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ABOUT THIS JOURNAL

Publication Policy
The Journal of Neurobehavioral Sciences (J Neuro Behav Sci) is a peer-reviewed open-access neuroscience journal without any publication fees. All editorial costs are sponsored by the Üsküdar University Publications and the Foundation of Human Values and Mental Health. Each issue of the Journal of Neurobehavioral Sciences is specially commissioned, and provides an overview of important areas of neuroscience from the molecular to the behavioral levels, delivering original articles, editorials, reviews and communications from leading researchers in that field. JNBS is published electronically and in the printed form 3 times a year by Uskudar University. The official language of JNBS is English. The average time from delivery to first decision is less than 30 days. Accepted articles are published online on average on 40 working days prior to printing, and articles are published in print at 3-6 months after acceptance. Please see our Guide for Authors for information on article submission. If you require any further information or help, please email us (jnbs@uskudar.edu.tr)

Aims & Scope
JNBS (J. Neuro. Behav. Sci) is a comprehensive scientific journal in the field of behavioral sciences. It covers many disciplines and systems (eg neurophysiological, neuroscience systems) with behavioral (eg cognitive neuroscience) and clinical aspects of molecules (eg molecular neuroscience, biochemistry), and computational methods in health.

The journal covers all areas of neuroscience with an emphasis on psychiatry and psychology as long as the target is to describe the neural mechanisms underlying normal or pathological behavior. Preclinical and clinical studies are equally acceptable for publication.

In this context; the articles and treatment results of computational modeling methods of psychiatric and neurological disorders are also covered by the journal.

JNBS emphasis on psychiatric and neurological disorders. However, studies on normal human behavior are also considered. Animal studies and technical notes must have a clear relevance and applicability to human diseases. Case Reports including current neurological therapies or diagnostic methods are generally covered by JNBS.

Besides; The scope of JNBS is not limited to the abovementioned cases, and publications produced from the interdisciplinary studies established in the following fields and with the behavioral sciences are included in the studies that can be published in JNBS.

- Cognitive neuroscience
- Psychology
- Psychiatric and neurological disorders
- Neurophysiology
- System neuroscience
- Molecular neuroscience
- Computational Neuroscience
- Neuromodulation, Neurolinguistic, Neuromarketing
- Biochemistry
- Computational and simulation methods and interdisciplinary applications in medicine
- Artificial Intelligence (AI) and interdisciplinary applications in medicine
- Brain imaging
- In vivo monitoring of electrical and biochemical activities of the brain
- Molecular Biology
- Genetics
- Bioinformatics
- Psychiatric Nursing

INSTRUCTIONS FOR AUTHORS
Prior to submission, please carefully read and follow the submission guidelines entailed below. Manuscripts that do not conform to the submission guidelines may be returned without review.

Submission
Submit manuscripts electronically (.doc format with including all figures inside) via the online submission system of our website (https://dergipark.org.tr/en/pub/jnbs).

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> İstanbul-Turkiye

General correspondence may be directed to the Editor's Office.

In addition to postal addresses and telephone numbers, please supply electronic mail addresses and fax numbers, if available, for potential use by the editorial and production offices.

Masked Reviews
Masked reviews are optional and must be specifically requested in the cover letter accompanying the submission. For masked reviews, the manuscript must include a separate title page with the authors' names and affiliations, and these ought not to appear anywhere else in the manuscript. Footnotes that identify the authors must be typed on a separate page. Make every effort to see that the manuscript itself contains no clues to authors' identities. If your manuscript was mask reviewed, please ensure that the final version for production includes a byline and full author note for typesetting.

Similarity Rate: The similarity of the submitted articles with the Ithenticate program is determined. The similarity rate should be below 20%.

Types of Articles: Brief Reports, commentaries, case reports and minireviews must not exceed 4000 words in overall length. This limit includes all aspects of the manuscript (title page, abstract, text, references, tables, author notes and footnotes, appendices, figure captions) except figures.

Brief Reports also may include a maximum of two figures.

For Brief Reports, the length limits are exact and must be strictly followed. Regular Articles typically should not exceed 6000 words in overall length (excluding figures).

Reviews are published within regular issues of the JNBS and typically should not exceed.

10000 words (excluding figures)

Cover Letters
All cover letters must contain the following: A statement that the material is original —if findings from the dataset have been

previously published or are in other submitted articles, please include the following information:

*Is the present study a new analysis of previously analyzed data? If yes, please describe differences in analytic approach.

*Are some of the data used in the present study being analyzed for the first time? If yes, please identify data (constructs) that were not included in previously published or submitted manuscripts.

*Are there published or submitted papers from this data set that address related questions? If yes, please provide the citations, and describe the degree of overlap and the unique contributions of your submitted manuscript.

*The full postal and email address of the corresponding author; *The complete telephone and fax numbers of the same;

*The proposed category under which the manuscript was submitted;

*A statement that the authors complied with APA ethical standards in the treatment of their participants and that the work was approved by the relevant Institutional

Review Board(s).

*Whether or not the manuscript has been or is posted on a web site;

*That APA style (Publication Manual, 6th edition) has been followed;

*The disclosure of any conflicts of interest with regard to the submitted work;

*A request for masked review, if desired, along with a statement ensuring that the manuscript was prepared in accordance with the guidelines above.

*Authors should also specify the overall word length of the manuscript (including all aspects of the manuscript, except figures) and indicate the number of tables, figures, and supplemental materials that are included.

Manuscript Preparation

Prepare manuscripts according to the Publication Manual of the American Psychological Association (6th edition).

Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the Manual.

Below are additional instructions regarding the preparation of display equations and tables.

Display Equations

We strongly encourage you to use MathType (third-party software) or Equation

Editor 3.0 (built into pre-2007 versions of word) to construct your equations, rather than the equation support that is built into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors.

To construct your equations with MathType or Equation Editor 3.0:

Go to the Text section of the Insert tab and select Object.

Select MathType or Equation Editor 3.0 in the drop-down menu.

If you have an equation that has already been produced using Microsoft Word 2007 or 2010 and you have access to the full version of MathType 6.5 or later, you can convert this equation to MathType by clicking on MathType Insert Equation. Copy the equation from Microsoft Word and paste it into the MathType box. Verify that your equation is correct, click File, and then click Update. Your equation has now been inserted into your Word file as a MathType Equation.

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Tables

Use Word's Insert Table function when you create tables. Using spaces or tabs in your table will create problems when the table is typeset and may result in errors.

Abstract and Keywords

All manuscripts must include an English abstract containing a maximum of 250 words typed on a separate page. (It should contain headings such as Background, Aims and Objectives, Materials and Methods, Results, Conclusion etc.) After the abstract, please supply up to five keywords or brief phrases.

References:

Vancouver is a numbered referencing style used in JNBS.

Citations to someone else's work in the text, indicated by the use of a number. A sequentially numbered reference list at the end of the document providing full details of the corresponding in-text reference.

General rules of in-text citation:

- A number is allocated to a source in the order in which it is cited in the text. If the source is referred to again, the same number is used.
- Use Arabic numerals (1,2,3,4,5,6,7,8,9).
- Either square [ ] or curved brackets ( ) can be used as long as it is consistent.
- In the publication, source numbers are indicated in parentheses or as superscripts at the end of the sentence - name - in which the source is used.
- If the sources with consecutive numbers are to be displayed at the same time, the first and last numbers are separated with "-"

According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1]
S variant is associated with the lower transcriptional activity of the promoter when compared to the L variant.[4,7-9,11]

The Reference Section:

• Journal Article:

Russell FD, Coppell AL, Davenport AP. In vitro enzymatic processing of radiolabelled big ET-1 in human kidney as a food ingredient. Biochem Pharmacol 1998;55(5):697-701. doi: 10.1016/s0006-2952(97)00515-7.

Gonen, M. Planning for subgroup analysis: a case study of treatmentmarker interaction in metastatic colorectal cancer. Controlled Clinical Trials 2003;24 : 355-363. doi: 10.1016/s0197-2456(03)00006-0.

• Authored Book:

Lodish H, Baltimore D, Berk A, Zipursky SL, Matsudaira P, Darnell J. Molecular cell biology. 3rd ed. New York: Scientific American; 1995.

Millares M, editor. Applied drug information: strategies for information management. Vancouver: Applied Therapeutics, Inc.; 1998.

Figures

Graphics files are welcome if supplied as Tiff, EPS, or PowerPoint files. Multipanel figures (i.e., figures with parts labeled a, b, c, d, etc.) should be assembled into one file.

The minimum line weight for line art is 0.5 point for optimal printing

PUBLICATION ETHICS AND PUBLICATION MALPRACTICE STATEMENT (ETHICAL GUIDELINES FOR PUBLICATION)

The publication of an article in the peer-reviewed journal JNBS is an essential building block in the development of a coherent and respected network of knowledge. It is a direct reflection of the quality of the work of the authors and the institutions that support them. Peer-reviewed articles support and embody the scientific method. It is therefore important to agree upon standards of expected ethical behaviour for all parties involved in the act of publishing: the author, the journal editor, the peer reviewer, the publisher and the society of society-owned or sponsored journals.

Uskudar University, as publisher of the journal, takes its duties of guardianship over all stages of publishing extremely seriously and we recognise our ethical and other responsibilities.

We are committed to ensuring that advertising, reprint or other commercial revenue has no impact or influence on editorial decisions. In addition, Editorial Board will assist in communications with other journals and/or publishers where this is useful to editors. Finally, we are working closely with other publishers and industry associations to set standards for best practices on ethical matters, errors and retractions - and are prepared to provide specialized legal review and counsel if necessary.

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(These guidelines are based on existing COPE's Best Practice Guidelines for Journal Editors.)

Reporting standards

Authors of reports of original research should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable. Review and professional publication articles should also be accurate and objective, and editorial 'opinion' works should be clearly identified as such.

Authors are required to state in writing that they have complied with the Declaration of Helsinki Research Ethics in the treatment of their sample, human or animal, or to describe the details of treatment.

Data access and retention

Authors may be asked to provide the raw data in connection with a paper for editorial review, and should be prepared to provide public access to such data (consistent with the ALPSP-STM Statement on Data and Databases), if practicable, and should in any event be prepared to retain such data for a reasonable time after publication.

Originality and plagiarism

The authors should ensure that they have written entirely original works, and if the authors have used the work and/or words of others, that this has been appropriately cited or quoted.

Plagiarism takes many forms, from 'passing off' another's paper as the author's own paper, to copying or paraphrasing substantial parts of another's paper (without attribution), to claiming results from research conducted by others. Plagiarism in all its forms constitutes unethical publishing behavior and is unacceptable.

Multiple, redundant or concurrent publication

An author should not in general publish manuscripts describing essentially the same research in more than one journal or primary publication. Submitting the same manuscript to more than one journal concurrently constitutes unethical publishing behavior and is unacceptable.

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Acknowledgement of sources

Proper acknowledgment of the work of others must always be given. Authors should cite publications that have been influential in determining the nature of the reported work. Information obtained privately, as in conversation, correspondence, or discussion with third parties, must not be used or reported without explicit, written permission from the source. Information obtained in the course of confidential services, such as refereeing manuscripts or grant applications, must not be used without the explicit written permission of the author of the work involved in these services.

Authorship of the paper

Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. Where there are others who have participated in certain substantive aspects of the research project, they should be acknowledged or listed as contributors.

The corresponding author should ensure that all appropriate coauthors and no inappropriate coauthors are included on the paper, and that all co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.

Hazards and human or animal subjects

If the work involves chemicals, procedures or equipment that have any unusual hazards inherent in their use, the author must clearly identify these in the manuscript. If the work involves the use of animal or human subjects, the author should ensure that the manuscript contains a statement that all procedures were performed in compliance with relevant laws and institutional guidelines and that the appropriate institutional committee(s) has approved them. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

Disclosure and conflicts of interest

All authors should disclose in their manuscript any financial or other substantive conflict of interest that might be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

Examples of potential conflicts of interest which should be disclosed include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Potential conflicts of interest should be disclosed at the earliest stage possible.

Fundamental errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and cooperate with the editor to retract or correct the paper. If the editor or the publisher learns from a third party that a published work contains a significant error, it is the obligation of the author to promptly retract or correct the paper or provide evidence to the editor of the correctness of the original paper.

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Publication decisions

The editor of a peer-reviewed journal is responsible for deciding which of the articles submitted to the journal should be published, often working in conjunction with the relevant society (for societyowned or sponsored journals). The validation of the work in question and its importance to researchers and readers must always drive such decisions. The editor may be guided by the policies of the journal's editorial board and constrained by such legal requirements as shall then be in force regarding libel, copyright infringement and plagiarism. The editor may confer with other editors or reviewers (or society officers) in making this decision.

Fair play

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Confidentiality

The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Disclosure and conflicts of interest

Unpublished materials disclosed in a submitted manuscript must not be used in an editor's own research without the express written consent of the author.

Privileged information or ideas obtained through peer review must be kept confidential and not used for personal advantage.

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Editors should require all contributors to disclose relevant competing interests and publish corrections if competing interests are revealed after publication. If needed, other appropriate action should be taken, such as the publication of a retraction or expression of concern.

It should be ensured that the peer-review process for sponsored supplements is the same as that used for the main journal. Items in sponsored supplements should be accepted solely on the basis of academic merit and interest to readers and not be influenced by commercial considerations.

Non-peer reviewed sections of their journal should be clearly identified.

Involvement and cooperation in investigations

An editor should take reasonably responsive measures when ethical complaints have been presented concerning a submitted manuscript or published paper, in conjunction with the publisher (or society). Such measures will generally include contacting the author of the manuscript or paper and giving due consideration of the respective complaint or claims made, but may also include further communications to the relevant institutions and research bodies, and if the complaint is upheld, the publication of a correction, retraction, expression of concern, or other note, as may be relevant. Every reported act of unethical publishing behavior must be looked into, even if it is discovered years after publication.

Duties of reviewers

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Contribution to editorial decisions

Peer review assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper. Peer review is an essential component of formal scholarly communication, and lies at the heart of the scientific method. JNBS shares the view of many that all scholars who wish to contribute to publications have an obligation to do a fair share of reviewing.

Promptness

Any selected referee who feels unqualified to review the research reported in a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

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Any manuscripts received for review must be treated as confidential documents. They must not be shown to or discussed with others except as authorized by the editor.

Standards of objectivity

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

Acknowledgement of sources

Reviewers should identify relevant published work that has not been cited by the authors. Any statement that an observation, derivation, or argument had been previously reported should be accompanied by the relevant citation. A reviewer should also call to the editor's attention any substantial similarity or overlap between the manuscript under consideration and any other published paper of which they have personal knowledge.

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Contents

Understanding Nightmare Disorder and A brief overview of required Psychological Interventions

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Dear Editor,

Nightmare disorder is a mental health condition characterized by repeated occurrences of extended, well-remembered, dysphoric dreams, often involving themes of threat, that result in awakening from sleep and significant distress and impairment[1] . A typical sleep occurs in two phases namely rapid eye movement stage (REM) and nonrapid eye movement stage (NREM), nightmares usually occur during REM stage of sleep cycle when brain activity nears the level of that when an individual is awake causing the experience to feel real. Research points to factors such as traumatic experiences, childhood adversities, suppression of thoughts, maladaptive beliefs, other medical conditions such as sleep apnea[2]. Though research points to multiple reasons for occurrence of nightmares, Spoormaker's cognitive model explains persistence of nightmares due to formation of nightmare scripts, the repeated elements in nightmares form structures patterns in dreamers experience. The scripts contain specific expected responses that get activated to dream elements, the cycle continues even after the original stressor fades.[3]

Individuals suffering from nightmare disorder experience immediate physical symptoms such as sweating, shortness of breath and intense emotions such as fear, anxiety, and distress. Nightmare disorder is also associated with wide range of complications such as apprehension to sleep, difficulty in onset of sleep and maintaining with consequences such as tiredness, concentration difficulties, drowsiness during daytime. In severe cases it can also lead to increased mental distress, anxiety, depression[4] maladaptive personality functioning[5]. A significant evidence suggests that nightmares are associated with suicidality and self – harm.[6]

Due to the growing recognition of the significant link between Nightmare Disorder and subsequent psychiatric issues, nightmares are now seen as a crucial focal point for treatment rather than merely a secondary symptom of other mental health problems such as PTSD, bipolar disorder, major depressive disorder. Medications such as prazosin, clonidine that work by promoting relaxation of nervous system and other medications such as like trazodone and atypical antipsychotics are also administered in treating nightmare disorder upon diagnosis and prescription by a qualified psychiatrist.[7]

Though prescribed drugs can help symptom management in treatment of nightmare disorder, psychological interventions remain essential in addressing root causes, effective management, and significant improvement in life quality of individuals suffering from nightmare disorder. Psychological treatments for nightmare disorder can have three approaches, treatments that emphasize on the subjective meaning of nightmares, the pathologic repetition of the nightmares and maladaptive beliefs about nightmares.[8] Interpreting and treating subjective meaning of nightmare content is prioritised In psychodynamic approach, through psychoanalysis, dream analysis, interpersonal therapy due to the belief that nightmares indicate a conflict that is unresolved.

