Current Topics Presented at the International Scientific Board of Experts on ADHD (ISBEA)

These presentations took place as part of the 8th Meeting of the International Scientific Board of Experts on ADHD (ISBEA) held on 21 September 2023 in Montpellier, France

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Received: 31st January 2024; Accepted: 5th March 2024

Abstract

Lifestyle factors such as diet and the presence of comorbid conditions can impact the diagnosis, course, and treatment of Attention Deficit Hyperactivity Disorder (ADHD). Children and adolescents with ADHD may have a different gut microbial composition when compared to neurotypical peers, although studies show a lack of consensus, identifying an urgent need for best practices. Results of TRACE, a dietary intervention study, indicated that long-term dietary treatment cannot fully replace Care As Usual for most children with ADHD and that an elimination diet is not advisable as part of ADHD treatment. Mood disorders are highly comorbid in ADHD, with 40—50% of all adult patients with ADHD having at least one depressive episode in their lifetime. ADHD also negatively affects quality of life and disease course in people with comorbid depression and increases suicidality. The ADHD-Major Depressive Disorder (MDD) phenotype is similar to bipolar depression (BD) and given the higher conversion risk in this phenotype, this might underlie the high comorbidity between ADHD and BD. However, in practice, ADHD is often overlooked in the presence of mood disorders. The high comorbidity of ADHD in MDD and BD suggests a rationale for formal screening and assessment in patients with MDD and BD. Both the mood disorder and ADHD should be adequately treated to improve patients' lives. Results presented here are from the 8th meeting of the International Scientific Board of Experts on ADHD.

KEYWORDS: ADHD; BIPOLAR DISORDER; COMORBIDITY; DEPRESSION; DIET; GUT MICROBIOME; NUTRITION; SUICIDE.

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Acknowlegements:
Thanks are given to Scientific Writers LTD., for medical writing assistance and Oruen LTD., for editorial support in the preperation of this article.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by impulsivity, hyperactivity, and poor attention capacity.[1] ADHD is a childhood-onset disorder with a prevalence of around 5–7% in childhood and 2–3% in adulthood.[2] ADHD is increasing among children and adolescents and places significant demands on paediatric specialist mental health services.[1] Guidelines recommend a multimodal treatment approach emphasising psychoeducation for patients, their families and caregivers.[1] Typical pharmacological treatment options for young people and adults include stimulant and non-stimulant medications.[1] New approaches towards the prevention and treatment of mental illness are needed, which can be delivered alongside or in the absence of traditional mental health care to reduce the global and growing burden of these conditions.[3] Several factors can impact the diagnosis, course, and treatment of ADHD. These include lifestyle factors such as diet and comorbid conditions.[2,3]

Although it is recognised that ADHD has a clear genetic component, non-genetic factors need to be considered to fully understand the disease.[3] There is evidence for a link between lifestyle factors such as smoking, lack of sleep, exercise, and diet on ADHD symptoms.[3] Comorbidity rates for psychiatric disorders are high, and for ADHD include mood disorders (MDD, BD), or substance use disorder (SUD).[2] Comorbidities suggest that one condition may be a risk factor for another and that they share a common aetiology.[2] Comorbidities impact quality of life and disease course, and affect treatment choices.[4-6]

1. ADHD, Nutrition and the Gut Microbiome

Studies suggest that the diet of ADHD individuals differs from their neurotypical peers as people with ADHD more frequently have a less healthy and pro-inflammatory Western diet.[7-9] This diet is high in fats and sugars and low in vegetable, fruit, and fibre intake. It is proposed that dietary interventions may ameliorate ADHD symptoms, including elimination diets and supplementation (probiotics, minerals, vitamins, PUFAs).[10]

The composition of the gut microbiota is influenced throughout neurodevelopment by external and host factors.[11] These include the diet of the individual, maternal and birth factors, feeding type and complementary feeding, and the use of antibiotics. The gut microbiome, containing commensal bacteria, is another non-genetic factor besides diet, disease, and physical activity, that could play a role in ADHD risk.[12] The microbiota are the ecological communities of commensal, symbiotic and pathogenic microorganisms found in and on all multicellular organisms. The microbiome is the combined genetic material of the microbiota. The gut microbiome influences different processes that range from immune function, neurotransmitter precursor production, hepatic function, blood pressure and blood-brain barrier function.[13]

