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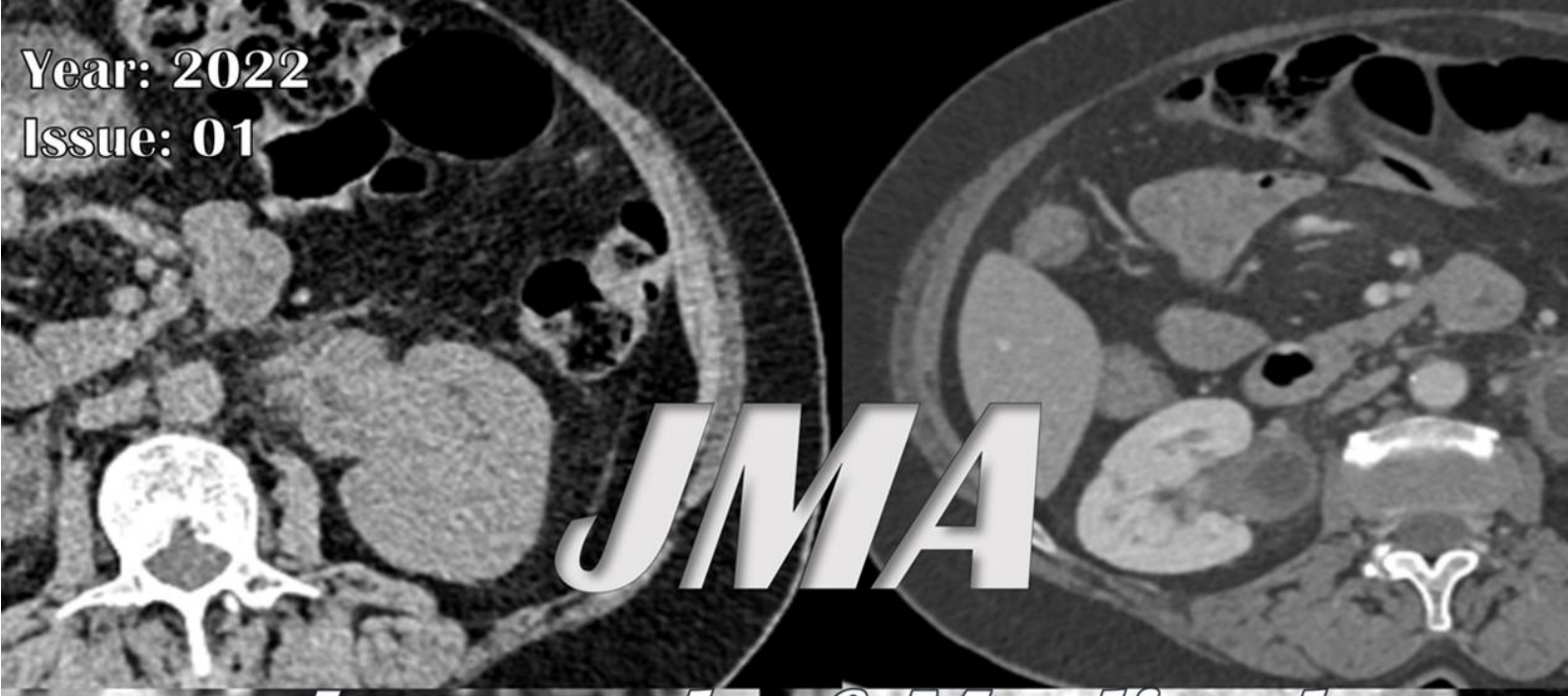

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JOURNAL OF MEDICAL ARCHIVES

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The most important criteria fo a manuscript to be accepted for publication are originality, high scientific quality, and citation potential. Manuscripts submitted for review must not have previously been presented or published in an electronic or printed medium. Manuscripts that have been submitted to another journal for evaluation and rejected for publication should be reported to the journal. Submission of previous reviewer reports will help to speed up the evaluation process. Manuscripts that have been presented at a meeting should include detailed information about the organization, such as the name, date, and location.

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Manuscripts submitted to Journal of Medical Archives will be peer-reviewed in a double-blind fashion. To ensure an unbiased evaluation process, each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields. The editorial board will appoint an external and independent editor to oversee the evaluation of manuscripts submitted by editors or members of the journal's editorial board. For all submissions, the Editor in Chief has the final say in the decision-making process.