According to Krakow et al.[9] the nightmare script phenomenon could also be understood as nightmares as learned behaviours that are result of traumatic and stressful events. Such pathological repetition of nightmares is targeted in Lucid dreaming therapy and by cognitive behavioural treatments like imagery rehearsal therapy (IRT), Exposure therapy, Systematic desensitization (SD) therapy, eye movement desensitization and reprocessing (EMDR) and Exposure, Relaxation, and Rescripting Therapy (ERRT). In Imagery rehearsal therapy (IRT), individuals change their nightmares into more positive dreams using mental imagery, the technique involves rehearsing alternative less distressing ending to nightmares, disrupting nightmare scripts by targeting the learned responses and behaviours.

Systematic desensitization is a therapeutic technique that gradually exposes individuals to their fears while they practice relaxation techniques and Exposure therapy, individuals confront their nightmares in controlled and safe setting until they no longer distress them, in the process anxiety and arousal symptoms are overridden by more adaptive behavioural, cognitive, and emotional processes. Exposure, Relaxation, and Rescripting Therapy (ERRT) combines elements of Imagery Rehearsal Therapy (IRT),

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Quick Response Code:

exposure therapy and relaxation techniques.

Lucid dreaming is a notably different approach where individuals become aware that they are dreaming by techniques such as reality testing and identifying dream signs. Once the individual achieves lucidity, they can intentionally change the direction of the dream to make it more positive or to explore different scenarios and exert some level of control over the dream narrative and environment. While some studies suggest that lucid dreaming may have therapeutic potential for addressing nightmares, more research is needed to fully understand its effectiveness and how it can be integrated into treatment approaches for nightmare disorders.

Psychologists play a crucial role in the management of nightmare disorders by carefully diagnosing and administering therapies according to expertise and individual needs. These therapies aim to reduce the frequency, severity, and distress associated with nightmares. However, some limitations can impact their ability to fulfil these roles effectively such as lack of awareness among people, shame, and inhibition to seek help, false beliefs regarding treatment, Research that explores more about such disorders, need for resources for Specialized and rigorous training for psychologists, Lack of Resources for psychologists in eliminating above barriers [10]. The impact of these limitations can be profound, potentially leading to persistent symptoms, increased distress, and a lower quality of life for individuals suffering from nightmare disorders. Addressing these barriers is essential for improving outcomes for patients with nightmare disorders. In conclusion, psychological treatment efficacy for nightmares is optimized when interventions empower individuals by directly addressing either the content of the nightmares or the emotional reactions associated with them, fostering a sense of control or mastery

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

There is no need for Ethics Committee approval.

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There is no conflict of interest to declare.

Author contribution area and rate (%)

Maddali Anvitha Lakshmi (30%): Contributed to writing a manuscript draft and literature search.

Neelam Sai Sahithi (30%): Contributed to writing a manuscript draft and literature search.

Pallerla Srikanth (20%): Contributed to the review and content of the manuscript

Ayesha Parveen Haroon (20%): Contributed to the review and content of the manuscript

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Impact of Adverse Childhood Experiences on the Treatment Journey of Women Facing Infertility

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Dear Editor,

Infertility in women is defined as the inability to conceive after a year of regular, unprotected sexual activity [1] .While technological advancements offer various medical interventions for treatment, infertility can stem from issues with ovulation, the uterus, fallopian tubes, or abdominal factors. Sometimes, the cause remains elusive despite thorough testing. However, infertility isn't solely a biological issue; adverse childhood experiences (ACE) also play a role. ACE encompass stressful or traumatic events during the first 18 years of life, such as domestic violence, substance abuse, parental mental illness, divorce, or incarceration, which can impact fertility beyond mere physiological factors.

ACE serve as a significant risk factor for the emergence of various psychological challenges and have been linked to the development of conditions like personality disorders, depression, anxiety, substance abuse, post-traumatic stress disorder, suicidal thoughts or actions, and psychotic episodes [2]. They can lead to social, emotional, and cognitive difficulties, as well as the adoption of health-compromising behaviors such as smoking, substance abuse, eating disorders, and unsafe sexual practices—often used as coping mechanisms. Notably, ACE don't just affect mental health but also impact physical well-being in adulthood. Research suggests that trauma and chronic stress, typical of ACE, can influence reproductive health and fertility. Some studies have highlighted potential gynecological issues associated with specific adverse childhood experiences; for instance, both physical and emotional abuse may elevate the risk of pelvic floor disorders and chronic pelvic pain due to stress.

A Longitudinal study conducted research involving 1652 women from the National Survey of Youth's 1997 cohort, revealing that those who had experienced stressful events during childhood were more likely to face infertility [3]. Similarly, an integrative review which examined 20 articles, suggested a potential link between pregnancy loss and infertility in women with a history of ACE. This review also highlighted related concepts such as racial and ethnic diversity, social determinants of health, modifiable risk factors, and stress assessments [4]. A cross-sectional study indicating that as the number of ACE increased, so did the likelihood of fertility difficulties. Those with four or more ACE had a 2.75 relative risk of infertility compared to those with no ACE [5]. Furthermore, mental health issues like depression, anxiety, and PTSD can intensify the emotional strain. Thus, comprehending the impact of ACE on infertility treatment among women is vital, given their potential effects on both mental and reproductive health outcomes.

The process of IVF treatment is intricate and comes with emotional and psychological challenges. Infertility can disrupt one's sense of self, leading to feelings of isolation, stigma, and judgment, ultimately resulting in a sense of inadequacy or shame. Moreover, IVF treatment entails significant financial investment and uncertainty, which can amplify financial stress, strain relationships, and worsen mental health conditions. A woman's past traumas and experiences significantly influence her IVF journey. Those with ACE typically contend with heightened levels of stress, anxiety, and depression, impacting their emotional well-being and coping mechanisms. Research indicates that this adversely affects treatment outcomes [6]. ACE often manifest as issues stemming from trauma, such as difficulties with trust or forming attachments, fear, and avoidance, further complicating decision-making processes.

Women who have experienced ACE may struggle to disclose sensitive information or articulate their needs during psychological assessments due to feelings of being overwhelmed or judged. Trusting medical professionals, adhering to treatment protocols, or feeling secure in medical environments may pose challenges. Hormonal fluctuations can intensify symptoms of depression, anxiety, and mood swings, complicating stress management during IVF medication and stimulation. Anderheim et al., noted that infertile women often engage in rumination during treatment, excessively dwelling on negative emotional responses, which can lead to heightened psychological strain [7]. They may find certain aspects of the IVF process, such as egg retrieval and embryo transfer, particularly triggering, especially if they have a history of

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physical or emotional trauma.

Hence, it's essential to evaluate ACE during the IVF process to understand patients' psychological backgrounds. This assessment can unveil potential trauma triggers, coping mechanisms, and emotional susceptibilities, enabling healthcare professionals to devise personalized treatment plans. SCREENIVF serves as an effective screening tool to distinguish between women entering IVF treatment with lower and higher risks of emotional issues during and after a treatment cycle. It serves as the initial step in triaging, determining the need for additional psychosocial support for women embarking on IVF. The subsequent step involves a more comprehensive diagnostic inquiry, which could identify those requiring further psychosocial interventions.

Early intervention can enhance well-being and treatment outcomes. The findings from the descriptive study indicate that psychological challenges among infertile women undergoing IVF treatment methods are particularly severe, creating a detrimental cycle [8]. On one hand, these psychological issues diminish patients' physical resilience and their response to infertility medical therapies, the persistence of infertility and potential setbacks in treatment exacerbate patients' psychological distress. This underscores the necessity for providing psychiatric care alongside infertility treatment. Successful navigation through IVF necessitates collaboration among various stakeholders. When patients disclose ACE, gynecologists can collaborate with psychologists. Psychologists can assess a woman's ACE history and identify any underlying mental health issues that might be exacerbated by IVF treatment.

Recognizing the importance of incorporating ACE assessment and intervention into infertility treatment is essential for enhancing patient outcomes. Tailored interventions and support can alleviate the emotional strain associated with infertility treatment. Future clinical approaches and research endeavors should prioritize the integration of ACE assessment and intervention into infertility treatment, emphasizing the necessity for holistic care addressing both physical and emotional dimensions of infertility. Exploring innovative strategies, fostering collaboration among stakeholders, and promoting trauma-informed care within fertility clinics are critical steps to ensure optimal care for women undergoing infertility treatment.

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Rare Presentation of Schmahmann's Syndrome in Dandy-Walkers Malformation - A Case Report

Abstract

The aim of this case report is to highlight the varied presentation of neurological disorders and the need for detailed evalution of the acute manisfestations of psychiatric symptoms. We report the case of a 17 year old boy presenting with complaints of acute onset of behavioural symptoms. We have briefly reviewed and discussed the clinical , diagnostic aspects of schmahmanns syndrome and therapeutic aspects of behavioural symptoms in dandy walkers malformation.

Keywords: Dandy Walker Malformation, Schmahmann's Syndrome, Disinhibition, Repetition, CCAS scale.

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Introduction:

Dandy Walker Malformation is a posterior fossa anomaly of the cranium, characterised by agenesis or hypoplasia of vermis; cystic enlargement of fourth ventricle with communication to a large cystic dilated posterior fossa; upward displacement of tentorium and torcula; and an enlarged posterior fossa. [1] First described by Dandy and Blackfan (1914), supplemented by Taggart and Walker (1942), it was introduced as its current description by Bender (1954).[2] Dandy Walker Complex (DWC) is a group of neurodevelopmental anomalies believed to occur between week 7-10 of gestation.[3] and comprise of Dandy-Walker Malformation(DWM), Dandy-Walker variant(DWV), mega-cisterna magna and posterior fossa arachnoid cyst.[4]

Clinical presentation of patients depends upon multiple factors, including severity of hydrocephalus, intracranial hypertension and underlying comorbidities. Symptoms including but not limited to developmental delays, macrocephaly, cognitive impairment, ataxia, hypotonia, occulomotor abnormalities, epilepsy and equilibrium disturbances may be seen in this condition. Association of psychosis and DMV, though rare, was reported by Sasaki et al. in pediatric patients.[5] Correlation between new onset of psychosis and cerebellar abnormalities in an adolescent patient have been hypothesised by Ryan et al. [6] Although the relationship between the two is still unclear due to lack of abundant data.

Another rare form of presentation of DWM is Schmahmann's syndrome which we will discuss in this case report.

Case Report:

Mr. ABC, 17 year old male, presented to the Psychiatry out-patient department of rural tertiary hospital with complaints of acute onset of repetitive and disinhibitory behaviour. He also had episodic outbursts of anger and irritability. Clinical history elicited from his family members included repetitive movements of tying shoe-laces, latching and unlatching the door. They also reported that he was undressing publicly, in front of the parents and other family members at times, which was not his usual behaviour. On further enquiry, there was history of delayed developmental milestones, memory disturbances and poor scholastic performance.

The patient was not a known case of any psychiatric disorders or medical diseases. No past history of similar episodes was noted. Family history yielded insignificant in this case.

On examimation mental status examination was within normal range and no focal significant neurological deficits were elicited. And it occurred in clear sensorium. Patient was conscious, co-operative and oriented in time, place and person.

On investigation, there were no signs of raised intracranial pressure now or evidences of macrocephaly in infancy. Due to its acute nature and episodic presentation, patient was evaluated further and neuroimaging studies were done, during which the following positive findings were seen on the Magnetic Resonance Imaging (MRI) scan of the brain - Hypoplasia of inferior cerebellar vermis was noted with prominent IVth ventricle. It was thus confirmed as Dandy Walker Malformation.[1] Subsequently, based on clinical history, laboratory investigations and neuroimaging studies, a diagnosis of Cerebellar Cognitive Affective Syndrome in a case of Dandy Walker Malformation was made.

Administration of the Cerebellar Cognitive Affective Scale (CCAS) by Hoche [7] confirmed the diagnosis of Schahmann's syndrome.

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He was treated with Injection Haloperidol and Promethazine hydrochloride I.M. stat. Then started on Tablet Risperidone, Tablet Lorazepam and 4 hourly Injection Normal Saline with Multivitamin concentrate infusion(MVI). Regular follow up with visits in case of fresh complaints, similar such episodes or any emergencies was advised.

Discussion:

In the current case scenario, acute onset repetitive and disinhibitory behaviours were the core symptoms of the patient on presentation. The most notable pathway out of the many that govern repetitive behaviours is the cortico-basal ganglia-thalamic pathway, which is also involved in the motor activities.[8]

The patient also was reported to have delayed developmental milestones and had poor academic performance along with episodes of anger outbursts and There was no past history of similar complaints. No history of fever, trauma was found. The differential diagnoses of Autism Spectrum Disorder (ASD), Obsessive Compulsive Disorder (OCD), Cerebellar Cognitive Affective Syndrome (CCAS) were made.

The patient had no prior complaints of deranged behaviour patterns, difficulty understanding social cues, impaired communication and lack of empathy which helped rule out ASD. The Y-BOCS questionnaire, along with clinical history helped rule out OCD as the patient did not have tics, obsessive thoughts and compulsions in the past.

On administration of the CCAS/ Schmahmann's scale, postive findings were noted for the same and diagnosis thus confirmed. Schmahmann's syndrome is characterized by four clusters of symptoms including: (a) impairment of executive functions such as planning, set-shifting, verbal fluency, abstract reasoning and working memory, (b) impaired visuo-spatial cognition, (c) personality changes with blunting of affect or abnormal behaviour, and (d) language deficits including agrammatism, wordfinding disturbances, disruption of language dynamics and dysprosodia.[9]

Neuroimaging done due to acute presentation of disinhibitory symptoms, involved an MRI scan of the brain which showed the findings of - Hypoplasia of inferior cerebellar vermis was noted with prominent IVth ventricle; with normal brain stem and cerebellum, normal cisterns, sulci and sellar/ parasellar structures. No evidence of hemorrhage or midline shift or mass lesions was seen. Intracranial vessels and dural venous sinuses displayed normal flow voids. Midbrain, pons, medulla, orbits, paranasal sinsues and calvarum appeared normal suggestive of Dandy-Walker Malformation.

Surprisingly, the only symptoms the patient had were of cerebellar and cognitive impairment. Classical findings of raised ICT were absent, and no reports of macrocephaly during infancy was made either.

Management included treating the patient with Injection Haloperidol 2.5 mg and Injection Promethazine hydrochloride 50 mg I.M. stat. He was then started on Tablet Risperidone 1 mg twice daily, Tablet Lorazepam 2 mg once daily. Patient was stabilised and monitored. There were improvement in the behavioural symptoms. The dose of resperidone was reduced to once daily and Tab Lorezepam was stopped on subsequent follow up after 20 days.

Conclusion:

Dandy Walker Malformation can also present with symptoms of Cerebellar cognitive affective syndrome. This case report highlights the importance of complete physical and neurological including imaging studies in a child or adolescent presenting with psychotic or behavioural symptoms. Awareness of psychiatric manifestation of congenital malformations will impact the diagnosis, treatment and prognosis of the individual.

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Kumari Padma (40%): Contributed with comments on manuscript organization and write up.

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Original Article

An Extensive Therapeutical Drug Monitoring Repository for Localized Population Pharmacokinetics Research

Abstract

Aim: The study's long-term goals, such as determining supratherapeutic ranges according to age distributions specific to the country, adjusting dosages for additional drugs used by patients in different disease groups, and providing the opportunity for etiological studies in the light of diagnosis and drug metabolism perspective, are of great importance in defining the study. **Method:** Population pharmacokinetics is a method expressed to evaluate processes such as absorption, distribution, metabolism, and elimination of a drug from an individual's blood-plasma concentration. In drug pharmacokinetic experiments, generating data without considering any pharmacokinetic differences among patients prevents the measurement or observation of variability among individuals in the population as a simple approach. The dose-concentration relationship is crucial for individualized dose adjustment. Additionally, the impact of other drugs used by the individual on metabolite levels and the metabolic interactions between drugs play a critical role in the development of personalized treatments. Population approaches provide a foundation that benefits the observation of these effects. The variability in drug metabolism among individuals forms one of the fundamental building blocks of personalized treatment approaches, specifically through Therapeutic Drug Monitoring (TDM), which plays an important role in determining the therapeutic range of drugs. **Materials**: In this study, drug metabolism findings of patients served at NP Istanbul Brain Hospital between 2010 and 2022 were examined within the repository created along with other patient-specific parameters. **Results and Conclusion**: The analysis results have been followed up longitudinally, partially demographically, and retrospectively. Thanks to the repository of NP Istanbul Brain Hospital, population pharmacokinetic analyses aimed in this study are being conducted for the first time globally and nationally in terms of scope. The repository has been studied with TDM for individualized treatment methods, and within this project, it is anticipated to perform phenotyping with the population pharmacokinetic approach.

Keywords: Pharmacokinetics, Population Pharmacokinetics, Psychiatric Drugs, Statistical Analysis, Therapeutic Drug Monitoring.

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Introduction

Therapeutic drug monitoring (TDM) is a method that allows clinicians to maintain patients' drug plasma concentrations in the target range through individual dose adjustment[2]. These methods accelerate the recovery of many patients and reduce medical costs[10]. TDM can be particularly beneficial for children and adolescents in the psychiatry and neurology patient group, pregnant women, the elderly, those with substance use disorders, forensic psychiatry patients, and patients with known or suspected abnormal pharmacokinetic curves[10].

Pharmacokinetics is a method expressed for the evaluation of processes such as absorption, distribution, metabolism and excretion (ADME) of compounds (such as drugs, medicinal biological substances and new chemical entities (NCE)) taken from the blood-plasma concentration of the individual[5, 9]. It is evaluated depending on the time course of concentration. Pharmacokinetics is concerned with what the compound does to the body, on the contrary, while pharmacodynamics (PD) is concerned with explaining the processes that the compound is exposed to by the body after ingestion and excretion[1].

