Therapeutic Approaches to Dysthymia

Artificial Intelligence (AI) in Psychiatry

An Assessment of Emotional State

Therapeutic Approaches to Dysthymia

Discovering Thoughts, Inventing Future
Global Journal of Medical Research: A Neurology and Nervous System
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<thead>
<tr>
<th><strong>Dr. Han-Xiang Deng</strong></th>
<th><strong>Dr. Pina C. Sanelli</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>MD., Ph.D</td>
<td>Associate Professor of Radiology</td>
</tr>
<tr>
<td>Associate Professor and Research Department</td>
<td>Associate Professor of Public Health</td>
</tr>
<tr>
<td>Division of Neuromuscular Medicine</td>
<td>Weill Cornell Medical College</td>
</tr>
<tr>
<td>Davee Department of Neurology and Clinical Neurosciences</td>
<td>Associate Attending Radiologist</td>
</tr>
<tr>
<td>Northwestern University Feinberg School of Medicine</td>
<td>NewYork-Presbyterian Hospital</td>
</tr>
<tr>
<td>Web: neurology.northwestern.edu/faculty/deng.html</td>
<td>MRI, MRA, CT, and CTA</td>
</tr>
<tr>
<td></td>
<td>Neuroradiology and Diagnostic Radiology</td>
</tr>
<tr>
<td></td>
<td>M.D., State University of New York at Buffalo, School of Medicine and Biomedical Sciences</td>
</tr>
<tr>
<td></td>
<td>Web: weillcornell.org/pinasanelli/</td>
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<tr>
<th><strong>Dr. Roberto Sanchez</strong></th>
<th><strong>Dr. Michael R. Rudnick</strong></th>
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<tbody>
<tr>
<td>Associate Professor</td>
<td>M.D., FACP</td>
</tr>
<tr>
<td>Department of Structural and Chemical Biology</td>
<td>Associate Professor of Medicine</td>
</tr>
<tr>
<td>Mount Sinai School of Medicine</td>
<td>Chief, Renal Electrolyte and Hypertension Division (PMC)</td>
</tr>
<tr>
<td>Ph.D., The Rockefeller University</td>
<td>Penn Medicine, University of Pennsylvania</td>
</tr>
<tr>
<td>Web: mountsinai.org/</td>
<td>Presbyterian Medical Center, Philadelphia</td>
</tr>
<tr>
<td></td>
<td>Nephrology and Internal Medicine</td>
</tr>
<tr>
<td></td>
<td>Certified by the American Board of Internal Medicine</td>
</tr>
<tr>
<td></td>
<td>Web: uphs.upenn.edu/</td>
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<tr>
<th><strong>Dr. Feng Feng</strong></th>
<th><strong>Dr. Seung-Yup Ku</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston University</td>
<td>M.D., Ph.D., Seoul National University Medical College, Seoul, Korea Department of Obstetrics and Gynecology</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Seoul National University Hospital, Seoul, Korea</td>
</tr>
<tr>
<td>72 East Concord Street R702</td>
<td></td>
</tr>
<tr>
<td>Duke University</td>
<td></td>
</tr>
<tr>
<td>United States of America</td>
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<tr>
<th><strong>Dr. Hrushikesh Aphale</strong></th>
<th><strong>Santhosh Kumar</strong></th>
</tr>
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<tbody>
<tr>
<td>MDS- Orthodontics and Dentofacial Orthopedics.</td>
<td>Reader, Department of Periodontontology, Manipal University, Manipal</td>
</tr>
<tr>
<td>Fellow- World Federation of Orthodontist, USA.</td>
<td></td>
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<tr>
<th><strong>Gaurav Singhal</strong></th>
<th><strong>Dr. Aarti Garg</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Master of Tropical Veterinary Sciences, currently pursuing Ph.D in Medicine</td>
<td>Bachelor of Dental Surgery (B.D.S.) M.D.S. in Pedodontics and Preventive Dentistr Pursuing PhD in Dentistry</td>
</tr>
<tr>
<td>Name</td>
<td>Education/Qualifications</td>
</tr>
<tr>
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</tr>
<tr>
<td>Sabreena Safuan</td>
<td>Ph.D (Pathology) MSc (Molecular Pathology and Toxicology) BSc (Biomedicine)</td>
</tr>
<tr>
<td>Arundhati Biswas</td>
<td>MBBS, MS (General Surgery), FCPS, MCh, DNB (Neurosurgery)</td>
</tr>
<tr>
<td>Getahun Asebe</td>
<td>Veterinary medicine, Infectious diseases, Veterinary Public health, Animal Science</td>
</tr>
<tr>
<td>Rui Pedro Pereira de Almeida</td>
<td>Ph.D Student in Health Sciences program, MSc in Quality Management in Healthcare Facilities</td>
</tr>
<tr>
<td>Dr. Suraj Agarwal</td>
<td>Bachelor of dental Surgery Master of dental Surgery in Oromaxillofacial Radiology. Diploma in Forensic Science &amp; Oodntology</td>
</tr>
<tr>
<td>Dr. Sunanda Sharma</td>
<td>B.V.Sc.&amp; AH, M.V.Sc (Animal Reproduction, Obstetrics &amp; gynaecology), Ph.D.(Animal Reproduction, Obstetrics &amp; gynaecology)</td>
</tr>
<tr>
<td>Osama Alali</td>
<td>PhD in Orthodontics, Department of Orthodontics, School of Dentistry, University of Damascus. Damascus, Syria. 2013 Masters Degree in Orthodontics.</td>
</tr>
<tr>
<td>Shahanawaz SD</td>
<td>Master of Physiotherapy in Neurology PhD- Pursuing in Neuro Physiotherapy Master of Physiotherapy in Hospital Management</td>
</tr>
<tr>
<td>Prabudh Goel</td>
<td>MCh (Pediatric Surgery, Gold Medalist), FISPU, FICS-IS</td>
</tr>
<tr>
<td>Dr. Shabana Naz Shah</td>
<td>PhD. in Pharmaceutical Chemistry</td>
</tr>
<tr>
<td>Raouf Hajji</td>
<td>MD, Specialty Assistant Professor in Internal Medicine</td>
</tr>
<tr>
<td>Vaishnavi V.K Vedam</td>
<td>Master of dental surgery oral pathology</td>
</tr>
<tr>
<td>Surekha Damineni</td>
<td>Ph.D with Post Doctoral in Cancer Genetics</td>
</tr>
<tr>
<td>Tariq Aziz</td>
<td>PhD Biotechnology in Progress</td>
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Artificial Intelligence (AI) in Psychiatry – A Summary
By Saagar S Kulkarni, Rohan S Kulkarni & Kathryn E Lorenz

Abstract- This bibliographic review appraises Artificial Intelligence (AI) theory’s applications in the field of psychiatry. Globally hundreds of millions of people suffer from mental disorders. Hundreds of thousands of people in the world commit suicide and also die from an illicit drug overdose due to addiction. Diagnosis and therapy of psychiatric disorders are complex, and machine/computer diagnostic tools for physicians are urgently needed to bolster their decision-making. This study includes various applications AI/machine learning algorithms in various sub-specialties of psychiatry. AI/ML-based psychiatry offers better value over conventional psychiatry in mood disorders, learning disabilities, children and adolescents’ mental illnesses, and substance abuse. However, numerous implementation challenges of AI in clinical psychiatric practice remain.

Keywords: AI and machine learning in mood disorders, AI and machine learning in substance abuse, AI and machine learning in mental illnesses in children and adolescents, AI and machine learning in learning disabilities.

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Keywords: AI and machine learning in mood disorders, AI and machine learning in mental illnesses in children and adolescents, AI and machine learning in learning disabilities.

I. Introduction

The key goal of this paper is to evaluate applications of Artificial Intelligence (AI) and machine learning in the field of psychiatry. The past thirty years have shown rapid progress in the use of AI to medical images based fields of radiology, neurology, pathology, and ophthalmology. In addition, as shown in Figure 1, AI has been an essential tool in various medicine-related applications.

Figure 1: AI In Medicine

In the field of psychiatry, as shown in Figure 2, AI has applications in disease determination, categorizing various psychiatric conditions, and various mood disorders.

Figure 2: AI in psychiatry
In this article, first were viewed Artificial Intelligence-based psychiatry research in various clinical situations that are included in Figure 2. Secondly, different ethical and social issues of AI Artificial Intelligence faces for use in psychiatric applications are discussed.

II. Artificial Intelligence or AI

By definition, Artificial Intelligence or AI is an intelligence that is not natural or is artificial. AI is founded on various statistical principles where a phenomenon is ‘learned’ by a machine. The phenomenon gets cleverer as more learning of it is managed. After a suitable quantity of this training, then, AI can be, as a human being, useful for making decisions. In this section important AI terms and ML-based algorithms are explained.

a) AI basics

In this section, important AI terms are briefly discussed.

Machine learning (ML) approach pools statistical modeling and computers together to learn from available data. ML is characterized into ‘supervised’ and ‘unsupervised’ learning.

1. Supervised learning method builds a forecast model of a known output and input data set. The model is then utilized to predict new output given new output information. This approach is well suited for both i) ‘classification’ model for output categories (e.g., a patient has an illness or patient does not is based on an MRI scan) and ii) ‘regression’ model where the output variable is continuous (e.g., patient’s weight).

2. Unsupervised learning approach groups data together, to comprehend the intrinsic structure of the data, based on their resemblances and when there is no output prediction variable and input data is not labeled. E.g., clustering patterns in a sample of patients with an illness that could lead to new drug therapy.

3. Semi-supervised learning is a blend of ‘Supervised’ and ‘Unsupervised’ learning approaches (e.g., conglomerate algorithms of ‘classification’ and ‘clustering’). Artificial Neural Networks or ANNs attains an output forecast that results from numerous independent phases of computations and weightings. ANN, similar to a neuron network in a brain, has a set of artificial layered/connected neurons to transfer data through the web.

b) ML Algorithms

Supervised Machine Learning modeling involves the splitting the available information into both ‘training’ (or ‘educating’) and ‘testing’ data sets for verification. In Supervised ML, the following algorithms are extensively utilized:

1. Regression: For ML, both ‘Linear regression’ (use of least squares regression line with the lowest error among the cause/independent variables and the effect/dependent variables), and ‘Logistic Regression’ (used for binary outcomes of ‘yes/no,’ or ‘no illness/illness’ with forecasters types of either categorical or continuous) methods are commonly used based on data characteristics.

2. Decision Tree (DT): The decision tree-based ML algorithm includes a set of rules that describes the pathway from the root to the leaves. The feature of interest is analyzed at the node while the output of the analysis is assigned at the branch.

3. Naive Bayes: ML algorithm based on Naive Bayes postulates that the characters under assessment are independent of each other.


5. k-Nearest Neighbor (k-NN): k-Nearest Neighbor based ML algorithm is utilized for data categorization of nonparametric grouping. The ‘k’ is defined as the square root of the number of incidences and its remoteness from a pre-selected point. Moreover, the categorization is established on the number of k neighbors.

6. Random Forest (RF): ML with Random Forest algorithm, which prevents ‘overfitting,’ is an efficient tool for an accurate estimate of classifiers. Nevertheless, the RF-based ML algorithms are less proficient than the SVM/or k-NN/logistic regression-based ML methods.

7. Convolutional Neural Networks (CNNs): ‘Convolution’ is a form of a mathematical function on two functions that produces a third function. Convolutional Neural Networks, feed-forward networks, learn by using numerous layers of nodes and several replications of both ‘analyzing’ and ‘weighting’ the patterns it recognizes in the images. The value/size of weights is decided based on how correctly it classifies a design or structure.

III. AI in Mood Disorders

Health professionals use ‘mood disorder,’ a mental health category, to generally label all categories of depression and bipolar disorders. However, a significant overlap in symptoms exists between these disorders. This is where AI and machine learning come into play with their potential to improve the accuracy of diagnosing different mood disorders.

a) AI In Depression

Having less concern in everyday activities, feeling unhappy or miserable, and other similar
indications for minimum two weeks may signal depression.

In 2020, Richter et al. research focused on a novel methodology to assess for dissimilarities in cognitive prejudices amid subclinical depressed and anxious persons. They, based on the stages of depression and anxiety indications, separated 125 people into four groups. A wide-ranging behavioral examination sequence revealed and measured numerous ‘cognitive–emotional’ biases. The authors developed sophisticated machine learning (ML) tools to scrutinize these outcomes. These techniques uncovered distinctive configurations that differentiate depression against anxiety. The model distinguished well between symptomatic members (with high signs of depression, anxiety, or both anxiety) compared to the control group with no symptoms. It resulted in a 71.44% classification prediction accuracy (specificity) for ‘high anxiety/high depression’ and 70.78% classification prediction accuracy(specificity) for ‘low anxiety and low depression. ’ In addition, the model yielded in classification prediction accuracy of 68% for ‘high depression’ while 74.18% for ‘high anxiety. ’

Li et al. in 2019 used electroencephalogram (or EEG to detect electrical activity in the brain using small, metal electrodes attached to the patient’s scalp) and ML to better diagnose depression amongst 28 individuals. The Mini-International Neuropsychiatric Interview (MINI) approach was utilized by the physicians as the measure by the authors for the identification of depression. Original features of ‘power spectral density’ and ‘activity’ were individually obtained by means of auto-regress model’ and the Hjorth algorithm with specific time frames. Two distinct methods of ‘ensemble learning’ and ‘deep learning’ processed these features. The ensemble learning used a deep forest transformation of the original features to new and a support vector machine (SVM) as a classifier. In the deep learning method, the authors added spatial data of EEG caps to both features and implemented Convolutional Neural Network (CNN) for recognition. Their approach yielded accuracy of 89% using the ensemble model and power spectral density. The deep learning method achieved 84.75% accuracy using the activity. The research showed that EEG could be utilized as a dependable gauge for recognizing depression.²

In 2018, Dinga et al.’s work assessed the predictive value of a varied range of clinical, biological, and psychological features for forecasting the progression of depression and targeted to detect the top predictors. The authors evaluated 804 patients with dysthymia or unipolar depression involving 81 of these features. The patients were clinically monitored for two years. The patients, applying a latent class growth analysis, were grouped into (i) the presence or lack of a depression, and (ii) disease course trajectory groups of rapid remission, gradual improvement, and chronic. The authors used a ‘penalized logistic regression’ to forecast depression progression and to also assess the predictive magnitude of distinct variables. They, established on the inventory of depressive symptomatology (IDS), estimated a swift reduction course of depression with an area under the Receiver Operating Characteristic (ROC) curve of 0.69 with 62% accuracy. Also, at follow-up, the existence of an MDD identification presented an area under ROC of 0.66 and 66% accuracy. Out of the sizeable set of considered parameters, only the IDS offered prognostic magnitude for course forecast on an individual level. Though the accuracy of course prediction was moderate at best.³

Chekroud et al. in 2016, came up with a procedure to evaluate whether patients with depression will attain symptomatic reduction from a twelve-week treatment of an antidepressant such as citalopram. The authors used self-reported data from 1,941 patients with depression from ‘ClinicalTrials.gov’ (number NCT00021528) to detect variables with the highest predictive of medical treatment results. They utilized these variables for training an ML model to forecast clinical depression remission. This model was externally confirmed by them in the escitalopram treatment group of 151 patients from a separate clinical trial (number NCT00590863). The ML model was trained with 25 self-reported variables, with the most predictive of treatment outcome, from 164 patients. The model, after internal cross-validation, predicted outcomes with an accuracy of 64.6% with p<0.0001. The external validation of the 151 patients from the escitalopram treatment group attained an accuracy of 59.6% with p=0.043. The model, when applied to a combined escitalopram-bupropion treatment group of 134 patients, resulted in an accuracy of 59.7% with p=0.023. However, when used for a combined venlafaxine-mirtazapine group of 140, the model displayed an accuracy of 51.4% with p=0.53, suggesting the model’s specificity to core mechanisms. The authors showed that use of the ML models by extracting available clinical test data can allow potential identification of patients prone to have a positive response to a specific antidepressant.⁴

In 2015, Patel et al., for accurate diagnosis and treatment of depression, studied numerous ML approaches with ‘multi-modal imaging’ and ‘non-imaging’ whole brain and network-based features as inputs. The authors recruited 33 older depressed and 35 late-life non-depressed individuals. Their demographics and cognitive ability scores were first documented, followed by attainment of their brain characteristics using multi-modal MRI. Linear and nonlinear ML methods were then examined by the authors for appraising models’ predictive accuracy. An ‘alternating decision trees’ method projected the highest accurate forecast models for late-life depression diagnosis with 87.27% accuracy, while the treatment response attained 89.47% accuracy. The diagnosis model included
measures of age, Mini-mental state examination score, and structural imaging (e.g., whole brain atrophy and global white matter hyperintensity burden). The treatment response model included measures of structural and functional connectivity. Thus multi-modal imaging coupled with a ‘non-imaging’ methods-based approach can predict depression diagnosis and treatment response for older age patients and allow custom-made depression treatment for them.⁵

In 2013, Hosseinifard et al.’s work demonstrated, based on 45 un-medicated depressed patients and 45 normal subjects, that nonlinear analysis of EEG is valuable method for discerning depressed patients and control subjects. From the EEG signal, the authors extracted four nonlinear features (Lyapunov exponent, Higuchi fractal, detrended fluctuation analysis, and correlation dimension. For differentiating the two groups, the authors, as the classifiers, used ‘k-nearest neighbor,’ ‘linear discriminant analysis’ and ‘logistic regression.’ The highest classification accuracy of 83.3% was achieved by correlation dimension and LR classifier. The authors improved their model when all nonlinear features were collectively applied to classifiers yielding a classification accuracy of 90% by LR classifier and all nonlinear features.⁶

b) AI in Bipolar Disorders (BD) and Schizophrenia (SZ)

Bipolar disorder is a circumstance when a person has phases of depression interchanging with phases of raised mood or mania. In comparison, an individual with schizophrenia interprets reality abnormally and has two or more symptoms out of: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms.

