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ORIGINAL CONTRIBUTION

Comorbidity prevalence and treatment outcome in children and adolescents with ADHD

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Abstract Although ADHD comorbidity has been widely studied, some issues remain unsolved. This multicenter observational study aims to examine comorbid psychiatric disorders in a clinical sample of newly diagnosed, treatment naïve children and adolescents with and without ADHD and, to compare treatment efficacy based on the type of comorbidity. We performed an analysis of the medical records of patients identified from the Regional ADHD Registry database, enrolled in 18 ADHD centers in the 2011–2016 period. 1919 of 2861 subjects evaluated (67%) met the diagnostic criteria for ADHD: 650 (34%) had only ADHD, while 1269 (66%) had at least one comorbid psychiatric disorder (learning disorders, 56%; sleep disorders, 23%; oppositional defiant disorder, 20%; anxiety disorders, 12%). Patients with ADHD of combined type and with severe impairment (CGI-S $\geq$5) were more likely to present comorbidity. 382 of 724 (53%) followed up patients improved after 1 year of treatment. ADHD with comorbidity showed greater improvement when treated with combined interventions or methylphenidate alone. Specifically, combined treatment showed significant superiority for ADHD with learning disorders (ES 0.66) and ODD (ES 0.98), lower for ADHD with sleep or anxiety disorders. Training intervention alone showed only medium efficacy (ES 0.50) for ADHD and learning disorders. This study was the first describing comorbidity patterns of ADHD in Italy, confirming, in a multicenter clinical setting, that ADHD is more often a complex disorder. Findings highlight important diagnostic, therapeutic, and service organization aspects that should be broadly extended to ensure an appropriate and homogenous ADHD management.

Keywords Comorbidity · Attention deficit hyperactivity disorder · Treatment outcome · Children · Adolescents

Lombardy ADHD Group members are moved to Acknowledgement.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobiological condition characterized by developmentally inappropriate and impairing patterns of inattention, hyperactivity, and impulsivity [1]. ADHD symptoms usually become more evident in school aged children, are more frequent in boys than girls and tend to persist into adulthood [2]. As for other psychiatric disorders occurring during the developmental age, the categorical and relatively simple symptomatological core of ADHD often does not appear alone. Frequently, a wide variety of concurrent psychiatric disorders contribute to the psychopathological status of children and adolescents with ADHD, with a well-established consensus among authors that the presence of

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overlapping psychiatric disorders is more likely to be the rule than the exception [3].

The medical term commonly used for this concurrence is comorbidity, even though the early meaning of the word as a "distinct additional clinical entity occurring during the clinical course of a patient having an index disease" [4] is clearly not fully applicable and appropriate to most psychiatric diagnoses. Indeed, the majority of those listed as comorbid conditions represents disorders, multifunctional impairments, and symptom constellations whose clustering together characterizes the clinical condition [5–7]. The first study evaluating a broad range of comorbid conditions in children with ADHD was published more than 30 years ago [8], and its main findings simply highlighted that ADHD is very often associated with other disorders, particularly depression and anxiety disorders, oppositional and conduct problems, and developmental disorders. No considerable evidence followed the study until more than 10 years later, when the emerging understanding of attention deficit disorders and comorbidities was summarized by Brown et coll. in a comprehensive manual [9]. It is now largely agreed that comorbidities are often one of the most important aspects of ADHD [10–15] and this has led, at least for ADHD, to the consideration of their impact on the outcome of the individual child in the longer term [16].

The overall prevalence of psychiatric disorders associated with ADHD in children and adolescents ranges from about 40 to 80% depending on the sample [11, 17–20], with higher rates in clinically referred ADHD children (67–87%) [3]. Thus, it seems rather clear that, in addition to an ADHD diagnosis, a clinician should consider a whole range of possible psychiatric conditions. The main disorders likely to co-occur with ADHD are: oppositional defiant disorder (ODD) (50–60%), conduct disorder (CD) (20–50% in children and 40–50% in adolescents), depression (16–26%) and anxiety (10–40%) disorders, bipolar disorders (11–75%), tic disorders (20%), obsessive compulsive disorders (6–15%), and autism spectrum disorders (65–80%) [11–13, 15, 21–23].

Other comorbidities, however, have also been observed in ADHD children and adolescents. A wide variety of learning difficulties are associated with ADHD, with over 45% having at least one or more significant impairments in reading, arithmetic or spelling [3, 24]. Several other problems, including, for example, social problems [25] or sleep disturbances [26], may be more common in ADHD than in the population without this condition. Comorbidity involving ADHD and learning disorders is frequent, ranging from 25 to 40% [3, 24]. A few studies point out the possibility of there being a specific learning disorder at first, which could later be complicated by a behavioral pattern of ADHD [27, 28]. Other authors note that learning disorders are almost a constant in ADHD children and adolescents; this may be due to the fact that inattention and hyperactivity, alone, could encourage the emergence of specific learning difficulties [29, 30]. Others, yet, claim that learning disorders and ADHD may occur together because of a shared genetic etiology and that a genetically mediated comorbid subtype may exist [29]. This hypothesis has been suggested also for many other neurodevelopmental disorders [31, 32]. Pennington proposed a probabilistic and multifactorial etiopathogenetical model to explain the high rate of overlap between different neurodevelopmental disorders [33]. Based on this dimensional perspective, ADHD was placed in the DSM-V section "neurodevelopmental disorders", including different disorders with high rates of comorbidity among them and with common onset in the developmental age [1]. These different explanations proposed are not mutually exclusive, but can be used as causal models of pathogenic pathways [29]. Literature data reveal that about 70% of children with ADHD show mild to severe sleep disorders [34]. In particular, ADHD patients experience much higher rates of sleep problems than their peers without ADHD [35]. The reported prevalence rates differ according to the subtype of ADHD, with a higher prevalence in the combined subtype and in patients with psychiatric comorbidity, which increase the risk of occurrence of sleep disorders [36]. On the other hand, some authors suggest that patients with severe sleep disorders develop subsequent ADHD symptoms [35], but more studies are needed to define the neurobiological basis of this possible casual relationship.