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For experimental, clinical, and drug studies, as well as some case reports, the Ethics Committee must approve research protocols in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, https://www.wma.net/. If necessary, the authors will be asked to provide ethics committee reports or an equivalent official document. For manuscripts involving human experimental research, a statement demonstrating that written informed consent was obtained from patients and volunteers after a detailed explanation of the procedures that they may be subjected to should be included. In animal studies, the measures taken to prevent pain and suffering of the animals should be clearly stated. In the Materials and Methods section of the manuscript, include information on patient consent, the name of the ethics committee, and the ethics committee approval number. It is the authors' responsibility to safeguard the patients' anonymity.
For photographs that may reveal the patients' identities, signed releases from the patients or their legal representatives should be enclosed, and publication approval should be provided in the Materials and Methods section.

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Title page: All submissions should include a separate title page that includes the following information:
The full title of the manuscript, as well as a short title (running head) of no more than 50 characters, the author's name(s), affiliations, highest academic degree(s), and ORCID IDs (s), Grant information, as well as detailed information on other sources of assistance,
The corresponding author's name, address, phone number (including mobile phone number), and email address Individuals who contributed to the manuscript's preparation but did not meet the authorship criteria are acknowledged.
Abstract: Except for Letters to the Editor and Images of Interest, all submissions must include an abstract. Subheadings should be used in the abstract of Original Articles (Objective, Materials and Methods, Results, and Conclusion). Please see Table 1 for word count requirements.
Keywords: At the end of the abstract, each submission must include a minimum of three and a maximum of six keywords for subject indexing. The keywords should be listed in their entirety, with no abbreviations. The keywords should be chosen from the National Library of Medicine's database of Medical Subject Headings https://meshb.nlm.nih.gov/search.
Manuscript Types
Original Article: This is the most important type of article because it contains original research and provides new information. The main text of original articles should be organized with subheadings such as Introduction, Materials and Methods, Results, and Discussion. Please see Table 1 for the Original Article limitations.
Statistical analysis is usually required to back up conclusions. Statistical analyses must be carried out in accordance with international standards for statistical reporting (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Under the Materials and Methods section, information on statistical analyses should be provided in a separate subheading, and the statistical software used during the process should be specified.
Units should be prepared using the International System of Units (SI).
Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or a high reputation in the topic of the journal's published research article. The journal selects and invites authors to provide such comments. Tables, figures, images, and other media are not included, nor are the abstract, keywords, and tables.
Review Articles: Reviews prepared by authors with extensive knowledge in a specific field and whose scientific background has resulted in a large number of publications with a high citation potential are encouraged. The journal may even invite these authors. Reviews should describe, discuss, and evaluate the current state of knowledge on a topic in clinical practice, and they should serve as a guide for future research. Review articles' main text should begin with an Introduction section and end with a Conclusion section. The remaining sections can be titled in a way that is relevant to the essence of the research. Please see Table 1 for the restrictions on Review Articles.
Case Reports: There is limited space in the journal for case reports, and reports on rare cases or conditions that pose diagnostic and treatment challenges, those offering new therapies or revealing knowledge not found in the literature, and interesting and educational case reports are accepted for publication. Subheadings in the text should include Introduction, Case Presentation, and Discussion. Please see Table 1 for a list of the limitations for Case Reports.
Letters to the Editor: This type of manuscript discusses important aspects of a previously published article that were overlooked or were missing. Articles on subjects within the scope of the journal that may be of interest to readers, particularly educational cases, may also be submitted in the form of a "Letter to the Editor." Readers can also submit "Letters to the Editor" with their thoughts on the published manuscripts. Abstracts, Keywords, Tables, Figures, Images, and other media should be avoided. The text should be free of structure. The manuscript being discussed must be properly cited within this manuscript.
Image of Interest: This type of submission should include an eye-catching image that will both challenge and inform readers, as well as contribute to their education. High-quality clinical images, radiology results, and surgical images are acceptable as submissions. Please see Table 1 for the restrictions on Images of Interest.
Table 1 shows the restrictions for each type of manuscript.