In order to explain the pharmacological activity profile of the compounds, the pharmacokinetic analysis is crucial. While a more common pharmacokinetic profile can be obtained especially in adults, it is rarer to have a certain profile in children, adolescents or the elderly[3]. Considering the fact that there is a certain gap in the literature on the pediatric population, in vivo pharmacokinetic models support appropriate dose and administration functions in order to identify the main metabolites and to have more information about human metabolism[1]. Pharmacokinetics enables the predictions about the absorption, distribution, metabolism and excretion of the compound *in silico*.

Population pharmacokinetics is used in drug studies to make adjustments by including all

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the features in the body, from organ functions to genetic changes, in order to determine the dose adjustment, dose scaling and correct dose rate for the individual in the population[16]. It is also an approach to make sense of the relationship between pharmacokinetics and pharmacodynamics. Because, as in drug development, the PK-PD relationship has a very important place in population pharmacokinetic studies[17]. The distribution of drug use in the population includes the estimation approaches to be made over this distribution.

Based on the pharmacokinetic method, it evaluates the differences in the processes of absorption, distribution, metabolism and excretion of the drug, which correspond to mathematical values between individuals[4]. It is expected that clinicians will adjust the dose by considering these differences. Pharmacokinetic studies are usually conducted by volunteers or selected by clinicians. However, this study design does not provide an accurate sample of population pharmacokinetic studies. While the most common limitation in population pharmacokinetic studies is the interindividual variability, the study conducted by volunteers or selected individuals prevents the limitation of this diversity[4]. Preventing this restriction is seen as a problem since an accurate population model will not be established.

In addition to demographic variables, measurable pathophysiological variables cause significant differences in therapeutic ranges, which may require re-adjustment of the dose to be administered to the individual[15]. Evaluation of all patients on the same parameters, regardless of environmental or pathophysiological variables in the patient, may lead to deviation from accurate estimates for pharmacokinetic characterization in the relevant population[9].

Population pharmacokinetics are widely used in drug development for precise dose adjustment through therapeutic drug monitoring[8, 9]. While the dose-concentration relationship is an important factor for drug dosing, interactions with other drugs used by the individual have a critical importance in the development of personalized treatments. Population approaches provide a useful basis for observing these effects. The drug metabolizing status that differs between individuals and TDM practice, which plays an important role in determining the therapeutic range of drugs, constitutes one of the basic building blocks of personalized treatment approach.

MATERIALS AND METHODS

The repository construction included the patient data, who received treatment and drug/metabolite blood plasma level tests at NPİSTANBUL Brain Hospital between 2010-2022. The local ethical approval was obtained from Üsküdar University Non-interventional Research Ethics Board (23.2.2023, 61351432/Feb 2023-20).

All patient information was stored in the local database, BİLMED, and the tests were performed in Medical Biochemistry Laboratory, Üsküdar University. The patient identity was hidden in the repository and only the ID number assigned to every patient in the system was included. The raw data included 26,324 patients (8963 inpatients, 20936 outpatients) and 174,387 total entries. Only a portion of the data included repeated entries per patient. Among these, 60.3% of entries belong to inpatients (n=105,194) and 39.7% to outpatients (n=69,193). The tests in the raw data included vitamin D (25-OH(D2+D3)) tests and genotypic profiling, which were omitted in the scope of this study.

The repository organization and descriptive statistical analysis was performed on Python-based protocols. The raw patient data was extracted from the system over 16 different parameters as follows. The descriptive analysis focused only on the Patient ID, Sex, Age, Admission and Test.

- **Patient ID [numerical] :** Unique ID number assigned by the system for every patient.
- **Sex [categorical] :** Sex of the patient. (Female (F), Male (M))
- **Age [numerical] :** Age of patient at the day of test
- **Date [date] :** Date of test
- **Admission [categorical]:** Admission at the day of test (Inpatient, Outpatient)
- **Height [numerical]:** Height of patient further organized in two options as in “m” and in “cm”.
- **Weight [numerical]:** Weight of patient at the day of test in “kg”.
- **Test [categorical] :** The name of the test (usually in the form of “drug” or “drug + metabolite”)
- **Doctor [categorical] :** The name surname of the doctor who entered the patient information.
- **Sample # [numerical] :** The unique ID for each test.
- **Test Result [numerical]:** The test results in the system in the form of “drug + metabolite” in the raw data is further organized into seperate entries as “drug” and “metabolite”.
- **DMIN - DMAX [numerical]:** The reference test result intervals in “ng/ml”.
- **Dose [numerical] :** The drug dose prescribed at the day of test, usually in mg/day.
- **Interaction [categorical] :** Other drugs that are prescribed simultaneously to the patient at the day of test
- **Diagnosis [categorical] :** The diagnosis of the patient at the day of test

RESULTS

The NPİstanbul Brain Hospital TDM database (2010-2022) contains drug/metabolite plasma level tests for 74 drugs and for vitamin D. The drugs organized in the repository grouped by their respective classes is given in Table 1. Genotypic profiling of Cyp1a2 (n=28), Cyp2d6 (n=30) and Cyp3a4 (n=27) enzymes were performed for a smaller portion of the patients in the database.

The drugs with the respective number of patients tested is given in Table 2. The drugs that were tested with the highest number of patients are risperidone (n=5397), olanzapine (n=4967) and valproic acid (n=4046). Further test profiles were obtained by the distribution over age, sex and admission. Among the inpatients, olanzapine (n=3749), risperidone (n=3630), quetiapine(n=2542), valproic acid (n=2039) and aripiprazole (n=1906) was the most commonly tested drugs. Aripiprazole was also the most commonly tested drug for outpatients (n=2598), followed by fluox-

Table 1: Drugs in NPİstanbul Brain Hospital TDM Database. The classes/types of drugs together with metabolizing enzymes and inhibited/induced enzymes are given. AKR: Aldo-keto reductase; CR: Carbonyl reductase; CYP: Human cytochrome P450 (CYP) enzymes; FMO: flavin monooxygenase; UGT: UDP-glucuronosyltransferase. (Hiemke ve ark., 2017)

Drugs	Class / Type	Metabolizing Enzymes	Inhibited enzymes	Inducer enzymes
Alprazolam	Anxiolytic	CYP3A4/5		
Amisulpride	Antipsychotic	More than 90% is excreted unchanged via the kidney		
Amitriptyline	Antidepressant	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A3, UGT1A4, UGT2B10		
Aripiprazole	Antipsychotic	CYP2D6, CYP3A4		
Atomoxetine	Drug for ADHD	CYP2C19, CYP2D6		
Biperiden	Antiparkinson	Unknown		
Bupropion	Antidepressant	CYP2C19, CYP2B6, CR	CYP2D6	
Carbamazepine	Anticonvulsant	CYP1A2, CYP2C8, CYP3A4/5, UGT2B7, epoxide hydrolase		CYP1A2, CYP2B6, CYP2C9, CYP3A4, UGT
Citalopram	Antidepressant	CYP2C19, CYP2D6, CYP3A4		
Chlorpromazine	Antipsychotic	CYP1A2, CYP2D6		
Clomipramine	Antidepressant	CYP1A2, CYP2C19, CYP2D6, CYP3A4, UGT2B10		
Clonazepam	Anxiolytic	CYP3A4		
Clozapine	Antipsychotic	CYP1A2, CYP2C19, CYP3A4		
Diazepam	Anxiolytic	CYP2B6, CYP2C19, CYP3A4, UGT2B7		
Disulfiram	Substance-related disorders	CYP1A2, CYP2A6, CYP2B6, CYP2E1, CYP3A4	CYP2E1	
Donepezil	Antidementia	CYP2D6, CYP3A4		
Duloxetine	Antidepressant	CYP1A2, CYP2D6	CYP2D6	
Escitalopram	Antidepressant	CYP2C19, CYP2D6, CYP3A4		
Fluoxetine	Antidepressant	CYP2B6, CYP2C9, CYP2C19, CYP2D6	CYP2D6, CYP2C19, CYP3A4	
Flupenthixol	Antipsychotic	CYP2D6		
Fluvoxamine	Antidepressant	CYP2D6, CYP1A2	CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4	
Gabapentin	Anticonvulsant	Not metabolized, renal excretion		
Haloperidol	Antipsychotic	CYP2D6, CYP3A4, AKR, UGT		
Lamotrigine	Anticonvulsant	UGT1A4, UGT3B7		UGT
Levetiracetam	Anticonvulsant	Not metabolized		
Lithium	Mood stabilizer	Renal clearance		

Lorazepam	Anxiolytic	UGT2B15		
Memantine	Antidementia	Scarcely metabolized		
Methylphenidate	ADHD medication	Carboxylesterase 1		
Mirtazapine	Antidepressant	CYP3A4, CYP1A2, CYP2D6		
Modafinil	ADHD medication	Amide hydrolase, CYP3A4		CYP1A2, CYP2B6, CYP3A4
Naltrexone	Substance-related disorders	AKR1C4		
Olanzapine	Antipsychotic	UGT1A4, UGT2B10, FMO, CYP1A2, CYP2D6		
Oxcarbazepine	Anticonvulsant	AKR, UGT2B15		
Paroxetine	Antidepressant	CYP2D6, CYP3A4	CYP2D6	
Pimozide	Antipsychotic	CYP1A2, CYP2D6, CYP3A4		
Piracetam				
Pregabaline	Anxiolytic	Not metabolized, renal excretion		
Quetiapine	Antipsychotic	CYP3A4, CYP2D6		
Reboxetine	Antidepressant	CYP3A4		
Risperidone	Antipsychotic	CYP2D6, CYP3A4		
Sertraline	Antidepressant	CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, UGT1A1		
Sulpiride	Antipsychotic	Not metabolized, renal excretion		
Topiramate	Anticonvulsant	UGT		
Trazadone	Antidepressant	CYP3A4, CYP2D6		
Trifluoperazine		UGT1A4		
Valproic Acid	Anticonvulsant	UGT1A3, UGT1A6, UGT2B7, CYP2A6, CYP2B6, CYP2C9, CYP219		
Venlafaxine	Antidepressant	CYP2C19, CYP2D6, CYP2C9, CYP3A4		
Vit D2 + D3	Vitamin D	CYP27A1, CYP2R1, CYP27B1, CYP24A1		
Vortioxetine	Antidepressant	CYP2D6, CYP3A4, CYP2A6, CYP2C		
Ziprasidone	Antipsychotic	CYP3A4		
Zuclopenthixol	Antipsychotic	CYP2D6		

Table 2. Drug test data available in the database with relevant number of tested patients. The table includes the total number of drugs in the database and the number of patients.

Drug	Number of Patients	Drug	Number of Patients
Risperidone	5397	Alprazolam	433
Olanzapine	4967	Levetiracetam	414
Valproic Acid	4046	Diazepam	355
Aripiprazole	3922	Topiramate	347
Sertraline	3815	Pimozide	301
Quetiapine	3267	Vortioxetine	271
Fluoxetine	2576	Naltrexone	269
Paroxetine	2324	Donepezil	208
Carbamazepine	1832	Memantine	201
Venlafaxine	1824	Piracetam	185
Escitalopram	1764	Amitriptyline	179
Haloperidol	1532	Ziprasidone	157
Oxcarbazepine	1381	Disulfiram	139
Zuclopenthixol	1311	Modafinil	133
Duloxetine	1241	Reboxetine	113
Lithium	1193	Metformin	90
Lamotrigine	1158	Mianserin	81
Methylphenidate	1141	Buspirone	76
Sulpiride	1086	Maprotiline	56
Fluvoxamine	1079	Moclobemide	55
Amisulpride	1030	Lacosamide	46
Gabapentin	957	Rivastigmine	39
Trifluoperazine	879	Acamprosate	34
Clonazepam	847	Buprenorphine	32
Clomipramin	842	Imipramine	29
Mirtazapine	831	Sertindole	21
Biperiden	715	Tianeptine	19
Clozapine	707	Milnacipran	17
Bupropion	691	Fluphenazine	14
Citalopram	675	Agomelatin	11
Chlorpromazine	626	Opipramol	11
Pregabaline	526	Phenobarbital	11
Atomoxetine	502	Zolpidem	7
Lorazepam	501	Pramipexole	2
Flupentixol	459	Dextromethorphan	1
Trazadone	453	Norbuprenorphine	1

Table 3. Drug tests available in the database grouped over admission and sex with respective number of tested patients. Distribution of the drug service received by the patients on the population according to the way of admission and gender, as the patients are subject to more than one drug use. M = male, F= female.

INPATIENT			OUTPATIENT		
TEST	SEX	#PATIENTS	TEST	SEX	#PATIENTS
Acamprosate	M	23	Acamprosate	M	5
	F	5		F	1
Agomelatin	M	1	Agomelatin	M	2
	F	5		F	3
Alprazolam	M	148	Alprazolam	M	77
	F	166		F	66
Amisulpride	M	420	Amisulpride	M	313
	F	275		F	173
Amitriptyline	M	39	Amitriptyline	M	44
	F	55		F	60
Aripiprazole	M	993	Aripiprazole	M	1442
	F	913		F	1156
Atomoxetine	M	127	Atomoxetine	M	284
	F	13		F	91
Biperiden	M	316	Biperiden	M	115
	F	291		F	44
Buprenorphine	M	26	Buprenorphine	M	5
	F	1		F	1
Bupropion	M	163	Bupropion	M	211
	F	103		F	255
Buspirone	M	22	Buspirone	M	18
	F	10		F	27
Carbamazepine	M	449	Carbamazepine	M	549
	F	511		F	552
Chlorpromazine	M	318	Chlorpromazine	M	80
	F	218		F	52
Citalopram	M	143	Citalopram	M	208
	F	99		F	254
Clomipramin	M	123	Clomipramin	M	369
	F	96		F	316
Clonazepam	M	349	Clonazepam	M	96
	F	346		F	86
Clozapine	M	297	Clozapine	M	303
	F	112		F	158
Dextromethorphan	M	1	Diazepam	M	36
				F	20
Diazepam	M	211	Disulfiram	M	70
	F	105		F	11
Disulfiram	M	71	Donepezil	M	37
	F	14		F	56
Donepezil	M	69	Duloxetine	M	423
	F	63		F	642

Duloxetine	M	97	Escitalopram	M	608
	F	141		F	675
Escitalopram	M	242	Fluoxetine	M	858
	F	330		F	1049
Fluoxetine	M	459	Flupentixol	M	100
	F	401		F	78
Flupentixol	M	203	Fluphenazine	M	3
	F	153		F	4
Fluphenazine	M	7	Fluvoxamine	M	450
	F	1		F	368
Fluvoxamine	M	238	Gabapentin	M	177
	F	181		F	206
Gabapentin	M	334	Haloperidol	M	223
	F	346		F	117
Haloperidol	M	853	Imipramine	M	12
	F	513		F	9
Imipramine	M	4	Lacosamide	M	28
	F	4		F	13
Lacosamide	M	6	Lamotrigine	M	276
	F	3		F	536
Lamotrigine	M	146	Levetiracetam	M	183
	F	346		F	160
Levetiracetam	M	49	Lithium	M	478
	F	41		F	408
Lithium	M	283	Lorazepam	M	34
	F	257		F	15
Lorazepam	M	201	Maprotiline	M	13
	F	261		F	26
Maprotiline	M	10	Memantine	M	39
	F	10		F	45
Memantine	M	78	Metformin	M	36
	F	61		F	34
Metformin	M	7	Methylphenidate	M	764
	F	14		F	268
Methylphenidate	M	89	Mianserin	M	18
	F	34		F	21
Mianserin	M	22	Milnacipran	M	3
	F	24		F	4
Milnacipran	M	10	Mirtazapine	M	162
				F	148
Mirtazapine	M	407	Moclobemide	M	32
	F	151		F	13
Moclobemide	M	9	Modafinil	M	47
	F	5		F	32
Modafinil	M	34	Naltrexone	M	44
	F	28		F	5
Naltrexone	M	210	Norbuprenorphine	M	1
	F	30			
Olanzapine	M	2254	Olanzapine	M	1136
	F	1495		F	732
Opipramol	M	2	Olanzapine	M	1136
	F	5		F	732
Oxcarbazepine	M	386	Opipramol	M	1
	F	452		F	3
Paroxetine	M	462	Oxcarbazepine	M	333
	F	334		F	358

Phenobarbital	M	2	Paroxetine	M	824
	F	3		F	902
Pimozide	M	81	Phenobarbital	M	3
	F	141		F	3
Piracetam	M	74	Pimozide	M	59
	F	104		F	56
Pramipexole	M	1	Piracetam	M	2
				F	6
Pregabaline	M	159	Pramipexole	F	1
	F	98			
Quetiapine	M	1533	Pregabaline	M	140
	F	1009		F	184
Reboxetine	M	23	Quetiapine	M	548
	F	19		F	488
Risperidone	M	2465	Reboxetine	M	36
	F	1165		F	51
Rivastigmine	M	12	Risperidone	M	1801
	F	8		F	788
Sertindole	M	1	Rivastigmine	M	9
	F	3		F	11
Sertraline	M	804	Sertindole	M	8
	F	548		F	9
Sulpiride	M	228	Sertraline	M	1260
	F	203		F	1477
Tianeptine	M	8	Sulpiride	M	431
	F	5		F	308
Topiramate	M	43	Tianeptine	M	4
	F	125		F	6
Trazadone	M	104	Topiramate	M	54
	F	125		F	160
Trifluoperazine	M	162	Trazadone	M	90
	F	476		F	152
Valproic Acid	M	1278	Trifluoperazine	M	137
	F	761		F	177
Venlafaxine	M	316	Valproic Acid	M	1721
	F	257		F	1129
Vortioxetine	M	38	Venlafaxine	M	622
	F	20		F	743
Ziprasidone	M	37	Vortioxetine	M	109
	F	53		F	116
Zolpidem	M	3	Ziprasidone	M	36
	F	2		F	57
Zuclopenthixol	M	794	Zolpidem	M	1
	F	322		F	1
			Zuclopenthixol	M	287
				F	131

Table 4: Median and MAD for age of patients per drugs. The median and MAD of age distribution per drug for female and male patients. The drugs with more than 50 patient data were included.