Despite the fact that ADHD comorbidity has been widely studied [11, 17–20], some issues remain unsolved. In fact, in clinical practice, comorbidities may mask the core symptoms of ADHD, or ADHD may be masked by comorbid conditions, thereby confusing the diagnostic process [37]. When making an ADHD diagnosis, it is important to exclude other disorders that might overlap with ADHD or mimic ADHD symptoms. Comorbid disorders, recognized or unrecognized, may also complicate the treatment process [11, 38] since most children with ADHD have co-occurring conditions that may complicate not only the clinical presentation, but also the choice of the most appropriate treatment strategy. A specific practice guideline pathway has been proposed by the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance to identify the key comorbidities and the different treatments priorities they require [39], simply suggesting that outcome is generally determined by the most serious comorbid condition. However, very little systematic research exists on sequencing of treatment for comorbidities, and this is generally handled on a case-by-case basis.

What is known about comorbidity is largely confined to ADHD of combined type [3]. Furthermore, to date, literature data are also sometimes inconsistent because of

differences in patients' age, sample selection (clinical or community) and size [40], and diagnostic instruments used to assess comorbid conditions. Moreover, only a few studies have been conducted with a multidimensional and multicenter approach [41, 42] analyzing the entire spectrum of psychiatric comorbidities and outcomes according to treatments received [12, 20].

The importance of recognizing the psychopathological profile of the comorbidities in ADHD has been patchily documented, but there is a limited amount of research addressing concerns on treatments efficacy remaining in need of exploration. This study aims to evaluate the prevalence rate of psychiatric comorbidity and treatment outcomes in children and adolescents with ADHD, aged 5–17 years, enrolled in the 18 ADHD reference centers of the Lombardy Region between June 2011 and August 2016. The objectives related to scope achievement specifically analyzing, documenting and evaluating co-occurring disorders in ADHD were expected to be achieved according to four specific aspects: prevalence rate and, prescribed and performed treatments, improved subjects rates and treatment efficacy related to the therapeutic approaches.

Methods

This study was designed as a review of patient medical records identified from the Regional ADHD Registry database. The research was approved by the Institutional Review Board of the IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri" in Milan, Italy, and written informed consent was obtained for all patients.

The local health setting

In the Lombardy Region, during the study period, a network of 34 Child and Adolescent Neuropsychiatric Services (CANPS) provides care at the hospital (tier three) and community (tier two) levels for children and adolescents with neurologic, neuropsychologic and/or psychiatric disorders, and for their families. About 15% of the Italian pediatric population live in this region. Regional health authorities are responsible for the accreditation of the ADHD reference centers in regional hospitals ("ADHD centers"), as specialized ADHD hubs (tier three) of the CANPS network. All CANPS community centers (tier two) take care of children with ADHD and their families, whereas ADHD centers are responsible for confirming the diagnosis and verifying the appropriateness of the therapeutic plan prescribed. ADHD centers are also responsible for the prescription of pharmacological therapies, their monitoring over time, and for inputting data into the registry. Moreover, ADHD centers ensure the interface with the family pediatricians for children on pharmacological therapy, guarantee the periodic visit and the management of the drug prescriptions, provide parent, teacher and child training directly.

The lombardy ADHD registry project

Following a previous, national, drug-oriented ADHD registry set up in 2007 [43, 44], in June 2011 an official, alternative regional registry was activated in the Lombardy Region. The Regional ADHD Registry was designed as a disease-oriented registry collecting information not only on ADHD patients treated with pharmacological therapy (as provided by the National Registry) but also on all patients who access ADHD centers for a diagnosis of suspected ADHD. Italian legislation [45] requires data on all ADHD patients receiving methylphenidate or atomoxetine treatment to be reported in the registry. The Regional Registry is part of a more general project aimed to ensure appropriate ADHD management for every child and adolescent once the disorder is suspected and reported, and includes commonly acknowledged diagnostic and therapeutic procedures as well as educational initiatives for health care workers (child neuropsychiatrists and psychologists) of the Lombardy Region's health care system who provide assistance to ADHD patients and their families. Initiatives focused on increasing knowledge on ADHD in parents, teachers, and family pediatricians were also part of the regional project [46–48].

The Regional ADHD Registry represents a distinctive tool, internationally, aimed to ensure the appropriate care of, and the safety of drug use in, ADHD children [46–48]. In practice, a strict diagnostic assessment of the disorder prior to treatment, as well as its systematic monitoring during both pharmacological treatment and behavioral interventions, must be guaranteed to ADHD patients who come to the attention of the 18 local ADHD centers. To define an optimal, evidence-based, shared strategy for diagnostic evaluation, an ad hoc assessment working group was created, involving a child neuropsychiatrist and a psychologist from each participating ADHD center and a group of researchers of the registry coordinating center (IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri"). More specifically, this strategy consisted of seven mandatory steps to be applied at the time of diagnostic evaluation: (1) the clinical anamnestic and psychiatric interview; (2) the neurological examination; (3) the evaluation of cognitive level by Wechsler Scales [49–51]; (4) the Schedule for affective disorders and schizophrenia for school-age children (K-SADS) [52] for a complete psychopathology overview and comorbidity assessment; (5) the child behavior checklist (CBCL) and/or the conners' parent rating scale-revised (CPRS-R)

rated by parents; (6) the conners' teacher rating scale-revised (CTRS-R) rated by teachers [53–55]; and 7) the clinical global impressions-severity scale (CGI-S) [56] to quantify symptom severity. This diagnostic pathway was agreed on, approved, and shared by all participating ADHD centers.

Following a diagnosis of ADHD, the registry was designed to guide the user by providing several, differently structured types of follow-up visits at periodic intervals to monitor the clinical outcome of the treatment strategies. These were carried out at 3 and 6 months after the diagnosis, and every 6 months afterward. Patients given methylphenidate were also monitored at 1 week and 1 month after the diagnosis (only after 1 month if they received atomoxetine).