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	35	6	5 or total of 10 images
Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1000	200	15	No tables	4 or total of 8 images
Letter to the Editor	500	No abstract	5	No tables	No media
Image of Interest	500	No abstract	5	No tables	2 or total of 4 images

Tables
Tables should be included in the main document, following the reference list, and numbered consecutively in the order they are referred to in the main text. Above the tables, a descriptive title must be placed. Footnotes should be used to define abbreviations used in the tables (even if they are defined within the main text). Tables should be created using the word processing software's "insert table" command and should be clearly laid out for easy reading. The data presented in the tables should not be a repetition of the data presented in the main text, but rather should supplement it.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted through the submission system as separate files (in TIFF or JPEG format). The files should not be embedded in the main document or in a Word document. If a figure has subunits, the subunits should not be merged to form a single image. Each subunit should be submitted through the submission system separately. Image labels (a, b, c, etc.) should not be used to indicate figure subunits. To support figure legends, thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images. The figures, like the rest of the submission, should be blind. Any information in the images that could be used to identify an individual or institution should be obscured. Each submitted image should have a minimum resolution of 300 DPI. All submitted figures should be clear in resolution and large in size (minimum dimensions: 100 100 mm) to avoid delays in the evaluation process. The legends for the figures should be listed at the end of the main document.

DIGITAL IMAGE GUIDE

Journal of Medical Archives requires that all digital files be prepared in accordance with the criteria outlined below.

A. Checklist for Image Preparation. Please use the checklist below to ensure that you have met the requirements for electronic image preparation. Throughout the guide, each category is elaborated on.

Grayscale images are created from black-and-white images (not black and white).

RGB color mode is used to save photographic images (not CMYK or indexed color).

The files are submitted in their native TIFF or EPS format, and they are not embedded in another program such as Microsoft Word, PowerPoint, or Excel.

Charts and illustrations created in Microsoft Office (Word, PowerPoint, and Excel) are submitted in native format and do not include embedded images.

SPSS, SigmaPlot, and ChemDraw charts are submitted as EPS images.

All graphics are sized to 100% of their print dimensions, eliminating the need for scaling (3.2" wide for 1-column figures and 6.4" wide for 2-column figures).

Images were scanned in accordance with our scanning guidelines.

Files are named in accordance with our recommended naming conventions.

B. Color It is critical to scan and save digital images in the correct color space when preparing them for publication.

1.Photographic images. Photographs, angiograms, echocardiograms, and other images should be scanned and saved in RGB color mode, even if they will be printed in grayscale. (The images will be converted to grayscale or CMYK color modes by the journal's compositors.). Color printing is expensive and not always necessary. If an image requires color for clarity, please notify the Journal editors.

2.Line art. Line drawings, charts, graphs, and ECG and EEG tracings, as well as other black-and-white images, should be scanned and saved in grayscale mode (not black-and white or color). (For SPSS charts, see Section C.2 on creating EPS file formats.) Refer to Section C.3.) for charts and graphs created in Microsoft Office.

3.Avoid ICC. ProfilesThere should be no ICC profiles in images.

C. File Format. Electronic images should only be submitted in TIFF or EPS format. See the guidelines for submitting artwork created in Microsoft Office programs (Word, PowerPoint, Excel).

1.TIFF (Tagged Image File Format). For photo-graphic images, TIFF is recommended. When preparing TIFF images, make sure to follow our scanning guidelines for the correct resolution. Please keep in mind that the Journal only accepts TIFF images that have been compressed with LZW; selecting this option will result in smaller files. TIFFs are created in most software programs by selecting File/Save as... or Export/TIFF or TIF. Consult your software's Help menu for more information.

2.EPS (Encapsulated Postscript). Line art, charts, and illustrations created with professional drawing programs such as Adobe Illustrator, SPSS, ChemDraw, CorelDraw, Sigma-Plot, and others should be saved in EPS format. When submitting EPS files for publication, keep the following guidelines in mind:

Text can be converted to outlines or fonts can be included/embedded. Only use Journal-approved fonts.

Any layers should be flattened.

Use line weights that are greater than 0.5 point.

Include an 8-bit preview/header with a 72-dpi resolution.

Color images should be saved in RGB mode.

An EPS file is created in most drawing programs by selecting File/Save as... or Export/EPS. Consult your software's Help menu for more information.

3.Microsoft Office (Word, Excel, PowerPoint). Charts and illustrations made in any Microsoft Office program are acceptable. Microsoft Office files with embedded images should not be submitted. Use the following guidelines when creating charts and illustrations:

Work in black and white rather than color.

Use black, white, and shades of gray for fill color instead of patterns.

Avoid using three-dimensional charts.

