

Gender differences in attention deficit hyperactivity disorder: an update of the current evidence

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Summary. The attention deficit hyperactivity disorder (ADHD) in women has recently received considerable attention, as research has shown an underestimation of the disorder in females, due to a difference in presentation compared to males: females have a higher risk of having ADHD, without those "disruptive" symptoms that determine the request for help. The purpose of the present narrative review is to identify the neglected clinical problems in the diagnostic and therapeutic intervention of women with ADHD and to analyze the associated comorbid problems. The conducted PubMed search and the relevant literature review on the topic show that the impairment of ADHD in women is underestimated due to the different ways the phenomenon manifests compared to traditional male's symptoms. This underestimation consequently leads to an inadequate treatment and has negative repercussions on the social context in which women are involved in.

Key words. Adult ADHD, comorbidity, gender differences, pregnancy, treatment, women.

Differenze di genere nel disturbo da deficit di attenzione e iperattività: un aggiornamento delle attuali evidenze.

Riassunto. Il disturbo da deficit di attenzione e iperattività (ADHD), di recente, ha ricevuto notevole attenzione, poiché la ricerca ha mostrato una sottostima del disturbo nella popolazione femminile, a causa della differente presentazione sintomatologica rispetto ai maschi: le femmine hanno un rischio maggiore di avere l'ADHD in assenza della sintomatologia dirompente. Lo scopo della presente rassegna narrativa era quello di identificare le problematiche cliniche spesso trascurate durante l'intervento diagnostico e terapeutico delle donne con ADHD e di analizzare i problemi di comorbidità associati. È stata condotta una ricerca su PubMed e, dall'analisi della letteratura, è emerso che la compromissione dell'ADHD nelle donne è sottostimata, sebbene le menomazioni funzionali sembrano influenzare maggiormente i contesti sociali in cui sono coinvolte.

Parole chiave. ADHD nell'adulto, donne, differenze di genere, gravidanza, trattamento, comorbidità.

Introduction

ADHD is one of the most common disorders diagnosed in childhood, characterized by problems related to attention, hyperactivity, and impulsivity; it is estimated that worldwide the disorder is prevalent in the child population, which represents 5.29% of the total population.

Recently, attention deficit hyperactivity disorder (ADHD) in women has received considerable attention, as research has shown an underestimation of the disorder in women due to a difference in symptom presentation compared to males. Women's probability of having ADHD is twice of males, despite the absence of "disruptive" symptoms that often lead to a request for help. However, scientific evidence shows that both sexes are affected by the disorder with the same severity and suffer the same disabling consequences.

Typically, women with ADHD without any childhood diagnosis discover their disorder only after one of their children is diagnosed with ADHD. When this is the case, the former can be invited for a pro-

fessional consultation, which is helpful to identify and finally recognize many of their behavioral patterns under a new perspective. Some ADHD women require intervention because their lives are "out of control", chaotic, they experience financial problems, difficulties in managing work, looking after their children, organizing the home, keeping in mind all the commitments of the family and the various commissions to be carried out. ADHD women frequently experience a dysphoric mood, anxiety disorders, and depression often complemented with eating problems and low self-esteem. The most common symptoms leading women to go to a specialist are typically depressive or stressful symptoms. In case ADHD is not recognized and properly treated, a chronicization of secondary disorders may arise¹.

Characteristics of ADHD, especially in women

ADHD is a psychopathological condition of neurodevelopment described by the leading international classification systems^{2,3}. It is usually diagnosed in childhood and often persists into adulthood, with

an estimated prevalence of ADHD in adult women of 3.2%. Although the disorder may have onset in childhood, diagnosis and treatment may be delayed until the presentation of clinical manifestations⁴.

ADHD is characterized by difficulties in two domains: inattention and hyperactivity-impulsivity. Three subtypes can be identified: predominantly inattentive, hyperactive-impulsive, and combined. Symptoms are stable over time, pervasive in various contexts, and cause severe impairment. While ADHD is present in childhood, its symptoms seem to take different evolutionary paths according to the different subtypes. In particular hyperactive-impulsive traits tend to fade away with advancing age, while inattentive symptoms persist. This development trajectory is common both in male and female populations.

The disorder seems to result from neurobiological dysfunctions that imply the persistence of problems relating to attention, agitation, and impulsivity that significantly compromise the proper functioning of everyday activities in the patients affected by it⁵. The prevalence of the disorder in the adult population ranges from 4% to 6%, and it is generally diagnosed in childhood with a prevalence rate of 11% and a male-female ratio of 3:1^{6,7}.

