiliated Hospital of Kunming Medical University, the First Hospital of Shanxi Medical University, First Affiliated Hospital of China Medical University, the Second Affiliated Hospital Zhejiang University, the Second Xiangya Hospital of Central South University, Xijing Hospital and Nanjing Drum Tower Hospital. The institutional review boards at each site approved the study. This study was approved by the Institutional Ethical Committee for Clinical Research of Shanghai Mental Health Center (2012BAI01B04), Shanghai, China. The research evaluators at each multicenter had undergone consistency training for this clinical investigation. Besides, all participants provided written informed consent prior to research entry according to the Declaration of Helsinki after the treatment had been chosen.

Inclusion and Exclusion Criteria

Participants aged ≥18 years old, currently under a major depressive episode, who were seeking care in inpatient or outpatient psychiatric departments, received screening interviews by trained research evaluators. Those who met DSM-IV TR criteria for the current episode of MDD would be eligible for inclusion as decided by a research psychiatrist. Overall exclusion criteria included (1) an imminent risk for suicide or homicide; (2) a lifetime diagnosis of bipolar disorder; (3) female patients during pregnancy or postpartum period; or (4) reception of modified electroconvulsive therapy within a month prior to study entry.

Variables

We divided the participants' data into the first visit patient group and the follow-up visit patient group. First-visit patients were recorded only once, whereas follow-up patients provided medication data and information for their first therapy and current therapy. The demographic information of recruited patients was collected with a self-designed case report form including age, gender, education level, number of episodes, treatment-resistant depression, marital status, vocational status, patient setting, and ethnicity.

Statistical Analyses

Statistical analyses were performed with SPSS version 17.0. Descriptive statistics include total and percentage of medicine use, as well as drug types. Skewed distribution data were represented by median (IQR).

Results

Sociodemographic Factors and Clinical Characteristics of the MDD Patients

A total of 3516 patients who suffered from significant depressive symptoms or a depressive episode were prescreened. After the clinical screening, 241 patients did not meet the criteria for a current major depressive episode or did not finish the assessment. Finally, 3275 patients finished the study and were collected in the present analysis except for six missing records in the statistics. See Table 2.

Comparison of the Current Status of Antidepressant Treatment Between First Therapy and Follow-Up Therapy Groups in 32 Centers

For the patients with switching treatment, the total course was 3.42 (±4.56) months. In the first-line recommendations, SSRIs accounted for the largest proportion (57.2%), followed by SNRIs (22.8%) and mirtazapine (7.0%) in the first therapy, while in the follow-up therapy the proportion were SNRIs (53.9%) followed by SSRIs (39.2%) and mirtazapine (9.8%). In the second-line recommendations, TCAs accounted for the largest proportion (3.6%), followed by trazodone

Table 2 Demographic and Clinical Information of the MDD Patients (n = 3269)

	Total (n = 3269)	**First visit Patient (n = 1346)**	**Follow-up Visit Patient (n = 1923)**
Age [Median(p25, p75)]	39.8 (31.0,50.8)	38.4 (29.2,45.9)	42.8 (32.6,53.5)
Gender (n, %)			
Male	1289 (39.4)	550 (40.9)	739 (38.4)
Female	1973 (60.4)	791 (58.8)	1182 (61.4)
Missing data	7 (0.2)	5 (0.4)	2 (0.1)
Education level (n, %)			
High School graduated	1840 (56.3)	705 (52.4)	1135 (59.0)
College degree	1185 (36.2)	551 (40.9)	634 (33.0)
Postgraduate degree	114 (3.5)	55 (4.1)	59(3.1)
Missing data	130 (4.0)	35 (2.6)	95 (4.8)
Number of episodes [Median(p25, p75)]	1 (1,2)	1 (1,1)	2 (1,3)
Treatment resistant depression (n, %)	153 (4.7)	14 (1.0)	139 (7.2)
Marrital status (n, %)			
Unmarried	671 (20.5)	332 (24.7)	339 (17.6)
Married	2384 (72.9)	944 (70.1)	1440 (74.9)
Divorced	109 (3.3)	39 (2.9)	70 (3.6)
Widowed	69 (2.1)	16 (1.2)	53 (2.8)
Missing data	36 (1.1)	15 (1.1)	21 (1.1)
Vocational status (n, %)			
Unemployed	749 (22.9)	273 (20.3)	476 (24.8)
Employed	1779 (54.4)	842 (62.6)	937 (48.7)
Student	200 (6.1)	95 (7.1)	105 (5.5)
Retired	443 (13.6)	104 (7.7)	339 (17.6)
Missing data	98 (3.0)	32 (2.4)	66 (3.4)
Patient setting (n, %)			
Outpatient	2283 (69.8)	1137 (84.5)	1146 (59.6)
Inpatient	982 (30.0)	208 (15.5)	774 (40.2)
Missing data	4 (0.1)	1 (0.1)	3 (0.1)
Ethnicity (n, %)			
Han population	3182 (97.3)	1314 (97.6)	1868 (97.1)
Non-Han population	66 (2.0)	22 (1.6)	44 (2.3)
Missing data	21 (0.6)	10 (0.7)	11 (0.6)