Only use Journal-approved fonts.

Use line weights that are greater than 0.5 point.

Submit the grouped image so that the datasheet can be accessed by the Journal compositors.

4.AVOID THE FOLLOWING:

Using graphics downloaded or saved from Web pages to submit.

Images with low resolution, regardless of how they appear on screen.

GIF files are being submitted. GIF files should never be used for publication.

Pre-printed photograph scanning (already published halftones). The printing process causes distortion in the photograph, which will be transferred to the scan.

TIFF generation within a Microsoft Office document.

Program for Scanning This proprietary program modifies the image's formatting so that it cannot be opened in our image evaluation program.

D.Resolution and Scanning

1.To ensure print quality, images must be scanned at the appropriate resolution. To select the proper scanning resolution, follow the guidelines below. Images scanned at a lower resolution will be rejected.

Photographic images with no text or arrows should be 300 dpi/ppi.

600 dpi/ppi for photographs with text or arrows

Line art in black and white: 1200 dpi/ppi
a.Scanning photographic images that do not contain text or arrows
Scanning in RGB mode
Scanning resolution should be 300 dpi/ppi.
Choose a target width of 7.5 cm for single-column figures and 15.5 cm for two-column figures.
Crop images as closely as possible; do not scan the margins.
Use the Journal of Medical Archives naming convention, save as a TIFF, and compress with LZW.
b.Photographic images with text or arrows are scanned.
Scanning in RGB mode
600 dpi/ppi scan (even if text or labels will be added after the image is scanned).
Choose a target width of 7.5 cm for single-column figures or 15.5 cm for double-column figures.
Crop images as closely as possible; do not scan the margins.
Use an approved font if you need to assassinate labels. You may be asked for an unlabeled version if the labels are pixilated.
Use the Journal of Medical Archives naming convention, save as a TIFF, and compress with LZW.
c.Scanning line art in black and White
Scanning in grayscale mode is recommended.
1200 dpi/ppi scan
Choose a target width of 7.5 cm" for single-column figures and 15.5 cm" for double-column figures. Images should be cropped closely; do not scan the margins.
Use an approved font if you need to add labels. You may be asked for an unlabeled version if the labels are pixilated.
Use the Journal of Medical Archives naming convention, save as a TIFF, and compress with LZW.
2.Scanning originals with widths less than the target width
Select the appropriate color space for the photograph or line art.
Determine the best solution. If an image's width is less than the target width, the scanning resolution must be increased to compensate. Divide the actual width by the target width to increase the resolution (either 7.5 cm or 15.5 cm). Round up to the nearest hundred by multiplying the answer by the target dpi. The scanning dpi will be determined by the outcome. Consider the following scenario: If an image is 2.4" wide and needs to be 300 dpi/ppi at 3", then 3 divided by 2.4 equals 1.251.25, 1.25 times 300 equals 375, and 400 is rounded up. As a result, if the 2.4" image is scanned at 400 dpi/ppi, the Journal can correctly convert the image to 3" wide at 300 dpi.
E. Naming Files
1. Naming convention For electronic images, please use the following naming convention:
Last name of the author + figure number file type
Okur1.eps or Okur1A.tif are two examples.
2.Revising images. When you revise an image and resubmit it to the Journal, you must include a version number to ensure that it is re-evaluated.
Smith1.eps, for example, would be saved as Smith1_ v2.eps the next time.
Allow the software program to add the file format extension at all times. Files that lack an extension will be rejected. You must use a software program to change a file format extension; renaming a file extension does not properly convert a file. For example, simply renaming a JPG file as TIFF does not convert it to a TIFF image. Opening a JPG file in Photoshop (or a comparable software program) and saving as a TIFF converts the file correctly.
Note: Using the Rename command, you can safely change the author's last name + figure number (i.e., anything before the "dot-file format" portion).
F. Approved Fonts.
For text in la- bels, graphs, and charts, please use one of the following fonts:
Adobe Garamond
Arial
Helvetica
Symbol
Times New Roman
Univers LT
G. Labels
1.Avoid using figure labels (A, B, C, etc.) on digital images; instead, include the letter in the figure file name (for example, Smith2B.tif)
2.If the images are part of an A, B, or C series, scan and submit each image individually.
H. How to Submit Images. During the initial submission, please submit your digital files through the journal's online manuscript system.
All acronyms and abbreviations used in the manuscript, both in the abstract and in the main text, should be defined at the outset. Following the definition, the abbreviation should be provided in parentheses.
When a drug, product, hardware, or software program is mentioned in the main text, product information, including the name of the product, the manufacturer, and the city and country of the company (including the state if in the United States), should be provided in parentheses in the following format: "General Electric, Milwaukee, WI, USA" "Discovery St PET/CT scanner"
All references, tables, and figures should be referred to within the main text and numbered consecutively in the order they are mentioned.
Limitations, drawbacks, and flaws of original articles should be addressed in the Discussion section before the conclusion paragraph.

