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Diagnosis and treatment of unipolar and bipolar depression in the early stage

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Abstract. Bipolar Disorder and Unipolar Depressive Disorder are both mental disorders that contain depressive episodes, and the patterns of depression are similar between the two diseases. People are likely to meet their clinicians for the first time when they experience depression while there is no significant evidence of the existence of mania episodes—the other episode of bipolar disorder. Therefore, it is likely that the clinicians misdiagnose the disorder, thus prescribing the wrong medication or applying therapies harmful to patients. For example, some antidepressants will stimulate the mania episode of bipolar patients, increasing the frequency of switch between extreme depression and mania, thus developing the results of bipolar disorder in the patients. At the same time, some mood stabilizers are not that effective to cure major depression compared to medication specialized in treating depression. This article aims at providing several diagnostic methods that can differentiate bipolar and unipolar disorders, and introducing some plausible therapies that work for the two disorders at the same time without severe harm or exacerbation.

Keywords: Bipolar Disorder, bipolar depression, diagnosis, unipolar depression, anti-depressant treatment.

1. Introduction

The increasing depression rate has been an important issue in recent years, and according to the data of American Psychology Association (APA), the pandemic has escalated the depression rate about four times, making it realized and taken seriously by more and more people [1]. At the same time, another psychological disorder called bipolar disorder (BD) is also affecting lots of people, making the patients suffer from shifts between extreme mania and depression episodes. Since depression episodes often happen as bipolar disorder patients' first and most prominent mood episode, and the symptoms are similar to those of unipolar depression disorder (UD), a lot of BD patients are misdiagnosed to have UD [2,3]. According to Psychiatry Professor Claire O'Donovan and Martin Alda, 8.4% of people who had been diagnosed as unipolar depression patients were given a new diagnosis of bipolar disorder after 2.3 to 13.1 years [4]. Meanwhile, only 20% of BD patients showing depressive episodes are diagnosed accurately within one year of their treatment [5].

However, the treatments toward BD and UD are quite different. Antidepressants are the most prescribed medication for UD patients, but they may have harmful side effects to BD patients [4]. Mania episode is the other extreme phase of BD, and patients are usually overly energetic, euphoric,

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and irritable during the mania phase that they may have risky activities thus eventually hurting themselves. Therefore, antidepressant medication may cause more frequent mania or hypomania switch for potential BD patients since the medication works to make people less upset but more active, thus possibly exacerbating mania [3,6]. Misdiagnosis and mistreatment may even lead to increasing suicide rates and worsened prognosis [7]. Therefore, it is important for the clinicians to provide accurate diagnoses in early stages when there is no significant manic episode taking place, thus being able to give the patients the most proper treatments.

This article is going to retrospectively discuss some plausible ways to distinguish UD and BD in the early stage, including application of patients' clinical characteristics, functional Magnetic Resonance Imaging (fMRI) biomarkers, and Electroencephalogram (EEG) and machine learning. Also, the article will introduce some kinds of therapy modes or medication usage that are helpful to both UD and BD patients and wouldn't lead to harmful side effects, so that they can be applied when information is limited for accurate diagnosis without worrying about further harm to the patients.

2. Diagnosis of unipolar depression and bipolar disorder accurately in the early stage

2.1. Clinical characteristic

There are some features that can help clinicians to judge whether a patient is more likely to suffer from unipolar depression or bipolar disorder. For example, the family history of getting BD can be referenced for diagnosis: recurrent incidence and the commencement of depressive symptoms at an early age can predict BD the best [4]. If the patient is under 30 years old, especially under 20 years old, it would be a risk factor for misdiagnosis [7]. Also, genetic factors play a role in BD development, and that people that have a first degree relative diagnosed with BD are 7 times more likely than normal people to have BD [7]. This kind of clinical characteristics can be easily obtained by clinicians through simply asking the patients, while some other factors may not be readily known at the first meeting between the patients and clinicians. For example, some factors that may predict BD are the frequent occurrence of depressive episodes, cyclothymic mood swings, resistance to antidepressants, and of course the appearance of mania or hypomania [7].

Since these risk factors may be detected after observation or self-report and won't be determined if them exist for a while, it may be better that the clinicians treat these patients carefully with treatments which are helpful to both BD and UD at first, and then check whether these risk factors reflect on the patients after several weeks. Common methods to check the manic symptoms include self-reporting mania scales, such as the Altman scale, the Internal State scale, and hypomania checklist [4]. In conclusion, just using clinical characteristics of the patient to judge whether they suffer from BD or UD is helpful for the prognosis, but it also has some disadvantages: the factors collected by clinicians or reported by patients aren't infallible, and that determining the condition of some factors is time-consuming. Therefore, it is necessary for the clinicians to turn to some more efficient and accurate methods related to brain imaging technology for diagnosis of BD.

