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**Treatment of Adults with Attention-Deficit/Hyperactivity Disorder:
A Systematic Literature Review**

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NURS 695: Alternate Plan Paper

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Abstract

Objective: To compare treatment with stimulant medications to nonstimulant medications and/or nonpharmacologic interventions on professional and interpersonal functioning in adults with attention-deficit/hyperactivity disorder (ADHD).

Method: Systematic literature review of five databases; 22 articles containing 323 studies (N=21,370) were included in this review.

Results: Psychostimulants remain the most studied treatment for adults with ADHD and boast larger effect sizes than nonstimulant and nonpharmacologic therapy. Among nonpharmacologic therapy, cognitive behavior therapy (CBT) has proven most successful in randomized controlled trials. Effects of CBT are enhanced when combined with pharmacotherapy.

Conclusions: Psychostimulants continue to be the most frequently prescribed treatment for adults with ADHD. Nonstimulant medications and nonpharmacotherapy remain used as an adjunct or alternative to psychostimulant therapy, but show promise in producing long-term improvements in professional and interpersonal functioning in adults with ADHD.

Keywords: ADHD, adult, stimulants, stimulant medication, nonstimulant medication, nonpharmacologic, pharmacologic, methylphenidate, atomoxetine, cognitive behavior therapy

Treatment of Adults with Attention-Deficit/Hyperactivity Disorder: A Systematic Literature Review

Attention-deficit/hyperactivity disorder (ADHD) is a condition that initially presents in childhood, affecting 5-7.2% of children (APA, 2013; Alyagon et al., 2020). While it was originally thought that the disorder would be outgrown, it is now known that up to 65% of children will continue to experience difficulty with attention and executive functioning into adulthood (Aoshima-Kilroy et al., 2017; Baird et al., 2019; De Crescenzo et al., 2017; Geffen & Forster, 2018; Goto et al., 2013; Lenzi et al., 2017; Schwarz, 2016; Smith et al., 2020). The condition affects more than 2.5% of adults in the United States and over 4% of adults worldwide (APA, 2013; Alyagon et al., 2020; Baird et al., 2019; Boland et al., 2020). Adults with ADHD may experience increased difficulty with relationships, academics, and maintenance of employment when compared to their peers (Boland et al., 2020; Corbisiero et al., 2018; Geffen et al., 2018; Goto et al., 2017). Comorbid substance use, anxiety, and mood disorders are present in up to 70% of adults with ADHD. Untreated adults with ADHD experience increased rates of accidental injury and premature mortality (Aoshima-Kilroy et al., 2017; APA, 2013; Boland et al., 2020; Corbisiero et al., 2018; De Crescenzo et al., 2017; Geffen et al., 2018; Lenzi et al., 2017).

The DSM-V (2013) defines ADHD as a neurodevelopmental disorder characterized by a “persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development”. It is characterized by the presence of at least one of the following criteria: Inattention or hyperactivity and impulsivity. Inattention is defined as having five or more of the following symptoms: Careless mistakes, difficulty sustaining attention, mind wandering, failure to complete tasks, difficulty with organization, avoidance of activities that require sustained

mental effort, often losing necessary objects, is easily distracted, and/or is often forgetful (APA, 2013). To meet the criteria for hyperactivity and impulsivity, at least five of the following symptoms must be present: Frequent fidgeting, inability to remain seated, restlessness, inability to engage in quiet activities, is often “on the go” and unable to be still for prolonged periods of time, talks excessively, engages in interrupting behaviors, and/or has difficulty waiting their turn patiently (APA, 2013). The symptoms required to meet the criteria for inattention, hyperactivity, or impulsivity make up the core symptoms of ADHD.

ADHD may be predominantly inattentive type, hyperactive/impulsive type, or may be a combined presentation of the two. The symptoms must be present prior to age 12, in two or more settings (home, school, work, extracurriculars, or leisure), and pervasively interfere with functioning (APA, 2013). While the condition may co-occur with other mental disorders, the symptoms should not occur exclusively with flare-ups of these disorders (APA, 2013). Adults with ADHD may present differently than children and complain of inattention, restlessness, and emotional dysregulation rather than disruptive behaviors; they also tend to be more talkative than their peers (Baird et al., 2019).

Standardized Tools

The standardized tools used to measure outcomes are highlighted in Table 4 of the appendix. The most common tools used were the Adult ADHD Self-Report Scale Symptoms Checklist (ASRS), Conners’ scales (both self- and observer-rated), Barkley scales, the Behavioural Rating Inventory for Executive Functioning (BRIEF-A), Wender scales, and Clinical Global Impressions (CGI) scales. Occupational functioning was measured using Endicott Work Productivity Scale (EWPS) and the Canadian Occupation Performance Measure (COPM). Various measures, in addition to structured interviews, were used to assess quality of

life, self-esteem, and self-efficacy. Standardized tools to measure comorbid conditions were used to determine levels of anxiety, depression, and suicidality, though these conditions were not studied in this review.

Pharmacologic Interventions

Psychostimulant Pharmacotherapy

Psychostimulant medications work by blocking reuptake of dopamine and norepinephrine, thus increasing synaptic concentration of these neurotransmitters (Aoshima-Kilroy et al., 2017). Use of these medications are considered the first-line treatment for adults with ADHD (Baird et al., 2019). Formulations may be immediate, intermediate, or long-acting and should be tailored to meet the individual's needs (De Crescenzo et al., 2017). Common side effects of these medications include anxiety, gastrointestinal upset, appetite suppression, headache, sleep disturbances, fatigue, and blunted affect (Aoshima-Kilroy et al., 2017; Baird et al., 2019). Because these medications promote vasoconstriction, they can increase blood pressure and may raise the risk of cardiovascular events including myocardial infarction (Aoshima-Kilroy et al., 2017). Rarely, these medications may instigate seizure, psychosis, suicidality, priapism, and hepatotoxicity (Aoshima-Kilroy et al., 2017). Caution should be exercised when prescribing these medications for persons who experience hyperthyroidism, glaucoma, epilepsy, or severe anxiety disorder. They should not be used within two weeks of taking an MAOI or with those who experience cardiomyopathy, abnormal QT interval (prolonged or shortened), Brugada syndrome, Wolff-Parkinson-White syndrome, anorexia, psychosis, or Marfan syndrome (Aoshima-Kilroy et al., 2017). Because they are classified as a Schedule II drug with high potential for misuse and diversion by the Food and Drug Administration, prescribers must take part in the Prescription Monitoring Program (Aoshima-Kilroy et al., 2017).

Psychostimulant medications have been used in pregnancy for women with moderate to severe symptoms. However, placental perfusion may be impacted by the vasoconstrictive actions of psychostimulant medications and their use is associated with an increased risk for pre-eclampsia (1.3 fold increase when taken in the first trimester) and pre-term birth (Cohen et al., 2017). Benefits of the medication must be weighed against the risks of not treating women with severe ADHD as untreated women may experience increased anxiety and aggression that may interfere with self-care during pregnancy (Cohen et al., 2017).

Nonstimulant Pharmacotherapy

Atomoxetine. Atomoxetine, a noradrenaline reuptake inhibitor, works by promoting neurotransmitters noradrenaline and dopamine in the prefrontal cortex thus improving attention (Aoshima-Kilroy et al., 2017; Geffen et al., 2018). Insomnia, sedation, dizziness, gastrointestinal dysfunction, sexual dysfunction, increased blood pressure, and anticholinergic effects (dizziness, dry mouth, urinary retention, and increased heart rate) are common side effects (Aoshima-Kilroy et al., 2017; AthenaHealth, 2020). Atomoxetine may cause liver damage and regular monitoring of liver function tests is necessary (Aoshima-Kilroy et al., 2017; AthenaHealth, 2020).

Bupropion. Bupropion is an aminoketone antidepressant. Its therapeutic effect is derived from its action of inhibiting reuptake of dopamine and noradrenaline (AthenaHealth, 2020; Verbeeck et al., 2017). Bupropion is structurally similar to psychostimulants, which translates to a similar, but less robust, action without the high risk of misuse and diversion that psychostimulants boast (Verbeeck et al., 2017). Headache, nausea, dry mouth, and insomnia are common side effects; additionally, bupropion lowers the seizure threshold, thus increasing seizure risk (AthenaHealth, 2020; Verbeeck et al., 2017). This medication may be effective for

the nearly 19% of adults with ADHD who experience comorbid major depression (CHADD, 2019).

Desipramine. Desipramine, a tricyclic antidepressant, inhibits norepinephrine and serotonin reuptake (AthenaHealth, 2020). It may be useful for adults who experience both major depressive disorder and ADHD. Desipramine has the potential for many adverse effects, the most common being drowsiness, anticholinergic effects (dry mouth, constipation, urinary retention), dizziness, palpitations, tachycardia, and gastrointestinal distress; it may also increase anxiety and agitation and cause restlessness and insomnia (AthenaHealth, 2020). Serious adverse effects include changes in blood pressure (hyper- or hypotension), cardiac arrhythmias, QT prolongation, torsades de pointes, and AV block. It may cause myocardial infarction, cerebrovascular accident, extrapyramidal symptoms and tardive dyskinesia, serotonin syndrome, psychosis, suicidality, hepatitis, and angioedema (AthenaHealth, 2020). Unlike psychostimulant medications, desipramine cannot be stopped abruptly. While taking the medication, providers should monitor therapeutic drug levels, suicidality, and behavior changes. Desipramine should be used with caution for anyone with a history of cardiovascular disease, electrolyte abnormalities, QT prolongation, torsades de point, arrhythmias, angle-closure glaucoma, seizure disorder, thyroid disease, diabetes mellitus, psychosis, Parkinson's disease, or alcohol abuse (AthenaHealth, 2020).