All collected data, i.e., those concerning the diagnostic evaluation and the systematic monitoring assessments described above, were analyzed monthly, and the findings were reported and periodically discussed with all 18 ADHD centers belonging to the Lombardy ADHD Group. In this study, to evaluate clinical outcome evaluation we used the improved subject rates and the treatment efficacy as measured by the CGI-Improvement and the CGI-Severity (pre- to post-treatment change, Δ Mean) scales, respectively.

This is a clinical multicenter study, in which all patients received a rigorous diagnostic assessment (according to national and international guidelines) [57, 58], approved by all involved clinicians and monitored by a registry-based data collection method. Here, we report clinical evaluation and treatment outcome data on new, treatment naïve patients who accessed the ADHD centers between June 2011 and August 2016 and were followed up for 1 year (12 ± 3 months) according to their comorbidity profile.

Data analysis

Descriptive statistics were summarized. We used Kruskal–Wallis or Chi-square tests to determine differences in population characteristics and between groups of subjects. Statistically significant differences were assessed at an alpha level of 0.05. We applied logistic regression analyses with stepwise selection and a significance level of 0.05 to, first, identify risk factors associated with ADHD and, secondly, with comorbidity, considering sociodemographic and anamnestic characteristics, ADHD subtypes, and symptom severity (only for the second step) as independent variables. To evaluate treatment efficacy, we also calculated standardized residuals (Std. Res) [59] and the Cohen's d effect size [60]. A standardized residual is the difference between the observed and expected values for a single treatment group: the larger the residual, the greater the contribution of the group to the magnitude of the resulting Chi-square obtained value. All statistical analyses were performed using SAS software (version 9.2).

Results

Diagnostic and therapeutic pathways of the sample are summarily presented in Fig. 1.

Prevalence rate

In all, 3030 children and adolescents from the 18 ADHD centers were evaluated for suspected ADHD, the majority (2861, 94%) had completed the diagnostic procedure at the time of data extraction (September 1, 2016) and were included in this study (Fig. 1). 1919 of 2861 new subjects evaluated (67%) met the diagnostic criteria for ADHD (M: 1635, 85%; F: 284, 16%). Of these, 650 (34%) received a diagnosis of ADHD only, while 1269 (66%) had at least one comorbid psychiatric disorder. 1106 of 1919 ADHD patients (58%) had ADHD of combined type (ADHD-C), 633 (33%) of inattentive type (ADHD-I), and 180 (9%) of hyperactive/impulsive type (ADHD-H). Comorbid psychiatric disorders were more frequent in patients with ADHD-C subtype (OR 1.54, IC 1.28–1.85) and in those with a CGI-S score equal to or greater than 5 (OR 2.46, IC 1.92–3.14).

Using logistic regression analyses with stepwise selection to determine differences in population characteristics and between groups, some anamnestic characteristics showed a statistically significant association ($p < 0.05$) with comorbidity in ADHD: lower age at diagnosis, having a family history of ADHD, and not being breastfed (Table 1).

Of the 2447 patients with at least one psychiatric disorder, 650 (27%) were diagnosed only with ADHD and 401 (16%) only with another psychiatric disorder, while 1396 (57%) had two or more mental disorders (1269 also ADHD). The rate of sleep disorders (23 vs. 13%; $p \leq 0.0001$) and oppositional defiant disorder (20 vs. 11%; $p \leq 0.0001$) was significantly higher in ADHD patients, while inverse data proportion was observed for anxiety disorders (12 vs. 19%; $p = <0.0001$) (Fig. 2). Overall, learning disorders (56%), sleep disorders (26%), oppositional defiant disorder (20%), and anxiety disorders (12%) were the more frequent disorders in ADHD subjects (Fig. 2).

Odds ratios and goodness-of-fit tests from logistic regression models for comorbid disorders with a statistically significant association (sleep disorders, oppositional defiant disorder, anxiety disorder) (Fig. 2) and sociodemographic and anamnestic variables (Table 1) in patients with ADHD and with other psychiatric disorders were performed to calculate the relative risk, excluding association bias related to differences on sociodemographic