(1.6%) in the first therapy, while those of trazodone (1.7%) followed by TCAs (0.5%) in the follow-up therapy. The rate of benzodiazepines was lower in the first therapy group than in the follow-up therapy group (19.0% vs 52.0%).

Within the TCM recommended by the Chinese Guidelines, the total use of Shuganjieyu capsules (0.3% vs 0.2%) or St John's Wort was few (0.1% vs 0.1%).

On the "without recommendations" list, compared to the first therapy, the total use of flupentixol and melitracen tablets (2.5% vs 1.1%) decreased in the follow-up therapy, while the use of antipsychotics (0.6% vs 17.2%) and mood stabilizers (0.1% vs 6.9%) increased.

The results also showed that SSRIs accounted for 57.2% (1099/1923) of first prescriptions for follow-up patients, while SSRIs accounted for 36.3% (489/1346) of first therapy among follow-up patients. Benzodiazepines accounted for 1.6% of first therapy among follow-up patients (n = 1923), but 46.1% (620/1346) among first-visit patients (n = 1346). See Table 3.

When the 1346 first visitors were not accounted in the first therapy group (Table 2), 1923 patients with their first visit and follow-up visit of treatment remained. A paired-sample design was conducted. In the first-line recommendations, SSRIs still accounted for the largest proportion (1099/1923, 57.2%), followed by SNRIs (438/1923, 22.8%) and mirtazapine (135/1923, 7.0%) compared to themselves of the proportion of SSRIs (753/1923, 39.2%), SNRIs (1037/1923, 53.9%) and mirtazapine (189/1923, 9.8%) in the follow-up therapy. In the second-line recommendations, TCAs

Table 3 Current Status of Antidepressant Treatment and Common Combined Antidepressants in 32 Centers

