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Differences in the Psychopharmacological Trajectories of School-Age Children with Attention-Deficit/Hyperactivity Disorder with and without Intellectual Disability

Diferenças nas Trajetórias Psicofarmacológicas de Crianças em Idade Escolar com Perturbação de Hiperatividade e Défice de Atenção com e sem Perturbação do Desenvolvimento Intelectual

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ABSTRACT

Introduction: Attention-deficit/hyperactivity disorder (ADHD) affects 5% - 7% of school-aged children, while intellectual disability (IDD) affects approximately 1% of the general population. Diagnosing and treating ADHD in individuals with IDD is challenging, not only due to communication difficulties but also because of psychiatric comorbidities that may be present. These factors can result in underdiagnosis of ADHD and increased prescribing of other psychotropic medications. The aim of this study was to determine differences in psychopharmacological treatment (number of prescribed psychostimulants, inefficacy, adverse effects) and in the number of comorbidities and other prescribed psychotropic drugs between patients with ADHD, with and without ID.

Methods: In the study, 845 children were included, divided into two groups: 574 with ADHD without ID and 271 with ADHD with ID. Microsoft® Excel® was used to calculate the Student's *t*-test, and statistical significance was assumed using the standard *p*-value of < 0.05.

Results: No significant differences were found in the average number of psychostimulants prescribed between groups ($p = 0.57$). Among those with ADHD without ID, 52.4% switched psychostimulants, while in the group with ADHD and ID, this change occurred in 56.1%. Statistically significant differences were found in the average number of other psychotropic medications prescribed per patient ($p < 0.05$) and in the number of antipsychotics prescribed ($p < 0.05$). Although our study showed more antipsychotic prescriptions for patients with ID compared to those without ID, some studies report similar use of antipsychotics between these groups. Additionally, the group with ID presented significantly more comorbidities than the group without ID ($p < 0.05$). These findings are aligned with the literature, which indicates a higher prevalence of psychiatric comorbidities in samples of patients with ID compared to those without ID (50% *vs* 18%).

Conclusion: Individuals with ID are diagnosed with more psychiatric comorbidities and are prescribed more psychotropic drugs. Additionally, more adverse effects and inefficacy with psychostimulants in ID populations require careful monitoring after initiation.

Keywords: Intellectual Disability; Antipsychotic Agents; Attention Deficit Disorder with Hyperactivity; Child; Psychotropic Drugs

RESUMO

Introdução: A perturbação de hiperatividade e défice de atenção (PHDA) afeta 5% - 7% das crianças em idade escolar, enquanto a perturbação do desenvolvimento intelectual (PDI) afeta cerca de 1% da população geral. Diagnosticar e tratar PHDA em indivíduos com PDI é desafiante, não só devido às dificuldades comunicacionais, como também às comorbilidades psiquiátricas que podem estar presentes, o que pode culminar no subdiagnóstico de PHDA e na maior prescrição de outros psicofármacos. Este estudo teve como objetivo determinar as diferenças no tratamento psicofarmacológico e no número de comorbilidades e de outros psicofármacos prescritos entre doentes com PHDA com e sem PDI.

Métodos: No estudo, foram incluídas 845 crianças, divididas em dois grupos: 574 com PHDA sem PDI e 271 com PHDA e com PDI. Foi usado o Microsoft® Excel® para calcular o teste *t* de *Student* e foi assumida a significância estatística usando o valor *standard* de $p < 0,05$.

Resultados: Não foram encontradas diferenças estatisticamente significativas no número médio de psicoestimulantes prescritos entre grupos ($p = 0,57$). Entre aqueles com PHDA sem PDI, 52.4% mudaram de psicoestimulante e, no grupo com PHDA e PDI, essa alteração ocorreu em 56.1%. Foram encontradas diferenças estatisticamente significativas no número médio de outros psicofármacos prescritos por doente ($p < 0,05$) e no número de antipsicóticos prescritos ($p < 0,05$). Apesar de o nosso estudo mostrar mais prescrições de antipsicóticos para doentes com PDI em relação aos doentes sem PDI, alguns estudos relatam um uso semelhante de antipsicóticos entre esses grupos. Além disso, o grupo com PDI apresentou significativamente mais comorbilidades do que o grupo sem PDI ($p < 0,05$). Este achado vai ao encontro da literatura, que mostra uma maior prevalência de comorbilidades psiquiátricas em amostras com PDI em comparação com amostras sem PDI (50% *vs* 18%).