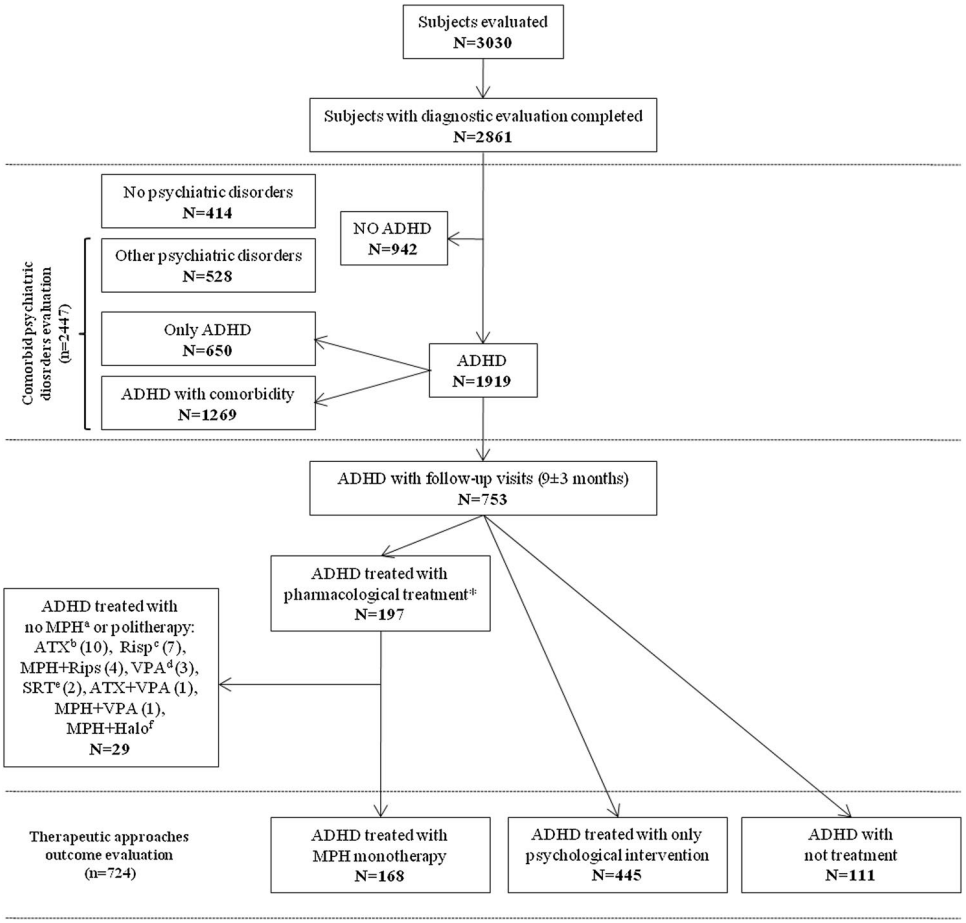

Fig. 1 Diagnostic and therapeutic pathways of the sample. *Subjects treated with pharmacological treatment alone or with associated psychological interventions; [a]methylphenidate; [b]atomoxetine; [c]risperidone; [d]valproic acid; [e]sertraline; [f]haloperidol

variables: an ADHD diagnosis was a significant risk factor for sleep disorders (OR 1.81, CI 95%: 1.31–2.51) and oppositional defiant disorder (OR 1.93, CI 95%: 1.37–2.72), while it was not a significant risk factor for the other mental disorders when all significant statistical variables in the bivariate model were controlled for. Moreover, the Hosmer–Lemeshow Chi-square test indicated that the observed data were not significantly different from expected values derived from each model ($p > 0.05$). Most models had a good estimation of predicted variables (concordance ≥ 0.57).

Therapeutic approaches

Data concerning the assessment and outcome of the therapeutic approaches were analyzed only for ADHD patients receiving care continuity at the ADHD center within a 1-year period (12 ± 3 months). Among patients receiving pharmacological treatment, with or without an associated psychological intervention, we chose to consider only those treated with methylphenidate ($n = 168$, 85%), thus, excluding those who received other psychotropic drugs or polytherapy ($n = 29$) to ensure a homogeneous treatment outcome evaluation (Fig. 1).

Prescribed and performed treatments

The rates of the different treatments prescribed (at the time of the diagnosis) and those received (during the 1-year period after the diagnosis) in 724 ADHD patients with and without psychiatric comorbidities were compared. The rate of psychological therapies (Psy) provided, i.e., training (Psy—Training) and other psychological (Psy—Other) interventions, decreased in both ADHD groups (with and without comorbidity) compared to what was prescribed upon diagnosis. ADHD patients with comorbidity, compared to those without, showed a slight increase in the rate of combined treatment received than that prescribed (from 25 to 26%), while a higher rate of ADHD patients without comorbidity (20%) did not receive any treatment compared to those with comorbidity (12%). The rate of the treatments prescribed and received in ADHD patients according to the more frequent comorbidities showed similar trends, except for the ODD group showing a lower decrease between the rate of the treatments prescribed and received

Table 1 Sociodemographic and anamnestic characteristics of the sample

Characteristics	ADHD ($N = 1919$)			NO ADHD ($N = 942$)			Total $N = 2861$ n (%)	Bivariate model p*
	ADHD only $N = 650$ n (%)	ADHD with comorbidity $N = 1269$ n (%)	ADHD total $N = 1919$ n (%)	No psyc disorders $N = 414$ n (%)	Other psyc disorders $N = 528$ n (%)	NO ADHD total $N = 942$ n (%)		
Mean age (SD) median	8.7 (2.4) 8	9.3 (2.5) 9	9.1 (2.5) 9	9.3 (2.5) 9	9.8 (2.5) 9	9.5 (2.5) 9	9.2 (2.5) 9	<0.0001
12–17 years	98 (15)	268 (21)	366 (19)	84 (20)	131 (25)	215 (23)	581 (20)	0.0071
Male	556 (86)	1.079 (85)	1.635 (85)	338 (82)	429 (81)	767 (81)	2.402 (84)	0.0091
Only child	167 (26)	307 (24)	474 (25)	92 (22)	120 (23)	212 (23)	686 (24)	0.1723
Born abroad	23 (4)	87 (7)	110 (6)	13 (3)	29 (5)	42 (4)	152 (5)	0.2704
Adopted	19 (3)	58 (5)	77 (4)	9 (2)	12 (2)	21 (2)	98 (3)	0.0205
School failures	19 (3)	78 (6)	97 (5)	16 (4)	36 (7)	52 (6)	149 (5)	0.3777
Employed parents	395 (61)	730 (58)	1125 (59)	261 (63)	307 (58)	568 (60)	1693 (59)	0.5119
Family history of ADHD	147 (23)	270 (21)	417 (22)	45 (11)	63 (12)	108 (11)	525 (18)	<0.0001
Dystocic delivery	166 (27)	322 (27)	488 (27)	92 (23)	128 (25)	220 (24)	708 (26)	0.1513
Preterm/low weight[b]	89 (15)	185 (16)	274 (16)	59 (15)	76 (16)	135 (16)	409 (16)	0.8788
Breastfeeding[c]	339 (65)	607 (62)	946 (63)	246 (69)	288 (66)	534 (68)	1480 (64)	0.0387
Motor delay	17 (3)	76 (6)	93 (5)	16 (4)	18 (3)	34 (4)	127 (5)	0.1699
Language delay	106 (17)	280 (23)	386 (21)	62 (15)	106 (21)	168 (18)	554 (20)	0.2230

*Test χ^2 used for categorical variables and Kruskal–Wallis for continuous variables

[a] Preterm (<37 sett), low weight (<2500 gr)