	Total First Therapy (n = 3269)	First Visit Patient (n = 1346)	First Therapy[a] (n = 1923)	Current Therapy[a] (n = 1923)
First-line recommendations				
SSRIs total	1242 (38.0%)	489 (36.3%)	1099 (57.2%)	753 (39.2%)
SSRIs monotherapy[b]	792 (24.2%)	362 (26.9%)	927 (48.2%)	430 (22.4%)
SNRIs total	1753 (53.6%)	716 (53.2%)	438 (22.8%)	1037 (53.9%)
SNRIs monotherapy	1259 (38.5%)	557 (41.4%)	333 (17.3%)	702 (36.5%)
Mirtazapine total	262 (8.0%)	73 (5.4%)	135 (7.0%)	189 (9.8%)
Mirtazapine monotherapy	51 (1.6%)	18 (1.3%)	50 (2.6%)	33 (1.7%)
Bupropion total	13 (0.4%)	5 (0.4%)	5 (0.3%)	8 (0.4%)
Bupropion monotherapy	3 (0.1%)	1 (0.1%)	3 (0.2%)	2 (0.1%)
Second-line recommendations				
TCAs total	12 (0.4%)	3 (0.2%)	70 (3.6%)	9 (0.5%)
TCAs monotherapy	1 (0.03%)	0 (0)	45 (2.3%)	1 (0.1%)
Trazodone total	46 (1.4%)	13 (1.0%)	30 (1.6%)	33 (1.7%)
Trazodone monotherapy	4 (0.1%)	1 (0.1%)	3 (0.2%)	3 (0.2%)
Quetiapine total	0 (0)	0 (0)	1 (0.1%)	0 (0)
Quetiapine monotherapy	0 (0)	0 (0)	0 (0)	0 (0)
Chinese medicine[c] monotherapy	1 (0.03%)	1 (0.1%)	6 (0.3%)	0 (0)
Shuganjieyu capsule	4 (0.1%)	0 (0)	6 (0.3%)	4 (0.2%)
St John's Wort	1 (0.03%)	0 (0)	1 (0.1%)	1 (0.1%)
Without recommendations				
Flupentixol and melitracen tablets monotherapy	31 (0.9%)	19 (1.4%)	48 (2.5%)	12 (0.6%)
Antipsychotics total	438 (13.4%)	107 (7.9%)	12 (0.6%)	331 (17.2%)
Antipsychotics monotherapy	5 (0.2%)	0 (0)	0 (0)	5 (0.3%)
Other traditional Chinese medicines	7 (0.2%)	1 (0.1%)	3 (0.2%)	6 (0.3%)
Mood stabilizers	202 (6.2%)	70 (5.2%)	1 (0.1%)	132 (6.9%)
Antidepressants+ benzodiazepines	1577 (48.2%)	601 (44.7%)	13 (0.7%)	976 (50.8%)

(*Continued*)

Table 3 (Continued).

	Total First Therapy (n = 3269)	First Visit Patient (n = 1346)	First Therapy[a] (n = 1923)	Current Therapy[a] (n = 1923)
Antidepressants+ mood stabilizers	196 (6.0%)	69 (5.1%)	1 (0.1%)	127 (6.6%)
Antidepressants+ flupentixol and melitracen tablets	25 (0.8%)	16 (1.2%)	14 (0.7%)	9 (0.5%)
Commonly combined antidepressants (total)	334 (10.2%)	92 (6.8%)	173 (9.0%)	242 (12.6%)
SSRIs + SNRIs	87 (2.7%)	26 (1.9%)	65 (3.4%)	61 (3.2%)
SSRIs + mirtazapine	75 (2.3%)	12 (0.9%)	50 (2.6%)	63 (3.3%)
SNRIs + mirtazapine	132 (4.0%)	42 (3.1%)	37 (1.9%)	90 (4.7%)
SNRIs + trazodone	18 (0.6%)	6 (0.4%)	3 (0.2%)	12 (0.6%)
SSRIs + trazodone	22 (0.7%)	6 (0.4%)	18 (0.9%)	16 (0.8%)
Recommendations for Clinical Specifiers				
Benzodiazepines[d]	1619 (49.5%)	620 (46.1%)	31 (1.6%)	999 (52.0%)
Antidepressants+ antipsychotics[e]	430 (13.2%)	107 (7.9%)	8 (0.4%)	323 (16.8%)

Notes: [a]Among follow-up patients; [b]Monotherapy was defined as one subject with or without combination of benzodiazepine; [c]Recommended by the Chinese Guidelines; [d]CANMAT recommendation for MDD with catatonic features (Level 3); [e]CANMAT recommendation for MDD with psychotic features (Level 1).

accounted for the largest proportion (70/1923, 3.6%) followed by trazodone (30/1923, 1.6%) compared to themselves of TCAs (9/1923, 0.5%) and trazodone (33/1923, 1.7%). See Figure 1.

Comparison of Commonly Combined Antidepressants Between First Therapy and Follow-Up Therapy Groups in 32 Centers

The rate of common antidepressant combinations in the first therapy was lower than that in the follow-up therapy (9% vs 12.6%), higher than that in the first-visit patient group (6.8%). See Table 3.

