The Role of Pharmacotherapy and Managed Care Pharmacy Interventions in the Treatment of ADHD

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Abstract

"Attention-deficit/hyperactivity disorder (ADHD)", which is one of most rampant neuro-developmental diseases, exerts a considerable influence on the relationships that people have with one another. In last 2 decades, there exists a significant increase in the quantity of clinical research and drugs those that have occurred licensed to address the symptoms of "attention-deficit hyperactivity disorder (ADHD)". Clinical research was conducted between the years 2001 and 2019 to study a variety of "pharmacological & non-pharmacological methods to the treatment of attention deficit hyperactivity disorder (ADHD)". Present research presents a quantitative summary of "the role of pharmacotherapy and managed care pharmacy intrusions in the treatment of ADHD" and variety of tactics through its analytical investigations. On clinicaltrial.gov, the researcher manually searched for the phrase "ADHD" and used the results of 695 interventional studies to compile the trial data that was used for this research. Alternatives to pharmaceutical treatments were investigated in almost eighty per cent of the research. These alternatives included a variety of behavioral intrusions, as of hypnotherapy, training at social skills, alterations to physical & sleep activity as well as deliberation. For the treatment of "attention-deficit hyperactivity disorder (ADHD)", there an increasing interest at devices exists, adjuvant, and alternative techniques. There is around twenty percent of all research that is related to the pharmaceutical industry. Among the various types of medications, the most common types are "alpha-2 adrenergic receptor agonists, selective norepinephrine reuptake inhibitors, and stimulants of the central nervous system". "Methylphenidate hydrochloride, lisdexamfetaminedimesylate, amphetamine sulfate, mixed amphetamine salts, and a combination of dexmethylphenidate hydrochloride and serdexmethylphenidate chloride" are some examples of the drugs that fall under this category. Pharmaceuticals such as "atomoxetine & viloxazine" are examples of such medications. The agonists' "guanfacine hydrochloride & clonidine hydrochloride" are two examples of these compounds. Treatments for "attention-deficit hyperactivity disorder (ADHD)" without first obtaining the "Food and Drug Administration (FDA)" include a typical "antipsychotics (such as quetiapine & aripiprazole) and antidepressants (such as vortioxetine & bupropion hydrochloride)". This research presents a review of "innovative pharmacological agents, non-pharmacological therapies, drug targets, and creative therapeutic choices". Additionally, a discussion of quantitative trends in clinical trials is included in this research.

Keyword: Pharmacotherapy, Managed Care, Pharmacy Intrusions, ADHD, Treatment

PREFACE

"Attention-deficit hyperactivity disorder (ADHD) is a neuro-behavioral illness that may be reliably diagnosed in children, adolescents, and adults". [15, 103] The worldwide prevalence of the illness is 2.5% in adults and 5% in children and adolescents [12, 83, 84] categorize "Attention Deficit Hyperactivity Disorder (ADHD)" into three principal subtypes: "ADHD-I, marked by a predominance of inattentive symptoms; ADHD-H, distinguished by a predominance of hyperactive-impulsive symptoms; and ADHD-C, characterized by a combination of equally symptom types". Anxiety, chronic stress, difficulties in establishing and sustaining relationships, as well as challenges in securing and retaining employment, are prevalent symptoms of "Attention Deficit Hyperactivity Disorder (ADHD)". Moreover, they have a higher propensity for involvement in severe traffic accidents, possess diminished educational attainment, are prone to distractions, and engage in drug usage [19].

Despite several factors, such as those related to the neurological system, environment, and genetics, [2, 89] being associated with "Attention Deficit Hyperactivity Disorder (ADHD)", its exact etiology remains elusive. Modifications to the normal regulation of neurotransmitters, as of "dopamine and norepinephrine", have been most commonly associated with the illness. Transporters [39, 74] and "G-protein coupled receptors (GPCRs)" [43, 53] represent significant categories of pharmacological targets, facilitating the actions of several neurotransmitters. The etiology of the condition is linked to certain areas of brain, as of "cerebellum, basal ganglia, anterior cingulate cortex, and prefrontal cortex (PFC)". Research utilizing "functional magnetic resonance imaging (fMRI)" indicates that patients with "attention deficit hyperactivity disorder (ADHD)" have variations in the structural development & functional stimulation of these regions. Numerous studies, suggest that various brain regions & their interconnections widely accepted as regulating mental processes including focus, thinking, memory, emotion, conduct, and actions. [69, 81 7, 8, 51,

"Symptoms of Attention Deficit Hyperactivity Disorder (ADHD)" encompass "inattention, impulsiveness, inadequate planning, and hyperactivity". Treatment alternatives for "Attention Deficit Hyperactivity Disorder (ADHD)" are broadening, with several approaches aimed at alleviating functional impairment and other primary symptoms.[19] Each nation possesses distinct regulations with the intent of overseeing "Attention Deficit Hyperactivity Disorder (ADHD)".[89] "Equally pharmacological and non-pharmacological methods" are established for the management of "Attention Deficit Hyperactivity Disorder (ADHD)". Initial category of drugs for treating "Attention Deficit Hyperactivity Disorder (ADHD) include stimulants, non-stimulants, & other sanctioned or unsanctioned pharmaceuticals".[18] If the initial two categories of stimulants neither work nor are well-tolerated, the subsequent third and fourth categories may be employed. Equally pharmaceutical and non-pharmacological methods have been extensively researched throughout the years.[89] This category comprises three principal areas: electronics, supplementary and alternative medicine, and psychological approaches.