2.2. fMRI detection

Along with the developed accuracy and sophistication of brain imaging, using fMRI is now reliable to differentiate BD and UD through observing some biomarkers that show different patterns under the circumstances of BD and UD patients. Resting state functional connectivity (rsFC) and regional homogeneity (ReHO) are widely studied in fMRI and are helpful to the classification of BD and UD. rsFC refers to the synchronization of brain activity between various areas during the resting state and ReHO is used to study and assess the similarity of the brain activities within a certain region.

2.2.1. Functional connectivity as the biomarker. The effectiveness on differentiating BD and UD of resting state functional connectivity (rsFC) has recently been, since BD patients' rsFC between frontopolar prefrontal cortex and insula is lower than UD patients', and that BD patients' rsFC between amygdala and hippocampus is higher [8]. Another study reveals that compared to UD patients,

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BD patients show lower rsFC between the left ventral striatum (VS) and left ventral tegmental area (VTA), which also contributes to the diagnosis [5]. According to the same study, the rsFC between the right VS and the right and left VTA is also lower in BD patients than UD patients [5]. Since VTA and VS are connected to the dopamine system, thus affecting motivation, cognition, and mood, BD patients that have lower rsFC between VTA-VS may represent that the depressive episode in BD is more severe than unipolar depression [5]. At the same time, since the main difference between BD and UD patients' reward circuit is just between VTA and VS, it can be explained why the depressive symptoms of BD and UD are similar.

Also, BD patients display higher FC in their frontoparietal network during depression, whereas UD patients show that in the default-mode network (DMN) as well as lower FC of their cingulo-opercular network during depression [8]. Through the application of multivariable pattern analysis, it is supported that the functional pattern of patients' somatomotor networks (SMN) and DMN can be utilized to identify BD and UD: for BD patients, their neural variability is declined in DMN but increased in SMN, and the condition is opposite for UD patients [8]. Since DMN contains various functions including episodic memory, contemplating the past or the future, and noticing the surroundings, patients with BD perform worse at tasks related to memory, attention, and I management compared to UD patients since their DMN is more damaged.

*2.2.2. Regional homogeneity as the biomarker.*Regional homogeneity (ReHO) value that represents the coordinated neuronal activity within brain areas that have similar functions is another widely used indicator to identify various mental disorders [9]. There is a significant difference between the ReHo values of patients with BD and UD in their right inferior temporal gyrus [9]. Since the difference is not related to patients' score in scales like Hamilton rating scale for depression-24 (HAMD-24) and Hamilton Anxiety Rating Scale (HAMA), it can be assumed that the difference is not related to the similar depressive episodes in BD and UD but more to the disorder respectively, thus being a proper and accurate biomarker to distinguish BD and UD [9].

There are also other biomarkers that can be detected by fMRI to diagnose between UD and BD. For example, BD patients have a lower amount of gray matter in their hippocampus and amygdala, while a greater amount of gray matter in their anterior cingulate cortex (ACC) than UD patients [5]. The connectivity of white matter between the medial orbitofrontal cortex (mOFC) and the nucleus accumbens (NAcc) and between amygdala and NAcc is related to the elevated probability of mania or hypomania occurrence, thus being helpful to diagnose BD [5].

It seems that there are various neuroimaging biomarkers able to identify between BD and UD at an early age through fMRI, but it still has some disadvantages. The first and more important shortcoming of using fMRI is its expense. As an advanced neuroimaging instrument, it costs about hundreds of dollars for a patient to take a scan, while not everybody is willing or able to spend money for fMRI scan just to detect the possibility of misdiagnosis. In addition, the reliability of fMRI is still in question since it is still uncertain how repeatable network results work on individuals, and that patients may generate physiological noise during the scan, confounding the data or image observed [10]. This confusion is inevitable, and even respiration is possible to result in misleading connection patterns without being fully detected and filtered out [10]. Therefore, it might still be a long time before the generalized application of fMRI that is affordable for most patients and able to differentiate BD from UD while ruling out the interference.

2.3. EEG and machine learning

Electroencephalogram (EEG) which is another neuroimaging method functions to capture the electrical activities of patients' brains. Since it is non-invasive and has good temporal resolution, it is also utilized to diagnose a number of psychological disorders including depression, anxiety, and BD [11]. According to previous research, Gamma pulse can be used to accurately identify depressive disorder, also differentiating UD and BD for some of its distinct qualities [11]. Additionally, depressed patients' frontal Theta asymmetry and frontal Theta power are significantly lower, which is helpful to

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detect UD [11]. To identify BD, a protein family named neurotrophins that shows different patterns within different BD phases can be referred to as the biomarker for BD [11].

