

Suicidality is most centrally situated within network of depression symptom criteria in unipolar depression patients with mood stabilizer in Asia

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ABSTRACT

Lithium and mood stabilizers are considered effective augmentation agents of antidepressants for treatment-resistant depression. Thus, this study aimed to estimate the network structure of depression symptom criteria among unipolar depression patients with mood stabilizers, using data from the Research on Asian Psychotropic Prescription Patterns for mood stabilizers (REAP-MS). We estimated a network of the 9 depression symptom criteria among 411 unipolar depression patients in Asia. Each of the depression symptom criteria was considered to be a dichotomous categorical variable. Suicidality (suicidal ideation or attempt) was the most centrally situated within the network of depression symptoms, followed by depressed mood, loss of energy, anhedonia and weight loss or gain. Contrastingly, concentration problem was the least interconnected. The depression symptom criteria were organized into 4 clusters by the community detection method. The findings suggest that suicidality may be one of the significant therapeutic target symptoms in unipolar depression patients with mood stabilizers.

1. Introduction

Lithium and anticonvulsant mood stabilizers (i.e., valproate, carbamazepine, lamotrigine) are recognized as effective adjunctive agents to an existing antidepressant for treatment-resistant depression (Park and Shen, 2023). Lithium is a proven unique anti-suicidal agent for patients with unipolar depression and contributes to reducing the relapse of mood disorder (Abou-Saleh et al., 2017). Thus, lithium has been typically used as an adjunctive treatment option to prevent suicide in patients with unipolar depression (Brus et al., 2019; Katz et al., 2022). Valproate (Ghabrash et al., 2016), carbamazepine (Schüle et al., 2009) and lamotrigine (Thomas et al., 2010) have been recommended as effective augmentation agents for treatment-resistant depression. Valproate is usually used as an antidepressant augmentation agent to achieve substantial clinical improvement over a relatively long period in patients with severe treatment-resistant depression (TRD) (Ghabrash et al., 2016). Carbamazepine augmentation can result in a greater clinical response rate in terms of treatment effectiveness in patients with unipolar depression (Zhang et al., 2008), although it can also affect the serum concentration of antidepressants (Schüle et al., 2009).

Lamotrigine augmentation can result in greater clinical improvement in more severe and longer illness among patients with TRD (Goh, et al., 2019). In the naturalistic French national study, among unipolar depression patients, poor responders to mood stabilizer augmentation have been characterized by a significantly higher level of suicidal ideation than the good responders (Hantouche et al., 2005).

Network analysis has been regarded as a relatively novel method to present psychopathology from the viewpoint of a “bottom-up” but not a “top-down” approach (Li et al., 2022; McNally et al., 2015). Thus, the network analysis research has presented findings partly inconsistent with the operational definition of major depression (Fried et al., 2018; Jang et al., 2024; Kendler et al., 2018; Park et al., 2020; Park and Kim, 2020). Although lithium and anticonvulsant mood stabilizers have been commonly used as augmentation agents for the pharmacotherapy of unipolar depression, the symptoms targeted can vary in the clinical treatment of depressive disorders (Abou-Saleh et al., 2017; Ghabrash et al., 2016; Schüle et al., 2009; Thomas et al., 2010). To the best of our knowledge, the symptomatology of unipolar depression patients with mood stabilizers has been little estimated through the network analysis. Thus, using the data from the Research on Asian Psychotropic Prescription Patterns for Mood Stabilizers (REAP-MS) (Chen et al., 2023), our study aimed to estimate the network structure of symptom criteria among unipolar depression patients with mood stabilizers in Asia. However, most studies only assessed depression based on the total or mean scores of standard scales, although depression consists of a cluster of different symptoms