The hypothesis is that brain homeostasis is (partly) determined by the interaction between the bacterial microbiome, diet, and the host's genome via the gut-brain axis.[14] There are 3 main modes of interaction between the gut, the entire nervous system, and the brain:

1. Activating the vagus nerve.
2. Activating the immune system.
3. Stimulating the endocrine system.

The latter includes the production of precursors for neurotransmitters as around 90% of all serotonin is produced by the gut.[13]

The EU project "Eat2beNICE" researched the impact of nutrition, lifestyle and physical activity on ADHD.[15] The aim was to evaluate if the variation of the human microbiota is associated with ADHD. Published research suggests there may be such an association, although limitations to research on microbiota and ADHD include a lack of consensus in published studies and that most publications are reviews.[16-19] There are issues with sample size and heterogeneity, sequencing methods and regions, and bioinformatics and statistics, questioning the robustness of the associations.

The first approach was via a meta-analysis of four adult ADHD case-control studies (IMpACT2, MIND-set, NeuroIMAGE, VHIR).[20] The study extracted bacterial DNA from stool samples and sequenced the 16s bacterial gene, which indicates the taxonomic cluster (genus) and abundance of bacteria present. The meta-analysis included genera with >10% selection probability in all four studies and >10% prevalence in at least one of the studies, yielding 28 genera with 21 prevalent in all 4 studies. Logistic regression analysis identified five genera associated with adult ADHD. Four were also associated with

adult ADHD using a different method, ANOVA-like Differential Expression (ALDEx2).[21] Two genera were found to be robustly associated in the meta-analysis. The study found that those genera that were more abundant in ADHD and associated with ADHD symptoms are involved in pro-inflammatory processes and might be considered risk-conferring, while the less abundant genera in the ADHD group were related to anti-inflammatory processes.

The second approach was using the Research Domain Criteria (RDoC) framework, investigating the correlation between the incidence or prevalence of gastrointestinal problems in people with psychiatric disorders. Research indicates that 40–60% of individuals with a psychiatric disorder have gastrointestinal symptoms (N=8037; Kox et al., in preparation). Patients with psychiatric disorders also show alterations in the gut microbiota composition.[12] To investigate, a transdiagnostic perspective was chosen using a dimensional approach incorporating comorbidity and heterogeneity, which is common in psychiatric disorders.

MIND-Set is a diagnostic study which aims to determine the shared and specific mechanisms of neurodevelopmental and stress-related psychiatric disorders.[22] The study asked whether there are associations between the gut microbiota and psychiatric symptoms across disorders. The study included 369 participants (272 patients, 97 controls) and found a high degree of comorbidity between symptom domains, including negative valence, social processes, cognitive systems, arousal/regulation and type of bacteria. The study was able to capture the behaviour regardless of the specific psychiatric diagnosis (e.g., schizophrenia, bipolar disorder, ADHD) and associate it with specific bacterial genera (Figure 1). Findings also revealed a correlation with immune response. The relative abundance of some bacteria and symptoms was associated with increased immune-mediated inflammatory disease and increased pro-inflammatory cytokines, while other bacteria and symptoms were associated with decreased immune-mediated inflammatory disease and decreased pro-inflammatory cytokines. Studies indicated that variation of the gut microbiome is associated with ADHD, although harmonisation across research designs is a necessary step to find robust association signals. In addition, data reduction (when possible) and multivariate approaches offer analytical flexibility for small (underpowered) studies. Feature selection approaches (i.e., randomised lasso) can help select informative features.

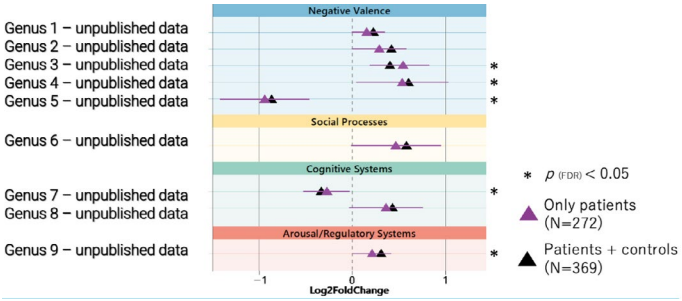

Figure 1. Results from Mind-Set study investigating the correlation between psychiatric behavioural symptom domains and the gut microbiome.