At the same time, EEG can be combined with machine learning, better diagnosing these mental disorders. Artificial Intelligence (AI) and Machine Learning (ML) are showing higher accuracy and deeper potential to provide clinical assistance, particularly in the mental health area, combined with the support of big data obtained through neuroimaging devices including fMRI and EEG. For instance, Convolutional Neural Network (CNN) is widely combined with EEG findings to identify major depressive disorder (MDD) or UD, especially with the assistance of One Dimensional Convolutional Neural Network and Long Short Term Memory (LSTM) [11]. To diagnose BD with machine learning, the feedforward neural network (FFNN) is widely utilized and can achieve an 87.75% accuracy when classifying BD, and multi-layer perceptron (MLP) as a class of FFNN can even identify BD sub types with a 91.83% classification accuracy [11]. Other commonly used machine learning models that diagnose BD are support vector machines (SVMs), artificial neural networks (ANNs), ensemble models, linear regression, and the Gaussian process model [12].

In previous study of classifying BD and UD, the researchers even developed a machine learning diagnostic algorithm relied on the data of participants' answers to World Health Organization World Mental Health Composite International Diagnostic Interview (CIDI) and their blood biomarkers, aiming at differentiating BD from UD or MDD. After training, the model developed is able to identify BD patients from people who are diagnosed with MDD recently with an accuracy of 0.83 on average [13]. Therefore, it is possible that more objective algorithmic methods can be developed in the future that can systematically detect biomarkers of the patients or the symptoms more associated with BD, thus decreasing the amount of misdiagnosis.

Although machine learning diagnosis can provide efficient and accurate classification of mental disorders that is relatively expense-saving, it still has some points that are worth considering. Nowadays, there is no one specific model followed by researchers or clinicians to identify BD, and the dataset used to study BD/UD classification is also not big enough. Since the technology of machine learning and neural networks is still under development and further improvement, it falls short of the model explainability required for quantitative research, thus unable to further develop repeatable and deterministic procedures that are therapeutically meaningful [11]. Also, there are some ethical problems such as whether patients are willing to provide their data for machine learning is questionable that may prevent machine learning from being generalized. However, it is plausible for clinicians to use machine learning to analyze patients' answers to questionnaires or scales, and it may find some new predictors after comparing a large number of patients' diagnosis and their answers.

3. Therapy helpful to both ud and bd

Since BD patients are likely to meet the clinicians for the first time when they only have depressive symptoms, they are frequently diagnosed with depression instead of BD, which affects the following treatments [11]. Although the depression episodes in BD and UD are similar, some medications for UD patients such as antidepressants may exacerbate the other episode—mania episode—of BD, increasing the risk of self-injury. Also, mood stabilizers that are mostly used to treat UD cannot be an adjunct to antidepressants to offset the risk of manic switch brought by antidepressants [6]. Therefore, since at present there is no one specific, time-saving, and accurate method that can be generalized to differentiate BD from UD the first time when patients meet the clinicians, it becomes more important for the clinicians to treat patients properly without exacerbating either UD or BD. Below are some medications or therapies that are effective to both BD and UD while not having serious side effects.

3.1. Lithium

Lithium is a kind of medication treatment that is mainly used to cure BD due to its outstanding ability to prevent depression and mania. Although it is not a typical treatment towards UD, it doesn't create harm to UD patients and is also effective on depressive episodes in UD [14]. Lithium has significant capability at its prophylaxis of repeating depressive episodes and anti-suicide effect, which shows its

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usefulness under emergent circumstances when patients have the thoughts of committing suicide [14]. In a study involving 123712 patients hospitalized for UD, individuals treated with lithium present a decrease in rehospitalization rates during the follow-up period of 7.7 years, which is not seen in those patients treated with antidepressants or other atypical antipsychotics [14]. According to previous research, even increasing lithium concentration in the drinking water in minute level can lower the rate of suicide [14]. Lithium has other properties that it can lower the risk of dementia, being neuroprotective and neurotropic, and improving the efficacy of other psychotropic drugs.

One thing that needs to be worried when prescribing lithium to patients is that not everyone responds optimally to it, which is related to patients' genetic loading. Actually, only around 30% of BD patients can fully respond to lithium, and patients with high major depression (MD) genetic loading are 1.5 times less likely than other patients to have optimal response under the treatment of lithium [15]. Lithium also brings some side effects, but some of these disadvantages can be corrected by other medications readily: the lowered thyroid hormone level and hypothyroidism can be moderated by supplementing thyroid hormone, the nephrogenic diabetes are treatable by carbonic anhydrase inhibitor acetazolamide or amiloride, and the heightened serum calcium can be against by measuring or neuroimaging parathyroid hormone and the glands, at most a surgery [14]. In other words, if it is assured that certain patients don't have high genetic loadings for MD, lithium treatment even in the long term can be effective and helpful to their mental health.