	FEMALE		MALE	
TEST	MEDIAN	MAD	MEDIAN	MAD
Alprazolam	48	15	44	15
Amisulpride	41,5	15	41	16
Amitriptyline	49,5	12,5	36,5	12,5
Aripiprazole	41,5	18,5	40	19
Atomoxetine	17	5	25,5	11
Biperiden	40	13	37	13
Bupropion	44,5	15	42,5	14,5
Carbamazepine	42	19	42	19
Chlorpromazine	42,5	15	39,5	13,5
Citalopram	50	20	44,5	17,5
Clomipramin	41	17	39,5	14,5
Clonazepam	45	18	44,5	18
Clozapine	49	18	42,5	16
Diazepam	43,5	14	43,5	14
Disulfiram	40	7	38,5	10
Donepezil	67,5	11,5	65	11
Duloxetine	49,5	17,5	45	14
Escitalopram	49	20	45,5	20
Fluoxetine	43	19	39,5	17
Flupentixol	37,5	12,5	37,5	12,5
Fluvoxamine	43,5	15,5	39,5	15,5
Gabapentin	46,5	18	43	15
Haloperidol	46,5	20,5	44,5	19,5
Lamotrigine	45	17	40,5	16
Levetiracetam	41,5	18	41,5	17,5
Lithium	43,5	15,5	44,5	16
Lorazepam	45,5	17	39,5	13
Memantine	70	10	65	13
Methylphenidate	26,5	11,5	29,5	12,5
Mirtazapine	49	18	46,5	17
Modafinil	43	12	35	13
Naltrexone	34	10	40	11
Olanzapine	47,5	21	47	21
Oxcarbazepine	40,5	17,5	37,5	17
Paroxetine	48	19	47	18
Pimozide	38,5	13	32,5	9
Piracetam	38	14	32	11
Pregabaline	49,5	16	44	14
Quetiapine	49	20	47	20
Reboxetine	45	12	37,5	11,5
Risperidone	41,5	19,5	43	21
Sertraline	48	21	46,5	20,5
Sulpiride	46,5	17,5	42,5	17
Topiramate	37,5	14	32,5	11,5
Trazadone	46	17	45,5	16
Trifluoperazine	44,5	17,5	39	13
Valproic Acid	41,5	20	43,5	20,5
Venlafaxine	46	17	47	17
Vortioxetine	44	13	42,5	13
Ziprasidone	36	11	34	9
Zuclopenthixol	39	15	38	14

Table 5 : Genotypic profiling of Cyp enzymes in the database per drugs.

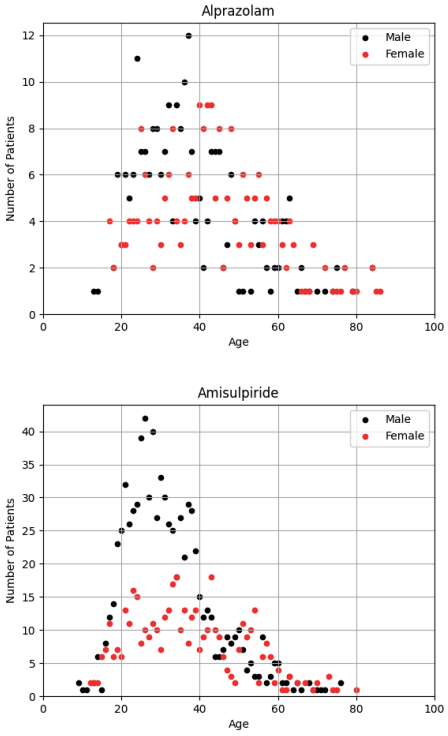
Drug	CYP1A2	CYP2D6	CYP3A4
Alprazolam	3	3	3
Amisulpride	7	7	8
Amitriptyline	3	2	2
Aripiprazole	14	17	17
Biperiden	4	4	4
Bupropion	4	4	2
Carbamazepine	6	7	6
Chlorpromazine	4	1	4
Citalopram	2	2	1
Clomipramin	3	4	2
Clonazepam	4	4	4
Clozapine	8	7	4
Diazepam	4	4	4
Disulfiram	0	1	1
Duloxetine	4	4	3
Escitalopram	5	5	5
Fluoxetine	7	8	7
Flupentixol	2	3	2
Fluvoxamine	9	10	10
Gabapentin	5	5	4
Haloperidol	7	7	6
Lamotrigine	4	3	1
Lithium	9	8	8
Lorazepam	4	4	4
Maprotiline	0	1	1
Metformin	1	1	1
Methylphenidate	2	4	3
Mianserin	1	1	0
Mirtazapine	3	2	2
Moclobemide	1	1	1
Modafinil	2	2	2
Naltrexone	1	1	1
Olanzapine	16	18	16
Oxcarbazepine	3	3	3
Paroxetine	4	5	5
Pimozide	1	0	1
Piracetam	1	0	1
Pregabaline	2	2	2
Quetiapine	13	16	16
Reboxetine	3	3	2
Risperidone	16	18	14
Sertraline	9	7	8
Sulpiride	1	2	2
Tianeptine	1	1	0
Topiramate	1	1	0
Trazadone	2	2	3
Trifluoperazine	1	1	0
Valproic Acid	14	16	16
Venlafaxine	6	6	5
Vit D2 + D3	7	6	6
Vortioxetine	2	1	1
Ziprasidone	0	0	1
Zolpidem	1	0	1
Zuclopenthixol	9	7	7

etine (n=1907), olanzapine (n=1868), paroxetine (n=1726) and escitalopram (n=1283). The test profile over the type of admission and sex for each drug is given in Table 3.

The drug combinations in the repository was evaluated over the the frequency of tests carried on the same patient. The raw combination frequencies were first normalized for each drug by the total number of patients that are tested, and then further normalized over the total sum of frequencies in the combination table. The frequencies are given as percentages in Supplementary Table. The drug pairs that are tested together for the same patient most frequently are risperidone-biperiden (36.4‰), olanzapine-haloperidol (34.3‰), olanzapine-lorazepam (32.5‰), quetiapine-diazepam (32‰), valproic acid-chlorpromazine (31.7‰), risperidone-flupentixol (30.6‰), valproic acid-biperiden (30.6‰), risperidone-disulfiram (30.2‰) and olanzapine-chlorpromazine (30.1‰).

The distribution of genotypic profiling for Cyp1A2, Cyp2D6 and Cyp3A4 over the prescribed drugs at the time of profiling is given in Table 6. Normalization was carried on the same way as described for drug combination frequencies.

The age profile for each drug is analyzed for the tests with more than 100 patients and was also grouped over sex (Figure 1) and age median for each drug is given in Table 4. The age distribution per drug was similar over sex and there were no statistically significant differences. The age distributions of the drugs are shown alphabetically in Figure 1A, Figure 1B, Figure 1C, Figure 1D, Figure 1E, Figure 1F, Figure 1G, Figure 1H, and Figure 1I. Generally the age distribution was skewed towards 30-40 years interval with heavy-tail distribution for the majority of the tested drugs. However, the distribution was skewed towards younger ages for atomoxetine (Figure 1A) and methylphenidate (Figure 1E), and to older ages for donepezil (Figure 1C) and memantine (Figure 1E). Table 5 presents the genotypic profiling of CYP enzymes in the database per drugs.



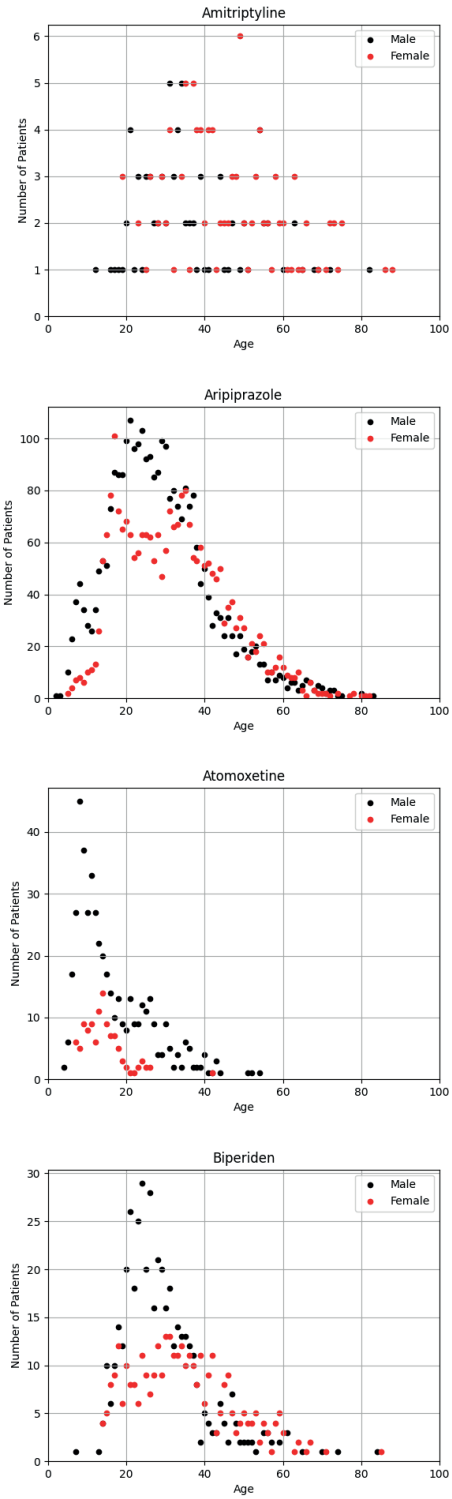
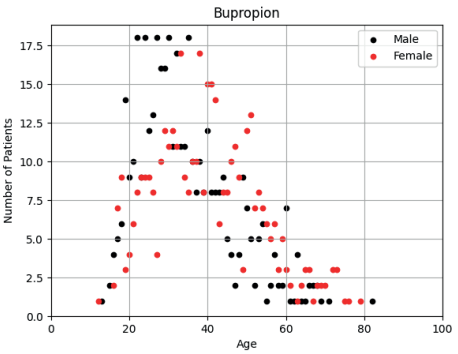
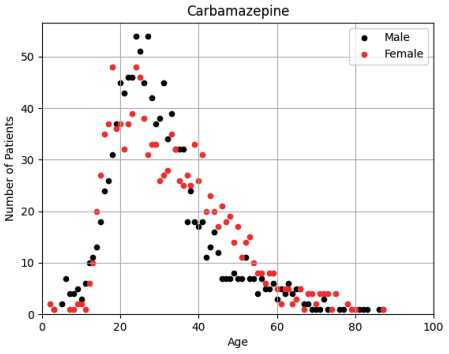
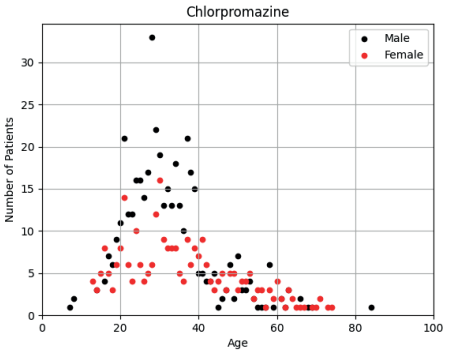
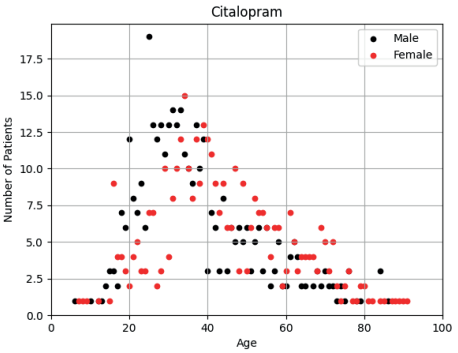


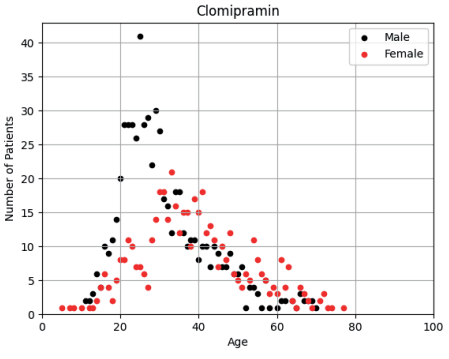
Figure 1.A: Age distribution of alprazolam, amisulpride, amitriptyline, aripiprazole, atomoxetine and biperiden.











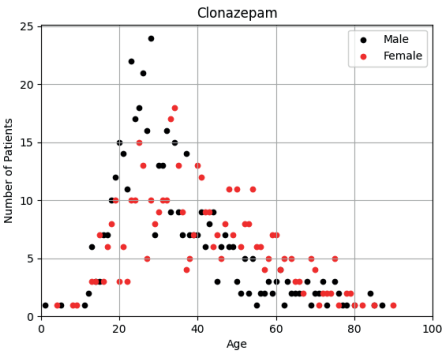
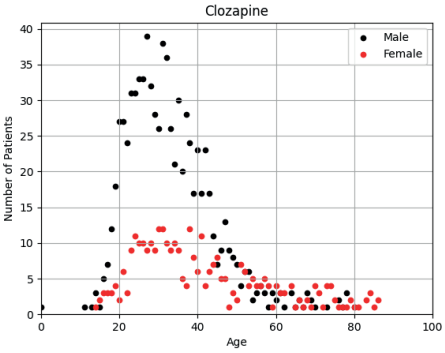
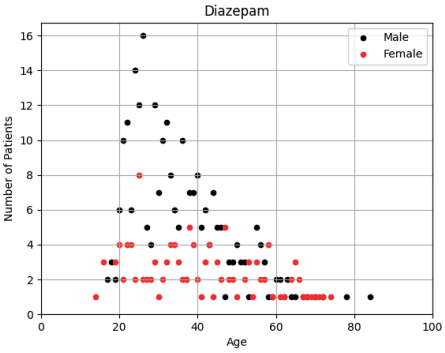
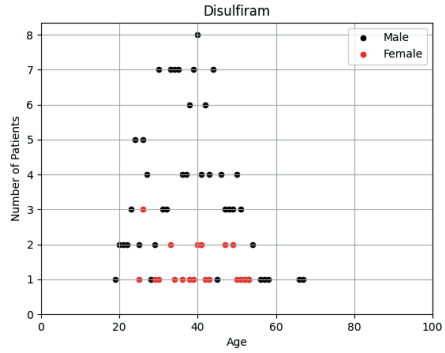
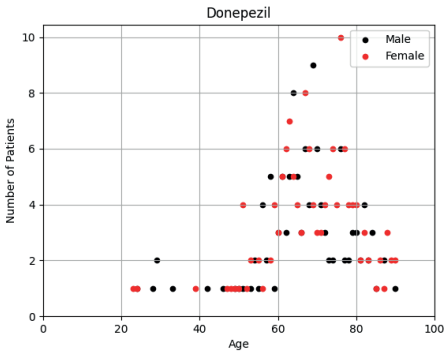


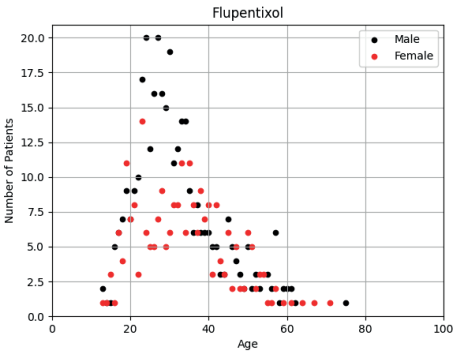
Figure 1.B: Age distribution of bupropion, carbamazepine, chlorpromazine, citalopram, clomipramine and clonazepam.