The studiesnotable reviews addressing the domain of ADHD treatment. In this comprehensive review of 190 studies, [18] analyze equally "pharmaceutical and non-pharmacological treatments for Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents". Findings indicated that behavioral therapy surpassed all other non-pharmacological approaches when it comes to overseeing "Attention Deficit Hyperactivity Disorder (ADHD)". Pharmacological intrusions for the disease shown optimal efficacy with stimulants such as "amphetamine and methylphenidate", but non-stimulants like clonidine, guanfacine, and atomoxetine were considered secondary options. Moreover, stimulants may have enhanced the advantageous effects of behavioral therapy for treatment.[18]The 2018 research conducted evaluated the

safety and efficacy of ADHD medications in adults, adolescents, and children. A thorough analysis of 133 studies determined that amphetamines for adults and methylphenidate for children and adolescents were the preferred pharmacological treatments for the short-term management of "Attention Deficit Hyperactivity Disorder (ADHD)". [7, 8, 51, 25]

Amphetamines demonstrate higher efficacy in treating adult ADHD, and they are the only compounds that surpass placebo in acceptability among adults, whereas methylphenidate exhibits greater acceptance in children and adolescents.[25] NICE recommendations [60] indicate a preference for methylphenidate over amphetamines in children and adolescents, and our research aligns entirely with these criteria. Nonetheless, the FDA endorses these medications for ADHD treatment without distinction. A meta-analysis of 54 studies thoroughly elucidated the non-pharmacological intrusions.[85]This initiative encompasses psychological treatments (cognitive training, neuro-feedback, behavioral intrusions) and nutritional therapy (restricted elimination diets, restriction of artificial food colorants, supplementation with free fatty acids). The alleviation of ADHD symptoms was accomplished with the administration of free fatty acid supplements and the elimination of artificial food colorants. [85] He indicated that further therapies need evidence of efficacy from blinded assessments. Furthermore, a thorough analysis of 32 studies investigating non-pharmacological therapy was conducted in 2019. [62] Cognitive behavior therapy was the preferred treatment for alleviating the fundamental behavioral symptoms of ADHD in most studies.

Supplementary intrusions for "Attention Deficit Hyperactivity Disorder (ADHD)" have demonstrated potential, including cognitive rehabilitation and remediation, mindfulness-based therapies, dialectical behavior therapy, and hypnotherapy. [62] To enhance comprehension of non-pharmacological intrusions for cognitive symptoms in ADHD patients, [54] performed a comprehensive assessment and meta-analysis. Physical exercise therapy, especially aerobic exercises, were identified as the most effective means of targeting and reducing cognitive symptoms of ADHD. "Cognitive training, neuro-feedback, biofeedback, and cognitive behavioral therapy (CBT)" appeared to be significantly advantageous as well. It was also determined that inhibition and flexibility were the cognitive capacities most adversely affected. Research examining trials that integrated pharmaceutical and non-pharmacological therapies revealed that the combination yielded minimal benefits. Furthermore, studies including just participants who did not receive any medication still yielded promising results. [54]

This research quantifies all ADHD treatment approaches that have undergone clinical trials from 2001 to 2019. The researcher's objective was to elucidate the diverse therapeutic options, their attributes, and the emerging trends in therapies garnering increased focus.

COLLECTION OF DATA & ANALYSIS

the study[92] assert that "clinicaltrials.gov" is one of the largest online platforms offering summary information on clinical trials across a wide range of illnesses and disorders. All trials used for this review were sourced from this database. We employed a comprehensive search technique and restricted our focus to interventional studies. We conducted a search for "ADHD under the Condition or Disease" column. The parts labeled "Other terms and Country" was left unfilled. The search engine at clinicaltrials.gov has automatically included synonyms for "ADHD, such as attention deficit, hyperactivity disorder, disorder hyperactivity, hyperkinetic disorder, hyperkinetic syndrome, and minimal brain dysfunction". All variants of "Attention Deficit Hyperactivity Disorder (ADHD)", encompassing mixed, mostly inattentive, and primarily hyperactive-impulsive types, were taken into account. The inclusion criterion did not include age or gender.

The analysis encompassed all trials performed until 2019. There were 1,184 endeavors in the initial search. Research detailing the application of pharmaceutical, non-pharmacological, or combined methods for the treatment of "attention deficit hyperactivity disorder (ADHD)" was crucial for inclusion in the review. The primary objective of the investigation should have been treatment. Researches involving persons with concurrent medical conditions, such as anxiety, depression, epilepsy, or any other disorder alongside ADHD, may also be deemed eligible for inclusion.

Studies lacking participant involvement were excluded from the analysis. Consequently, 398 publications were excluded from consideration, whereas 695 researches were preserved for this review. For each trial examined, data was obtained from clinicaltrials.gov on the following: "NCT number, study title, status, investigated condition, intervention, phase, completion date, and date of initial findings report". It was essential to revise specific studies due to inappropriate or confusing allocation of their stages. Due to the uncertainty regarding the successful advancement of trials to later stages, we chose to employ an earlier phase in studies with a dual-phase design (e.g., Phase 1|Phase 2). Whenever the phase was designated as "Not applicable" or "Early Phase 1", the researcher classified it as Phase 1. The researcher employed the term "stage" (e.g., exploratory stage and pivotal stage) for devices since, according to the FDA's classification, the term "phase" is inaccurate.[32] "Pilot, feasibility, and first-in-human investigations" constitute the exploratory phase. The number of participants in the clinical trial dictated the stage to which the research was assigned. After categorizing relevant papers, the researcher assessed and classified the treatment methodologies employed in the selected studies. The researcher employed the subsequent classification:

A) Non-pharmacological treatments

Innovative & different approaches:

- Polyunsaturated fatty acids, vitamins, minerals, amino acids, herbal treatments, homeopathic remedies, and nutritional supplements.
- Diverse modalities include physical exercise, massage therapy, acupuncture, hypnosis, yoga, tai chi, mindfulness, chiropractic care, osteopathic treatment, and more mind-body activities.