Nonpharmacologic Interventions

Nonpharmacologic therapy may be used as an alternative to pharmacotherapy by persons who are unable to tolerate, whose symptoms are inadequately controlled by, or who do not wish to take medication. While there are many nonpharmacologic options for symptom control in adults with ADHD including hypnotherapy, neurofeedback, self-monitoring, and psychotherapy

in the form of cognitive behavior therapy (CBT); CBT has been the most studied. CBT was developed in the 1960's; however, only recently has this therapy been integrated into ADHD treatment (CHADD, 2021). CBT addresses ADHD symptoms by teaching organizational, executive functioning, and emotional regulation skills (CHADD, 2021). Mindfulness meditation has been used to improve emotional regulation (Bachman et al., 2016; De Crescenzo et al., 2017). Non-invasive brain stimulation has been FDA approved to treat depression and obsessive/compulsive disorder and has been postulated to improve ADHD symptoms (Alyagon et al., 2020).

While psychostimulants have been recommended by guidelines as the first-line therapy for ADHD in adults, these medications carry the risk of adverse effects. Up to 50% of adults taking psychostimulant medication discontinue their use within three years (Smith et al., 2020; Verbeeck et al., 2017). For those who do continue psychostimulant therapy, many are left with incomplete symptom coverage, unwanted side-effects, and difficulty functioning during times when medication is not taken (Cherkasova et al., 2016). The purpose of this literature review is to compare treatment using psychostimulant medications to nonstimulant medications and/or nonpharmacologic interventions on professional and interpersonal functioning in adults with attention-deficit/hyperactivity disorder (ADHD).

Method

Databases

A literature search was performed using five electronic databases, including Academic Search Premier, CINAHL, PubMed, ProQuest: Nursing and Allied Health Database, and PsychArticles. These databases were chosen based on their content of health-related and

neuropsychiatric-related articles. Descriptions of each database can be found in Table 1 of the Appendix.

Study Selection and Search Strategies

The protocol for critically appraising evidence outlined by Melnyk and Overholt (2019) guided this systematic review of the literature. The search terms are outlined in Table 2 of the Appendix. The search was limited to scholarly, peer-reviewed articles in the English language. Studies published between January 2015 and January 2021 were eligible for consideration in order to provide the most recent research available. Articles considered for inclusion must have 1) included pharmacologic and/or nonpharmacologic therapy for adults with ADHD and 2) evaluated observed and/or perceived effects to symptoms and professional and/or interpersonal functioning using standardized tools. Exclusion criteria included studies that involved children or adolescents, and those that investigated ADHD with comorbid psychiatric conditions, substance abuse, or pregnancy. Articles that were not available in full text were also excluded.

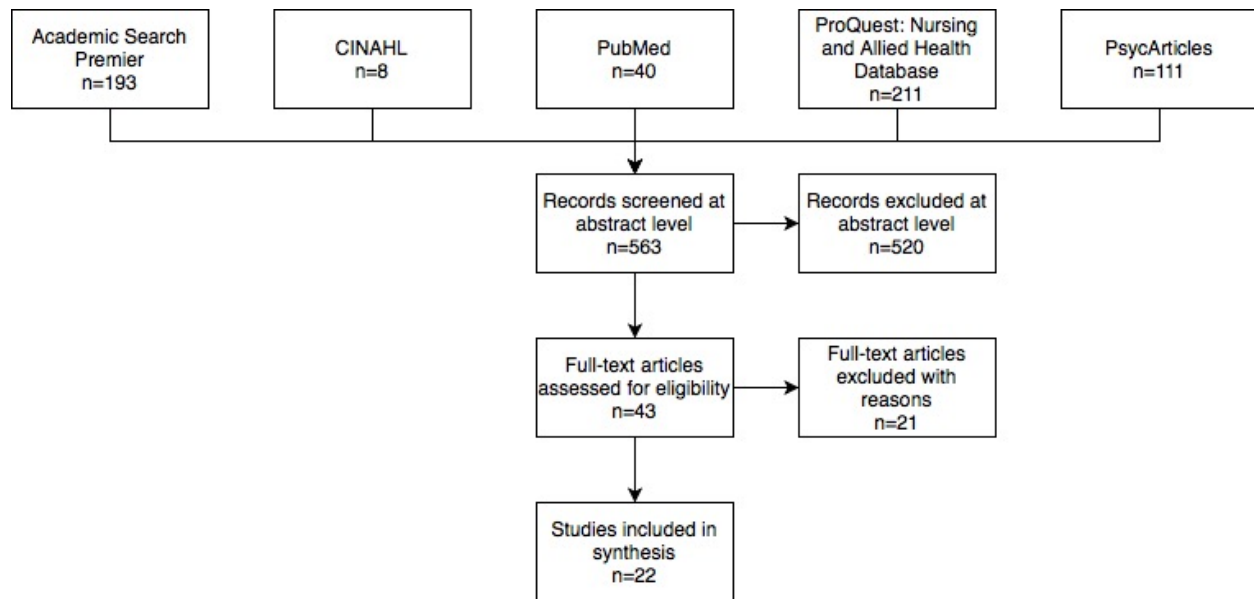
As shown in the Figure 1, a search of the included databases resulted in 563 articles, which were screened at the abstract level and reduced to 43 articles. Those remaining articles were read in their entirety and 21 were excluded according to the criteria noted above with detailed reasons outlined in Table 3 of the Appendix. Twenty-two articles met final inclusion criteria for this review. Reference Table 4 for details regarding each study that was included.

The studies contained data from around the world. Of the 22 articles, five were conducted in North American, seven were from Europe, two were from the Middle East, and one study was completed in Asia. The remaining articles either did not specify the country the study took place in or drew from multiple countries.

Close observation was given to study design, intervention, and primary and secondary outcomes. Of the 22 studies included, 21 were quantitative. One qualitative study was included to provide insight on what drives adults with ADHD to choose and maintain treatment. Due to the small size of this qualitative study, caution should be used generalizing the data to larger populations. Risk of inherent bias was present in many of the studies due to concealment of randomization process. An additional limitation to this review was the volume of included studies. Multiple meta-analyses were included in this review and some of the studies were duplicated within these analyses. Enacting more strict search parameters or limiting meta-analyses would have yielded a more manageable dataset.

Figure 1

Prisma Flow Diagram



Literature Review

Study Characteristics

Publication Dates

2015-2016	3
2017-2018	11
2019-2021	7

Geographical Location

North America	5
Europe	7
Middle East	2
Asia	1
Multiple Countries or Otherwise Unspecified	7

Treatment

Total Studies: 342

Sample Size	N=21,370
Stimulant Therapy	N=9,944
Nonstimulant Therapy	N=5,500
Non-pharmacotherapy	N=164
Multi-Modal	N=92

Effects of Interventions

Stimulant Medication

Psychostimulant therapy is the most studied therapy for adults with ADHD. Their use is associated with improved core symptom control and increased attention (Fuermaier et al., 2016).

Methylphenidate has been shown to be more efficacious in improving cognitive function, work

productivity, and emotional dysregulation leading to improved quality of life when compared to other psychostimulants, nonstimulant medications, and placebo (Goodman et al., 2017; Lenzi et al., 2018). These improvements were shown through both provider- and self-rated standardized tools. While Baird et al. (2019) found that amphetamine use was not effective in improving global functioning or reducing co-existing anxiety and/or depression symptoms, a meta-analysis by Boland et al. (2020) discovered the opposite – psychostimulant use showed protective effects on mood disorders ($p < 0.001$) and risk-behaviors with significant improvements to overall functioning compared to no medication ($p < 0.001$). A meta-analysis by Elliot et al. (2020) revealed that use of any ADHD pharmacotherapy (psychostimulant or nonstimulant medications) was associated with a statistically significant improvement in executive functioning (95% CI [-7.15, -4.29]) with low risk of harms (95% CI [0.67, 2.18]). While psychostimulants boast larger effects than nonstimulant medications or nonpharmacologic therapy ($p < 0.00001$), their use is also associated with more frequent adverse events ($p = 0.006$) (Cunill et al., 2016).

Nonstimulant Medication

While nonstimulant medications are more efficacious than placebo at reducing core ADHD symptoms, they are not as effective as psychostimulant medications in randomized controlled trials (De Crescenzo et al., 2017). Atomoxetine is the most studied among the nonstimulant medications. It has been shown to reduce core ADHD symptoms and improve executive functioning with fewer adverse effects than psychostimulant medications ($p < 0.001$) (Goto et al., 2017). Those receiving atomoxetine also experienced improvements in quality of life ($p < 0.001$), life outlook ($p < 0.05$), productivity ($p < 0.001$), and relationships ($p = 0.007$) (Goto et al., 2017). According to a study by Verbeeck et al. (2017), bupropion proved superior to placebo in reducing core ADHD symptom severity (95% CI [-0.86, -0.15]) with similar

tolerability to placebo (95% CI [0.35, 4.10]), though the evidence was of low quality. Bupropion and desipramine may be a useful treatment when considering pharmacotherapy for adults who have co-existing mood disorder as their primary use is for the treatment of depression.