Conclusão: Em suma, indivíduos com PDI apresentam mais comorbilidades psiquiátricas e recebem mais prescrições de psicofármacos. Além disso, a possibilidade de ocorrerem mais efeitos adversos e a ineficácia dos psicoestimulantes nas populações com PDI exigem uma monitorização cuidadosa após o seu início.

Palavras-chave: Antipsicóticos; Criança; Perturbação do Desenvolvimento Intelectual; Perturbação de Hiperatividade e Défice de Atenção; Psicotrópicos

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KEY MESSAGES

- Strengths: This study comprises a large sample (845 children) comparing ADHD with and without ID with a detailed analysis of comorbidities and pharmacological trajectories.
- Learning Points: There is evidence of higher prescription rates of antipsychotics and multiple psychotropic medications in children with ID. It is important to closely monitor adverse effects with multidimensional assessment.
- Limitations: This is a retrospective study with data extracted from potentially incomplete electronic records. This study lacks of adjustment for potential confounding factors and risk of clinical follow-up loss.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder, which affects approximately 5% - 7% of school-age children.[1] It is characterized by persistent inattention and/or hyperactivity and impulsivity with functional impairment in at least two contexts.[2]

Both psychopharmacological and behavioral interventions are options to manage ADHD symptoms. Stimulant medications, such as methylphenidate and lisdexamfetamine, have been first-line treatment options to target hyperactivity and attentional difficulties.[3] Furthermore, atomoxetine, a non-stimulant medication, has been used in place of stimulant medications, mainly when adverse effects of stimulant medications are poorly tolerated.[4]

The literature has shown that almost 66% of children with ADHD have at least one co-occurring condition, including anxiety, depression and/or sleep disorders.[5] In fact, among children with ADHD, up to 70% experience sleep problems. Fortunately, most ADHD patients have transient sleep problems, and only 10% have persistent problems over a 12-month period.[6] Since sleep problems have been associated with more severe ADHD symptoms, it is even more important to identify and manage sleep problems in children with ADHD. Efron *et al* found that 22% of children with ADHD were taking melatonin or clonidine for managing sleep problems.[7] The literature showed that children with ADHD have a significantly higher rate of impaired sleep compared to their healthy peers across most subjective sleep domains (e.g., bedtime resistance, sleep onset, night awakenings due to restlessness or movements, daytime sleepiness). Attention-deficit/hyperactivity disorder frequently co-occurs with primary sleep disorders such as restless legs syndrome, sleep apnea, and insomnia. Commonly, both pharmacological and non-pharmacological interventions are needed for treating sleep problems in children with ADHD.[8]

Intellectual disability (ID) is another neurodevelopmental disorder and is characterized by cognitive difficulties (reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, and learning from experience) as well as difficulties in conceptual, social, and practical areas of living.[2] The estimated prevalence rate of ID is around 1%.[9] There is a higher burden of psychiatric and neurodevelopmental disorders in people with ID, namely ADHD, with a prevalence rate between 6% and 16% in this population, which means three times higher than in the general population.[10]

The Wechsler Intelligence Scale for Children (WISC-III) is used to assess the intelligence quotient (IQ) between the ages of 6 and 16. It is an individually administered intelligence test that includes three composite IQ scores (Full Scale IQ, Verbal IQ, and Performance), four index scores (Verbal Comprehension Index, Perceptual Organization Index, Processing Speed Index, and Freedom from Distractibility Index) and 13 subtests (Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Coding, Picture Arrangement, Block Design, Object Assembly, Symbol Search, and Mazes).[11]

Diagnosis and treatment of ADHD in people with ID can be challenging because lower intellectual functioning can affect attention and behavior. Moreover, communication difficulties and psychiatric comorbidities could make the ADHD diagnosis even harder.[12] Missed diagnosis and lack of ADHD treatment in people with ID have shown to increase the use of other psychotropic medications such as antipsychotics.[13] Therefore, treatment of ADHD in people with ID is important to improve quality of life, reduce functional impairment, and prevent overuse of psychotropic medications.[12]