2. Methods

2.1. Study overviews

As described elsewhere (Chen et al., 2023), the REAP-MS is the largest international collaborative research system exploring for the use of psychopharmacological treatment in Asia, involving ten Asian countries/special administrative regions including China, India, Indonesia, Malaysia, Myanmar, Singapore, South Korea, Taiwan and Thailand. Prior to the initiation of the REAP-MS, the investigators had several meeting to ensure consistency of the data collection. The REAP-MS collected data describing the clinical characteristics (i.e., symptom criteria of major depression) and psychotropic medication prescription patterns of mood stabilizer-using psychiatric patients who are diagnosed with any mental disorder except bipolar disorder (codes F31.0-F31.9 in the International Classification of Diseases, 10th revision [ICD-10]) (World Health Organization (WHO), 1992) from January 2019 to October 2019. Ethical reviews for study protocol and informed consent forms were approved by the institutional review boards of all the study centers, including Taipei City Hospital, Taipei, Taiwan (receipt number: TCHIRB-10605117-E). All the study participants completed the written informed consent for the REAP-MS. The psychiatric diagnoses

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was made with ICD-10 criteria. In addition, mood stabilizer was defined with the “antiepileptics (N03)” code in the Anatomical and Therapeutic Chemical (ATC) classification of [WHO Collaborating Centre for Drug Statistics Methodology \(2018\)](#). In terms of the definition of mood stabilizer using the ATC classification, the exceptional conditions were as follows: Lithium (N05AN) was included as a mood stabilizer but anti-psychotic based on its main clinical use for treating elevated mood symptoms in the REAP-MS, whereas it was defined with the “psycho-analeptics (N05)” code. Clonazepam (N03AE01) was included as an anxiolytic but not a mood stabilizer based on its main clinical use for treating anxiety symptoms in the REAP-MS, whereas it was defined with the “antiepileptics (N03)” code. In addition, using the nine symptom criteria for major depression (i.e., depressed mood [DEP], anhedonia [ANH], weight loss or gain [WEI], insomnia or hypersomnia [SOM], psychomotor agitation or retardation [AGI], loss of energy [ENE], feelings of worthlessness or guilt [GUI], decreased concentration or indecisiveness [CON], suicidal ideation or attempt [SUI]), defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) major depression ([American Psychiatric Association, 2013](#)), mood stabilizer-targeted symptoms of depressive symptoms were evaluated. Thus, 1557 psychiatric patients concurrently using mood stabilizers were enrolled in the REAP-MS.

To estimate the network structure of symptom criteria among unipolar depression patients with a mood stabilizer, we used the data from the study participants who met the following inclusion criteria: (i) the ICD-10 diagnosis of a depressive episode (F32), recurrent depressive disorder (F33) or persistent depressive disorder (F34) ([WHO, 1992](#)), which was corresponding to the DSM-5 major depression and dysthymia ([American Psychiatric Association, 2013](#)), by clinical psychiatrists at the individual research centers, (ii) the availability of the nine symptom criteria for major depression, defined by the DSM-5. The exclusion criteria were as follows: (i) severe physical disease and inability to read or write, (ii) the comorbidity of organic mental disorder, substance use disorder, schizophrenia-spectrum disorder and intellectual disability. Finally, 411 unipolar depression patients with mood stabilizers were included in our study.

2.2. Statistical analysis

R-package qgraph ([Epskamp et al., 2012](#)) was used to estimate the network structure of the DSM criteria for major depression based on polychoric correlations. In terms of network analysis, the nodes and edges represented symptoms and associations among symptoms, respectively. All the DSM criteria for major depression were regarded as dichotomized-categorical variables. A unidirectional network was estimated because of the cross-sectional characteristic of the REAP-MS. The least absolute shrinkage and selection operator (LASSO) ([Tibshirani, 1996](#)) was used to control the false-positive edges and set very small edges to zero. Graphical LASSO (GLASSO) was used to define the relationship levels between the two symptoms, which is controlled for all other relationships within the network. The extended Bayesian Information Criteria were used to minimize the shrinkage parameter and recover the underlying network accurately. The Fruchterman-Reingold algorithm was used to situate strongly connected nodes. The correlation stability coefficient (CS-coefficient) indicated the maximum proportion of cases that could be eliminated to obtain a 95 % probability that the ranking correlation between the original network and the case-subset network would have a significant effect (0.7). Interpreting centrality indices with a CS coefficient > 0.25 was recommended. Node strength centrality indicated the sum of all associations of a given node with all other nodes and was considered a common and stable central metric in network analysis ([Opsahl et al., 2010](#)).