Devices:

- "Transcranial direct current stimulation (tDCS)"
- "Transcranial random noises stimulation (tRNS)"
- "Repetitive transcranial magnetic stimulation (rTMS)"
- "Direct transcranial magnetic stimulation (dTMS)"
- "External trigeminal nerve stimulation (eTNS)"

Psychological:

- Behavior management intrusions (e.g., parental and teacher training, student programs for social and organizational skill development, cognitive behavioral therapy, and analogous methodologies)
- Intrusions encompassing cognitive training (e.g., attention enhancement, neuro-feedback, working memory development, etc.)
- Counseling for mental health

B) Pharmacological treatments

Non-stimulant medications:

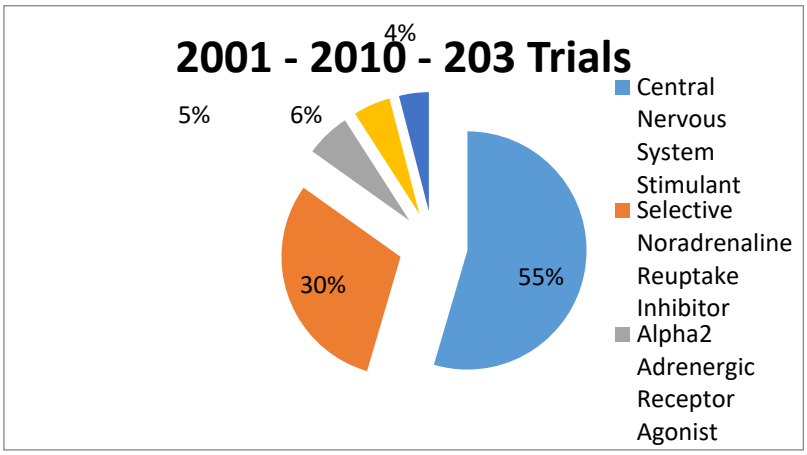
- Guanfacine and clonidine are examples of alpha-2 adrenergic receptor agonists.
- Atomoxetine, a selective norepinephrine reuptake inhibitor, along with other approved and unapproved pharmacological agents for "Attention Deficit Hyperactivity Disorder (ADHD)": Hydrochloride salts of antidepressants (e.g., "bupropion, venlafaxine, desipramine")
- Class I antipsychotics (e.g., "risperidone, olanzapine, aripiprazole")

Stimulant medications:

"Medroxyphenidate hydrochloride, lisdexamfetaminedimesylate, dexmethylphenidate hydrochloride, and other norepinephrine and dopamine reuptake inhibitors".

C) Combined Treatments

All data related to INN, agent type, agent class, target type, mechanism of action, and FDA approval for drug-based research were obtained from the following sources: "go.drugbank.com, genome.jp, uniprot.org, and fda.gov".



Aside from transdermal systems (such as "amphetamine and methylphenidate"), the researcher excluded other doses and pharmaceutical kinds from consideration. The classification was employed to categorize all devices identified in clinical studies.

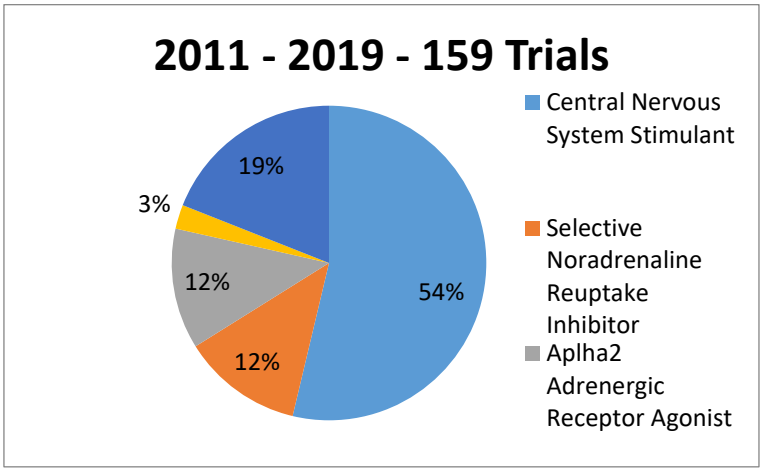


Fig. 1: The figure displays data on the number of trials conducted on the most popular classes of pharmaceuticals used to treat "attention deficit hyperactivity disorder (ADHD)" during two time periods: 2001–2012 and 2013–2019.