Moreover, ADHD and ID share some comorbidities, such as sleep disorders.[14] In fact, studies with adults with ID showed that they have an incidence of sleep disorders between 8.5% to 34.1%, with a serious sleep problem rate of 9.2%. According to a meta-analysis, there is evidence that melatonin enhances total sleep time and reduces the number of wake-ups per night in people with intellectual disabilities.[15]

This study aimed to understand whether there were significant differences between patients with ADHD with and without ID: in the psychopharmacological trajectory (number of prescribed psychostimulants, inefficacy, and adverse effects of psychostimulant medication), in the number of comorbidities, and in the prescribing of other psychotropic drugs.

METHODS

This study was conducted at the Childhood and Adolescence Mental Health and Psychiatry Department of Unidade Local de Saúde de Santo António. The study included all children aged 6 to 12 years old (inclusive) who had been referred to a Child Psychiatry consultation between 2013 and 2022, had received a diagnosis of ADHD according to the DSM-5, and had been treated with psychostimulant medication.

Data were collected by accessing the electronic clinical records of the selected patients. The study collected the following variables: sociodemographic information – age at the first consultation (6 - 12), sex (male or female) –, type of prescribed psychostimulant medication (immediate-release methylfenidate, extended-release methylphenidate, modified-release methyphenidate, lisdexamfetamine, atomoxetine), reason to change the psychostimulant (adverse effects, ineffectiveness, or both), other prescribed psychotropic drugs (antipsychotics, antidepressants, benzodiazepines), comorbid psychiatric diagnosis [oppositional defiant disorder (ODD)], specific learning disorders, sleep disorders, elimination disorders, communication disorders, autism spectrum disorder (ASD), anxiety disorders, depressive disorders), and IQ (40 - 130).

The Ethics Committee of Unidade Local de Saúde de Santo António approved this study.

Study sample definition

At the beginning of the study, 1453 children were identified. Of those, 608 were excluded: 431 children were excluded because they did not have WISC-III results in their electronic clinical files; 172 children were excluded because they scored between 70 and 79 on the WISC-III. In this context, it is important to note that ID implies an IQ below 70, although in WISC-III an IQ between 70 and 79 is already considered below normal. Finally, five children were excluded because they scored over 130 on the WISC-III, which is considered higher than normal IQ (giftedness). The final