Conclusions and Outlook

Children and adolescents with ADHD might have a different microbial composition when compared to neurotypical peers. However, there is a lack of consensus on studies of children and adults identifying an urgent need for best practice approaches. Further understanding regarding the role of the gut microbiota in ADHD could open new avenues for early intervention and improved management of the disease which includes the effect of diet, e.g., probiotic treatments. Specific diets may be designed which could target specific beneficial ADHD microbiota. Future research is needed to investigate if gut microbiota is linked to the risk of developing ADHD and what are the exact altered routes of communication between the brain and the gut microbiome involved in ADHD.

2. Treatment of ADHD with Care as usual versus an Elimination diet (TRACE) Study

Studies suggest that the diet of ADHD individuals may differ from their neurotypical peers[7-9] and contain a high percentage of fats and sugars and a low vegetable, fruit, and fibre intake. The elimination diet has been studied as an intervention to ameliorate symptoms of ADHD,[7] consisting of only hypoallergic foods consumed over 2–5 weeks. Results from studies indicated that approximately 33% of participants were responders. Criticisms included the uncontrolled nature of the study designs, the diet was too difficult to adhere to, adverse effects were not measured, and long-term effects were unknown.

The TRACE study investigated the short-term and long-term results of dietary intervention, taking criticism of previous elimination studies into account.[7] The TRACE study randomised children between an elimination diet (n=84) or a healthy diet (n=81) as an active control. The study also included a non-randomised comparative arm with children following Care As Usual (CAU, n=58). Participants were prospectively followed up until one year after entering the study. The elimination diet excluded foods that might evoke a hypersensitive reaction, while healthy diets were based on nutritional guidelines from the World Health Organisation.[10] Inclusion criteria were for participants to be 5–12 years of age with a diagnosis of ADHD with or without comorbidities, and having an adequate mastery of the Dutch language. Exclusion criteria included having adequately controlled ADHD, eating disorders, diabetes, and following another restrictive diet such as being vegetarian or vegan.

Participants were mostly boys (78%), with an average age of approximately 8 years and an average IQ of approximately 100. A substantial proportion (~40%) had oppositional defiant disorder (ODD) and severe internalising disorder (~32%). All groups had a high prior belief in a treatment they were dedicated to. Parents who preferred a dietary treatment had a higher belief in the relationship between food and behaviour. Although the study was designed as a 3-arm study, investigators were unable to recruit enough participants in the CAU group. The participants were overall healthy and comparable with the general population of children in the Netherlands and had similar energy and nutrient intake.

The primary outcomes of the study were multi-dimensional, multi-rater assessments, combining parent and teacher ratings. Measures included inattention, hyperactivity, impulsivity, and emotion regulation. Prior studies suggested that the diet may be particularly effective in reducing irritability, which is not captured by the ADHD symptom dimensions. A 30% improvement in symptoms was considered improvement whereas a 30% increase in problematic symptoms indicated a deterioration. Responses included improvement, partial improvement, mixed response (parents and teachers disagreed), non-response, and deterioration.

After 5 weeks, results of the study indicated good adherence (96%) by participants to the diet with few adverse events. Responses showed that the elimination diet did not outperform the healthy diet, with fewer children on an elimination diet showing full or partial response compared with children following the healthy diet (Figure 2). The results for children following a healthy diet were comparable to those receiving CAU. Overall, parents observed larger effects of treatment than teachers, particularly on emotional dysregulation symptoms. Secondary outcomes indicated improvements in health in both dietary intervention groups, including somatic complaints, blood pressure, heart rates, and BMI. There were signs of deterioration of health in the CAU group. There was an overall increase in parental stress in all conditions.