Tomasik et al. in 2021, based on blood biomarker data and an online questionnaire, developed a diagnostic algorithm to decrease the misidentification of ‘Bipolar Disorder’ (BD) as ‘Major Depressive Disorder’ (MDD). Their model utilized data from patients aged 18-45 years with depressive symptoms. In order to establish their depression diagnosis, phone interviews were conducted after patients answered an online questionnaires and provided dried blood samples for biomarker assessment. The authors applied ‘Extreme Gradient Boosting’ followed by nested cross-validation to train and validate models distinguishing BD from MDD in individuals who self-described diagnosis of MDD. The area under the ROC curve for splitting participants with ‘BD diagnosed as MDD’ from those with ‘truthful MDD’ was 0.92 with a 95% Confidence Interval of 0.86–0.97. Validation in cases of participants without previous diagnosis of mood disorder diagnosis produced area under the ROC of 0.89 and 0.90 for distinguishing newly identified BD and subclinical low mood from MDD, respectively. Validation in participants with previous BD identification showed 86% sensitivity. The authors’ algorithm thus accurately recognized patients with BD in numerous clinical circumstances, which could assist in accurate clinical identification and management of BD.⁷

In 2021, Siqueira Rotenberg et al.’s research analyzed ML approaches as a likely forecaster in BD-related depressive relapses. The authors applied ML algorithms of RF, SVM, Multi-layer Perceptron, and Naïve Bayes, to a group of 800 patients (507 with depressive relapses and the remaining 293 without). The ML algorithms’ prediction ranged between 61 and 80% in terms of F-measure. The RF approach’s performance was the best, with 68% for a relapse cohort and 74% without. Thus, ML algorithms can assist in clinical decision-making for patients requiring BD management.⁸

Fernandes et al. in 2020, using immune and inflammatory biomarkers in peripheral blood and cognitive biomarkers utilizing ML, established a model with probabilistic multi-domain data integration in order to predict the identification of BD and schizophrenia (SZ) based on 416 participants. Their model for ‘with the BD’ vs. ‘without’ displayed a sensitivity of 80% and specificity of 71%. For ‘with the SZ’ vs. ‘without’, the model produced sensitivity and specificity of 84% and 81%, respectively. However, the model was moderately effective for the discriminating between BD and SZ with a sensitivity of 71% and specificity of 73%.⁹

In 2019, Belizario et al. work focused on understanding if Predominant polarity (PP) is a vital specifier of BD. The authors applied ML algorithms to establish a patient’s PP but without including the number and polarity of past incidents, and searched for the links between PP and demographic/clinical factors. Clinical and demographic characteristics were gathered from 148 BD patients using a tailored questionnaire. The authors utilized the RF algorithm to categorize patients into either ‘depressive’ or ‘manic’ PP and uncover which factors were linked to the specifier.

The model produced an area under the ROC curve of 74.72% in categorizing patients into either ‘depressive’ or ‘manic’ PP. The top factors selected by the model included: age at the first depressive episode, number of hospitalizations, BD Type II, manic onsets, and delusions. Additionally, anxiety disorders, alcohol dependence, eating disorders, and substance dependence appeared to be linked with PP. The research work demonstrated that the ML could assist in a patient’s PP diagnosis.¹⁰

In 2018 Perez Arribas et al. applied a ‘signature-based’ learning method to a cohort of 130 participants (48 with BD, 31 with borderline personality disorder, and 51 control) who, using a bespoke smartphone app, daily submitted for one-year mood ratings. The model was used to record the progressing interrelations amongst the distinctive features of mood and use this information to categorize participants’ diagnosis and to forecast...
succeeding mood status. The model could differentiate amongst the three participant cohorts, with categorization accuracy of classified 75% into the correct diagnostic cohort versus with 54% utilizing standard methods. Additionally, succeeding mood scores were accurately forecasted with higher than 70% accuracy. The forecast of mood was most accurate in the control group (89–98%), followed by bipolar disorder (82–90%) and borderline personality disorder (70–78%). The authors thus successfully demonstrated the signature method to analyze mood data in terms of diagnostic classification and prediction of future mood.¹¹

Schnacket al. in 2014 work focused on utilizing MRI scans to distinguish SZ from BD. Their study included scans, using a 1.5 T MRI scanner, of 198 participants (66 each with SZ, with BD, and the healthy/control). Three SVMs, based on their gray matter density images, were trained to distinguish patients with SZ from the control group, patients with SZ from those with BD, and patients with BD from the control cohort. The model separated a) SZ patients from BD patients with an accuracy of 88%, and b) patients with SZ from control participants with an accuracy of 90%. The approach was moderately accurate is separating BD patients from the control cohort with correct categorization (accuracy for BD 53% and control 67%). Application of 1.5 T MRI scanner-based models on a validation set from a 3 T MRI scanner provided average categorization accuracies of 76% (control vs. SZ), 66% (BD vs. SZ), and 61% (control vs. BD). This research work, based on structural MRI scans, showed that the accurate separation of SZ from BD using gray matter pathology could aid in the differential diagnosis of these disorders.¹²

AI in Suicidality with Mood Disorders

Suicide, an individual taking their own life, is a catastrophic response to traumatic life circumstances. A majority of all suicides are by individuals who agonize from mood disorders. Thus, avoidance of suicide among those who suffer from mood disorders is a key to preventing a suicide.

In 2021 Hong et al.’s research assessed a group of 66 adolescents and young adults with MDD diagnosis. They obtained T1-weighted MRI scans which were categorized utilizing the SVM algorithm to separate ‘suicide attempters’ from people with ‘suicidal ideation but without attempts.’ Their model identified suicide attempters and individuals with ‘suicidal ideation but without attempts’ with an accuracy of 78.59%, the sensitivity of 73.17%, and specificity of 84.0%. For the ‘suicide attempters,’ the Positive Predictive Value (PPV) of suicide attempts was 88.24%, while the Negative Predictive Value (NPV) was 65.63%. The authors were able to derive the top 10 ranked classifiers for a suicide attempts. The outcomes of this research specified that structural MRI-based information could be beneficial for the categorization of suicide possibility among MDD patients.¹³

Agne et al. in 2020 work focused on understanding the reasons why patients with obsessive-compulsive disorder (OCD) have a higher risk of suicide attempts vs. the general population. The authors used the ML method to find out if the driver(s) of the higher suicide attempts include the sociodemographic factors and comorbidities. The analysis included 959 patients with OCD using an elastic net model to identify the forecasters of suicide attempts utilizing sociodemographic and clinical factors. The occurrence of suicide attempts in the sample authors studied was 10.8%. The model yielded a) previous suicide planning, b) previous suicide thoughts, c) lifetime depressive episodes, and d) intermittent explosive disorder as relevant predictors of suicide attempts. The elastic net model with an area under the curve of 0.95 thus provided a high accuracy performance algorithm.¹⁴

In 2019, Carson et al. developed a ML algorithm utilizing natural language processing of electronic health records to detect suicidal conduct among youths those are hospitalized for psychiatric issues. A total of 73 individuals from the northeastern US, with an electronic health record, available before hospitalization, who responded to a survey for a record of suicide attempts in the past year before the hospitalization were selected for this study. The clinical notes from these records prior to inpatient admission were processed for phrases linked with the suicide attempt. The authors then applied the RF machine learning approach to develop a categorization model. The model demonstrated i) a sensitivity of 0.83, ii) specificity of 0.22, iii) area under the curve of 0.68, iv) a PPV of 0.42, v) NPV of 0.67, and vi) an accuracy of 0.47. The phrases highly linked with suicide attempts are grouped around terms related to suicide, psychotropic medications, psychiatric disorders, and family members. This research thus displayed a reasonable achievement of a natural language processing method in the identification of suicide attempts among hospitalized youths with a psychiatric background.¹⁵

In 2017, Jihoon et al.’s work focused on if the data from multiple clinical scales have categorization power for detecting actual suicide attempts. Five hundred seventy-three participants with disorders of depression and anxiety completed questionnaires, including 31 psychiatric scales, concerning their record of suicide attempts. The authors first trained an ANN classifier with total of 41 factors (31 psychiatric scales and ten sociodemographic factors), followed by a ranking of the impact of each factor on the categorization of suicide attempts. The model demonstrated an accuracy of detecting suicide attempts of 94% in one month, 91% in one year, and 87% in a lifetime. The areas under the ROC curves for suicide attempts detection were 0.93 for one month, 0.87 for
one year, and 0.89 for a lifetime. The questionnaire regarding ‘Emotion Regulation’ had the highest impact among all factors. This ML-based research thus demonstrated that self-reported clinical scales could be valuable for the categorizing of suicide attempts.16

Passos et al.’s study in 2016 looked at various clinical risk variables to calculate the likelihood of an individual attempting suicide. Demographic and clinical variables based data from 144 patients, who were diagnosed with a mood disorder, was used for training an ML algorithm. This algorithm was then used by the authors in classifying new individuals as either ‘suicide attempters’ or ‘non-attempters.’ Three different ML algorithms were applied and assessed. All these algorithms separated ‘suicide attempters’ from ‘non-attempters’ with forecast accuracy ranging from 65% to 72% with p value <0.05. The Relevance Vector Machine (RVM) algorithm correctly forecasted the behavior of 103 of the 144 subjects producing 72% accuracy and an AOC of 0.77 with a p-value <0.0001. The critical predictor factors in discriminating ‘suicide attempters’ comprised of a) prior hospitalizations for depression, b) a record of psychosis, c) cocaine dependency, and d) posttraumatic stress disorder. Thus, the authors were able to identify demographic and clinical risk factors for suicide attempts in individuals with mood disorders.17

IV. AI IN ADDICTION

Despite harmful consequences, uncontrolled consumption of either a substance (e.g., drugs, alcohol, food) or a medium (e.g., technology). The person’s capacity to function in day-to-day life can become compromised with addiction even though the individuals know the habit is producing or will produce complications.

In 2021, Gao et al.’s study focused on a ‘proteome-informed’ ML algorithm to uncover an almost ideal compounds for anti-cocaine dependence. The authors using 32 ML different models, performed over 60K experimental drugs for side effects and repurposing possibilities. All of the current drug candidates did fail in both cross-target and Absorption/Distribution/Metabolism/Excretion/Toxicity (ADMET) screenings. However, the ML algorithms recognized numerous ‘nearly optimum’ possibilities for additional optimization.18

Choi et al.’s research in 2021 aimed to categorize predictor factors (e.g., environmental causes, social, and mental) that produce nicotine dependence in youth who consume e-cigarettes or hookah consumers and construct nicotine dependence fore cast models using ML algorithms of a) RF with Relief F and b) Least Absolute Shrinkage and Selection Operator or LASSO. These ML-based prediction models utilized data from the 2019 National Youth Tobacco Survey participants of 6,511 who were recognized as ever consumed either e-cigarettes or hookah. A final analysis based on 193 predictor factors showed a) witnessed e-cigarette use in their household, and b) perception of their tobacco use as top factors that could be utilized in public alertness for policymakers.19

In 2021 Wang et al.’s work focused on developing SVM models to recognize internet addiction and evaluate the effectiveness of cognitive behavior therapy (CBT) founded on ‘unbiased functional connectivity density or FCD. Total of 57 participants (27 with IA and 30 with healthy control or HC) provided resting-state fMRI before and after eight-week CBT meetings. The discriminatory FCDs were calculated as the characters of the support vector classification model to identify persons with IAs from the HCs. The authors’ model effectively separated participants with IA with an accuracy of 82.5% from HCs with an area under the curve of 0.91. Furthermore, FCDs of potential neuroimaging biomarkers for IA were confirmed as a) hyperactive-impulsive habit system, b) hypoactive-reflecting system, and c) sensitive interoceptive reward awareness system.20

In 2019, Symons et al.’s research efforts analyzed the performance of ML models vs. medical professionals to forecast alcohol addiction results in patients after CBT. Twenty-eight ML models were built and trained utilizing a)demographic and b) psychometric assessment data from 780 patients who had gone through a 12-week, abstinence-based CBT program for alcohol addiction. Additional 50 patients for prediction were assessed by i) ten addiction therapy experts, and with ii) twenty-eight trained ML models. The highest accuracy ML model of 74%was far superior vs. the four least accurate therapists, with 51% to 40% accuracy. However, the model’s robustness was low as the area under the ROC curve was only 0.49. The mean aggregate predictive accuracy of these 28 ML models was slightly better (56.6%) than the ten clinical therapists (56.1%). Thus the research showed that the highest performing prediction models have the potential to help the therapists in clinical settings.21

V. AI IN FORENSIC PSYCHIATRY

Forensic psychiatry tends toward a heavy emphasis on science, and forensic psychiatrists identify and handle mental disorders in the framework of the criminal judicial system.

In 2022, Hoffmann et al., using ML methods, explored aggression in 370 offender inpatients with schizophrenia spectrum disorders (SSDs). The SVM based models yielded the best accuracy out of all ML models, with an accuracy of 77.6% and an area under the ROC curve of 0.87. The most predictive factors in separating ‘aggressive’ from ‘non-aggressive’ in inpatients were a) negative behavior toward other
In 2021 Watts et al. applied ML techniques to predict the type of criminal wrongdoings in psychiatry patients, at an individual level. Multiple ML models (Random Forest, Elastic Net, SVM) were built and trained based on 1,240 patients in the forensic psychiatric health system. Using only 36 clinical factors, sexual crimes were forecasted by the authors, from both ‘non-violent’ and ‘violent’ offenses with a sensitivity of 82.4% and specificity of 60.0%. The authors, utilizing a binary classification model with 20 clinical factors, forecasted sexual and violent acts, with 83.3% sensitivity and 77.4% specificity. Furthermore, using 30 clinical factors, non-violent and sexual offenses can be separately forecasted with 74.6% sensitivity and 80.7% specificity. These results indicate that ML models can display higher accuracy than the current risk assessment tools (which also cannot individually predict) with the area under the ROC curve between 0.70 and 0.80. However, a considerable subset of patients in this analysis had a history in the criminal system preceding an official diagnosis. Thus, many of the factors that forecast these behaviors might result from the problems of past offenses.

Philipp et al., in 2020, using ML, investigated 569 predictor factors for their forecasting power for either ‘coercion’ or ‘no coercion’ in 358 patients (131 who did experience coercion while 227 who did not). The data was split (70/30%) first to find the best ML model (70% of data) and the remainder data (30%) for extracting most essential factors from the best model found. The best model had a balanced accuracy of 73.3% and an area under the ROC curve (a predictive power) of 0.85 with the top five prediction factors of a) threat of violence, b) actual violence toward others, c) the application of direct coercive measures during past psychiatric inpatient treatments, d) the PANSS poor impulse control, e) uncooperativeness, and hostility. This research confirmed prior discoveries and added detail on variables revealing the use of coercion.

**VI. AI in Personality Disorders**

Kinds of personality disorders are categorized into three groups/clusters, founded on similar features and indications. These personality disorders are:

1. Cluster A is categorized by odd, eccentric thought processes and, or conduct,
2. Cluster B is categorized by the overly emotional thought processes and, or unpredictable conduct,
3. Cluster C is categorized by anxious, fearful thought processes and, or conduct.

In 2014, Randa et al. built an ‘expert system,’ which mimics the ‘expert rational’ in deciphering a problem, of personality disorders to help assist in the early identification of the illness. The authors used a ‘Certainty Factor’ method to estimate the likelihood of someone is suffering from this illness. They demonstrated an approach to establishing the types of personality disorders founded on symptoms experienced. Their calculations based on the method of Certainty Factor displayed a 77.2% confidence level.

Berdahl, in 2010, developed a framework for etiology of Borderline Personality Disorder (BPD) by building a NN with restrictions from a) neuroanatomy, b) neurophysiology, and c) behavior. The NN models showed how various brain make-ups could interrelate during BPD. These NN simulations indicated that long-term depression (LTD) in the brain structures might clarify various BPD symptoms.

Hayat et al. in 2019 investigated aback propagation neural network (BPPN) model for the early discovery of type B personal disorder. The model used 43 data points for training and 34 for testing. The model’s output was cataloged into four identification classifications of type B personal disorder: i) anti-social, ii) borderline, iii) histrionic, and iv) narcissistic. The model achieved an accuracy of 90.7% in training and 97.2% in testing. The authors thus showed a high accuracy BPPN model to diagnose type B personal disorder.

**VII. AI in Child and Adolescent Psychiatry**

The child and adolescent psychiatric fields focus on the identification and the management of disorders of i) thinking, and ii) feeling and, or behavior disturbing children, adolescents, and their families.

