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ADHD IN ADULTS: Comorbidity with bipolar disorder and substance abuse

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INDEX

INTRODUCTION

Despite an increasing attention received in the last decades, attention-deficit/hyperactivity disorder (ADHD) in adults has continued to be understudied and underdiagnosed. Empirical researches have addressed most of the controversial issues and has supported the persistence of ADHD in adults. Epidemiological and clinical studies indicated that ADHD and comorbid disorders that often coexist in childhood continue into adulthood, leading to a medical and economic burden; even if the extent of the burden of ADHD is unknown, it worsens when the disorder and cormorbid disorders are untreated (Biederman J., 2004).

ADHD is characterized by a continuous history of hyperactivity, forgetfulness, distractibility, impulsiveness and/or inattention, starting from the early childhood and at a more severe extent than whatever may be usual in peers. Originally described in pediatric populations, it is widely recognized in adults. A recent 10-year follow-up study examined the age-dependent persistence of ADHD in young patients during the transition from adolescence into early adulthood. At follow-up ADHD was considered persistent if subjects met full or subthreshold (more than half of the symptoms required for a full diagnosis) DSM-IV diagnostic criteria. The study followed-up 110 patients with ADHD and 105 non-ADHD

controls. While 65% of children with ADHD no longer met full DSM-IV criteria for ADHD at the 10-year follow-up, 78% of subjects showed at least one or more relevant symptoms, or failed to attain functional remission (Global Assessment of Functioning, GAF score < or =60). Persistence of ADHD as described here was associated with higher rates of psychiatric co-morbidity, more family history of mood disorders and higher levels of educational and interpersonal impairments than controls (Biederman J et al., 2010).

ADHD teenager patients are more likely to be prone to accidents like dog-bites and burns, and display an unhealthy lifestyle: smoking, alcohol and drug abuse, risky sexual lifestyle, chronic sleep problems with delayed falling asleep and awakening. Criminality in adulthood, especially when associated with substance abuse and antisocial personality, is predicted by ADHD and comorbid conduct disorder in childhood.

While the disorder in children is mostly described as a disorder involving hyperactivity and impulsiveness, in adulthood ADHD inattention prevails on externalizing features, with a higher rate of psychiatric comorbidities, including major depressive disorder, bipolar disorder (BD), anxiety disorders and substance abuse (Klassen LJ. et al., 2010). In recent years, evidence has been growing regarding high levels of comorbidity between ADHD and other disorders, including mood and anxiety and

conduct disorders. Thus, ADHD diagnosis seems to comprehend different groups of conditions, rather than a single homogeneous clinical entity, with potentially different etiopathogenetic substrates and different outcomes. Follow-up studies of children with ADHD indicate that subgroups of subjects with ADHD and comorbid disorders have a poorer outcome as evidentiated by significantly greater social, emotional, and psychological difficulties (Spencer TJ, 2006).

Wender (1998) provided a list of adult behaviours linked to childhood ADHD (see also Weiss & Murray, 2003; Asherson, 2005). Motor hyperactivity may be replaced by a subjective sense of restlessness, difficulty in relaxing and settling down and dysphoria when inactive. Attention deficits may as well persist in a lack of concentration on detail, the need to re-read materials several times, forgetting activities and appointments, losing things and losing the thread of conversations. Thoughts are unfocused and ‘on the go’ all the time. Mood changes are represented by rapid shifts into depression or excitability, irritability and temper outbursts that interfere with relationships. Disorganisation is prominent, tasks are not completed, problem-solving strategy is lacking and time management is particularly poor. Enduring impulsivity leads to problems in teamwork, abrupt initiation and termination of relationships, and liability to set up quick decisions without full analysis of the situation (Asherson et al., 2007).

ADHD is estimated to affect approximately 5.29% of school-aged children and is therefore the most common childhood onset psychological disorder. A conservative estimation of the annual society cost of ADHD in childhood and adolescence is USD 42.5 billion in the U.S. Global sales of ADHD medicines could reach USD 4.3 billion by 2012. Despite the prevalence, high heritability and costs of ADHD, biological markers do not exist and diagnosis is made on the basis of screening interviews. The individuation of biomarkers could permit an early and reliable diagnosis and an appropriate therapeutic approach. Lack of markers likely stems from several factors that complicate ADHD research and the assessment of pharmacological responses (Wallis D., 2010)

Instruments for diagnosing ADHD in childhood are well validated and reliable, but the diagnosis of ADHD in adults remains problematic (Barkley RA., 2009). Discussions about the appropriateness of DSM-IV criteria for adult ADHD are controversial, since they were designed for and based on studies on children (Davidson MA., 2008). Recent publications indicate that diagnosing ADHD in adulthood using DSM-IV is hampered if the number of symptoms does not achieve the threshold for diagnosis or if onset prior to the DSM-IV age at onset criterion cannot be established (Faraone SV., et al, 2006). Several physicians focus on major psychiatric diseases (major depressive disorder, bipolar disorder,

anxiety disorders and substance abuse) but not on ADHD (Goldstein 2009).

Therefore, many symptoms that are directly attributable to ADHD are often mistakenly associated with other psychiatric conditions and consequently not fully treated (Fischer et al., 2007; Kessler et al., 2006). Treating ADHD has been shown to decrease the severity of comorbid substance abuse, although in severe cases, treating substance abuse first might be necessary to ensure treatment compliance (Newcorn et al., 2007). Considering the current lack of empirical data on treatment of ADHD and comorbidities, patients should be managed on a case-by-case basis, with the most severe condition given treatment priority.

The comorbid presentation of people suffering from ADHD and BD (ADHD/BD) is associated with a more severe disease course, more severe mood disorder symptoms, and lower functional scores. Importantly, the co-segregation of these two conditions makes ADHD diagnosis challenging because its symptoms are often mistakenly assumed to be part of BD. As a result, patients with comorbid ADHD/BD are under-diagnosed and under-treated. Optimal diagnosis, understanding and treatment of the comorbid condition are important, as ADHD/BD has been associated with significant functional impairment and suboptimal treatment responses when compared to ADHD or BD populations without comorbidity. (Chokka, 2010; Halmoy, 2010).

HISTORICAL ASPECTS

One of the first reference to a hyperactive or ADHD child (Fidgety Phil) was in the poems of the German physician Heinrich Hoffman in 1865, who wrote poems about many of the childhood maladies who saw in his medical practice (Stewart, 1970). But scientific credit is typically awarded to George Still and Alfred Tredgold for being the first authors to focus with serious clinical attention on the behavioral condition in children that most closely approximates what is today known as ADHD.

Still, he believed these children displayed a major “defect in moral control” in their behavior that was relatively chronic in most cases. In some cases, these children acquired the defect as a consequence of an acute brain disease, and it might remit on recovery from the disease. In the chronic cases, he noted a higher risk for criminal acts in later development in some of them, though not all. Although this defect could be associated with intellectual retardation, as it was in 23 of the cases, it could also arise in children of near normal intelligence as it seemed to happen in the remaining 20.

The history of interest in ADHD in North America can be traced back to the outbreak of an encephalitis epidemic in 1917–1918 when clinicians had to face a number of children who survived this brain infection yet with significant behavioral and cognitive sequelae (Cantwell, 1981;

Kessler, 1980; Stewart, 1970). Numerous papers reported these sequelae (Ebaugh, 1923; Strecker & Ebaugh, 1924; Stryker, 1925), and they included many of the characteristics we now incorporate into the concept of ADHD. Such children were described as being impaired in their attention, regulation of activity, and impulsivity, as well as other cognitive abilities, including memory, and were often noted to be socially disruptive. Symptoms of oppositional and defiant behavior as well as delinquency and conduct disorder also arose in some cases. Post-encephalitic Behavior Disorder, as it was called, was clearly the result of brain damage. The large number of children affected resulted in significant professional and educational interest in this behavioral disorder. Its severity was such that many children were recommended for care and education outside the home and normal educational facilities. Despite a rather pessimistic view of the prognosis of these children, some facilities reported significant success in their treatment using simple behavior modification programs and increased supervision (Bender, 1942; Bond & Appel, 1931).

The association of a brain disease with behavioral pathology apparently led early investigators to study other potential causes of brain injury in children and their behavioral manifestations. Birth trauma (Shirley, 1939); other infections such as measles (Meyer & Byers, 1952), lead toxicity (Byers & Lord, 1943), epilepsy (Levin, 1938), and head injury (Blau,

1936; Werner & Strauss, 1941) were studied in children and were found to be associated with numerous cognitive and behavioral impairments, including the triad of ADHD symptoms noted earlier. Other terms introduced during this era for children displaying these behavioral characteristics were “organic driveness” (Kahn & Cohen, 1934) and “restlessness” syndrome (Childers, 1935; Levin, 1938). Many of the children seen in these samples were also mentally retarded or more seriously behaviorally disordered than are children who are today diagnosed as ADHD. Only several decades later, however, investigators would have attempted to make out the separate contributions of intellectual delay, learning disabilities, or other neuropsychological deficits from those of the behavioral deficits to the maladjustment of these children. Even so, scientists at that time discovered that activity level was often inversely related to intelligence in children, increasing as intelligence declined—a finding supported in many subsequent studies (Rutter, 1989). It should also be noted that a large number of children in these older studies were, in fact, brain damaged or had signs of such damage (epilepsy, hemiplegias, etc.).

Another significant series of papers on the treatment of hyperactive children appeared in 1937–1941. These papers were to mark the beginnings of medication therapy (particularly stimulants) for behaviorally disordered children as well as the field of child psychopharmacology in

general (Bradley, 1937; Bradley & Bowen, 1940; Molitch & Eccles, 1937). Originally Initiated to treat headaches that resulted from pneumo-encephalograms during research studies of these disruptive youth, the administration of amphetamine turned out in a noticeable improvement in their behavioral problems and academic performance. Later studies also confirmed such a positive drug response in half or more of hyperactive hospitalized children (Laufer, Denhoff, & Solomons, 1957). As a result, by the 1970s, stimulant medications were gradually becoming the treatment of choice for the behavioral symptoms now associated with ADHD. And so they remain today.

In the 1950s, researchers began a number of investigations into the neurological mechanisms underlying these behavioral symptoms, the most famous of which was probably that by Laufer et al. (1957). These writers referred to ADHD children as having Hyperkinetic Impulse Disorder and stated that the central nervous system (CNS) deficit occurred in the thalamic area. Here, poor filtering of stimulation occurred, allowing an excess of stimulation to reach the cortex. The evidence was based on a study of the effects of the photo-Metrozol method in which the drug Metrozol is administered while flashes of light are presented to the child. The amount of drug required to induce a muscle jerk of the forearms along with a spike-wave pattern on the electroencephalogram serves as the measure of interest. Laufer et al. (1957) found that

hyperactive inpatient children required less Metrozol than nonhyperactive inpatient children to induce this pattern of response. This finding suggested that hyperactive children had a lower threshold for stimulation likely in the thalamic area.

In the late 1950s and early 1960s, critical reviews began appearing questioning the concept of a unitary syndrome of brain damage in children. They also pointed out the logical fallacy that if brain damage resulted in some of these behavioral symptoms, these symptoms could be pathognomonic of brain damage without any other corroborating evidence of CNS lesions. Leading among these critical reviews were those of Birch (1964), Herbert (1964), and Rapin (1964), who questioned the validity of applying the concept of brain damage to children who had only equivocal signs of neurological involvement, not necessarily damage. A plethora of research followed on MBD children (see Rie & Rie, 1980, for reviews); in addition, a task force by the National Institute of Neurological Diseases and Blindness (Clements, 1966) recognized at least 99 symptoms for this disorder. The concept of MBD would die a slow death as it eventually became recognized as vague, over-inclusive, of little or no prescriptive value, and without much neurological evidence (Kirk, 1963).

As dissatisfaction with the term “MBD” was occurring, clinical investigators shifted their emphasis on the behavioral symptom thought

as the main characteristic of the disorder – i.e., hyperactivity. And so the concept of a hyperactive child syndrome arose, described in the classic papers by Laufer and Denhoff (1957) and Chess (1960) and other reports of this era (Burks, 1960; Ounsted, 1955; Prechtl & Stemmer, 1962). Chess defined hyperactivity as follows: “The hyperactive child is one who carries out activities at a higher than normal rate of speed than the average child, or who is constantly in motion, or both”. Chess’s article was historically significant for several reasons: (1) it emphasized activity as the defining feature of the disorder, rather than speculative underlying neurological causes, as other scientists of the time would also do, (2) it stressed the need to consider objective evidence of the symptom beyond the subjective reports of parents or teachers, (3) it took the blame for the child’s problems away from the parents, and (4) it separated the syndrome of hyperactivity from the concept of a brain-damaged syndrome. Other scientists of this era emphasized similar points (Werry & Sprague, 1970). It was recognized that hyperactivity is a behavioral syndrome that could arise from organic pathology but could also occur in its absence. Even so, it would continue to be viewed as the result of some biological difficulty rather than due solely to environmental causes. Hence arose the beginning of a belief that would be widely held among clinicians into the 1980s – that hyperactivity (ADHD) was outgrown by adolescence.

Also noteworthy in this era was the definition of hyperactivity given in the official diagnostic nosography at the time, the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II; American Psychiatric Association, 1968). It employed only a single sentence describing the hyperkinetic features and, in the wake of Chess, stressed the view that the disorder was developmentally benign: “The disorder is characterized by overactivity, restlessness, distractibility, and short attention span, especially in young children; the behavior usually diminishes by adolescence”.

It is likely during this period, or even earlier, that the perspective of hyperactivity in North America began to diverge from that in Europe, and particularly in Great Britain. In North America, hyperactivity would become a behavioral syndrome recognized mostly by greater-than-normal levels of activity, would be viewed as a relatively common disturbance of childhood, would not necessarily be associated with demonstrable brain pathology or mental retardation, and would be more of an extreme degree in the normal variation of temperament in children. In Great Britain, the earlier and narrower view of a brain-injured child syndrome would continue into the 1970s -- hyperactivity or hyperkinesis was seen as an extreme state of excessive activity of an almost driven quality, was highly uncommon, and usually occurred in conjunction with other signs of brain damage, such as epilepsy, hemiplegias, retardation,

or a clearer history of brain insult, such as trauma or infection (Taylor, 1988). The divergence in views would lead to large discrepancies between North America and Europe in their estimations of the prevalence of the disorder, their diagnostic criteria, and their preferred treatment modalities. A rapprochement between these views would not occur until well into the 1980s (Rutter, 1988, 1989; Taylor, 1986, 1988).

As Ross and Ross (1976) noted in their exhaustive and scholarly review of the era, the perspective on hyperactivity in this historical period was that it remained a brain-dysfunction syndrome, although of a milder magnitude than previously believed. The disorder was no longer ascribed to brain damage; instead a focus on brain mechanisms prevailed. The disorder was also viewed as having a predominant and relatively homogeneous set of symptoms, prominent among which was excessive activity level or hyperactivity. Its prognosis was now felt to be relatively benign as it was often outgrown by puberty. The recommended treatments now consisted of short-term treatment with stimulant medication and psychotherapy in addition to the minimum-stimulation types of classrooms recommended in earlier years.

Research in the period from 1970 to 1979 took a quantum leap forward, with more than 2,000 published studies existing by the time the decade ended (G. Weiss & Hechtman, 1979). Numerous clinical and scientific textbooks (Cantwell, 1975; Safer & Allen, 1976; Trites, 1979; Wender,

1971) appeared along with a most thorough and scholarly review of the literature by Ross and Ross (1976). Special journal issues were devoted to the topic (Douglas, 1976; Barkley, 1978), along with numerous scientific gatherings (Knights & Bakker, 1976, 1980). Clearly, hyperactivity had become a subject of serious professional, scientific, and popular attention.