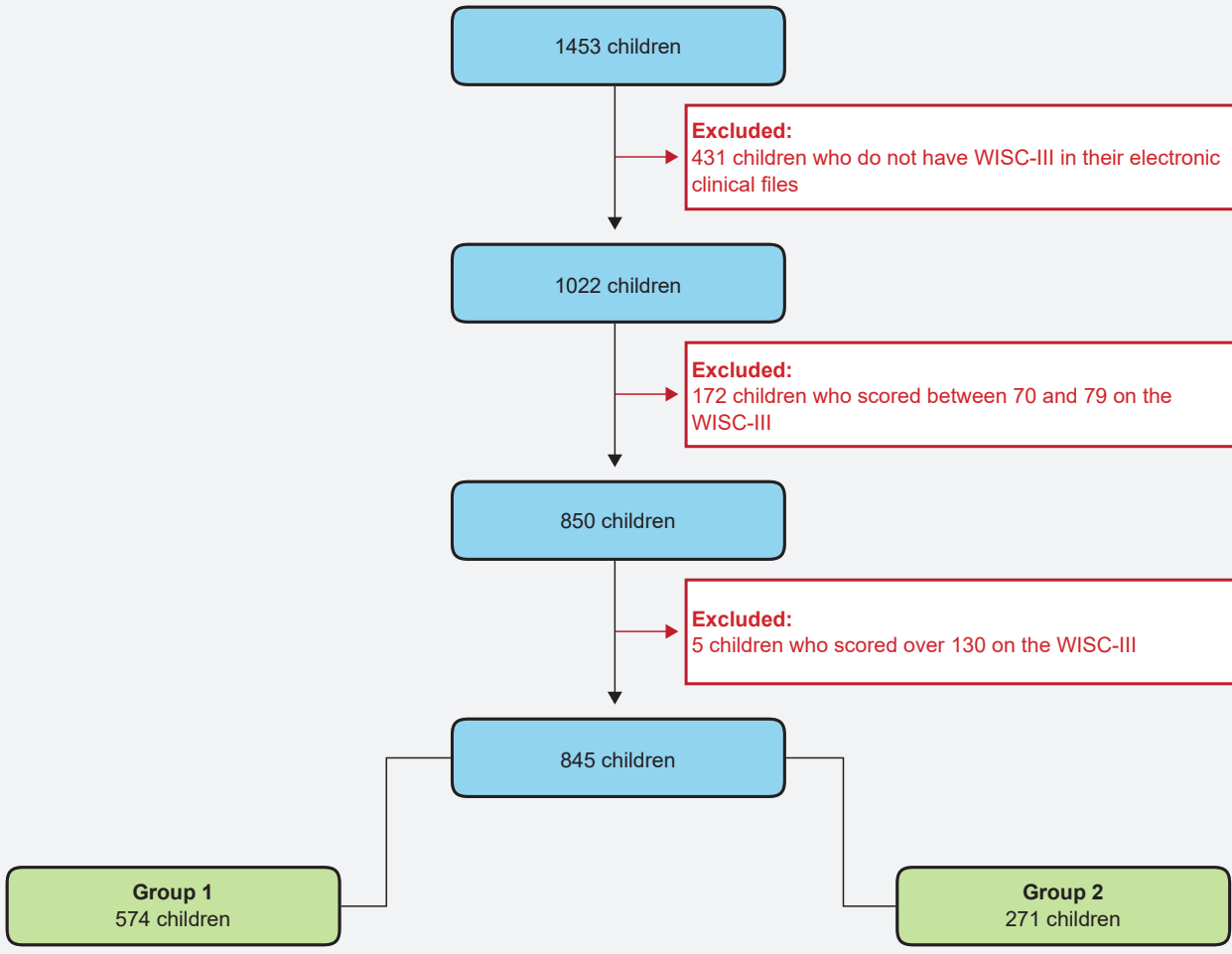

Figure 1 – Flowchart for study sample definition

sample size for the study was 845 children (Fig. 1).

Statistical analysis

The prescribed first-line medication, the need to change the psychostimulant medication or not, the reason for changing the psychostimulant medication, the class of other prescribed psychotropic drugs, and the comorbid diagnoses were coded as categorical variables.

The descriptive and simple comparative analysis was then performed using Microsoft® Excel®. Categorical variables were characterized by their absolute and relative frequencies. Microsoft® Excel® was also used to calculate Student's *t*-tests and calculate the various *p*-values of the experiment. The standard threshold of less than 0.05 was adopted for statistical significance.

RESULTS

Socio-demographic characteristics of the study population

In the group of children without ID, the average age was 8.1 years. This group was composed of 420 male children (73.2%) and 154 female children (26.8%). The average IQ in this group was 95.2 points, with a minimum IQ of 80 and a maximum IQ of 130.

Table 1 – First-line prescribed medicines by group

First-line medication		No. (%) of patients
ADHD without ID	Immediate-release methylphenidate (Rubifen®)	227 (39.5%)
	Extended-release methylphenidate (Concerta®)	176 (30.7%)
	Modified-release methylphenidate (Ritalina®)	140 (24.4%)
	Lisdexamfetamine	27 (4.7%)
	Atomoxetine	4 (0.7%)
ADHD with ID	Immediate-release methylphenidate (Rubifen®)	135 (49.8%)
	Modified-release methylphenidate (Ritalina®)	69 (25.5%)
	Extended-release methylphenidate (Concerta®)	58 (21.4%)
	Lisdexamfetamine	8 (2.9%)
	Atomoxetine	1 (0.4%)

Table 2 – Reasons to switch medication

Reasons to switch medication		No. (%) of patients
ADHD without ID	Ineffectiveness	217 (72.1%)
	Adverse effects	36 (12.0%)
	Ineffectiveness + adverse effects	48 (15.9%)
ADHD with ID	Ineffectiveness	102 (67.1%)
	Adverse effects	20 (13.2%)
	Ineffectiveness + adverse effects	48 (19.7%)