[b] ≥3 months

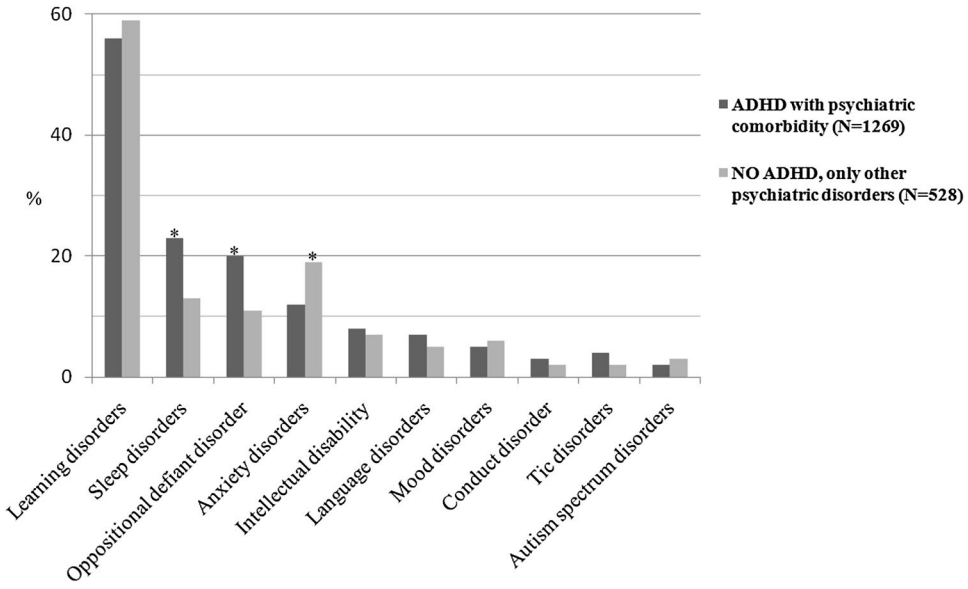

Fig. 2 Psychiatric disorders in patients with and without ADHD. *Test X^2 ($p < 0.05$)

compared to other groups. Only treatments that were actually received in the clinical practice and during the study period (12 ± 3 months) were considered in the outcome evaluation.

Improved subject rates

Clinical outcome evaluation of ADHD patients after one year of therapy, as measured by the CGI-Improvement scale, was evaluated. Overall, in the ADHD group ($N = 724$), 141 (20%) and 241 (33%) patients showed great and minimal improvement, respectively, while 299 (41%) showed no significant clinical change and 43 (6%) worsened. Results show similar rates in both ADHD with and without comorbidity groups, while, when considering each type of psychiatric comorbidity as a separate group, some differences arose. The ADHD group with an associated sleep disorder showed a higher rate of much improved subjects (28%), while the groups with ADHD with a comorbid ODD or anxiety disorder showed higher rates of worsened subjects of 11 and 13%, respectively.

Findings of the Chi-square test for each treatment (counting the number of improved patients, CGII <3) in these following ADHD groups: only ADHD, ADHD with comorbidity, ADHD with most frequent comorbidities, i.e., learning, sleep, ODD, and anxiety disorders, and ADHD Total, are shown in Fig. 3. A statistical difference between treatment groups was found in ADHD with comorbidity ($p < 0.001$), ADHD + Learning disability ($p = 0.004$), ADHD + ODD ($p = 0.019$) groups and in all ADHD ($p < 0.001$). Residual analysis was then applied to identify which specific treatment made the greatest contribution to the Chi-square test's significance (Fig. 3). Overall, combined treatment proved superior, showing a significant value in the overall ADHD group (ADHD Total), which is equivalent to stating that subjects who received MPH + Psy were significantly more likely to improve compared to other treatment groups. In ADHD with comorbidity, subjects treated with combined treatment (MPH + Psy) and those treated with MPH alone had positive values, indicating that there were more improved subjects in these groups than would be expected by chance. Although other treatments showed positive residual values, no significant findings were found.

Moreover, we evaluated whether a more severe symptomatology could have acted as moderator for the improvement rate: no differences were observed in the improvement rates for all treatment groups after stratifying for CGI-Severity at the baseline evaluation (CGIS <5 vs ≥5) ($p > 0.05$).

Treatment efficacy

We also analyzed outcome data as measured by the CGI-Severity scale (pre- to post-treatment change, Δ Mean). Figure 4 includes the effect sizes (ES) for each treatment group relative to a control condition, such as those subjects who did not receive any treatment. A common way to interpret effect sizes proposed by Cohen (1969) [60] considers an ES of 0.2 as "small", 0.5 as "medium" and "large enough to be visible to the naked eye", and an ES of 0.8 or more as "large" and "grossly perceptible and therefore large".

Comparing only ADHD with ADHD with comorbidity groups, pharmacological treatment alone (MPH) showed a medium ES (0.63) for patients with only ADHD and a large ES (0.89) for ADHD with comorbidity, while the combined treatment (X) shows a large, and statistically significant,