In 2022 Dobias et al. utilized individual sociodemographic factors and depression symptoms as predictors to study the capacity to forecast ‘whether’ and ‘where’ adolescents (ages 12-17) get mental healthcare. The authors analyzed data from the 2017 National Survey of Drug Use and Health as a characteristic sample of non-institutionalized individuals in the US. The analysis included both RF and elastic net-based ML models. The model’s assessment was based on data from total of 1,671 youths (inpatient, outpatient, and other) with raised depressive symptoms. Only 53% of these youths sought care of any kind. Using the two predictors, the RF models explained no ‘pseudo-out-of-sample’ deviance in youth accessing any depression treatment, while elastic net models performed slightly better, explaining 0.80–2.50% ‘pseudo-out-of-sample’ deviance for access to all depression treatments. This research thus showed considerable limits in our ability to forecast ‘whether’ and ‘where’ youths access mental healthcare.
Haque et al.’s research in 2021 focused on ML algorithms for detecting depression among children and, or youths aged four to 17 years and factors that contribute to the illness. In this research, for modeling, multiple available datasets from 2013-14 for the Australian children and youths were used. In the depression recognition step, MF algorithms based on RF, XGBoost, Decision Tree, and Gaussian Naive Bayes were used. The RF-based ML algorithm was the best in forecasting depressed categories by 99% with an accuracy of 95%.29

In 2021, Price et al. studied the association between childhood maltreatment and structural alterations in the brain. They utilized ML based on elastic net regularized regression to detect if and how brain structure differed among young adults (18-21 years of age) with and without a record of mistreatment. A total of 384 individuals completed an evaluation of juvenile trauma experience and a structural MRI. A model which included five subcortical volumes, seven cortical thicknesses, and 15 surface areas yielded an area under the ROC curve of 0.71 with a p-value less than 0.001. The individuals with a mistreatment past had smaller surface areas and cortical thicknesses predominantly in 'frontotemporal' areas. They also displayed more enormous cortical thicknesses in occipital regions and larger surface areas in frontal regions. This research clearly demonstrated that childhood abuse is associated with numerous measures of structure in the brain.30

To diagnose anxiety and depression, McGinnis et al. in 2018 proposed the application of a 90-second fear induction task during which time an individual’s motion is monitored using a wearable sensor that is commercially available. In contrast, current diagnostic approaches for detecting the illness takes days. A multitude of ML models was utilized by the authors to extract from one 20-second phase of the task to forecast diagnosis. The best model demonstrated a diagnostic accuracy of 75%, comparable to current diagnostic methods, however, at a relatively insignificant fraction of the time and cost.31

In 2017 Saxe et al. studied if ML methods can generate predictive categorization models for childhood Posttraumatic Stress Disorder (PTSD) and also if explicit factors can be recognized for the disorder. The authors applied ML forecasting categorization methods to 105 biopsychosocial risk variables. The variables were based on data which was collected from 163 injured hospitalized children that were diagnosed with PTSD three months after their discharge. A forecasting categorization model was realized by the authors with meaningful accuracy. A model built based on subsets of possibly causally relevant characters achieved similar forecasting ability paralleled to the best model constructed with all factors. The authors found that the Causal Discovery Character Choice-based methods recognized 58 factors, of which ten were classified as very stable. Thus authors using ML algorithms could establish both forecasting categorization models for childhood PTSD and categorize numerous causal factors.32

VIII. AI in Attention Deficit Hyperactivity Disorder (ADHD)

An individual with attention deficit hyperactivity disorder (ADHD) condition has differentiations in brain development and brain activity, from a normal brain, which disturbs attention, the ability to sit static, and self-discipline. It is critical to diagnose children with displaying substantial losses and symptoms of ADHD at an early age as early detection and treatment may lead to more effective, and shorter treatment.

In 2011, Delavarian et al. explored the use of AI in diagnosing children with different behavioral disorders. By using the Matlab toolbox for pattern recognition known as “Ptools,” the authors examined a total of 16 different classifiers and their accuracies in differentiating between childhood conditions that present with similar symptoms. The specific disorders included ADHD, depression, anxiety, comorbid depression and anxiety, and conduct disorder (i.e., the outputs). The study involved 306 children, and 38 common symptoms of childhood behavioral disorders were used as inputs. The authors concluded, from the data collected, that the nearest mean classifier was the most accurate classifier, with an accuracy of 96.92%. Not only was it the most accurate of the classifiers examined, but it was also significantly more accurate in diagnosing children with behavioral disorders compared to not using a classifier at all (87.51%). The authors showed that the use of specific classifiers can help aid in improving the correct diagnosis of childhood behavioral disorders. This is key, as correctly identifying patients with these disorders at earlier stages in life will allow for earlier interventions and subsequently improved outcomes.33

In 2010, Anuradha et al.’s research applied the SVM Algorithm in diagnosing ADHD. The Support Vector Machines are a frequently utilized artificial intelligence technique; by constructing a hyperplane or sets of hyperplanes in a high-dimensional space, the authors used this technique to classify a group of 100 children, ages 7-10 years old, as either having or not having ADHD. The input to the SVM Algorithm was primarily in the form of answers to a questionnaire. The questionnaire consisted of 6 yes-or-no questions, with values of 1 given to “yes” answers and 0 assigned to “no” answers. After the input data was fed into the Algorithm, the output was recorded as either “1” for diagnosis of ADHD or “0” for no diagnosis of ADHD. According to the data reported in this study, the SVM Algorithm was correct in diagnosing/not diagnosing
ADHD 88.7% of the time when comparing the output from the Algorithm to the diagnoses made by trained physicians. (While this study design assumes that the physicians are correct in their diagnoses, it is promising that this Algorithm can match the diagnosis of trained physicians nearly 90% of the time).\(^{34}\)

Ariyarathne et al. in 2020, based on a CNN model, proposed using fMRI data of the “resting brain” in conjunction with seed-based correlation analysis to classify and identify children with ADHD. Seed-based correlation analysis works by computing the functional connectivity between different regions within the brain. Four specific brain regions were studied, including the Medial Prefrontal Cortex (MPC), Posterior Cingulate Cortex (PCC), Left Temporoparietal Junction (LT), and Right Temporoparietal Junction (RT). From the seed-based correlation analysis of these brain regions, a Convolution Neural Network (CNN) was used as a pattern recognition classifier to distinguish between patients with ADHD and patients without ADHD (controls). According to the results, the accuracy of classification of patients with ADHD was highest in the Medial Prefrontal Cortex (MPC) region of the brain at 85.21%. This should not come as a surprise, claimed the researchers, as the primary region of the brain implicated with ADHD is the prefrontal cortex.\(^{35}\)

**IX. AI in Geriatric Psychiatry**

Geriatric psychiatry, the practice of psychiatry in older adults, is a vital field of psychiatry. Many of aging-related body changes (e.g., blood and nervous system) might escalate an individual’s probability to suffer depression, mental impairment, and dementia.

In 2021 Yadgir et al.’s study focused on ways to categorizing patients, aged above 59 years, with a high risk of Cognitive Impairment (CI) using ML-based on factors accessible from electronic health records (EHRs). The authors used records of 1,736 adults who were dismissed from three emergency departments (EDs). Each adult’s CI was estimated by the authors, based on the ‘Blessed Orientation Memory Concentration’ (BOMC) test conducted in the ED. A ‘nested cross-validation’ framework was utilized to assess ML algorithms. Using BOMC scores, 121 (7% of 1,736) adults tested positive for potential CI. The top-performing ML algorithm, of XGBoost, forecasted BOMC positivity with an area under the ROC curve of 0.72. With a categorization threshold of 0.4, the model yielded 0.73 sensitivity, 0.64 specificity, an NPV of 0.97 and a PPV of 0.13. This work showed that an ML algorithm built on EHR data could separate patients at higher risk for CI.\(^{36}\)

Hemrungroj et al., using a neural network algorithm, in 2021, looked at the Thai population for the categorization of amnestic mild cognitive impairment (aMCI) and Alzheimer’s disease (AD). The authors used Montreal Cognitive Assessment (MoCA) to study incorporated 60 AD patients, 61 aMCI patients, and 60 healthy controls (HCs). The authors, using their model, discriminated against aMCI patients from AD patients with an area under the ROC curve of 0.94, and HC with an area under the ROC curve of 0.81. The ML method exhibited that i) ‘aberrations in recall’ was the most significant feature of aMCI vs. HC, and ii) ‘aberrations in visuospatial skills’ and ‘executive functions’ were the top features of AD versus aMCI. Furthermore, impairments in a) recall, b) language, and c) orientation distinguished AD from aMCI. However, d) attention, e) concentration, and f) working memory did not. Thus the authors demonstrated that the ML algorithm based on ‘MoCA’ is a suitable cognitive assessment tool for the Thai population for the identification of aMCI and AD.\(^{37}\)

In 2019 Facal et al.’s research explored the effect of cognitive reserve (CR) in transforming from mild cognitive impairment (MCI) to dementia using both traditional and ML-based approaches. Using Petersen criteria for diagnosis, 169 participants who completed the longitudinal study were divided into three MCI subgroups, and a healthy control group. The authors utilized nine ML categorization algorithms to analyze collected data for prediction concerning ‘converter’ and ‘nonconverter’ participants from MCI to dementia. The top-performing ML models were i) the gradient boosting classifier with accuracy of 0.93, F1 of 0.86, and Cohen \(\kappa\) of 0.82, and ii) the RF classifier with an accuracy of 0.92, F1 of 0.79, and Cohen \(\kappa\) of 0.71. The authors, using ML techniques, demonstrated the protective role of CR as an arbitrator of conversion to dementia. Furthermore displaying that the participants with a) extra years of education and b) more outstanding vocabulary scores lived longer, deprived of developing dementia.\(^{38}\)

Zilcha-Mano et al., in 2018, used ML algorithms to identify predictors for antidepressant medication vs. placebo results in drug trials. 174 participants, with unipolar depression of age 75 and above, were randomly allocated to a pill (citalopram) or placebo. The authors used ML with ‘recursive partitioning’ algorithm to categorize the most robust arbitrators of placebo vs. medication response. The highest signal finding between medication and placebo in support of drugs was for patients with a lower education level (less than equal to 12 years) who experienced a longer duration of depression since their first incident. On the other hand, for individuals with higher education (more than 12 years), the placebo almost outpaced medication. Despite efforts to categorize characteristics associated with medication–placebo differences in antidepressant trials, few reliable findings have emerged to influence participant selection in drug development settings and differential therapeutics in clinical practice. Limitations in the methodologies used, mainly searching for a single moderator while treating all other variables as noise,
may partially explain the failure to generate consistent results. The present study tested whether interactions between pretreatment patient characteristics, rather than a single-variable solution, may better predict who is most likely to benefit from placebo versus medication. The authors, for older patients with unipolar depression, recommended considering individuals’ education level and length of their depression in drug trials and also in clinical settings.  

X. CHALLENGES AND OPPORTUNITIES FOR AI IN PSYCHIATRY

AI by itself could not replace human empathy. Therefore, collaborations between ML and psychiatrists can be effective in diagnosis and treatment. AI-based technology might enhance psychiatrist’s efficiency and improve patient care, while reducing treatment costs. However, AI-based diagnosis in psychiatry is still not generally used in clinical practices as there are many legal, privacy, and ethical matters that impede its acceptance.

XI. CONCLUSION

AI has the power to amplify clinical productivity due to its propensity to handle a vast amount of data suitable for automation. There exists a significant overlap in symptoms between mental disorders. AI is not going to substitute psychiatrists; instead, it can provide psychiatrists with insights that can streamline treatment. AI with the potential to improve the accuracy of diagnosing different mood disorders and can assist psychiatrists in providing proper illness detection and subsequent treatment.

REFERENCES Références Referencias


Artificial Intelligence (AI) in Psychiatry – A Summary


Therapeutic Approaches to Dysthymia

By Carolina Soutto Mayor Mangini, Leonardo Bicudo Conti, Lucas Chen Cheng, Pedro Torquato Shibuya & Vinicius Costa Salemme

Universidade Santo Amaro

Abstract- Introduction: Dysthymia is a psychic disorder defined by chronic lowering of mood, with a minimum duration of two years, in which fluctuating moments of the emotional state occur. Unlike the clinical picture of "major depressions", dysthymia has milder manifestations, which occur in a non-episodic manner. Even with milder symptoms, dysthymia ends up having a significant impact on patients lives, since, in the vast majority of cases, the diagnosis is made too late. It is a disease that affects 3 to 6% of the world population, mainly individuals in early adulthood, being twice as common in women than in men. The prognosis of this psychic disorder is associated with the chronicity of the disease and the possible comorbidities resulting from the depressive condition.

Keywords: treatment; pathophysiology; dysthymia; psychiatric disorders; depression; antidepressant drugs.


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Therapeutic Approaches to Dysthymia

Abordagens Terapêuticas Para Distimia

Aproximaciones Terapéuticas A La Distimia

Carolina Soutto Mayor Mangini a, Leonardo Bicudo Conti a, Lucas Chen Cheng b, Pedro Torquato Shibuya c, & Vinicius Costa Salemme d

Resumo- Introdução: O termo “distimia” diz respeito a um transtorno psíquico definido pelo rebaixamento crônico do humor, com duração mínima de dois anos, nos quais ocorrem momentos flutuantes do estado emocional. Diferentemente dos quadros clínicos de “depressões maiores”, a distimia possui manifestações mais leves, que ocorrem de maneira não-episódica. Mesmo com sintomas mais leves, o quadro clínico acaba sendo significadamente impactante na vida dos pacientes, uma vez que, na grande maioria dos casos, o diagnóstico é feito muito tarde. É uma doença que acomete de 3 a 6% da população mundial, principalmente indivíduos no início da vida adulta, sendo duas vezes mais comum em mulheres do que em homens. O prognóstico desse transtorno psíquico se associa à cronicidade da doença e às possíveis comorbididades advindas do quadro depressivo.

Objetivo: O objetivo deste trabalho é analisar a literatura coletada a respeito de distimia e as possíveis abordagens terapêuticas para a patologia.


Discussão: Pode-se utilizar qualquer tipo de antidepressivo para o tratamento do transtorno distímico, mas, dados apontam uma maior eficácia dos fármacos inibidores seletivos da recaptação de serotonina, dos antidepressivos tricíclicos e dos inibidores da monoaminooxidase. Além disso, as psicoterapias que se demonstraram mais eficientes para o tratamento da distimia foram a cognitiva e a comportamental.

Conclusão: O diagnóstico precoce da distimia deve ser realizado cautelosamente, diferenciando-o de transtornos de depressão maior e, uma vez estabelecido, deve-se considerar uma abordagem terapêutica baseada na associação da farmacoterapia e da psicoterapia. Essa terapia associada é a mais eficaz para o controle sintomatológico da doença e para uma melhora na qualidade de vida do paciente.

Palavras-Chave: tratamento; fisiopatologia; distimia; transtornos psiquiátricos; depressão; fármacos antidepressivos.

Resumen- Introducción: El término “distimia” hace referencia a un trastorno psíquico definido por el decaimiento crónico del estado de ánimo, con una duración mínima de dos años, donde se presentan momentos fluctuantes del estado emocional. Diferentemente de los cuadros clínicos de “depresiones mayores”, la distimia tiene manifestaciones más leves, que se presentan de manera no episódica. Incluso con síntomas más leves, el cuadro clínico acaba teniendo un impacto importante en la vida de los pacientes, ya que, en la gran mayoría de los casos, el diagnóstico se realiza muy tarde. Es una enfermedad que afecta del 3 al 6% de la...
depressão é uma patologia definida como um transtorno afetivo, que possui repercussões mentais, corporais e comportamentais (1). O termo “depressão” foi utilizado pela primeira vez em 1960, a fim de caracterizar um estado de desânimo ou perda de interesse na vida e, atualmente, é designado para descrever sintomas de apatia; irritabilidade; perda de interesse e falta de motivação; tristeza, podendo ou não estar acompanhada de crises de choro; agitação ou retardo psicomotor; alterações no sono; perda ou ganho de apetite; desinteresse sexual; sentiment constantes de culpa; pensamentos de morte e possíveis tentativas suicidas; desolação e de redução do comportamento adaptativo do sujeito (2,3,4,5).

Segundo a Classificação Internacional de Doenças, a depressão pode ser diagnosticada a partir da presença de alguns sintomas, manifestados durante um período, com certa frequência e intensidade (4). A síndrome pode ser especificada como um transtorno misto de ansiedade e depressão (CID-10 F41.2); como uma reação depressiva breve, prolongada ou mista de ansiedade e depressão (CID-10 F43); como episódios depressivos leves, moderados, graves com ou sem sintomas psicóticos (CID-10 F32); como transtornos depressivos recorrentes (CID-10 F33); e como distimia (CID-10 F34.1), quando caracterizada como um transtorno de humor persistente (4).

O conceito de distimia é definido por um rebaixamento crônico do humor, com duração de pelo menos 2 anos, que pode ser seguido de momentos flutuantes do estado emocional (7, 8, 9). Esse não se enquadrar no critério de “transtorno recorrente” ou de “depressões maiores”, uma vez que a intensidade de suas manifestações são mais leves e essas ocorrem de maneira não-episódica (4, 6, 7). A principal característica da patologia é o baixo grau de sintomas que, mesmo sendo menos agressivos, acabam causando um grande impacto na vida dos pacientes, dado que se trata de um quadro crônico negligenciado (7).