References

The APA style must be used for both in-text citations and references.
When citing publications, the most recent and up-to-date publications should be used. The accuracy of references is the responsibility of the authors. The DOI number should be provided if an advance-of-print publication is cited. Journal titles should be abbreviated in accordance with the Index Medicus/MEDLINE/PubMed journal abbreviations. All authors should be listed when there are six or fewer authors. If there are more than six authors, the first six should be listed, followed by "et al." References should be cited in the main text of the manuscript using Arabic numbers in parentheses. The following examples show reference styles for various types of publications.
Journal Article: Aydin, S., Fatihoglu, E., & Kacar, M. (2019). Intrathyroidal ectopic thymus tissue: a diagnostic challenge. La radiologia medica, 124(6), 505-509.
Book Section: Baker, F. M., & Lightfoot, O. B. (1993). Psychiatric care of ethnic elders. In A. C. Gaw (Ed.), Culture, ethnicity, and mental illness (pp. 517-552). Washington, DC: American Psychiatric Press.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.
Conference Proceedings: Bowden, F.J., & Fairley, C.K. (1996, June). Endemic STDs in the Northern Territory: Estimations of effective rates of partner change. Paper presented at the Scientific Meeting of the Royal Australian College of Physicians, Darwin.
Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Naranjo Arévalo, A. M. (2021). Clinical utility of the pediatric scale for the definitive diagnosis of appendicitis vs mesenteric adenitis. Riobamba, 2019-2020 (Bachelor's thesis, Universidad Nacional de Chimborazo).
Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ https://www.cdc.gov/ncidodlElD/cid.htm

REVISIONS

When submitting a revised version of a paper, the author must include a detailed "Response to the Reviewers" that details how each issue raised by the reviewers has been addressed and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made), as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days of the decision letter's date. If the revised manuscript is not submitted within the time frame specified, the revision option may be canceled. If the submitting author(s) believe that more time is needed, they should request it before the initial 30-day period expires.
Professional language editors copy-edit accepted manuscripts for grammar, punctuation, and format. When a manuscript's publication process is completed, it is published online on the journal's website as an ahead-of-print publication before it is included in the journal's scheduled issue. The corresponding author is sent a PDF proof of the accepted manuscript, and their publication approval is requested within two days of receiving the proof.

JOURNAL OF MEDICAL ARCHIVES

Original Articles:

Review Article

JOURNAL OF MEDICAL ARCHIVES

DRUGS USED IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Abstract:

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, attention deficit, and impulsivity. Today, methylphenidate (MPH), which is the first choice as a stimulant in the treatment of ADHD, was first produced in 1944 and introduced to the market under the name Ritalin in 1954. ADHD heritability is estimated to be around 70–80%. ADHD is thought to be associated with dysfunctions of neurotransmitter systems in the brain. Among these neurotransmitters, dopamine and noradrenaline are prominent. The left prefrontal cortex is frequently affected in ADHD. Studies are showing that the brain volumes of children with ADHD are lower in all regions compared to the control group. Psychostimulants, including MPH and amphetamine, are first-line pharmacotherapy for patients with ADHD. Alpha-2 agonists such as clonidine and guanfacine can be used to treat ADHD in children and adolescents. Atomoxetine and alpha-2 receptor agonists (eg guanfacine and clonidine) are effective but less so than psychostimulants. Other medications used for ADHD include antidepressants (eg, bupropion, trazodone), atypical antipsychotics (eg, risperidone, aripiprazole), and mood stabilizers (eg, carbamazepine). New drugs with new mechanisms of action are needed, as a significant proportion of patients treated with currently approved drugs do not respond and/or show insufficient efficacy.