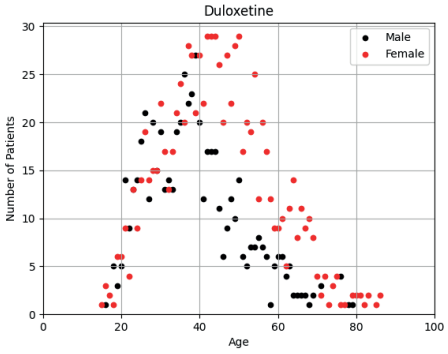


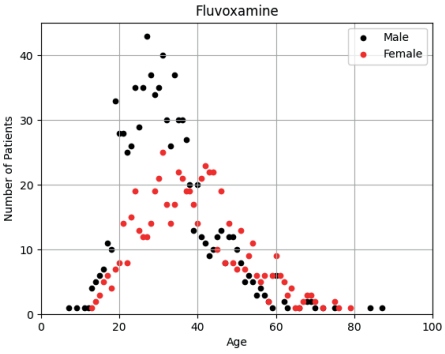


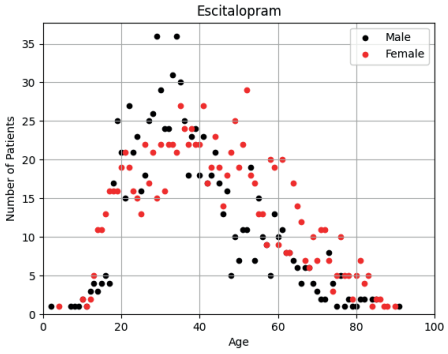












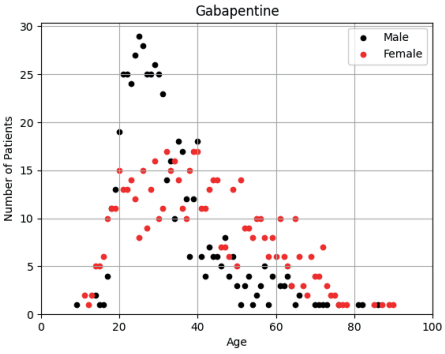
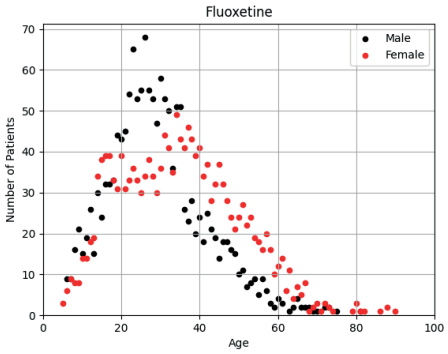
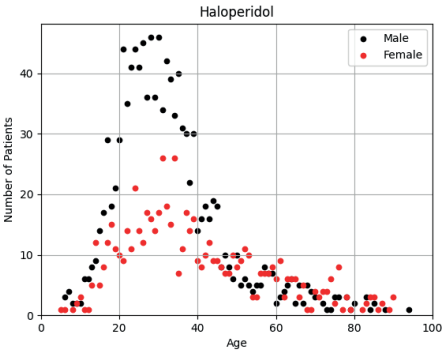


Figure 1.C: Age distribution of clozapine, diazepam, disulfiram, donepezil, duloxetine and escitalopram.





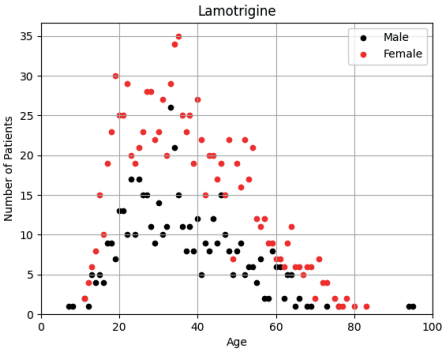
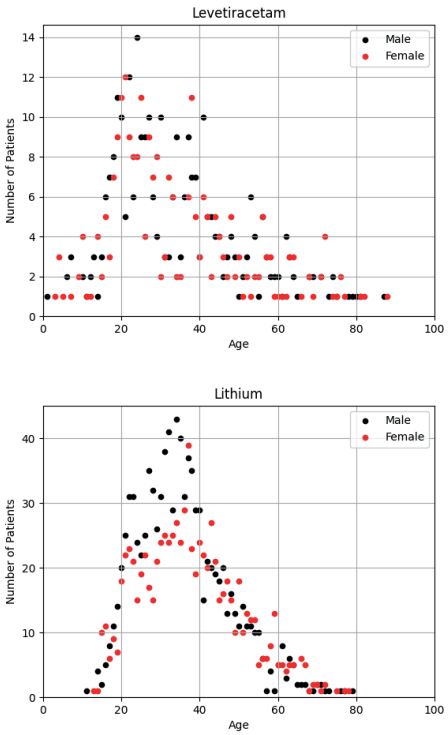
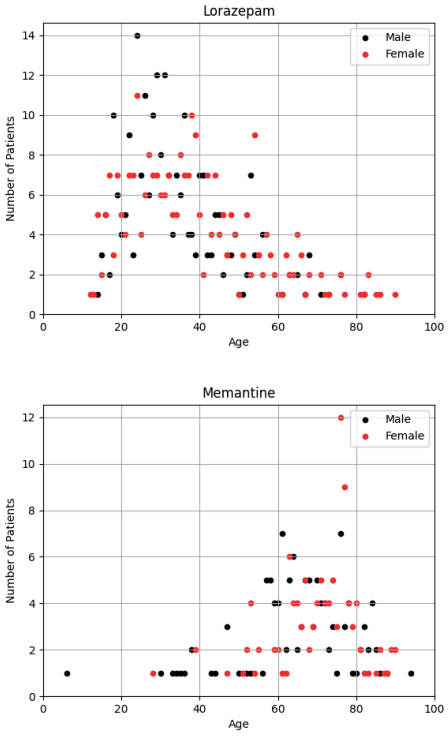


Figure 1.D: Age distribution of fluoxetine, flupentixol, fluvoxamine, gabapentin, haloperidol, lamotrigine.





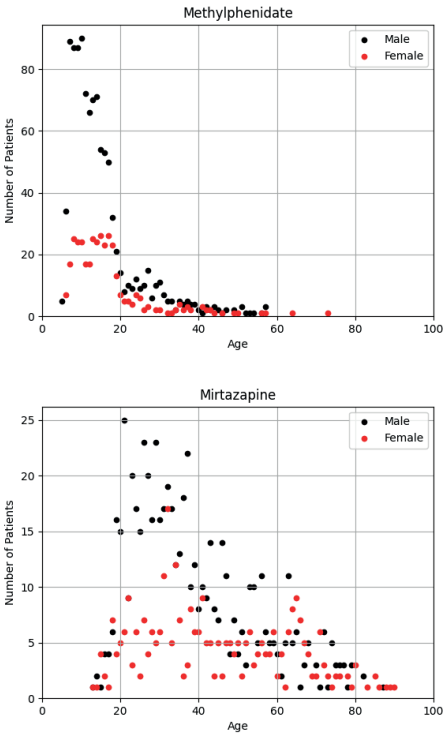
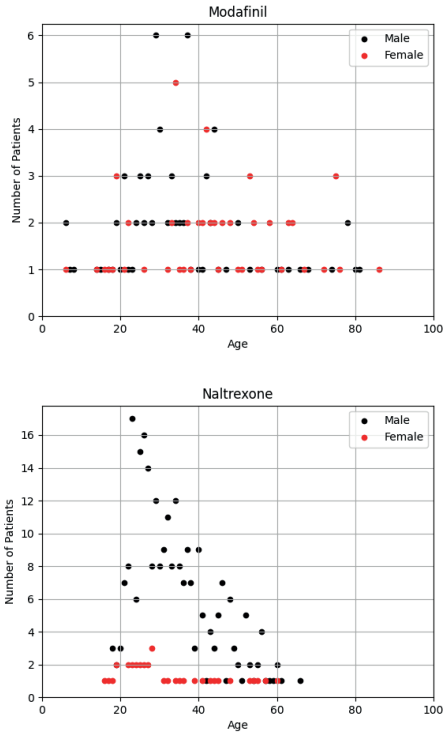


Figure 1.E: Age distribution of levetiracetam, lithium, lorazepam, memantine, methylphenidate and mirtazapine.



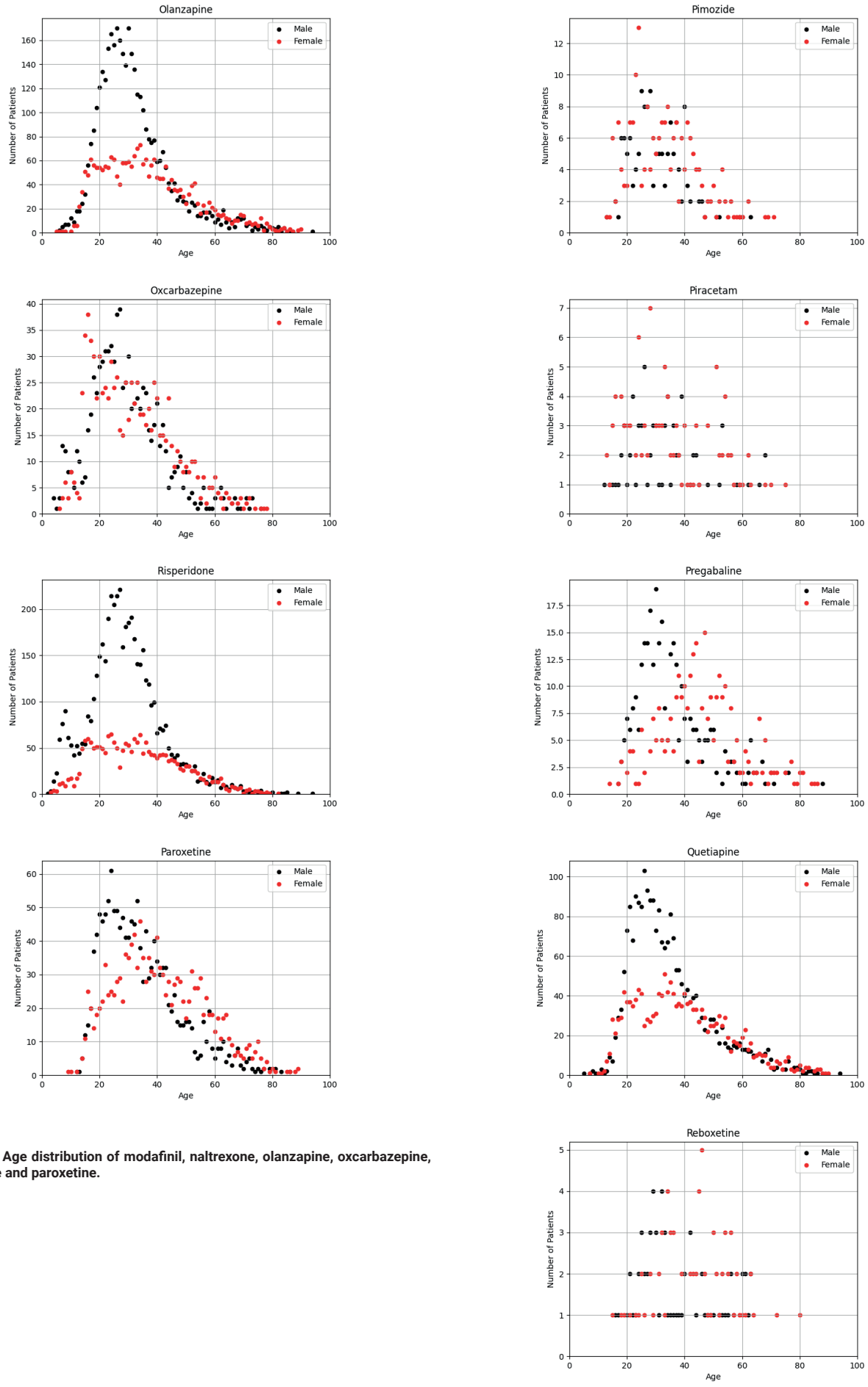
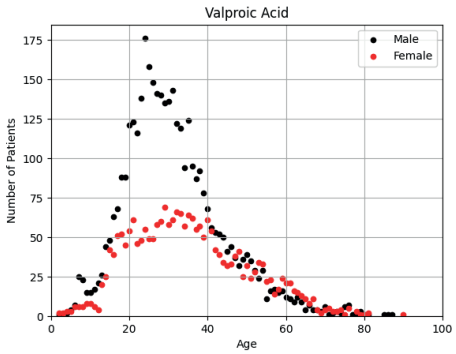


Figure 1.F: Age distribution of modafinil, naltrexone, olanzapine, oxcarbazepine, risperidone and paroxetine.



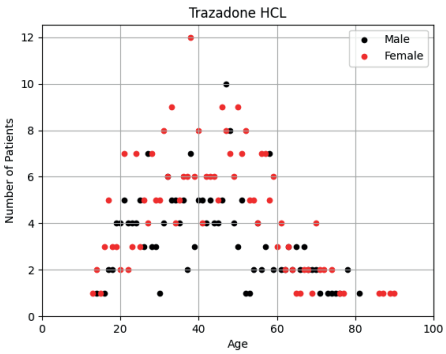
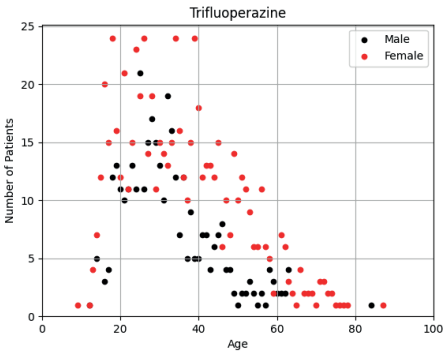
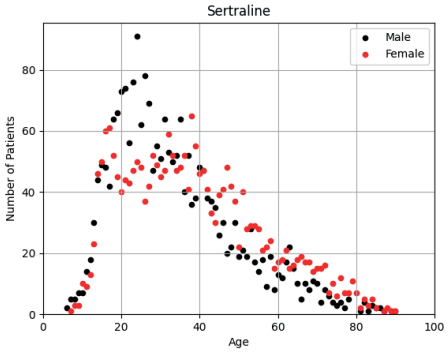
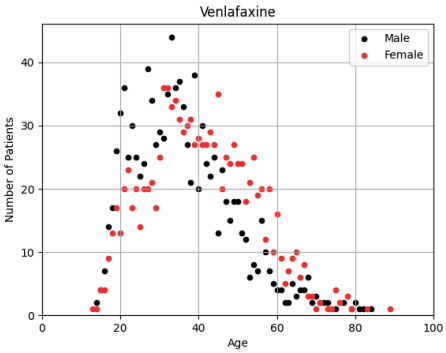


Figure 1.G: Age distribution of pimozide, piracetam, pregabalin, quetiapine, reboxetine and valproic acid.







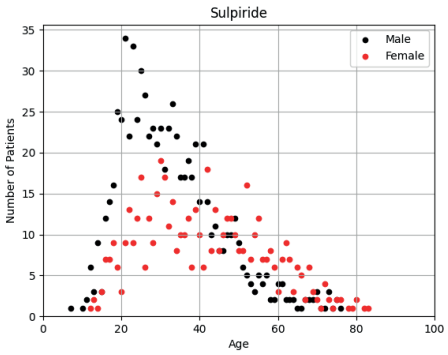
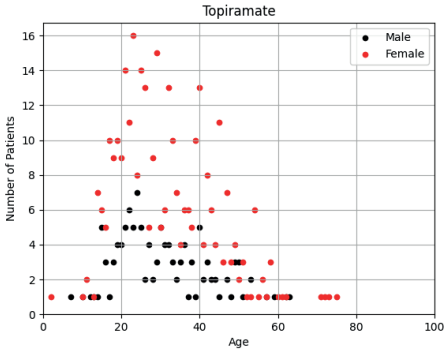
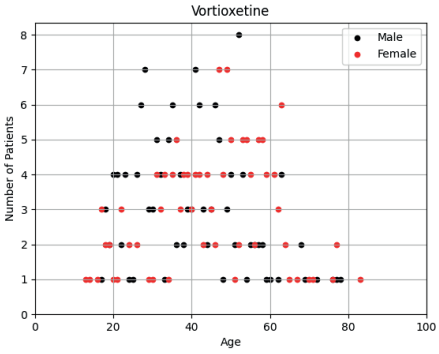


Figure 1.H: Age distribution of sertraline, sulpiride, topiramate, trazodone HCL, trifluoperazine, and venlafaxine.





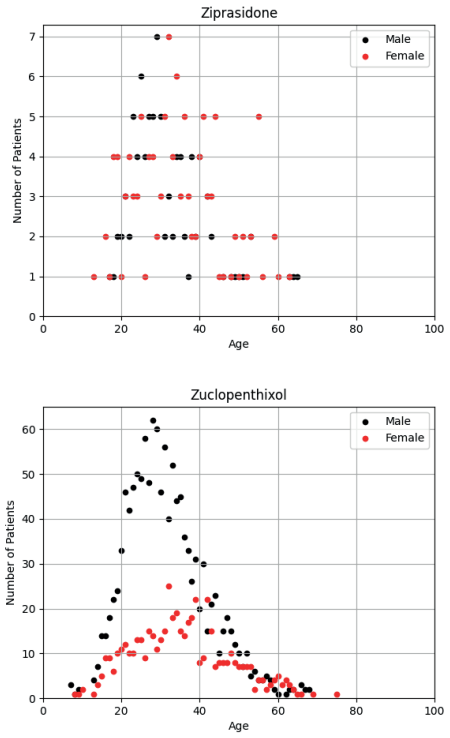


Figure 1.I: Age distribution of vortioxetine, ziprasidone and zuclopenthixol.

DISCUSSION

Population pharmacokinetics in conjunction with TDM enables the progress of personalized medicine. Pharmacokinetics is vital in particular, to demonstrate the demographic, biological, or physiopathological profiles within the population, as individual variability stands as a prominent factor within personalized medicine.

Establishing well-structured data repositories that can reflect and combine patient variability is an essential first step for detail pharmacokinetic analysis in a population. The data repository established with this study enables classification over age, sex and diagnosis. Furthermore, the data from inpatients enable continuous analysis of variations within individual over a period of time, that is more trustable due to being monitored by the experts. Therefore, follow-up studies on population pharmacokinetics for each drug can be incorporated with the existing information on multiple drug use, personal history, genetical variations and electrophysiological data. Detailed repositories enable data elimination due to ,e.g., drug interactions but also outcomes of these drug interactions with respect to population, especially when combined with genotypic profiling.