Sarcasso, niilismo, exigência e reclamação excessiva são algumas das principais características de pacientes com transtorno distímico, além de tensão, rigidez e resistência às intervenções terapêuticas (7, 8, 9). É comum que os indivíduos acometidos por distimia aparentem ter um comportamento social estável, mas questiona-se a veracidade dessa estabilidade, dado que autores notaram um alto investimento de energia em atividades laborais e reduzido em relacionamentos interpessoais (7, 8, 9).

A patologia possui etiologia complexa e multifatorial, contando com mecanismos de hereditariade, predisposição, temperamento, estilos de vida, gênero e estressores biológicos e psicológicos (7). Trata-se de uma doença que acarreta de 3 a 6% da população mundial, principalmente indivíduos no início da vida adulta, sendo duas vezes mais comum em mulheres do que em homens (7, 8).

Assim como outros casos de depressão, os pacientes com distimia acabam por procurar auxílio médico muito tempo depois do início dos sintomas e, quando o fazem, apresentam queixas mal definidas, como letargia, fadiga e mal-estar (7). Comumente o paciente e seus familiares confundem o transtorno com o estado cotidiano do sujeito, associando seus sinais e sintomas à experiência habitual do paciente (8). Portanto, o diagnóstico de distimia deve ser realizado cautelosamente, uma vez que os pacientes podem apresentar outras comorbidades, dificultando a percepção clínica de sintomas de distimia e, assim, negligenciando diagnósticos desta patologia psíquica (7).

A fim de realizar o diagnóstico adequado do quadro distímico, utiliza-se o Manual de Diagnóstico e Estatística da Associação Psiquiátrica Americana, em sua 4a edição (DSM-IV), o qual determina os seguintes critérios (9):  

1. Humor deprimido na maior parte do dia, por pelo menos dois anos. Em crianças e adolescentes, o
humor pode ser irritável e a duração de pelo menos um ano;
2. Presença enquanto deprimido de dois ou mais dos seguintes sintomas: aumento ou diminuição do apetite, insônia ou hipersonia, baixa energia ou fadiga, baixa auto-estima, diminuição da concentração ou indecisão, desesperança;
3. Durante o período de dois anos (um para crianças e adolescentes) do transtorno, nunca ter ocorrido remissão dos sintomas 1 e 2 por mais de dois meses consecutivos;
4. Durante os primeiros dois anos (um para crianças e adolescentes), não ter ocorrido um Episódio Depressivo Maior, isto é, o quadro atual não ser melhor classificado como Transtorno Depressivo Maior Crônico ou em remissão parcial;
5. Nunca ter ocorrido um Episódio Maníaco, Misto ou Hipomaníaco e nunca ter preenchido os critérios para ciclotimia;
6. O transtorno não ocorre exclusivamente durante o curso de um transtorno psicótico crônico, como Esquizofrenia ou Transtorno Delirante;
7. Os sintomas não ocorrem devido ao efeito fisiológico direto de alguma substância (drogas ou medicações) ou devido diretamente a alguma condição médica geral (hipotireoidismo, por exemplo);
8. Os sintomas causam sofrimento significativo ou prejuízo no funcionamento social, ocupacional ou em outras áreas significativas.

(American Psychiatry Association, 1994)

Uma vez realizado o diagnóstico de distimia, deve-se atentar à sub-divisão do mesmo, sendo a patologia classificada como "precoce", quando iniciada antes dos 21 anos de idade e "tardia" após isso (9). Não se sabe ao certo qual dos dois tipos de distimia é prevalente, mas dados apontam que o prognóstico da doença está relacionado às possíveis comorbidades associadas ao transtorno psíquico, sendo muito comum a evolução para um episódio de depressão maior ou para um transtorno bipolar do tipo II. Alguns poucos casos podem, inclusive, associar-se a transtornos de bipolaridade tipo I (9). 25% dos pacientes com distimia não atingem uma remissão total dos sintomas, assim, relaciona-se o prognóstico da patologia à cronicidade da doença (9).

II. OBJETIVO

O objetivo deste trabalho é analisar a literatura coletada sobre a distimia e as possíveis intervenções terapêuticas para o tratamento da patologia. Para isso, visa-se realizar uma profunda discussão sobre depressão, atentando-se à sua fisiopatologia e suas diversas classificações, e, posteriormente, realizar um estudo detalhado a respeito dos fármacos antidepressivos e seus mecanismos de ação, para assim concluir quais tipos de fármacos e terapias são ideias para o tratamento da distimia.

III. JUSTIFICATIVA

Uma vez que a distimia é uma patologia que costuma ser sub-diagnosticada e, ao mesmo tempo, bastante incapacitante social e fisicamente, deve-se aprofundar os estudos sobre o assunto. A doença se desenvolve de forma gradual e, na maioria das vezes, o médico só é procurado quando os sintomas já estão bastante avançados, assim, uma comunidade médica com conhecimento avançado sobre o assunto pode ser apta a realizar um diagnóstico precoce e melhorar o prognóstico do paciente.

A ocorrência de comorbidades ao transtorno distímico e a taxa de pacientes que não conseguem ter remissão total dos sintomas são índices que escancaram a importância da patologia. Portanto o estudo detalhado acerca do diagnóstico e tratamento da distimia é indispensável, assim como o engajamento de psiquiatras e demais médicos em realizar uma análise clínica bem direcionada que vise distinguir exatamente qual tipo de transtorno de humor o paciente apresenta.

IV. MÉTODOS


V. DISCUSSÃO

- Fisiopatologia da depressão

Existem diversas teorias que explicam a fisiopatologia da depressão, mas, baseando-se em estudos mais recentes, a principal teoria para o mecanismo da doença é chamada de “monoaminérgica” (10, 11). O sistema monoaminérgico tem sua origem em núcleos no mesencéfalo e no tronco cerebral, e se propaga pelo córtex e pelo sistema límico (10, 11). Considerando a anatomia desse sistema, a teoria propõe que a instalação de um quadro depressivo ocorre em função de uma menor produção de aminas biogênicas cerebrais, sendo essas a serotonina, noradrenalina e/ou dopamina (10,11,12).

O estudo que defende essa teoria leva em consideração alguns fatores. O primeiro deles é o fato...
da serotonina e da noradrenalina, juntos com a acetilcolina, estarem diretamente relacionadas às áreas corticais e subcorticais do cérebro humano e, assim, possuam atuação nos mecanismos de regulação do sono, humor, apetite, atividades psicomotoras, entre outros (10,11). Além disso, outro fator significativo foi o resultado de estudos que comprovavam a eficácia de fármacos inibidores da monoaminoxidase (IMAO) em pacientes com sintomas depressivos, dado que, quando eram medicados, seus índices de serotonina e de noradrenalina aumentavam e eram restabelecidos (10,11). Por fim, outros estudos analisaram a reação de pacientes após tratamento com fármacos antidepressivos tricíclicos, que foram responsáveis por indicar que essas pessoas adoecidas tinham, como consequência ao tratamento, suas atividades sinápticas indicar que essas pessoas adoecidas tinham, como consequência ao tratamento, suas atividades sinápticas

Outra teoria relevante para a fisiopatologia da depressão se baseia na participação do imunológico para o desenvolvimento da patologia (10). Essa defende que os sintomas depressivos ocorrem em função do aumento na produção de citocinas pró-inflamatórias, uma vez que essas podem atuar como neuromoduladores e, assim, intervir nos aspectos neuroquímicos, neuroendócrinos e comportamentais dos transtornos de humor (10, 13). Essa relação entre o sistema imune e o sistema nervoso central ocorre por meio de atividades de neutrófilos e macrófagos; por meio da redução na atividade de células natural killer; e pela resposta de linfócitos a mitógenos (10, 13).

Ao se tratar da distimia, sua fisiopatologia não é totalmente compreendida (18). Associa-se a doença a heranças genéticas, principalmente em casos de transtorno distímico precoce, ou seja, antes dos 21 anos de idade (18).

- Classes dos antidepressivos e seus mecanismos de ação

**Inibidores da monoaminoxidase (IMAO):** atuam por meio da inibição da enzima monoaminoxidase. Essa enzima é responsável pela eliminação dos neurotransmissores localizados dentro dos neurônios, fazendo com que permaneçam por mais tempo na fenda sináptica (14). A enzima monoaminoxidase possui dois mecanismos de ação, a MAO-A é responsável pelo metabolismo de norepinefrina, serotonina e tiromina; enquanto a MAO-B metaboliza, com mais eficácia, a dopamina (15). Os fármacos inibidores da MAO podem ser irreversíveis e, além disso, alguns conseguem bloquear as duas formas da enzima (15). Sendo assim, como representantes dos antidepressivos IMAO não seletivos e irreversíveis, tem-se: Iproniazida; Isocarboxazida; Tranilcipromina; Fenelzina. Dos seletivos e irreversíveis: Clorgilina. E por fim, dos inibidores reversíveis da MAO-A: Brofaromina; Moclobemida; Toloxatona; Befloxiqatona (14). Para finalizar, os efeitos colaterais apresentados por essa classe de fármacos, são: hipotensão, cefaleia, sonolência, boca seca, ganho de peso, distúrbios sexuais e até mesmo hepatite, parkinsonismo, anorexia (14,15,16).

**Inibidores não-seletivos da recaptação de monoaminas (ADTs):** agem de modo que bloqueiam a recaptação de monoaminas, sendo as principais a norepinefrina (NE) e serotonina (5-HT), além da dopamina (DA) em menor proporção (13,14). O exato mecanismo de ação dos fármacos ADTs ainda é desconhecido, mas sabe-se que esses são responsáveis por aumentar a eficácia da transmissão monoaminérgica por meio do aumento da concentração sinápica de serotonina e noradrenalina, que ocorre em função do bloqueio da recaptação dessas monoaminas (13). Dessa forma, ocorre a dessensibilização de receptores b1 adrenérgicos, serotoninérgicos 5-HT2 e 5HT1A, presentes no sistema nervoso central (13). Os principais fármacos representantes dessa classe são: Imipramina, Desipramina, Clomipramina, Amitriptilina, Nortriptilina, Doxepina, Maprotilina (13,16). O bloqueio dos receptores é o fator que desencadeia os efeitos colaterais, que se manifestam de maneiras típicas:

- **Anticolinérgicos:** boca seca, vista turva, aumento da pressão ocular, retenção urinária, taquipneia, constipação, ganho de peso, disfunções sexuais;
- **Histaminérgicos:** sonolência, sedação, fadiga, tontura, náusea, ganho de peso, hipotensão e potencialização de drogas depressoras centrais;
- **Alfa-1-adrenérgicos:** hipotensão postural, taquipneia, congestão nasal, cefaleia, disfunção erétil, vertigem e tremores;
- **Serotoninérgicos:** fadiga, cefaleia, alterações no sono, irritabilidade, ganho de peso, hipotensão e disfunção sexual. (13,16)

**Inibidores seletivos da recaptação de serotonina (ISRSs):** inibem de forma eficaz e seletiva a recaptação de serotonina, causando uma potencialização da neurotransmissão serotoninérgica (13,16). Os fármacos dessa classe são: Fluoxetina, Paroxetina, Sertralina, Citalopram, Fluvoxamina e Escitalopram. Seus principais efeitos colaterais são: náusea, êmese, dispneia, dor abdominal, diarréia, perda de apetite, perda ou ganho de peso, ansiedade, agitação, insônia, pressão ocular, retenção urinária, taquicardia, constipação, ganho de peso, confusão e disfunções sexuais;

**Inibidores seletivos da recaptação de 5-HT/NE (ISRSNs):** realizam um potente bloqueio serotoninérgico, combinado a um leve efeito de recaptação de noradrenalina (13, 16). Esses fármacos agem de maneira rápida na “downregulation” de receptores beta-adrenérgicos, junto à adenosina monofosfato cíclica (13, 16). As drogas representantes dessa classe são: Venlaxina, Milnaciprano e Duloxetina. Seus principais efeitos colaterais são: náuseas, tonturas, sonolência,
hipertensão, sudorese abundante, tremores, diminuição da libido, anorgasmia, retardo ejaculatório e impotência (13,16).

Inibidores da recaptação de 5-HT e antagonistas alfa-2 (ISRAs): inibem a recaptação de noradrenalina e serotonina, de modo que, a longo prazo, promovem a dessensibilização e diminuição do número de receptores beta-adrenérgicos e 5-HT2 (13). Seus representantes são: Nefazodona e Trazodona. Os efeitos colaterais causados por esses fármacos são: cefaléia, boca seca, sonolência, náuseas, obstrução intestinal e ataxia; também foram relatados turvação de visão, dispepsia, fraqueza e rash cutâneo (13,16).

Inibidores seletivos da recaptação de noradrenalina (ISRNs): atuam sobre a atividade seletiva da recaptação de noradrenalina, com atividade antagonista de alfa-2 (13,16). O fármaco representativo dessa classe de antidepressivos é a Reboxetina. Seus principais efeitos colaterais são: taquicardia, impotência, hesitação ou retenção urinária, insônia, sudorese excessiva, constipação intestinal e boca seca (13,16).

Inibidores seletivos da recaptação de dopamina (ISRDs): aumentam a liberação de noradrenalina corpórea e, concomitantemente, inibem “in vitro” a captação neuronal de noradrenalina e dopamina (13,16). A droga pertencente a essa classe é a Bupropiona, que possui como efeitos colaterais: agitação, ansiedade, rash cutâneo, diminuição do apetite, boca seca e constipação intestinal (13,16).

Antidepressivo noradrenérgico e específico serotonérgico (NaSSA): a ação desses fármacos ocorre por meio do aumento de atividades noradrenérgicas e serotoninérgicas centrais. Possui afinidade com receptores histamínicos e isso explica sua atividade sedativa (13,16). O fármaco representante é a Mirtazapina e tem como efeitos colaterais: agitação, ansiedade, rash cutâneo, diminuição do apetite, boca seca e constipação intestinal (13,16).

A distimia e seu tratamento

Todos os pacientes com depressão devem ser rastreados pensando no diagnóstico de distimia e, para isso, recomenda-se que o adoecido seja bem informado sobre a distinção entre os dois transtornos, atentando-o às principais características: início insidioso, sintomas que crescem e decrescem no período de dois anos, podendo, inclusive, haver breves períodos de humor normal (17). Os adoecidos com o transtorno distímico apresentam sintomas mais subjetivos, distúrbios psicomotores menos dramáticos ou neurovegetativos, incluindo anormalidades de sono, apetite e níveis de energia (18).

O tratamento da distimia pode ser baseado na farmacoterapia isolada; na psicoterapia isolada; ou na combinação de ambas formas terapêicas (17,18). A abordagem terapêutica baseada, exclusivamente, na farmacoterapia já se demonstrou eficaz no tratamento da distimia (17). Estudos apontam que pacientes com o transtorno distímico respondem bem a tratamentos com fármacos inibidores seletivos da recaptação de serotonina (ISRAs), antidepressivos tricíclicos (ADTs) e inibidores da monoaminoxidase (7,18). Nesses casos, o uso dos ISRAs é mais recomendado, dado que a resposta terapêutica é semelhante à dos outros medicamentos, mas esses são melhores tolerados pelo organismo (18).

Foi-se relatado também um sucesso terapêutico com o uso de agentes noradrenérgicos, como a Mirtazapina, Nefazodona, Venlafaxia, Duloxetine e Bupropiona (18). Além disso, um estudo verificou a eficácia terapêutica do uso de antipsicóticos de segunda geração para o tratamento da distimia, mas esses possuem menor tolerabilidade e, consequentemente, causam efeitos colaterais significativos, tais como: sedação, ganho de peso ou anormalidades de dados laboratoriais, como o aumento da prolactina (18). Evidências também indicaram efeitos benéficos do uso de Amissulpirida em baixas doses (18).

Uma vez que a distimia possui como uma de suas principais comorbidades a ansiedade, estudou-se também o uso de benzodiazepínicos, a fim de controlar esse sintoma (9). Porém, a melhora da sintomatologia depressiva com o uso de benzodiazepínicos ainda não foi comprovada. Assim, atualmente recomenda-se o uso do antidepressivo tricíclico amitriptilina, ao invés de benzodiazepínicos, para pacientes moderadamente deprimidos com altos níveis de ansiedade associada, uma vez que causam menos risco de abuso e possuem sua eficácia comprovada (9).

Apesar dos dados expostos, Dunner defende em seu artigo “Dysthymia and double depression” que o uso de qualquer antidepressivo é eficaz para o tratamento de distimia, sendo necessária uma análise detalhada de cada paciente, atentando-se aos efeitos colaterais de cada fármaco, às comorbidades do indivíduo e cronicidade da doença (8,9,19).

A duração da farmacoterapia no tratamento de distimia ainda não foi estabelecida, porém, é recorrente que os pacientes necessitem de um tratamento contínuo, por longos períodos. Nesses casos, deve-se considerar as mudanças de antidepressivos e/ou ajustes nas doses dos fármacos, a fim de evitar que os pacientes enfrentem momentos de recaídas e/ou de perda da eficácia da medicação ao longo do tempo (17).