3. Results

3.1. General descriptions of the study participants

In [Table 1](#), among the 411 study participants, the sociodemographic characteristics, clinical characteristics, mood stabilizer using distributions and response frequency distributions of the DSM symptom criteria for major depression have been listed.

3.2. Estimated network structures of the DSM symptom criteria for major depression

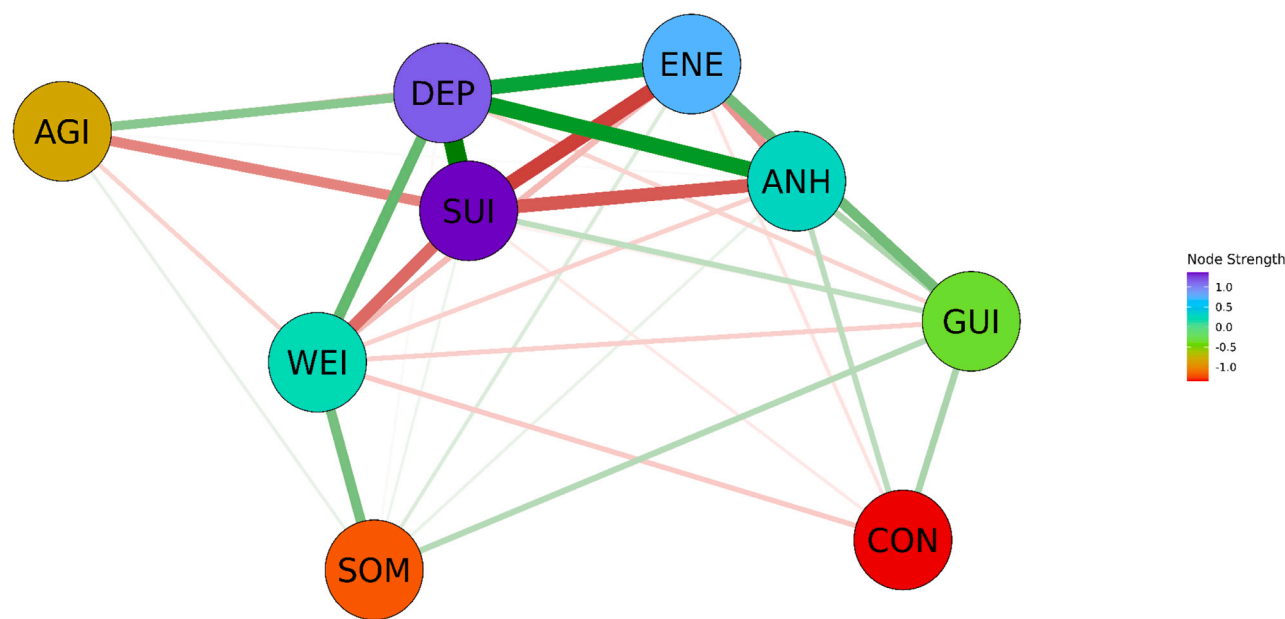
In [Fig. 1\(a\)](#), among the 411 study participants, the network construction of the DSM symptom criteria for major depression revealed that 33 of 36 possible edges were estimated to be > 0. Several strong interconnections between the edges were identified within the network, including DEP-SUI (weight = 0.914), DEP-ANH (0.730), DEP-ENE (0.497), ENE-GUI (0.459), WEI-SOM (0.442) and DEP-AGI (0.383) interconnections. In [Fig. 1\(b\)](#), an inspection of the node strength centrality of the DSM symptom criteria for major depression presented that SUI was the most centrally situated symptom domain, followed by DEP,