Another important outcome for the follow-up studies from this repository would be establishing the dosing intervals, i.e. supratherapeutical dosing, with respect to age. While it is possible to locate a PK profile, particularly for adults, within the literature, the likelihood of encountering a PK profile for infants and children is quite low when age ranges are categorized as infants, children, adolescents, adults, and elderly patients. Particularly, the illnesses that manifest during childhood, the drugs administered, or the treatment modalities employed in line with the diagnoses have a lasting impact on an individual's future life. It should also be noted that some drugs might interfere with early neurodevelopmental processes when administered at younger ages, which requires close and careful monitoring to maintain therapeutic levels during childhood. The absence of PK profiles for commonly used drugs in children can potentially lead to neurodevelopmental complications. The inclusion of a pediatric therapeutic range in metabolizer phenotyping would be advantageous for pediatric personalized medicine. In this regard, addressing the literature gap regarding pediatric therapeutic ranges in TDM studies is crucial. This effort can help mitigate the risk of neurodevelopmental disorders resulting from drug use in children. The determination of the supratherapeutic range is of great significance, just as the identification of the therapeutic range within the population is crucial. Overdose exposure in poor metabolizers can lead to various complications or even reach critical levels. Hence, the possibility of an individual's demise is one of the potential scenarios.

Through the repository established in this study, the goal is to elucidate the repository's purpose, allowing patients to access the correct treatment and focus on the objectives of personalized medicine. The repository encompasses various drugs and distinct diagnostic groups. In the TDM-specific treatment process for individuals, there exists a substantial gap in local studies. The aim is to extend the phenotyping study to encompass a larger population in our country in collaboration with the repository maintained by NPİSTANBUL Brain Hospital to enable better and more personalized therapeutical interventions.

FUTURE PERSPECTIVE

The need for a foundation created by genotypic analyses arises in the presence of multiple enzyme contents in drug metabolism. The genotyping conducted in Table 5 serves as an example for prospective studies. It is believed that there should be an intensification of interest in genotyping studies to obtain outputs from metabolic analyses. It is anticipated that enhancing the genetic analysis infrastructure in the design of studies for further development and progression of this research will be beneficial. Extracting individual genetic panels of patients is considered a fundamental requirement for focusing on personalized treatment studies. It is suggested that efforts should be directed towards increasing and contributing to the database for the creation of these panels.

Patient informed consent:

Patient informed consent was obtained.

Ethics committee approval:

The local ethical approval was obtained from Üsküdar University Non-interventional Research Ethics Board (23.2.2023, 61351432/Feb 2023-20).

Conflict of interest:

There is no conflict of interest to declare.

Financial support and sponsorship:

No funding was received.

Author contribution subject and rate:

Elif Çakır (25%) Data curation, software, investigation, formal analysis, writing – original draft

Pınar Öz (30%) Conceptualization, methodology, software, validation, project administration, writing- review and editing

Murat Özdemir (15%) Conceptualization, resources, supervision

Selma Özilhan (15%) Conceptualization, resources, supervision

Nevzat Tarhan (15%) Conceptualization, supervision, funding acquisition

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Legend	
Acomprosate	Ac
Agomelatin	Ag
Alprazolam	Al
Amisulpiride	As
Amitriptyline	Am
Aripiprazole	Ar
Atomoxetine	At
Biperiden	Bi
Buprenorphine	Bn
Bupropion	Bp
Buspirone	Bs
Carbamazepine	Ca
Chlorpromazine	Ch
Citalopram	Ci
Clomipramin	Cm
Clonazepam	Cn
Clozapine	Cz
Dextrometorphan	De
Diazepam	Da
Disulfiram	Ds
Donepezil	Do
Duloxetine	Du
Escitalopram	Es
Fluoxetine	Fx
Flupentixol	Fp
Fluphenazine	Fh
Fluvoxamine	Fv
Gabapentine	Ga
Haloperidol	Ha
Imipramine	Im
Lacosamide	Lc
Lamotrigine	Lm
Levetiracetam	Le
Lithium	Li
Lorazepam	Lo
Maprotiline	Ma
Memantine	Mm
Metformin	Mf
Methylphenidate	Mp
Mianserine	Ma
Milnacipran	Mn
Mirtazapine	Mr
Moclobemide	Mc
Modafinil	Md
Naltrexone	Na
Norbuprenorphine	No
Olanzapine	Ol
Opipramol	Op
Oxcarbazepine	Ox
Paroxetine	Pa
Phenobarbital	Ph
Pimozide	Pm
Piracetam	Pi
Pramipexole	Pr
Pregabaline	Pg
Quetiapine	Qu
Reboxetine	Re
Risperidone	Ri
Rivastigmine	Rv
Sertindole	Si
Sertraline	Sr
Sulpiride	Su
Tianeptine	Ti
Topiramate	To
Trazadone	Ta
Trifluoperazine	Tf
Valproic Acid	Va
Venlafaxine	Ve
Vit D2	V2
Vit D2 + D3	V23
Vit D3	V3
Vortioxetine	Vo
Ziprasidone	Zi
Zolpidem	Zo
Zuclopenthixol	Zu

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Bn								0	0	2	0	0	0	2	1	0	0	0	0	0	1	2	0	0	0	12	1	0	0	1	0	1	1	0
Bp									14	69	26	34	25	41	12	0	30	9	8	65	75	147	10	0	53	52	34	1	0	78	3	54	34	3
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Ca											119	42	51	117	64	0	53	20	13	62	141	183	68	3	82	161	214	0	19	146	100	129	76	5
Ch												24	41	91	73	0	43	5	7	21	53	70	65	2	47	81	210	0	1	66	3	99	66	5
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Cz																0	17	1	17	11	49	80	77	1	64	53	175	0	2	41	9	69	42	3
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Le																																5	4	1
Li																																	56	6
Lo																																		2
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Am	2	2	3	1	0	19	2	4	2	0	55	1	8	43	0	9	5	1	27	51	4	24	0	0	35	23	0	4	7	19	35	25	0	78	0	6	3	0	11	Am
Ar	28	23	259	21	5	153	10	35	59	0	990	1	368	333	2	88	87	0	73	956	28	1044	2	7	796	185	2	124	104	184	1118	363	0	1400	0	35	60	1	406	Ar
At	0	0	79	0	0	19	0	5	15	0	107	0	31	28	0	4	3	0	14	52	0	186	0	0	69	7	0	6	6	11	83	9	0	198	0	4	5	0	9	At
Bi	10	10	9	5	2	35	5	4	38	0	321	2	92	80	1	39	3	0	18	294	2	422	1	2	121	57	1	26	13	51	355	38	0	193	1	5	29	0	312	Bi
Bn	0	0	0	0	0	6	0	0	0	1	5	0	6	3	0	0	0	0	3	2	0	6	0	0	2	0	0	0	2	1	2	1	0	7	0	0	0	0	0	Bn
Bp	5	4	34	5	1	59	5	17	35	0	128	0	60	89	0	9	5	0	39	154	10	126	2	1	136	68	2	26	36	38	111	97	0	193	0	15	6	0	27	Bp
Bs	0	2	4	1	0	14	1	2	5	0	32	0	9	29	0	2	2	0	6	21	0	14	0	1	15	5	1	2	4	13	16	18	0	44	0	7	2	1	2	Bs
Ca	12	8	50	7	0	73	3	12	53	0	624	2	218	153	3	68	39	0	36	429	7	712	1	3	276	90	0	63	42	194	375	122	0	879	1	15	25	1	185	Ca
Ch	5	4	11	2	0	37	3	4	23	0	305	2	102	44	2	39	18	1	18	288	2	296	1	2	99	50	1	32	29	69	322	49	0	242	0	7	19	3	231	Ch
Ci	15	6	9	7	2	42	1	5	30	0	134	0	56	59	0	9	2	0	26	114	9	138	4	0	54	91	4	21	35	31	94	45	0	139	0	9	11	0	40	Ci
Cm	5	3	3	4	0	28	3	7	6	0	144	0	45	167	1	20	11	0	21	127	6	160	1	1	163	79	1	16	17	48	116	65	0	182	0	2	19	0	34	Cm
Cn	21	11	11	5	3	96	3	13	16	0	329	2	88	159	2	31	23	1	72	340	11	259	2	2	218	127	2	34	47	85	250	125	0	371	0	18	20	1	115	Cn
Cz	19	6	6	4	0	21	2	7	7	0	229	1	43	53	1	42	15	0	12	199	6	312	7	1	94	50	2	18	8	34	206	38	0	297	0	5	17	0	148	Cz
De	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	1	1	1	0	1	0	0	0	0	0	0	0	1	De
Da	7	1	12	5	1	70	2	8	47	0	149	1	54	68	0	9	10	0	37	184	5	123	0	0	79	43	3	6	25	34	114	55	0	155	0	2	5	3	55	Da
Ds	0	0	5	0	0	21	0	2	18	0	38	0	26	21	0	4	0	0	9	30	1	68	0	0	34	4	1	2	7	13	27	12	0	115	1	3	2	1	2	Ds
Do	89	1	1	4	0	22	0	8	1	0	76	0	11	17	0	1	3	0	11	88	1	35	7	0	84	16	0	1	16	10	24	24	0	74	0	9	0	0	7	Do
Du	14	9	17	11	0	71	6	25	11	0	125	1	57	114	0	11	7	0	137	165	9	84	0	1	144	141	5	34	71	56	121	94	0	214	0	17	12	0	30	Du
Es	37	16	23	14	1	105	1	14	32	0	394	2	143	125	0	34	23	0	55	281	16	290	5	1	155	139	5	37	77	148	237	127	0	522	2	18	11	3	68	Es
Fx	14	18	152	10	3	118	5	30	42	0	491	2	182	189	0	45	53	1	66	390	23	588	2	3	227	174	3	85	82	153	311	192	0	795	2	27	36	1	108	Fx
Fp	2	3	8	3	1	21	1	3	15	0	165	0	41	34	1	36	10	0	10	167	0	228	0	0	74	39	0	20	9	30	175	20	0	122	0	0	17	0	107	Fp
Fh	1	0	0	0	0	0	0	0	0	0	6	0	2	0	0	1	0	0	0	4	0	10	0	0	3	1	0	1	0	1	7	4	0	4	0	0	1	0	3	Fh
Fv	9	17	12	11	3	47	8	21	12	0	229	0	78	161	1	36	18	0	50	240	20	236	2	1	225	182	2	19	40	56	186	125	0	256	0	16	17	0	75	Fv
Ga	21	19	38	8	0	102	3	20	38	0	441	4	139	165	1	59	17	1	73	324	11	319	3	1	208	84	5	37	47	188	236	133	0	554	1	29	20	0	90	Ga
Ha	42	18	19	6	0	63	3	12	37	0	852	0	156	96	3	55	64	0	29	609	7	714	7	1	216	73	1	42	25	88	562	62	0	884	1	11	31	1	325	Ha
Im	0	1	2	0	0	1	0	2	0	0	4	0	3	6	0	0	0	0	0	1	0	5	0	0	4	4	1	0	1	0	3	1	0	9	0	1	0	0	1	Im
Lc	1	0	0	0	0	1	0	0	0	0	6	0	1	3	0	0	0	0	0	2	0	5	0	0	4	0	0	5	0	0	18	1	0	20	0	0	1	0	2	Lc
Lm	13	16	20	11	3	60	6	17	6	0	359	4	118	190	2	31	21	1	33	312	19	256	1	1	204	73	2	41	51	166	249	186	0	446	0	21	25	2	89	Lm
Le	5	1	1	3	0	13	0	2	4	0	34	0	34	14	0	2	0	0	8	34	1	43	1	1	23	12	0	22	4	11	111	8	0	100	0	3	4	0	10	Le
Li	8	12	20	4	2	48	6	18	12	0	459	0	107	97	0	34	14	0	27	423	16	403	1	3	134	55	2	37	23	88	435	126	0	442	1	17	31	0	199	Li
Lo	12	5	6	7	1	55	3	7	21	1	264	1	79	97	0	17	14	0	28	223	3	172	2	1	88	53	5	12	30	76	170	55	0	260	0	9	11	1	98	Lo
Ma	0	0	3	1	0	8	2	2	0	0	5	0	4	11	0	2	4	1	8	20	4	8	0	0	11	9	0	1	4	4	9	8	0	11	0	1	2	0	3	Ma
Mm		1	0	6	0	28	0	3	2	0	92	1	11	24	0	4	2	0	13	70	2	47	19	0	59	14	0	1	19	8	32	24	0	81	0	6	1	0	7	Mm
Mf			1	0	0	0	0	2	0	0	24	0	8	8	1	8	4	0	6	22	1	26	0	0	15	9	1	7	7	9	24	9	0	53	0	5	3	0	15	Mf
Mp				0	1	22	2	14	10	0	111	0	52	36	0	2	2	0	16	61	8	331	0	0	172	18	0	10	8	27	140	26	0	213	0	5	10	0	16	Mp
Ma					6	11	0	1	2	0	30	0	8	21	0	0	2	0	11	22	1	16	1	0	18	18	1	3	9	4	12	19	0	28	0	4	1	0	6	Ma
Mn						3	0	0	1	0	5	0	2	2	0	0	1	0	1	2	1	4	0	0	1	6	0	0	0	1	3	2	0	7	0	0	1	0	1	Mn
Mr							3	17	50	0	287	1	62	214	0	11	25	0	73	219	12	181	4	2	208	85	4	9	53	65	117	181	0	389	1	17	8	3	48	Mr
Mc								4	1	0	10	0	3	8	0	2	1	0	1	8	4	7	0	0	9	4	0	2	2	3	6	4	0	8	0	2	1	0	4	Mc
Md									8	0	31	0	15	22	0	0	1	0	17	35	5	26	2	0	29	19	0	5	10	9	23	39	0	62	0	14	4	0	11	Md
Na										0	93	1	68	33	0	7	0	0	23	116	1	125	0	0	72	26	2	9	15	11	70	29	0	132	1	4	3	1	49	Na
No											0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No
Ol												5	469	548	1	161	96	0	134	1140	22	1849	16	8	788	210	4	71	92	433	1503	348	0	2723	3	45	33	5	670	Ol
Op													1	1	0	0	0	0	0	2	0	2	0	0	3	0	0	0	2	3	0	1	0	7	0	0	0	0	0	Op
Ox														136	1	54	25	0	34	374	8	580	1	1	228	92	5	45	37	195	296	101	0	619	0	14	23	1	145	Ox
Pa															0	34	33	0	91	428	25	367	1	3	231	245	2	28	94	167	301	187	0	663	0	34	17	0	87	Pa
Ph																1	0	0	0	3	0	2	0	0	2	0	0	0	0	1	4	0	0	7	0	0	0	0	2	Ph
Pm																	0	0	8	84	3	141	0	1	47	23	0	16	4	48	98	23	0	151	0	2	11	0	55	Pm
Pi																		0	7	72	3	85	0	0	29	19	0	6	10	24	36	20	0	179	0	7	3	1	25	Pi
Pr																			0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	Pr
Pg																				129	6	106	1	0	116	74	3	18	43	39	73	90	0	182	0	17	4	1	20	Pg
Qu																					31	1312	11	3	622	226	5	106	112	250	1105	331	0	1411	3	36	61	6	539	Qu
Re																						25	0	0	42	15	1	2	12	6	16	27	0	43	0	4	1	0	3	Re
Ri																							3	7	814	171	4	98	77	220	1566	234	0	2605	5	25	51	3	687	Ri
Rv																								0	16	4	0	0	2	0	4	1	0	12	0	0	1	0	0	Rv
Si																									8	2	0	1	2	2	7	4	0	4	0	0	1	0	1	Si
Sr																										245	4	74	124	175	499	239	0	1070	1	34	30	2	175	Sr
Su																											5	27	48	62	213	126	0	271	0	16	16	0	89	Su
Ti																												1	2	2	4	3	0	4	0	2	0	0	1	Ti
To																													25	47	95	47	0	104	0	2	18	0	29	To
Ta																														45	61	96	0	144	2	16	6	1	12	Ta
Tf																															193	93	0	582	0	17	12	0	57	Tf
Va																																230	0	1265	1	20	67	3	640	Va
Ve																																	0	535	1	38	16	0	61	Ve
V2																																		1	1	0	0	0	0	V2
V23																																			6	110	66	6	480	V23
V3																																				0	0	0	0	V3
Vo																																					4	0	8	Vo
Zi																																						0	41	Zi
Zo																																							0	Zo
	Mm	Mf	Mp	Ma	Mn	Mr	Mc	Md	Na	No	Ol	Op	Ox	Pa	Ph	Pm	Pi	Pr	Pg	Qu	Re	Ri	Rv	Si	Sr	Su	Ti	To	Ta	Tf	Va	Ve	V2	V23	V3	Vo	Zi	Zo	Zu	

Supplementary Table : Normalized frequency of drug combinations in data repository.