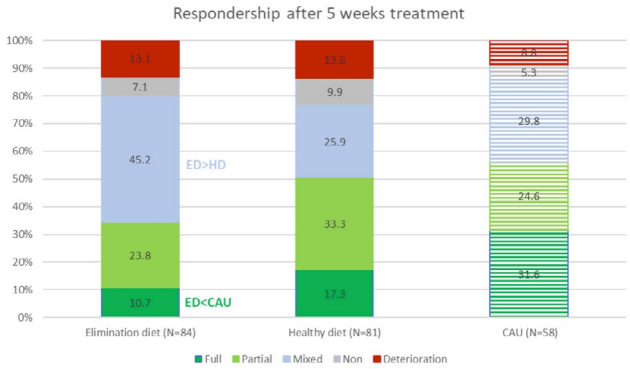

Figure 2. Response after 5 weeks of dietary treatment in children with ADHD in the TRACE study (primary outcome). Abbreviations: ED, Elimination Diet; CAU, Care As Usual.

The study concluded that after 5 weeks:

1. A short-term dietary treatment for ADHD in children is feasible and safe.
2. Treatment with an elimination diet is not superior to treatment with a healthy diet.
3. ADHD is probably not rooted in food-allergies/-sensitivities for the majority of children.
4. Inconclusive effectiveness of ADHD treatment is common (rater disagreement in ~30%).

After 5 weeks, participants who showed improvement or partial improvement were offered to continue with their diets. Although not advised to do so, other responders were also allowed to continue with their diet. After 1 year, 90% of participants continued their diet, which was comparable across treatment groups. After 1 year, the healthy diet continued to outperform the elimination diet. A large proportion (48%) of the parents and teachers in the elimination diet group disagreed in their responses. There was no significant difference between

a healthy diet and CAU. Results after 1 year also indicated that for most children, diet is not a sufficient standalone treatment for ADHD. More improvement was seen with a combination of a healthy diet with CAU than with the elimination diet.

Predictors of favourable adherence and response to diet are presented in **Table 1**:

	Predictors
Child	Younger age, symptom severity (combined presentation with irritability and emotional dysregulation) Rater agreement between parent and teacher (not significant: IQ, sex, nutritional habits, physical health)
Parent	Positive prior expectancy, good mental health, e.g., low stress levels and good quality of life
Parent-Child Relationship	Warmth, feeling competent/able
Social and Economic Status	Parents' education, 2-parent household

Conclusions and Outlook

The overall conclusions of TRACE were:

1. Long-term dietary treatment cannot fully replace CAU for most children with ADHD.
2. Treatment with an elimination diet is not advisable as part of ADHD treatment.
3. A healthy diet as an optional start of ADHD treatment is advisable for school-aged children.
4. When treating ADHD, parental factors (e.g., treatment preference, resilience) are equally important as child factors.

3. ADHD Comorbidity: Depression and Suicidality

Epidemiology

As stated earlier in this report, studies suggest that the diet of ADHD individuals may differ from their neurotypical peers[7-9] and contain a high percentage of fats and sugars and a low vegetable, fruit, and fibre intake. The elimination diet has been studied as an intervention to ameliorate symptoms of ADHD,[7] consisting of only hypoallergic foods consumed over 2–5 weeks. Results from studies indicated that approximately 33% of participants were responders. Criticisms included the uncontrolled nature of the study designs, the diet was too difficult to adhere to, adverse effects were not measured, and long-term effects were unknown.

Depression is among the most common comorbidities of ADHD, particularly in adults, according to administrative data from the German Statutory Health Insurance Database (4 million children and adults accessing care).[23] The risk for mood disorders is 5 times higher in patients with ADHD than those without ADHD across all age groups, and gender ratio is approximately 1:1. The largest risk is found in males aged 31 years or over, who have a 19-fold higher risk for mood disorders compared with individuals with no diagnosis of ADHD.[23] These data support the need to screen males aged 30–50 years presenting with depressive symptoms, for ADHD. Using a meta-analysis of all population-based studies, a five-fold increased risk for depression in patients with ADHD was found (Figure 3).[2]

Using the German claims dataset in newly diagnosed adults with ADHD, comparing patients who received guideline adherent therapy (defined by having a stimulant prescription for more than six months, n=624) with those who did not receive guideline adherent therapy (n=1756), patients with comorbid depression were more likely to receive guideline adherent treatment, and higher specialist care.[24] These findings may either indicate higher ADHD severity, suggest that comorbid depression may index disease severity, or increased presentation to secondary care specialists in the comorbid situation. Data also show that depression prevalence decreased after ADHD treatment initiation, from 65% to 53% in those who received guideline adherent treatment.[24] These data suggest that ADHD treatment also impacts the prevalence of comorbid depression.