The researcher employed the "Unspecified device class" to classify devices that did not conform to any of the preceding categories. In the analysis of trials incorporating several therapies (such as parent training, vitamins, and massage), each therapy was considered individually. It is important to note that our major focus was on patterns in clinical trials, and the data obtained from the research may not accurately represent the actual use of methods in clinical practice. It is crucial to acknowledge the limitations of these quantitative evaluations. The patient's prior or concurrent use of medication, psychotherapy, or other therapies for ADHD was not always evident. Consequently, it is plausible that several ADHD treatments designated as singular were, in fact, a mix of therapies. Moreover, as several researches encompassed multiple circumstances, it is probable that ADHD was not the principal focus of each experiment, perhaps resulting in misleading findings on certain trends in the data. Certain drugs could not be categorized into a single class since they were just proposed in the research without explicit identification. Conversely, there were studies that used non-pharmacological approaches and therapeutic sessions, including behavioral parent training, working memory enhancement, and "transcranial direct current stimulation (tDCS)". Nevertheless, the research description did not consistently specify the particular equipment or therapy employed, as of "Soterix Medical tDCS device or the Magstim Super Rapid2 stimulator". Such cases required the separate evaluation of each therapy and device. It is important to note that the majority of alternative and extra processes, along with psychological methods, are classified as "Not Applicable." Despite the potential for data misinterpretation, the researcher designated these studies as "Phase 1" for the sake of simplicity. A comprehensive classification of these data must be employed in future targeted assessments of behavioral therapies. [64] indicate that the National Institutes of Health (NIH) recommends classifying behavioral therapy studies based on their contexts, with research settings as the most fundamental and community settings as the least fundamental. Excluding the clinicaltrials.gov database, no other sources or clinical trial registries were evaluated for the inclusion of clinical studies in the analysis.

CLASSIFICATIONS OF DRUGS EVALUATED IN CLINICAL TRIALS MOST OFTEN

Considering the significant significance of medicine in ADHD treatment, we analyzed two time frames (2001–2010 and 2011–2019) and presented the most prevalent pharmaceutical classes together with the frequency of their applications.

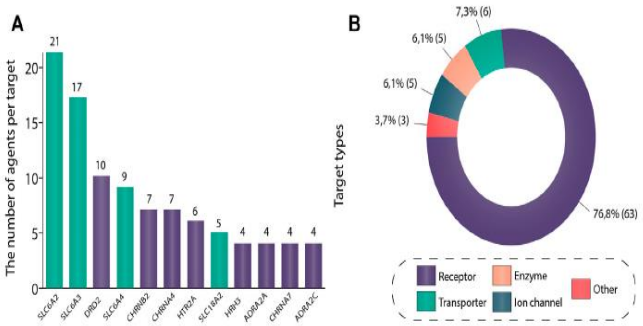


Fig. 2: (A) Standardized pharmacological targets for attention deficit hyperactivity disorder. (B) CARTPT (Cocaine- and amphetamine-regulated transcript protein), and M (Matrix protein 2)

The five most prevalent categories were "central nervous system stimulants, alpha-2 adrenergic receptor agonists, antidepressants, selective norepinephrine reuptake inhibitors, and atypical antipsychotics". The researcher identified a notable discrepancy between the groups administered stimulants and those that were not. Among 212 therapies, CNS stimulants were identified; of these, 74 intrusions comprised antidepressants, atypical antipsychotics, and alpha2 adrenergic receptor agonists. Selective noradrenaline reuptake inhibitors constituted 76 treatments over equally periods, rendering them the second largest class. From 2001 to 2010, there were 61 intrusions for this group; however from 2011 to 2019, only 15 intrusions occurred. This is a considerable decrease. The number of studies for atypical antipsychotics fell from eleven between 2001 and 2010 to three between 2011 and 2019. Conversely, alpha2 adrenergic receptor agonists and stimulants had no notable fluctuations and remained quite stable. Between the first and subsequent time periods, antidepressants were the sole type of medicine to exhibit an increase, rising from nine to twenty-three treatments.

POTENTIAL MEDICINAL PRODUCT SITES

The researcher examined the goals of the ADHD drug. Figure 2A illustrates the predominant pharmacological targets employed in ADHD clinical studies. The targets encompass: "sodium-dependent noradrenaline transporter (21 agents), sodium-dependent dopamine transporter (17 agents), D(2) dopamine receptor (10 agents), sodium-dependent serotonin transporter (9 agents), neuronal acetylcholine receptor subunit alpha-4 (7 agents), neuronal acetylcholine receptor subunit beta-2 (7 agents), 5-hydroxytryptamine receptor 2A (6 agents), synaptic vesicular amine transporter (5 agents), neuronal acetylcholine receptor subunit alpha-7 (4 agents), alpha-2C adrenergic receptor (4 agents), alpha-2A adrenergic receptor (4 agents), and histamine H3 receptor (4 agents)". The majority of pharmaceuticals primarily target the SLC6A2, SLC6A3, and SLC6A4 genes, which encode the sodium-dependent transporters for noradrenaline, dopamine, and serotonin, respectively. Pharmaceutical agents that serve as reuptake inhibitors alter neurotransmission to restore levels of noradrenaline, dopamine, and serotonin in the brains of persons with "Attention Deficit Hyperactivity Disorder (ADHD)". A crucial aspect to highlight is that these targets are predominantly addressed by the primary category of medications approved for the treatment of ADHD, namely stimulants. Amphetamine-type stimulants, approved for the treatment of "Attention Deficit Hyperactivity Disorder (ADHD)", affect monoamine buildup by targeting the synaptic vesicular amine transporter (SLC18A2), a vesicular protein. [91]

In cases where stimulants are ineffective, alpha-2 adrenergic agonists provide a viable alternative. This class of drugs functions by obstructing noradrenaline and dopamine neurotransmission by the binding

to Alpha-2A adrenergic receptors (ADRA2A, ADRA2C). Patients experiencing adverse effects from stimulants, including irritability, tic emergence or worsening, insomnia, diminished appetite, or significant growth suppression, may obtain treatment with an alpha-2 agonist medication. Furthermore, individuals with a predisposition to or a history of stimulant addiction or misuse should refrain from using stimulants. This include individuals with tic disorders, cardiovascular diseases (including congenital heart anomalies, genetically predisposed elevated risk for sudden cardiac death, unstable hypertension, or coronary artery disease), or any cardiac complications. When stimulants fail to deliver sufficient relief, combinations with alpha-2 adrenergic agonists are occasionally advised. [21, 47] The predominant ADHD medicines available today focus on monoamine transporters to elevate brain monoamine levels (Table 1).