O uso exclusivo da psicoterapia, para o tratamento da distimia, também pode ser eficaz (17). Estudos defendem que existem diversos tipos de psicoterapias que podem ser utilizadas como ferramenta para o transtorno psíquico, tais como a...
psicoterapia cognitivo-comportamental, a psicoterapia interpessoal e a psicodinâmica (17,18). Além disso, o Sistema de Análise Comportamental Cognitiva de Psicoterapia (CBASP) tem se demonstrado eficaz para o tratamento de quadros crônicos de depressão. Esse se baseia em uma técnica estruturada para instruir os pacientes com depressão crônica a lidar com encontros interpessoais problemáticos, tornando-os aptos a usar algoritmos de solução de problemas sociais para lidar com suas dificuldades interpessoais (18). O procedimento é chamado de “análise situacional” e seu foco principal são as interações interpessoais, abordando-as de uma forma mais direta e estruturada, diferentemente do que ocorre na psicoterapia interpessoal e na terapia cognitiva (18). No entanto, estudos apontam dificuldade com o tratamento da psicoterapia exclusiva, alegando que esse é mais eficaz quando combinado com a farmacoterapia (9,17,18,19).

Por fim, a intervenção terapêutica mais aceita atualmente e considerada mais eficaz é a que combina a farmacoterapia com a psicoterapia, sendo preferencialmente a cognitiva ou comportamental (7,8,17,18,19). A farmacoterapia se demonstra mais eficiente em abordar os sintomas depressivos e, concomitantemente a isso, a psicoterapia pode auxiliar o indivíduo a melhorar a sensação de bem-estar, satisfação e autoestima (8). Dessa forma, o planejamento terapêutico combinado pode ser mais eficaz em promover uma melhor qualidade de vida das pessoas distímicas (8).

A eletroconvulsoterapia (ECT) é um procedimento que se demonstrou eficaz para pacientes com depressão maior que não respondem aos antidepressivos (9). Porém, uma vez que a distímia tem caráter leve, a resposta dos pacientes ao procedimento é bastante improvável, apenas em casos que apresentem comorbidades associadas (9).

VI. Conclusão

A distímia é uma doença crônica que cursa com períodos flutuantes, oscilando entre o humor normal do indivíduo e recáidas depressivas, com duração de pelo menos dois anos. Trata-se de uma patologia bastante incapacitante, que pode demandar um tratamento por toda a vida e, dessa forma, esse deve ser idealizado com cautela.

A fim de propor uma intervenção terapêutica eficaz, deve-se realizar o diagnóstico do transtorno o mais precocemente possível, atentando-se às diferenças entre distímia e depressão maior. Uma vez que o diagnóstico foi estabelecido, o médico deve planejar uma abordagem terapêutica baseada na associação da farmacoterapia e da psicoterapia. A escolha dos medicamentos e do tipo de terapia deve ser realizada considerando as particularidades de cada paciente, mas, por meio dessa abordagem, o indivíduo poderá ter o controle de sua sintomatologia e, ao mesmo tempo, uma melhora na qualidade de vida.

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Physical Neuro-Urological Examination in Patients with Spinal Cord Injury Revisited

By Wyndaele Jean Jacques & Wyndaele Michel

University Antwerp Belgium

Abstract- Study design: Retrospective cohort study

Objectives: To show that combining neuro-urological examinations in the lumbosacral area permit to refine the neurological diagnosis by evaluating ascending and descending spinal cord pathways, sacral reflex arcs and the status of the related muscles.

Setting: University Antwerp Belgium.

Methods: Evaluation of perineal sensation with light digital touch (SENSPER), anal sphincter tone (AST) and voluntary contraction (ASC), anal reflex (ASR), bulbocavernosus reflex (BCR) were done in patients with SCI as part of urodynamic testing.

Results: 121 individuals were included, 80 males and 41 females, age 46 ± 16 years old, with different levels and completeness of SCI, determined with ASIA/ISCoS International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). The examination was done 6.6 ± 12 years post lesion. The findings did not differ between gender or age, except that ASR was more frequently absent in women and ASC diminished with increasing age.

Keywords: SCI, neuro-urological, physical examination, sensation, reflexes, contraction.

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Physical Neuro-Urological Examination in Patients with Spinal Cord Injury Revisited

Clinical Neuro-Urological Examination in SCI

Wyndaele Jean Jacques & Wyndaele Michel

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Results: 121 individuals were included, 80 males and 41 females, age 46 ± 16 years old, with different levels and completeness of SCI, determined with ASIA/ISCoS International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). The examination was done 6.6 ± 12 years post lesion. The findings did not differ between gender or age, except that ASR was more frequently absent in women and ASC diminished with increasing age. As expected SENSPER and ASC were related with The American Spinal Injury Association Impairment Scale (AIS), but the other tests were not. Repeating the tests with a long interval gave reproducible results. A positive relation was found between the results of SENSPER and ASC, between AST and ASR/ BCR, and between ASR and BCR.

Conclusions: The different components of the physical neuro-urological examination give complementary information on parts of the peripheral innervation and ascending and descending nervous pathways from and towards the lower part of the spinal cord, and on the pelvic floor muscular status. Their combination permits to gain detailed information on the nervous structures involved in SCI.

Keywords: SCI, neuro-urological, physical examination, sensation, reflexes, contraction.

Data Archiving and Data Availability: The data are in the patient files. Data from the database are available on request to the corresponding author, blinded for patient name and file number and other information that might consist a breach of confidentiality.

I. Introduction

Besides inspection and palpation of the genitalia, a physical neurological examination is part of the neuro-urological diagnosis in patients with a suspected or known neuropathy such as a spinal cord injury (SCI). The examination comprises different techniques: sensation of touch of the dermatomes in the perineal area (SENSPER), scoring of the tone of the anal sphincter (AST), voluntary contraction of the anal sphincter/pelvic floor muscles (ASC), anal (ASR) and bulbocavernous (BCR) reflexes, and the cremaster reflex. The tests are not invasive, and inform about parts of the afferent and efferent peripheral innervation, the related pathways in the spinal cord, and the pelvic floor muscular status (Table 1)[1]. When the reasons for the tests are explained, consent is easily obtained. The assessment of SENSPER includes a test of the patient’s compliance and reliability by asking for sensation without touching[2].

We looked at data from such examinations (except cremaster reflex) in a cohort of patients with SCI. Our aim was to show that combining neuro-urological examinations in the lumbosacral area permits to refine the neurological diagnosis by evaluating ascending and descending spinal cord pathways, sacral reflex arcs and the status of the related muscles.

II. Materials and methods

This is a retrospective study on a consecutive cohort of SCI patients, investigated in a standardised way, when they presented for urodynamic evaluation during a period of 2 years. Patient age and sex, cause of SCI, and their neurological status determined following the ASIA/ISCoS International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) were gathered, with the American Spinal Injury Association Impairment Scale score (AIS)(2). No data were included from patients who did not have a urodynamic investigation. The tests were performed 8 ±12 years after SCI as part of regular follow up (n=77) or as part of an extra evaluation (n=44), e.g. for changed spasticity, increase in AD.

The evaluation of the somatosensory afferent innervation was done in the dermatomes S3-S5 with light
touch, blinded for the patient and with fake touching introduced to check for reliability. The findings were scored as 0= absent, 1= present in all dermatomes and 2= present in part of the dermatomes or only on one side, for which the details are given. In the results. Then followed four tests with an intrarectal fingertip: the AST was graded by gentle lateral stretching (0= absent with flaccid muscle and sometimes open anus, 1= weak with little resistance, 2= strong resistance); the ASC was scored as 0= no contraction possible, 1= contraction possible, 2 =strong contraction. Distinction was made with a reflex contraction provoked by the introduction of the finger. The ASR was elicited by making a brisk lateral movement of the fingertip in the anus and was considered positive if the sphincter grabbed the finger (0= absent, 1= present but not strong, 2= strong).Finally, the BCR was elicited with a brisk squeezing of the glans penis/clitoris and the same scoring system was used as for ASR [1].The differentiation between scores 1 and 2was subjective but made by experienced physicians.

Institutional Review Board permission was granted (Edge 001176).

Statistical analysis was done with SPSS28, using Chi-Square (value, df, p value) for categorical, ANOVA for age, and Kappa (k, p value) for comparison of the outcome of two different tests. Statistical significance was set at p<0.05.

III. Results

The cohort consists of 121patients, 80 males and 41 females, age 47 ± 16 years old. The examination was done 6.6 ± 12 years post SCI. AIS was determined 8 ± 17 days before the test.

There was no significant difference between gender (Chi-Square for SENSPER (5.55, df 2, p=0.062), AST(1.33, df 2, p=0.514), ASC (3.21, df 2, p= 0.200), BCR (5.05, df 2, p=0.80). The ASR reflex was statistically more absent in women: 54% (22/41) vs in 41% (33/80) of men (12.18, df 2, p=0.002). No influence of age was found on the neuro-urological physical examinations ANOVA for all (but one) test (SENSPER p=0.218; AST p=0.0.751; ASR p= 0.192; BCR p= 0.485; ASC became weaker with raising age (p =0.002).

The findings of the physical examination in the groups with different spinal cord level and lesion type are presented in table 1, together with the innervation used for the sensation, tone, contraction and reflexes tested.

The outcome of the SENSPER was unreliable in 7 patients not included in the study cohort. When the neuro-urological findings were compared in complete and incomplete lesions, a positive statistical significance(chi-square) was found for SENSPER (65.51,df 2, p<0.001). In complete lesions 20/67, 30% had touch sensation; in incomplete lesions SENSPER in all dermatomes or in part of them was present in 49/54 (91%) and absent in 5 (9%). Absence of S4-S5 sensation was found in 5 patients with incomplete lesion (1 cervical, 2 thoracic, 1 thoracolumbar and 1 cauda). Twenty patients had sensation but only in parts of the dermatomes (Table 1 score= 2): S3 present both sides and S4-S5 absent in 12 patients, S3 present at one side with S4-S5 absent in 5 patients, S4-S5 present only one side 2 patients, S5present only one side 1patient.Interpretation of ASC was uncertain because of interfering spasticity in 2 patients examined in the same period, who were not included in the cohort:ASC was possible in 3/67 (4.5%) of the complete lesions and in 40/54 (74 %) of the incomplete lesions.

A comparison between complete and incomplete lesions is given for each test in table 1. To evaluate if the different tests gave similar results Kappa was done . Between ASR and BCR an almost perfect relation was found in complete (k 0.810 p<0.001) and a good relation in incomplete (k 0.734 p<0.001).

Significant similarity (p<0.05)was in complete lesions found between SENSPER-ASC and AST- ASR but both with a low k (0.118 and 0.202 respectively). In incomplete, significance in similarity of outcome in AST-ASC and AST-BCR had medium k of 0.294 and 0.261 respectively.

The tests were repeated in 31patients who had not shown changes in their neurological status (determination of AIS was done mean 5 days before the second urodynamics and compared with the one done at the time of the first urodynamics, with an interval of 32±31 weeks). All tests were highly reproducible (Table 3).

IV. Discussion

A neuro-urological physical examination includes testing of motor, sensory, muscular and reflex function in the lower sacral segments(table 1).

In our cohort the relation between AIS and SENSPER was highly positive, as would be expected as sacral sensation is used to help determine AIS. But in a number of complete lesions SENSPER was positive, and in a number with incomplete lesion SENSPER was absent. The reasons may be: unsuspected change in the neurological situation since the last determination of AIS, sensation present in part of the perineal area not examined in the original scoring (especially S3 versus S4-S5), insufficient attention to pitfalls and not introducing fake tests, insufficient cooperation of the patient, and presence of multiple lesions [1-3]. A SCI patient may strongly want to feel without being able to do so. Doubtful outcome of SENSPER was found in some patients examined during the same period who reported sensation while not being touched, but they were not included in this study. Finnerup et al evaluated
sensation evoked by painful or repetitive stimulation below injury level in patients with a clinically complete (AIS A) lesion. Their findings suggest retained sensory communication across the injury in complete SCI, and they suggested the term ‘sensory discomplete’ (4).

Muscle tone is the continuous and passive-partial contraction of the muscle or the muscle’s resistance to passive stretch during the resting phase [5]. If the AST is slack (our score 0), it mostly indicates peripheral motor denervation while a normal or strong tone (our score 1 and 2) points to decentralization. Previous interventions on the anus or lower bowel must be considered, and an overfilled rectal canal at the time of the examination must be avoided. We found the AST globally not related to the AIS score. We also did not find a relation between AST and ASC, while AST was positively related to ASR (minor significance in incomplete/mediocre in incomplete) and BCR (mediocre overactivity, that 63.0% (58 of 92) had a normal bulbocavernousus reflex (BCR) response (19).

The BCR is multisynaptic, mediated mostly by the roots S2–4, occasionally with synapses as high as L5 [15–16]. The efferent innervation can include S5 [16]. Impulses from the glans penis and the frenulum run via the dorsal nerve of the penis/clitoris or perineal nerve, mostly through the dorsal roots and back from the motor neurons and pudendal nerves to the external anal sphincter and bulbocavernosus muscles [17–18]. Wang et al. showed in suprasacral SCI patients with detrusor overactivity, that 63.0% (58 of 92) had a normal bulbocavernousus reflex (BCR) response (19).

ASR and BCR were in our study statistically significantly related (p > 0.001), likely due to the similar innervation involved in both reflexes. But some differences between ASR and BCR were seen and may be caused by a difficulty to elicit, especially the BCR, as seen in healthy individuals [20–21].

The presence of sacral reflexes below the level of injury is key to determining an UMN lesion, absence of sacral reflexes defines a lower motor neuron (LMN) lesion [22].

Extrapolation from the neurological examination to the nature of the neurogenic LUTD is only possible to a certain extent. Wyndaele found a correlation between different levels of SCI, the function of the bladder neck and sphincter, and the ACR and BCR. Higher lesions corresponded more with a reflex lower urinary tract and somatic motor activity, lower lesions more with areflexia. With a lesion between thoracic 10 and lumbar 2 as many reflective as a-reflective dysfunctions were found. Detrusor and striated sphincter reflexia/areflexia corresponded significantly with the presence/absence of bulbocavernosus and anal reflexes. The presence or absence of perineal sensation of light touch has been shown to correspond significantly with the presence or
absence of sensation in the lower urinary tract [23]. In SCI patients with thoracolumbar fractures pinprick sensation in the perineal area was shown to have negative predictive value: absence of pinprick sensation predicted poor bladder recovery [24]. Alexander et al found that subjects with greater preservation of sensation in S3-S5 reported greater ability to initiate and control voiding [25].

For a detailed diagnosis of the LUT function after SCI clinical examination alone is not sufficient [23], as also concluded by Moslavec et al [26]. Dartos-cremaster reflex is predictive of some aspects of sexual and bladder neck function in men [27]. It has in our study been done in a few patients only and was thus not included in the results.

Pavese et al could predict urinary continence and complete bladder emptying 1 year after traumatic SCI with the full prediction model relying on lower extremity motor score (LEMS), light-touch sensation in the S3 dermatome of ISNCSI, and SCIM subscale respiration and sphincter management [28]. In patients with ischemic SCI the same model was also useful to predict functional bladder outcome [29].

We conclude that different techniques of lumbosacral physical examination give each a complementary information in the neurological diagnosis after SCI. Our results show that in most tests a different outcome is seen. Only BCR and ASR gave good to perfect similarity in the results. But their outcome can be different as seen in some of our cohort. Combining the tests permit to evaluate ascending and descending spinal cord pathways, sacral reflex arcs and the status of the related muscles. Limitations of our study are that it is retrospective, the interpretation of the tests is done manually by clinicians and is subjective based on experience. Electrodiagnostic tests and cerebral imaging permit semiobjective and objective measurements which are today not often done outside research.

Statement of Ethics: We certify that all applicable institutional and governmental regulations concerning the ethical use of the data were followed during this research.

Conflicts of Interest: the authors have no conflicts of interest.

Author Contributions:
- Wyndaele Jean Jacques collected the file data, put them in a database, made evaluations and wrote the text.
- Wyndaele Michel contributed to data interpretation and read and corrected the text.

Funding: there was no funding for this study

Acknowledgement: We thank E Roelandt for her help with the statistics.

References Références Referencias

Table 1: Results of the Examination in Patients with a Different AIS Score and Lesion Level

<table>
<thead>
<tr>
<th>Nervous system related to the tests</th>
<th>SENSPER</th>
<th>AST</th>
<th>ASC</th>
<th>ASR</th>
<th>BCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afferent: pudendal S3-S5 through fasciculi gracilis towards brain (ref 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efferent: pudendal nerve and supraspinal nuclei (ref 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spinal cord levels and lesion type</th>
<th>Complete</th>
<th>Total</th>
<th>Complete</th>
<th>Total</th>
<th>Complete</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1-C8</td>
<td>13</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>T1-T9</td>
<td>25</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>T10-L1</td>
<td>8</td>
<td>-</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>L2-S3</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Conus/cauda</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>47</td>
<td>8</td>
<td>12</td>
<td>10</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1-C8</td>
<td>1</td>
<td>21</td>
<td>3</td>
<td>2</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>T1-T9</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>T10-L1</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>L2-S3</td>
<td>-</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Cauda</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>total</td>
<td>5</td>
<td>41</td>
<td>8</td>
<td>11</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Global total</td>
<td>52</td>
<td>49</td>
<td>20</td>
<td>21</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>

Chi Square between complete and incomplete:
- 65.51, df 2, p<0.001
- More absent in complete
- 1.42, df 2, p= 0.491
- No difference
- 14.470, df 2, p<0.01
- More absent in complete
- 1.156, df 2, p = 0.561
- No difference
- 0.344, df 2, p= 0.842
- No difference

SENSPER= touch sensation perineal dermatomes S3-S5=0 absent, 1= present,2= present in only parts of area; AST= tone anal sphincter; ASC= voluntary contraction anal sphincter; ASR= anal sphincter reflex; BCR= bulbocavernous reflex. ASC, ASR and BCR are graded as 0= absent, 1=not strong, 2=strong. For AST: 0= absent with flaccid muscle and sometimes open anus, 1= weak with little resistance, 2= strong resistance. Complete = AIS A, incomplete= AIS B-D. - = no patient with this finding.