Nonpharmacologic Therapy

Multiple nonpharmacologic therapies were studied in this literature review. Various forms of psychotherapy have been shown to be beneficial in reducing core ADHD symptoms for individuals with mild ADHD or those with incomplete symptom management despite pharmacotherapy (Groß et al., 2019). CBT has the most support as a viable treatment for adults with ADHD, however results are not as rapid as pharmacotherapy and effect sizes remain much smaller than treatment with psychostimulants alone (Smith et al., 2020). And while it has been shown to be effective, there are few studies that compare CBT without the addition of pharmacotherapy (Groß et al., 2019). When used in addition to pharmacotherapy, CBT has been shown to significantly reduce core ADHD symptoms and improve both occupational and social functioning when compared to standard treatment with pharmacotherapy alone (Dittner et al., 2018; Groß et al., 2019). The medium-to-large effects of CBT are apparent regardless of whether or not pharmacotherapy is used (Knouse et al., 2017). Improved perceived anxiety, depression, and distress are secondary benefits of CBT in adults with ADHD (Dittner et al., 2018). Additional secondary benefits include improved time-management, organization, and planning skills, as well as increased knowledge and motivation for self-care (Smith et al., 2020). A further finding is continued statistically significant effects up to 18 months after treatment had ended when compared to usual care (Groß et al., 2019). Conversely, Corbisiero et al. (2018) found that the addition of CBT to stimulant pharmacotherapy was no more effective than standard clinical management consisting of 30 minutes of medication counseling and supportive therapy by

trained clinicians; this finding was, however, an outlier compared to the majority of the research described above.

Mindfulness meditation and mindfulness-based CBT were shown to significantly improve self-regulation, attention, and emotional control (Bachman et al., 2016; De Crescenzo et al., 2017; Janssen et al., 2018). When combined with pharmacotherapy, mindfulness-based CBT significantly reduced perceived and clinician-rated core ADHD symptoms with effects lasting through six months of follow-up (Janssen et al., 2019). While immediate effects on executive functioning were not observed with mindfulness-based CBT, this domain was improved at the six-month follow-up (Janssen et al., 2019).

Interventions targeting executive functioning skills such as establishing a routine, organization, and time management was shown to improve outcomes in women with ADHD (Gutman et al., 2020). Additional interventions that have been shown to improve executive functioning include stress management and environmental control by reducing distractions (Gutman et al., 2020). Prefrontal brain stimulation, similar to what has been used for mood disorders, has shown some promise in one small study. However, the treatment may cause physical discomfort and the long-term effects remain unknown (Alyagon et al., 2020). Other nonpharmacologic approaches, such as hypnotherapy and neurofeedback were not shown to be effective when compared to sham therapy (Smith et al., 2020).

Gaps in Literature

Multi-modal therapy is recommended for adults with ADHD. However, there is a paucity of studies that evaluate the long-term outcomes of multimodal therapy on symptom control and overall functioning. Additionally, little information exists on barriers to psychotherapy uptake among adults with ADHD.

Discussion

Current guidelines recommend long-acting psychostimulant medication (methylphenidate) as first-line treatment for adults with ADHD who have significant impairment in at least one domain (ADHD Institute, 2019; National Institute for Health and Care Excellence (NICE), 2019). Use of such medications may result in more than 30% improvements in core symptom reduction (Grade B recommendation) (Baird et al., 2019). Nonstimulant medications remain second-line treatment for adults with ADHD, and may be used in place of or as an adjuvant to psychostimulant medications. Multimodal therapy, including psychotherapy, is also recommended, though not widely utilized (ADHD Institute, 2019; Geffen et al., 2018; Groß et al., 2019; Lenzi et al., 2017; NICE, 2019). The risks and benefits of ADHD treatment in adults should be carefully considered and the decision on how to treat the symptoms should occur through shared decision making (Boland et al., 2020; Druedahl & Sporrang, 2018; Elliot et al., 2020; Groß et al., 2019; Verbeeck et al., 2017).

Pharmacotherapy has proven both safe and efficacious through numerous randomized controlled trials. Both memory and executive function, as well as emotional dysregulation, may be improved, though not normalized, using psychostimulant medications (Fuermaier et al., 2016; Lenzi et al., 2018). Unfortunately, benefits cease when the medication is discontinued or a dose is missed, and effects may be reduced over time. The addition of psychotherapy, specifically CBT, may be a means of bridging this gap and providing skills to improve long-term executive functioning which leads to improved social, occupational, and global functioning (Fuermaier et al., 2016; Janssen et al., 2019). While studies highlight that psychotherapy is less efficacious than pharmacotherapy, these options for treatment should be shared for all those who cannot tolerate or do not wish to undergo pharmacotherapy, or offered in addition to pharmacotherapy

for enhanced core symptom control (Cherkasova et al., 2016; Dittner et al., 2018; Groß et al., 2019; Knouse et al., 2017). Discontinuation rates of psychostimulant therapy may be upwards of 50% for reasons ranging from feelings of not being oneself and unsatisfactory symptom control to bothersome adverse effects (Druehl et al., 2018; Verbeeck et al., 2017). Discontinuation rates may be mitigated with the addition of psychotherapy as pharmacotherapy provides immediate relief while individuals learn skills to cope with their ADHD (Alyagon, 2020; Cunill et al., 2016). It is worth noting that one study by Corbisiero et al. (2018) did not show CBT to be any more efficacious than standard clinical management when used in addition to pharmacotherapy. This study's findings, however, were contrary to the remaining studies in this review. It should be noted that there were obvious limitations of this study including small sample ($N=43$) and uneven distribution of comorbid conditions between the control and intervention groups.

In fact, Druehl et al. (2018) found that many adults desired nonpharmacologic treatment for their ADHD but felt that they lacked knowledge about their options. Despite scientific studies boasting the effectiveness of therapies such as CBT, mindfulness, or skills training and recommendations for multimodal therapy, nonpharmacologic options remain a largely underutilized treatment for adults with ADHD in the United States. The key is to offer transparency in the course of treatment; while medications often provide immediate results, the effects of nonpharmacologic therapeutic options are more gradual, yet also longer lasting (De Crescenzo et al., 2017). Additionally, psychotherapy may be substantially costlier than pharmacotherapy (Druehl et al., 2018).

Limitations

While this review of literature was useful in uncovering the continued needs for research on nonpharmacologic and multimodal therapy in adults with ADHD, it did not address how to approach treatment of ADHD in adults with co-morbid substance use disorder. Substance use disorder has been shown to increase the risk of stimulant misuse (De Crescenzo et al., 2017).

Implications for Future Practice

Recommendations for Clinical Practice

Primary care nurse practitioners and other medical providers should address biases related to diagnosis of adult ADHD and treatment with psychostimulant medications. Additionally, providers should increase their knowledge of nonpharmacologic therapies to use in addition to pharmacotherapy to optimize symptom management and professional and interpersonal functioning.

Recommendations for Research

Further research is needed on the long-term outcomes of treatment with psychostimulants compared with psychotherapy. Is CBT not well-utilized due to lack of knowledge on its efficacy or due to lack of providers who practice this form of therapy? Further research is warranted to explore barriers to CBT in adults with ADHD.

Recommendations for Health Policy

Currently, there is a scarcity of professionals trained to implement CBT for those diagnosed with ADHD. Increasing provider training in CBT, coping skills, and executive functioning training may translate to increased uptake of multi-modal therapy in adults with ADHD.

Conclusions

Psychostimulants remain the first-line treatment option for adults with ADHD, with nonstimulant medications and nonpharmacologic options considered second-line treatments that should be used in addition to psychostimulants or for those who are unable to tolerate psychostimulants. Nonpharmacologic options may also be considered as first-line treatment for individuals who express concern over a desire to not become reliant on medications. Regardless of the therapeutic option chosen, the patient's individual concerns and life situation should be considered and the choice should be made through shared decision making after risks and benefits of all options have been discussed.

In the absence of referral for psychotherapy, primary care nurse practitioners caring for adults with ADHD may provide counseling on nonpharmacologic interventions to manage their symptoms to enhance pharmacotherapy. Education on environmental management, such as establishing routines, working in a quiet, clutter-free setting, and minimizing distractions, coupled with stress-management techniques may be used to complement pharmacotherapy. Ensuring that primary care providers managing adults with ADHD are following the most current evidence and prescribing multimodal therapy is paramount in arming adults with ADHD with the tools they require to successfully manage their disorder.

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Appendix

Table 1

Database Search Description

Database (or Search Engine)	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
1. Academic Search Premier	Full Text; Peer Reviewed; English Language; Research Article	2015-2020	Provides citations and abstracts to articles, as well as full text of articles from over 4,600 publications, covering almost every academic subject.
2. CINAHL	Full text; Peer Reviewed; English Language; Research Article	2015-2020	Provides full text access to e-books about nursing and 29 core nursing journals. Also provides citations and abstracts to articles, books, dissertations, proceedings, and other materials about all aspects of nursing and allied health, including cardiopulmonary technology, emergency service, health education, medical/laboratory, medical assistant, medical records, occupational therapy, physical therapy, physician assistant, radiologic technology, social service/health care, and more.
3. PubMed	Full text; Peer Reviewed; English Language; Research Article	2015-2020	Provides citations, abstracts, and selected full text to articles about "medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences."
4. ProQuest: Nursing and Allied Health Database	Full Text; Peer Reviewed; English Language; Research Article	2015-2020	Provides citations, abstracts, and selected full text to articles about all aspects of nursing and allied health.
5. PsycArticles	Full Text; Peer Reviewed; English Language; Research Article	2015-2020	Provides full-text articles from journals published by the American Psychological Association, the APA Educational Publishing Foundation, the Canadian Psychological Association, and Hogrefe & Huber. The database includes all material from the print journals with the exception of advertisements and editorial board lists.