The D(2) dopamine receptor and the 5-hydroxytryptamine receptor 2A are the primary targets of antipsychotics. These receptors correspond to the genes DRD2 and HTR2A, respectively. [6, 52] Antipsychotics are used to treat a variety of mental health conditions. All of the medications that were found in our investigation have been allowed for the treatment of schizophrenia; however, there is not a single medicine from this category that has been approved for the treatment of "Attention Deficit Hyperactivity Disorder (ADHD)" as of yet. Participants in the research comprised people who were using medications for the treatment of dementia. These medications target the alpha-4, beta-2, and alpha-7 subunits of the neuronal acetylcholine receptor (CHRNA4, CHRNB2, and CHRNA7, respectively). The same is true for "Attention deficit hyperactivity disorder (ADHD)"; no FDA-approved medication targeting these receptors has been approved. Despite this, we found that each of these objectives occurred significantly more frequently than others. Because of the high prices, low success rates, and the complexities involved in the process of developing and discovering new drugs, the industry is shifting its focus toward the repurposing of the medications that are currently available. According to [72, 50, 45,] this new breakthrough is in line with a similar upward trend in the field of drug discovery everywhere in the world.

HRH3, also known as the histamine receptor H3, is another potential area of research. Arousal, suppression of pituitary hormone release, motivation, memory, goal-oriented behavior, and the sleep-wake cycle are some of the cognitive functions that have been linked to histamine. [63, 61, 64, 48] Histamine has also been proven to be associated with a wide range of neuropsychiatric disorders and behaviors. It has been shown by previous studies [79, 77, 75] that specifically targeting the histamine receptor H3 using genetic and pharmacological methods may have the potential to modify aggression, circadian rhythms, anxiety, memory, and social behavior. In addition, it has the potential to alleviate cognitive impairments that are associated with neurodegenerative diseases. Based on these findings, it appears that the manipulation of histamine receptor H3 might potentially offer a unique strategy to the treatment of mental illnesses such as "Attention deficit hyperactivity disorder (ADHD)". It is important to note that the clinical effects of HRH3 medication for "Attention Deficit Hyperactivity Disorder (ADHD)" are rather disheartening. Previous studies [14, 45, 103] have shown that three of the four pharmacological drugs that were examined, namely "PF-03654746, Bavisant, and MK-0249", did not demonstrate a substantial improvement in ADHD symptoms until they were tested in phase 2 clinical trials. In the phase 1 clinical study for the remaining medication, betahistine, [59] found that the medication was well tolerated and did not cause any notable side effects. Despite this, no more study including this medication in people who have "Attention deficit hyperactivity disorder (ADHD)" has been conducted since that time.

TABLE - 1: Drugs approved for ADHD and other indications encountered in clinical trials

Agent name	Agent type	Agent class	Approval overall	Approval ADHD	Targets	First approved indication
Memantine hydrochloride	Small molecule	Dementia therapeutic agent	2003	-	GRIN1; GRIN2A; GRIN2B; GRIN2C; GRIN2D; GRIN3A; GRIN3B	Dementia of the Alzheimer's type
Methylphenidate hydrochloride	Small molecule	CNS stimulant	1955	1955	SLC6A3	ADHD
Methylphenidate transdermal system	Small molecule	CNS stimulant	2006	2006	SLC6A3	ADHD
Lisdexamfetamine dimesylate	Small molecule	CNS stimulant	2007	2007	SLC6A2; SLC6A3	ADHD
Viloxazine	Small molecule	Selective noradrenaline reuptake inhibitor	2019	2019	SLC6A2	ADHD
Amiloride hydrochloride	Small molecule	Diuretic	1981	-	SCNN1A; SCNN1B; SCNN1G; SCNN1D	Congestive heart failure; Hypertension
Amphetamine sulfate	Small molecule	CNS stimulant	1984	1984	SLC18A2; SLC6A2; SLC6A3; CARTPT; TAAR1; VMAT2; MAOA; MAOB	ADHD
Dextroamphetamine sulfate		CNS stimulant	1976	1976	SLC18A2; SLC6A2; SLC6A3	ADHD
Dexmethylphenidate hydrochloride		CNS stimulant	2001	2001	SLC6A3; SLC6A2	ADHD
Mixed amphetamine salts		CNS stimulant	2001	2001	SLC18A2; SLC6A2; SLC6A3	ADHD
Atomoxetine		Selective	2002	2002	SLC6A2	ADHD