Table 1

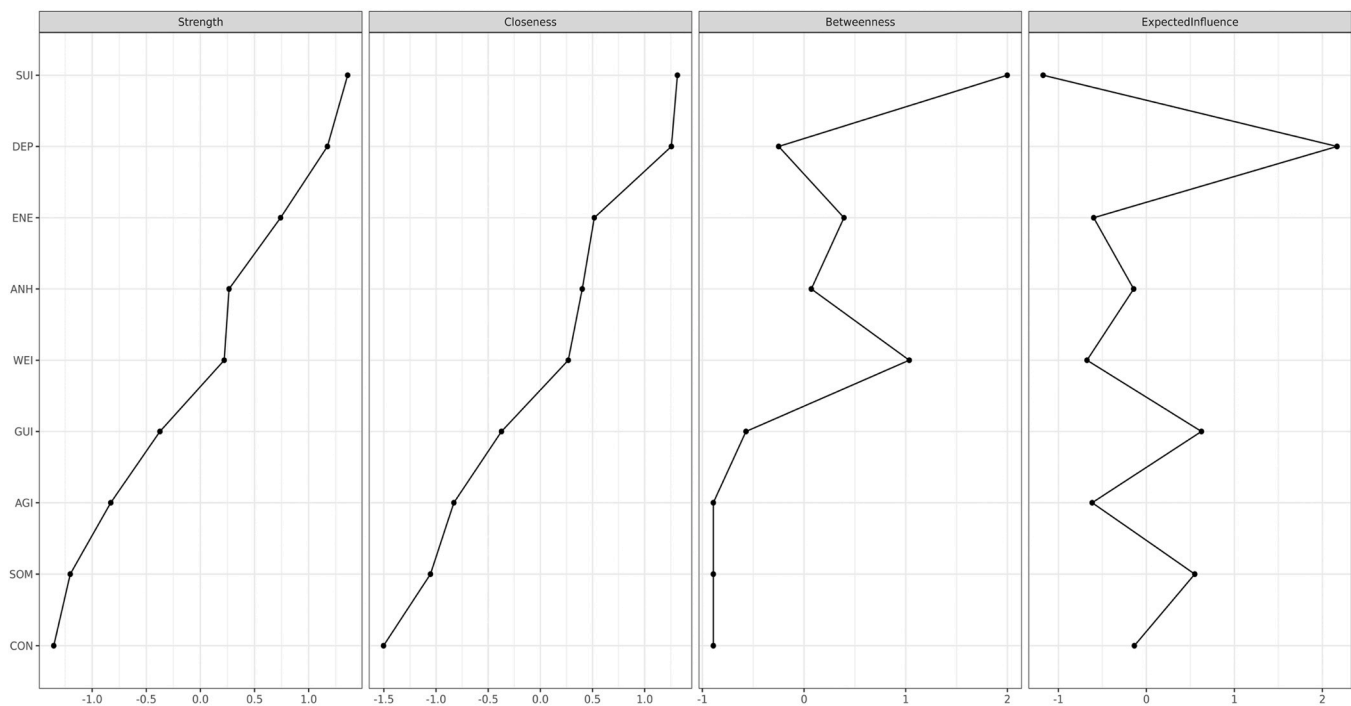
General descriptions of the study participants (n = 411).

	mean (SD) or n (%)
Age, years old	40.8 (17.1)
Female	242 (58.9)
Outpatient	331 (80.5)
Country	
China	126 (30.7)
India	35 (8.5)
Indonesia	4 (1.0)
Korea	118 (8.7)
Malaysia	10 (2.4)
Myanmar	22 (5.4)
Pakistan	4 (1.0)
Singapore	9 (2.2)
Taiwan	47 (11.4)
Thailand	36 (8.8)
ICD-10 diagnosis	
Depressive episode (F32)	170 (41.4)
Recurrent depressive disorder (F33)	231 (56.2)
Persistent depressive disorder (F34)	10 (2.4)
Duration of illness	
Less than 6 months	125 (30.5)
6–12 months	109 (26.4)
1–5 years	132 (32.1)
More than 5 years	45 (10.9)
Physical comorbidity	77 (17.4)
Mood stabilizer	
Carbamazepine	20 (4.9)
Lamotrigine	39 (9.5)
Lithium	91 (22.1)
Oxcarbazepine	6 (1.4)
Valproate	250 (60.8)
Other mood stabilizer	
Gabapentin	3 (0.7)
Phenobarbital	1 (0.2)
Phenytoin	1 (0.2)
Pregabalin	6 (1.4)
Topiramate	7 (1.7)
DSM symptom criteria for depressive episode	
Depressed mood	91 (7.6)
Anhedonia	34 (2.8)
Weight loss or gain	19 (1.6)
Insomnia or hypersomnia	185 (15.4)
Psychomotor agitation or retardation	33 (2.8)
Loss of energy	55 (4.6)
Feelings of worthlessness or guilt	30 (2.5)
Decreased concentration or indecisiveness	113 (9.4)
Suicidal ideation or attempt	49 (4.1)

DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; SD, standard deviation



(a) Estimated network structure



(b) Standardized node strength centrality, betweenness centrality and closeness centrality

Fig. 1. Estimated network structure of the DSM symptom criteria for major depression among unipolar depression patients with mood stabilizers (n = 411). Green lines represent positive associations, whereas red lines represent negative associations between the connecting nodes. The thickness of the lines represents the strength of the edges. Nodes represent the depressive symptoms evaluated with the PHQ-9. AGI, psychomotor agitation or retardation; ANH, anhedonia; CON, decreased concentration or indecisiveness; DEP, depressed mood; ENE, loss of energy; GUI, feelings of worthlessness or guilt; SOM, insomnia or hypersomnia; SUI, suicidal ideation or attempt; WEI, weight loss or gain.

ENE, ANH and WEI. Contrastingly, CON was the least interconnected symptom domain within the network. A community detection method organized the depression symptom criteria into 4 clusters including DEP-AGI-SUI, WEI-SOM, ANH-CON and ENE-GUI. Node strength centrality and edge-weight accuracies was supported by an interpretable levels of CS-coefficient of 0.272 and 0.267, respectively.

4. Discussion

In summary, our findings have shown that suicidal ideation or attempt is the most central domain within the network of the DSM symptom criteria in unipolar depression patients with mood stabilizers. Thus, it can be proposed that suicidality is the most essential therapeutic

target symptom among unipolar depression patients with mood stabilizers, although lithium can be used as an anti-suicidal augmentation option for treatment-resistant depression (Abou-Saleh et al., 2017; Ghabrash et al., 2016; Schüle et al., 2009; Thomas et al., 2010). The findings are partly consistent with the proven anti-suicidal effectiveness of mood stabilizers (especially lithium) (Abou-Saleh et al., 2017). In our study, lithium and valproate were used by 22.1 % and 60.1 % of the study participants, respectively. It is known that anticonvulsant mood stabilizers (i.e., valproate, carbamazepine, lamotrigine) have a less anti-suicidal effect than lithium (Tondo and Baldessarini, 2016), whereas the use rate of valproate has been three times of that of lithium in our study. The discrepancy may be partly explained by the assumption that lithium is less preferred than valproate because of its prominent side effect profiles. However, Abou-Saleh et al. (2017) have proposed that lithium can be prophylactically used to prevent suicide for two episodes of depressive episode within five years. Herein, it is possible to draw some hypotheses from these findings: First, suicidality may be the most essential symptom in the depressive symptom network of patients with unipolar depression who have currently used mood stabilizers, although lithium and anticonvulsant mood stabilizers have been used as augmentation agents for various depressive symptom targets. Second, both lithium and anticonvulsant mood stabilizers may be used as augmentation options to prevent and treat suicidality in patients with unipolar depression, although lithium has been relatively less used than valproate, according to our findings. Thus, it may be concluded that suicidality is the most important symptom domain in the treatment of treatment-resistant unipolar depression, irrespective of the use of any mood stabilizers.

Our study has a limitation as follows: First, the estimated centrality may be biased because of the dichotomous-categorical characteristic of the DSM symptom criteria (Fried et al., 2018; Kendler et al., 2018). However, the Pearson correlation between standard deviation and node strength centrality of the criteria among the study participants was considered negligible ($r = 0.04$). Second, the potential effects of mood stabilizer dosages, classes of antidepressants, and other pharmacological treatment characteristics can be adjusted in terms of network structure estimation. Therefore, their effects on the findings could not be considered.

Despite the limitation, partly inconsistent with the DSM construct of major depression, suicidality has been proposed as the most influential symptom within the network of symptom criteria among unipolar depression patients with mood stabilizers. In other words, in this network analysis model, suicidality was identified as the most central symptom. Additionally, the important edges involving suicidality can be prioritized as treatment targets together with "suicidality" according to network analysis theory.

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Declaration of Competing Interest

Seon-Cheol Park, an editorial board member of the Asian Journal of Psychiatry, was not involved in the evaluation of or decision to publish this article.

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