Table 2

Data Abstraction Process

Date of Search	Key Words	Results in Academic Search Premier	Results in CINHAL	Results in PubMed	Results in ProQuest: Nursing and Allied Health Database	Results in PsycArticles
11/2/2020	“ADHD”, “adult”	39,790	515	1,772	4,952	
11/2/2020	“ADHD”, “adult”, “stimulants”	5,517	65	265	1,054	
11/2/2020	“ADHD” AND “adult” AND “stimulant medication” AND “nonstimulant medication” NOT “child, adolescent”	44	0	8 (6)	4 (0)	
11/6/2020	“ADHD” AND “adult” AND “nonpharmacologic”	165	0	27	42	
11/6/2020	“ADHD” AND “adult” AND “nonpharmacologic” NOT “child” NOT “children” NOT “adolescent”	11(0)	0	9 (7)	9 (1)	
11/18/2020	“ADHD”, “adult”					1,273
11/18/2020	“ADHD”, “adults”, “stimulants”					187
11/18/2020	“ADHD” AND “adult” AND “stimulant medication” AND “nonstimulant medication” NOT “child, adolescent”					0
11/18/2020	“ADHD” AND “adult” AND “nonpharmacologic”					2 (0)
11/18/2020	“ADHD” AND “adult” AND “nonpharmacologic” NOT “child” NOT “children” NOT “adolescent”					0
11/18/2020	“ADHD” AND “adult” AND “pharmacologic” NOT “child” NOT “adolescent”					18 (0)
11/19/2020	“ADHD” AND “adult” AND “methylphenidate” AND “cognitive behavior therapy”	1,403	2 (1)			39 (3)
11/19/2020	“ADHD” AND “adult” AND “methylphenidate” AND “cognitive behavior therapy” NOT “child” NOT “adolescent”	85 (7)		4 (2)		39 (0)
1/17/2021	“atomoxetine” AND “ADHD” AND “adult” NOT “child” NOT “adolescent” NOT “pediatric”	97 (3)	6 (1)	19 (1)	198 (5)	13 (0)

***BOLD** = articles reviewed for match with systematic review inclusion criteria after title and abstract review

Table 3

Characteristics of Literature Included and Excluded

Reference	Included or Excluded	Rationale
Alyagon, U., Shahar, H., Hadar, A., Ygael, N. B., Lazarovits, A., Shalev, H., & Zangen, A. (2020). Alleviation of ADHD symptoms by non-invasive right prefrontal stimulation is correlated with EEG activity. <i>Neuroimage: Clinical</i> , 26(102206). https://doi.org/10.1016/j.nicl.2020.102206	Included	Semi-blinded randomized controlled trial Non-invasive electromagnetic stimulation treatment in participants with ADHD Limitations: small study size, non-comorbid participants, ill-represented group, lacked diversity
Aoshima-Kilroy, A., Banu, S., Udoetuk, S., Shah, A. A., & Moukaddam, N. (2017). To prescribe or not? pharmacological options in adult attention-Deficit/Hyperactivity disorder. <i>Psychiatric Annals</i> , 47(6), 303-308. http://dx.doi.org.ezproxy.mnsu.edu/10.3928/00485713-20170510-01	Excluded	Informational article. Consideration of inclusion in introduction but not suitable for literature review
Bachmann, K., Lam, A. P., & Philipsen, A. (2016). Mindfulness-based cognitive therapy and the adult ADHD brain: A neuropsychotherapeutic perspective. <i>Frontiers in Psychiatry</i> , 27(7), 117. https://doi.org/10.3389/fpsy.2016.00117	Included	Review of information Use of mindfulness as a treatment modality for ADHD; limitations, amount of mindfulness needed for optimal response Limitations: review of literature, lack of RTCs
Baird, D., & Hoffman, A. (2019). Use of amphetamines for attention-deficit/hyperactivity disorder in adults. <i>American Family Physician</i> , 100(5), 278-279. Retrieved on November 20, 2020 from https://www.aafp.org/afp/2019/0901/p278.html	Included	Systematic review of efficacy of amphetamine use in adults with ADHD
Biederman, J., DiSalvo, M., Woodworth, K. Y., Fried, R., Uchida, M., Biederman, I., Spencer, T. J., Surman, C., & Faraone, S. V. (2019). Toward operationalizing deficient emotional self-regulation in newly referred adults with ADHD: A receiver operator characteristic curve analysis. <i>European Psychiatry</i> , 63(1):e21. https://doi.org/10.1192/j.eurpsy.2019.11	Excluded	Focus of the article was on deficient emotional self-regulation (DESR) and how this impacts ADHD symptoms. The article does not add to the research of appropriate therapy to enhance outcomes
Boland, H., DiSalvo, M., Fried, R., Woodworth, K. Y., Wilens, T., Faraone, S. V., & Biederman, J. (2020). A literature review and meta-analysis on the effects of ADHD medications on functional outcomes. <i>Journal of Psychiatric Research</i> , 123, 21–30. https://doi.org/10.1016/j.jpsychires.2020.01.006	Included	The meta-analysis includes individuals across the lifespan revealing benefits and risks associated with ADHD medication, including functional outcomes Limitations: inclusion of registry studies and are unable to infer causality or effects of pharmacotherapy
Cherkasova, F., French, L. R., Syer, C. A., Cousins, L., Galina, H., Kashani, Y. A., & Hechtman, L. (2016). Efficacy of cognitive behavioral therapy with and without medication for adults with ADHD: A randomized clinical trial. <i>Journal of Attention Disorders</i> , 24(6), 889–903. https://doi.org/10.1177/1087054716671197	Included	Comparison of group CBT alone versus combine with medication on ADHD symptoms and functional outcomes in adults Limitations: absence of blinded independent evaluations of treatment outcomes; significant differences between CBT alone and CBT+M groups in sex and underlying anxiety; lack of “sham” treatment

Reference	Included or Excluded	Rationale
Coogan, A. N., Schenk, M., Palm, D., Uzoni, A., Grube, J., Tsang, A. H., Kolbe, I., McGowan, N. M., Wandschneider, R., Colla, M., Oster, H., Thome, J., & Faltraco, F. (2019). Impact of adult attention deficit hyperactivity disorder and medication status on sleep/wake behavior and molecular circadian rhythms. <i>Neuropsychopharmacology</i> , 44(7), 1198-1206. https://doi.org/10.1038/s41386-019-0327-6	Excluded	Small study on the effects of ADHD and medications to treat the condition on sleep and circadian rhythms, did not evaluate the impact of medications on functional status
Cohen, J. M., Hernández-Díaz, S., Bateman, B. T., Park, Y., Desai, R. J., Gray, K. J., Paterno, E., Mogun, H., & Huybrechts, K. F. (2017). Placental complications associated with psychostimulant use in pregnancy. <i>Obstetrics and Gynecology</i> , 130(6), 1192-1201. https://doi.org/10.1097/AOG.0000000000002362	Excluded	Exclude for literature review; pregnancy appears an outlier in the research and will omit from the review. Consideration of mentioning the risks of stimulant use during pregnancy (pre-eclampsia, placental abruption, growth restriction, preterm birth) in introduction or discussion
Corbisiero, S., Bitto, H., Newark, P., Mörstedt, B. A-, Elsässer, M., Kammermann, J. B-, Künne, S., Nyberg, E., Fallahpour, M. H-, & Stieglitz, R. D. (2018). A comparison of cognitive-behavioral therapy and pharmacotherapy vs. pharmacotherapy alone in adults with attention-deficit/hyperactivity disorder (ADHD) -- A randomized controlled trial. <i>Frontiers in Psychiatry</i> , 9(571). http://doi.org/10.3389/fpsy.2018.00571	Included	Comparison of CBT with medication versus medication alone on ADHD symptoms and functional outcomes in adults
Cunill, R., Castells, X., Tobias, A., & Capellà, D. (2016). Efficacy, safety and variability in pharmacotherapy for adults with attention deficit hyperactivity disorder: A meta-analysis and meta-regression in over 9000 patients. <i>Psychopharmacology</i> , 233(2), 187-197. http://dx.doi.org.ezproxy.mnsu.edu/10.1007/s00213-015-4099-3	Included	Systematic review and meta-analysis of RCTs comparing pharmacologic treatments in adults with ADHD
De Crescenzo, F., Cortese, S., Adamo, N., & Janiri, L. (2017). Pharmacological and non-pharmacological treatment of adults with ADHD: A meta-review. <i>Evidence - Based Mental Health</i> , 20(1), 4. http://dx.doi.org.ezproxy.mnsu.edu/10.1136/eb-2016-102415	Included	Systematic review of treatments for adults with ADHD including both pharmacologic and nonpharmacologic therapies
Demiral, S. B., Tomasi, D., Wiers, C. E., Manza, P., Kojori, E. S-, Studentsova, Y., Wang, G., & Volkow, N. D. (2018). Methylphenidate's effects on thalamic metabolism and functional connectivity in cannabis abusers and healthy controls. <i>Neuropsychopharmacology</i> , 44(8), 1389-1397. https://doi.org/10.1038/s41386-018-0287-2	Excluded	Did not meet inclusion criteria as participants experienced cannabis use disorder, not ADHD
Dittner, H., Hodsoll, J., Rimes, K. A., Russell, A. J., & Chalder, T. (2018). Cognitive-behavioural therapy for adult attention-deficit hyperactivity disorder: A proof of concept randomised controlled trial. <i>Acta Psychiatrica Scandinavica</i> , 137(2), 125-137. https://doi.org/10.1111/acps.12836	Included	Randomized controlled trial comparing treatment as usual to treatment as usual plus cognitive behavior therapy
Druehdahl, L. C., & Sporrang, S. K. (2018) Managing complexity: Exploring decision making on medication by young adults with ADHD. <i>Pharmacy (Basel)</i> , 6(2), 33. https://doi.org/10.3390/pharmacy6020033	Included	Qualitative study exploring experiences of young adults with ADHD related to their treatment decisions