Keywords: Attention Deficit Hyperactivity Disorder, Methylphenidate, New Drugs

INTRODUCTION

a) Up-To-Date Information

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, attention deficit, and impulsivity. It is observed more frequently in boys than in girls (1). It is estimated that the percentage of ADHD in childhood is 5% worldwide (2). The disease may continue into adulthood.

Behavioral and executive problems, anxiety problems, depression, autism spectrum disease, Tourette Syndrome, learning disorder, and eating disorders can accompany ADHD in children with ADHD (3).

Bipolar disorder, major depressive disorder/dysthymia, anxiety disorder, and personality disorders can be seen in adults (4).

b) History

In 1775, German physician Melchior Adam Weikard published a book describing attention disorders (5).

Today, methylphenidate (MPH), which is the first choice as a stimulant in the treatment of ADHD, was first produced in 1944 (6) and introduced to the market under the name Ritalin in 1954 (7).

PATHOGENESIS OF ADHD

a) Genetic Factors

ADHD heritability is estimated to be around 70–80% (8, 9). Children with a sibling with ADHD are more likely to develop ADHD than other children. It is thought that genetic factors play a role in determining whether the disease will continue into adulthood (10).

b) Environmental Factors

Alcohol use during pregnancy, very premature birth, low birth weight, child neglect, abuse, social exclusion and deprivation, certain infections during pregnancy, birth and early childhood, such as measles, chickenpox, encephalitis, varicella zoster, measles and enterovirus, exposure to certain toxic substances in childhood, traumatic brain injury are among environmental factors leading to the development of ADHD (11).

Emotional abuse from families and the poor education system could take a role in the development of the disease apart from the personal development of children (12).

In recent years, studies have been carried out on the relationship between intestinal microflora and ADHD (13, 14).

c) ADHD Pathophysiology

ADHD is thought to be associated with dysfunctions of neurotransmitter systems in the brain. Among these neurotransmitters, dopamine and noradrenaline are prominent.

The dopamine and noradrenaline pathways are associated with several cognitive pathways (15).

d) Major Changes Observed in Brain Structure in ADHD

The left prefrontal cortex is frequently affected in ADHD. Children with ADHD have a marked overall volume reduction in certain brain regions.

Magnetic Resonance Imagining (MRI) is the most commonly used method to measure brain structures. Studies have reported that there can be macro and microstructural pathophysiological changes in patients with ADHD. Studies are showing that the brain volumes of children with ADHD are lower in all regions compared to the control group (16, 17).

DRUGS

Catecholamines may have a role in the control of attention at the level of the cerebral cortex. Various stimulant medications have been used in the treatment of attention deficit hyperactivity disorder (ADHD) and are particularly indicated for moderate to severe cases. There are different drugs used in ADHD (18).

Psychostimulants, including MPH (MPH) and amphetamine, are first-line pharmacotherapy for patients with ADHD. MPH actions include dopamine and norepinephrine transporter inhibition, agonist activity at the serotonin type 1A receptor, and redistribution of vesicular monoamine transporter 2. MPH is effective in children with ADHD and is the most widely used treatment agent (19). The effects of amphetamine include inhibition of dopamine and norepinephrine transporter, vesicular monoamine transporter 2, and monoamine oxidase activity. Both MPH and amphetamine are generally associated with an acceptable range of side effects as they are predominantly mild and/or transient.

Common side effects include decreased appetite, sleep disturbances, increased blood pressure and heart rate, headaches, irritability, and stomach pain (20).

Atomoxetine is a selective inhibitor of the norepinephrine reuptake transporter. Therefore, its mechanism of action is mediated by the potentiation of norepinephrine levels at noradrenergic synapses. It is used in the treatment of ADHD. Atomoxetine has a United States (US) boxed warning for suicidal ideation in children and adolescents. An analysis of multiple studies revealed increased suicidal ideation in children and adolescents treated with atomoxetine (0.4%) compared with those treated with placebo (0%). Children and adolescents who start using atomoxetine should be closely monitored for suicidal ideation and changes in behavior. Clinicians should always perform a risk-benefit analysis before prescribing atomoxetine (21).

Alpha-2 agonists such as clonidine and guanfacine can be used to treat ADHD in children and adolescents. The reduced firing of presynaptic neurons that release norepinephrine to the prefrontal cortex improves the impulsive and hyperactive behavior seen in attention-deficit/hyperactivity disorder (22). Sedation is a common side effect of both clonidine and guanfacine (23). Atomoxetine and alpha-2 receptor agonists (eg, guanfacine and clonidine) are effective but less so than psychostimulants (24).