Table 3 – Most frequent adverse effects reported in each group

Adverse effects		No. (%) of patients
ADHD without ID	Loss of appetite	37 (44.0%)
	Apathy	26 (30.9%)
	Abdominal pain	11 (13.1%)
	Insomnia	11 (13.1%)
	Aggressiveness/agitation	11 (13.1%)
ADHD with ID	Loss of appetite	17 (25.0%)
	Apathy	13 (19.1%)
	Aggressiveness/agitation	8 (11.8%)
	Tics	7 (10.3%)
	Headache	6 (8.8%)

Note that some patients reported more than one adverse effect.

In the group of children with intellectual disability, the average age was 8.3 years. This group was composed of 194 male children (71.6%) and 77 female children (28.4%). The average IQ in this group was 62.5 points, with a minimum IQ of 40 and a maximum IQ of 69. In this group, 259 patients (95.6%) had a mild intellectual disability, with an IQ between 50 and 69, and 12 patients (4.4%) had a moderate ID, with an IQ between 35 and 49.

Clinical characteristics of the study population (Tables 1 - 6)

The average number of psychostimulants prescribed per child in the group without ID was 1.7. On the other hand, the average number of psychostimulants prescribed per child in the group with ID was 1.8. The means of both groups were compared using the t-test and the difference was not statistically significant (*p*-value = 0.57).

The most frequent first-line medication in the group without ID were immediate-release methylphenidate (Rubifen®) in 227 patients (39.5%), followed by extended-release methylphenidate (Concerta®) in 176 patients (30.7%), modified-release methylphenidate (Ritalina®) in 140 patients (24.4%), lisdexamfetamine in 27 patients (4.7%) and atomoxetine in four patients (0.7%). Similarly, the most common first-line medication prescribed in the group with ADHD and ID was immediate-release methylphenidate (Rubifen) in 135 patients (49.8%), followed by modified-release methylphenidate (Ritalina) in 69 patients (25.5%), extended-release methylphenidate (Concerta) in 58 patients (21.4%), lisdexamfetamine in 8 (2.9%) and atomoxetine in only one patient (0.4%).

In the group without ID, a total of 301 patients (52.4%) had to change treatment. In particular, 217 patients (72.1%) changed medication due to ineffectiveness, 36 patients (12.0%) changed medication due to adverse effects and 48 patients (15.9%) changed medication due to both ineffectiveness and adverse effects. In the group with ID, a total of 152 patients (56.1%) needed to change medication.

Table 4 – Other psychotropic medications and melatonin preparations prescribed by group

Other psychotropic medications		No. (%) of patients
ADHD without ID	Antipsychotics	121 (21.1%)*
	Antidepressants	60 (10.4%)
	Benzodiazepines	46 (8.0%)
	Melatonin preparations	81 (14.1%)
ADHD with ID	Antipsychotics	103 (38.0%)*
	Antidepressants	41 (15.1%)
	Benzodiazepines	23 (8.4%)
	Melatonin preparations	33 (12.2%)

*: statistically significant differences

Table 5 – Number of comorbidities by group

Type of comorbidities		No. (%) of patients
ADHD without ID	No	108 (18.8%)
	One	242 (42.2%)
	Two	150 (26.1%)
	Three	54 (9.4%)
	Four	14 (2.4%)
	Five	3 (0.5%)
	Six	2 (0.4%)
	Seven	1 (0.2%)
ADHD with ID	Only ID	83 (30.6%)
	ID + one comorbidity	118 (43.5%)
	ID + two comorbidities	49 (18.1%)
	ID + three comorbidities	15 (5.5%)
	ID + four comorbidities	5 (1.9%)
	ID + five comorbidities	1 (0.4%)

Table 6 – Type of comorbidities by group

No. of comorbidities		No. (%) of patients
ADHD without ID	ODD	195 (34.0%)
	Specific learning disorders	190 (33.1%)
	Sleep-wake disorders	93 (16.2%)
	Anxiety disorders	77 (13.4%)
	Elimination disorders	62 (10.8%)
	Communication disorders	52 (9.1%)
	ASD	44 (7.7%)
ADHD with ID	ODD	103 (38.0%)
	Sleep-wake disorders	39 (14.4%)
	Anxiety disorders	31 (11.4%)
	Communication disorders	30 (11.1%)
	Elimination disorders	29 (10.7%)
	ASD	29 (10.7%)

ASD: autism spectrum disorder; ODD: oppositional defiant disorder

In the case of 102 patients (67.1%), they changed medication due to ineffectiveness. Furthermore, 20 patients (13.2%) changed medication due to adverse effects and 48 children (19.7%) changed medication due to both ineffectiveness and adverse effects.