N-Butanol Fraction of Curcuma Longa (Turmeric) Ameliorates Lead Acetate-Induced Altered Sensory Motor Activity, Oxidative Stress and Histopathological Changes in the Frontal Cortex of Wistar Rat Pups

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Abstract

Background: Lead acetate (Pb) exposure during frontal cortex development is associated with developmental toxicity later in life, causing both morphological and functional alterations. *Curcuma longa*, however, has been suggested to possess neuroprotective qualities that could lessen these adverse effects. ***Objective*:** Assessed the frontal cortex following treatment with *Curcuma longa*. ***Materials and Methods*:** Twenty adult female Wistar rats and ten adult male Wistar rats were matched during the proestrous phase of the estrous cycle in order to mate and create five groups of six (n=6) in a 4:2 (4 females to 2 males) ratio. Gestational day 0 was marked as the confirmation of pregnancy based on if sperm is present and a vaginal plug in the vaginal smear. Four (n=4) pregnant Wistar rats were put together. Group 1 (control) rats were given 2 milliliters per kilogram of distilled water. Pb was given at a dose of 120 mg/kg to Group 2. Group 3 rats were given 120 mg/kg of lead and 100 mg/kg of vitamin C. The animals in Group 4 received 750 mg/kg of Curcuma longa and 120 mg/kg of Pb. The animals in Group 5 rats were given 1500 mg/kg of Curcuma longa and 120 mg/kg of Pb. From gestational day 7 to day 21 (14 days), the medication was administered orally. The animals were allowed to litter naturally. At postnatal day (PND) 1, some pups were euthanized using chloroform inhalation and their brains were harvested for Oxidative stress markers, histology, histochemical assessments. While some pups were kept for Cliff avoidance test at PND 4-7. ***Results*:** The study found that lead acetate (Pb) exposure during gestation significantly decreased the mean turning latency in the cliff avoidance test and increased lipid peroxidation (MDA) levels, while decreasing antioxidant enzyme levels (SOD, CAT, GSH) compared to the control group. These neurological and oxidative changes were mitigated by co-administration of Curcuma longa, with a notable improvement in the cliff avoidance test performance and restoration of the altered histological and histochemical markers. The results suggest that *Curcuma longa*, a natural antioxidant, has neuroprotective properties that can counteract the adverse effects of lead toxicity during gestational development**.** ***Conclusion*:** *N-Butanol* Fraction of *Curcuma Longa* ameliorated lead-induced neurotoxicity in rat pups.

Keywords: *Curcuma Longa*, lead acetate, cliff avoidance, biochemical, histology, histochemistry

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Introduction

Naturally occurring elements, metals are usually found in the forms of their related compounds. They are widely used in industry and have the potential to harm people's health due to exposure to the environment and at work [1]. Heavy metals such as arsenic (As), mercury (Hg), lead (Pb) and cadmium (Cad) remain in the environment and have a variety of detrimental consequences when their specific density exceeds 5 g/cm3[2].

Lead (Pb) has been used as a heavy metal for millennia to make a variety of products, and its uses are still prevalent today. Children and developing fetuses are especially susceptible to the disastrous health effects that exposure to lead can have. Numerous industries, including coating, refining, glazing, and ceramics, use lead extensively. Furthermore, it is also employed in the production of radiation shields, cookware, building insulation, cable wrapping, water pipelines, and military applications. Lead is released into the environment by these actions, and it subsequently accumulates in many human organs, with the brain being the primary organ to target[3].

Lead poisoning, or lead toxicity, is a condition caused by elevated levels of heavy metals in the body that can influence behavior and cause biochemical alterations in the body. Cognitive and memory impairments, anxiety-related conditions, disruptions in social and sexual functioning, as well as imbalances in neurotransmitter systems are some examples of the changes that can occur. Among the symptoms of lead poisoning are headaches, anemia, irritability, convulsions, coma, and death in severe cases[4].

Lead can interfere with the formation of red blood cells and disturb numerous biological systems, including proteins, because it can produce compounds with large functional chemical groups. Therefore, if lead is swallowed or inhaled, it can be harmful to one's health. The detrimental impacts of lead exposure on children's growth and maturation continue to be a major global concern because the developing brain is most susceptible to the potentially long-term effects of lead exposure, which can cross

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Ethics committee approval: The study obtained ethical endorsement from the Ahmadu Bello University Committee on Animal Care and Use, with the approval number ABUCAUC/2022/049, ensuring the research was conducted in agreement with institutional procedures and regulations for the use and care of animals.

the placental and blood-brain barriers and be further exacerbated by maternal bone turnover during pregnancy[1].

Children absorb lead more quickly than adults do, which results in more physical harm[6]. Even at low exposures, this is detrimental to children's cognitive development[7]. Children with blood lead levels below 10 mg/dL have lower IQs, according to studies[8]. Children are susceptible to harmful consequences from even extremely low levels of lead exposure due to their rapid brain growth[9]. Although there is no safe threshold, the Centers for Disease Control (CDC) advises <5 mg/dL to prevent harm[10]. Child cognition is significantly impacted by maternal blood <6.5 mg/dL, and 24-month cognitive development is inversely associated with prenatal exposure <5 mg/dL[9]. Although some studies show the benefits of low prenatal lead exposure, the data are still mixed, necessitating additional study into the consequences of even slight prenatal lead exposure [11].

Turmeric may mitigate the damage that lead poisoning causes to the brain cortex of Wistar rats, according to studies[12]. Turmeric's primary component, curcumin, is mostly known for its health advantages. Turmeric has several positive properties, such as antioxidant activity and anti-inflammatory, anti-cancer, and anti-ulcer properties[13]. Hence, turmeric shows promise as a therapeutic agent against a number of chronic conditions, such as diabetes, cancer, allergies, rheumatoid arthritis, and Alzheimer's disease. Since turmeric has a low toxicity profile and has been used medicinally for a long time, there is growing interest in developing modern pharmaceuticals made from this spice to help treat a variety of illnesses[13].

Material and Methods

The study obtained ethical approval from the Ahmadu Bello University Committee on Animal Care and Use, with the approval number ABUCAUC/2022/049, ensuring the research was carried out in agreement with institutional procedures and regulations for the use and care of animals.

Plant extraction

The n-butanol fraction of *Curcuma longa* was prepared in Faculty of Pharmaceutical Sciences in the Department of Pharmacognosy and Drug Development, Ahmadu Bello University, Zaria. The rhizome of *Curcuma longa* was collected, cut into pieces, sun-dried, and powdered using a laboratory mortar and pestle. The powdered rhizome was macerated in ethanol for 36 hours, with occasional shaking. The resultant mixture was then filtered, and the filtered liquid was carefully evaporated to complete dryness using a water bath maintained at a temperature of 55±5 degrees Celsius. The ethanol extract was then partitioned using n-butanol under the same conditions. The n-butanol fraction, a dark-brown gummy exudate, was obtained with a yield of 5.68% and was kept in the refrigerator pending experimentation. These procedures were performed as depicted by Bulus et al. [14].

Determination of estrous cycle and pregnancy

The Wistar rats' estrous cycle was monitored using the vaginal smear/cytology method, as described by Ajayi et al. [15]. Every day vaginal lavages with normal saline were used to determine each female rat's estrous cycle stage under a light microscope. During the pro-estrous stage, marked by the presence of epithelial cells, and the estrous stage, marked by the presence of cornified cells, the female rats were retained in cages with sexually active male rats of the same strain. Sperm presence in a vaginal smear was used to check pregnancy or by the use of a vaginal plug [15].

Experimental design

Twenty (20) pregnant Wistar rats were alienated into five groups (Group I-V), n= 4; Group I (control) was given 2 ml of distilled water; Group II was given 20%/kg body weight of the LD_{50} of lead acetate (Hamza *et al*., 2017); group III were administered 100mg/kg Vitamin C + 20%mg/kg Pb; group IV were given 15% LD_{50} BFCl + 20% mg/kg Pb; group V were administered 30% LD_{50} BFCl + 20% mg/kg Pb. All dosing was carried out through the oral route and done one time daily on gestation days 6-21 (14 days) which are the critical developmental days of the frontal cortex. Some of the pups were sacrificed on postnatal day (PD1) while others were kept for behavioral analysis (PND 4-7).

Cliff avoidance reflex

The study assessed reflex and neuromotor growth in the rat pups using the method described by Olopade and Shokunbi[16]. The front paws, digits, and nose of each pup were placed on the edge of a stage that was elevated one meter from the ground beginning on postnatal days (PND) 4 and 7. With a maximum time of 40 seconds, the amount of time the pup needed to remove its nose and paws from the precipice was measured in seconds. A 40-second lag was noted if the puppy was unable to turn away from the cliff. As stated by Dubovicky et al.[17], it was also noted if the animal was capable of completing the task or not.

Animal Euthanization

On postnatal day 1 (PND1), a subset of pups (n=8) from each group were anesthetized using chloroform inhalation and then decapitated. For four of these pups from each group, the entire head was fixed in 10% formal saline for 48 hours to be used for histological studies. For the remaining four pups per group, a midsagittal incision was made to open the skull and harvest the brains. These brains were then homogenized in phosphate buffer for the analysis of oxidative stress biomarkers. The brain homogenates were collected in sample bottles, placed on ice blocks, and refrigerated for further biochemical studies. All animal sacrifices were performed in the Human Anatomy Department (Neuroscience laboratory), Ahmadu Bello University, Zaria.

Biochemical analysis

After centrifuging the homogenized brain samples, small portion of the supernatant were taken out for biochemical analysis to evaluate biomarkers of oxidative stress, such as the level of lipid peroxide (malondialdehyde, MDA), the antioxidant enzymatic activity of catalase (CAT), and glutathione (GSH), and superoxide dismutase (SOD). The Department of Human Anatomy at Ahmadu Bello University in Zaria conducted these investigations. Using ELISA kits from WKEA Med Supplies Corp., China, the concentrations of MDA and the activity of SOD, CAT, and GSH were assessed in the samples by the methodology described by Okey and Ayo[18].

Histochemical and Histological studies

The fixed heads of the pups were removed, and a midsagittal incision was made to open the skulls and harvest the brains. The fixed brains were then taken to the Histology Unit, Anatomy Department at Ahmadu Bello University, Zaria, for tissue processing and staining. Hematoxylin and Eosin staining was carried out using the methods described by Drury et al.[19], while Creysl Fast Violet staining was conducted following the method of Carson[20]. All these histological procedures were performed in the Faculty of Basic Medical Sciences of Human Anatomy Department, Ahmadu Bello University, Zaria.

Quantification of Nissl substance distribution

The staining intensity of the Creysl Fast Violet (CFV)-stained micrographs (digital microscopic images) was measured using a computer running Image J, an image analysis software from the National Institutes of Health (NIH) in the United States, by the manufacturer's instructions[21]. To limit any bias due to non-identical image quality, such as differences in image acquisition settings and exposure times, the Image J region of interest (ROI) manager tool was employed to analyze specific areas of the micrographs[22,23]. The modal gray data for three ROIs were gotten, and the means were calculated and examined [21,24].

Data analysis

The data obtained were stated as mean ± standard error of the mean (SEM). To analyze the differences between and within the groups, an analysis of variance (ANOVA) was performed, afterward the Tukey post hoc test. Data of $p<0.05$ were deemed statistically substantial. The data analysis was done using the graph pad prism software.

Results

Cliff avoidance reflex

The comparison of the initial and final turning latency showed a substantial decrease ($p<0.05$) in the mean turning latency in Group IV (750 mg/kg BFCl + 120 mg/kg Pb), suggesting an improvement in the sensory-motor maturation (Figure 1A). When the final cliff avoidance test was compared across the groups, there was a notable rise ($p<0.05$) in the mean turning latency in Group II (120 mg/kg Pb) compared to the control group (2 ml/kg H2O), which indicated a delay in sensory-motor maturation (Figure 1B).

Biochemistry of antioxidant enzyme activity and lipid peroxide levels

The malondialdehyde (MDA) assay was used to estimate the lipid peroxidation levels, while the antioxidant enzymatic activity was assessed by assaying for superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) in the brain tissue. The results showed a substantial decrease ($p<0.05$) in the SOD levels across the groups when compared to the control (Figure 2B). Additionally, there was a notable decline ($p<0.05$) in the catalase level in Group II (120 mg/kg Pb), Group III (100 mg/kg vitamin C), and Group V (1500 mg/kg BFCl) in relation to the control group. Conversely, there was a significant increase ($p<0.05$) in the catalase level in the 750 mg/kg BFCl group when compared to the 120 mg/kg Pb group (Figure 2C). Furthermore, there was a outstanding decrease ($p<0.05$) in the GSH levels across the groups in relation to the control group (Figure 2D).

Haematoxylin and Eosin (H and E) stain features

Histological examination of the frontal cortex (layer III and layer V) of the Wistar rat pups in the control group (2 ml/kg of H2O) showed a nearly normal histoarchitecture (Figure 3A). In contrast, the frontal cortex of Group II exposed to lead (120 mg/kg) demonstrated pathological changes in layer III and layer V, such as pyknosis and cytoplasmic vacuolation (Figure 3B). The frontal cortex of Group III treated with 100 mg/kg vitamin C + 120 mg/kg Pb revealed mild distortions, including pyknosis and cytoplasmic vacuolation, in layer III and layer V (Figure 3C). The frontal cortex of Group IV treated with lead (120 mg/kg) and a low dose of BFCl (750 mg/kg) showed mild distortion of the cytoarchitecture in layer III and layer V (Figure 3D). Lastly, the frontal cortex of Group V treated with 1500 mg/kg BFCl + 120 mg/kg Pb exhibited mild distortion in the histoarchitecture of the layer III and layer V, such as pyknosis and cytoplasmic vacuolation (Figure 3E).

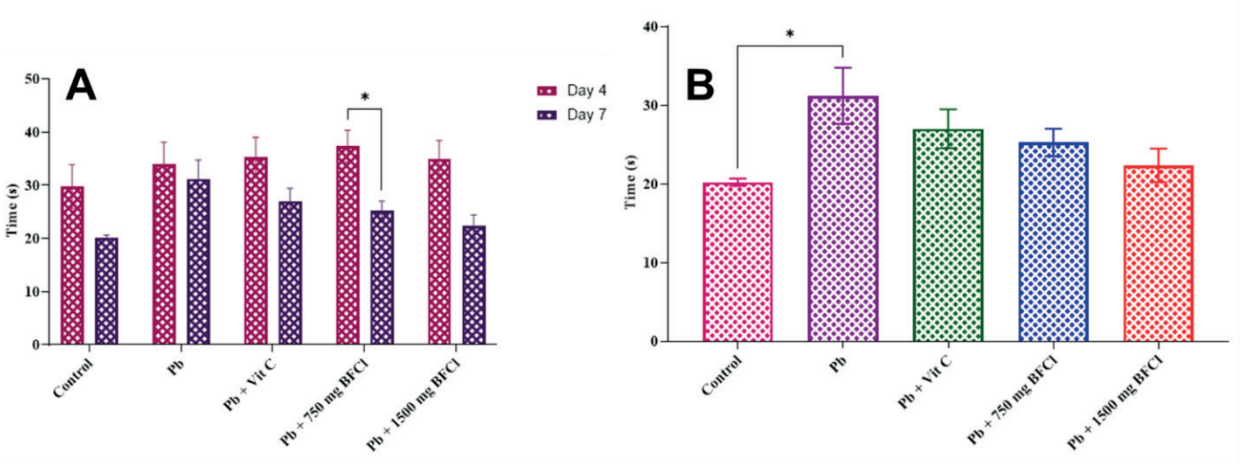

Figure 1: Cliff avoidance test. Effect of BFCl on (A) Initial and Final Cliff Avoidance test of the Wistar rat pups. (B) Final Cliff Avoidance test of the Wistar rat pups. n=7; mean ± SEM, One-way ANOVA, Tukey post hoc test, *=p<0.05 when compared to the control group. Pb= Lead acetate, Vit C= Vitamin C, BFCl=n-Butanol Fraction of *Curcuma longa*.