By the early 1970s, the defining features of the hyperactive or hyperkinetic child syndrome were broadened to include what investigators previously felt to be only associated characteristics, including impulsivity, short attention span, low frustration tolerance, distractibility, and aggressiveness (Marwitt & Stenner, 1972; Safer & Allen, 1976). Others (Wender, 1971, 1973) persisted with the excessively inclusive concept of MBD in which even more features, such as motor clumsiness, cognitive impairments, and parent–child conflict, were viewed as hallmarks of the syndrome and in which hyperactivity was unnecessary for the diagnosis. As noted earlier, the diagnostic term "MBD" would fade from clinical and scientific usage by the end of this decade, resulting in no small part of the scholarly tome by Rie and Rie (1980) and critical reviews by Rutter (1977, 1982). These writings emphasized the lack of evidence for such a broad syndrome. The symptoms were not well defined, did not significantly correlate among themselves, had no well-specified etiology, and displayed no common

course and outcome. The heterogeneity of the disorder was overwhelming and the conceptualization of an MBD with little or no evidence of neurological abnormality was far and wide criticized (Wender, 1971). Moreover, even in cases of well-established cerebral damage, the behavioral sequelae were not uniform across cases and hyperactivity turned out only in a minority of cases. Hence, contrary to 25 years of theorizing about this point, hyperactivity was not a common sequelae of brain damage, truly brain-damaged children did not display a uniform pattern of behavioral deficits, and children with hyperactivity rarely had substantiated evidence of neurological damage (Rutter, 1989). Wender (1971) described the essential psychological characteristics of children with MBD as consisting of six clusters of symptoms: (1) motor behavior, (2) attentional–perceptual cognitive function, (3) learning difficulties, (4) impulse control, (5) interpersonal relations, and (6) emotion.

Wender theorized that these six domains of dysfunction could be best accounted for by three primary deficits: (1) a decreased experience of pleasure and pain, (2) a generally high and poorly modulated level of activation, and (3) extroversion. A consequence of item (1) is that MBD children would prove less sensitive to both rewards and punishments, making them less susceptible to social influence. The generally high and poorly modulated level of activation was thought to be an aspect of poor

inhibition. Hyperactivity, of course, was the consummate demonstration of this high level of activation. The problems with poor sustained attention and distractibility were conjectured to be secondary aspects of high activation. Emotional overreactivity, low frustration tolerance, quickness to anger, and temper outbursts resulted from the poor modulation of activation. These three primary deficits, then, created a cascading of effects into the larger social ecology of the child, resulting in numerous interpersonal problems and academic performance difficulties.

Like Still (1902), Wender gave a prominent role to the low level of inhibition. He believed it could explain both the activation and the attention problems, as well as the excessive emotionality, low frustration tolerance, and hot temperedness of these children. It is therefore quite unclear why deficient inhibition was not made to be a primary symptom in this theory in place of high activation and poor modulation of activation.

Unlike Still, however, Wender does not say much about normal developmental processes with respect to the three primary areas of deficit and thus does not clarify more precisely what may be going awry in them to give rise to these characteristics of MBD. The exception may be represented by the hypothesized lowered sensitivity to reinforcement and punishment. A higher-than-normal threshold for pleasure and pain,

as noted earlier, was thought to create these insensitivities to behavioral consequences.

At this time, disenchantment developed over the exclusive focus on hyperactivity as the sine qua non of this disorder (Werry & Sprague, 1970). Significant at this historical juncture would be the presidential address of Virginia Douglas to the Canadian Psychological Association (Douglas, 1972). She argued that deficits in sustained attention and impulse control were more likely to account for the difficulties seen in these children than just hyperactivity. These other symptoms were also seen as the major areas on which the stimulant medications used to treat the disorder had their impact. Douglas's paper is historically significant in other ways as well. Her extensive and thorough battery of objective measures of various behavioral and cognitive domains, heretofore unused in research on ADHD, allowed her to rule in or out various characteristics felt to be typical for these children in earlier clinical and scientific lore. For instance, Douglas found that hyperactive children were not necessarily and uniformly more reading or learning disabled, did not perseverate on concept learning tasks, did not manifest auditory or right–left discrimination problems, and had no difficulties with short-term memory. Most important, she and Susan Campbell demonstrated that hyperactive children were not always more distractible than normal

children and that the sustained attention problems could emerge in conditions in which no significant distractions existed.

Douglas (1980a, 1980b, 1983; Douglas & Peters, 1979) later elaborated, refined, and further substantiated her model of hyperactivity; thus, her model culminated in the view that four major deficits could account for symptoms of ADHD: (1) the investment, organization, and maintenance of attention and effort; (2) the inhibition of impulsive responding; (3) the modulation of arousal levels to meet situational demands; and (4) an unusually strong inclination to seek immediate reinforcement. This perspective initiated or guided a substantial amount of research over the following 15 years.

Douglas's paper and the subsequent research published by her team were so influential that they were probably the major reason the disorder was renamed Attention-Deficit Disorder (ADD) in 1980 with the publication of DSM-III (American Psychiatric Association, 1980). In this revised official taxonomy, deficits in sustained attention and impulse control were formally recognized ~~as~~ of greater significance in the diagnosis than hyperactivity. The shift to attention deficits rather than hyperactivity as the major difficulty of these children was useful, at least for a while, because of the growing evidence that hyperactivity was not specific of this particular condition but could be noted in other psychiatric disorders (anxiety, mania, autism, etc.), that there was no clear

delineation between normal and abnormal levels of activity, that activity was in fact a multi-dimensional pattern, and that the symptoms of hyperactivity were quite situational in many children (Rutter, 1989). But also this re-appraisal would have shown its weakness when a decade later similar objections began to be raised about the pattern of attention (multidimensional, situationally variable, etc.). Yet, some research showed that at least deficits in vigilance or sustained attention could be used to discriminate this disorder from other psychiatric disorders (Werry, 1988).

Another hallmark of this era was the widespread adoption of the parent and teacher rating scales developed by C. Keith Conners (1969) for the assessment of symptoms of hyperactivity, particularly during trials on stimulant medication. For at least 20 years, these simply constructed ratings of behavioral items would be the “gold standard” for selecting children as hyperactive for both research purposes and treatment with medication. The scales would also come to be used for monitoring of treatment responses during clinical trials.

Also significant during this decade was the effort to study the social–ecological impact of hyperactive/inattentive behavior. This line of research set about evaluating the effects produced on family interactions by the hyperactive child. Originally initiated by Campbell (1973, 1975), this line of inquiry dominated the research over the following decade

(Barkley & Cunningham, 1979; Cunningham & Barkley, 1978, 1979; Danforth et al., 1991), particularly evaluating the effects of stimulant medication on social exchanges. These studies showed that hyperactive children were much less compliant and more oppositional during parent–child exchanges than normal children and that their mothers were more demanding, commanding, and negative than mothers of normal children. These difficulties would increase substantially when the situation changed from free play to task-oriented demands. Studies also demonstrated that stimulant medication resulted in significant improvements in child compliance and decreases in maternal control and directiveness. Simultaneously, Humphries, Kinsbourne, and Swanson (1978) reported similar effects of stimulant medication, all of which suggested that much of parental controlling and negative behavior toward hyperactive children were the result rather than the cause of the children's poor self-control and inattention. At the same time, Carol Whalen and Barbara Henker at the University of California, Irvine, demonstrated similar interaction conflicts between hyperactive children and their teachers and peers as well as similar effects of stimulant medication on these social interactions (Whalen & Henker, 1980; Whalen, Henker, & Dotemoto, 1980). This line of research was substantially increased in the following decade and was expanded by Charles Cunningham and others to include studies of peer interactions

and the effects of stimulants on them (Cunningham, Siegel, & Offord, 1985).

Finally, this decade should be credited with the emergence of clinical and research interests in the existence of MBD or hyperactivity in adult clinical patients. Initial interest in adult MBD can be traced back to the latter part of the 1960s, seemingly arising as a result of two events. The first of these was the publication of several early follow-up studies demonstrating persistence of symptoms of hyperactivity/MBD into adulthood in many cases (Mendelson et al., 1971; Menkes, Rowe, & Menkes, 1967). The second was the publication by Harticollis (1968) of the results of neuropsychological and psychiatric assessments of 15 adolescent and young adult patients (ages 15–25) seen at the Menninger Clinic. The neuropsychological performance of these patients suggested evidence of moderate brain damage. Their behavioral profile suggested many of the symptoms that Still initially identified in ADHD children, particularly impulsiveness, overactivity, mood lability, and proneness to aggressive behavior and depression. Some of the cases appeared to have demonstrated this behavior uniformly since childhood. Horticollis speculated using psychoanalytic theory that this condition arose from an early and possibly congenital defect in the ego apparatus in interaction with busy, action-oriented, successful parents.

The following year, Quitkin and Klein (1969) reported on two behavioral syndromes in adults that may be related to MBD. The authors studied 105 patients at the Hillside Hospital in Glen Oaks, New York, for behavioral signs of “organicity” (brain damage), behavioral syndromes that might be considered soft neurological signs of CNS impairment, as well as the results of electroencephalogram (EEG), psychological testing, and clinical presentation and history that might differentiate these patients from other types of adult psychopathology. The results were interpreted as being in conflict with the widely held beliefs at the time that hyperactive–impulsive behavior tends to wane in adolescence. On the contrary, the authors argued that some of these children continued into young adulthood with this specific behavioral syndrome. Later into this decade, Morrison and Minkoff (1975) similarly argued that adult patients with explosive personality disorder or episodic dyscontrol syndrome may have been hyperactive children. They also suggested that antidepressant medications might be useful in their management, echoing the same suggestion made earlier by Huessy (1974) in a letter to the editor of a journal that both antidepressants and stimulants may be the most useful medications for the treatment of these hyperkinetic or MBD adults. But the first truly scientific evaluation of the efficacy of stimulants with adults having MBD must be credited to Wood, Reimherr, Wender, and Johnson (1976). They used a double-blind, placebo-

controlled method to assess response to methylphenidate in 11 of 15 adults with MBD followed by an open trial of pemoline (another stimulant), and the anti-depressants imipramine and amitryptiline. The authors found that 8 of the 11 tested on methylphenidate had a favorable response whereas 10 of the 15 tested in the open trial showed a positive response to either the stimulants or antidepressants. The work of Pontius (1973) in this decade is historically notable for her proposition that many cases of adult MBD demonstrating hyperactive and impulsive behavior may arise from frontal lobe and caudate dysfunction. Such dysfunction would lead to “an inability to construct plans of action ahead of the act, to sketch out a goal of action, to keep it in mind for some time (as an overriding idea) and to follow it through in actions under the constructive guidance of such planning”.

The decade closed with the prevailing view that hyperactivity was not the only or most important behavioral deficit seen in hyperactive children but poor attention span and impulse control were equally if not more important in explaining their problems. Brain damage was relegated to an extremely minor role as a cause of the disorder, at least in the realm of childhood hyperactivity/MBD, although other brain mechanisms, such as under-arousal or under-reactivity, brain neurotransmitter deficiencies (Wender, 1971), or neurological immaturity (Kinsbourne, 1977) were viewed as promising. Greater speculation about potential environmental

causes or irritants emerged, particularly diet and child rearing. Thus, the most recommended therapies for hyperactivity were not only stimulant medication but widely available special education programs, classroom behavior modification, dietary management, and parent training in child management skills. A greater appreciation for the effects of hyperactive children on their immediate social ecology was beginning to emerge, as was the impact of stimulant medication in altering these social conflicts. However, the sizable discrepancy in North American and European views of the disorder remained, with North American professionals continuing to recognize the disorder as more common, in need of medication, and more likely being an attention deficit while those in Europe viewed it as uncommon, defined by severe overactivity, and associated with brain damage. Those children in North America being diagnosed as hyperactive or attention deficit would likely be diagnosed as conduct disorder in Europe where treatment would be psychotherapy, family therapy, and parent training in child management. Medication would be disparaged and little used. Nevertheless, the view that attention deficits were equally as important in the disorder as hyperactivity was beginning to make its way into European taxonomies (e.g., International Classification of Diseases, ninth revision [ICD-9], World Health Organization, 1978). Finally, some recognition occurred in this decade that there were adult equivalents of childhood hyperactivity or MBD that

they might be indicative of frontal-caudate dysfunction, and that these cases responded to the same medication treatments that had earlier been suggested for childhood ADHD—the stimulants and antidepressants.

The exponential increase in research on hyperactivity characteristic of the 1970s continued unabated into the 1980s, making hyperactivity the most studied childhood psychiatric disorder. More books were written, conferences convened, and scientific papers presented during this decade than in any previous historical period. This decade would become known for its emphasis on attempts to develop more specific diagnostic criteria, the differential conceptualization and diagnosis of hyperactivity from other psychiatric disorders, and, later in the decade, critical attacks on the notion that inability to sustain attention was the core behavioral deficit in ADHD.

Marking the beginning of this decade was the publication of DSM-III (American Psychiatric Association, 1980) and its radical reconceptualization (from that in DSM-II) of the Hyperkinetic Reaction of Childhood to that of Attention-Deficit Disorder (with or without Hyperactivity). The new diagnostic criteria were noteworthy not only for their greater emphasis on inattention and impulsivity as defining features of the disorder but also for their creation of much more specific symptom lists, an explicit numerical cutoff score for symptoms, specific guidelines

for age of onset and duration of symptoms, and the requirement of exclusion of other childhood psychiatric conditions as better explanations of the presenting symptoms. This was also a radical departure from the ICD–9 criteria set forth by the World Health Organization (1978) in its own taxonomy of child psychiatric disorders which continued to emphasize pervasive hyperactivity as a hallmark of this disorder.

In that revision (DSM-III-R, American Psychiatric Association, 1987) only the diagnostic criteria for ADD+H were stipulated. ADD–H would no longer be officially recognized as a subtype of ADD but would be relegated to a minimally defined category: Undifferentiated ADD. This reorganization was associated with an admonition that far more research on the utility of this subtyping approach was necessary before its place in this taxonomy could be identified.

At the same time that the DSM-III criteria for ADD (+/–H) were gaining in recognition, others attempted to specify research diagnostic criteria (Barkley, 1982; Loney, 1983).

Concurrently, Loney (1983) and her colleagues had been engaged in a series of historically important studies that would differentiate the symptoms of hyperactivity or ADD+H from those of aggression or conduct problems (Loney, Langhorne, & Peternite, 1978; Loney & Milich, 1982). Following an empirical/statistical approach to developing research diagnostic criteria, Loney demonstrated that a relatively short list of

symptoms of hyperactivity could be empirically separated from a similarly short list of aggression symptoms. Taylor's (1989) statistical approach to studying clusters of behavioral disorders pointed out that hyperactivity syndrome may represent a valid diagnostic entity, independent from other disorders, particularly conduct problems. This conceptualization required that the symptoms of hyperactivity and inattention are excessive and handicapping children, occur in two of three broadly defined settings (e.g., home, school, and clinic), are objectively measured rather than subjectively rated by parents and teachers, develop before age 6, last at least 6 months, and exclude children with autism, psychosis, or affective disorders (depression, anxiety, mania, etc.).

Also important in this era was the attempt to identify useful approaches to subtyping other than those just based on the degree of hyperactivity (+H/–H) or aggression associated with ADD. A significant though under-appreciated line of research by Roscoe Dykman and Peggy Ackerman at the University of Arkansas distinguished between ADD children with and without learning disabilities, particularly reading impairments. Their research (Ackerman, Dykman, & Oglesby, 1983; Dykman, Ackerman, & Holcomb, 1985) and that of others (McGee, Williams, Moffit, & Anderson, 1989) showed that some of the cognitive deficits (verbal memory, intelligence, etc.) formerly attributed to ADHD were actually more a function of the presence and degree of language/reading difficulties than

of ADHD. And, although some studies showed that ADHD children with reading disabilities are not a distinct subtype of ADHD (Halperin, Gittelman, Klein, & Rudel, 1984), the differential contributions of reading disorders to the cognitive test performance of ADHD required that subsequent research studies carefully select subjects with pure ADHD not associated with reading disability. If they did not, then they at least should identify the degree to which reading disorders exist in the sample and their effects on the cognitive test results.