Research suggests that the prevalence ratio of M/F disorder is inaccurate and that females with the disorder are underdiagnosed despite having similar levels of impairment to males⁸. Although the identification of symptoms in males is more recognizable as characterized by impulsivity and inattention, females presenting exclusively attention-related issues without significant hyperactivity may not be identified as needing specific assessment and therefore they often do not benefit from adequate treatment. Indeed, several studies highlighted that the predominantly inattentive and disorganized symptomatology by part of the female population is often attributed to anxiety and depression⁹, rather than being recognized as a characteristic of the prevalent presence of ADHD.

Moreover, other common conditions in the female population with ADHD further complicate the symptom picture. Symptoms such as insomnia, chronic pain, generalized anxiety disorder, depressive disorders, low self-esteem, and suicidal ideation are indeed often attributed to these comorbidities.

In males, as the symptoms are usually more easily recognized, the identification and treatment are quicker compared to females' ones. As previously stated, symptoms for the latter are more frequently associated with internalizing pathologies rather than ADHD.

Moreover, fetal exposure to some environmental components, such as alcohol and drugs, during pregnancy influences the onset of the disease¹⁰. In addition, gestational hypertension, preterm birth,

and low birth weight can be considered risk factors, although further studies are needed to highlight a direct correlation between ADHD and exposure to environmental risk factors.

ADHD Comorbidity

Comorbid conditions are widespread among the entire adult population and include anxiety, depression, bipolar, eating disorders, OCD, substance use disorders, personality disorders, and impulsive control disorders. Nevertheless, some externalizing disorders, such as oppositional defiant disorder, comorbid with conduct disorder, and antisocial behavior, are more prevalent in men.

The less obvious and evident disclosure of ADHD in girls and women through atypical diagnostic criteria may hide a potential underlying ADHD behavior.

Thus, women may be more likely to receive a primary diagnosis for internalizing disorders or personality disorders, which in turn may delay the proper diagnosis and appropriate treatment.

Broadly focusing on eating disorders, evidence shows a potential association with ADHD and a higher prevalence of them among women rather than men¹¹.

Many studies have shown, for instance, a possible association between ADHD and obesity in adults. In particular, the results of the study by Schweickert et al.¹² indicate that ADHD correlates significantly with severe binge eating patterns within a sample of 55 women, with an average of 38.9 years and an average BMI of 39.2.

The hypotheses suggest that ADHD could be responsible for weight gain due to the disorganization of normal eating behavior, which may have led to binge eating. The authors further suggest that attentional and organizational difficulties lead people to compensate for the frustration of these symptoms with compulsive eating¹². The executive function deficits and working memory deficits present in the obese patients in the sample also suggest an impairment in the ability to track impulsive binge eating¹³.

Women with ADHD, who have an early onset have more prolonged episodes of depression and higher rates of suicide than women without ADHD^{14,15}.

A different genetic influence between the sexes and diversity in the neuroendocrine factors affecting the dopaminergic system (estrogen and thyroid) appear to be associated with an increased prevalence of depression in women with hormonal changes¹⁶. According to the literature, pregnant women with ADHD symptoms have a higher probability of developing internalizing symptoms and exceptionally higher risks of postpartum depression symptoms^{17,18}.

Furthermore, research shows that ADHD is asso-

ciated with worse clinical outcomes in women with bipolar disorder¹⁹ and that women with ADHD have more difficulties than men in various social settings²⁰.

One Japanese research investigated gender differences in sociodemographic and clinical characteristics of adults with ADHD. In the Japanese clinical trial, there was a high rate of psychiatric comorbidity and more marital and occupational functional impairments in the women sample than in men with the same pathology²¹.

This finding may be significant for public health because ADHD persisting into adulthood for women is associated with depression, anxiety, self-harm, substance use, and eating disorders. Adult women with ADHD can experience various difficulties at work due to their symptoms in personal and family life. Many report relationship problems that cause chronic feelings of frustration and guilt.

Often women with ADHD are unemployed or find low-skilled jobs resulting in a low earning capacity²².

A longitudinal study focusing on girls between the ages of 8 and 30 found that women with ADHD diagnosed in childhood were more likely than their peers to have little or no academic or professional skills, have poorly paid work, need benefits, live in temporary housing, and have a low income²³. Hence, ADHD has a substantial and long-term impact on a person's ability to perform routine daily activities and, in particular, women with ADHD who are starting work may need support in understanding an organization's needs, job role and staff structure, how to manage interpersonal conflicts, their time, plan and prioritize homework.

The deficit of executive functions in ADHD seems to play a fundamental role in behavioral self-regulation at various levels, such as in defining priorities, organizing and starting work; supporting and shifting attention to the various tasks; regulating the state of vigilance, commitment, and speed of processing during the execution of a task; management of frustration and regulation of emotions; working memory deficit and difficulty in accessing memory recall, so ADHD qualifies as a disability²⁴.