Table 2: Outcome of the Tests in Groups of at Least 7 Patients with the Same Level of Lesion and Complete or Incomplete Lesion

<table>
<thead>
<tr>
<th>Level injury</th>
<th>Number of patients</th>
<th>SENSPER</th>
<th>AST</th>
<th>ASC</th>
<th>ASR</th>
<th>BCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 0 1 2 0 1 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5 Complete</td>
<td>3 3 - - - 1 2 3 -</td>
<td>1 1 1 1 1 1 1 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5 Incomplete</td>
<td>4 1 3 - - 4 - 3</td>
<td>1 2 2 - 2 2 -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D8 Complete</td>
<td>5 5 - - - 3 2 5 -</td>
<td>1 2 2 2 2 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D8 Incomplete</td>
<td>2 - - - - 2 - 2 -</td>
<td>1 1 - 1 1 -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 Complete</td>
<td>2 2 - - - 2 - 2</td>
<td>- 1 1 - 1 1 -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 Incomplete</td>
<td>5 1 2 3 2 5 -</td>
<td>- 4 1 - 4 1 -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cauda Complete</td>
<td>4 1 1 2 1 2 1 4 -</td>
<td>- 4 - 4 - 4 -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cauda Incomplete</td>
<td>3 1 2 - 2 1 - 3</td>
<td>- 2 1 - 2 1 -</td>
<td></td>
<td></td>
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</tr>
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</table>
Table 3: Results of Repeated Testing with an Interval of Mean 32 Weeks in 31 Patients who had Unchanged AIS Scores (%).

<table>
<thead>
<tr>
<th>Test</th>
<th>No change</th>
<th>Appearance while originally absent</th>
<th>Disappearance while originally present</th>
<th>Total</th>
<th>Missing values</th>
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<tbody>
<tr>
<td>SENSPER</td>
<td>26 (84%)</td>
<td>4</td>
<td>1</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>24 (83%)</td>
<td>1</td>
<td>4</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>ASC</td>
<td>27 (90%)</td>
<td>3</td>
<td>-</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>ASR</td>
<td>16 (59%)</td>
<td>7</td>
<td>4</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>BCR</td>
<td>16 (67%)</td>
<td>6</td>
<td>2</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>
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Distressed: An Assessment of Emotional State of Young Adults during a COVID Wave

By Sehaj Gill & Preetinder Gill

Eastern Michigan University

Abstract- Purpose: The COVID-19 pandemic has resulted in a heavy toll on public health. The adverse health outcomes have affected the public physically, mentally and emotionally. Waves during the pandemic have resulted in lockdowns that limited people’s ability to interact socially. Due to the novel nature of the disruptions the emotional effects of COVID related lock downs have not been adequately studied. This study assessed the effects of the Jan-Feb 2022 COVID wave related lockdown on young adults aged 18 to 25 in the 11 counties that form the Detroit Metro area in the State of Michigan in the United States of America.

Methods: A survey instrument was developed using well validated Depression Anxiety Stress Scales-21 (DASS-21) along with other questions related to demographics, impact of COVID and methods used for obtaining advice. The survey was electronically shared with the target population in the Detroit Metro area with the help of Centiment, a market research company.

Keywords: depression, anxiety, stress, pandemic, social impact, modes for seeking advice, covid-19 lockdown.

GJMR-A Classification: DDC Code: 614.5 LCC Code: RA644.S17

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Distressed: An Assessment of Emotional State of Young Adults during a COVID Wave

Sehaj Gill & Preetinder Gill

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Results: The data analyses show that the target population in the Detroit Metro area suffered from high levels of depression, anxiety, and stress. This was significantly higher for people who identified their gender as other than male or female. Females also had a higher level of stress than males. It was found the COVID lockdown correlated with higher levels of depression and stress. Further, statistically significant high levels of worry and aggressive behaviors were reported as manifestation of the COVID lockdown. Finally, the target population turned to the internet portals and friends and health professionals at a statistically significant level to seek advice.

Conclusion: The Jan-Feb 2022 COVID lockdown had significant impact on the emotional state of young adults in the Detroit Metro area. Also, the study identified common manifestations of distressed emotional state in people aged 18 to 25 years.

Keywords: depression, anxiety, stress, pandemic, social impact, modes for seeking advice, covid-19 lockdown.

1. Introduction

The outbreak of the novel coronavirus, officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a Public Health Emergency of International Concern by the World Health Organisation (WHO) in January 2020. (World Health Organization, 2022; Hotez, 2020; Kenny & Mallon 2021) The disease associated with SARS-CoV-2 is called COVID-19.1 In March 2020, WHO declared COVID-19 a global pandemic. (Cucinotta & Vanelli, 2020) As of June 17, 2022, over 535 million confirmed cases of COVID-19, including over 6 million deaths have been reported. (World Health Organization, 2022) Typical symptoms include fever, cough and tiredness. Other symptoms can include, but are not limited to, loss of taste or smell, headaches, and nausea. (Mayo Foundation, 2022)

Besides the direct health effects, COVID-19 has affected human well-being in many other ways. Several virus variants have resulted in waves that have been typically accompanied with lockdowns. (Fisayo & Tsukagoshi, 2021; Zhang et al, 2021) The lockdowns in particular and the pandemic in general have had a severe impact on the world economy and triggered the largest global economic crisis in more than a century. (World Bank Group, 2022) The median global GDP dropped by 3.9% from 2019 to 2020. (Oum, 2022) Social distancing has been one of the main ways in which communities around the world tried to slow down the spread of the disease. (Qian & Jiang, 2020) Disruption of normal social connections along with economic disruptions plausibly have had detrimental and diverse psychological effects on various segments of the public. (Singh & Singh, 2020; Ruben & Wessely, 2020) Little is known about the psychological effects. (Canet-Juric et al, 2020; Schelhorn et al, 2022) Studies have been conducted to assess these effects on pregnant women, people with preexisting mental health conditions, incarcerated individuals, migrant workers, international students, children and young adults. (Fakari & Simbar, 2020; Li & Zhang, 2020; Cloud et al, 2020; Liem et al, 2020; Zhai & Du 2020; Buheji et al 2020; Shanahan et al 2022) More studies are still needed to fully understand the mental and emotional effects of COVID-19 on various segments of the public across all geographical areas. (Cipolletta et al, 2022; Liu et al, 2020; Yildirim et al, 2021) This study addresses the dearth of research in assessing the emotional state of young adults during a COVID-19 wave in the Detroit Metro area.

II. Material and Methods

Detroit residents between the ages of 18 and 25 self-reported their conditions via a survey instrument hosted on Centiment, Co, an online survey platform that
helps to target specific demographics for researchers. (Centiment, 2022) Data were collected between January 19, 2022, and February 7, 2022. The Detroit Metro area was experiencing a COVID wave during the same time. (State of Michigan, 2022) 522 people from the target population responded to the survey. 412 people completed the survey. There are approximately 600,000 people between the ages of 18 and 25 that reside in the Detroit Metro area. (Detroit Regional Chamber, 2022) 384 samples would be needed to achieve 95% confidence level with a 5% margin of error for statistical analysis. (Australian Bureau of Statistics, 2022) The collected responses are greater than the sample size target.

The survey instrument has 4 sections. The first section covered responder demographics. The second section is adapted from the Depression, Anxiety and Stress Scales (DASS-21). The DASS-21 “is a set of three self-report scales designed to measure the emotional states of depression, anxiety and stress. Each of the three DASS-21 scales contains 7 items, divided into subscales with similar content. The depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The stress scale is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset / agitated, irritable / over-reactive and impatient”. Scores for depression, anxiety and stress are calculated by summing the scores for the relevant items. (Motor Accident Insurance Commission, Australia, 2016; Lovibond & Lovibond, 1996) DASS-21 responses are summarized as extremely severe, severe, moderate, mild, and normal.

The third section is based on the Pew Research Center’s Teen Survey. (Jiang, 2020) The questions in this section cover the usage of electronic devices by the sampled population. The fourth section was derived from C.S. Mott Children’s Hospital National Poll on Children’s Health. (Freed, n.d.) This survey measures effects of COVID-19 restrictions on teens, who rely on their peer and social connections for emotional support. In total, the survey instrument had 46 multiple choices questions.

Descriptive analysis of the data collected was performed to better understand the demographics of the participants. Descriptive analysis also included breakdown of responses per question. Analysis of variance (ANOVA) was used to explore whether there are any statistically significant differences between various groups. Further, ANOVA was used to investigate the relationships between depression, anxiety, stress, and self-reported impact of COVID-19 on social interactions. Finally, ANOVA was used to investigate how young adults in the Detroit Metro area tried to deal with problems related to their emotional states.

### III. Results

49% of the respondents identified as female, 46% identified as male. 54% of the respondents self-reported themselves as white or Caucasian, 35% as black of African American, 9% as Latino or Hispanic, 7% as Asian, 3% as Native American or Alaskan Native and 1% as Native Hawaiian or Pacific Islander. A breakdown of respondent by age is shown in table 1.

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>82</td>
<td>16%</td>
</tr>
<tr>
<td>19</td>
<td>50</td>
<td>10%</td>
</tr>
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<td>20</td>
<td>65</td>
<td>12%</td>
</tr>
<tr>
<td>21</td>
<td>88</td>
<td>17%</td>
</tr>
<tr>
<td>22</td>
<td>58</td>
<td>11%</td>
</tr>
<tr>
<td>23</td>
<td>45</td>
<td>9%</td>
</tr>
<tr>
<td>24</td>
<td>58</td>
<td>11%</td>
</tr>
<tr>
<td>25</td>
<td>68</td>
<td>13%</td>
</tr>
<tr>
<td>Other/Undisclosed</td>
<td>8</td>
<td>2%</td>
</tr>
</tbody>
</table>

In response to DASS-21 portion of the survey, most respondents reported their levels as normal. Specifically, 38.8% reported normal depression levels, 37.4% reported normal anxiety levels and 47.6% reported normal stress levels. On the other hand, 26.9% of respondents reported their depression as extremely severe or severe, 36.2% of respondents reported their anxiety as extremely severe or severe and 18.9% of respondents reported their stress as extremely severe or severe. Additionally, it can be concluded that largest number of people reported higher than normal levels of depression, anxiety, and stress. A complete breakdown of the relevant responses is included in table 2. A Pearson correlation analysis for the three emotional states was performed. The states demonstrate a high degree of correlation. The correlation analysis is shown in table 3. Furthermore, moderate degree of statistically significant correlation, with coefficients between 0.24 and 0.39, were found between the levels of emotional states and various detrimental behaviors reported by the
respondents. Results of the associated Pearson correlation analysis are also shown in Table 3.

### Table 2: Descriptive Analysis for Emotional States

<table>
<thead>
<tr>
<th>Level</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>Percent</td>
<td></td>
</tr>
<tr>
<td>Extremely Severe</td>
<td>57</td>
<td>13.8%</td>
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<tr>
<td>Severe</td>
<td>54</td>
<td>13.1%</td>
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</tr>
<tr>
<td>Subtotal</td>
<td>111</td>
<td>26.9%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>102</td>
<td>24.8%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>39</td>
<td>9.5%</td>
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<tr>
<td>Normal</td>
<td>160</td>
<td>38.8%</td>
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</tr>
<tr>
<td>Grand Total</td>
<td>412</td>
<td></td>
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</tr>
</tbody>
</table>

### Table 3: Pearson Correlation Analysis for Emotional States and Detrimental Behaviors

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Anxiety</th>
<th>Stress</th>
<th>Sleep issues</th>
<th>Worry</th>
<th>Sadness</th>
<th>Changes in appetite</th>
<th>Aggressive behavior</th>
<th>Withdrawing from family</th>
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</thead>
<tbody>
<tr>
<td>Depression</td>
<td>0.67</td>
<td>0.68</td>
<td></td>
<td>0.30</td>
<td>0.39</td>
<td>0.39</td>
<td>0.24</td>
<td>0.37</td>
<td>0.30</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.68</td>
<td>0.73</td>
<td></td>
<td>0.32</td>
<td>0.35</td>
<td>0.30</td>
<td>0.24</td>
<td>0.36</td>
<td>0.21</td>
</tr>
<tr>
<td>Stress</td>
<td>0.30</td>
<td>0.32</td>
<td>0.30</td>
<td>0.40</td>
<td>0.41</td>
<td>0.39</td>
<td>0.25</td>
<td>0.39</td>
<td>0.24</td>
</tr>
<tr>
<td>Worry</td>
<td>0.39</td>
<td>0.35</td>
<td>0.38</td>
<td>0.40</td>
<td>0.55</td>
<td>0.28</td>
<td>0.28</td>
<td>0.24</td>
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</tr>
<tr>
<td>Sadness</td>
<td>0.39</td>
<td>0.30</td>
<td>0.36</td>
<td>0.41</td>
<td>0.55</td>
<td>0.28</td>
<td>0.38</td>
<td>0.29</td>
<td>0.37</td>
</tr>
<tr>
<td>Changes in appetite</td>
<td>0.24</td>
<td>0.24</td>
<td>0.25</td>
<td>0.39</td>
<td>0.28</td>
<td>0.38</td>
<td>0.25</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>0.37</td>
<td>0.36</td>
<td>0.39</td>
<td>0.31</td>
<td>0.24</td>
<td>0.29</td>
<td>0.25</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Withdrawing from family</td>
<td>0.30</td>
<td>0.21</td>
<td>0.24</td>
<td>0.23</td>
<td>0.27</td>
<td>0.37</td>
<td>0.34</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

*p values < 0.05 in all cases*

Over 62% of the respondents reported that the COVID-19 wave that was prevalent during the data collection phase has very negative or somewhat negative impact on their social interactions. A complete breakdown of the responses is included in Table 4. Respondents used various modes of communication to interact with their family members, friends or loved ones. Most common modes of communications reported were phone calls, social media, gaming platforms and in-person interactions. A complete breakdown of the responses is included in table 5. During the COVID-19 wave prevalent during the data collection phase 53.6% respondents reported experiencing sleep issues, 56.8% respondents reported experiencing worry, 53.2% respondents reported experiencing sadness, 38.6% respondents reported experiencing changes in appetite, 24.8% respondents reported experiencing aggressive behavior and 32.3% respondents reported withdrawing from family. Further, to seek emotional support 57.8% of respondents looked for information on internet portals, 32% used mobile applications, 37.6% looked for professional help and 68.4% talked to people in the family and/or friends.

### Table 4: Responses for the Survey Question “How would You Rate the Impact of the Current/Latest COVID-19 Wave on your Social Interactions?”

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Negative</td>
<td>127</td>
<td>30.8%</td>
</tr>
<tr>
<td>Somewhat Negative</td>
<td>132</td>
<td>32.0%</td>
</tr>
<tr>
<td>Subtotal</td>
<td>259</td>
<td>62.9%</td>
</tr>
<tr>
<td>No Impact</td>
<td>114</td>
<td>27.7%</td>
</tr>
<tr>
<td>Somewhat Positive</td>
<td>27</td>
<td>6.6%</td>
</tr>
<tr>
<td>Very Positive</td>
<td>12</td>
<td>2.9%</td>
</tr>
<tr>
<td>Grand Total</td>
<td>412</td>
<td></td>
</tr>
</tbody>
</table>
ANOVA was performed to assess whether levels of depression, anxiety and stress varied by gender. It was found that the p-values of the F-tests were less than 0.05, hence it can be concluded that there are statistically significant differences between the means from one level of gender to another at the 95.0% confidence level. The multiple range tests showed that the levels varied significantly between the following groups. People who self-reported their gender as other had statistically significant higher levels of depression and anxiety when compared to people who self-reported their gender as male or female. People who self-reported their gender as female or other had statistically significant higher levels of stress when compared to people who self-reported their gender as male. Results of the ANOVA are shown in tables 6, 7, 8. Multiple Ranges tests are shown in tables 9, 10, 11. The results of ANOVA didn’t show any statistically significant differences related to respondents’ race.