Others in this era attempted to distinguish between pervasive and situational hyperactivity where the former was determined by the presence of hyperactivity at home and school and the latter referred to hyperactivity in only one of these settings (Schachar, Rutter, & Smith, 1981). It would be shown that pervasively hyperactive children were likely to have more severe behavioral symptoms, greater aggression and peer relationship problems, and poor academic achievement. A revision of DSM-III (DSM-III-R; American Psychiatric Association, 1987) incorporated this concept into an index of severity of ADHD. British scientists even viewed pervasiveness as an essential criterium for the diagnosis of a distinct syndrome of hyperactivity (see earlier). However, research appearing at the end of the decade (Costello, Loeber, Stoutheimer-Loeber, 1991) demonstrated that such group differences were more likely the result of differences in the source of the information

used to classify the children (parents versus teachers) than to actual behavioral differences between the situational and pervasive subgroups. This did not mean that pervasiveness might not be a useful means of subtyping or diagnosing ADHD but that more objective means of establishing it were needed than just comparing parent and teacher ratings on a questionnaire.

Later in the decade, in an effort to further improve the criteria for defining this disorder, the DSM was revised (American Psychiatric Association, 1987) as noted above, resulting in the renaming of the disorder as Attention-Deficit Hyperactivity Disorder. The revisions were significant in several respects. First, a single item list of symptoms and a single cutoff score replaced the three separate lists (inattention, impulsivity, and hyperactivity) and cutoff score in DSM-III. Second, the item list was now based more on empirically derived dimensions of child behavior from behavior rating scales and the items and cutoff score underwent a large field trial to determine their sensitivity, specificity, and discriminating power to distinguish ADHD from other psychiatric disorders and normal children (Spitzer et al., 1990). Third, the need was stressed that one had to establish the symptoms as developmentally inappropriate for the child's mental age. Fourth, the coexistence of affective disorders with ADHD no longer excluded the diagnosis of ADHD. And, more controversially, the subtype of ADD without Hyperactivity was removed

as a subtype and relegated to a vaguely defined category, Undifferentiated ADD, which was in need of greater research on its merits. ADHD was now classified with two other behavioral disorders (Oppositional Defiant Disorder and Conduct Disorder) in a supra-ordinate family or category known as Disruptive Behavior Disorders in view of their substantial overlap or comorbidity in clinic-referred populations of children.

During this decade, Herbert Quay adopted Jeffrey Gray's neuropsychological model of anxiety (Gray, 1982, 1987, 1994) to explain the origin of the poor inhibition evident in ADHD (Quay, 1987, 1988, 1997). Gray identified both a behavioral inhibition system as well as a behavioral activation system as being critical to understanding emotion. He also stipulated mechanisms for basic nonspecific arousal and for the appraisal of incoming information that must be critical elements of any attempt to model the emotional functions of the brain. According to this theory, signals of reward serve to increase activity in the behavioral activation system (BAS), thus giving rise to approach behavior and the maintenance of such behavior. Active avoidance and escape from aversive consequences (negative reinforcement) likewise activate this system. Signals of impending punishment (particularly conditioned punishment) as well as frustrative nonreward (an absence of previously predictable reward) increase activity in the behavioral inhibition system

(BIS). Another system is the fight–flight system, which reacts to unconditioned punitive stimuli.

Quay's use of this model for ADHD stated that the impulsiveness characterizing the disorder arose from diminished activity in the brain's BIS. This model predicted that those with ADHD could be less sensitive to such signals, particularly in passive avoidance paradigms (Quay, 1987). The theory also specifies predictions that can be used to test and even falsify the model as it applies to ADHD. Finally, Quay predicted increased rates of responding by those with ADHD under fixed-interval or fixed-ratio schedules of consequences. Some of these predictions were supported by subsequent research; others either remained to be investigated more fully and rigorously or have not been completely supported by the available evidence (see Milich, Hartung, Martin, & Haigler, 1994; Quay, 1997). Nevertheless, the theory remains a viable one for explaining the origin of the inhibitory deficits in ADHD and continues to be deserving of further research.

Another noteworthy development in this decade was the greater sophistication of research designs attempting to explore the unique features of ADHD relative to other psychiatric conditions rather than just in comparison to normal. As Rutter (1983, 1989) noted repeatedly, the true test of the validity of a syndrome of ADHD is the ability to differentiate its features from other psychiatric disorders of children, such

as affective or anxiety disorders, learning disorders, and particularly conduct disorders. Those studies that undertook such comparisons indicated that situational hyperactivity was not consistent in discriminating among psychiatric populations but that difficulties with attention and pervasive (home and school) hyperactivity were more reliable in doing so and were often associated with patterns of neuropsychological immaturity (Firestone & Martin, 1979; Gittelman, 1988; McGee, Williams, & Silva, 1984a, 1984b; Rutter, 1989; Taylor, 1988; Werry, 1988).

The emerging interest in comparing ADD children with and without Hyperactivity (+/–H) furthered this line of inquiry by demonstrating relatively unique features of each disorder in contrast to each other (see Chapter 3) and to groups of learning-disabled and normal children (Barkley, DuPaul, & McMurray, 1990, 1991). Further strengthening the position of ADHD as a psychiatric syndrome was evidence from family aggregation studies that relatives of ADHD children had a different pattern of psychiatric disturbance from those children with Conduct Disorder or mixed ADHD and Conduct Disorder (Biederman, Munir, & Knee, 1987; Lahey et al., 1988). Purely ADHD children were more likely to have relatives with ADHD, academic achievement problems, and dysthymia, whereas those children with Conduct Disorder had a greater prevalence of Conduct Disorder, antisocial behavior, substance abuse,

depression, and marital dysfunction among their relatives. This finding led to speculation that ADHD had a different etiology from conduct disorder. The former was said to arise out of a biologically based disorder of temperament or a neuropsychological delay; the latter from inconsistent, coercive, and dysfunctional child rearing and management, ~~was~~ frequently associated with parental psychiatric impairment (Hinshaw, 1987; Loeber, 1990; Patterson, 1982, 1986).

The 1980s also witnessed some advances in the tools of assessment in addition to those for treatment. The Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983, 1986) emerged as a more comprehensive, more rigorously developed, and better-normed alternative to the Conners Rating Scales (Barkley, 1987). It would become widely adopted in research on child psychopathology in general, not just in ADHD, by the end of this decade. Other rating scales more specific for ADHD were also developed, such as the ACTeRS (Ullmann et al., 1984), the Home and School Situations Questionnaires (Barkley & Edelbrock, 1987; DuPaul & Barkley, 1992), the Child Attention Profile (see Barkley, 1987), and the ADHD Rating Scale-IV (DuPaul, 1991).

Gordon (1983) developed, normed, and commercially marketed a small, portable, computerized device that administered two tests believed to be sensitive to the deficits in ADHD. One was a CPT measuring vigilance and impulsivity and the other was a direct reinforcement of low rates

(DRL) test assessing impulse control. This test became the first commercially available objective assessment device for evaluating ADHD children. Although the DRL test showed some promise in early research (Gordon, 1979), it was subsequently shown to be insensitive to stimulant medication effects (Barkley, Fischer, Newby, & Breen, 1988) and was eventually de-emphasized as useful in the diagnosis for ADHD. The CPT task, by contrast, showed satisfactory discrimination of ADHD from normal groups and was sensitive to medication effects (Barkley et al., 1988; Gordon & Mettelman, 1988). Although cautionary statements would be made that more research evidence was needed to evaluate the utility of the instrument (Milich, Pelham, & Hinshaw, 1985) and that its false-negative rate (misses of legitimate ADHD children) might be greater than that desired in a diagnostic tool, the device and others like it (Conners, 1995; Greenberg & Waldman, 1992) found a wide clinical following by the following decade.

Developments also continued in the realm of treatments for ADHD. Comparisons of single versus combined treatments were more common during the decade (Barkley, 1989c), as was the use of more sophisticated experimental designs (Hinshaw, Henker, & Whalen, 1984; Pelham, Schnedler, Bologna, & Contreras, 1980) and mixed interventions (Satterfield, Satterfield, & Cantwell, 1981). Several of these developments in treatment require historical mention. The first was the

emergence of a new approach to the treatment of ADHD: cognitive-behavioral therapy, or CBT (Camp, 1980; Douglas, 1980a; Kendall & Braswell, 1985; Meichenbaum, 1988). Founded on the work of Russian neuropsychologists (Vygotsky and Luria), North American developmental and cognitive psychologists (Flavell, Beach, & Chinsky, 1966), and early cognitive-behavioral theories (Meichenbaum, 1977), these approaches stressed the need to develop self-directed speech in impulsive children to guide their definition of and attention to immediate problem situations, to generate solutions to these problems, and to guide their behavior as the solutions were performed. Self-evaluation, self-correction, and self-directed use of consequences were also viewed as important (Douglas, 1980a, 1980b). Although first reports of the efficacy of this approach appeared in the late 1960s and the 1970s (Bornstein & Quevillon, 1976; Meichenbaum & Goodman, 1979), it was not until this decade that the initial claims of success with nonclinical populations of impulsive children were more thouroughly tested in clinical populations of ADHD children. The initial results were disappointing (Abikoff, 1987; Gittelman & Abikoff, 1989). Generally, they indicated some degree of improvement in impulsiveness on cognitive laboratory tasks but insufficient to be detected in teacher or parent ratings of school and home ADHD behaviors and certainly not as effective as stimulant medication (Brown, Wynne, & Medenis, 1985). Many continued to see some promise in

these techniques (Barkley, 1981, 1989b; Meichenbaum, 1988; Whalen, Henker, & Hinshaw, 1985), particularly when they were implemented in natural environments by important caregivers (parents and teachers); others ended the decade with a challenge to those who persisted in their support of this approach to provide further evidence for its efficacy (Gittelman & Abikoff, 1989). Such evidence would not be forthcoming (see Chapter 15). Later, even the conceptual basis for the treatment came under attack as being inconsistent with Vygotsky's theory of the internalization of language (Diaz & Berk, 1995).

A second development in treatment was the publication of a specific parent-training format for families with ADHD and oppositional children. A specific set of steps for training parents of ADHD children in child behavior management skills was developed (Barkley, 1981) and refined (Barkley, 1987, 1997b). The approach was founded on a substantial research literature (Barkley, 1997b; Forehand & McMahon, 1981; Patterson, 1982) demonstrating the efficacy of differential attention and time-out procedures for treating oppositional behavior in children—a behavior frequently associated with ADHD.

A similar increase in more sophisticated approaches occurred in this era in relation to the classroom management of ADHD children (Barkley, Copeland, & Sivage, 1980; Pelham et al., 1980; Pfiffner & O'Leary, 1987; Whalen & Henker, 1980). These developments were based on earlier

promising studies in the 1970s with contingency management methods in hyperactive children (Allyon et al., 1975; see Chapter 15 for the details of such an approach). Although these methods may not produce the degree of behavioral change seen in the stimulant medications (Gittelman et al., 1980), they provide a more socially desirable intervention that can be a useful alternative when children have mild ADHD and cannot take stimulants or their parents decline the prescription. More often these methods serve as an adjunct to medication therapy to further enhance academic achievement.

Finally, medication treatments for ADHD expanded to include the use of the tricyclic antidepressants, particularly for those ADHD children with characteristics that contraindicated using a stimulant medication (e.g., tic disorders or Tourette syndrome) or for ADHD children with anxiety/depression (Pliszka, 1987). The work of Joseph Biederman and his colleagues at Massachusetts General Hospital (Biederman, Gastfriend, & Jellinek, 1986; Biederman, Baldessarini, Wright, Knee, & Harmatz, 1989) on the safety and efficacy of the tricyclic medications encouraged the rapid adoption of these drugs by many practitioners (see Ryan, 1990), particularly when the stimulants, such as Ritalin (methylphenidate), were receiving such negative publicity in the popular media (see the next section). Simultaneously, initially positive research reports appeared on the use of the antihypertensive drug, clonidine, in

the treatment of ADHD children, particularly those with very high levels of hyperactive–impulsive behavior and aggression (Hunt, Caper, & O'Connell, 1990; Hunt, Minderaa, & Cohen, 1985)

history of this disorder, chief among them being the increase in research on the neurological and genetic basis of the disorder and on ADHD as it occurs in clinic-referred adults.

Researchers have long-suspected that ADHD was associated in some way with abnormalities or developmental delays in brain functioning. Supporting such an interpretation are numerous neuropsychological studies showing deficits in performance by ADHD children on tests that were presumed to assess frontal lobe or executive functions (Barkley, 1997b; Barkley et al., 1992; Goodyear & Hynd, 1992, for reviews). Moreover, psychophysiological research in earlier decades had suggested brain underactivity, particularly in functioning related to the frontal lobes (Hastings & Barkley, 1978; Klorman, 1992). And thus there is good reason to suspect that delayed or disturbed functioning in the brain, and particularly the frontal lobes, may be involved in this disorder.

In 1990, Alan Zametkin and his colleagues at the National Institute of Mental Health (NIMH; Zametkin et al., 1990) published a landmark study. The authors evaluated brain metabolic activity in 25 adults with ADHD who had a childhood history of the disorder and who also had children with the disorder. The authors used positron emission tomography

(PET), an exceptionally sensitive technique for detecting states of brain activity and its localization within the cerebral hemispheres. The results of this study indicated significantly reduced brain metabolic activity in adults with ADHD relative to a control group, primarily in frontal and striatal regions. Such results were certainly consistent in many, though not all, respects with the earlier demonstrations of reduced cerebral blood flow in the frontal and striatal regions in children with ADHD (Lou et al., 1984, 1989). Significant in the Zametkin et al. (1990) study, however, was its use of a much better defined sample of ADHD patients and its focus on adults with ADHD. Although later attempts by this research team to replicate their original results using teenagers with ADHD were consistent with these initial results for girls with ADHD, no differences were found in boys with ADHD (see Ernst, 1996, for a review). Sample sizes in these studies were quite small, however, almost ensuring some difficulties with the reliable demonstration of the original findings. Despite these difficulties, the original report stands out as one of the clearest demonstrations to date of reduced brain activity, particularly in the frontal regions, in ADHD.

At the same time as the NIMH research using PET scans was appearing, other researchers were employing magnetic resonance imaging (MRI) to evaluate brain structures in children with ADHD. Hynd and his colleagues were the first to use this method and they focused on the total

brain volume as well as specific regions in the anterior and posterior brain sections. Children with ADHD were found to have abnormally smaller anterior cortical regions, especially on the right side, and they lacked the normal right–left frontal asymmetry (Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulis, 1990). Subsequent research by this team focused on the size of the corpus callosum, finding that both the anterior and posterior portions were smaller in children with ADHD (Hynd et al., 1991); however, in a later study, only the posterior region was significantly smaller (Semrud-Clikeman et al., 1994). Additional studies were reported by Hynd et al. (1993), who found a smaller left caudate region in children with ADHD, and Giedd et al., (1994), who found smaller anterior regions of the corpus callosum (rostrum and rostral body).

More recently, two research teams published studies using MRI with considerably larger samples of ADHD children (Castellanos et al., 1994, 1996; Filipek et al., 1997). These studies documented significantly smaller right prefrontal lobe and striatal regions in children with ADHD. Castellanos et al. (1996) also found smaller right-sided regions of structures in the basal ganglia, such as the striatum, as well as the right cerebellum. Filipek et al. (1997) observed the left striatal region to be smaller than the right. Despite some inconsistencies across these studies, most have implicated the prefrontal-striatal network as being

smaller in children with ADHD with the right prefrontal region being smaller than the left. Such studies have placed on a considerably firmer foundation the view that ADHD does, indeed, involve impairments in the development of the brain, particularly in the prefrontal-striatal regions, and that the origin of these differences from normal are likely to have occurred in embryological development (Castellanos et al., 1996). Advances in neuroimaging technology continue to provide exciting and revealing new developments in the search for the structural differences in the brain that underlie this disorder. For instance, the advent of functional MRI with its greater sensitivity for localization of activity has already resulted in a number of newly initiated investigations into possible impairments in these brain regions in children and adults with ADHD.