		noradrenaline reuptake inhibitor				
Guanfacine hydrochloride		Alpha2 adrenergic receptor agonist	1986	2009	ADRA2A	Hypertension
Clonidine hydrochloride		Alpha2 adrenergic receptor agonist	1974	2010	ADRA2A; ADRA2B; ADRA2C	Hypertension
Molindone hydrochloride		Typical antipsychotic	1974	-	DRD2	Schizophrenia
Modafinil		CNS stimulant	1998	-	SLC6A3	Narcolepsy; OSA; SWD
Galantamine hydrobromide		Dementia therapeutic agent	2001	-	ACHE; CHRNA7	Dementia of the Alzheimer's types
SDX CL/d-MPH Cl		CNS stimulant	2019	2019	SLC6A3; SLC6A2	ADHD
Quetiapine		Atypical antipsychotic	1997	-	HTR2A; DRD2	Schizophrenia
Naltrexone hydrochloride		Opiate antagonist	1984	-	OPRD1; OPRM1; OPRK1; SIGMAR 1	Opioid dependence
Ramelteon		Sedative-hypnotic	2005	-	MTNR1A ; MTNR1B	Insomnia
Amantadine		Antiparkinson agent	1966	-	M; GRIN3A; DRD2	Parkinson's disease
Bupropion hydrochloride		Antidepressant	1985	-	SLC6A2; SLC6A3	Major depressive disorder
Vortioxetine		Antidepressant	2013	-	SLC6A4; HTR3A; HTR7; HTR1B; HTR1A	Major depressive disorder
Aripiprazole		Atypical antipsychotic	2002	-	DRD2; HTR2A	Schizophrenia
Mazindol		Anoretic	1973	-	SLC6A2; SLC6A3; SLC6A4	Duchenne muscular dystrophy

Varenicline		Smoking cessation aid	2006	-	CHRNA4	Smoking addiction
Droxidopa		Antiparkinson agent	2014	-	ADRA1A; ADRA1B; ADRA1D; ADRA2A; ADRA2B; ADRA2C; ADRB1; ADRB2; ADRB3	Neurogenic orthostatic hypotension
Carbidopa		Antiparkinson agent	2014	-	DDC	Parkinson's disease
Duloxetine hydrochloride		Antidepressant	2004	-	SLC6A4; SLC6A2	MDD; GAD; DPNP; Fibromyalgia; CMP
Zolpidem tartrate		Sedative-hypnotic	1992	-	GABRA1	Insomnia
Eszopiclone		Sedative-hypnotic	2004	-	GABRA1; GABRA2; GABRA3; GABRA4; GABRA5; GABRA6; GABRB1; GABRB2; GABRB3; GABRD; GABRE; GABRG1; GABRG2; GABRG3; GABRP; GABRQ	Insomnia
Buspirone hydrochloride		Anxiolytic agent	1986	-	HTR1A; DRD2	Anxiety disorders
Valproate sodium		Anticonvulsant agent	1996	-	HDAC9	Complex partial seizures; Simple and complex absence seizures
Risperidone		Atypical antipsychotic	1993	-	DRD2; HTR2A	Schizophrenia
Brexpiprazole		Atypical	2015	-	HTR1A;	MDD;

		antipsychotic			DRD2; HTR2A; ADRA2C; ADRA1B	Schizophrenia
Divalproex sodium		Anticonvulsant agent	1983	-	HDAC9	Complex partial seizures; Simple and complex absence seizures
Olanzapine		Atypical antipsychotic	1996	-	HTR2A; DRD2	Schizophrenia; BD-I; Agitation associated with schizophrenia/BD-I
Oxytocin	Biotech	Uterotonic agent	1980	-	OXTR	Initiation or improvement of uterine contractions
Fluvoxamine maleate	Small	Antidepressant	1994	-	SLC6A4	OCD

After classifying the targets according to the diagram shown in Figure 2B, we find that receptors make up 63% of the total, transporters make up 7%, enzymes make up 6%, ion channels make up 6%, and proteins make up 4%. A clear quantitative dominance of receptor targets is depicted in Figure 2B with this illustration. More than eighty percent of the pharmacological target categories encompassed by the trials that were included have equally receptor and transporter types. There has been a discernible rise in the investigation of novel medications, with receptors being identified as a primary target. [76] This is in line with the trends that have been observed.

PRESENT STATE OF ADHD CLINICAL TRIALS

Comparatively, the number of pharmaceutical substances has substantially decreased, going from eleven in 2005 to only one in 2019. This is in contrast to the growing popularity of gadgets, psychological approaches, and alternative and complementary therapies. Numerous other sorts of methodological approaches are greatly outnumbered by psychological tactics, as is clear. With an average of 36 new treatments being introduced each year, the years 2010 and 2019 had the highest number of new treatments introduced. A pharmaceutical medicine kicked off its clinical trial in 2001, the same year that the database was first established. It was in the year 2002 that the first psychological procedures were introduced, and in the year 2004, complementary and alternative approaches were introduced. In 2009, the first evaluation of devices was carried out. In general, the number of one-of-a-kind non-pharmacological procedures has increased by a factor of three in comparison to the number of pharmacological approaches. This is mostly due to the fact that medicines do not include a diverse range of many compounds.

It was necessary for us to conduct an analysis of the annual distributions of the experimental phase as the next step in the process. The quantitative data are depicted, which includes the total number of studies

that have been carried out following the year 2001 as well as the fluctuations in the number of studies that have occurred during each phase from 2001 to 2019. The number of trials had a substantial increase in 2005, then remained relatively stable from 2010 to 2013, and then experienced a little decrease between 2017 and 2018. Additionally, there is a sporadic rise in the number of clinical studies that are at the phase 1 stage. There were 32 phase 1 trials at their highest point in the year 2019. In 2007, there was a jump in the number of trials for phase two, which was followed by a continuous decline until the year 2019. The quantity of these studies saw a significant decrease after reaching a peak of 22 studies in the third phase in 2005 and 25 studies in the fourth phase. This fall occurred after the third phase reached its peak. The growth in the number of phase 1 studies demonstrates that there are an increasing number of treatments available for "Attention deficit hyperactivity disorder (ADHD)". It may be deduced from the fact that a sizeable proportion of these individuals do not advance to the second phase of clinical trials that the drugs have a poor success rate.