Reference	Included or Excluded	Rationale
Elliott, J., Johnston, A., Husereau, D., Kelly, S. E., Eagles, C., Charach, A., Hsieh, S., Bai, Z., Hossain, A., Skidmore, B., Tsakonias, E., Chojecki, D., Mamdani, M., & Wells, G. A. (2020). Pharmacologic treatment of attention deficit hyperactivity disorder in adults: A systematic review and network meta-analysis. <i>PloS One</i> , 15(10), e0240584–e0240584. https://doi.org/10.1371/journal.pone.0240584	Included	Meta-analysis of pharmacologic treatments for adults with ADHD
Fuermaier, A. B. M., Tucha, L., Koerts, J., Weisbrod, M., Lange, K. W., Aschenbrenner, S., & Tucha, O. (2017). Effects of methylphenidate on memory functions of adults with ADHD. <i>Applied Neuropsychology: Adult</i> , 24(3), 199-121. https://doi.org/10.1080/23279095.2015.1124108	Included	Treatment with methylphenidate in adults with ADHD improves, but does not normalize, memory function.
Geffen, J., & Forster, K. (2018). Treatment of adult ADHD: A clinical perspective. <i>Therapeutic Advances Psychopharmacology</i> , 8(1), 25-32. https://doi.org/10.1177/2045125317734977	Included	Synthesis of information Clinical perspective of treatment options for adult individuals with ADHD. Guideline for practice
Goodman, D. W., Starr, H. L., Ma, Y. W., Rostain, A. L., Ascher, S., & Armstrong, R. B. (2017). Randomized, 6-week, placebo-controlled study of treatment for adult attention-deficit/hyperactivity disorder: Individualized dosing of osmotic-release oral system (OROS) methylphenidate with a goal of symptom remission. <i>Journal of Clinical Psychiatry</i> , 78(1), 105-114. https://doi.org/10.4088/JCP.15m10348	Included	Use of osmotic-release oral system (OROS) methylphenidate on symptom reduction in adults with ADHD
Goto, T, Hirata, Y., Takita, Y., Trzepacz, P. T., Allen, A. J., Song, D., Gau, S. S., Ichikawa, H., Takahashi, M. (2017). Efficacy and Safety of Atomoxetine Hydrochloride in Asian Adults With ADHD. <i>Journal of Attention Disorders</i> , 21(2), 100–109. https://doi.org/10.1177/1087054713510352	Included	RCT of safety and efficacy of atomoxetine in adults with ADHD. Limitations include exclusion of comorbid psychiatric conditions which authors note limits generalizability of results to many individuals experiencing ADHD. Study used a flexible-dose design which made it challenging to determine safety and efficacy
Groß, V., Lücke, C., Graf, E., Lam, A. P., Matthies, S., Borel, P., Sobanski, E., Rösler, M., Retz, W., Jacob, C., Colla, M., Huss, M., Jans, T., Kis, B., Hamid, M. A., van Elst, L. T., & Philippen, A. (2019). Effectiveness of psychotherapy in adult ADHD: What do patients think? Results of the COMPAS study. <i>Journal of Attention Disorders</i> , 23(9), 1047–1058. https://doi.org/10.1177/1087054717720718	Included	Study of patient perspectives on psychotherapy for adults with ADHD
Gutman, S. A., Balasubramanian, S., Herzog, M., Kim, E., Swirnow, H., Retig, Y., & Wolff, S. (2020). Effectiveness of a tailored intervention for women with attention deficit hyperactivity disorder (ADHD) and ADHD symptoms: A randomized controlled study. <i>American Journal of Occupational Therapy</i> , 74(1), 1-11. https://doi.org/10.5014/ajot.2020.033316	Included	Randomized controlled study investigating reduced perceived stress and ADHD symptoms and enhanced perceived performance of and satisfaction with desired occupational roles and activities in a sample of women Limitation of small sample size, low statistical power; lack of formal diagnosis in 4 of the women
Huang, F, Qian, Q., & Wang, Y. (2015). Cognitive behavioral therapy for adults with attention-deficit hyperactivity disorder: study protocol for a	Excluded	Study protocol, no results generated

Reference	Included or Excluded	Rationale
randomized controlled trial. <i>Trials</i> , 16(1), 161–161. https://doi.org/10.1186/s13063-015-0686-1		
Imagawa, H., Nagar, S. P., Montgomery, W., Nakamura, T., Sato, M., & Davis, K. L. (2018). Treatment patterns, health care resource utilization, and costs in Japanese adults with attention-deficit hyperactivity disorder treated with atomoxetine. <i>Neuropsychiatric Disease Treatment</i> , 14, 611-621. https://doi.org/10.2147/NDT.S150261	Excluded	Retrospective analysis of insurance claims data revealing patterns of medication adherence, discontinuation, and use of other medications. Not relevant to clinical question
Jain, R., & Katic, A. (2016). Current and investigational medication delivery systems for treating attention-deficit/hyperactivity disorder. <i>Primary Care Companion for CNS disorders</i> , 18(4). https://doi.org/10.4088/PCC.16r01979	Excluded	Full text not available
Janssen, L., Kan, C. C., Carpentier, P. J., Sizoo, B., Hepark, S., Schellekens, M. P. J., Rogier, A., Donders, T., Buitelaar, J. K., & Speckens, E. M. (2019). Mindfulness-based cognitive therapy v. treatment as usual in adults with ADHD: A multicentre, single-blind, randomised controlled trial. <i>Psychological Medicine</i> , 49(1), 55–65. https://doi.org/10.1017/S0033291718000429	Included	An exploration of the utility of mindfulness-based therapy versus treatment as usual in adults with ADHD
Joseph, A., Cloutier, M., Guérin, A., Nitulescu, R., & Sikirica, V. (2016). Treatment outcomes after methylphenidate in adults with attention-deficit/hyperactivity disorder treated with lisdexamfetamine dimesylate or atomoxetine. <i>Patient Preference Adherence</i> , 10, 391-405. https://doi.org/10.2147/PPA.S98498	Excluded	Retroactive cohort study examined medication continuation rates among adults receiving pharmacotherapy for ADHD
Karlstad, Ø., Zoëga, H., Furu, K., Bahmanyar, S., Martikainen, J. E., Kieler, H., & Pottegård, A. (2016). Use of drugs for ADHD among adults – A multinational study among 15.8 million adults in the Nordic countries. <i>European Journal of Pharmacology</i> , 72, 1507-1514. https://doi.org/10.1007/s00228-016-2125-y	Excluded	The purpose explored use of pharmacotherapy for ADHD without the perceived efficacy of treatment. Consideration of use in introduction.
Kiepek, N., Beagan, B., & Phelan, S. (2019). Substance use to enhance occupational performance and experience: A critical interpretive synthesis. <i>Cadernos De Terapia Ocupacional Da UFSCar</i> , 27(4), 843-857. doi:http://dx.doi.org.ezproxy.mnsu.edu/10.4322/2526-8910.ctoAR1926	Excluded	Excluded for literature review as the information does not meet inclusion requirements. However, the article highlights the use of non-prescribed stimulant medications for cognitive enhancement (20% of university students)
Klassen, L. J., Blackwood, C. M., Reaume, C. J., Schaffer, S., & Burns, J. G. (2018). A survey of adult referrals to specialist attention-deficit/hyperactivity disorder clinics in Canada. <i>International Journal of General Medicine</i> , 11, 1-10. https://doi.org/10.2147/IJGM.S145269	Excluded	The article focuses on recommending family practitioners diagnose and manage care for adults with ADHD instead of referring to specialists. Referral should be reserved for complex case management
Knouse, L. E., Teller, J., & Brooks, M. A. (2017). Meta-analysis of cognitive-behavioral treatments for adult ADHD. <i>Journal of Consulting and Clinical Psychology</i> , 85(7), 737-750. http://doi.org/10.1037/ccp0000216	Included	Meta-analysis of CBT for adults with ADHD
Lenzi, F., Cortese, S., Harris, J., & Masi, G. (2018). Pharmacotherapy of emotional dysregulation in adults with ADHD: A systematic review and meta-	Included	Systematic review and meta-analysis of effects of pharmacotherapy on emotional dysregulation in adults with ADHD. Limitations