ADHD IN CHILDREN AND ADOLESCENTS

ADHD is a neurobehavioral developmental disorder. It is primarily characterized by "the co-existence of attentional problems and hyperactivity, with each behavior occurring infrequently alone" and symptoms starting before seven years of age.

ADHD is the most commonly studied and diagnosed psychiatric disorder in children, affecting about 3 to 5 percent of children globally and

diagnosed in about 2 to 16 percent of school aged children (Kessler et al, 2006). It is a chronic disorder with 30 to 50 percent of individuals diagnosed in childhood continuing to have symptoms in adulthood. Adolescents and adults with ADHD tend to develop coping mechanisms to compensate for some or all of their impairments. It is estimated that 4.7 percent of American adults live with ADHD. Standardized rating scales such as WHO's Adult ADHD Self-Report Scale can be used for ADHD screening and assessment of the disorder's symptoms severity.

ADHD is diagnosed two to four times more frequently in boys than in girls, though studies suggest this discrepancy may be partially due to subjective bias of referring teachers. ADHD management usually involves some combination of medications, behavior modifications, lifestyle changes, and counseling. The clinical picture can be difficult to be differentiated from other disorders, increasing the likelihood that the diagnosis of ADHD may be missed. Additionally, most clinicians have not received formal training in the assessment and treatment of ADHD, particularly in adult patients (Barkley 2006).

ADHD and its diagnosis and treatment have been considered controversial since the 1970s. The controversies have involved clinicians, teachers, policymakers, parents and the media. Topics include the definition of the disorder, its causes, and the use of stimulant medications in its treatment. Most healthcare providers accept that

ADHD is a genuine disorder with debate in the scientific community focusing mainly on how it is diagnosed and treated. The American Medical Association concluded in 1998 that the diagnostic criteria for ADHD are based on extensive research and, if applied appropriately, lead to the diagnosis with high reliability.

ADHD may accompany other disorders such as anxiety or depression. Such combinations can greatly complicate diagnosis and treatment. Academic studies and research in private practice suggest that depression in ADHD appears to be increasingly prevalent in children as they get older, with a higher rate of increase in girls than in boys, and to vary in prevalence on the basis of the subtype of ADHD. Where a mood disorder complicates ADHD it would be prudent to treat the mood disorder first, even if parents often wish to have the ADHD treated first, because the response to treatment is quicker (Barkley, 2006).

Inattention and "hyperactive" behavior are not the only problems in children with ADHD. ADHD exists alone in only about 1/3 of the children diagnosed with it. Many co-existing conditions require other strategies of treatment and should be diagnosed separately instead of being grouped in the ADHD diagnosis. Some of the associated conditions are:

- Oppositional defiant disorder (35%) and conduct disorder (26%) which both are characterized by antisocial behaviors such as stubbornness, aggression, frequent temper tantrums, deceitfulness, lying, or stealing,

inevitably linking these comorbid disorders with antisocial personality disorder (ASPD); about half of those with hyperactivity and ODD or CD develop ASPD in adulthood.

- Borderline personality disorder, which was, according to a study on 120 female psychiatric patients diagnosed and treated for BPD, associated with ADHD in 70 percent of the sample (Krull KR, 2007).
- Primary disorder of vigilance, which is characterized by poor attention and concentration, as well as difficulties in staying awake. These children tend to fidget, yawn and stretch and appear to be hyperactive in order to remain alert and active.
- Mood disorders. Boys diagnosed with the combined subtype have been shown likely to suffer from a mood disorder (Bauermeister, J., et al. 2007)
- Bipolar disorder. As many as 25 percent of children with ADHD have bipolar disorder. Children with this combination may demonstrate more aggression and behavioral problems than those with ADHD alone (Krull KR, 2007).
- Anxiety disorder, which has been found to be common in girls diagnosed with the inattentive subtype of ADHD (Bauermeister, J., et al. 2007)

- Obsessive-compulsive disorder. OCD is believed to share a genetic component with ADHD as well as many of its characteristics (Krull KR, 2007).

Methods of treatment often involve some combination of behavior modification, life-style changes, counseling, and medication. A 2005 study found that medical management and behavioral treatment is the most effective ADHD management strategy, followed by medication alone, and then behavioral treatment (Jensen PS et al, 2005) While medications have been shown to improve behavior when taken over the short term, they have not been shown to alter long term outcomes. Medications have at least some effect in about 80% of subjects.

The evidence is strong for the effectiveness of behavioral treatments in ADHD. It is recommended as first choice in those who have mild symptoms and in preschool aged children (Kratochvil et al, 2009). Psychological therapies include psychoeducation, behavioral therapy, cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), family therapy, school-based interventions, social skills training and parent management training.

Parent training and education have been found to have short term benefits (Pliszka S, 2007)). Family therapy has shown to be of little use in the treatment of ADHD, though it may be worth noting that parents of children with ADHD are more likely to divorce than parents of children without

ADHD, particularly when their children are younger than eight years old. Several ADHD specific support groups exist as informational sources and to help families cope with challenges associated with dealing with ADHD.

Methylphenidate (Ritalin) 10 mg tablets stimulant medications are the medical treatment of choice (Wigal SB, 2009). There are a number of non-stimulant medications, such as atomoxetine, which may be used as alternatives. There are no good studies of comparative effectiveness among various medications, and there is a lack of evidence on their effects on academic performance and social behaviors. While stimulants and atomoxetine are generally safe, there are side effects and contraindications related to their use (Wigal SB, 2009)). Medications are not recommended for preschool children, as their long-term effects in such young people are unknown. There is very little data on the long-term adverse effects or benefits of stimulants for ADHD (King S et al,2006).Guidelines on when to use medications vary internationally, with the UK's National Institute of Clinical Excellence, for example, only recommending use in severe cases, while most United States guidelines recommend medications in nearly all cases.

As far as prognosis is concerned, children diagnosed with ADHD have significant difficulties in adolescence, regardless of treatment. In the United States, 37 percent of those with ADHD do not get a high school graduation even though many of them will receive special education services (Barkley

2006). In the US, less than 5 percent of individuals with ADHD get a college degree compared to 28 percent of the general population. Children with ADHD are at high risk of adverse life events once they become teenagers. These events include road accidents, different kind of injuries, early sexual activity, and teen pregnancy. Russell Barkley states that adult ADHD impairments affect "education, occupation, social relationships, sexual activities, dating and marriage, parenting and offspring psychological morbidity, crime and drug abuse, health and related lifestyles, financial management, or driving. ADHD can be found to produce diverse and serious impairments". The proportion of children meeting the diagnostic criteria for ADHD drops by about 50 percent over three years after the diagnosis. This occurs regardless of the treatments used and also occurs in untreated children with ADHD.ADHD persists into adulthood in about 30 to 50 percent of cases (Kessler et al, 2006). Subjects affected are likely to develop coping mechanisms as they mature, thus compensating for their ADHD.

EPIDEMIOLOGY

The study of the prevalence of ADHD in Western countries has provided very different results, due to the heterogeneity of diagnostic approaches, particularly between the USA and Europe. Even if the greatest

prevalence of the disorder in the United States has been linked to the exposure to high-technology products (synthetic food additives, leaded petrol, dyes), it is very likely to be due to a different diagnostic sensitivity.

ADHD is highly prevalent among the general population. It is believed that 3-7% of school age subjects are affected with a 4:1 ratio between males and females (10% vs. 2%). The prevalence observed among preschool age children is 2-8% and it rises to 4-12% among primary school children, diminishing to approximately 6% in adolescence (Kessler et al., 2006).

Vast amounts of evidence suggest a higher prevalence of inattentive forms in females, and hyperactive and impulsive forms in males among whom it is possible to encounter a more frequent comorbidity with externalizing disorders (Oppositional-defiant disorder, Conduct disorder).

ADHD in the US constitutes about 30-40% of users of developmental age psychiatry services, and it is present in 40-70% of psychiatric patients subjected to treatment. In the mid-80s about 2-4% of the American school population received psychiatric treatment with psychostimulants, while at the end of the 80s public campaigns by the Scientist Church had caused a reduction in the clinical use of this category of drugs (Safer and Krager, 1992).

Between 1990 and 1995 there was a new 2,5-fold increase in the use of stimulants in the United States.

As far as adul population is concerned**,** until a few years ago studies were limited to a rough estimation based on data on prevalence and prognosis in childhood, taking into account that the symptomatology tend to persist in 50% of cases and that the disorder does not occur ex novo in adults (Harpin, 2005; Hechtman, 2000; Mannuzza et al., 1993).

Recently, epidemiological studies, such as the *National Comorbidity Survey*, carried out on an adult population of 10.000 subjects, show a prevalence of 4,4% with a higher frequency in the predominantly inattentive type when compared to the other two types (Kessler et al., 2006); these data have been confirmed in subsequent studies (Klassenm, 2010; Wilens, 2009).

In a study carried out on a sample of 102 subjects from a penitentiary, 25,5% of them met the diagnostic criteria for ADHD. This data reflect the highest incidence of psychopathology and psychiatric comorbidity in prisoners.

NOSOLOGY AND DIAGNOSIS

Before the introduction of the operational criteria of DSM III (1980), the syndrome was considered to be composed of behavioural, motor, cognitive and sensory-perceptual deficits, including a wide variety of symptoms such as hyperactivity, inattention, distractibility, impulsiveness,

lability of mood, irritability, prematuraty, disobedience, hostility, dyslexia, or other learning disabilities.

With DSM III, hyperactivity is no longer seen as a cornerstone of the syndrome, while inattention (attention deficit disorder) is considered a primary element together with impulsivity and hyperactivity as complementary elements.

For these reasons DSM III is defined as an attention deficit disorder (ADD). In the third revised edition of DSM III-R, (1987), hyperactivity is diagnostically re-emphasised and the syndrome is defined as "Attention deficit hyperactivity disorder".

With the publication of DSM IV (1994), the attention deficit regains its importance. Impulsivity and hyperactivity remain included in the list of criteria.

DSM IV places ADHD into the sphere of childhood and adolescent disorders with a division into three types:

1. predominantly inattentive;
2. predominantly hyperactive- impulsive,
3. combined.

In DSM III-R there are no criteria for the diagnosis of a residual or persistent form in adulthood, while DSM IV specifically defines “ADHD in partial remission” in adolescents and adults who no longer meet the full

criteria. ICD 10 instead offers a diagnosis of “hyperkinetic syndrome” characterised by impulsivity, aggressiveness and inattention, often accompanied by a history of perinatal or neonatal damage.

The DSM-IV-TR criteria (Table 1) for the diagnosis of ADHD are valid only for children and adolescents, yet when extended to adults it can be seen that their sensitivity and specificity are somewhat limited.

Criterion A requires the persistence of at least 6 symptoms of inattention and/or hyperactivity-impulsivity for a period of at least 6 months, with an intensity that causes maladjustment and which is in contrast with the level of development. Criterion B sets the age of onset of some symptoms that cause impairment under 7 years of age. Criterion C indicates the presence of a malfunction in two or more contexts (work, school, family). Several authors (Heiligenstein et al., 1998; Barkley, 2006) stress that the symptomatological pattern of an adult affected by ADHD often changes in time and is mainly characterised by the attenuation of some symptoms (hyperactivity and impulsivity) and by the chronicity and persistence of others (inattention). In addition, comorbidity with other psychiatric pathologies such as mood disorders, anxiety and disorders deriving from use of substances can hide the attention deficit and the impulsivity, thus favouring an underestimation of the disorder. Finally, problems that patients run into in adulthood arise within contexts and situations (marriage, children, work) that differ from those in age of

development with a different emotional and practical impact. Studies that adopt the DSM-IV-TR criteria exclude some potential cases of ADHD that do not fully meet the criteria, although they do show maladjustment in several areas. In fact, it has been noticed that the presence of at least 6 symptoms of inattention and/or hyperactivity- impulsivity is an excessively restrictive and not a very realistic criterion in the adult population. For this reason there are many studies which adopt alternative diagnostic systems such as the *Utah criteria for adult ADHD* proposed by Wender (Table 2).

Several authors have also highlighted the need of specific diagnostic criteria based on the age of the subject, validated by studies exclusively carried out on adults (Murphy and Barkley 1996; Faraone et al., 2000).

Self-assessment scales, such as the *Conner's Adult ADHD Rating Scales (CAARS)* and *Wender Utah Rating Scales (WURS)*, or others that require the presence of a family member, such as *ADHD Rating Scales-IV*, can be used for an adult. The use of neuropsychological tests *(Stroop tasks e Continuous performance tests)* is aimed to evaluate cognitive functions and they can also be useful in monitoring the effectiveness of treatments.

Nosographic problems of ADHD in adults include: full correspondence with the diagnostic criteria of DSM-IV, appropriateness of the development of symptoms, age criterion, validity of the diagnosis of

ADHD not otherwise specified (NOS), comorbidity with other mental disorders.

Currently the diagnosis in an adult can be formulated only if all the criteria of ADHD for children are fullfilled. If this condition is not fully satisfied, subjects can be classified as ADHD NOS. In most cases this category comprehends *late-onset* ADHD and *subthreshold* ADHD. In the first case the patient meets all the criteria of ADHD for children except the onset before 7 years of age. In the second case the patient has never received a diagnosis of ADHD as a child; however, there are persistent and disabling symptoms.

Most patients with late-onset ADHD (83%) reported that the symptoms first appeared before the age of 12 (Faraone et al., 2006). This would suggest that the age criterion currently used in DSM-IV is too restrictive.

The presence of a psychiatric comorbidity can complicate the diagnosis because symptoms of diferent disorders may be overlapping. For instance, bipolar-disorder is often characterised by hyperactivity, inattention, loquacity, work impairment and impulsiveness, which are symptoms of ADHD as well (Klassen, 2010).

For patients with SUD (substance use disorder) there are further specific issues: alcohol and substance abuse can sham symptoms of ADHD, it may be more difficult to find the overall data necessary for the diagnosis, and finally, the diagnosis of ADHD is relatively unknown and rarely

advanced by health workers charged with the treatment of substance abuse.

Many substances themselves can cause the appearance of symptoms similar to those of ADHD. Cocaine causes psychomotor agitation and restlessness, and similar phenomena can occur also in syndromes caused by abstinence.

Patients affected by SUD usually find it difficult to recall their childhood symptoms because of cognitive impairment related to the chronic and ongoing use of alcohol and substances such as opiates, marijuana and methamphetamines.

COMORBIDITY

A high percentage of subjects affected by ADHD suffer from another psychiatric disorder. This percentage would be 80% in adults (Klassen at al, 2010). The literature refers to comorbidity with many conditions such as oppositional-defiant disorder, conduct disorder, obsessive-compulsive disorder, substance use disorder, mood disorders, anxiety disorders, Tourette's syndrome, learning disabilities, mental retardation, and borderline personality disorder.

It is estimated that 25-75% of adolescents affected by ADHD also meet the criteria for Oppositional Disorder and Conduct Disorders (Barkley, 2006), and that this condition is associated with a worse prognosis in terms of adaptation and responding to treatments. In a vast case history of subjects between 9 and 16 years old affected by ADHD, mood disorder was found in 48% of the cases, oppositional and conduct disorder in 36% and anxiety disorder in 36% (Bird et al., 1993). In a study carried out from 1988 to 2003, 280 patients affected by ADHD were compared to 142 patients with a negative diagnosis, all aged between 6 and 18 years. At the end of the study, the subjects affected by ADHD showed a higher risk of developing bipolar disorder, major depressive disorder or conduct disorder (Biederman, 2009).