The phases of clinical trials for medical devices are broken down into their respective distributions. It is interesting to note that the testing of devices did not begin until 2009, and that initially, just two studies were carried out. Nine investigations were conducted in 2019, ten years after the organization's establishment, with the purpose of measuring the total number of clinical trials. With regard to the 51 research, 39 are currently in the exploratory phase, while the remaining investigations are currently in the critical phase. It is possible that the limited number of devices that have progressed to the pivotal stage or acquired FDA clearance is the reason why there are so many studies that are still in the exploratory phase addressing devices for the treatment of "Attention deficit hyperactivity disorder (ADHD)".

QUANTITATIVE TENDENCIES IN CLINICAL STUDIES IN THEIR FIRST, EXPLORATORY STAGES

In the first round of study, we are interested in determining which treatments offer the most benefits. A summary of the patterns that were seen in phase 1 clinical trials of a number of different medications, instead of using the word "Phase 1" to refer to the gathering of devices, the phrase "exploratory stage" was taken. Psychological intrusions are the primary component of Phase 1 therapies, and when looking at historical patterns, it is clear that the frequency of these procedures has greatly grown from 2008 to 2019. To ascertain which psychological therapies are essential to this development, we categories them into three subcategories: behavior management intrusions, cognitive training intrusions, and psycho-educational intrusions. The predominant psychological intrusions, encompassing 115 researches during the analyzed period, are behavior management therapies. Cognitive training treatments, with 78 studies, are the second largest category. Ultimately, there were seven studies concerning the smallest cohort—psycho-education.

BEHAVIORAL & PHYSICAL INTRUSIONS FOR ADHD

Psychological treatments and complementary and alternative therapies are two primary types of non-pharmacological intrusions, in addition to devices. Our data indicate that, over the past decade, there has been an increase in research on CAM treatments, with the domain of physical activity (PA) experiencing the most significant growth. A range of methodologies has been employed as experimental intrusions for the treatment of ADHD, encompassing "aerobic exercise, treadmill training, sprint interval training, baduanjin practice, taekwondo practice, MOVI KIDS, ImPuls, equine-assisted activities", and various therapies. It is well accepted that individuals with ADHD have worse cognitive performance attributable to reduced levels of the neurotransmitters dopamine and norepinephrine in the brain. An enhancement in the availability and

neurotransmission of catecholamines within cerebral networks may serve as a possible pharmacological strategy for alleviating ADHD symptoms, resulting in advancements in executive functions. Numerous studies have shown that it enhances academic performance, behavioral problems, emotional management, planning, and problem-solving abilities. Research indicated substantial reduction in symptoms of anxiety, depression, aggressiveness, and social difficulties in certain investigations. It is reasonable to propose that physical exercise may serve as an additional feasible technique for the treatment of ADHD, despite the absence of robust data evidencing its usefulness. Behavioral therapies may be the primary catalyst for the proliferation of psychological therapy. Prominent among these clinical investigations are NCT03628781 and NCT04402528. Behavioral therapy proved effective in alleviating ADHD symptoms. Regrettably, psychological treatments sometimes prove ineffective owing to problems such as a shortage of skilled therapists, inadequate financing, and geographical limitations. Consequently, to assist persons with ADHD in surmounting these challenges and mitigating functional impairment, the Mehealth for ADHD program incorporates several behavioral therapies. Pediatricians may enhance the care provided to their ADHD patients and increase the utilization of behavioral treatment with Mehealth for ADHD, a secure online platform grounded in scientific evidence. Besides serving as a unique instrument for optimizing ADHD therapy, it also enhances patient communication, accelerates diagnosis, and improves efficiency. This therapy has just completed two clinical trials involving a total of 200 people.

DISCUSSION & CONCLUSION

This meta-analysis of 695 studies about “Attention Deficit Hyperactivity Disorder (ADHD)” in children, adolescents, and adults provides comprehensive quantitative data on pharmacological and non-pharmacological treatment methods. The overall number of diverse non-pharmacological therapies is thrice more than the number of distinct treatments utilizing pharmaceutical drugs. Psychological treatments have outperformed all other non-pharmacological intrusions in clinical investigations. Moreover, several technologies have been employed in various research studies, and the prevalence of complementary and alternative medicines has increased over the past decade. “Methylphenidate hydrochloride, methylphenidate transdermal system, lisdexamfetaminedimesylate, amphetamine sulfate, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, mixed amphetamine salts, dexmethylphenidate hydrochloride / serdexmethylphenidate chloride, atomoxetine, guanfacine hydrochloride, clonidine hydrochloride, viloxazine”... Alongside the medications previously approved, five other treatments are presently undergoing clinical testing. The medications include “ADAIR, PDC-1421, centanafadine, OPC-64005, and prospecta”. One medicine from each class has progressed to phase 1, two drugs from each class have advanced to phase 2, and one drug from each class has attained phase 3, accordingly. Furthermore, three drugs already approved for other indications and currently under investigation in ADHD clinical trials include “molindone hydrochloride, risperidone, and brexpiprazole. Furthermore, the clinical development of two drugs, dasotraline and Fasoracetam”, was discontinued. “Methylphenidate hydrochloride, lisdexamfetaminedimesylate, amphetamine sulfate, and mixed amphetamine salts are central nervous system stimulants utilized in the treatment of Attention Deficit Hyperactivity Disorder (ADHD)”. These medications function by inhibiting certain transporters in the brain, chiefly those responsible for the transit of dopamine and norepinephrine. “Bupropion hydrochloride, vortioxetine, duloxetine hydrochloride, edivoxetine, reboxetine, fluvoxamine maleate, PDC-1421, dasotraline, ampreloxetine”, and countless additional antidepressants represent a significant array of unique pharmaceuticals now in clinical trials. Patients with ADHD who did not respond favorably to stimulants or experienced unpleasant side effects may consider antidepressants as an alternative treatment. The two drugs exhibit a same mode of action and

target identical receptors, including the sodium-dependent noradrenaline transporter and the sodium-dependent dopamine transporter.