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F-Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between groups</td>
<td>30.21</td>
<td>3</td>
<td>10.07</td>
<td>3.95</td>
<td>0.0085</td>
</tr>
<tr>
<td>Within groups</td>
<td>1040.42</td>
<td>408</td>
<td>2.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F-Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between groups</td>
<td>20.54</td>
<td>3</td>
<td>6.85</td>
<td>3.28</td>
<td>0.0210</td>
</tr>
<tr>
<td>Within groups</td>
<td>851.91</td>
<td>408</td>
<td>2.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F-Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between groups</td>
<td>25.87</td>
<td>3</td>
<td>8.62</td>
<td>5.84</td>
<td>0.0006</td>
</tr>
<tr>
<td>Within groups</td>
<td>602.06</td>
<td>408</td>
<td>1.48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Sig.</th>
<th>Difference</th>
<th>+/- Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female - Male</td>
<td>-0.28</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Female - Other</td>
<td></td>
<td>1.22</td>
<td>0.97</td>
</tr>
<tr>
<td>Female - Prefer Not to Say</td>
<td>0.63</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td>Male - Other</td>
<td></td>
<td>1.50</td>
<td>0.97</td>
</tr>
<tr>
<td>Male - Prefer Not to Say</td>
<td>0.90</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td>Other - Prefer Not to Say</td>
<td>-0.59</td>
<td>1.59</td>
<td></td>
</tr>
</tbody>
</table>

* denotes a statistically significant difference.
Table 10: Multiple Range Tests for Depression by Gender

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Sig.</th>
<th>Difference</th>
<th>+/- Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female - Male</td>
<td>-0.26</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Female - Other</td>
<td>1.01</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Female - Prefer Not to Say</td>
<td>0.04</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>Male - Other</td>
<td>1.27</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Male - Prefer Not to Say</td>
<td>0.30</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>Other - Prefer Not to Say</td>
<td>-0.97</td>
<td>1.44</td>
<td></td>
</tr>
</tbody>
</table>

* denotes a statistically significant difference.

Table 11: Multiple Range Tests for Stress by Gender

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Sig.</th>
<th>Difference</th>
<th>+/- Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female - Male</td>
<td>-0.39</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Female - Other</td>
<td>0.72</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Female - Prefer Not to Say</td>
<td>0.39</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Male - Other</td>
<td>1.12</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Male - Prefer Not to Say</td>
<td>0.78</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Other - Prefer Not to Say</td>
<td>-0.33</td>
<td>1.21</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA did not highlight any statistically significant differences between levels of depression, anxiety, stress, and self-reported impact of COVID-19 on social interactions. All p-values were greater than 0.05. Similarly, the analysis did not demonstrate any statistically significant difference in the impact of COVID-19 based on gender or race. Tables 12, 13, 14 show that respondents turned to internet portals and professionals for help with their emotional states at statistically significant levels.

Table 12: Analysis of Variance for Depression - Type III Sums of Squares

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F-Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN EFFECTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Advice from internet</td>
<td>23.35</td>
<td>1</td>
<td>23.35</td>
<td>11.71</td>
<td>0.0007</td>
</tr>
<tr>
<td>B: Help from app</td>
<td>1.01</td>
<td>1</td>
<td>1.01</td>
<td>0.51</td>
<td>0.4775</td>
</tr>
<tr>
<td>C: Help from professional</td>
<td>12.61</td>
<td>1</td>
<td>12.61</td>
<td>6.32</td>
<td>0.0123</td>
</tr>
<tr>
<td>D: Help from family and friend</td>
<td>4.92</td>
<td>1</td>
<td>4.92</td>
<td>2.47</td>
<td>0.1169</td>
</tr>
</tbody>
</table>

All F-ratios are based on the residual mean square error.

Table 13: Analysis of Variance for Anxiety - Type III Sums of Squares

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F-Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN EFFECTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Advice from internet</td>
<td>48.13</td>
<td>1</td>
<td>48.13</td>
<td>20.62</td>
<td>0.0002</td>
</tr>
<tr>
<td>B: Help from app</td>
<td>7.10</td>
<td>1</td>
<td>7.10</td>
<td>3.04</td>
<td>0.0819</td>
</tr>
<tr>
<td>C: Help from professional</td>
<td>13.97</td>
<td>1</td>
<td>13.97</td>
<td>5.99</td>
<td>0.0148</td>
</tr>
<tr>
<td>D: Help from family and friend</td>
<td>0.82</td>
<td>1</td>
<td>0.82</td>
<td>0.35</td>
<td>0.5536</td>
</tr>
</tbody>
</table>

All F-ratios are based on the residual mean square error.

Table 14: Analysis of Variance for Stress - Type III Sums of Squares

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F-Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN EFFECTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Advice from internet</td>
<td>20.64</td>
<td>1</td>
<td>20.64</td>
<td>14.22</td>
<td>0.0002</td>
</tr>
<tr>
<td>B: Help from app</td>
<td>0.02</td>
<td>1</td>
<td>0.02</td>
<td>0.01</td>
<td>0.9085</td>
</tr>
<tr>
<td>C: Help from professional</td>
<td>4.25</td>
<td>1</td>
<td>4.25</td>
<td>2.93</td>
<td>0.0879</td>
</tr>
<tr>
<td>D: Help from family and friend</td>
<td>0.004</td>
<td>1</td>
<td>0.004</td>
<td>0.00</td>
<td>0.9608</td>
</tr>
</tbody>
</table>

All F-ratios are based on the residual mean square error.
IV. Discussion

The analyses show that emotional states of young adults in the Detroit Metro area were concerning. The emotional states were worse for genders other than male. The COVID-19 wave, and the associated lockdown also seems to have coincided with several detrimental behaviors. The young adults used various modes of communication to keep their social interactions active. They turned to various avenues to seek help for their emotional states.

V. Conclusion

Public health administrators could use the findings of this study to develop effective remedial programs. At individual level, young adults should keep channels of communications open via various modes with loved ones and professionals to help elevate their emotional states. The study is the first of its kind for the Detroit Metro area. Additional studies should be conducted in other geographical areas to develop a comprehensive understanding of the emotional states of young people in general and during pandemic lockdowns in specific. Further longitudinal studies will also help deepen the depth of knowledge. Regardless, of the COVID-19 related lockdown the emotional states of young people in the Detroit Metro area were found to be distressed.

Acknowledgments

The authors acknowledge the support of their family in completing this research study.

Disclosure

The authors report no conflicts of interest in this work.

References Références Referencias


Abbreviations: Df: Degrees of Freedom
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Exploring the Mechanism of Tripterygium Wilfordii Treating Epilepsy based on Network Pharmacology

By Yuewang & Xiali

University of Chinese Medicine

Abstract- Introduction: This study explored the action mechanism of tripterygium wilfordii active ingredients in the treatment of epilepsy by using network pharmacology.

Methods: TCMSP database was used to screen the active components and genes of Tripterygium wilfordii. On-line text mining server (GeneCards) was used to query epilepsy genes, and the genes of epilepsy and tripterygium wilfordii were standardized and intersected. The mapped genes were imported into Cytoscape software, and the relationship network of "drugs-ingredients-diseases-targets" was obtained. Based on David database, gene ontology (G0) function enrichment analysis and (KEGG) pathway enrichment analysis were performed on the target. And construct KEGG path relation network. On-line database String constructs protein-protein interaction PPI network, and imports relational network layout into Cytoscape software to obtain core sub-network. AutoDockTools and AutoDockVina software are used for molecular docking, and Pymol is used for docking visualization.

Results: There are 21 kinds of active ingredients of Tripterygium wilfordii, including kaempferol, β-sitosterol, triptolide and other active ingredients. 72 cross genes were obtained.

Keywords: tripterygium wilfordii, epilepsy, network pharmacology.

GJMR-A Classification: DDC Code: 616.853 LCC Code: RC372
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Results: There are 21 kinds of active ingredients of Tripterygium wilfordii, including kaempferol, β-sitosterol, triptolide and other active ingredients. 72 cross genes were obtained. Through pathway construction and enrichment analysis, it was found that the potential mechanism may be related to cell proliferation, differentiation, apoptosis, GABA-mediated pathway and so on. The docking results showed that the binding energies of the core targets were all small -5 kcal mol-1, which indicated that there was a good affinity between genes and components.

Conclusion: Tripterygium wilfordii has the characteristics of multi-components, multi-targets and multi-pathways in treating epilepsy. It provides theoretical basis and basis for new drug development and experimental research.

Keywords: tripterygium wilfordii, epilepsy, network pharmacology.

I. INTRODUCTION

Epilepsy is one of the most common chronic brain diseases affecting more than 70 million people around the world. It greatly affects the quality of life of patients and poses a serious threat to their health [1-2]. At present, antiepileptic drug therapy is the most important clinical treatment scheme. Although it can alleviate the symptoms of patients, it can't inhibit the development of epileptic process, and long-term use will also cause various adverse reactions, which will also reduce the drug sensitivity [3]. For short-term clinical seizures of epilepsy, 60% ~ 70% of patients can achieve seizure-free symptoms [4], but there is no satisfactory treatment plan for long-term treatment of epilepsy [5]. Therefore, it is of great clinical significance to develop drugs with high curative effect, good safety and little side effects and new treatment methods.

Traditional Chinese medicine (TCM) is effective in treating epilepsy, with few side effects and wide clinical application. Therefore, this study aims to explore the mechanism of TCM tripterygium wilfordii in treating epilepsy and provide new drug ideas for the treatment of epilepsy. It is a woody vine of Tripterygium wilfordii belonging to Celastraceae. It is cold in nature, bitter in taste and poisonous, and belongs to the four meridians of heart, liver, stomach and kidney. It has the effects of promoting blood circulation, removing blood stasis, clearing away heat and toxic materials, and is distributed in the middle and lower reaches of the Yangtze River [6]. It was first published in Shennong's Materia Medica, and is named Mangcao, which is mainly used for treating scalp wind, carbuncle, breast swelling and hernia [7]. There are detailed records in the Compendium of Materia Medica, which can treat swelling, edema, swelling, jaundice, chronic malaria, poison in the mouth of fish, etc [8]. Studies have shown that triptolide has protective effect on neurons of KA-induced epileptic rats [9]. Moreover, Tripterygium wilfordii polyglycoside can effectively improve the learning and memory ability of epileptic rats induced by PTZ, which is closely related to the up-regulation of Ng and PKC expression levels in hippocampus of rats [10].

Looking at the existing literatures about the effective components of Tripterygium wilfordii, it can be found that there is still a lack of overall and systematic understanding of the anti-epileptic mechanism of Tripterygium wilfordii. In this study, the target of Tripterygium wilfordii was found out through its active ingredients and fused with the epileptic target, and the potential target of Tripterygium wilfordii in treating epilepsy was obtained. The signal pathway or metabolic pathway related to Tripterygium wilfordii in treating...
epilepsy was obtained through function and pathway enrichment analysis, which provided a new idea and direction for comprehensively and systematically expounding the action mechanism of Tripterygium wilfordii in treating epilepsy.

II. MATERIALS AND METHODS

a) Prediction of Active Components and Targets of Tripterygium wilfordii

The effective components and targets of Tripterygium wilfordii were searched in TCMSP database with keywords "tripterygium wilfordii", "leigongteng" and "thunder god vine". Taking oralbioavailability (OB) ≥ 30% and drug-likeness property (DL) ≥ 0.18[11] as screening criteria, the active ingredients of Tripterygium wilfordii were obtained. According to the active components of Tripterygium wilfordii, the corresponding target protein was predicted in TCMSP platform, and then the protein was imported into UniProt database (https://www.Uniprot.org/) for gene standardization.

b) Prediction of Epileptic Targets

Through the online text mining server Genecards (https://www.genecards.org/), the target of epilepsy is predicted, and the data is arranged and duplicated to get the target related to epilepsy.

c) Prediction of Tripterygium wilfordii’s effect on Epileptic Targets

The online software Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) was used to intersect the active components of Tripterygium wilfordii with epilepsy-related targets, and the potential targets of the interaction between Tripterygium wilfordii and epilepsy were obtained.

d) Build a "drug-ingredient-disease-target" relationship network

After arranging the active ingredients and potential targets of Tripterygium wilfordii, the network of "Tripterygium wilfordii-active ingredients-epilepsy-potential targets" was initially obtained by guiding people to Cytoscape 3.9.0 software for visualization.

e) Gene Enrichment Analysis

David database was used to analyze the potential targets by GO and KEGG, and to explore the possible biological function and main signal pathway of Tripterygium wilfordii in treating epilepsy. In this study, the first 20 GO biological functions and KEGG enrichment pathways of enrichment results were selected by using P from small to large as screening conditions.

f) Construction of "Target-KEGG" Pathway Relationship Network

Import the KEGG path relationship file into Cytoscape 3.9.0 software, calculate the Degree value, and adjust the size of nodes according to the Degree value, and further obtain the "target-KEGG path" relationship network diagram.

g) Construction of Protein-Protein Interaction Network (PPI Network)

In order to understand the interaction among proteins, the potential targets of Tripterygium wilfordii for epilepsy treatment were input into online database String (https://string-db.org/) to construct a network, and the interaction network between potential target proteins was obtained. The tsv file of PPI network relationship was obtained, and the file was imported into Cytoscape 3.9.0 software for PPI protein interaction analysis. Use plug-in Cyto hubba to screen core targets. Build a core network diagram.

h) Component-Target Molecule Docking

Molecular docking of the screened core target and its corresponding active components was carried out to verify the binding activity between components and targets. Firstly, the protein crystal structure of the core target was downloaded from RCSB PDB database.
Exploring the Mechanism of Tripterygium Wilfordii Treating Epilepsy Based on Network Pharmacology

(http://www1.rcsb.org/), and the original ligand and water molecule were removed by PyMol. In addition, the components were introduced into ChemBio3D Ultra for energy minimization. Then, AutoDockTools is used for file conversion before docking, and then AutoDockVina is used for molecular docking. Finally, the sample with the lowest free energy is selected as the docking sample, and it is visualized by PyMol.

III. Results

a) Search the Active Ingredients and Targets of Tripterygium Wilfordii

According to the search conditions, the active components of Tripterygium wilfordii were searched, and 26 kinds of active components of Tripterygium wilfordii were obtained. The structures of the obtained components were verified by Pubchem database, and finally 21 components with complete information were obtained, as shown in Table 1. And its effective active ingredients were input into TCMSP platform to search for 148 targets of active ingredients of Tripterygium wilfordii.

<table>
<thead>
<tr>
<th>ID</th>
<th>Ingredient</th>
<th>OB%</th>
<th>DL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOL000296</td>
<td>hederagenin</td>
<td>36.91</td>
<td>0.75</td>
</tr>
<tr>
<td>MOL000449</td>
<td>Stigmasterol</td>
<td>43.83</td>
<td>0.76</td>
</tr>
<tr>
<td>MOL003184</td>
<td>1S1827-74-9</td>
<td>45.42</td>
<td>0.53</td>
</tr>
<tr>
<td>MOL003185</td>
<td>(1R,4aR,10aS)-5-hydroxy-1-(hydroxymethyl)-7-isopropyl-8-methoxy-1,4a-dimethyl-4,9,10,10a-tetrahydro-3H-phenanthren-2-one</td>
<td>48.84</td>
<td>0.38</td>
</tr>
<tr>
<td>MOL003196</td>
<td>Tryptophenolide</td>
<td>48.50</td>
<td>0.44</td>
</tr>
<tr>
<td>MOL003229</td>
<td>Triptin B</td>
<td>34.73</td>
<td>0.32</td>
</tr>
<tr>
<td>MOL003231</td>
<td>Triptoditerpenic acid B</td>
<td>40.02</td>
<td>0.36</td>
</tr>
<tr>
<td>MOL003245</td>
<td>Triptonoditerpenic acid</td>
<td>42.56</td>
<td>0.39</td>
</tr>
<tr>
<td>MOL003248</td>
<td>Triptonoterpenone</td>
<td>48.57</td>
<td>0.28</td>
</tr>
<tr>
<td>MOL003280</td>
<td>TRIPTONOLIDE</td>
<td>49.51</td>
<td>0.49</td>
</tr>
<tr>
<td>MOL000358</td>
<td>beta-sitosterol</td>
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<tr>
<td>MOL000422</td>
<td>kaempferol</td>
<td>41.88</td>
<td>0.24</td>
</tr>
<tr>
<td>MOL004443</td>
<td>Zhebeiresinol</td>
<td>58.72</td>
<td>0.19</td>
</tr>
<tr>
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<td>40957-99-1</td>
<td>57.20</td>
<td>0.62</td>
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<tr>
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<td>Celalocinnine</td>
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<tr>
<td>MOL003217</td>
<td>Isoxanthohumol</td>
<td>56.81</td>
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<tr>
<td>MOL005828</td>
<td>nobiletin</td>
<td>61.67</td>
<td>0.52</td>
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<tr>
<td>MOL003187</td>
<td>triptolide</td>
<td>51.29</td>
<td>0.68</td>
</tr>
<tr>
<td>MOL003206</td>
<td>Celafurine</td>
<td>72.94</td>
<td>0.44</td>
</tr>
<tr>
<td>MOL003224</td>
<td>Tripdiotolinde</td>
<td>78.72</td>
<td>0.72</td>
</tr>
<tr>
<td>MOL003225</td>
<td>Hypodiolide A</td>
<td>76.13</td>
<td>0.49</td>
</tr>
</tbody>
</table>

b) Potential Targets of Tripterygium Wilfordii in the Treatment of Epilepsy

6007 targets related to epilepsy were retrieved. 3170 epileptic targets with a probability greater than or equal to 0.5 were selected, and the acquired tripterygium wilfordii targets and epileptic targets were standardized in Uniprot database. Using software venny2.1, 148 targets with tripterygium wilfordii active ingredients and 3170 epileptic-related targets were mapped and crossed, and 72 potential targets with tripterygium wilfordii for epilepsy treatment were obtained as a result, as shown in Figure 1.
c) **Construction of "Drug-Ingredient-Disease-Target" Network**

After the intersection, the potential targets were introduced into Cytoscape 3.9.0 software, and a "drug-component-disease-target" relationship network was constructed. It was found that each component was closely related to epilepsy through genes, as shown in Figure 2. The line segments among various factors represent the interaction relationship, and the more line segments, the stronger the interaction relationship.