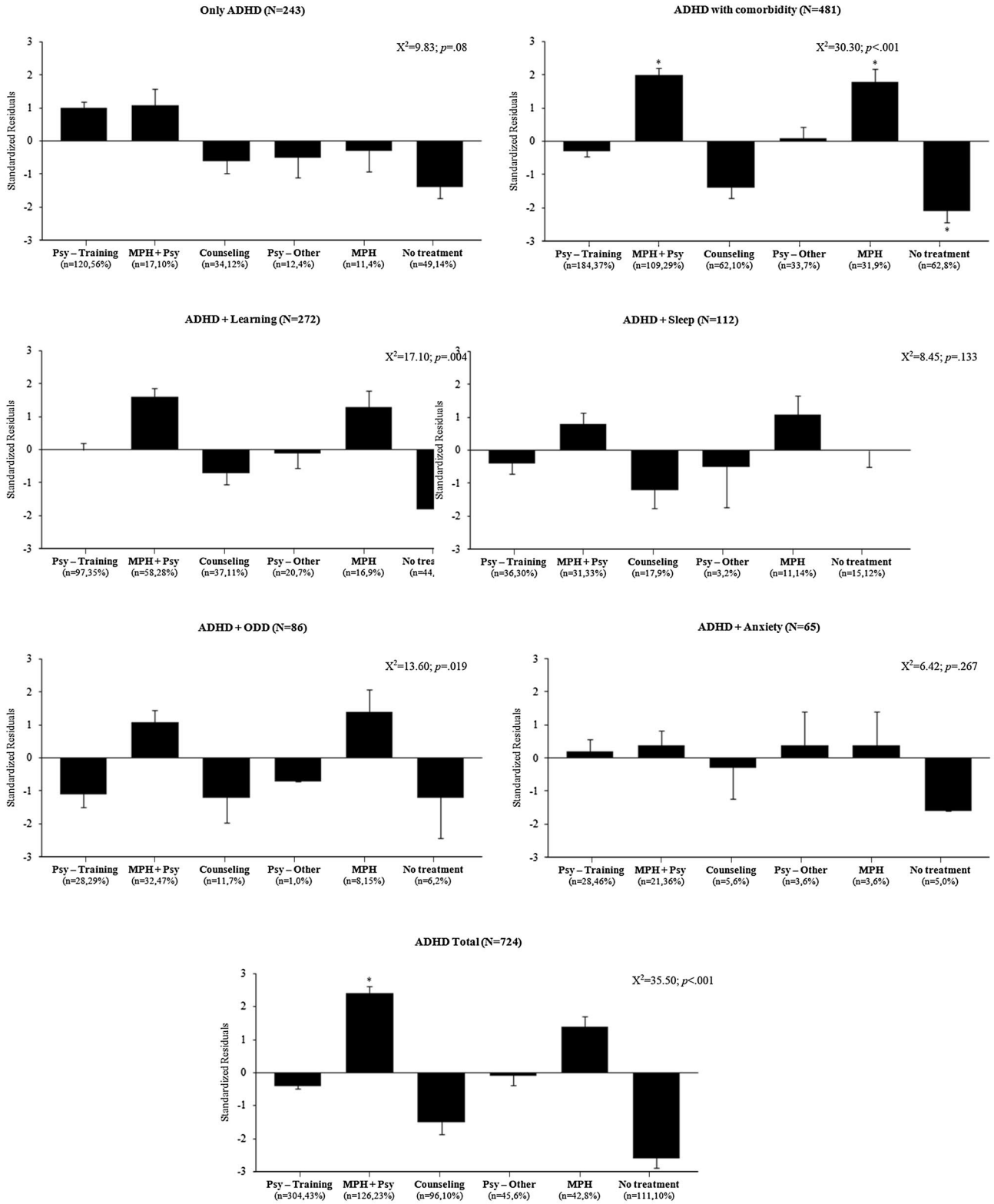

Fig. 3 Clinical improvement (CGI-I $\leq$3) in ADHD with and without comorbidities according to treatment received (Std. Res). *Statistically significant

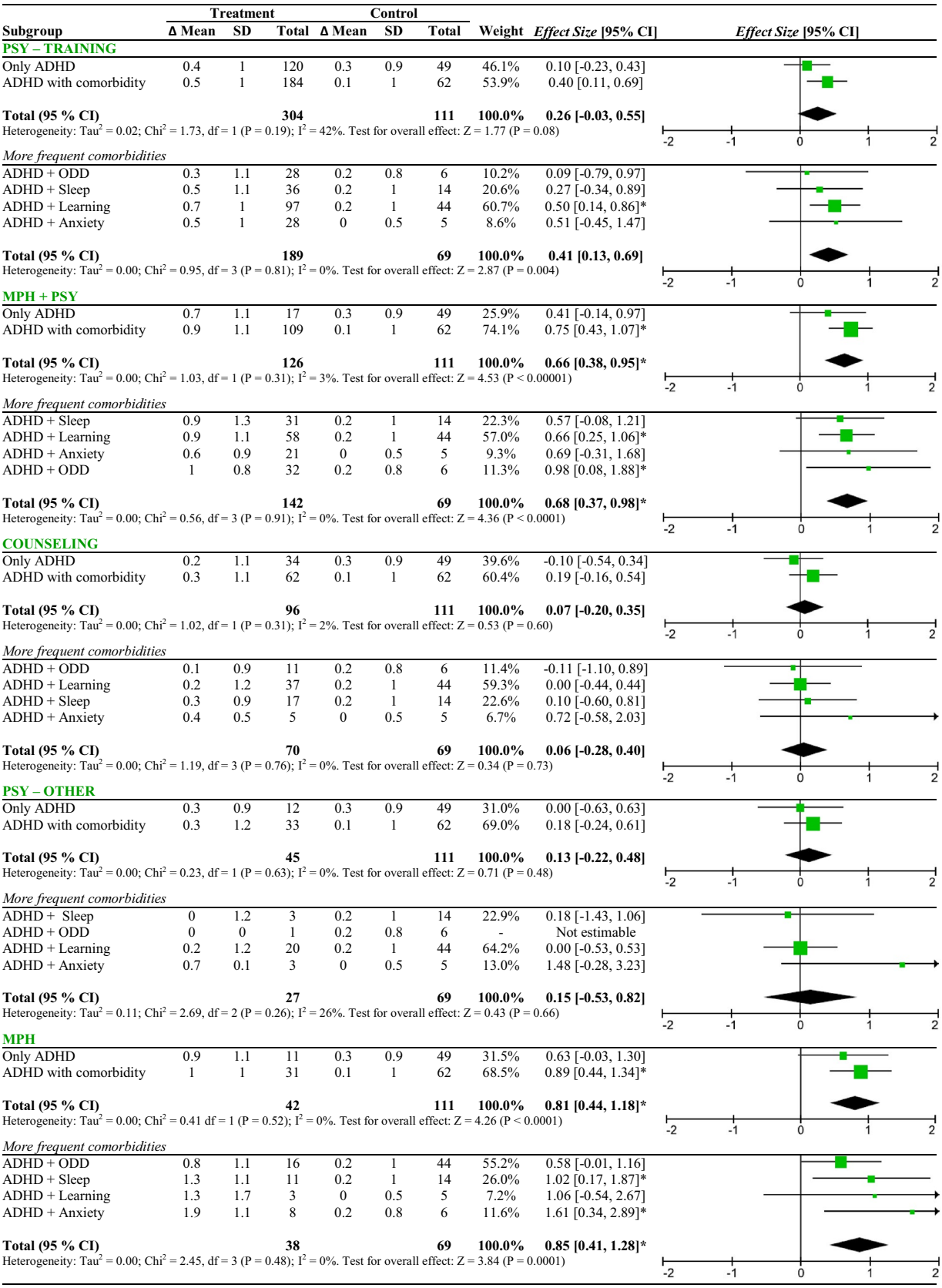

Fig. 4 Treatment outcomes (Effect size) on global functional impairment (CGI-S mean pre–post) of ADHD patients with and without comorbidities according to treatment received