Moreover, we calculated the kind(s) of antidepressants (SSRIs, SNRIs, mirtazapine, bupropion, TCAs, and trazodone) used in MDD treatment. An average of 1.85 medications was administered to each MDD patient, 7% accepted psychotherapy, while the use of more than one drug reached up to 62.9% (49.5% for two medications, and 13.5% for more than two medications). See Figure 2.

Discussions

Through this survey, the proportion of SSRIs (57.2%) were the first choice in the first therapy, while the proportion of those drugs decreased during the follow-up therapy, which was replaced by SNRIs (53.9%), suggesting that SNRIs were the most considered alternative drugs. Antidepressant switching is also one of the alternative treatment strategies adopted in MDD patients who have no remission despite the adequate trial of antidepressant(s).[2] We endorse this kind of opinion that follows the evidence-based support by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, because the results indicate that a switch to sertraline is a cost-effectiveness treatment option, comparing with a switch to venlafaxine in MDD patients after unsuccessful treatment with citalopram for economic evaluation.[2] Nevertheless, the switch options of bupropion, sertraline, and venlafaxine were not significantly different from each other in terms of cost-effectiveness.[18] The actual difference of using conditions could be variations of drug prices in different countries due to the self-regulation of pharmaceutical industry.[19] From the perspective of pharmacology, the switch to a different mechanism of antidepressants would contribute to affecting different signs and symptoms.[20,21] This variation strategy may provide more chances of cure[22] when comparing the effects of sertraline with duloxetine,[23] rather than those of venlafaxine with escitalopram.[22] In the first-line recommendations, the prescription of bupropion was surprisingly low, even lower than the second-line recommendations except for quetiapine. Efforts remain to be made to promote the