Pharmacotherapy of ADHD

ADHD therapy is multimodal, using pharmacological, psychotherapeutic, and supportive approaches. The drugs currently available for the are summarized below (table 1).

ADHD treatment:

- stimulants, such as methylphenidate (MPH), dexamethylphenidate, dextroamphetamine (DEX), mixed amphetamine salts (MAS), pemoline, and modafinil;
- non-stimulating drugs mainly include atomoxetine, bupropion, and alpha2-adrenergic agonists.

Table 1. Recommendations for medication in ADHD with a focus on the female gender.

Medication recommendations
• Treatment monitoring may require deviation from conventional outcomes from rating scales and behavior management. Individualized targets (e.g., emotional lability, academic attainment) may be more appropriate.
• Prescribers need to consider interactions between ADHD and other medications for comorbid conditions, where applicable.
• Where mood problems are apparent but not pervasive, it is advisable to treat ADHD symptoms and monitor for improvement before considering or initiating treatment for mood disorders.
• Appetite suppression as a side effect of stimulant medication should be considered if eating disorders are a concern.
• Risks of substance use while on ADHD medications should be considered and discussed with patients.
• Treatment with ADHD medications is generally not advised during pregnancy or breastfeeding.
• Treatment re-evaluation is recommended during and after crucial periods of hormonal change (menopause, pregnancy).
• Psychoeducation on pharmacological treatment options and treatment targets for parents and affected girls may help to improve adherence and engagement.
• Regular review is required throughout development and may be especially important at critical transitions.

There is also a vast literature on the use of tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), SSRIs, and atypical antipsychotics. Their effectiveness against the core symptoms of the disorder is poor, and they are mainly used to treat comorbidities²⁵. Controlled clinical trials demonstrate the efficacy of stimulants in the treatment of ADHD symptoms in adulthood²⁶.

Adverse effects such as increased heart rate and blood pressure, reduced appetite, and sleep are often associated with the administration of methylphenidate therapy and other stimulants¹⁰. Serious cardiovascular complications are rare with 0.2-0.4% increased risk compared to the general population documented in a single study. Particular attention should be paid exclusively to the risk of arrhythmias in case of congenital heart diseases²⁷⁻²⁹.

Treatment with atomoxetine is associated with a positive effect on ADHD symptoms in adults with an effect size between 0.33 and 0.40³⁰.

The use of atomoxetine would be preferable in patients in whom the rapid onset of the therapeutic response is not essential and in need of long-term stabilization, in patients with comorbidities.

ADHD and pregnancy

In order to stabilize maternal symptoms and minimize the risk of harmful effects on the fetus, the objectives of the treatment of pregnant ADHD women should include the correct management and prevention of possible mood and anxiety disorders; coordination between integrated obstetrics/gynecology and psychiatry teams.

Pharmacological options include stimulants (Methylphenidate, Amphetamine, Dexamphetamine, Lis-dexamfetamine) and non-stimulants such as bupropion and atomoxetine¹⁶. In some cases, switching from the stimulant drug to bupropion can be a middle path in case of symptoms of ADHD and depression in comorbidities. Prospective birth outcome data, available in the pregnancy registry of women treated with bupropion, suggest that malformation rates due to bupropion exposure are similar to those of the general population, although they are not as effective as stimulants in the treatment of ADHD³¹.

In a 2017 cohort study in a population of 453 women treated with atomoxetine, there was no evidence of risks of preeclampsia, placental abruption, or preterm birth³².

Supportive Interventions in ADHD

Despite the extensive literature on adults with ADHD, only a few have focused on examining the specific tailored interventions for affected women.

Studies have shown that women with ADHD tend to have difficulties in work, school, parenting skills, and marital relationships²². Adequate planning of the daily organizational activities can be complex due to internal and external stress factors women face³³. Furthermore, while men with ADHD may often rely on the assistance of their spouses or other family members to compensate for the typical deficits of the disorder, studies have shown that women with ADHD tend to deal with symptoms in a more isolated way³⁴. The situation for women is further deteriorated due to the underestimated share of those diagnosed or misdiagnosed, making it more difficult to provide specific interventions³⁵.

To promote effective interventions, Gutman et al.³⁶ have developed manualized guidelines to enhance planning strategies in women with ADHD.

He developed a tailor-made intervention for each woman, based on their main difficulties and according to their social role, especially in their daily routines or natural environment.

Women were helped in planning their daily routines through an occupational therapy path, by organizing spaces in everyday life environments, developing skills to manage time in a more straightforward, and recognizing and managing external and internal

distractors. Finally, programmed breaks, mindfulness, breathing exercises, and meditation were used to develop strategies and skills of emotional regulation in stressful situations.