When analysing data from samples that primarily look at MDD, in a meta-analysis of 52 studies (n=16 897), the prevalence of ADHD in MDD was 28% (95% confidence interval [CI]: 19–39) in childhood, 17% (95% CI, 12–24) in adolescence, and 7% (95% CI: 4–11) in adulthood, indicating that ADHD was 3 times more common in MDD compared with controls, and more so in childhood and adolescence than in adulthood.[25]

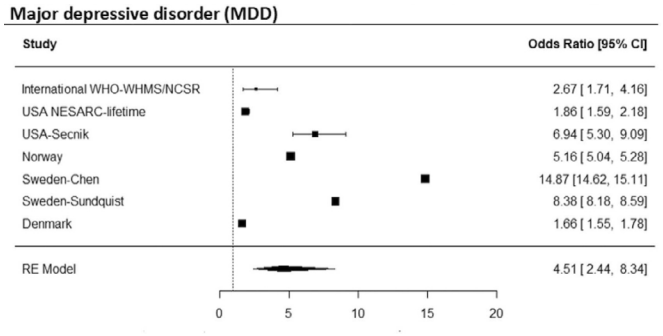

Figure 3. Meta-analysis of population-based ADHD comorbidity studies. Adapted from results by Hartman et al.[2] Panel shows pooled and study specific relative risk (odds ratio, OR) of MDD in individuals with ADHD compared with individuals without ADHD. Positive OR values indicate a higher risk in individuals with ADHD. The diamond shape at the bottom of the panel is the pooled difference between adults with and without ADHD.
Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; CI, confidence interval.

In a meta-analysis of BD and ADHD (24 studies, n=222 000), the lifetime prevalence of bipolar disorder in patients with ADHD was 8.4% as compared with 1–2% in the general population; approximately 8-fold higher than in the general population and with a point prevalence of 3.8% (12 studies, n=14 000).[26] The study found no significant influence of age, sex, sample size, or diagnostic manual used. Conversely, in patients diagnosed with BD, the lifetime prevalence of ADHD is 18% (24 studies, n=402 000), with a point prevalence of 21% (12 studies, n=11 000).[26] The effects were smaller in large, epidemiological samples as compared with case-control samples (25% vs. 8%, P<0.001).[26] These data indicate that in addition to comorbid depression there is also comorbid BD in ADHD and suggest a rationale for formal screening and assessment in patients with BD for ADHD.

Phenotype and Course

The likelihood of comorbid depression and anxiety increases with ADHD severity. Studies show that comorbid MDD significantly impacts quality of life of people with ADHD and that the reduction in quality of life is mediated by depressive symptoms.[4,5] Severity of ADHD correlates with the prevalence of MDD over the lifetime. However, ADHD is often overlooked when comorbid MDD is present indicating the importance of screening for comorbidities and initiating adequate treatment to improve patient lives.[5]

Studies indicate that the phenotype of depression is different in ADHD. The BRIDGE-2-MIX study found that ADHD-MDD has "bipolar-like" features, including a higher number of (hypo)manic symptoms during MDD, a higher prevalence of mixed or atypical depression, a common MDD onset before 20 years of age, a positive family history for (hypo)mania, a history of manic switch during antidepressant medication, a higher number of affective episodes, more bipolar specifiers and a higher number of other psychiatric comorbidities.[27] The question of whether it is a subtype of depression or the effect of ADHD symptoms on depressive symptoms remains to be answered and longitudinal studies are needed to elucidate this. The clinical take-home message is that patients with ADHD have a higher risk of depression prompting the need to assess for the presence of the other disorder when patients present with symptoms for either disorder.

A large study in the Netherlands in staged MDD patients (n=1851) found that more severe stages of depression were associated with more symptoms of ADHD.[28] ADHD symptoms were associated with an early onset, more episodes and hospitalisations, suicidality and self-harm, and irritability.[29] The study found that a higher MDD severity was associated with more ADHD symptoms. The research again highlights the importance of looking for the presence of ADHD in therapy-resistant depression.