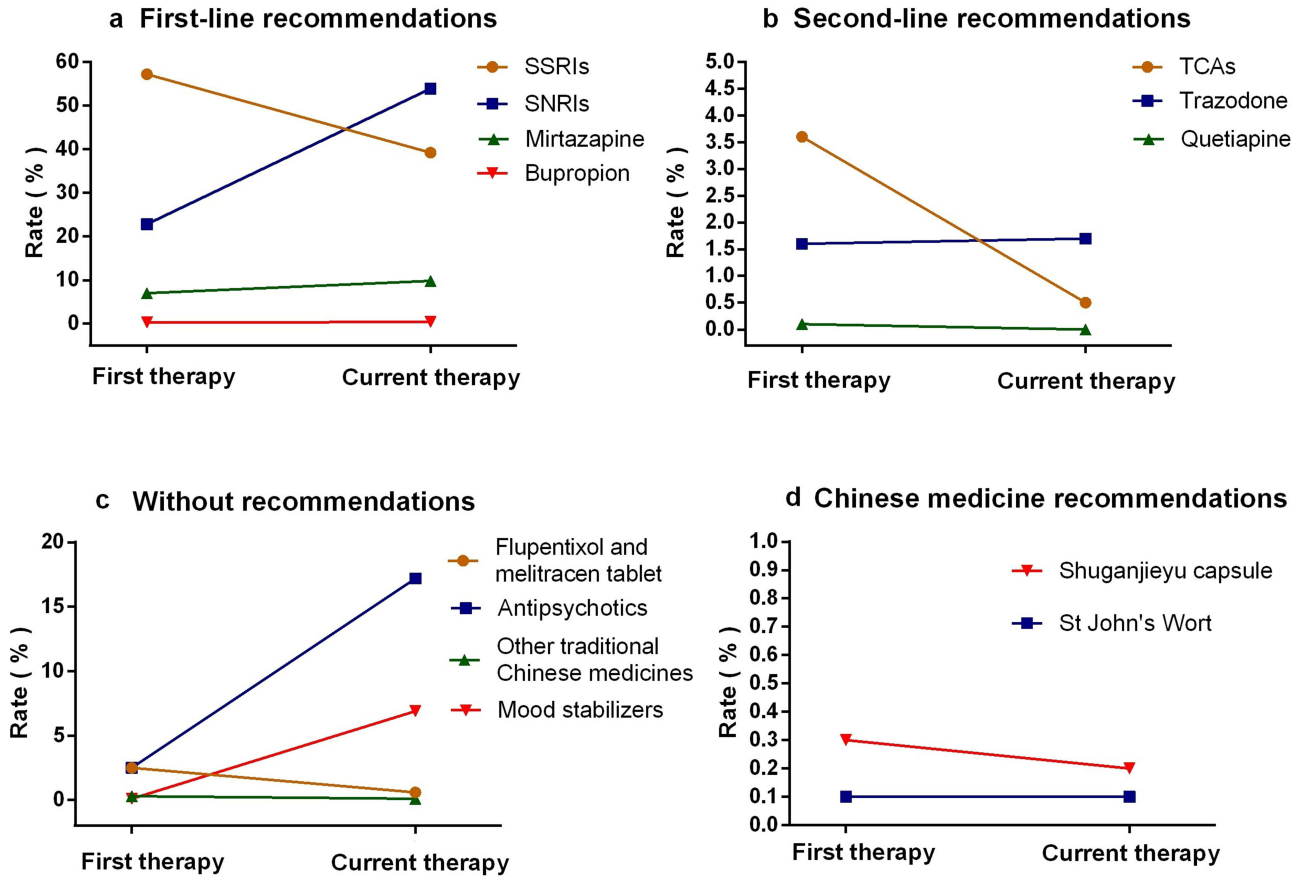

Figure 1 Line chart of switching antidepressants in their first visit and follow-up visit of treatment (n = 1923). The sub-figures respectively show the first-line recommendations (**a**), the second-line recommendations (**b**) and the "without recommendations" list (**c**) by CANMAT 2016 and the Chinese medicine recommendations (**d**) by PTDDC 2015.

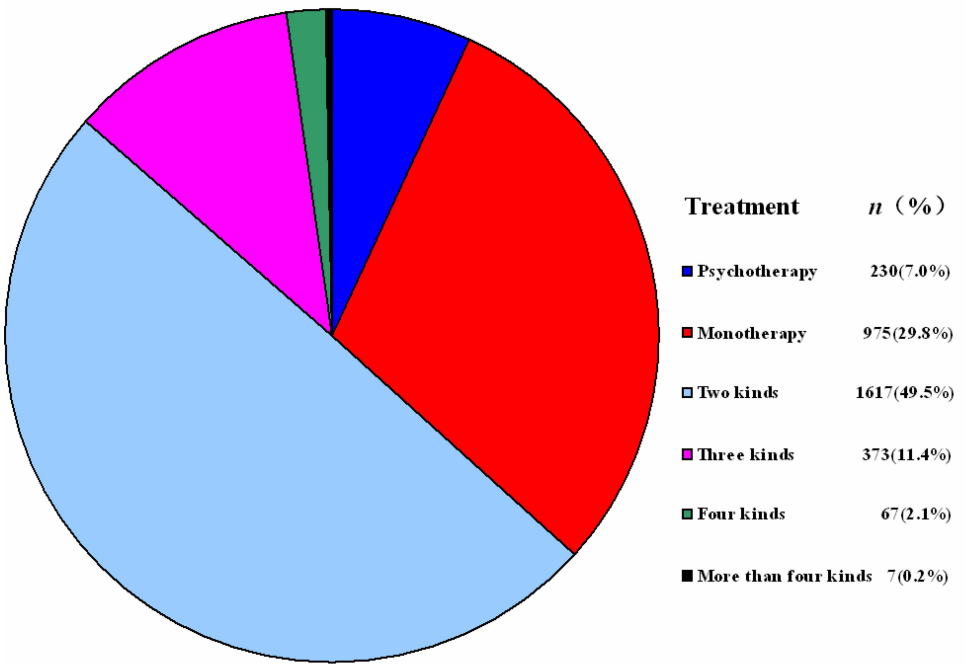

Figure 2 Statistics of psychotherapy or kind(s) of pharmacotherapy (n = 3269).