Our study found that the rate of side effects requiring changes was higher in the group with intellectual disability (13.2% + 19.7%) compared to the group without ID (12.0% + 15.9%). On the other hand, in terms of ineffectiveness, our study showed that a higher percentage of individuals without ID had to change medication due to ineffectiveness (72.1% + 15.9%) when compared to individuals with ID (67.1% + 19.7%).

The most frequent adverse effects in the group with ADHD without ID were loss of appetite (37/84; 44.0%), apathy (26/84; 30.9%), abdominal pain (11/84; 13.2%), insomnia (11/84; 13.1%) and aggressiveness/agitation (11/84; 13.1%). On the other hand, in the group with ID, the most frequent adverse effects were loss of appetite (17/68; 25.0%), apathy (13/68; 19.1%), aggressiveness/agitation (8/68; 11.8%), tics (7/68; 10.3%) and headaches (6/68; 8.8%).

Furthermore, the average number of other psychotropic drugs prescribed per patient in the group without ID was 0.55. Whereas the average number of other psychotropic drugs per patient in the group with patients with ID was 0.98. The means of both groups were compared using the *t*-test, and the difference was statistically significant (*p*-value < 0.05). The maximum number of other psychotropic drugs prescribed per patient in the group without ID was 9 and the maximum number of other psychotropic drugs prescribed per patient in the group with ID was 11.

Furthermore, the most prescribed pharmacological class after psychostimulants in group 1 was the antipsychotic class (prescribed in 121 patients; 21.1%), followed by the antidepressant class (prescribed in 60 patients; 10.4%) and the benzodiazepine class (prescribed in 46 patients; 8.0%). On the other hand, in the group of children with ADHD and ID, the psychotropic drugs prescribed along with psychostimulant medication were, in decreasing order of frequency: antipsychotics (in 103 patients; 38.0%), antidepressants (in 41 patients; 15.1%) and benzodiazepines (in 23 patients; 8.4%). Considering that the most prescribed pharmacological class after psychostimulants was antipsychotics, we compared the means of the number of antipsychotics prescribed in each group (0.29 in group 1 and 0.58 in group 2) using a *t*-test and the difference was statistically significant (*p*-value < 0.05).

In our study, the most prescribed drug class after psychostimulants was antipsychotics. However, the percentage of patients prescribed an antipsychotic in the ID group was higher than in the non-ID group (38.0% *vs* 21.1%). Additionally, the average number of antipsychotics prescribed in the ID group was significantly higher than in the group of individuals with normal IQ (0.58 *vs* 0.29; *p*-value < 0.05). Nevertheless, there is a 2016 study that showed that there were equal frequencies in the use of antipsychotics in patients with ADHD with and without ID.[16]

In the group of individuals without ID, melatonin preparations were prescribed to 81 individuals (14.1%). On the other hand, in the group of individuals with ADHD and ID, melatonin prescriptions were given to 33 individuals (12.2%). In our study, more melatonin preparations were prescribed to individuals without ID compared to those with ID (14.1% *vs* 12.2%). The difference in the prescribing of melatonin preparations between groups was not statistically

significant (Z-value = 0.655). This finding is different from what was found in the study by Osunsanmi *et al*, where a modestly higher prescribing of melatonin preparations was observed in the group with ID.[16]