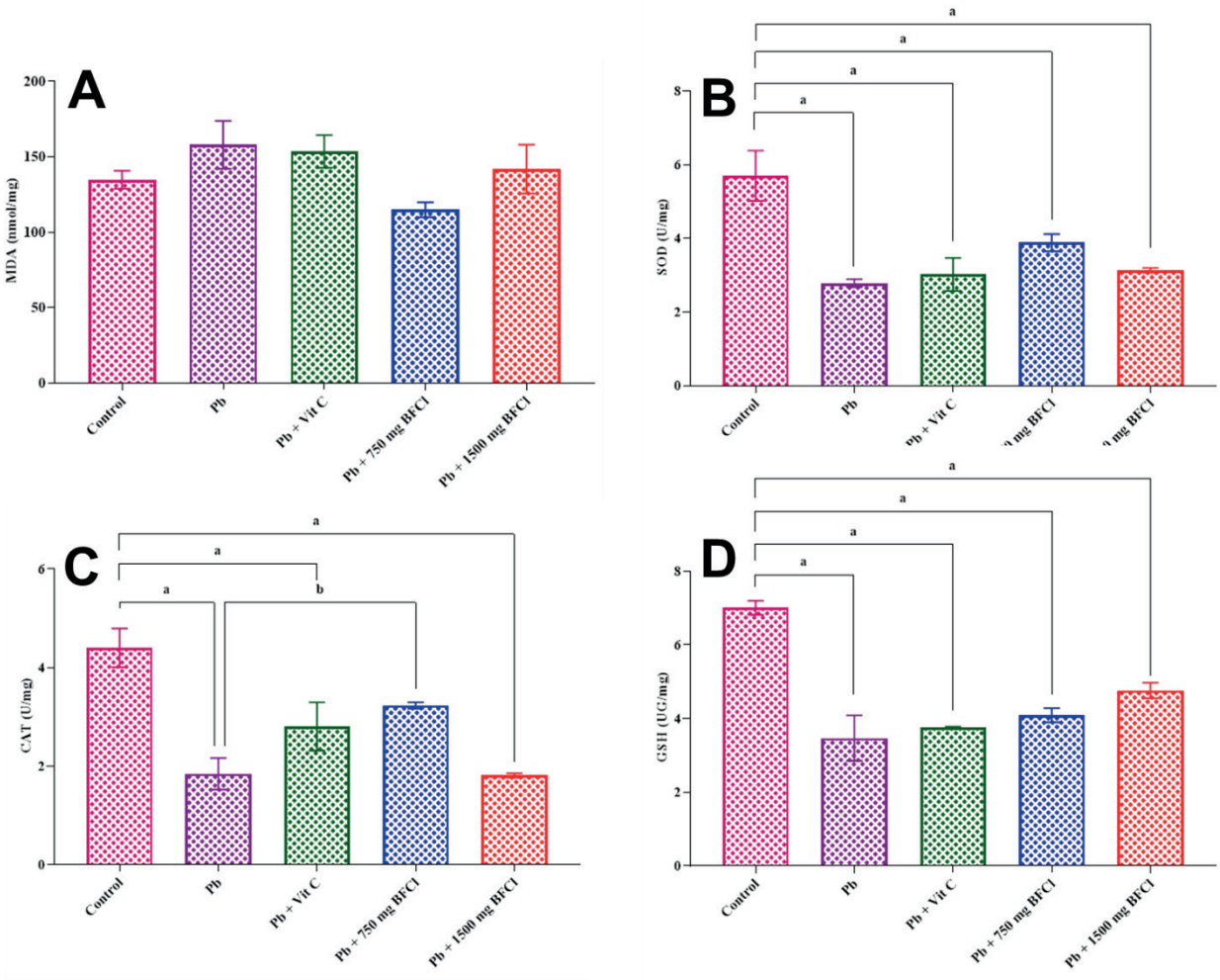

Figure 2: Bar charts of Oxidative stress parameters (A) MDA, (B) SOD, (C) CAT, and (D) GSH, of Wistar rats following administration of lead acetate and treatment with N-Butanol Fraction of Curcuma Longa prenatally. n=4; mean ± SEM, one-way ANOVA, Tukey post hoc test, a =p<0.05 when compared to the control group. Pb= Lead acetate, Vit C= Vitamin C, BFCl=n-Butanol Fraction of Curcuma longa.

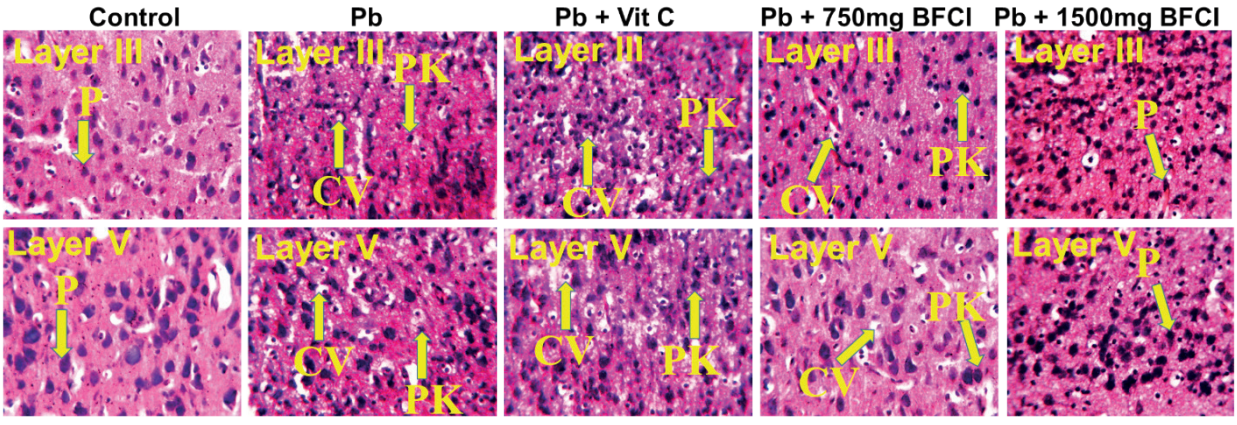

Figure 3: Composite micrographs of Wistar rat pups frontal cortex layer III and V of (A) Control group showing normal histoarchitecture. (B) Lead acetate group showing distortion in the histoarchitecture. (C) Group III showing distortion in the histoarchitecture. (D) Group IV showing mild distortion of the histoarchitecture. (E) Group V showing improvement in the histoarchitecture. H and E, Mg = x250. Pyramidal cells (P); Cytoplasmic Vacuolation (CV); Pyknosis (Pk). Pb= Lead acetate, Vit C= Vitamin C, BFCl=n-Butanol Fraction of Curcuma longa.

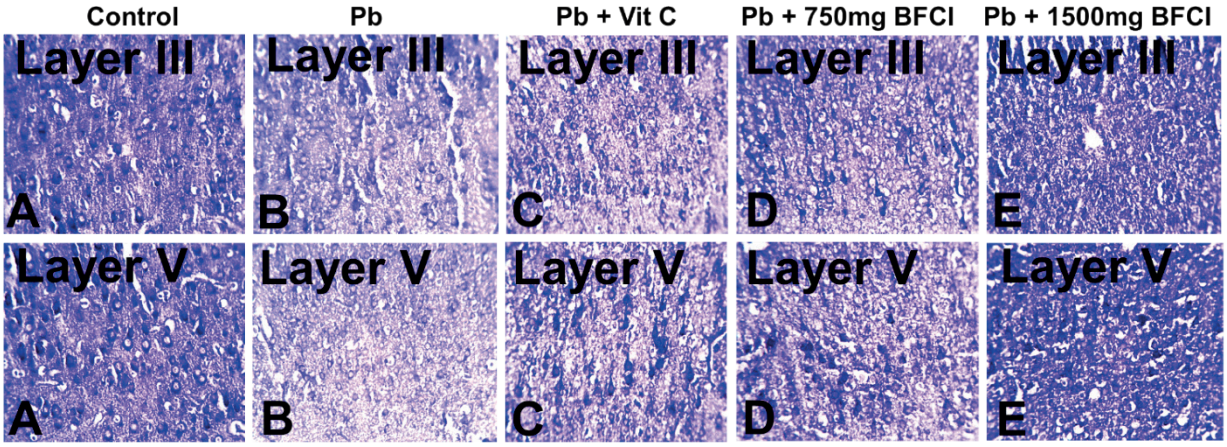

Figure 4: Photomicrograph of Wistar rat pup frontal cortex layer III and V stained by Cresyl violet, mag X250. (A) Control group (2ml/kg H20), showing staining intensity of Nissl bodies. (B) Group II (120 mg/kg Pb) showing reduced staining intensity of Nissl bodies. (C) Group III administered Vit C + 120 mg/kg Pb, showing reduced staining intensity of Nissl bodies. (D) Group IV (750 mg/kg BFCl + 120 mg/kg Pb) showing increase staining intensity of Nissl bodies. (E) Group IV (1500 mg/kg BFCl + 120 mg/kg Pb) showing increase staining intensity of Nissl bodies. Pb= Lead acetate, Vit C= Vitamin C, BFCl=n-Butanol Fraction of Curcuma longa.

Cresyl Fast Violet stain (CFV) features

The frontal cortex sections of the Wistar rat pups in the control group (2 mg/kg of distilled water) (Figure 4A), 750 mg/kg BFCl + 120 mg/kg Pb (Figure 4D), and 1500 mg/kg BFCl + 120 mg/kg Pb (Figure 4E) showed intense staining for Nissl substances in the frontal cortex, with distinctive appearance of the layer III and V regions. In contrast, Group II (120 mg/kg Pb) revealed reduced staining intensity of layer III and layer V when n relation to the control group and BFCl-treated groups, with numerous chromatolytic cells (Figure 4B). Examination of the frontal cortex of Group III (100 mg/kg vitamin C + 120 mg/kg Pb) revealed reduced staining intensity in layer III and layer V with few chromatolytic cells when compared to the BFCl-treated groups (Figure 4C).

Discussion

Studies have shown that the harm that lead poisoning does to the brain cortex of Wistar rats may be lessened by using turmeric[12]. Curcumin, the main ingredient in turmeric, is primarily responsible for its health benefits. Turmeric has several advantageous qualities, including anti-cancer, anti-inflammatory, and anti-ulcer properties in addition to its antioxidant activity[13]. Thus, turmeric has potential as a treatment for several chronic illnesses, including Alzheimer's disease, diabetes, cancer, allergies, and rheumatoid arthritis. Turmeric has been used medicinally for a long time and has a low toxicity profile, thus there is rising interest in creating contemporary medications manufactured from this spice to help treat a range of illnesses[13].

In this work, the cliff avoidance test, a measure of sensory-motor maturation in the growing frontal cortex was used to assess motor activities. Lead, one of such heavy metals that is identified to be harmful to the brain, especially in developing brains, and can induce lesions in the frontal lobes. The results of the cliff avoidance test displayed that prenatal dose of 750 mg/kg of the Curcuma longa extract (BFCl) enhanced the recorded mean turning latency, suggesting an enhancement in sensory-motor maturation. In contrast, prenatal exposure to 120 mg/kg of lead acetate destructively had an effect on the average turning expectancy, indicating a delay in sensory-motor maturation. These discoveries are consistent with the study of Usman et al. [26], who discovered similar effects of aluminum exposure during pregnancy on the cliff avoidance response in developing brains. Overall, the study demonstrated the potential neuroprotective and cognitive-enhancing effects of Curcuma longa, a plant rich in flavonoids, in animal models exposed to neurotoxicants during prenatal development. These results add to the rising body of research supporting the therapeutic potential of natural plant-based medicines to lessen the harmful effects of environmental contaminants on brain development and function.

This study also looked at the effects of *Curcuma longa* (BFCl) n-butanol fraction on oxidative stress and antioxidant enzyme activity in Wistar rat pup's frontal cortex treated with lead acetate during prenatal development. Mammalian cells are more sensitive to the redox status of both the extracellular and intracellular environments because they have developed in an oxidizing environment. Numerous cellular functions, including as signal transmission, metabolism, development, apoptosis, and detoxification systems, are influenced by the redox state of the intracellular environment. hydrogen peroxide (H2O2), hydroxyl radical (HO) and Superoxide (O2) are examples of reactive oxygen species (ROS) that have been shown to restrict the activity of a biological component.

The study found no striking variance in malondialdehyde (MDA) levels across the groups, but in the group receiving 750 mg/kg BFCl and 120 mg/kg lead acetate, the MDA level was reduced compared to the other groups. This decrease might be explained by the antioxidant qualities of *Curcuma longa*'s n-butanol fraction, which might have caused the antioxidants to be released to lessen the effects of lead acetate poisoning and lipid peroxidation in the frontal cortex. Additionally, a substantial ($p<0.05$) decline in SOD (superoxide dismutase) activity was noted in all treatment groups in relation to the control group. The discovered histological abnormalities in the frontal cortex and possible oxidative stress may have caused this decrease in SOD activity. Other possible causes include the harmful effects of lead acetate, rising oxidative activities, and lowering antioxidant activities. This outcome is consistent with studies conduct-

ed by Abu-Taweel et al.[12], who discovered that a SOD deficiency may worsen cerebral vascular hypertrophy and dysfunction. Interestingly, the group receiving 750 mg/kg BFCl and 120 mg/kg lead acetate showed an rise in SOD levels in relation to the other groups. Usman et al.[27] attributed this improvement to the antioxidant capabilities of BFCl, which may have assisted in reducing the activity of free radicals in the tissue.

The antioxidant enzyme level, catalase (CAT) was significantly reduced ($p<0.05$) in Groups II, III, and V compared to the control group. However, there was a significant increase ($p<0.05$) in CAT levels in Group IV, which received 750 mg/kg of the n-butanol fraction of Curcuma longa (BFCl) and 120 mg/kg of lead, compared to Group II, which was given only 120 mg/kg of lead. As indicated by the elevated CAT levels, a lower dose of BFCl was able to lessen the effects of lead toxicity, suggesting that the administration of BFCl is dose-dependent. This outcome is in line with the research done by Benammi et al. [28], who discovered that *Curcuma longa* is an effective neuroprotective agent against neurotoxicity triggered by lead.

Furthermore, the research found that the level of reduced glutathione (GSH) was strikingly lowered ($p<0.05$) in the treated groups in relation to the control group. It is well known that GSH's antioxidant qualities, which include directly scavenging radical species, depend on its thiol moiety[29]. This implies that the high level of GSH in the frontal cortex of the Wistar rat pups may have caused oxidative stress. Moreover, GSH is essential for cell proliferation [30].

Interestingly, the study found that the groups receiving 750 mg/kg BFCl + 120 mg/kg lead acetate and 1500 mg/kg BFCl + 120 mg/kg lead acetate were able to ameliorate the effect of lead acetate toxicity better than the group receiving 100 mg/kg vitamin C + 120 mg/kg lead acetate when in relation to the group receiving only 120 mg/kg lead acetate (Group II). This suggests that the n-butanol portion of *Curcuma longa* has higher scavenging activity than vitamin C, according to Bulus et al. [14]. Overall, the alterations in antioxidant enzyme activities and oxidative stress markers suggest that *Curcuma longa*'s n-butanol fraction possesses antioxidant properties that may be capable to mitigate the damaging effects of lead acetate exposure on the developing frontal brain.

Researches have shown that exposure to lead acetate causes histological abnormalities in the rat cerebral cortex, including an increase in apoptosis associated with oxidative stress[3]. However, a number of studies have shown that curcuma longa, often known as turmeric, has anti-inflammatory and memory-enhancing properties, suggesting that it may be helpful in the management and avoidance of neurodegenerative diseases[28]. Additionally, it has been shown that Curcuma longa reduces oxidative stress, inflammation, and apoptosis to protect the diabetic brain[31].

The present study used microscopic analysis with hematoxylin and eosin staining to examine the histoarchitecture of the frontal cortex in Wistar rat pups. The control group (2 ml/kg H2O) exhibited a nearly normal histological structure in layers III and V of the frontal cortex. In contrast, the group exposed to 120 mg/kg of lead acetate (Group II) showed pathological changes, such as neurodegenerative alterations like pyknosis and cytoplasmic vacuolation. Improvements in the histoarchitecture of the frontal cortex neuronal cells were observed in a dose-dependent manner in the groups that received vitamin C (100 mg/kg, Group III) and the n-butanol fraction of *Curcuma longa* (BFCl) at 750 mg/kg (Group IV) or 1500 mg/kg (Group V) in combination with 120 mg/kg of lead acetate. Previous studies that indicated exposure to lead acetate can alter the brain's histoarchitecture and have a deleterious effect on the brain's functional integrity [32, 33] are consistent with these findings. The antioxidant properties of BFCl have been the subject of numerous studies, which may explain the advantages shown in the groups that received it [14, 31].

Histochemical assessment of the frontal cortex using Cresyl fast violet stain revealed pathological changes, such as pyknosis, cytoplasmic vacuolation, and reduced staining intensity of Nissl bodies in the 120 mg/kg lead acetate group. Nissl bodies are a significant part of the cytoplasm of neurons and are thought to be a reliable sign of neurocyte damage[34]. The frontal cortex of Wistar rat pups treated with vitamin C and BFCl exhibited a dose-dependent rise in the staining intensity of Nissl bodies in layers III and V, indicating that BFCl had a neuroprotective effect against lead acetate-induced tissue damage. The above results have also been reported by earlier studies that examined the cerebral and cerebellar cortices of Wistar rats exposed to lead and discovered similar structures[35–37]. Anterograde and retrograde amnesia may be exacerbated by reduced neurotransmitter synthesis caused by Nissl body degeneration, which may impair impulse transmission to prefrontal cortex cells[3]. Niu et al.[34] also found that there was a striking reduction in Nissl body expression in the lead treatment group in relation to the control group in their study on the effects of lead and fluoride on adult rats' locomotor activity and Nissl body expression in their brains. Similar to this, Olatomide et al. [38] study on the influence of postnatal lead exposure on the growing hippocampal tissue of pups of Wistar rat exposed to lead acetate showed that the hippocampal tissue of exposed pups had changed cytoarchitecture and had less Nissl material staining than that of the control group.

Additionally, several studies have revealed varying degrees of alterations to the Nissl substance following the injection of lead[39.40]. These findings support the current investigation's findings about changes in Nissl body staining and neuronal degeneration associated with lead exposure.

Conclusion

The findings from this study disclosed that the *N-Butanol* Fraction of *Curcuma Longa* (Turmeric) was able to ameliorate lead acetate-induced altered sensory-motor activity, oxidative stress, and histopathological changes in the frontal cortex of Wistar rat pups.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

The study obtained ethical endorsement from the Ahmadu Bello University Committee on Animal Care and Use, with the approval number ABUCAUC/2022/049, ensuring the research was conducted in agreement with institutional procedures and regulations for the use and care of animals.

Conflict of interest:

There is no conflict of interest to declare.

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Author Contributions subject and rate

Isaiah Israel Bakenneso (30%): Data collection, analyses and design the research.

Sunday Abraham Musa (25%): Supervision and research organization.

Abubakar Addamu Sadeeq (25%): Supervision and research organization.

Ekpo Ubong Udeme (20%): Analyses and research organization.

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