coverage of bupropion in China from the aspects of efficiency and security.[24] On the opposite, obsolete knowledge is another phenomenon. We found in the statistics that many hospitals still adhere to compound preparations such as flupentixol and melitracen tablets (1.7%, total) in that the efficacy was exhibited in MDD patients accompanied with chronic somatic diseases.[25] The flupentixol/melitracen combination was used to be the most frequently prescribed compounds in China.[26] However, in the current developed process of atypical antipsychotics and second-generation antidepressants, we can see the trend that this type of drug has been phased out for decades due to the irrational fixed-dose combination,[27] which has been prohibited for sale or use in many countries. There are many regions in China where knowledge dissemination mainly depends on the succession of teachings from a master to his disciples. Although many treatment strategies are out-of-date, it is common for people to adhere to the Confucian principle of "honoring the teacher and respecting his teachings" rather than evidence-based medicine.

The gap between 57.2% of first SSRI prescriptions for follow-up patients and 36.3% of first-visit patients may come from many first-visit patients who record their medical history from the beginning of taking medicine. It takes a while of adaptation for patients to establish treatment compliance at outpatient clinic.[28] Moreover, MDD patients who tend to seek medical help from general hospitals[29] were more likely to suffer from urinary system complaints, headache, sensory system complaints, trunk pain, and nervous system complaints.[14] These symptoms were likely to be prescribed benzodiazepines or medications for treating physical illnesses, instead of antidepressant by physicians. After a follow-up referral to a psychiatric specialist, the phenomena of seeking rapid relief were adjusted within a reasonable range. The onset of MDD will be probably defined when they come to a psychiatric hospital. That may explain why so many first benzodiazepine prescriptions were not accounted for follow-up patients. CANMAT recommends for MDD with catatonic features, but benzodiazepine use is very common (49.5%) in China, obviously not for catatonic features.

Compared with the CANMAT guideline, drug uses without recommendations were observed in our survey. The commonly combined pharmacotherapy was directly selected for the first treatment (9%), while antipsychotics (17.2%) and mood stabilizers (6.9%) adjunctive therapy to antidepressant therapy was increased in the follow-up treatment. In the cross-sectional study, the use of two or more drugs reached up to 62.9%, so the prescription of multiple antidepressants is still a common problem, especially in East Asia.[30] This trend may result from consideration for a synergistic effect of antipsychotics in the treatment of MDD,[31] but the combined pharmacotherapy also increases the risk of side effects caused by psychotropic medications.[32] Drug–drug interactions and clinical considerations should be adequately integrated to construct a co-administration of medical therapy.[33,34] For the reason above, the antipsychotics (except for quetiapine) and mood stabilizers are inconsistent with the CANMAT guideline.[9,35] Meanwhile, we have also noticed that lithium, as a classic mood stabilizer, would likely to be inappropriate for patients with a partial response to the first antidepressant trial. However, if the patient has failed several treatment strategies, lithium would be recommended for adjunctive medication for nonresponse or partial response to an antidepressant in the CANMAT guideline.[9]

Polypharmacy is a worldwide issue in psychiatry.[36] Our study calculated the clinical prescriptions of psychiatry in 32 centers. In the cross-sectional study, an average of 1.85 medications were administered to each MDD patient, while those taking two or more medications reached up to 62.9%. Polypharmacy leads to many disadvantages for patients with MDD. Polypharmacy treatment not only increases the incidence and severity of side effects, but also increases the burden of treatment costs.[37] According to Healthy People 2020, prescription of multiple medications is the No. 1 drug safety priority to Americans' aging population, in which the proportion of Asian Americans was 48%.[38] The main reason may be an inadequate understanding of pharmacodynamics and pharmacokinetics of commonly used psychiatric medications. We found these problems in their records, including an irrational fixed-dose combination (flupentixol and melitracen tablets), antipsychotics (eg, a low dose of olanzapine, perphenazine, clozapine or chlorpromazine), and a mood stabilizer (eg, lithium or valproate) compared with the CANMAT guideline. Furthermore, some irrationally combined uses of drugs were prescribed in the follow-up therapy, such as SSRIs with SNRIs or SNRIs with mirtazapine.[39] SSRIs or SNRIs are first-line pharmacotherapies for MDD, which inhibit many common cytochrome enzymes,[40] so they may have drug interactions. Because more than half of the patients with MDD starting treatment did not remit after an adequate trial with the first agent, they will need a second-line therapy.[41] Therapeutic alliance always prefers drug combinations rather than switch the existing ineffective medication(s), which made the rate of drug combination increase from 7% to 12.6% in MDD patients who returned to those psychiatric departments. This phenomenon needs more than a theoretical