3.2. Subcutaneous esketamine

Ketamine and esketamine are usually referred to as anesthetic medications with high safety factor and effectiveness, but researchers have recently explored their potential as new therapies for UD and BD's depressive episode [16]. Ketamine can efficiently reduce the depressive symptoms in two hours after the infusion and the effects can peak in 24 hours, and the high efficiency has established its position in BD and UD treatment [16]. In a study, esketamine is given to both UD and BD patients to observe the medication's impact on their symptoms, and it is observed that the efficacy of esketamine doesn't vary between the BD group and UD group, lowering their Montgomery—Asberg Depression Rating Scale (MADRS) scores significantly [16]. The MADRS score reveals patients' risk of suicide, which keeps decreasing after exposed to esketamine treatment, and reduces further after repeated administrations [16].

Every 15 minutes, the safety of the esketamine is monitored through measurement of the trial participants' blood pressure and pulse rates, and it shows that adverse reactions are quite mild that didn't affect the participation [16]. The average blood pressure and average pulse rate didn't differ with the change of esketamine doses which are 0.5, 0.75, and 1.0mg/kg, proving that the safety of using esketamine as treatment for UD and BD is guaranteed [16].

3.3. Electroconvulsive (ECT) therapy

ECT is an effective treatment that is more widely used as treatment of UD, but it is also applicable for BD. It is especially helpful to treat certain clinical symptoms, such as psychotic depression, serious attempt to commit suicide, and depression recalcitrant to treatment [17]. Through comparison of ECT's effect on BD and UD patients, it is found that ECT works better and more efficiently for BD patients than UD patients [17]. However, ECT is effective equally for the clinical remission of both BD and UD, which doesn't change due to the existence of mania episodes, confirming ECT's usability on BD patients.

Despite its splendid impression on BD and UD remission and its antisuicidal property, ECT is essentially only used on a tiny percentage of patients with severe depression since it has the potential for some negative side effects. ECT may lead to manic switch of BD patients, but the treatment of this symptom during ECT course is continuing ECT until the phase turns neutral [17]. In addition, ECT potentially results in cognitive impairment, which is usually memory impairment that happens on the day of treatment, but some patients may experience permanent retrograde amnesia [17,18]. Therefore,

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it is unlikely that ECT therapy can be generalized to all patients with BD or UD, especially the patients whose symptoms are not serious enough due to the possible risk brought by its usage.

3.4. Light therapy

Light therapy or phototherapy is primarily applied for seasonal affective disorder (SAD), of which the milder form is also known as the winter blues. Since the natural light resource is important and positively correlated to people's mood, SAD may occur in winter when the light resource decreases, and phototherapy works by exposing patients to intense light sources some time every day [18]. According to previous studies, light therapy as the adjunct of antidepressants carried out at midday is helpful to BD patients, offering a stable and strong antidepressant response [19]. Within the six weeks' study, patients experiencing bright light therapy at noon show 68.2% rate of remission, and reported lower depressive levels, better global functioning, and no extreme mood switch [19]. However, the effect of using dim red light or holding phototherapy in the morning is far less significant, which reveals the importance of light intensity and the timing when patients receive phototherapy [19]. In addition, the effect of light therapy on BD patients in the study presents a large increase after week 4, thus indicating that light therapy may need to be applied perseveringly to achieve its optimal effect.

4. Conclusion

The article has introduced how clinicians may be able to diagnose BD and UD accurately in an early stage when the mania symptoms haven't presented yet. However, these diagnosing methods all have some limitations or disadvantages, and the most generalizable way is for the clinicians to detect possible risk of BD based on patients' clinical characteristics and demographics such as family history of BD. When the disorder of patients is not clear, it may be necessary for the clinicians to apply treatments that are helpful and cause no harm to both BD and UD, instead of treating patients with antidepressants that exacerbate BD. Some applicable treatments include lithium, ketamine/esketamine, ECT, and light therapy. Although these treatments may have some drawbacks, the clinicians can use it as a reference, combining these treatments with other methods, with the aim of causing least harm to BD and UD patients in the early stage.

At present, research on BD and UD is still not enough to develop a generalized treatment or diagnostic approach, but the situation may change if there is an expanded sample size and more clinical research about BD and UD patients, especially if the researchers can cooperate with mental hospitals. However, new medication's effect on patients involves ethical issues, which may make certain research difficult to proceed and is the common problem for all drug developments. Present studies haven't found an efficient, affordable, and 100% accurate way to classify BD and UD, but the potential of machine learning to differentiate BD and UD is worth expecting. Along with the development of technology and understanding of mental disorders, it can be believed that in the short future, better medication and diagnostic methods can be developed to treat UD and BD.

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