Reference	Included or Excluded	Rationale
analysis. <i>Neuroscience and Biobehavioral Reviews</i> , 84, 359–367. https://doi.org/10.1016/j.neubiorev.2017.08.010		include lack of differentiation between individuals with and without comorbid conditions and inability to analyze outcomes based on ADHD subtype
Levin, F. R., Mariani, J. J., Specker, S., Mooney, M., Mahony, A., Brooks, D. J., Babb, D., Bai, Y., Eberly, L. E., Nunes, E. V., & Grabowski, J. (2015). Extended-release mixed amphetamine salts vs placebo for comorbid adult attention-deficit/hyperactivity disorder and cocaine use disorder: A randomized clinical trial. <i>JAMA Psychiatry</i> , 72(6), 593-602. https://doi.org/10.1001/jamapsychiatry.2015.41	Excluded	Did not meet inclusion criteria due to comorbid cocaine use
Pettersson, R., Staffan, S., Söderström, K. E., & Nilsson, K. W. (2017). Internet-based cognitive behavioral therapy for adults with ADHD in outpatient psychiatric care: A randomized trial. <i>Journal of Attention Disorders</i> , 21(6), 508–521. https://doi.org/10.1177/1087054714539998	Excluded	Sample size was small with low power. The trial did not factor in medication use, which some participants used and some did not. Though the study did show an improvement in those using an internet-based CBT program, I did not feel that the study was robust.
Ramsay, J. R. (2017). The relevance of cognitive distortions in the psychosocial treatment of adult ADHD. <i>Professional Psychology: Research and Practice</i> , 48(1), 62-69. http://doi.org/10.1037/pro000010	Excluded	Article does not meet inclusion requirements as the article addresses cognitive distortions and mindsets as a foundation for understanding treatment of adults with ADHD. While the information is useful to practice, it does not generate new information on the treatment of adults with ADHD
Savulich, G., Thorp, E., Piercy, T., Peterson, K. A., Pickard, J. D., & Sahakian, B. J. (2019). Improvements in attention following cognitive training with the novel "Decoder" game on an iPad. <i>Frontiers in Behavioral Neuroscience</i> , 13(2), 1-8. https://doi.org/10.3389/fnbeh.2019.00002	Excluded	The article used a sample of adults with no psychiatric diagnosis (past or current), including ADHD
Smith, V. N., Merwood, A., Hand, D., Brandling, J., Greenwood, R., Skinner, L., Law, S., Patel, V., & Rai, D. (2020). Non-pharmacological interventions for adult ADHD: A systematic review. <i>Psychological Medicine</i> , 50(4), 529–541. https://doi.org/10.1017/S0033291720000069	Included	Systematic review of nonpharmacologic interventions for adults with ADHD
Suzuki, C., Ikeda, Y., Tateno, A., Okubo, Y., Fukayama, H., & Suzuki, H. (2019). Acute atomoxetine selectively modulates encoding of reward value in ventral medial prefrontal cortex. <i>J Nippon Medical School</i> , 86(2), 98-107. https://doi.org/10.1272/jnms.JNMS.2019_86-205	Excluded	Randomized, placebo controlled within-subjects cross-over trial Explores the effects of atomoxetine in the adult reward center of the brain, but not the adult with ADHD
van Elst, L. T., Maier, S., Klöppel, S., Graf, E., Killius, C., Rump, M., Sobanski, E., Ebert, D., Berger, M., Warnke, A., Matthies, S., Perlov, E., & Philipsen, A. (2016). The effect of methylphenidate intake on brain structure in adults with ADHD in a placebo-controlled randomized trial. <i>Journal of Psychiatry & Neuroscience</i> , 41(6), 422-430. https://doi.org/10.1503/jpn.150320	Excluded	RCT on the effect of methylphenidate on brain structure which does not meet inclusion requirements. Consideration of use in introduction
Verbeeck, W., Bekkering, G. E., Van den Noortgate, W., & Kramers, C. (2017). Bupropion for attention deficit hyperactivity disorder (ADHD) in	Included	Systematic review assessing the efficacy of bupropion as therapy for adults with ADHD

Reference	Included or Excluded	Rationale
adults. <i>Cochrane Database Systematic Review</i> , 10(10). https://doi.org/10.1002/14651858.CD009504.pub2		
Weyandt, L. L., Oster, D. R., Marraccini, M. E., Gudmundsdottir, B. G., Munro, B. A., Rathkey, E. S., & McCallum, A. (2016). Prescription stimulant medication misuse: Where are we and where do we go from here? <i>Experimental and Clinical Psychopharmacology</i> , 24(5), 400-414. http://doi.org/10.1037/pha0000093	Excluded	Article addresses prescription stimulant medication misuse that is not specific to adults with ADHD
Yang, Z., Kelly, C., Castellanos, F. X., Leon, T., Milham, M. P., & Adler, L. A. (2016). Neural correlates of symptom improvement following stimulant treatment in adults with attention-Deficit/Hyperactivity disorder. <i>Journal of Child and Adolescent Psychopharmacology</i> , 26(6), 527-536. http://dx.doi.org.ezproxy.mnsu.edu/10.1089/cap.2015.0243	Excluded	The study examined the effects of amphetamines on the prefrontal cortex of the brain. Consideration of inclusion into the introduction
Zimmermann, M. B., Diers, K., Strunz, L., Scherbaum, N., & Mette, C. (2019). Listening to Mozart improves current mood in adult ADHD - A randomized controlled pilot study. <i>Frontiers in Psychology</i> , 10(1104). https://doi.org/10.3389/fpsyg.2019.01104	Excluded	The study focused on emotional lability associated with ADHD and not functional status

Table 4

Literature Review Table of All Studies Included

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Alyagon U., Shahar H., Hadar A., Barnea-Ygael N., Lazarovits A., Shalev H., & Zangen A. (2020). Alleviation of ADHD symptoms by non-invasive right prefrontal stimulation is correlated with EEG activity. <i>Neuroimage: Clinical</i> , 26(102206). https://doi.org/10.1016/j.nicl.2020.102206	To evaluate whether targeting the right prefrontal cortex (rPFC) with multiple sessions of repetitive transcranial magnetic stimulation (rTMS) will affect clinical symptoms in adults suffering from ADHD	N=43 drug-free adults with ADHD; Israel	I	Conners' Adult ADHD Rating Scale (CAARS); Barkely Adult ADHD Rating Scale (BAARS-IV); Behavioral Rating Inventory for Executive Functioning (BRIEF-A); Beck Depression Inventory (BDI)	rTMS; active control; sham treatment	rTMS resulted in significant improvement of symptoms (p=0.00085)	rTMS is a safe and effective treatment for ADHD
Bachmann, K., Lam, A. P., & Philipsen, A. (2016). Mindfulness-based cognitive therapy and the adult ADHD brain: A neuropsychotherapeutic perspective. <i>Frontiers in Psychiatry</i> , 27(7), 117. https://doi.org/10.3389/fpsy.2016.00117	To highlight the mechanisms of mindfulness meditation.	5 neuroimaging studies; 3 clinical studies; Germany	I		Mindfulness-based cognitive therapy	Mindfulness meditation may reduce distractibility while cognitive therapy aids in improving coping and executive functioning skills.	Mindfulness meditation as a neurobehavioral intervention may help adults with ADHD to improve self-regulation.
Baird, D., & Hoffman, A. (2019). Use of amphetamines for attention-deficit/hyperactivity disorder in adults. <i>American Family Physician</i> , 100(5), 278-279. Retrieved on November 20, 2020 from https://www.aafp.org/afp/2019/0901/p278.html	To evaluate the safety and efficacy of amphetamines in adults with ADHD	19 randomized controlled trials with N=2,521 adults with ADHD; US	I			Amphetamines provide a clinician rated 30% reduction in ADHD symptoms when compared with placebo (Strength of recommendation: B)	While amphetamines may reduce clinician-rated symptoms in adults with ADHD, they were not found to improve global functioning or reduce accompanying symptoms of anxiety and depression. Use of amphetamines are not without risk of adverse effects, including increased anxiety, depressed mood, nausea, vomiting, headache, fatigue, insomnia, hypertension, and flushing.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Boland, H., DiSalvo, M., Fried, R., Woodworth, K. Y., Wilens, T., Faraone, S. V., & Biederman, J. (2020). A literature review and meta-analysis on the effects of ADHD medications on functional outcomes. <i>Journal of Psychiatric Research</i> , 123, 21–30. https://doi.org/10.1016/j.jpsychires.2020.01.006	To conduct a systematic review and meta-analysis of literature from large databases and registries to assess the effects of ADHD medication on associated functional outcomes.	40 articles included in literature review; 21 studies included in meta-analysis; No country stated	I			Pharmacotherapy is associated with a decreased risk of negative ADHD-associated functional outcomes.	Early diagnosis and treatment of individuals with ADHD may improve functional outcomes.
Cherkasova, F., French, L. R., Syer, C. A., Cousins, L., Galina, H., Kashani, Y. A-, & Hechtman, L. (2016). Efficacy of cognitive behavioral therapy with and without medication for adults with ADHD: A randomized clinical trial. <i>Journal of Attention Disorders</i> , 24(6), 889–903. https://doi.org/10.1177/1087054716671197	Evaluate the effects of group CBT alone versus combined with medication on ADHD symptoms and functional outcomes in adult patients.	88 adults with ADHD; N=46 without medication; N=42 with medication; Canada	I	Cognitive behavior therapy with and without medication; Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAARD-D); Barkley Current ADHD Symptoms Scale; Conners' Adult ADHD Rating Scale (CAARS); Barkley Childhood ADHD Symptoms Scale; Wender Utah Rating Scale; Wechsler Adult Intelligence Scale-III; Wechsler Memory Scale-III; Wide Range Achievement Test-3	CBT – 12 sessions at 1.5 hours each administered by a PhD-level therapist; Medication – methylphenidate or amphetamine, gradually increased over the course of the study	CBT, both with and without medication, resulted in significant improvements relative to baseline in ADHD symptoms and functional outcomes; CBT with medications was superior to CBT alone in reducing both self- and observed ADHD symptoms immediately while CBT alone improve more gradually. The CBT only group continued to improve after discontinuation of the CBT intervention, while this was not observed with the CBT plus medication group.	CBT without medication is a viable option for those who cannot, or do not wish to, take stimulant medications.
Corbisiero, S., Bitto, H., Newark, P., Mörstedt, B. A-, Elsässer, M., Kammermann, J. B-, Künne, S., Nyberg, E., Fallahpour, M. H-, & Stieglitz, R. D. (2018). A comparison of cognitive-behavioral therapy and	To analyze the contribution of psychotherapy to the treatment of adult ADHD patients.	N=43 ADHD patients; N=20 CBT + med; N=23 SCM + med; Switzerland	I	Methylphenidate; CBT Structured clinical interview for DSM-IV (SCID-I and SCID-II); Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID); Conners' Adult ADHD Rating Scale (CAARS);	Methylphenidate 20 mg/day, titrated up every 4 days to a level of 0.5-1.3 mg/kg daily. If	Individualized CBT program was not able to outperform standard clinical management (SCM).	More information is needed to determine the effects of CBT therapy in addition to pharmacotherapy in adults with ADHD