discussion of the psychopharmacological effects of the drug combination. Instead, there needs to be high-quality clinical research in China to investigate this phenomenon, which is supposed to be converted into guidelines.

In addition, we found that unrealistic treatment expectations might exist in this survey, leading a therapeutic alliance to prefer "good drugs" (such as newly imported antidepressants), "strong drugs" (such as antipsychotics as a synergistic agent), "fast drugs" (such as benzodiazepines) or "TCM" [Following the principles of "Monarch", "Minister", "Assistant", and "Guide" (君臣佐使)].[37] A 10-years cohort study showed that patients with MDD starting treatment might be expected to spend three-quarters of the next decade in euthymia, and the remaining period in subthreshold or threshold depression.[42] Nowadays in China, patients and their guardians are unwilling to wait for the gradual improvements afforded by most antidepressants,[37] so doctor-patient alliance should make efforts to reach a rational agreement on their following treatment compliance, especially when the doctor has not prepared them for the slow onset of treatment effects.[38]

Additionally, the dominant position of a psychiatrist may increase the dosage and type of medication. Indeed, patients' lack of relevant knowledge leaves their psychiatrists dominate the negotiations about treatment. The use of psychotropic medications can be an unintended (or intended) method of increasing patient compliance.[37] Urgent need for improving mental health care should be a more collaborative model instead of the current psychiatrists' dominant position. This issue is acute in psychiatry because of its relatively subjective judgment and slow development in comparison with that of other medical specialties.

TCM has a distinctly Chinese characteristic with its theoretical rationality. Shuganjieyu capsule and St. John's Worts (called Hypericum monogynum in China) were recommended to be used in mild-to-moderate depression by evidence-based supports[43,44] according to the Chinese guideline, while the CANMAT guideline for complementary and alternative medicine treatments indicated St. John's wort as a second-line recommendation for moderate to severe MDD,[45] so we put them into the consideration of our study. However, it was also found in the study that some TCM with the formula of "君臣佐使" failed to be collected due to a large number of drug materials. Therefore, to some extent, TCM has also increased the use of medications, and it still has a long way to attend further from a transnational perspective to the innovations of this period, as well as to be approved and recommended by international guidelines in the future.[46]

Limitations

The real-world antidepressant combinations may be less than what we calculated within our research data, for as many of these may have been "combined" during a cross-titration (eg, switching an SSRI to SNRI) with no intention of dual SSRI-SNRI therapy. Furthermore, many patients may have previously been treated with antidepressants. As a real-world practice, first therapy cannot be equal to the real "first", which depends on their accurate medical history provided.

Acknowledgment

The authors would like to acknowledge and thank all the participants in this study and all the members of the NSSD team. The authors also thank Lu Yang for proofreading the final edition.

Funding

The National Key Research and Development Program of China (2016YFC1307100), the National Natural Science Foundation of China (91232719, 81771465, 81930033), Shanghai Key Medicine Specialties Program (ZK2019A06), Shanghai Clinical Research Center for Mental Health (SCRC-MH, 19MC1911100), the Scientific Research Project of Hongkou District Health Commission (2101-03) and Excellent Talent Training Program of Shanghai Hongkou Mental Health Center (2023XKDTR01).

Disclosure

The authors report no conflicts of interest in this work.

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