For some authors, ADHD and conduct disorder are two indistinguishable clinical entities because of a complete symptomatological overlap, whereas for others they are partially or totally independent. The latter hypothesis is supported by researches that compare family aggregation models and cognitive performances. Loney and coll. have observed that the co-presence of ADHD and conduct disorder in childhood evolves into aggressive behaviour and tendency to commit crimes during adolescence. Vice versa, ADHD without conduct disorder can evolve into cognitive and school deficits (Loney, 1980; Mc Gee et al., 1984). Other studies have shown that children affected by ADHD in comorbidity with

conduct disorder have a worse course and less therapeutic response than children affected by ADHD without conduct disorder (Biederman et al., 1991). It is interesting to make a comment about the gender difference in these disorders. Conduct disorders are two times more common in males than in females. Moreover, they are often the main reason why male children affected by ADHD can be identified and treated. Therefore, it is probable that some female children may not be diagnosed with this disorder. Considering that the prevalence rates of ADHD in children vary by sex in ratio between 3:1 and 10:1, it is easy to suspect that this difference may be partly justified by the lack of identification of a certain number of cases in female subjects (Biederman, 2004).

A similar difference can be encountered in Antisocial Personality Disorder (diagnosed in adults), since men affected by ADHD receive this diagnosis more frequently than women. With regards to the prevalence of Oppositional-Defiant Disorder, the rates are almost identical in both sexes, both in childhood and in adulthood (Biederman, 2004).

The literature widely reports an overlapping between ADHD and learning disabilities. Bad school performance in children affected by ADHD may be linked to inattention and impulsivity (characteristics of the disorder), to cognitive deficits or other factors such as a social disadvantage and demoralization. ADHD and learning disabilities are probably separate

entities, since the former is a behavioural disorder while the latter include deficits of various cognitive processes such as language, reading, writing, or calculation. In addition, many children affected by ADHD do not have learning problems and not all children affected by a learning disability have ADHD.

Several studies point out a strong comorbidity between ADHD and anxiety disorders in adults, underlining a prevalence of Generalized Anxiety Disorder in 24-43% of patients (Barkley et al., 1996; Minde et al., 2003; Shekim et al., 1990). In 2006, Togersen and coll. noticed in their patients affected by ADHD a life-time prevalence of panic disorder in 13% and of social phobia in 18% of them. But there are also studies where no significant comorbidity between ADHD and anxiety disorders in adults was found (Murphy e Barkley, 1996; Barkley et al., 2001).

The research data on comorbidity between ADHD and Obsessive-Compulsive Disorder are controversial. Obsessive-compulsive personality traits can be found in a certain number or patients (Nadeau 2005). However, many adults affected by ADHD feel the need to be strict and inflexible in order to inhibit traits of impulsivity, or become indecisive and unable to make decisions that, when taken, are impulsive and disastrous.

Tourette's Disorder is characterised by the presence of multiple motor tics with onset before the age of 18. Patients affected by this disorder

show symptoms of ADHD in 50% of the cases (Comings and Comings 1990). Symptoms of the disorder generally appear between 2 and 15 years of age. Studies carried out on children with a case history of ADHD and Tourette's Disorder have shown that the symptoms of ADHD appear earlier than those of Tourette's Disorder (Comings, Comings et al. 1989).

ADHD AND BIPOLAR DISORDER

With regards to comorbidity with a mood disorder, major depression seems to be highly prevalent among children affected by ADHD, particularly in those with a conduct disorder (Angold et al., 1999). For adults, several researches show comorbidity between major depression and ADHD between 16 – 31% of all cases (Barkley et al., 2006; Biederman et al., 1993; Schubiner et al., 1995). Yet there are some follow-up studies that have documented an increased risk of depression in hyperactive children monitored until adulthood (Weiss et al., 1993).

There is a significant comorbidity between ADHD and bipolar disorder, and it has been hypothesised that the former can be, at least in some cases, a prodromal form of the latter (Bizzarri, Rucci et al. 2007). Ryden and coll. noted how the clinical impact of a diagnosis of ADHD in children and adolescents on the course of Bipolar Disorder persists in a

pejorative sense in adulthood, regardless of whether the criteria for the diagnosis of ADHD continue or not to be satisfied (Ryeden, 2009).

The symptomatic overlap between ADHD and bipolar disorder sometimes makes it difficult to formulate a differential diagnosis between the two conditions. Although there are several symptoms in common such as loquacity, distractibility, impulsive behaviour, hyperactivity, low critical capacity and underestimation of existential problems, it is clinically possible to point out some differences.

The symptoms of ADHD tend to assume a chronic course, while in bipolar disorder the course is episodic. Patients affected by ADHD do not experience a rise in purposive activity, a reduced need of sleeping nor hypertrophic self-esteem, which are all characteristics of the main phases of Bipolar Disorder. Finally, mania may present psychotic symptoms such as hallucinations and delusions which are absent in subjects affected by ADHD.

Compared to bipolar disorder, the symptoms of ADHD are characterised by an earlier onset, a persistent course, absence of euphoria, elation and psychotic phenomena, and generally less severe hyperactivity and impulsivity if compared to mania. Despite these differential features, controversies remain on the symptomatic overlapping and on the possible diagnostic difficulties in epidemiological and clinical studies.

Sentissi and coll. evaluated the prevalence of comorbid ADHD in bipolar patients during euthymic phase reporting a rate of 30% (Sentissi, 2008). Sachs G.S. et al. have suggested that Bipolar Disorder + ADHD can be considered a diagnostic subtype within the bipolar spectrum, characterised by a heavy genetic load and very early onset mood (Sachs et al., 2000). This is in line with the clinical observation that in subjects affected by bipolar disorder and ADHD, a worse outcome in terms of quality of life, global adaptation and risk of suicide is recorded (Tamam et al., 2008; Klassen, 2010). On this subject, it is important to note that these patients are poorly compliant to treatments (Klassen, 2010). Finally, it should be kept in mind that bipolar disorder in ADHD may be triggered by stimulants and antidepressants (Faedda e Teicher, 2005; Ross, 2006), even if data in this field are controversial.

The rates of comorbidity of Bipolar Disorder in subjects affected by ADHD are extremely variable, from 5,1% to 47,1%. This heterogeneity can be attributed to the diagnostic criteria in use, to the different selection methods of case histories, and to the scarcity of case histories. For the same reasons, also the prevalence of ADHD in subjects affected by Bipolar Disorder varies widely, from 9,5% to 21,2%.

ADHD AND SUBSTANCE USE DISORDER

Substance Use Disorder (SUD) is widely diffused among the general population and it is estimated that 27% of adult population suffers from it (Kandel et al., 1997). Of them, 15-25% show symptoms of ADHD (Wilens, 2004), three times higher a percentage than that found among the general population. Similarly, ADHD seems to constitute a risk factor for the development of SUD. In fact, the percentage of patients affected by SUD among adults with ADHD is more than 40%, basically three times the prevalence rate of SUD among the general population, estimated at around 14,6% (Kessler, Adler et al. 2006).

From a comparison of 120 adults affected by ADHD with 268 adults not affected by ADHD, with an average age of 40 years, it was found that the life-time prevalence of SUD was present in 52% of patients with ADHD and in 27% of those without it (Biederman et al., 1995). Further studies have shown that adults affected by ADHD in comorbidity with Bipolar Disorder or Conduct Disorder are at a higher risk of getting a SUD (Wilens et al., 1998).

In short, the source literature is unanimous in stating that there is a mutual connection between SUD and ADHD, and that patients with both disorders are subjects to a worse outcome. Arias and colleagues have

found out from a sample of 1761 adults diagnosed with an addiction to cocaine and/or opioids that more comorbidities with other psychiatric disorders can be found in subjects affected by ADHD, together with a worse course of the illness identified by a higher numbers of hospitalisations, suicide attempts and self-harming behaviour (Arias et al., 2008). In this case history, bipolar disorder type I was associated with ADHD in 18.5% of all cases. The same research shows how ADHD affects the clinical picture of SUD, determining an earlier onset (11.4 years vs. 13.2 years old) and addiction to a larger number of substances (3.5 vs 2.9).

Generally, SUD is more severe in patients affected by ADHD. Carrol e Rounsaville have compared subjects who are addicted to cocaine and ADHD with subjects who are addicted to cocaine but do not suffer from the disorder. The former appeared to be younger at the time of observation and treatment, the addiction had an earlier onset, and they used larger quantities of the substance more frequently (Carroll e Rounsaville, 1993). Similarly, Schubiner et al. (2000) have reported a greater number of car accidents and an earlier treatment for SUD in adults affected by ADHD compared to subjects without ADHD.

In an attempt to explain the connection between these two disorders it is necessary to take into account that according to a developmental prospective ADHD manifests itself before SUD. It is therefore improbable

that a SUD could be a risk factor for ADHD. Yet it is not clear to what degree ADHD could be considered a precursor of a SUD. In a large case-control study (2003), Katusic and colleagues supervised 363 youths with ADHD from the age of 5 until adolescence, compared and paired with 726 check-ups. The obtained results showed that the presence of ADHD was associated with a three-fold increase in the risk of SUD with an earlier onset of this disorder. From a longitudinal study carried out by Molina and Pelham (2003) on 142 adolescents compared with 100 checkups, it appears that the severity of the inattentive symptoms of ADHD would be linked to the increased risk of SUD. This data is significant if the frequent persistency of inattentive symptoms in young adults is considered together with the greater risk for the development of SUD in this age.

The presence of ADHD also seems to have an influence on the progression of SUD. ADHD and the comorbidities linked to it speed up the passage from use of “soft” drugs and alcohol to a “hard” drug addiction. Finally, the presence of ADHD seems to compromise the prognosis of SUD. Wilens and coll. compared 130 adults affected by ADHD and SUD with 71 subjects affected by SUD but without ADHD. The remission rate and duration of SUD differed significantly between the two groups: SUD had an average duration of three years more and

the time required to achieve SUD remission was more than double in subjects with ADHD (Wilens, Biederman et al. 1998).

Assessing the link between ADHD and SUD, familiar studies are interesting, as they suggest a common genetic matrix between the two disorders. A family aggregation between ADHD in children and SUD in first and second degree relatives has been known already for some time (Cantwell, 1972). It has emerged from controlled studies that the children of subjects affected by SUD are highly affected by ADHD and cognitive and behavioural features compatible with the disorder, including a low attention capacity, impulsivity, aggressivity and hyperactivity (Stanger et al., 1999).

Judging by the available data, the mechanisms through which the presence of ADHD would favour the development of SUD are surely numerous, and much remains to be understood. Arias et al. suggest that ADHD may be associated with a more severe phenotypic expression of SUD because of the presence of higher levels of impulsivity and novelty-seeking in affected subjects than in those not affected (Arias et al., 2008). There are some researches that identify the self-medication of depressive, anxious and aggressive symptoms as a possible explanation of SUD. A recent study by Wilens and colleagues took into account a population of subjects affected by ADHD, both adolescents and adults, comparing them with a control group in order to understand the

motivations behind drug use. Self-medication plays an important role. The majority of the subjects used the substance to control their mood, to sleep, or without any specific reason. However, there were no differences between subjects with ADHD and members of the control group, nor have differences been found regarding the choice of a specific drug (Wilens et al., 2008).

PREDICTORS OF PERSISTENCE IN ADULTHOOD

Persistence and chronic evolution in adulthood have been reported in 50-80% of patient suffering ADHD. Comorbidity with other mental disorders in childhood is the first predictor of persistence in adulthood, in particularly Conduct Disorder, Mood Disorders, Substance Use Disorder and their early onset. Obviously a child-adolescent with ADHD and comorbid conditions is frequently resistant to treatments, a factor that may contribute to the chronic evolution.

A recent study describes clinical outcomes of youngsters with ADHD (Langley K et al, 2010). The study population was composed by 126 school-aged children (mean age 9.4 years, s.d. = 1.7) that were reassessed after 5 years, during the adolescence (mean age 14.5 years, s.d. = 1.7), for ADHD, conduct disorder and other antisocial behaviours. Most adolescents (69.8%) continued to meet full criteria for ADHD, were

known to psychiatric services and exhibited high levels of antisocial behaviour, criminal activity and substance use problems. Maternal childhood conduct disorder predicted offspring persistence of ADHD; maternal childhood conduct disorder, lower child IQ and social class predicted offspring conduct disorder.

Children with attention-deficit/hyperactivity disorder (ADHD) are at risk for adverse outcomes such as substance abuse and criminality, particularly if they develop conduct problems. Little is known about early predictors of the developmental course of conduct problems among children with ADHD. Parental psychopathology and parenting were assessed in 108 children who first met DSM IV criteria for ADHD at 4-7 years of age. When demographic variables and baseline ADHD and conduct problems were controlled, maternal depression predicted conduct problems 2-8 years following the initial assessment, whereas positive parenting during the structured parent- child interaction task predicted fewer future conduct problems. These findings suggest that maternal depression is a risk factor, whereas early positive parenting is a protective factor, for the developmental course of conduct problems among children with ADHD (Chronis et al, 2007).

An interesting study (Berlin L et al, 2003) examined whether inhibition measured as early as preschool age can predict more general executive functioning and ADHD symptoms at school age. In contrast to previous

studies, the present study focused specifically on ADHD symptoms rather than general disruptive behavior problems, and boys and girls were studied separately. The main result was that inhibition was strongly related to ADHD symptoms both at school and at home for boys, but only in the school context for girls. Early inhibition was also significantly related to the development of deficit in executive functions, and a positive correlation was found between executive functions and ADHD symptoms, although only for boys. The strong relationship between inhibition, executive functioning and ADHD symptoms for boys compared to girls could suggests that either the predictors of ADHD are different for the two sexes, or girls are more often equipped with some factor that protects them from developing ADHD symptoms, despite poor executive functioning. However, it is also possible that relations are just more difficult to be demonstrated for girls than for boys due to their lower incidence of disruptive behavioural problems.

Using data based on self-, parent, and teacher reports, Crystal DS and collegues (2001) assessed various aspects of psychopathology in a large sample of control children and those with ADHD. Confirmatory factor analysis was employed to extract response bias from latent constructs of aggression, anxiety, attention problems, depression, conduct disorder, and hyperactivity. These latent constructs were then entered into logistic regression equations to predict membership in

control versus ADHD groups, and to discriminate between ADHD subtypes. Results of the regression equations showed that higher levels of attention problems and aggression were the best predictors of membership in the ADHD group relative to controls. Logistic regression also indicated that a higher degree of aggression was the only significant predictor of membership in the ADHD-Combined group compared to the ADHD-Inattentive group. However, when comorbid diagnoses of Oppositional Defiant Disorder and Conduct Disorder were controlled for in the logistic regression, greater hyperactivity rather than aggression was the sole variable with which to distinguish the ADHD-Combined from the ADHD-Inattentive subtype.

RESEARCH CONTRIBUTE

OBJECTIVES

Co-morbidity among ADHD, SUD and BD has been reported in clinical and epidemiological studies. However, few investigations were carried out to detect and characterize ADHD in adult patients with SUD and BD observed in psychiatric settings.

For this purpose we evaluated the prevalence of symptoms belonging to the ADHD spectrum in two samples of adult patients affected by SUD and by BD; we also explored the clinical and epidemiological features associated with ADHD in such populations.

STUDY 1

Comorbid ADHD in 97 Bipolar Disorder patients: prevalence and clinical features.

METHOD

For this research we have selected a series of 97 consecutive patients from out-patient and Day-Hospital services of the Department of Psychiatry at University of Pisa in a period of 12 months. The patients had a diagnosis of Bipolar Disorder type I or II according to DSM-IV-TR criteria. All patients gave their informed consent for the participation and the protocol of the study was approved by the ethics committee of Pisa University.

The clinical data was carefully collected through a semi-structured interview. For the baseline interview, approximately an hour was needed and half an hour for the subsequent visits. The interview was conducted by two psychiatrists with at least five years experience in the diagnosis and treatment of mood disorders. Each psychiatrist had followed a training program for using interviewing tools, which included direct observation of experienced interviewers, supervision during the interviews and tests of inter-rater reliability.