Evidence on the phenotype of BD in ADHD comes from Mayo Clinic Bipolar Biobank study (N=2198: BD + childhood ADHD [cADHD], n=350; BD + adult ADHD [aADHD]: n=254; BD without ADHD: n= 1594), which found that BD + cADHD patients were younger, more often male, more often had comorbid anxiety disorders and substance abuse disorder (SUD) (P<0.001), and poorer response to lithium and lamotrigine (P<0.007).[30] In addition, a meta-analysis of 43 studies found ADHD with BD more often present in males (odds ratio [OR]=1.46; P<0.001), unemployed people (OR=1.45; P=0.045), and single people (OR=0.62; P=0.014).[31] Comorbid ADHD was associated with earlier onset of BD (standardised mean difference [SMD]= −0.36; P<0.001), and more BD episodes (SMD = 0.35; P=0.007; especially depressive and mixed episodes). It was also associated with a higher number of suicide attempts (OR= 1.83; P<0.001), higher comorbidity with generalised anxiety disorder, panic, social phobia, eating

disorders, antisocial personality disorder (OR = 3.59; P=0.004) and SUD (OR = 2.29; P<0.001).[31]

One complication is that many symptoms of ADHD mirror those of the bipolar prodrome, which is characterised by irritability, aggressiveness, sleep disturbances, depression, hyperactivity, anxiety, and mood swings, complicating a differential diagnosis.[32] Using personal history, family history, episodicity, and childhood onset presentation is important in differentiating them. ADHD, for instance, is unlikely in patients presenting their first symptoms at the age of 40 years. A second differential diagnosis is bipolar mixed states, which presents as depression and mania with suicidal thoughts, hopelessness, depressed mood, irritability, racing thoughts, and increased drive, which can also look like ADHD. The episodic course of BD is an important factor in the differential diagnosis between both disorders.

A seminal study investigated the development of bipolar disorder symptoms in patients with MDD.[33] Over 500 patients with MDD were included and followed up for 30 years. The study found around 20% (N=108) of patients experienced hypomania or mania, resulting in revision of diagnoses for 12.2% to bipolar II and 7.5% to bipolar I disorder. Risk is particularly high in patients who have BD symptoms at intake, with the risk for an MDD patient developing bipolar disorder within five years being 40%. The phenotype of these patients overlaps with ADHD patients and may explain the higher BD switch risk with ADHD and MDD comorbidity, and the 8-fold higher risk of ADHD and disorder comorbidity. Consequently, patients with ADHD may have a higher risk of developing MDD and BD which affects treatment choices, including the rationale for using mood stabilisers and second-generation antipsychotics instead of mania-inducing agents.

Patients with ADHD are also at increased risk of suicide,[34,35] with odds ratios for attempted suicide and completed suicide of approximately 3.5 and 6.0, respectfully.[34] In a third study, looking at mortality in ADHD, all-cause death was increased in ADHD and increased with the number of psychiatric comorbidities. The study suggests an interplay between ADHD, comorbid mental disorders, and suicide attempts. A possible explanation for this would be that increased impulsivity and uncontrolled immediate actions increase the likelihood of acting upon suicidal ideation.

A systematic review of 40 studies identified the following risk factors for suicidal behaviours in ADHD: ADHD symptom severity and persistence, female gender, childhood & parental influences, social functioning, comorbid psychiatric disorders (especially depression), increased impulsivity, and emotional dysregulation.[36] The study concludes that overall, ADHD emerges as an independent risk factor for suicidal spectrum behaviours. ADHD also correlated with suicidal behaviours in adolescents (k=6; n=22445; d=0.54 (0.34–0.75); P<0.001).[36, 37] In addition, many studies link the genetic risk of ADHD and suicide.

Causes

When looking at possible causes for the correlation between ADHD, MDD, and suicidality, almost every environmental MDD risk factor can be found more often in ADHD: these include traumatic life events, adverse childhood events, disturbance in parental bonding, unstable relationships, repeated social rejection, repeated failure, obesity, substance use, other somatoform psychiatric conditions. There is also an overlap in affected brain regions, most notably the reward system (involving the prefrontal cortex, PFC). Increased impulsivity in ADHD may lead individuals to act upon their suicidal ideation leading to increased suicide attempts.