In terms of comorbid psychiatric diagnoses, the average number of comorbidities in the group without ID was 1.4 diagnosis, with a maximum of seven comorbid diagnoses. Of the total, 108 patients (18.8%) did not have comorbidities. On the other hand, 242 patients (42.2%) presented another diagnosis, 150 children (26.1%) were diagnosed with two more mental disorders, 54 patients (9.4%) were diagnosed with three more mental disorders, 14 children (2.4%) presented another four diagnoses, three patients (0.5%) had five more diagnoses, two patients (0.3%) were diagnosed with six more mental disorders and only one child (0.2%) was diagnosed with seven other mental disorders. The most frequent comorbidities found in this group, according to DSM-5, were ODD (34.0%; 195/574), followed by specific learning disorders (33.1%; 190/574), sleep-wake disorders (16.2%; 93/574), anxiety disorders (13.4%; 77/574), elimination disorders (10.8%; 62/574), communication disorders (9.1%; 52/574) and ASD (7.7%; 44/574).

In terms of comorbid psychiatric diagnoses, the average number of comorbidities in the group with ID was 2.1 diagnoses, with a maximum of 6 comorbid diagnoses. In this group, 83 patients (30.6%) had only ADHD and ID, 118 children (43.5%) were diagnosed with one more mental disorder besides ADHD and ID, 49 patients (18.1%) had two more diagnoses besides ADHD and ID, 15 patients (5.5%) were diagnosed with three more mental disorders besides ADHD and ID, five children (1.8%) had four more diagnoses besides ADHD and ID and, finally, only one patient (0.4%) was diagnosed with five more diagnoses besides ADHD and ID. The most frequent comorbidities found in the group with ID, according to DSM-5, were ODD (38.0%; 103/271), followed by sleep-wake disorders (14.4%; 39/271), anxiety disorders (11.4%; 31/271), communication disorders (11.1%, 30/271), elimination disorders (10.7%; 29/271) and ASD (10.7%; 29/271). The means of the two groups in terms of number of comorbidities were compared using the t-test, and the difference was statistically significant (p-value < 0.05).

In our study, only 29 individuals with ADHD and ID had ASD (8.9%). However, there is a study with adult individuals that showed a prevalence of 73% of ASD in those with ADHD and ID. Furthermore, in this study, they found that anxiety disorders were the most common mental disorder reported (n = 65, 15%) followed by depression (n = 43, 10%).[17] The prevalence of anxiety disorders (11.4%) and depression (3.7%) in our study was considerably lower.

In a study with children and adolescents with ID, the most common comorbid psychiatric disorders were ADHD (64.9%), ODD (21.6%), anxiety disorders (18.0%), nocturnal enuresis (16.2%), conduct disorder (10.8%) and depressive disorder (6.3%).[16] In our study, we found a higher prevalence of ODD (38.0% *vs* 21.6%) but a smaller prevalence of anxiety disorders (11.4% *vs* 18.0%), depressive disorders (3.7% *vs* 6.3%) and elimination disorders (10.7% *vs* 16.2%).

DISCUSSION

There were no significant differences in psychostimulant prescribing between groups (1.7 *vs* 1.8 per child). Immediate-release methylphenidate was most common in both groups. Medication changes due to ineffectiveness were higher in the non-ID group (72.1%) compared to the ID group (67.1%), whereas changes due to adverse effects were higher in the ID group (33.0%) than in the non-ID group (27.9%).

The average number of other psychotropic drugs prescribed per patient was significantly higher in the ID group (0.98 *vs* 0.55). Antipsychotics were the most prescribed class after psychostimulants, more so in the ID group (38.0% *vs* 21.1%).

Comorbid psychiatric diagnoses were more prevalent in the ID group (average 2.1 diagnoses *vs* 1.4). Oppositional defiant disorder was most common in both groups, but the prevalence of other disorders varied between groups.

Unlike other studies in the literature, such as the study by Osunsanmi *et al*, where extended-release methylphenidate was the first-line ADHD treatment in individuals with ADHD and without ID (33.6% in both groups),[16] in our study immediate-release methylphenidate was the most commonly used first-line treatment in both groups. A possible explanation for this difference in our study is the fact that immediate-release methylphenidate in Portugal has a significantly lower cost compared to extended-release methylphenidate (the cost of a Rubifen® package with 50 tablets is €5.35 *versus* the cost of a Concerta® package with 30 tablets that is €15.49). Furthermore, this study focused on children who started the treatment before adolescence, which may have contributed to starting the treatment with lower doses, as the lowest dose of immediate-release methylphenidate is 5 mg, while the lowest dose of extended-release is 18 mg.