Because data collection depended largely, as far as the anamnestic information, on what the patients were able to remember, all the information was verified by the project research coordinator in order to obtain a consensus agreement with the psychiatrists interviewers . When questions arose, patients were contacted for further clarification. In almost all cases, the patient medical records were reviewed and missing information was gathered from family members or previous health care assistants. The following rating tools have been used: ASRS-v 1.1. (Adult ADHD Self-Report Scale) and DCTC (Diagnostic, Clinical and Therapeutic Checklist). The latter is a semi-structured interview developed for the diagnosis of the major clinical syndromes of Axis I and II, based on the criteria in DSM-IV for specific nosographic entities. It allows systematic demographic, clinical and dialysis information. Patients with various origins, were divided almost equally between spontaneously referred patients (self-referrals), or on the advice of their physicians or of any specialists including psychiatrists. The DCTC allows to evaluate the development over timer of psychiatric symptoms using the CGI and social adaptation through the GAF and the Sheehan Disability Scale. The DCTC also allows to record comorbidity Axis I of the patient and possible drug therapies taken. Information on previous treatments and changes in the therapy proposed during the assessment were also collected.

For the evaluation of the ADHD, the patients had to fill out the Adult ADHD Self-Report Scale (ASRS-v1.1). This self-assessment tool consists of 18 items that explore the symptoms presented in the previous 6 months. The first 6 items allow you to make a diagnostic screening for the presence of ADHD in adults. The diagnosis is then prescribed when scores reach highs above a predetermined range in more than 4 of the first 6 items and that the onset of symptoms is seen before the age of 7 years old.

Statistical analysis

The epidemiological and clinical characteristics were compared between two groups: positive diagnosis of Attention Deficit Disorder and Hyperactivity Disorder (ADHD) and negative for that diagnosis (non-ADHD). The comparative analysis for the epidemiological, clinical and symptomatic characteristics of the different subgroups was performed using one-way-ANOVA for dimensional variables (post-hoc comparisons were made using the Bonferroni test) and cross-tabulation for the categorical variables. We have used a 2 tail significance levels with a threshold $p < 0.5$.

RESULTS

Our sample of 97 patients with Bipolar Disorder I and II is composed of 58 males (58.9%) and 39 females (40.2%); 19 out of 97 patients (19.6%) meet the DSM-IV-TR criteria, scored an appropriate level to the scale ASRS to be diagnosed ADHD and reported the onset of ADHD symptoms before reaching the age of 7.

Among subjects diagnosed with ADHD, males are more represented (63.2%, n = 12). The average age is 39.7 ± 13.8 for subjects with ADHD and 42.6 ± 14.2 for subjects without ADHD. In the group diagnosed with ADHD the unmarried prevail (47.4%, n = 9) and the percentage of separated or divorced is higher than for the non-ADHD group (21.1%, vs 7.7%, p = 0.2). While comparing the two groups no significant differences emerged with regard to employment, although patients with ADHD were found to have lower levels of education. The 47.4% (n = 9) of them achieved middle school or lower education level, 42.1% (n = 8) received a high school diploma and only 10.5% (n = 2) holds a BA (Table 3)

In comparison with the non-ADHD group, patients with ADHD show higher rates of depressive episodes (26.3%, n = 5 vs 14.1%, n = 11, p = 0.2) and manic episodes (26.3%, n = 5 vs 20.5%, n = 16 ns). None of the patients with ADHD was in remission at the time of the recruitment,

while 5.1% (n = 4) of patients in the non-ADHD group were in remission (Nieremberg et al., 2005).

Depressive episodes were significantly more frequent among patients with a diagnosis of Bipolar Disorder II and ADHD (42.1%, n = 8 vs 30.8%, n = 24, p = 0.3). None of the patients from this group was in remission, while in the non-ADHD 2.6% (N = 2) of patients with Bipolar Disorder II was in remission (Table 4).

Patients with ADHD reported significantly higher rate of lifetime comorbidity with Substance Use Disorder (SUD) (31.6%, n = 6 vs 17.9%, n = 14, p = 0.2). There are also differences in regard to the specific abuse such as alcohol (21.1%, n = 4 vs 9%, n = 7, p = 0.1), THC (15.8% vs 5.1%, n = 3 , n = 4, p = 0.1), cocaine (15.8%, n = 3 vs. 5.1%, n = 4, p = 0.1) (Fischer et al., 2007; Klessler et al. , 2006; Ohlmeier et al., 2007). No significant difference is found by comparing the rates of abuse of MDMA and heroin (Table 4).

A significantly higher proportion of patients with ADHD reported comorbidity with Impulse Control Disorder (15.8%, n = 3 vs. 3.8%, n = 3, p = 0.1) and Generalized Anxiety Disorder (10.5%, n = 2 vs 2.6%, n = 2, p = 0.1) (Table 4) (Kessler et al., 2006).

Patients with ADHD have a higher percentage of Depression (36.8%, n = 7 vs 17.9%, n = 14), Dysphoric Mania (10, 5%, n = 2 vs 7.7%, n = 6)

Mixed State (42.1%, n = 8 vs 29.5%, n = 23). There is also in this group a lower percentages of patients in Eutimia (5.3%, n = 1 vs 34.6%, n = 27) compared to non-ADHD group. The difference is statistically significant with p = 0.1 (Table 5).

We evaluated the previous response to the antidepressants. Patients with ADHD reported higher rates of mood Instability during treatment with antidepressants and resistance (Table 5).

As for global adaptation measured by the Global Assestment of Functioning scale (GAF), patients with ADHD reported lower scores (47.1 ± 19.5 vs 52.2 ± 24.9). The Shean Disability Scale shows a significantly worse functioning behavior in a family adjustment with patients with ADHD (5.2 ± 2.4 vs 3.9 ± 2.2, p = 0.04) and no statistical difference in “Social” and “Occupational Functioning” (Table 5).

The CGI-Bipolar show no differences for “Mania”, “Anxiety” and “Psychosis”. (Table 5). As expected Patients with ADHD have reported significantly higher mean scores in all items and total scores with ASRS scale compared to non-ADHD patients (41.6 ± 9.8 vs 23.4 ± 9.4 p = 0.0) (Table 6). We have then performed an exploratory factor analysis (Table 7) of the 18 items of this scale to evaluate how the various items are grouped together in our population. The results of the analysis suggest that items can be grouped into four factors that explain 56.33% of the

variance. In particular, the first factor, which has a Eingenvalue of 2,8 and explains 15.6% of the variance, can be defined "Hyperactivity / Impulsivity" and comprises the following items:

5 (0,586) Shaking hands or feet when the subject has to sit for a long time.

6 (0,633) Feeling overly active or constraint to do something as if driven by a motor.

12 (0,536) Needing to get away from a situation in which one must be present.

13 (0,643) Feeling non-rested or agitated.

14 (0,666) Having difficulty to relax

The second factor that has a Eingenvalue of 2,8 and explains 15,6% of the variance, can be defined “inattention” and comprises the following items:

4 (0,456) To avoid or delay the execution of a task that requires reasoning.

7 (0,674) Making errors due to distraction while performing a difficult or tedious project.

8 (0,684) Having difficulty to sustain attention during a tedious or repetitive job.

9 (0,636) Having difficulty concentrating on what is being said by the interlocutor.

11 (0,786) Being distract from surround environment: noises and activities.

The third factor, "Lack of organization", has a Eingenvalue of 2,6, explains 14,3% of the variance, and comprises the following items:

1 (0,680) Having difficulty in focusing and developing details of any a project.

2 (0,804) Having difficulty in arranging objects while performing a task that requires organization.

3 (0,510) Having trouble remembering appointments and deadlines.

7 (0,600) Being distracted while performing a difficult and tedious project.

10 (0,456) Loosing things, or having difficulty finding them.

The fourth factor that has a Eingenvalue of 1,9 and explains 10,7% of the variance, "Intrusiveness", comprises the following items:

15 (0,754) Talking too much in social situations.

16 (0,694) Breaking-off a conversation when the other person has yet to finish talking.

18 (0,584) Interrupt others when they are very busy.

DISCUSSION

In our sample of patients with Bipolar Disorder, the prevalence of co-morbid ADHD is 19,6% (19 vs. 97). This finding is consistent with the previous literature (Barkley 2006, Klassen et al., 2010). The ASRS scale

used to inquire the ADHD symptoms in adults has been effective in identifying those subjects who showed these same symptoms during childhood. This enabled the formulation of the ADHD diagnosis in adulthood and the comparison of clinical features with bipolar patients without ADHD. The persistence of ADHD symptoms seems to negatively affect the overall adaptation to adult life, in particular due to the interference of the cognitive deficits that tend to have a chronic condition influencing the patient's relational system(Biederman and Faraone, 2006). Even in our group with ADHD diagnosis we witnessed this figure, in fact the unmarried, the separated and divorced prevailed and the same for lower levels of education in respect to the non-ADHD group. The clinical condition that requires the simultaneous presence of DB I and ADHD is, in our sample, associated with a greater number of depressive episodes in health history which reaches statistical significance in respect to subjects from the non-ADHD group (26.3%, n = 5 vs 14.1%, n = 11, p = 0.2). And this is also observed when considering patients diagnosed with DB II + ADHD vs the non-ADHD (42.1%, n = 8 vs 30.8%, n = 24, p = 0.3). None of the patients in group BD + ADHD at the time of the visit was in a state of Eutimio, or did not have a state of symptomatic remission (Nieremberg et al., 2005). Patients with ADHD recorded significantly higher proportion of lifetime comorbidity with Substance Use Disorder (SUD) (31.6%, n = 6 vs 17.9%, n = 14, p = 0.2)

where in particular those substances were: alcohol, cocaine and cannabis also as described by other authors. (Fischer et al., 2007; Kessler et al., 2006; Ohlmeier et al., 2007) The only substances that do not differ in the two groups studied were Heroin and MDMA. The latter in the American studies is frequently associated with ADHD, however in our area cocaine is more consumed, due to its spread and the fact that it is easily available compared to MDMA. In a recent study conducted in Spain (Ferrer et al., 2010) in a group of adult patients with Borderline Personality Disorder (BPD) a comorbidity with ADHD of 69% was found, and by comparing the BPD + ADHD group in respect to those without ADHD, showed a statistically significant greater rate of association with substance use disorder (59.4% vs. 38.4%). In addition, the BPD + ADHD subjects show a correlation with the aspect "impulsiveness" which is less frequent in subjects without ADHD, however characterized by the presence of symptoms of mood and anxiety spectrum. Another study investigating the presence of ADHD in patients with major depressive episodes and bipolar disorder highlights the frequency of clinical observations of ADHD greater in bipolar disorder versus unipolar depression (17.6% vs. 5.4%). The DB + ADHD group is associated with an earlier onset of disease, a higher number of comorbidities and a marked consequent reduction in quality of life. (McIntyre et al. 2010) A further research conducted on 211 individuals diagnosed with ADHD

emphasizes the association between the severity of symptoms and negative events of life regardless of associated comorbidities. (Garcia et al., 2010). Patients with coexisting DB, ADHD and SUD present inevitably increased severity of the clinical picture in general showing a worse prognosis and a poor response to treatment. Until we verify a state of abstinence of substances it is difficult to treat ADHD and the DB. In particular, the abuse of cocaine and in general the conditions of multi-drug abuse are less responsive to standard psychopharmacological treatment, but once abstinence achieved, we arrive to the psycho-affective equilibrium stabilization mainly through the use of mood regulators, and finally symptoms of ADHD can be treated. The DB + ADHD group also differs to a significantly higher proportion of comorbidity with Impulse Control Disorder (15.8%, n = 3 vs. 3.8%, n = 3, p = 0.1) and Disorder Generalized Anxiety (10.5%, n = 2 vs 2.6%, n = 2, p = 0.1) (Kessler et al., 2006). The course and prognosis of Bipolar Disorder is influenced by the association of both ADHD and other psychiatric disorders presence. Obviously a medical condition in which cognitive and deficit symptoms persist of executive functions leads to numerous problems in terms of school/work environment and family environment. In fact, Kessler and his colleagues, in a recent study, examined the symptoms that most characterize ADHD in adults, 131 subjects with ADHD compared to 211 controls, observing, through a

logistic regression, that the pathognomonic psychopathological item appears to be a deficit of executive functions rather than the symptoms of inattention. The latter does not represent a distinctive diagnostic element as overlapping with other pathological conditions and therefore nonspecific (Kessler et al., 2010). Finally, our study describes a population of bipolar which, compared by the association with ADHD show a more severe psychopathology and a worse level of overall functioning compared to non-ADHD group. By documenting the clinical impact of ADHD in DB, it is noted that like any comorbidity influences the course, the prognosis and especially therapeutic management. If it is better to limit the use of antidepressants in the DB, in the event of comorbidity DB + ADHD, scrutiny must be greater. In our sample we observed the mood instability and irritability appearance after taking psychotropic medication therapy based mainly on serotonergic antidepressants (SSRI) in both groups. However, there are some patients with DB and DB + ADHD that are getting a clinical efficacy from such treatment. They are the subjects who, for the most part, have anxiety disorder in combination, such as Panic Disorder and Generalized Anxiety Disorder. Or subjects who maintain a good psycho-affective balance by following an appropriate stabilizing therapy with lithium salts and / or antiepileptic, which doe not undergo through hypo / mania changes during treatment with SSRI or with other antidepressants. More

scientific researches are needed to explore these therapeutic implications especially in terms of comorbidity between DB and ADHD.

STUDY 2

ADHD in 109 patients with Sustance Use Disorder

METHODS

A sample of 109 consecutive out-patients with Substance Use Disorder was selected among the outpatiens attending the Ser.T. (literally “Servizio per le Tossicodipendenze”) of Viareggio (LU) and the outpatient Services of “Incontro” and “Ce.I.S.” Therapeutic Community, based in Pistoia and Livorno respectively, over a period of about 12 months.

Informed consent was provided by all patients, and the study protocol was approved by the Ethic Committee of the University of Pisa.

Clinical data were collected by means of an in-depth semi-structured interview; the basal evaluation lasted 1 hour approximately. The interviews were conducted by two specialists with minimum 5 years experience in dealing with diagnosis and treatment of Affective and Substance Use Disorders.

The methodology of evaluation and the instrument utilized were the same described in the Study 1

Statistical Analysis

Epidemiological and Clinical characteristics as well as ADHD symptomatology detected by means of ASRS were compared in the two groups of patients: those with (ADHD) and without (no-ADHD) a diagnosis of ADHD. Comparative analysis for epidemiological, clinical and symptomatological characteristics of the different subgroups was accomplished using logistic regression analysis and cross-tabulation for categorical variables. The significance level chosen was $p < 0.5$ (two-tailed). Exploratory Factor analysis for ASRS items was conducted using Varimax rotation and forcing a three-factor solution.

RESULTS

Among the 109 patients affected by SUD (81 males and 28 females), 20 (18,35%) report a diagnosis of ADHD according to DSMIV and ASRS-v1.1. No difference can be observed between ADHD and no-ADHD patients as regards age, sex, marital status, employment and education. (Table 8). The two groups do not show differences for substances in use as well (Table 9), even though in the no-ADHD group the share of cannabis-abusers is higher (27%vs10%). As regards lifetime psychiatric comorbidity (Table 9), ADHD patients show larger prevalence of Bipolar Disorder (80% vs 43.2%, OR 8.84, p.003) and current manic of mixed episode at the time of observation (40% vs 16.9%, OR 3.29, p=.027). No

significant difference between ADHD and No-ADHD patients has been observed in terms of prevalence of comorbid Anxiety Disorders and Impulses Control Disorders. As expected, the CGI-bipolar scores (Table 9) reported by ADHD patients were generally higher for items such as “Mania” (0.95, ds=1.43 vs 0.52, ds=0.91; OR 1.42, p=.097) and “Mixed Simptoms” (1.40, ds=2.01 vs 0.69, ds=1.42; OR 1.23, p=.071), the differences ar not statistically significant.

ADHD patients did not differ from No-ADHD patiens as regards social, familial or professional adjustment, as measured by Sheehan Disability Scale and GAF (Table 9).

As concern the response to previous antidepressant treatment (Table 10): no significant differences can be observed in “manic switch” and “mood instability”, but ADHD patients report more frequently “resistance to treatment” (15% vs 3.4%, chi-square 4.25, p=.039) and “irritability” (35% vs 15.7%, □hi-square 3.90, p=.048).