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
pharmacotherapy vs. pharmacotherapy alone in adults with attention-deficit/hyperactivity disorder (ADHD) -- A randomized controlled trial. <i>Frontiers in Psychiatry</i> , 9(571). http://doi.org/10.3389/fpsy.2018.00571				Conners' ADHD Adult Rating Scale Self-Report Short Version (CAARS-S:S); Conners' Adult ADHD Rating Scale Observer Long Version (CAARS-O:L); Wender-Reimherr Adult Attention Deficit Disorder Rating Scale (WRAADD); ADHD Self-Rating Behavior Questionnaire (ADHD-SR); Sheehan's Disability Scale (SDS); Adult Attention-Deficit/Hyperactivity Disorder Quality-of-Life Scale (AAQoL); General Perceived Self-Efficacy Scale (SWE); Rosenberg Self-Esteem Scale (RSES); Psychotherapy Motivation Questionnaire (FMP); Bern Post Session Report	methylphenidate was not tolerated, an equivalent dose of Concerta was given; CBT 10-12 sessions individualized to ADHD		
Cunill, R., Castells, X., Tobias, A., & Capellà, D. (2016). Efficacy, safety and variability in pharmacotherapy for adults with attention deficit hyperactivity disorder: A meta-analysis and meta-regression in over 9000 patients. <i>Psychopharmacology</i> , 233(2), 187-197. http://dx.doi.org.ezproxy.mnsu.edu/10.1007/s00213-015-4099-3	To further understand the factors underlying the variability in the results of RTCs assessing pharmacological interventions for adults with ADHD.	44 studies involving N=9952 patients; Atomoxetine=12 studies/N=3703; Bupropion=5 studies/N=329; Dexamphetamine=1	I	Systematic review of RCTs	Stimulant therapy; nonstimulant therapy; psychotherapy	Pharmacological treatment was efficacious in reducing ADHD symptoms ($p<0.00001$) with stronger effect size with stimulant medications (Diff SMD=0.18, $p=0.017$); treatment with pharmacologic agents was associated with more frequent adverse effects ($p=0.006$).	Efficacy of stimulant medication is greater than non-stimulant medications. Must weight possible symptom relief with risks of adverse effects from treatment with stimulant medications. Providers must monitor for decreased efficacy of pharmacotherapy over time.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
		study/N=49 ; Dexamethyl phenidate= 1 study/N=22 1; Desipramin e=1 study/N=43 ; Lisdexamfe tamine=3 studies/N= 613; Mixed amphetami ne salts=3 studies/N= 655; Methylphen idate OROS=10 studies/N= 2,340; Other methylphen idate formulation =10 studies/N= 1,657; Modafinil= 1 study/N=33 8 Multiple countries/ Multiple sites					
De Crescenzo, F., Cortese, S., Adamo, N., & Janiri, L. (2017). Pharmacological and non-pharmacological treatment of	To provide a reliable summary of the best available information to	40 studies; N=778,298; No country specified	I	Systematic reviews; recent guidelines on adult ADHD	Pharmacotherapy; nonpharmacologic therapy;	Stimulant medications (amphetamines) have higher efficacy than other forms of therapy.	Risks-versus-benefits of stimulant medications should be considered when treating adults with ADHD.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
adults with ADHD: A meta-review. <i>Evidence - Based Mental Health</i> , 20(1), 4. http://dx.doi.org.ezproxy.mnsu.edu/10.1136/eb-2016-102415	inform practice in adults with ADHD.				multimodal therapy		
Dittner, H., Hodsoll, J., Rimes, K. A., Russell, A. J., & Chalder, T. (2018). Cognitive-behavioural therapy for adult attention-deficit hyperactivity disorder: A proof of concept randomised controlled trial. <i>Acta Psychiatrica Scandinavica</i> , 137(2), 125–137. https://doi.org/10.1111/acps.12836	Investigate efficacy, patient acceptability, and feasibility of formulation-based CBT for adults with ADHD	60 participants ; 19 participants in the CBT group were on medication, 26 participants in the TAU group were on medication. Medication =stimulant or atomoxetine; UK	I	Barkley Current Symptoms Scale; Work and Social Adjustment Scale	16 sessions CBT	Significant improvement of symptoms as well as improved self-rated anxiety and depression, global distress, and patient satisfaction	When added to treatment as usual, CBT had greater success in reducing ADHD symptoms and improving occupational and social functioning than treatment as usual (medication management) alone.
Druedahl, L. C., & Sporrang S. K. (2018). Managing complexity: Exploring decision making on medication by young adults with ADHD. <i>Pharmacy (Basel)</i> , 6(2), 33. https://doi.org/10.3390/pharmacy6020033		10 adults age 22-29 years of age; Denmark	VI	Focus group Individual Interviews		Three major themes were revealed through analysis of date: 1) Patient's right to choose ADHD medication as treatment 2) Patient's decision of whether or not to treat ADHD with medication 3) Factors affecting patient's decision on whether to take ADHD medication or not	Understanding the factors influencing treatment choices helps prescribers empower patients
Elliott, J., Johnston, A., Husereau, D., Kelly, S. E., Eagles, C., Charach, A., Hsieh, S., Bai, Z., Hossain, A., Skidmore, B.,	Assess the relative effects of individual pharmacologic treatments for	81 trials; N=12,423; Country not specified	I		Stimulant pharmacotherapy; Non-stimulant	High or unclear risk of bias in many studies; few differences between medications. Atomoxetine was associated with improved patient-reported clinical	The choice between ADHD pharmacotherapies may depend on individual patient considerations; future studies should assess long-term

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Tsakonas, E., Chojecki, D., Mamdani, M., & Wells, G. A. (2020). Pharmacologic treatment of attention deficit hyperactivity disorder in adults: A systematic review and network meta-analysis. <i>PloS One</i> , 15(10), e0240584–e0240584. https://doi.org/10.1371/journal.pone.0240584	adults with ADHD				pharmacotherapy	response and quality of life compared with placebo. No significant difference in risk of serious adverse events or treatment discontinuation between ADHD pharmacotherapies and placebo, however the proportion of participants who withdrew due to adverse events was significantly higher among participants who received any ADHD pharmacotherapy.	effects of individual pharmacotherapies
Fuermaier, A. B. M., Tucha, L., Koerts, J., Weisbrod, M., Lange, K. W., Aschenbrenner, S., & Tucha, O. (2017). Effects of methylphenidate on memory functions of adults with ADHD. <i>Applied Neuropsychology: Adult</i> , 24(3), 199-121. https://doi.org/10.1080/23279095.2015.1124108	Explore the impact of methylphenidate (MPH) on memory functions of adults with ADHD	N=108; MPH group N=36; Non-MPH group N=36; healthy adults without ADHD N=36; Germany	II		MPH	Nonmedicated adults with ADHD showed considerable impairments in memory function related to executive control; adults treated with MPH showed improved memory function compared to the nonmedicated group; healthy adults without ADHD showed the best memory function.	Pharmacotherapeutics improve memory functions in adults with ADHD, however they are still impaired when compared with healthy controls. Nonpharmacologic therapy, in addition to pharmacotherapy, is likely necessary to improve memory functions.
Geffen, J., & Forster, K. (2018). Treatment of adult ADHD: A clinical perspective. <i>Therapeutic Advances in Psychopharmacology</i> , 8(1), 25-32. https://doi.org/10.1177/2045125317734977 .	To recognize the importance of adult ADHD, overcome anxiety about the diagnosis, and prevent marginalization of vulnerable patients. Informational guideline.		I			Stimulant therapy is first-line for adults with ADHD. Drug holidays are not necessary for adults. Non-stimulant therapy is second-line for adult ADHD and may be introduced as 1) monotherapy in patients not suited to stimulant therapy; 2) augmenting treatment in combination with stimulants; or 3) treatment for comorbid conditions. Combined pharmacotherapy and psychosocial therapy (CBT) is recommended.	Practitioners should employ combined pharmacotherapy and psychosocial therapy for adults with ADHD.
Goodman, D. W., Starr, H. L., Ma, Y. W., Rostain, A. L., Ascher, S., & Armstrong, R. B. (2017). Randomized, 6-week,	To evaluate the efficacy and safety of individualized dosing within	N=357; OROS methylphenidate	I	Adult ADHD Investigator Symptom Rating Scale (AISRS);	OROS MPH, 18 mg/day increasing to individualized dose of 36	OROS MPH produced a significantly greater decrease in ADHD symptoms than placebo (P<.001). Significantly more individuals achieved remission on	Use of OROS methylphenidate may help adults with ADHD achieve remission.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
<p>placebo-controlled study of treatment for adult attention-deficit/hyperactivity disorder: Individualized dosing of osmotic-release oral system (OROS) methylphenidate with a goal of symptom remission. <i>Journal of Clinical Psychiatry</i>, 78(1), 105-114. https://doi.org/10.4088/JCP.15m10348</p>	<p>the approved dose range for osmotic-release oral system (OROS) methylphenidate hydrochloride in adults with ADHD</p>	<p>(MPH), N=141; Placebo, N=138 US</p>		<p>Clinical Global Impressions-Improvement (CGI-I); Central Nervous System Vital Signs (CNSVS); Continuous Performance Test (CPT); Shifting Attention Test (SAT); Symbol Digit Modalities Test; Behavior Rating Inventory of Executive Function-Adult (BRIEF-A); Adults ADHD Impact Module (AIM-A); Endicott Work Productivity Scale (EWPS); Dyadic Adjustment Scale (DAS); Pittsburgh Sleep Quality Index (PSQI); Epworth Sleepiness Scale (ESS); InterSePT Scale for Suicidal Thinking (ISST-Plus)</p>	<p>mg, 54 mg, or 72 mg/day until AISRS <18 or limit of tolerability; Matching placebo</p>	<p>symptoms using OROS MPH than the placebo (P=.0008). OROS methylphenidate did not appear to negatively impact sleep compared to placebo, however self-reported feelings of insomnia.</p>	
<p>Goto, T, Hirata, Y., Takita, Y., Trzepacz, P. T., Allen, A. J., Song, D., Gau, S. S., Ichikawa, H., Takahashi, M. (2017). Efficacy and safety of atomoxetine hydrochloride in Asian adults with ADHD: A 10-week randomized double-blind placebo-controlled Asian study. <i>Journal of Attention Disorders</i>, 21(2), 100–109.</p>	<p>To examine the efficacy and safety of atomoxetine in adult ADHD patients from Japan, Korea, and Taiwan.</p>	<p>N=195 intervention ; N=196 placebo; Asia</p>	<p>I</p>	<p>CAARS-Inv; quality of life (QoL); executive function (EF)</p>	<p>Atomoxetine</p>	<p>With atomoxetine there was a reduction in CAARS-Inv and improvements in QoL and EF</p>	<p>Atomoxetine is an effective and tolerable treatment for adults with ADHD with low risk for adverse effects.</p>