Genetic factors also play an important role. Individuals with ADHD have an adjusted HR=4.1 for subsequent development of MDD.[38] Mendelian randomisation shows that genetic liability for ADHD is causally related to MDD (OR=1.2).[38] There is a high overall genetic correlation between mental disorders, including schizophrenia, MDD, BD, and ADHD.[39-41] ADHD shows the strongest genetic correlation with MDD and PTSD. The most parsimonious explanation would be that common genetic correlation captures a vulnerability that is not disease specific. Data from genome-wide association studies (GWAS) point to specific risk loci for ADHD, with 5600 casual genetic variants (polygenicity) identified, and with a genetic correlation of r=0.45 with MDD, indicating a high number of shared genetic variants.[42] These genetic data also show that DSM criteria are not sufficient in describing psychiatric disorders. The future may hold a disease mechanism-driven classification system, encompassing the subjective experience or the clinical phenotype.

Treatment

Stimulant therapy may prevent depression in later life.[43-45] In one study, ADHD medication was associated with a 40% reduced long-term risk for depression (HR=0.58).[46] In addition, a longer duration of ADHD medication was shown to lower the risk.[46] ADHD medication was also associated with reduced rates of concurrent depression.[46] Similarly, in a large sample from Taiwan, longer methylphenidate use indicated significant protective effects against developing depressive disorder (OR=0.91).[45] The clinical message is that ADHD needs to be treated adequately to reduce its negative consequences.

How should ADHD with depression be treated? A consensus-derived diagnostic algorithm for ADHD was designed by a panel of psychiatrist-clinicians with expertise in child and adolescent ADHD and mood disorders, adult mood disorders, and adult ADHD.[6] The panel recommended a general screen for the assessment of possible ADHD, even when there are other psychiatric presentations. The panel recommended treating the depression in the first instance. A study looking at adult ADHD with MDD comorbidity, comparing group psychotherapy, individual counselling, medication, and placebo, found there was no significant effect of any treatment on depressive symptoms.[47] However, the study was not sufficiently powered for the investigation, and patients were not selected for MDD comorbidity.

There is some clinical guidance on the basic principles of treating ADHD and depression in the absence of adequately powered clinical studies.[6] While ADHD can be diagnosed during depressive episodes, this should be confirmed during euthymia and the burden and relevance of ADHD on a person's life should be assessed. It is recommended to adequately treat the depressive episode, followed by an assessment of the relevance of ADHD and subsequent treatment of ADHD when needed using stimulants.

Potentially beneficial due to the effects on ADHD are venlafaxine,[48] bupropion,[49] and nortriptyline.[50] Selective serotonin reuptake inhibitors and other tricyclic antidepressants do not influence ADHD symptoms,[48] while atomoxetine,[51] duloxetine,[52] and reboxetine[53] monotherapies have no effect on depressive symptoms. A small, randomised trial investigating the combination of antidepressant and stimulant medication (SSRI plus atomoxetine or methylphenidate) in ADHD with comorbid partially responsive MDD resulted in a decrease in depressive symptoms across various measures.[54] However, this study was not placebo-controlled and suggests combination treatment may be safe, feasible and effective, although more studies are needed. Due to the risk of inducing mania, when BD is suspected, the use of mood stabilisers such as lithium is recommended, and careful assessment is needed before initiating monotherapy with stimulants.[55,56]

Conclusion

ADHD and MDD are substantially comorbid, with 40–50% of all adult patients with ADHD having at least one depressive episode in their lifetime.[2] Studies indicate that the more severe the symptoms of ADHD, the more severe is MDD and vice-versa.[28] The presence of comorbid ADHD and mood disorders has an important impact on quality of life with suicide being the most severe consequence.[34] ADHD-MDD phenotype is bipolar-like, leading to higher rates of ADHD-BD.[32,33] Causes of ADHD-MDD comorbidity are both genetic and environmental, with GWAS indicating a high number of shared genetic variants between both disorders.[42] Although ADHD-MDD can be diagnosed during a depressive episode, it should be confirmed during euthymia.[6] Studies show that stimulant treatment of ADHD reduces the risk for later-life MDD supporting early diagnosis and screening to improve patients' lives.[5] If clinically relevant, ADHD comorbid with MDD should be treated with stimulants (care should be taken when patients are treated with monoamine oxidase inhibitors).[43-45] Psychoeducation is key in treating ADHD and comorbid disorders, including advice for developing coping skills and raising awareness.[1]

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