Even if based on a limited sample, results show a reduction in perceived stress and symptoms typical of ADHD, which in turn translates into greater satisfaction associated with women's social roles and greater effectiveness in daily activities. This study may be taken as evidence that non-pharmacological support can be effective in the control of symptoms.

Socio-economic costs in mental health and ADHD

According to the World Health Organization, mental health has always been considered an essential component of health. However, its inclusion among the UN Sustainable Development Goals (SDGs) took place only in September 2015, as a stepping stone in acknowledging the burden of mental illness at a global level.

More in detail, the relevance of such recognition pertains not only to the increased awareness of its consequences on health, but it crucially highlights its huge socio-economic consequences.

Good mental health may indeed be defined as a facilitator of socio-economic development, as it enables individuals to fulfill themselves, work productively, and thus contribute to the community's life. On the other hand, if not properly handled, mental health may severely impact individuals due to the relevant social stigma associated with these pathologies^{37,38}, as well as having negative repercussions on the public sphere.

In this sense, mental health is strictly intertwined with well-being, and their relationship affects several sectors while cyclically increasing inequalities in educational attainments, health, productivity and income, social inclusion, housing, and poverty^{39,40}.

For this reason, at the international level, the awareness of properly treating mental illness is increasing. The WHO's Mental Health Action Plan 2013-2020 as well as The Health at a Glance Europe 2018 report make a strong case for promoting mental health, based on a life-course approach.

Psychiatric diseases in the last 10 years have "dramatically" increased, impacting significantly both public health and the economic side⁴⁰.

The economic costs may be both direct and indirect: direct costs impact the health systems and social security programs, while indirect ones refer to lower employment rates or lower productivity. Overall, both costs were estimated to amount to more than 4% of GDP across European countries in 2018³⁹, while the Lancet Commission⁴⁰ estimated a loss of 16 trillion in economic output between 2011 and 2030 for the global economy.

The Italian scenario aligns with the international one, with depression being the most common mental disorder in the country: 2.8 million people declared to have suffered from depression in 2015⁴¹.

More in detail, ISTAT estimates that about 15% of the adult population with a severe depressive or chronic anxiety disorder have been referred to a psychiatrist or psychologist between 2014-2015, with a higher prevalence in adults between 18 and 64 years (20.5 %).

Considering this data is relevant for the current article because, as discussed in the previous sections, women with ADHD disorder often display precisely these symptoms, namely anxiety and depression. In light of these comorbidities, available data on depression and anxiety may be used as a proxy for ADHD's potential socioeconomic costs.

Among the working population, those with chronic mental illness suffer from severe limitations in carrying out daily activities (25.4%), while this share significantly drops for those suffering from different chronic diseases (4.6%). The gap is even more significant when looking at the different levels of productivity or efficacy of daily activities (57.7% vs 9.8%) and at their attention deficit (57.4% vs 10.2%)⁴¹.

Moreover, severe and chronic anxiety and depression disorders negatively affect the number of days away from work (+18.7%) compared to the rest of the working population.

Furthermore, those suffering from anxiety or depressive disorders resort more frequently to treatment, both to a general practitioner or a specialist (93.1% and 75.2% respectively), compared to those with other chronic or acute diseases (85.6% and 64.2%).

The use of drugs is higher as well for the first group of the population (77.1%) compared to those with different chronic diseases (62.9%)^{41,42}.

According to the mental health Atlas (2017) published by the WHO, in 2017 low-income countries spent around 1\$ USD on mental health per capita, while high-income ones reached an average of 80\$ USD per capita. Italy's expenditure amounted to 71 euros per capita in 2016 and 75.5 euros in 2017.

Additionally, the country spent up to 3.6 billion in 2016 for territorial psychiatric assistance, which represents almost 3.2% of the overall health public expenditure.

Conclusions

ADHD is the most commonly studied childhood psychiatric disorder, and, as such, a significant amount is known about how it appears and what impairments are likely to coexist alongside it. Nevertheless, the literature on ADHD in the adult population is scarce and presents several limitations, *inter alia*,

data availability, small sample sizes, referral biases, and a lack of diagnostic assessment standards⁴³.

Moreover, the sexes are unequally represented⁴³, as most of these studies focused on men with ADHD rather than women. This is due to the fact that while men typically manifest disruptive and externalizing disorders, women's symptoms are not immediately reconducted to ADHD. Indeed, as previously discussed, they usually appear as internalizing disorders.

Underestimating the share of women with ADHD often leads to treatments that focus only on the main symptoms, without tracing them back to the potential underlying ADHD.

Future research should take into account that other than traditional symptoms, internalizing disorders may as well be related to ADHD. This acknowledgment may reduce underestimation in women affected by the disease and allow for better and tailored treatments.

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