ES (0.75) for ADHD with comorbidity. Other treatments showed lower ES values for these groups. According to more frequent comorbidities (ODD, anxiety, learning and sleep disorders), on the other hand, we found: for subjects with comorbid learning disorders, medium ESs of the Psy—Training treatment alone (0.50) and of the combined treatment (MPH + Psy, 0.66); for those with ODD, a large ES (0.98) of the MPH + Psy treatment; and very large ESs for ADHD with anxiety (1.61) and with sleep (1.02) disorders when they received MPH alone (Fig. 4).

Discussion

Prevalence rate

In our sample of Italian children and adolescents with ADHD, most of the patients (66%) resulted as having one or more comorbid psychiatric disorders, in strong agreement with previous studies [6, 13, 14, 21, 61–65]. This rate is consistent with studies that found that ADHD without comorbidity is rare [66], even in the general population sample [14]. Among the sociodemographic and anamnestic characteristics, the variables that resulted significantly associated with a higher risk of presenting a co-occurring disorder in ADHD were a lower age at diagnosis, having a family history of ADHD, and not being breastfed. These results were somewhat expected following data from previous reports evaluating risk factors for psychiatric disorders in a large population sample [67–70]. Moreover, ADHD patients show a higher risk of presenting two or more psychiatric comorbidities compared to subjects with other psychiatric disorders, although with lower rates than those reported in the MTA study [13] (21% in our study vs 40% in the MTA study).

Consistently with other reports, most of our patients with ADHD had other psychiatric conditions more frequently compared to subjects with other mental disorders. On the broad spectrum of possible co-existing problems likely to occur in individuals diagnosed with ADHD [3], in our ADHD sample the most common comorbid conditions were specific learning disorder, sleep problems, oppositional defiant disorder and anxiety disorders, with slightly different prevalence rates compared to previous reports [6, 15, 24, 34, 36, 64, 71]. In particular, in our ADHD sample ODD co-occured in 20% of cases; this rate was slightly lower than that of other studies showing association rates varying from 25 to 50% [10, 61, 62, 65], with a higher prevalence in population studies (61%) compared to clinical sample studies (39%) [63]. This difference may be related to the Italian context, based on the findings of previous studies that found an overall lower rate of externalizing disorders (1%) in the developmental age compared to those estimated in other countries [72]. The general population prevalence in children and adolescents is 6.5% for anxiety disorders and 2.6% for depressive disorders [73]; similar results emerged from our study's entire sample. The association between anxiety disorders and ADHD, on the other hand, ranges from 10 to 40% [13, 14, 74] in clinic-referred children and is consistent with our results. Moreover, consistent with our findings, perspective, longitudinal studies across the lifespan show that the risk of anxiety disorders in ADHD children and adolescents is no greater than in control groups, but, in young adulthood, shows a large rise in those whose ADHD persists to age 27 [75]. This inconsistence in the literature data is probably due to the fact that most research merges all types of anxiety disorders together.

The co-occurrence of other psychiatric comorbidities is less frequent. The prevalence rate of depressive disorder associated with ADHD (5%), e.g., was lower than expected, based on other reports that indicated association rates of between 20 and 30% [13, 75–77]. Our finding, however, may be explained by the fact that the risk of depression among ADHD patients seems to be largely mediated by the co-occurrence of conduct disorders [78–80] whose incidence is very low in our sample (3%).

In all the children with two or more psychiatric disorders, the ADHD group showed two age peaks, at 8 and 12 years, compared to a single peak in subjects without ADHD. This data could be explained by the fact that the onset of most comorbid disorders occurred earlier when an ADHD diagnosis was present. This issue has been reported previously, for example in obsessive compulsive [81] and bipolar disorders [82]. In our sample, subjects with ADHD-C subtype showed higher rates of psychiatric comorbidity, more significant global functional impairment, and higher drug prescription rates. The overlap between the presence of comorbid conditions and clinical global severity is consistent with recent data confirming that comorbidity strongly impacts on the level of functional impairment [83]. Moreover, subjects with comorbidity, and who therefore show higher impairment, also more frequently receive a prescription of pharmacological treatment in combination with psychological intervention, as is to be expected given the Italian National guidelines [58].

Therapeutic approaches

Among ADHD patients receiving care continuity for 1 year, the performed treatment rate changed according to the type of prescribed treatment and to the presence and type of psychiatric comorbidity.

Prescribed and performed treatments

Overall, training and other psychological treatments were performed less frequently than prescribed at the time of diagnosis in, both, patients with and without comorbidity. While ADHD without comorbidity had a higher rate of subjects not receiving any treatment, ADHD with comorbidity showed an increase in the rate of subjects treated with combined therapy and, more specifically, ADHD with ODD was the group that more frequently received the treatment prescribed. These results were expected, not only for the above-mentioned reasons concerning the clinicians' compliance to guidelines, but also for the existing, and well known, critical issues related to the services organization and their sustainability in responding to care needs [84]. It is known worldwide that only a very limited number of children and adolescents with mental health needs has access to care, and Italy is no exception: access to services occurs only in 1 case every 4 for children with a neuropsychiatric disorder [85]. The waiting lists for diagnosis and treatment represent a major issue to be resolved in clinical practice and could be a possible explanation of the difference found between prescribed and received treatments [84].