Figure 1: Map of Tripterygium wilfordii epilepsy target. Blue circle represents Tripterygium wilfordii epilepsy target, yellow circle represents epilepsy target, and gray ellipse represents potential tripterygium wilfordii epilepsy target.

![Figure 1](image1.png)

**Figure 2:** Green circle represents the target, orange inverted V represents the active ingredient of Tripterygium wilfordii, green diamond represents epilepsy, and purple represents Tripterygium wilfordii.

![Figure 2](image2.png)

d) **GO Function Enrichment Analysis and KEGG Pathway Enrichment Analysis**

The functional enrichment of GO is mainly divided into three parts: biological process (BP), cellular component (CC) and molecular function (MF). According to the order of P value, the first 20 enrichment items are selected respectively. Among them, the mechanism of tripterygium wilfordii in treating epilepsy mainly involves biological processes such as GABA signaling pathway, cell composition such as synapse, mitochondria and plasma membrane raft, and molecular functions such as steroid binding, protease binding, protein binding, gated ion channel activity and GABA-A receptor activity. See Figure 3- Figure 5 for specific GO comments.
The enrichment results of KEGG pathway mainly include: cancer pathway, lipid and atherosclerosis signaling pathway, platinum resistance signaling pathway, Kaposi’s sarcoma-associated herpes virus infection signaling pathway, chemical carcinogenesis-receptor activation signaling pathway, human cytomegalovirus infection signaling pathway, IL-17 signaling pathway, AGE-RAGE signaling pathway in diabetic complications, fluid shear stress and atherosclerosis signaling pathway, pulmonary tuberculosis signaling pathway, dopaminergic synapse and neuroactive ligand- . See Figure 6- Figure 7.
**Fig. 6:** The enrichment of KEGG pathway and the gradual change from red to blue represent the increasing P value.

**Fig. 7:** KEGG bubble diagram. The larger the circle, the more genes are enriched, and the darker the red color, the lower the P value.

e) **Build KEGG Channel Relationship Network**

Calculate the degree values of the first 20 enriched KEGG pathways and potential targets by using Cytoscape3.9.0 software, and adjust the size and color of the nodes with the degree values to construct the "target -KEGG pathway" relationship network diagram, as shown in Figure 8. Results It was found that Tripterygium wilfordii might play a therapeutic role on epilepsy through multiple active ingredients, multiple targets and multiple ways.

**Fig. 8:** Purple represents KEGG pathway, the larger the inverted V, the darker the color, the more enrichment pathways, and the larger the square, the darker the color, the more participating pathways.
f) **PPI Network Construction and Core Target Prediction**

The 72 potential targets of tripterygium wilfordii and epilepsy are entered into the String database, and the PPI relationship network diagram is shown in Figure 9. The results showed that there were direct or indirect interactions among potential targets. The PPI network consisted of 72 nodes and 562 edges, with an average node degree of 15.8. The interaction results of PPI protein showed that protein domain and GABA receptor were found in its features, and it was speculated that Tripterygium wilfordii might play a role in epilepsy through GABA receptor system. Use Cyto hubba plug-in to screen out the core targets among potential targets and obtain the core sub-network. See figure 10. There are eight core targets in the core network, such as AKT1, ESR1, TP53, FOS, CYP3A4, MMP9, TNF and CASP3. These targets are also important targets in KEGG relationship network, and they play an important role not only in KEGG relationship network, but also in PPI network.

![Figure 9: PPI protein interaction network diagram, the sphere represents the target, the connection between the targets represents the interaction, and the more line segments, the stronger the effect.](image)

![Figure 10: Core Target Map](image)


g) **Component-Target Molecule Docking**

According to the above screening steps, the related core genes were obtained, and the core genes were molecular docked with the components. The results are shown in Table 2. It was found that all the other core genes can be docked except CASP3 gene, and the binding energy is less than -5 kcal mol-1, which indicates that the core targets have good binding activity with the corresponding active components. The smallest binding energy of the core target is the docking of CYP3A4 with kaempferol, and the binding energy is-
8.39 kcal mol\(^{-1}\). The results show that tripterygium wilfordii can treat epilepsy through gene regulation components and action pathways. The docking mode was visualized by PyMol, and it was found that there were hydrogen bonding forces in these docking structures, which also indicated that the spatial matching degree of components and proteins was good. As shown in Figure 11.

**Table 2**: Docking information of core target molecules, in which the binding energy unit is kcal mol\(^{-1}\).

<table>
<thead>
<tr>
<th>Number</th>
<th>Gene name</th>
<th>Ingredient</th>
<th>Docking position</th>
<th>Binding energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AKT1</td>
<td>kaempferol</td>
<td>SER-56, GLN-61,</td>
<td>-6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GLN-59</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ESR1</td>
<td>isoxanthohumol</td>
<td>HIS-206, TYR-213</td>
<td>-7.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nobiletin</td>
<td></td>
<td>-7.43</td>
</tr>
<tr>
<td>3</td>
<td>MMP9</td>
<td>nobiletin</td>
<td>ALA-191, GLN-227</td>
<td>-7.58</td>
</tr>
<tr>
<td>4</td>
<td>TP53</td>
<td>triptolide</td>
<td>ARG-267</td>
<td>-7.57</td>
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<tr>
<td></td>
<td></td>
<td>nobiletin</td>
<td>GLY-154</td>
<td>-6.61</td>
</tr>
<tr>
<td>5</td>
<td>TNF</td>
<td>kaempferol</td>
<td>ALA-134, ASN-46,</td>
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<tr>
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<td></td>
<td></td>
<td>TRP-28, GLY-24,</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>ILE-136</td>
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<td>triptolide</td>
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<td>CYP3A4</td>
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<td>GLU-234, ARG-106</td>
<td>-8.39</td>
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</tbody>
</table>

**Fig. 11**: Molecular Docking Diagram

**IV. Discussion**

Epilepsy is a serious neurological disease caused by the disorder of the physiological structure or function of the brain. More than half of the patients with epilepsy have one or more complications [12]. Mental diseases (such as depression, anxiety, psychosis, autism) and physical diseases (such as type 1 diabetes, arthritis, peptic ulcer, chronic obstructive pulmonary disease) are all related to long-term seizures [2]. However, the long-term use of antiepileptic drugs has great adverse reactions, and about 50% of patients can't control seizures well by using only one antiepileptic drug [13]. A large number of experiments and clinical studies show that the effect of integrated traditional Chinese and western medicine on epilepsy is better than that of chemical medicine alone [14]. Chinese medicine believes that epilepsy is closely related to pathological factors such as wind, blood stasis, phlegm and fire. The treatment should distinguish the attack period from the recovery period, and grasp the principle of “treating the target when it is urgent, and treating the root when it is slow”. In the recovery period, the treatment is mainly to soothe the liver and regulate qi, strengthen the spleen and soothe the nerves, and replenish qi and nourish yin [15]. Finding new drugs to treat epilepsy is our constant pursuit. In recent years, network pharmacology of traditional Chinese medicine (TCM) with "multi-component targeted network" as its main research mode has become increasingly popular, which mainly reveals the drug-gene-disease network relationship by predicting the targeted distribution and pharmacological effects of TCM compounds. Based on the concept of multi-component, multi-target and multi-way action of traditional Chinese medicine, this study studied the main components, targets, biological functions and signal
pathways of Tripterygium wilfordii through network pharmacology technology, in order to reveal its mechanism of action in treating epilepsy.

In this study, 21 kinds of active components and 72 potential anti-epileptic targets of Tripterygium wilfordii were screened by network pharmacology technology, and the network of "drug-component-disease-target", "target -KEGG" and "PPI network" were constructed. Eight core targets including AKT1, ESR1, TP53, FOS, CYP3A4, MMP9, TNF and CASP3 were screened out. The same active ingredient of Tripterygium wilfordii can act on multiple targets; The same signal pathway can enrich multiple targets; The same target can correspond to multiple active ingredients and participate in multiple signal pathways.

The results of network analysis show that tripterygium wilfordii mainly includes kaempferol, β-sitosterol, lignan, triptolide, tripterygium wilfordii polyglycoside and other active components as potential components for treating epilepsy. Studies have shown that flavonoids have antioxidant effect and can protect cells from oxidative stress. This study includes kaempferol, a flavonoid compound. Kaempferol can combine with benzodiazepines on GABA-A receptor to protect the brain from oxidative stress and has anti-epileptic effect [16]. Tripterygium wilfordii can protect neurons from apoptosis induced by kainic acid in rats by inhibiting the expression of MHC-ⅰ, ⅱ molecules in microglia and immune response [17]. Tripterygium wilfordii can also down-regulate the expression of caspase-3 and caspase-9 proteins in hippocampus of epileptic rats induced by kainic acid, thus inhibiting neuronal apoptosis [18]. Tripterygium wilfordii can inhibit neuronal apoptosis in epileptic rats by up-regulating Bcl-2 and down-regulating Bax protein expression [19]. Tripterygium wilfordii extract can inhibit the activation and proliferation of microglia, and its molecular mechanism may be related to the down-regulation of NF-KB protein and mRNA expression in microglia [20].

According to related research, β-sitosterol has obvious anticonvulsant effect among the main active components of Tripterygium wilfordii [21-22]. Experiments have proved that β-sitosterol has neuroprotective effect on hippocampal neurons with epileptic discharge [23]. The latest research found that the mechanism of tripterygium wilfordii polyglycoside inhibiting inflammatory factors may be related to MAPK signal transduction pathway and VEGF signal transduction pathway. Neuroinflammation and oxidative stress are closely related to epilepsy. Some effective anti-inflammatory and antioxidant drugs in animal models have been applied clinically, and have shown therapeutic effects on epilepsy patients.

Both PPI core targets and enrichment pathways confirm that the main components of Tripterygium wilfordii may be related to target regulation. Neuron-activated biomarker protein kinase subtype B 1(Akt1) is a serine/threonine kinase activated by oxidative stress, which is closely related to seizures [24-25]. It can participate in protein synthesis in hippocampal synaptic plasticity and control many pathological signal processes of epilepsy. Therefore, intervention of Akt/MTOR pathway with AKT subtype specific inhibitors may provide a way for the treatment of epilepsy. In addition, the level of interleukin-6(IL-6), a pro-inflammatory cytokine, was confirmed to increase significantly after epilepsy [27-29]. The level of cysteine aspartic protease 3 (Caspas3) encoded by CASP3 was also confirmed to be significantly increased in the serum of epileptic patients [30]. It was found that the expression of miRNA-141 in epileptic patients was up-regulated, which induced neuronal apoptosis and increased the expression level of Caspase-3/9 and p53 protein. miRNA-141 was involved in epilepsy by targeting p53 to inhibit apoptosis [31]. VEGFA is over-expressed in patients with drug-resistant temporal lobe epilepsy, suggesting that it is involved in the pathological process of epilepsy [32]. Seizures significantly inhibit the plasticity of synapses, and the short-term plasticity mainly depends on the fluctuation and steady state of calcium levels in synapses [33]. The neuroprotective effect of ESR1 is mainly through its influence on synaptic plasticity [34]. ZHANG et al. [35] found that mice lacking FOS expression had more severe seizures, increased neuronal excitability and neuronal cell death, and FOS regulated the expression of GLUR6 and brain-derived neurotrophic factor (BDNF) in vivo and in vitro. As an important factor of apoptosis after brain injury, HIF-1α may provide a new target for the treatment of epilepsy [36]. Under hypoxia, HIF-1α is widely expressed in neurons, glial cells and ependymal cells in the central nervous system. Li Yanmei [37] and others found that the homozygous mutation of CYP3A4*1G may be related to drug resistance in children with epilepsy with hereditary or unknown etiology. Screening CYP3A4*1G genotype is one of the important methods to guide the selection of antiepileptic drugs and to judge and predict the therapeutic effect of antiepileptic drugs in children with hereditary or unknown etiology. Liu Dandan [38] studies have shown that seizures in the acute stage of viral encephalitis are related to the increased levels of IL-1β, IL-6 and TNF-α in cerebrospinal fluid. Therefore, the core target of this study is closely related to regulating the occurrence and development of epilepsy treated by effective components of Tripterygium wilfordii.

In order to further analyze the signal pathways and biological processes involved in tripterygium wilfordii therapeutic targets, the KEGG signal pathways and GO biological processes of tripterygium wilfordii therapeutic targets were enriched. Among them, oxidative stress and neuronal apoptosis are both related to seizures. There is evidence that in some animal
epilepsy models, antioxidant therapy can reduce the nerve damage caused by oxidative free radicals, thus playing an anti-epileptic role [39-40]. At present, most antiepileptic drugs play an antiepileptic role mainly by regulating voltage-gated ion channels, enhancing C-aminobutyric acid-mediated inhibition, regulating synaptic release, or blocking ionic glutamate receptors. Therefore, the function of synapses is closely related to epilepsy [41]. It has also been reported that the level of catecholamine in striatum decreased during the incubation period in the seizure model induced by sodium glutamate [42]. The activity of neurotransmitter receptor is also closely related to the occurrence of epilepsy. It has been found that stimulating vagus nerve can enhance the activity of inhibitory neurotransmitter receptor a-aminobutyric acid receptor, thus inhibiting the occurrence of epilepsy [43]. The results of GO bioaccumulation analysis in this paper provide bioinformatics basis for potential target therapy of epilepsy predicted by Tripterygium wilfordii. The results of KEGG enrichment analysis showed that Tripterygium wilfordii might be related to epilepsy through IL-17 signaling pathway, human cytomegalovirus infection and tumor necrosis factor signaling pathway. The above reports on the effective active ingredients of Tripterygium wilfordii are basically consistent with the predicted results of the enrichment analysis of Tripterygium wilfordii target and KEGG signal pathway and GO biological process in this study.

V. Conclusion

The selected targets, their biological functions and enriched signal pathways are closely related to the regulation of biological changes of epilepsy. However, many components selected from Tripterygium wilfordii are regulated by the core targets, which play a role in treating epilepsy. Further, it is suggested that the active ingredients of Tripterygium wilfordii may exert its therapeutic effect by acting on a variety of biological changes in the development of epilepsy. Its core target is closely related to the development of epilepsy, and the biological functions and enriched signal pathways of potential targets are also closely related to the mechanism of epilepsy. This study preliminarily expounded the molecular mechanism of tripterygium wilfordii in treating epilepsy, which provided a theoretical basis for new drug research and a new idea for treating epilepsy with traditional Chinese medicine. However, further experimental verification is still needed.

Author Contributions

X.L. and Y.W. participated in the design of this study, and they both performed the statistical analysis. X.L. carried out the study and collected important background information. Y.W. drafted the manuscript. All authors read and approved the final manuscript. X.L. and Y.W. carried out the concepts, design.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

First of all, I would like to thank my alma mater, Changchun University of Traditional Chinese Medicine, and then I would like to thank Mr. Li Wannan for his suggestions on this research.

Data availability

The data used to support the findings of this study is available from the corresponding author upon request.

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We typeset manuscripts using advanced typesetting tools like Adobe InDesign, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

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Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

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2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author’s email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s)’ names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted must not have been submitted or published elsewhere and all authors must be aware of the submission.

**Declaration of Conflicts of Interest**

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

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- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures
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2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

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Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.
Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27” x 11” , left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word “Abstract” in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper’s subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned un refereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.
**Format Structure**

*It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.*

All manuscripts submitted to Global Journals should include:

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The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

**Author details**

The full postal address of any related author(s) must be specified.

**Abstract**

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

**Keywords**

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

**Numerical Methods**

Numerical methods used should be transparent and, where appropriate, supported by references.

**Abbreviations**

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

**Formulas and equations**

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

**Tables, Figures, and Figure Legends**

Tables: Tables should be cautiously designed, uncrowed, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.
Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Electronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/photos) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.
6. **Bookmarks are useful**: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. **Revise what you wrote**: When you write anything, always read it, summarize it, and then finalize it.

8. **Make every effort**: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. **Produce good diagrams of your own**: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. **Use proper verb tense**: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. **Pick a good study spot**: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. **Know what you know**: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. **Use good grammar**: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. **Arrangement of information**: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. **Never start at the last minute**: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. **Multitasking in research is not good**: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. **Never copy others' work**: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. **Go to seminars**: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. **Refresh your mind after intervals**: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.
20. **Think technically:** Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. **Adding unnecessary information:** Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts.

22. **Report concluded results:** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. **Upon conclusion:** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

**Informal Guidelines of Research Paper Writing**

**Key points to remember:**
- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

**Final points:**

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

*The introduction:* This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

*The discussion section:* This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

*General style:* Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

*To make a paper clear:* Adhere to recommended page limits.
Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don’t address the reviewer directly. Don’t use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

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The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study’s tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

*Materials may be reported in part of a section or else they may be recognized along with your measures.*

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that’s all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer’s interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.
Results:
The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:
- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:
- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:
As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:
If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:
The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

**Approach:**

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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