Our results are aligned with the existing literature in terms of side effects in the group with ID compared with the group without ID, which also indicates a higher-than-usual rate of side effects in children with intellectual disabilities.[18] Another study from 1991 showed that children with ADHD and ID who received short-acting methylphenidate were at higher risk of showing side effects such as tics and social withdrawal.[19] A more recent study showed that psychostimulants were associated with sleep difficulties, loss

of appetite and weight loss.[20] However, a systematic review from 2018 concluded that adverse effects from treatment with methylphenidate in children with ID ranged somewhere between 12% and 24%, although in some studies the rate was as high as 40% for some adverse effects,[21] which is comparable to the reported rate of adverse effects reported among non-ID children, which is on average around 12.5% - 24%.[22] This is consistent with a more recent study from 2020 that showed no major differences in type, nature, frequency, and intensity of side effects between the general and ID populations.[12]

Our ineffectiveness' rates are not consistent with previous studies in which, among patients with an IQ of 70 or less, only one of 17 patients achieved a Clinical Global Impression I (CGI-I) score of 1 or 2 thus being considered 'responder'; *versus* 20 of 26 patients with IQ 85 or greater.[12] In fact, a response rate to short-acting methylphenidate of 45% to 66% was shown for children with ADHD and ID, which is below the response rate for children with ADHD alone. Interestingly, an IQ above 50 predicted a better response to stimulants, while very low (severe, profound) IQ levels predicted a poorer response.[23]

A 2019 study found that 39.6% of children and adolescents with ID had one comorbid psychiatric disorder, 26.1% had two comorbidities, 10.8% had three comorbid psychiatric disorders, 1.8% had four comorbidities and another 1.8% had five comorbid diagnoses.[24] In terms of the number of comorbidities, we found that 30.6% of the children with ID had one comorbidity (ADHD), 43.5% were diagnosed with two more mental disorders, 18.1% had three comorbidities, 5.5% were diagnosed with four mental disorders besides ID, 1.8% had five comorbidities and only one patient (0.5%) were diagnosed with six mental disorders besides ID and ADHD.

The literature is indeed consistent in showing that the prevalence of comorbid psychiatric disorders is higher in ID samples than in samples with normal IQ. Dekker *et al* showed that 50% of children and adolescents with ID had a comorbid psychiatric disorder, while only 18% of children and adolescents with normal IQ had a psychiatric comorbidity.[25] Furthermore, Emerson *et al* showed that this prevalence was 36% for individuals with ID and 8% for individuals without ID.[26]

This study has the limitations of retrospective studies, and its findings should therefore be considered with caution. The evaluation of these cases relies solely on the available information in the clinical electronic reports which may be incomplete. Additionally, some children from our cohort may have become disengaged from our hospital's care and are currently receiving follow-up treatment at alternative healthcare facilities, posing challenges in terms of accessing comprehensive clinical information pertaining to these individuals.

Moreover, no adjustments were made for potential confounding factors between the two groups. As a result, caution must be exercised when interpreting the conclusions, as causal inferences cannot be drawn from the findings.

CONCLUSION

This study shows that individuals with ID have significantly more psychiatric comorbidities. Furthermore, it was concluded that the group with ID was prescribed more psychotropic medications, mainly antipsychotics, which were prescribed 1.5 times more often in this group compared to the group without ID. In the case of ADHD, diagnosing it is especially challenging in patients with ID due to some symptom overlap, so it is crucial to ask parents and teachers about ADHD symptoms and their impact on the child's functioning to establish an appropriate diagnosis and treatment plan. Finally, it is important to note that in the population with ID, there may be more adverse effects and greater inefficacy with psychostimulant medication, which require close monitoring after being started. To monitor possible side effects, the prescriber should assess blood pressure, heart rate, and weight at each appointment. Furthermore, the prescriber should ask about sleep habits, appetite, and other somatic symptoms such as headache and gastrointestinal distress.

AUTHOR CONTRIBUTIONS

FBM: Study design, data acquisition and analysis, writing of the manuscript.

VMM: Study design, writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

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VMM has declared that no competing interests exist.

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