Our data also show that patients with ADHD and ODD more frequently receive the treatment prescribed. This could be explained by the fact that ODD symptoms are largely known to increase the clinical severity and to worsen long-term outcomes [86], but also to be the major reason for difficulties in the daily management of patients at school and in other life contexts. This, in turn, could result in a priority need to be answered from different perspectives. It is, in fact, clinically reasonable that patients with high comorbidity and impairment are considered a priority for intervention and, therefore, show a greater correspondence between received and prescribed treatments, and a lower percentage of no treatment when compared to ADHD alone. Moreover, a higher rate of ADHD subjects with comorbidity receive a pharmacological therapy alone compared to those with only ADHD, probably related to the fact that clinical service resources fail to ensure all psychological treatments prescribed. Despite this, it is important to note that not all clinical and environmental factors that could be playing a substantial role in the therapeutic strategy, nor a possible change in these factors during the 1-year period, could be considered in our study because, in order to increase the number of variables considered, a higher number of enrolled patients would have been needed.

Improved subject rates

ADHD subjects, with and without comorbidity, receiving combined treatment had a higher subject improvement rate compared to that of the other treatment groups. Interestingly, the improvement rate did not seem to be related to clinical severity at baseline, which could mean that appropriate and different therapeutic choices were made according to the different severity levels at the time of diagnosis. Defining specific, different therapeutic approaches according to CGI-Severity at baseline was one of the objectives of the Lombardy ADHD treatment group, and, thus, seems to have been achieved. Nonetheless, this aspect needs to be verified with larger numbers.

The clinical improvement rate according to specific comorbidities showed that combined therapy was superior for ADHD with learning disorders and with sleep disorders compared to training intervention alone, as expected considering the effect of the pharmacological treatment on sleep [26] and on learning disorders—improving attention allows improvement in learning skills [39].

On the other hand, according to our results, subjects with ADHD and anxiety disorders need to be treated with psychological interventions other than training, rather than with combined therapy, in order to reach a greater improvement. In this case, our data seem to be in contrast with previous findings: March and coll. [87]—MTA study—indeed, show that the increase in treatment effect size is relatively greater for behavioral and, more robustly, for combined treatment, when comparing ADHD with and without anxiety disorders. The findings, however, are not fully comparable because in our study "other psychological treatment" is a heterogeneous treatment group including not only behavioral treatment, but also psychoanalytic, psychodynamic, and familiar psychological approaches.

Treatment efficacy

Our results are in line with the main results of the most important study on the efficacy of treatments for ADHD—the MTA study [88]—according to which the combined treatment did not yield significantly greater advantages than pharmacological therapy alone for core ADHD symptoms, but may have provided advantages for positive functioning outcomes. In our sample, we considered the improvement rate in clinical global functioning, as measured by CGI scales (CGIs), to measure treatment outcomes. In the interpretation of our findings, however, we need to consider not only the strengths of CGI scales (overall clinician-determined summary measures taking into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function) [89], but also their weaknesses, i.e., clinician only, subjectivity, and heterogeneous confidence intrinsic to the use of these scales.

Nonetheless, taking into account these limitations, and consistently with the results of previous reviews [89–92] we could also conclude that, in our sample, combined treatment and pharmacological therapy are well-established interventions for ADHD also in an observational clinical practice context, with a large ES, followed by training treatments, with an almost medium effect size. However, a lower ES for pharmacological treatment alone was found in the group with ADHD only, but this could probably be due to the lower number of subjects with ADHD only that have been treated with pharmacological therapy alone, since it is known, indeed, that small samples are particularly susceptible to inflated effect size estimates [93].

Finally, these results should be considered with caution considering to some limitations related to the specific methodological study design, which was not a randomized controlled trial (RCT), but an observational study conducted in the clinical practice context. The service organization variables may have had an impact on the possibility to ensure treatments prescribed and to fully follow clinical guidelines, and this may, in turn, be a bias in estimating the efficacy and efficiency of the treatments performed. Moreover, an important aspect that would require to be investigated is the clinical outcome of each specific comorbidity through the collection, i.e., change in symptoms severity, clinical evaluation over the time (chronicity, improvement, recovery,…). But this is another analysis we expect to perform further and according to database adjustment. Lastly, although the Regional ADHD Registry, as part of a larger, multimodal project, represents a distinctive tool for ensuring appropriate diagnostic and therapeutic pathways of care in ADHD children, our findings refer specifically to the population with ADHD accessing ADHD centers since only these hubs input data into the Registry.

Conclusion

Our findings confirm, in a multicenter observational study involving a large sample of children and adolescents, that ADHD is more often a complex disorder with a high rate of associated comorbid conditions [94]. This study was the first to describe the comorbidity patterns of ADHD in the Italian context and to highlight certain important clinical and service organization aspects that should be extended to other national ADHD centers to ensure an appropriate and homogenous care management of ADHD in Italy. First, the high prevalence of associated psychiatric conditions warrants that these problems be systematically and specifically investigated, diagnosed, and, especially, taken into consideration as the main guide for choosing among the available therapeutic options. Secondly, as parents are frequently not aware of the longitudinal course of the ADHD disorder, especially when complicated by psychiatric comorbidity, clinicians should consider the best evidence-based treatment to improve outcome, informing and actively involving families and patients (if possible) in the decision making process. Third, given the demonstration of this relevant rate of co-existing psychiatric conditions in ADHD, it would be appropriate that clinicians working in ADHD centers not only have expertise in ADHD, but also have clinical skills in most neuropsychiatric disorders, as previously reported [9, 95]. Finally, clinicians should consider the full spectrum of neurodevelopmental disorders, anxiety, and mood disorders as possible differential diagnoses of ADHD. Neurodevelopment disorders in children and adolescents, such as ADHD, are multifactorial disorders and have shared characteristics and several risk factors in common [96]. This raises the need for accurate clinical evaluations regarding the specificity of underlying etiological factors, the degree of functional impairment of the core symptoms and different comorbidities, and, consequently, of appropriate treatment. In our opinion, this will be the challenge for future clinical care and research in the area.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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