As expected, the ASRS score calculated with 6 items (15.05, ds=3.2 vs 7.38, ds=3.50 ; OR 8.99, p=.000) and with 18 items (41.2, ds=6.75 vs 24.46, ds=9.35; OR 7.56, p=.000) was significantly higher in ADHD patients. In addition all ASRS items discriminates between the two diagnostic groups, with OR values ranging from 7.44 for item 4 to 1.52 for item 10.

The factor analysis (Table 11) of the ASRS 18 items indicates a 3 factor solution, accounting for 47,73% of the total variance. The first factor, “Attention deficit”, with an Eingenvalue of 3.2, account for 17.9% of the total variance, and encompasses items 3 -*Having trouble remembering appointments and deadlines*- (.451), 4 (.590), 5 (.406), 7 (.722), 8 (.682), 9 (.534), 10 (.715), 11 (.473), 12 (.484). The second factor, “Hyperactivity-Impulsivity”, with an Eingenvalue of 2.8, account for 15.5% of the variance, and comprised the items 5 - *Shaking hands or feet when the subject has to sit for a long time*- (576), 6 (.429), 11 (.501), 15 (.695), 16 (.771), 17 (.415), 18 (.570). The third factor, “Disorganization”, with an Eigenvalue of 2.6, account for 14.3% of the variance and comprised the items 1- *Having difficulty in focusing and developing details of any a project*- (.722), 2 (.692), 4 (.527), 6 (.473), 9 (.583), 13 (.514), 14 (.466).

DISCUSSION

In our sample of 109 patients with SUD, 18 % present a diagnosis of adult ADHD. This finding is consistent with other studies: the prevalence of ADHD in SUD patients is about three times higher than in general population (Levin 1998), (King, Brooner et al. 1999), (Clure, Brady et al. 1999). On the other hand, the rate of SUD in ADHD patients can reach up to 40% (Kalbag and Levin 2005), substantially higher than what is

observed in general population (about 14,6% - Kessler, Adler et al. 2005). Some authors report that ADHD diagnosis is associated with early onset and severe course of SUD, with increased number of relapses and longer time elapsed for remission (Carroll and Rounsaville 1993), (Wise, Cuffe et al. 2001), (Stein, Marx et al. 2004) , (Wilens, Biederman et al. 1997). In recent study by Arias et al. (Arias, Gelernter et al. 2008), a sample of 1761 SUD patients was studied and the results showed generally larger use of substances in probands with ADHD. In our study no difference could be detected bewteen the ADHD and the no-ADHD group, partly on account of the limited numerosity of our sample, but probably also because of the type of abuser patients, who were mostly opioid addicts with high rates of polyabuse. For the same reason, no statistical differences have been observed in the analysis of socio-demographic variables. Some authors have suggested that patients with ADHD may use stimulants such as cocaine, to reduce symptoms typical of their disorder, however no significant difference in the type of substance used in SUD patients with and without ADHD is detected either in our sample or in other studies available in current literature (Biederman, Wilens et al. 1995).

In absence of convincing evidence addressing the issue of self-medication, it is more reasonable to propose that the use of substances in ADHD patients is facilitated by impulsivity typical of their disorder

(Arias, Gelernter et al. 2008) and by the increased presence of comorbidity for mood disorders. The analysis of comorbid psychiatric disorders shows that the Bipolar Disorder (BD) is more common in the ADHD group compared to the no-ADHD: as much as 80% of patients with ADHD had a Bipolar Disorder. A greater rate of BD in patients with ADHD and SUD compared to no-ADHD SUD has also been reported by Arias et al. (Arias, Gelernter et al. 2008) but with lower prevalence (5.25% for Bipolar Disorder type I, vs 65% in the sample in question). This difference may be largely accounted for the different methodological procedures, setting recruitment, numerosity and severity of the selected patients. The same authors reported a higher frequency of conduct disorder and antisocial personality disorder, but these diagnosis were not investigated in our study, and post-traumatic stress disorder, which we did not detect most probably due to limited sample size.

Patients with ADHD report high rates of a positive family history for BD (Dilsaver, Henderson-Fuller et al. 2003); (Secnik, Swensen et al. 2005). On the other hand ADHD is often diagnosed in patients with Bipolar Disorder (Tamam, Karakus et al. 2008), (Sentissi, Navarro et al. 2008); (Tamam, et Tuglu al. 2006); (Sachs, Baldassano et al. 2000). The comorbidity for ADHD is particularly high in pediatric samples, reaching 38 - 98% (Tamam, Karakus et al. 2008); (Sachs, Baldassano et al. 2000), and decreases in adult population up to 9-35% (Tamam, Karakus

et al. 2008); (Nierenberg, Miyahara et al. 2005), (Sentissi, Navarro et al. 2008); (Tamam, Tuglu et al. 2006). In this study, subjects with BD and ADHD appear to have worse course than no-ADHD, they have a higher rate of manic or mixed episodes at the time of observation with a generally greater severity (although this finding does not reach the statistical significance).

In current literature there are no studies that compare abuser bipolar patients with and without comorbid ADHD, but it is well known that, in general, BD individuals with ADHD have a worse course of illness than non-ADHD BD individuals: the onset of manic symptoms is early (Kent and Craddock 2003), (Wingo and Ghaemi, 2007); (Nierenberg, Miyahara et al. 2005); (Masi et al. 2006); (Sachs, Baldassano et al. 2000), (Jaideep et al., 2006), possibly as earlier as 3-5 years (Nierenberg et al. 2005); (Masi et al., 2006). In addition there is a worse course (Wingo and Ghaemi, 2007); (Nierenberg, Miyahara et al. 2005); (Tamam, Tuglu et al. 2006), higher rates of bipolar disorder type I (Nierenberg, Miyahara et al. 2005), a higher frequency of depressive episodes (Tamam, Tuglu et al. 2006) and manic episodes (Nierenberg, Miyahara et al. 2005), with shorter intervals free from disease (Nierenberg, Miyahara et al. 2005). This has led to the hypothesis that bipolar disorder comorbid with ADHD is actually a distinct phenotype (Faraone, Biederman et al. 1997).

Familiarity studies seem to confirm this hypothesis. (Faraone and Biederman 1994); (Wozniak, Biederman et al. 1995).

Finally, we investigated the response to antidepressants in the studied sample, and patients with ADHD have greater resistance to treatment and irritability compared with No-ADHD subjects. In literature it is reported that patients with ADHD and substance abuse may benefit from treatments based on bupropion, with improvement of both ADHD symptoms and craving for substances (Riggs, Leon et al. 1998); (Wilens, Spencer et al. 2001), (Levin, Evans et al. 2002); (Wilens, Prince et al. 2003), other studies show positive response to methylphenidate (Levin, Evans et al. 1998).

In the present study a distinction was not made as regarded response to different antidepressants, but most of the subjects had taken SSRIs. The data in our possession may suggest a poorer response to SSRI antidepressants in patients with SUD and ADHD, but the findings may be due the higher rate of individuals affected by BD in SUD patients with ADHD. Further researches with larger samples are in order to clarify this aspect.

Factor analysis of the ASRS scale suggests that, in a population of patients with substance abuse, those items that explore symptoms of ADHD are mainly distributed in three groups: disattention, hyperactivity-impulsivity and disorganization. The factor of attention deficit is the most

important in our series of adult patients with SUD; this finding is consistent with findings from other studies (Heiligenstein, Conyers et al. 1998), (Fischer, Barkley et al. 2007); (Barkley, Fischer et al. 2006), according to which the attention deficit component keeps stable and is maintained through the years, while the hyperactivity tends to decrease. In our patients, hyperactivity and impulsiveness are associated in a unique factor that has a similar weight to the disorganization factor. In the adult with SUD, difficulties with attention and organization seem to take a particular significance constituting an essential part of the simptomatologic picture. These results can also be explained, at least in part, with cognitive impairment related to chronic use of psychotropic substances. Another possibility is that the severity of inattention is the variable that best correlates with an increased risk for developing SUD in individuals with ADHD, as already supported by other authors (Molina and Pelham 2003); (Wilens 2004).

STUDY 3

Comorbid ADHD in a clinical sample of patients with Sustance Use Disorder and Bipolar Disorder

METHODS

A sample of 147 consecutive patients was selected among the outpatients attending the Day Hospital and Ambulatory Unit of the Clinica Psichiatrica, University of Pisa, the inpatients and outpatiens attending the Hospital and Ambulatory Service of Psichiatry in Ospedale della Versilia and Ser.T. Ambulatory (literally “Servizio per le Tossicodipendenze”, that is Service for Addiction Disorders) in Viareggio and the Ambulatory of “Incontro”, a Therapeutic Community based in Pistoria, over a period of about 12 months.

According to DSM-IV-TR [1] criteria by means of SCID-I [2], 50 patients were diagnosed Bipolar Disorder type I or II (BIP) and 53 were diagnosed Substance Use Disorder, while 44 were Dual Diagnosis patients.

Informed consent was provided by all patients, and the study protocol has been approved by the Ethic Committee of University of Pisa.

The methodology and the evaluation instruments utilized for the present study were the same described in the Study 1.

Statistical Analysis

Epidemiological and Clinical characteristics as well as ADHD symptomatology detected by means of ASRS were compared in the three groups of patients: SUD (n=53), BIP (n=50), SUD+BIP (n=44). Comparative analysis for epidemiological, clinical and symptomatological characteristics of the three subgroups was accomplished using one-way ANOVA for dimensional variables (Bonferroni test was implemented as well for post-hoc comparisons) and cross-tabulation for categorial variables. The significance level chosen was $p < 0.5$ (two-tailed).

RESULTS

Our sample of 147 patients consisted of 95 males (64.6%) and 52 females (43.4%). (Table 12). Individuals belonging to BIP subgroup showed highest mean age (42.9+15.0) while SUD showed the lowest (24.8+9.6). Subgroup SUD+BIP showed a mean age of 34.9+6.8, an intermediate value between the other 2 subgroups. As regards sex distribition, the BIP subgroup included fewer males in comparison to SUD and SUD+BIP (46%, 71.7% and 77.3% respectively). SUD and

SUD+BIP patients included mostly unmarried individuals whilst the BIP subgroup had a larger number of married patients. No differences were shown regarding employment, whereas education level was lower in SUD+BIP.

As regards the diagnostic profile at the time of observation (Table 13), the BIP subgroup included more patients in current manic episode or remission, while SUD+BIP patients presented a higher number of mixed episodes, even though this difference did not reach statistical significance. Prevalence of Bipolar Depression was similar in BIP and SUD+BIP subgroups.

Diagnosis of Alcohol Abuse was more frequent in SUD patients whilst SUD+BIP patients presented Cocaine Use Disorder more frequently, both differences did not reach statistical significance though; Heroin Addiction was similarly represented in SUD and SUD+BIP (30.2% vs 36.4%).

Most patients presented at least one concomitant mental disorder. Specifically, SUD+BIP patients showed higher ratios of comorbidity than the other two groups, reaching statistic significance for prevalence of Cocaine and stimulants, Alcohol Use and Substances polyabuse.

GAF scores indicated a better general functioning in SUD patients (61.8+20) while BIP and SUD+BIP patients obtained lower scores (52.4+22.4 vs 55.7+12.2 respectively). Social Adaptation as measured

by means of Sheehan Disability Scale in the three functional areas of work, family and social relationships did not show statistically significant differences in the three groups, indicating moderately impaired levels of adaptation in all patients.

From a psychopathological perspective, the global clinical evaluation of severity (obtained through the CGI) showed higher scores in BIP and SUD+BIP in comparison to SUD patients for depression, mixed state and psycosis. The BIP group showed higher scores in mania scale and lower scores in the impulsivity scale in comparison to the other two groups.

23 patients (15.6%) reported diagnostic scores in ASRS accompanied by a history of ADHD in childhood, thus permitting a diagnosis of Adult ADHD. An additional 24 patients (16.3%) showed high scores but did not report a history of ADHD in childhood.

From the comparison among the 3 groups (Figure 1) 13 (29.5%) patients with SUD+BIP reported a history of ADHD in contrast with only 4 (7.5%) SUD and 6 (12%) BIP patients. The difference was statistically significant.

Most items (15 over 18) of ASRS (Table 14) did not show significant difference between the 3 subgroups even though SUD+BIP patients reported higher mean scores in all explored variables. Only three items showed significant difference: Item 2, “difficulty getting things in order when you have to do a task that requires organization” and Item 17,

“difficulty waiting your turn in situations when turn taking is required” show significantly higher scores in SUD+BIP patients in comparison to the other 2 groups. Item 14, “difficulty unwinding and relaxing when you have time to yourself”, differentiates BIP and BIP+SUD from SUD.

As regards the total score of the first 6 Items, the most important in terms of diagnostic specificity, SUD+BIP showed higher scores than the other 2 groups as well as in ASRS total score.

DISCUSSION

Our sample of 147 patients with Bipolar Disorder, Substance Use Disorder or Dual Diagnosis present ADHD comorbidity in about 15% of the cases; an analogous ratio of patients reports high scores in ASRS but does not report onset in childhood as required for diagnosis.

The rate of comorbidity observed in our study is consistent with those reported by other authors (Kessler et coll., 2006) with different diagnostic instruments on similar samples.

Comorbidity with ADHD is found in about a quarter of Dual Diagnosis (SUD+BIP) patients, this represents a rate higher than those found in patients with either SUD or BIP disorder alone. This finding is consistent with the results of other studies (Tamam L. e coll., 2008).

As regards demographic variables, the subgroups with SUD included a preponderance of unmarried individuals, while Bipolar patients were more frequently married. This finding is compatible with the different mean ages in the three subgroups, with BIP patients being older than the others.

The three groups showed no difference regarding employment, whilst education was significantly poorer in SUD+BIP. This result is coherent with the impaired school performance associated to a history of ADHD in childhood. Other authors (Barkley, 2008) reported poor levels of education in adult ADHD patients.

As regards diagnosis, patients did not differ for the specific substance used, even though alcohol was more frequent in SUD patients whereas Cocaine Use Disorder prevailed in SUD+BIP.

As expected, most patients presented at least one psichiatric comorbidity. In SUD+BIP patients, for instance, high rates of comorbidity were reported. Cocaine and stimulants use, Alcohol Use and Polyabuse characterized Dual Diagnosis patients.

This finding is in line with previous observations (Levin F.R., 2007; Tamam L. e coll., 2008) implying that the associations with ADHD and Mood Disorders seem to identify a specific SUD subgroup whose features are increased severity, tendency to poliabuse and to chronic course.

As regards the symptom profile at time of observation, BIP patients more frequently presented a current manic episode or remission, while SUD+BIP reported a larger number of mixed episodes. The global clinical assessment of severity showed larger presence od Depressive, Mixed and Psychotic symptoms in BIP and SUD+BIP patientes. As expected from diagnosis, BIP patients reported more severe manic symptoms and lower levels of impulsivity in comparison to both the other two groups.

The association between Mixed symptoms, SUD+BIP and ADHD bears remarkable clinical interest and important implications from a therapeutic point of view.

As regards ADHD specific symptomatology, Dual Diagnosis patients reported high scores in all the explored areas and more commonly reported “ difficulty getting things in order when you have to do a task that requires organization” and “difficulty waiting your turn in situations when turn taking is required”. Both items required for diagnosis and total ASRS score suggested an increased severity of various aspects of ADHD such as lack of attention, impulsivity and difficulty in organization. “Difficulty unwinding and relaxing” was more frequently associated to Mood Disorders instead.

LIMITATIONS

Our research has some methodological limitations that need be taken into account for the interpretation of the results. The data collection is retrospective and recollection bias can affect the diagnosis and onset of symptomatology. However, this bias is shared by all three groups in study. Moreover, the retrospective diagnosis of ADHD is probably underepresented, as it is scarcely identified and reported in our country. More importantly, our sample shows substantial heterogeneity in terms of sex, age and provenance, as this concerns the interpretation of our results. For instance, the differences in age and sex could affect the relative prevalence of ADHD. Our BIP patients present higher mean age and are more frequently female, therefore the prevalence of ADHD might be lower if compared to a sample matched for demographic characteristics. By contrast, Substance Use is very common in young male bipolar patients.