Conversely, these medications have not received FDA approval for this application. There is a notable increase in cognitive training and behavior management trials. Treatment for “Attention Deficit Hyperactivity Disorder (ADHD)” generally commences in early childhood, involving the collaboration of parents, educators, and other caregivers. The skills acquired by children to manage their symptoms throughout their lives significantly contribute to the efficacy of behavioral therapies, including parent training, school-based intrusions, and peer-based intrusions, in alleviating ADHD symptoms. If a conclusive diagnosis remains unattainable, several therapies may be contemplated due to their considerable safety. A wide array of therapy solutions exists to target certain age demographics. Cognitive treatments effectively treat “Attention Deficit Hyperactivity Disorder (ADHD)” by targeting the fundamental cognitive deficiencies that hinder patients' learning and critical thinking abilities. These impairments encompass inhibitory control, working memory, planning, and cognitive flexibility. The increase in non-pharmacological research may be due to ADHD treatments addressing individuals across their developmental stages, allowing for adjustments as they transition from childhood to adulthood, thus impacting the most challenging behavioral symptoms during this period. Non-pharmacological therapy may be customized for children as they mature to address their specific developmental needs and contexts. Parent training is the most endorsed non-pharmacological intervention for preschoolers, whereas equally parent training and classroom intrusions are the preferred therapies for school-aged children.

The number of non-pharmacological research may rise due to the substantial costs associated with pharmacological clinical trials. Nonetheless, not all patients will endure or be capable of enduring pharmaceutical treatments. Pharmacological intrusions for “Attention Deficit Hyperactivity Disorder (ADHD)” may offer transient alleviation; nevertheless, sustained management through behavioral therapies and skill development is crucial. Additionally, some non-pharmacological intrusions target specific challenges faced by persons with ADHD. These encompass therapies aimed at improving academic achievement, social skills therapy, and training for working memory and attention. Pharmacological therapy for “Attention Deficit Hyperactivity Disorder (ADHD)” remains limited; however medications continue to be the primary treatment option. Pharmacological and behavioral intrusions function collaboratively or independently to enhance the neurotransmission of dopamine and noradrenaline in the brain, forming the foundation of contemporary therapy. The quantity of drugs approved for the treatment of “Attention Deficit Hyperactivity Disorder (ADHD)” is relatively limited (12 unique chemicals), predominantly consisting of derivatives of “amphetamine sulfate & methylphenidate hydrochloride”. Furthermore, these medicines only focus on a limited number of targets. In 2019, the combination of the central nervous system stimulants “dexmethylphenidate hydrochloride and serdexmethylphenidate” was approved for the treatment of “Attention Deficit Hyperactivity Disorder (ADHD)”. The domain of pharmacological therapy for ADHD remains in its nascent phase of research. Furthermore, during the past three years, researchers have employed several pharmaceutical candidates – “PDC-142, centanafadine, and tipepidine” as experimental therapies. “Innovative drug formulations (ADAIR) and prospective targets (HRH3)” are significant catalysts for progress in the sector, alongside the necessity to tackle issues such as poor adherence, non-tolerability, and limited short-term effectiveness. ADHD can also be addressed with a combination of methods. Our findings align precisely with previous studies indicating that behavioral therapy combined with methylphenidate hydrochloride substantially alleviated ADHD symptoms. This discovery is especially significant considering that most licensed ADHD drugs are stimulants and that the majority of psychology research has been on behavior control techniques. The sole non-pharmacological treatment demonstrating

statistically significant outcomes in clinical trials was behavior therapy, with parent training being the most extensively researched psychological intervention. Furthermore, a combination of behavioral treatment and stimulants proved to be more efficacious than stimulants used in isolation. Pharmacological intervention modulates monoamine neurotransmission in the brain, whereas behavioral therapy aims to ameliorate specific maladaptive behaviors such as aggression, subpar academic achievement, and strained familial and social connections. The reduction of ADHD symptoms was significantly enhanced by a combination of methylphenidate hydrochloride and non-stimulant medications such as "atomoxetine, clonidine, and guanfacine". However, more exploration of therapeutic combinations is essential.

"Pharmaceuticals, behavioral management techniques, cognitive training programs, supplementary therapies, devices, and mind-body intrusions" represent a selection of the numerous options for addressing "Attention Deficit Hyperactivity Disorder (ADHD)". The improper use of stimulant medications, the limitation of behavioral therapies to merely address behavioral issues without tackling the underlying cause of ADHD, insufficient funding, and logistical obstacles encountered by families contribute to the growing diversity of ADHD treatments. Further research is required to elucidate the precise pathways by which non-pharmacological therapies, including devices, influence the pathophysiology of ADHD and associated symptoms, whether individually or synergistically. Individuals with ADHD often delay seeking therapy until the illness has significantly affected their life, despite the presence of all symptoms at that stage. Consequently, the domain of early disorder diagnosis and prevention is expected to increase in importance. Ultimately, considering the primary rationale for treating ADHD is to enhance long-term outcomes such as social interactions and job prospects, it is imperative to examine the effects of equally present and future treatment options (including non-pharmacological approaches) on these domains across time.

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