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
https://doi.org/10.1177/1087054713510352							
Groß, V., Lücke, C., Graf, E., Lam, A. P., Matthies, S., Borel, P., Sobanski, E., Rösler, M., Retz, W., Jacob, C., Colla, M., Huss, M., Jans, T., Kis, B., Hamid, M. A., van Elst, L. T., & Philipsen, A. (2019). Effectiveness of psychotherapy in adult ADHD: What do patients think? Results of the COMPAS study. <i>Journal of Attention Disorders</i> , 23(9), 1047–1058. https://doi.org/10.1177/1087054717720718	Efficacy of psychological and pharmacological ADHD treatments as evaluated by observer-rated and patient-rated symptom change	7 study sites in Germany; N=433	II	Patient-rated ADHD symptoms, CAARS-S:L; Clinical Global Assessment-Efficacy (CGA-E); Observer-rated CAARS-O:L; CGI-I; CGA-E	Group therapy (dialectical behavior therapy (DBT) and cognitive behavior therapy (CBT), 22 sessions; clinical management CM) individual counseling without structured behavior intervention or homework, 22 sessions; pharmacologic treatment (double blinded) with methylphenidate (MPH) sustained release starting at 10 mg/day and increased to maximum dosage of 1.3 mg/kg or placebo	ADHD-specific group psychotherapy outperformed non-ADHD specific individual counseling post-treatment ($P < .0001$) and at follow-up ($P = .004$).	Group ADHD therapy may be an effective approach to symptom improvement
Gutman, S. A., Balasubramanian, S., Herzog, M., Kim, E., Swirnow, H., Retig, Y., & Wolff, S. (2020). Effectiveness of a	To determine whether a 7-week tailored occupation-based	N=11 intervention ; N=12 control;	I	Adult attention deficit hyperactivity disorder self-report scale; Perceived stress scale;	7 week individual 1-hour sessions	The intervention group revealed statistical improvement in perceived stress, ADHD symptoms, COPM, and satisfaction ($P = .000$)	An intervention focusing on routine establishment, organization, time management, stress management, and sensory regulation in home and community may be helpful for women

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
tailored intervention for women with attention deficit hyperactivity disorder (ADHD) and ADHD symptoms: A randomized controlled study. <i>American Journal of Occupational Therapy</i> , 74(1), 1-11. https://doi.org/10.5014/ajot.2020.033316	intervention can reduce perceived stress and ADHD symptoms and enhance perceived performance of and satisfaction with daily roles and activities among women with ADHD	US		Canadian Occupational Performance Measure			with ADHD, though more research is warranted.
Janssen, L., Kan, C. C., Carpentier, P. J., Sizoo, B., Hepark, S., Schellekens, M. P. J., Rogier, A., Donders, T., Buitelaar, J. K., & Speckens, E. M. (2019). Mindfulness-based cognitive therapy v. treatment as usual in adults with ADHD: A multicentre, single-blind, randomised controlled trial. <i>Psychological Medicine</i> , 49(1), 55–65. https://doi.org/10.1017/S0033291718000429	To investigate the efficacy of mindfulness-based cognitive therapy (MBCT) plus treatment as usual (TAU) versus treatment as usual (TAU) alone in reducing core symptoms in adults with ADHD	N=120; MBCT, N=60; TAU, N=60; Netherlands	I		Mindfulness-based cognitive therapy	MBCT + TAU revealed a significant reduction in clinician-rated ADHD symptoms and the effect was maintained until 6-month follow-up. No improvements were shown in the domain of executive function post-treatment, however there were improvements at the 6 month follow-up.	Mindfulness-based cognitive therapy may be an effective treatment option in addition to treatment as usual for adults with ADHD looking for enhanced symptom improvement.
Knouse, L. E., Teller, J., & Brooks, M. A. (2017). Meta-analysis of cognitive-behavioral treatments for adult ADHD. <i>Journal of Consulting and Clinical Psychology</i> , 85(7), 737-750. http://doi.org/10.1037/ccp0000216	To examine effects of cognitive-behavior therapy (CBT) versus controls in adults with ADHD.	32 studies; Country not specified	I		Cognitive-behavior therapy	CBT is associated with medium-to-large effects on ADHD symptoms. Effects of CBT were comparable for participants regardless of medication status or treatment format.	CBT is a viable option for symptom reduction in adults with ADHD.
Lenzi, F., Cortese, S., Harris, J., & Masi, G. (2018). Pharmacotherapy of emotional	To assess the effects of ADHD	23 double-blinded RCTs for	I	Systematic review and meta-analysis of RCTs	Methylphenidate (MPH); lisdexamfetamine	MPH significantly more efficacious in reducing severity of emotional dysregulation	Analysis reveals that medication was more efficacious than placebo at reducing both provider- and self-rated

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
dysregulation in adults with ADHD: A systematic review and meta-analysis. <i>Neuroscience and Biobehavioral Reviews</i> , 84, 359–367. https://doi.org/10.1016/j.neubiorev.2017.08.010	medications on emotional dysregulation in adults with ADHD.	the qualitative review and 21 for the meta-analysis; N=4,724 Stimulant N=1,549 Non-stimulant N=1,230 Placebo N=1,945 Country not specified			mine, atomoxetine, and placebo	symptoms compared to placebo, SMD=0.34); atomoxetine showed a low effect size (SMD=0.24); lisdexamfetamine small-to-medium effect size (SMD=0.34) increasing to moderate effect when removing cross-over studies (SMD=0.50)	symptoms of emotional dysregulation. The effect is shown to be less than the reductions of core ADHD symptoms (impulsivity, distractibility, etc.). It is not clear if mood stabilizing medications would be more effective at controlling symptoms of emotional dysregulation in adults with ADHD.
Smith, V. N-, Merwood, A., Hand, D., Brandling, J., Greenwood, R., Skinner, L., Law, S., Patel, V., & Rai, D. (2020). Non-pharmacological interventions for adult ADHD: A systematic review. <i>Psychological Medicine</i> , 50(4), 529–541. https://doi.org/10.1017/S0033291720000069	To review evidence-based non-pharmacological treatment options for adults with ADHD who are still experiencing symptoms or for those who have made the informed choice not to start medication	32 studies; N=2,366; Country not specified	I		Individual CBT; Group CBT; Internet CBT; Hypnotherapy; Working Memory Training; Mindfulness and Meditation; Psychoeducation; Cognitive Training; Neurofeedback; Self-monitoring; Self-help	Majority of individuals found symptom improvement with CBT treatment.	CBT is a viable option for symptom reduction in adults with ADHD.
Verbeek, W., Bekkering, G. E., Van den Noortgate, W., & Kramers, C. (2017). Bupropion for attention deficit hyperactivity disorder (ADHD) in adults. <i>Cochrane Database Systematic</i>	To assess the effects and safety of bupropion for the treatment of adults with ADHD	6 studies; N=438; US and Iran	I		Bupropion use for adults with ADHD; placebo	Low-quality evidence that bupropion decreased the severity of ADHD symptoms and moderately increased the proportion of participants achieving a significant clinical improvement in ADHD	More research is needed to determine the efficacy of bupropion as a treatment for adults with ADHD.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
<i>Review, 10(10).</i> https://doi.org/10.1002/14651858.CD009504.pub2						symptoms. Tolerability of bupropion is similar to placebo.	