Other medications used for ADHD include antidepressants (eg, bupropion, trazodone), atypical antipsychotics (eg, risperidone, aripiprazole), and mood stabilizers (eg, carbamazepine). These drugs are not approved by the US Food and Drug Administration for the treatment of ADHD and are used off-label when psychostimulants, atomoxetine or alpha-2 receptor agonists are ineffective or for the treatment of comorbid conditions (25).

NEW PHARMACOLOGICAL APPROACHES TO ADHD

Due to the complex nature of ADHD, all relevant factors, such as the severity of symptoms, presence of comorbidities, which periods of the day should relieve symptoms, and the patient's preferences, should be considered when selecting the appropriate pharmacological treatment agent (26). New drugs with new mechanisms of action are needed, as a significant proportion of patients treated with currently approved drugs do not respond and/or show insufficient efficacy (27).

a) Serdexmethylphenidate (SDX)

MPH is a racemic mixture of two enantiomers, dexmethylphenidate (d-MPH) and 1-methylphenidate (1-MPH); data from animal models and other studies have shown that the d-MPH isomer provides the main pharmacological contribution in the treatment of ADHD (28). SDX is a prodrug in that it is pharmacologically inactive until converted to an active form primarily in the lower gastrointestinal tract (28). d-MPH is the main active metabolite of SDX and the precise mechanism of this conversion has not yet been clarified (29). In a study, SDX was shown to serve as a d-MPH prodrug with lower abuse potential than d-MPH when administered via the most common stimulant abuse routes (30).

b) Viloxazine

Viloxazine (QELBREE™), a norepinephrine reuptake inhibitor, is being developed by Supernus Pharmaceuticals for the treatment of ADHD. This is a new extended-release (ER) formulation of an older pharmacological agent for which extensive safety data are available (31).

Viloxazine improved the severity of ADHD symptoms in children aged 6-11 years with ADHD when administered orally at low doses in a randomized, double-blind, placebo-controlled, multicenter,

phase III study (32). The most common adverse reactions in viloxazine recipients (occurring in ≥ 2% and at a rate greater than in placebo recipients) were somnolence, headache, upper respiratory tract infection, decreased appetite, fatigue, abdominal pain, nausea, vomiting, insomnia, irritability and pyrexia. Also as a noradrenergic drug, it can cause manic or mixed episodes in patients with bipolar disorder. Before initiating viloxazine therapy, patients should be screened for the risk of bipolar disorder (33).

c) Centanafadine

Centanafadine has been reported to be a novel reuptake inhibitor of serotonin, norepinephrine, and dopamine, leading to stimulation of norepinephrine and dopamine, and therefore potentially useful in the treatment of ADHD (34).

For adults with ADHD in phase 3 randomized controlled trials, centanafadine has demonstrated efficacy in relieving symptoms in as little as 1 week. The relatively quick onset of efficacy should make centanafadine a valuable nonstimulant tool for the treatment of ADHD. Centanafadine is safe and well tolerated, with a limited abuse potential across the clinical trial program, including in phase 3 randomized controlled trials (35).

CONCLUSION

ADHD is a disease that varies in terms of symptoms and although it has been known for years, its pathophysiology is not fully understood. Therefore, difficulties are encountered in the treatment of the disease. Since dysfunctions in neurotransmitter systems, especially dopamine and noradrenaline, are thought to be the primary cause in ADHD pathophysiology, neurotransmitter systems are especially targeted in its treatment. Although the role of MPH, which is used as the first choice in the treatment of ADHD, in the treatment of the disease is not known, it is aimed to treat the disease with its effects on the dopamine and noradrenaline systems. Due to the undesirable effects, potential for addiction and limited effectiveness of MPH, research on alternative treatment methods continues. Serdexmethylphenidate, Viloxazine and Centanafadine, which have come to the fore for this purpose, have also targeted dopamine, noradrenaline and serotonin systems. Although it has been determined in clinical studies that these new drugs can cause regression on ADHD symptoms and show rapid efficacy, undesirable effects have also been observed in the treatment with these drugs, and the data we have about these drugs are limited. Undoubtedly, further studies is needed on the subject. With different drugs and different approaches to treatment, the way to find more effective treatment methods and to clarify the pathophysiology of the disease will be opened.

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