In addition, patients were recruited from Ser.T, communities and tertiary care centers, therefore the observations are related to a sample with remarkably serious psychopathology, not necessarily representative of patients with SUD belonging to the general population. Another limitation is related to the fact that, since the study was accomplished by expert

clinical evaluators, they were not blind with respect to the diagnosis. The use of standardized tools of assessment, however, reduces this limit.

CONCLUSION

The persistence of ADHD in adulthood is a complex underdiagnosed clinical condition. In most adult patients, ADHD is associated with another mental disorder and can be concealed by its presence; comorbidity will affect clinical presentation, severity, natural course, prognosis and treatment.

Substance Use Disorders and Mood Disorders are frequently associated with Adult ADHD. Our patients with BD and ADHD appear to have a worse course with a large number of manic or mixed episodes at the time of observation and greater severity of sintoms. Our results are consistent with those obtained from a study of Bernardi and colleagues on a sample of 100 patients aged between 18 and 30 years with a diagnosis of Bipolar Disorder in remission. The study shows that 18% of patients present lifetime and 10% current comorbidity of ADHD + BD and that this event is characterized by an earlier onset of mood disorder, a greater number of affective episodes and greater impulsivity compared to bipolar patients without ADHD. This findings suggest the possibility that patients with bipolar disorder who have a diagnosis of ADHD in adulthood represent a clinically distinct phenotype (Bernardi et al., 2010).

Similarly, we found that one fifth of our sample of bipolar adults has a current diagnosis of ADHD, and that these patients are characterized by a greater number and more severe depressive episodes, resulting in a marked interference in global adaptation, when compared with ADHD subjects without bipolar. To complicate the clinical picture in BD + ADHD group, they are often associated with the Substance Use Disorder and the Impulse Control Disorder.

The STUDY 2 indicate high prevalence of symptoms of ADHD in an adult population with Substance Use Disorder: about 1 patient in 5 reported symptoms compatible with a diagnosis of ADHD. In our sample, there are no differences between groups with and without ADHD in the type of substance used, partly because of the limited sample size, but probably also for the type of patients, predominantly opioid-dependent and burdened by a high rate of poli-drug abuse. Patients with ADHD, compared with patients with substance abuse without ADHD, reported more frequent comorbid BD and history of resistance or irritability in response to antidepressants.

Factor analysis of the ASRS scale, in patients with substance abuse, reveals that symptoms of ADHD are distributed in three main dimensions: inattention, hyperactivity-impulsivity and disorganization.The Inattention is the most important factor, while hyperactivity and impulsivity are associated in a single factor that has a weight similar to

the disorganization factor. Inattention and difficulties in organization therefore seem to assume a significant importance in SUD, being an essential part of the symptomatological picture.

Substance Use Disorder is widespread in general population (Kandel e coll., 1997) and a remarkable part of these individuals shows symptoms of ADHD (Wilens, 2004). On the other hand, ADHD is a risk factor for Substance Use in itself.

In STUDY 3, 1 Dual Diagnosis patient out of 4 reported childhood history of ADHD and more than 1 patient out of 2 presented corresponding symptoms at the time of observation. Our data are consistent with the observation that SUD in ADHD patients features an earlier onset, a longer duration and a faster progression towards substance polyabuse (Wilens 1998, 2003). In addition, the risk for developing a SUD is increased by the comorbidity of ADHD and Bipolar Disorder.

Differential diagnosis between ADHD and Bipolar Diroder is hardly manageable for the substantial symptomatologic overlap between the two conditions. Prolonged hypomania, especially in teenagers and young adults, is not easily distinguished from hyperactivity and impulsivity observed in ADHD, and many cases may be affected by both conditions concomitantly. The comorbidity also seems to increase the risk to develop SUD dramatically.

Our study confirms the observation that the relationship between adult ADHD and Substance Use Disorder is conveyed by the association with conduct disorders and antisocial personality disorder. Our data are consistent with the hypothesis that this relationship may also be facilitated by the presence of Bipolar Disorder. In conclusion, Bipolar Disorder, ADHD, Conduct Disorder and Substance Use Disorder may share a common diathesis conveyed by hyperactivity-impulsivity.

Further prospective studies are needed to confirm our observations and to evaluate the influence of ADHD symptoms on course and treatment response.

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TABLE 1 (*DSM –IV TR Criteria ADHD*)

A. Either (1) or (2):

(1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention:

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not have seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities
(2) six (or more) of the following symptoms of hyperactivityimpulsivity have been persistent for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity:

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness
Diagnostic Criteria For ADHD – DSM-IV-TR
Provided By ADHDFamilyOnline.com Reference: (APA [*DSM-IV-TR*] 2000)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often “on the go” or often acts as if “driven by a motor”
(f) often talks excessively
Impulsivity:
(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairments were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinical significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code Based On Type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type:
if both Criteria A1 and A2 are met for the past 6 months
314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type:
if Criterion A1 is met but Criterion A2 is not met for the past 6 months
314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

Table 2. Utah Criteria for Adult Attention-Deficit/Hyperactivity Disorder

I. Diagnosis retrospective of ADHD in childhood A. Interview to parents (DSM-IV criteria) B. Interview to patient, to find these symptoms 1-2: 1) Hyperactivity in childhood 2) Disattention in childhood
II. Characteristic adulthood: five symptoms more, Disattention Hyperactivity Lability Irritability No tollerance to stress Disorganization Impulsivity
III. No for depression, psychosis and personalty disorder.

A Parent Rating Scale of Childhood Behaviour
B Wender Utah Rating Scale self-report

Table 3. Demographic aspects in patient affected by Bipolar Disorder with or without ADHD.

	ADHD N = 19	No – ADHD N = 78	t or χ^2	p
Age, mean (sd)	39,7 (13,8)	42,6 (14,2)	.786	.434
Gender: male, n (%)	12 (63,2)	46 (59)	.11	.739
Civil status, n (%)				
Unmarried	9 (47,4)	32 (41)		
Married	5 (26,3)	38 (48,7)		
Separated / Divorced	4 (21,1)	6 (7,7)		
Widow	1(5,3)	2(2,6)	4,9	.181
Education, n (%)				
University	2 (10,5)	10 (12,8)		
High school	8 (42,1)	33 (42,3)		
Low school	9 (47,4)	34 (43,6)	.4	.949

Table 4. Diagnostic aspects in patient affected by Bipolar Disorder with or without ADHD.

	ADHD N = 19	No – ADHD N = 78	t or χ^2	P
Psychiatric Diagnosis, n (%)				
Bipolar Disorder I Depressive Episode	5 (26,3)	11 (14,1)	1,7	.198
Bipolar Disorder I Mixed State	5 (26,3)	25 (32,1)	0,2	.628
Bipolar Disorder I Manic	5 (26,3)	16 (20,5)	0,3	.582
Bipolar Disorder I Remission	--	4 (5,1)	1	.313
Bipolar Disorder II Depressive Episode	8 (42,1)	24 (30,8)	0,9	.346
Bipolar Disorder II Remission	--	2 (2,6)	0,5	.481
Congruent psychotic characteristic	1 (5,3)	7 (9,0)	0,3	.598
Incongruous psychotic characteristic	2 (10,5)	4 (5,1)	0,8	.381
Alcol	4 (21,1)	7 (9)	2	.137
MDMA	1 (5,3)	4 (5,1)	0,01	.981
THC	3 (15,8)	4 (5,1)	2,6	.107
Heroin	1 (5,3)	4 (5,1)	0,01	.981
Cocaine	3 (15,8)	4 (5,1)	2,6	.107
SUD	6(31,6)	14(17,9)	1,7	.188
Panic Disorder	6 (31,6)	22 (28,2)	0,1	.771
Social Phobia	--	4 (5,1)	1	.313

OCD	1 (5,3)	5 (6,4)	0,04	.852
GAD	2 (10,5)	2 (2,6)	2,5	.118
Bulimia	--	1 (1,3)	0,2	.620
Impulse Control Disorder	3 (15,8)	3 (3,8)	3,8	.053

Table 5. Clinical aspects in patient affected by Bipolar Disorder with or without ADHD.

	ADHD N = 19	No – ADHD N = 78	t or χ^2	p
Current Mood, n (%)				
Depression	7 (36,8)	14 (17,9)		
Euthymia	1 (5,3)	27 (34,6)		
Disphoric Mania	2 (10,5)	6 (7,7)		
Euphoric Mania	1 (5,3)	6 (7,7)		
Mixed State	8 (42,1)	23 (29,5)	8,6	.126
Pregress response to antidepressant, n (%)				
Swicth ipo/manic	3 (15,8)	17 (21,8)	0,3	.562
Mood Instability	5 (26,3)	18 (23,1)	0,9	.766
Resistence to treatment	4 (21,1)	12 (15,4)	0,4	.551
Irritability	4 (21,1)	22 (28,2)	0,4	.528
GAF, mean (ds)	47,1 (19,5)	52,2 (24,9)	- 0,8	.410
Sheehan Disability Scale, mean (sd):				
School/work	5,7 (2,5)	4,6 (2,6)	1,7	.095
Social	5,8 (2,4)	4,8 (2,5)	1,7	.089
Family	5,2 (2,4)	3,9 (2,2)	2,1	.040
CGI- Bip, mean (sd)				
Manic Severity	1,9 (1,9)	1,6 (1,6)	0,8	.422
Depressive Severity	2,5 (1,3)	2,1 (1,5)	1,0	.316

Mixed Severity	1,4 (1,3)	1,6 (1,7)	- 0,5	.641
Anxious Severity	2,4 (1,9)	1,9 (1,6)	1,0	.318
Hympulsivity Severity	1,7 (1,7)	1,3 (1,5)	1,1	.264
Psychosis Severity	1,05 (1,6)	1,4 (2,6)	- 0,5	.595

Table 6. ASRS scores comparison in patient affected by Bipolar Disorder with or without ADHD.

	ADHD N = 19	No – ADHD N = 78	f or χ^2	p
Items, mean (sd)				
1- Having difficulty in focusing and developing details of any a project.	2,5 (0,9)	1,1 (1,1)	5,2	.000
2- Having difficulty in arranging objects while performing a task that requires organization.	2,6 (1,1)	0,9 (1,0)	6,4	.000
3- Having trouble remembering appointments and deadlines	2,5 (1,2)	1,1 (1,2)	4,6	.000
4- To avoid or delay the execution of a task that requires reasoning.	3,1 (0,8)	1,2 (1,0)	7,4	.000
5- Shaking hands or feet when the subject has to sit for a long time.	3,0 (1,3)	1,3 (1,2)	5,7	.000
6- Feeling overly active or constraint to do something as if driven by a motor.	2,4 (1,4)	1,0 (1,3)	4,1	.000
7- Making errors due to distraction while performing a difficult or tedious project.	2,6 (0,8)	1,4 (1,0)	4,9	.000
8- Having difficulty to sustain attention during a tedious or repetitive job.	2,6 (1,1)	1,6 (1.1)	3,7	.000
9- Having difficulty concentrating on what is being said by the interlocutor.	2,5 (1,0)	1,3 (1,1)	4,5	.000
10- Loosing things, or having difficulty finding them.	2,5 (1.3)	1,5 (1,1)	3,2	.002
11- Being distract from surround environment: noises and activities.	2,1 (1,1)	1,5 (1,0)	2,2	.030
12- Needing to get away from a situation in which one must be	1,8 (1,2)	0,9 (1,1)	2,9	.004

present.				
13- Feeling non-rested or agitated.	2,7 (1,0)	2,1 (1,1)	2,3	.026
14- Having difficulty to relax	2,2 (1,3)	1,5 (1,1)	2,6	.011
15- Talking too much in social situations.	1,7 (1,3)	1,5 (1,3)	.826	.411
16- Breaking-off a conversation when the other person has yet to finish talking.	2,1 (0,9)	1,3 (1,1)	2,5	.016
17-Difficulty to wait your turn	1,4 (1,3)	1,2 (1,2)	.671	.504
18- Interrupt others when they are very busy.	1,3 (1,1)	1,0 (1,0)	1,1	.278
Score Total, mean (sd)	41,6 (9,8)	23,4 (9,4)	7,5	.000

Table 7. Factor analisys of ASRS items in 97 patients with Bipolar Disorder

Item ASRS	Factor 1 Hyperactivity/ Hympulsivity	Factor 2 Inattention	Factor 3 Disorganization	Factor 4 Intrusivity
1- Having difficulty in focusing and developing details of any a project.	.078	.205	.680	- .008
2- Having difficulty in arranging objects while performing a task that requires organization.	.118	.201	.804	.218
3- Having trouble remembering appointments and deadlines	.317	.381	.510	- .225
4- To avoid or delay the execution of a task that requires reasoning.	.375	.456	.254	.252
5- Shaking hands or feet when the subject has to sit for a long time.	.586	.277	-.024	.069
6- Feeling overly active or constraint to do something as if driven by a motor	.633	- .127	.174	.360
7- Making errors due to distraction while performing a difficult or tedious project.	.073	.674	.600	.077
8- Having difficulty to sustain attention during a tedious or repetitive job.	.069	.684	.378	.154
9- Having difficulty concentrating on what is being said by the interlocutor	.394	.636	.192	- .029
10- Loosing things, or having difficulty finding them	.386	.316	.456	.086
11- Being distract from surround environment: noises	.052	.786	.178	.008

and activities				
12- Needing to get away from a situation in which one must be present.	.536	.115	- .012	.325
13- Feeling non-rested or agitated.	.643	.223	.282	- .011
14- Having difficulty to relax	.666	- .003	.300	.040
15- Talking too much in social situations.	.085	.012	.027	.754
16- Breaking-off a conversation when the other person has yet to finish talking.	.122	- .002	.236	.694
17- Difficulty to wait your turn	.473	.339	- .243	.306
18- Interrupt others when they are very busy	.324	.316	- .227	.584
Eingenvalue	2,8	2,8	2,6	1,9
% of Variance	15,6	15,6	14,3	10,7

Table 8. Demographic aspects in patient affected by Substance Use Disorder, with ADHD (ADHD) or without ADHD (noADHD)

	ADHD N= 20	noADHD N= 89	f or hi2	p
Age, mean (sd)	35,10 (7,66)	34,74 (8,46)	0,17	ns
Gender, male, n (%)	16 (80,0)	65(73,0)	0,42	ns
Civil status n (%)				
Unmarried	17 (85,0)	61(68,5)		
Married	1 (14,6)	13 (14,6)		
Separated o divorced	2 (10,0)	15 (16,9)	2,28	ns
Work, n (%)				
Student	2 (10,0)	5 (5,6)		
Disoccupied	4 (20,0)	16 (18,0)		
Housewife	0 (0,0)	1 (1,1)		
Worker	11(55,0)	34 (38,2)		
Trader	0 (0,0)	7 (7,9)		
Employed	1 (5,0)	14 (15,7)		
Free lance	2(10,0)	11 (12,4)		
Pensioned	0 (0,0) 1	(1,1)	5,11	ns
Education, n (%)				
University	1 (5,0)	2 (2,2)		
High school	3 (15,0)	33 (37,1)		
Low school	16 (80,0)	54 (60,6)	5,30	ns

Table 9. Diagnostic and clinical aspects in patient affected by Substance Use Disorder, with ADHD (ADHD) or without ADHD (noADHD)

	ADHD N=20	noADHD N=89	t or hi2(df=1)	p
Substance lifetime				
Alcol	8 (40.0)	31 (34.0)	1.25	ns
Cocaine	7 (35.0)	34 (38.2)	.87	ns
Heroine	10 (50.0)	58 (65.0)	.53	ns
THC	2 (10.0)	24 (27.0)	.30	ns
MDMA	2 (10.0)	10(11.2)	.88	ns
Comorbidity lifetime. n (%)				
MDD	0 (0.0)	2 (2.2)	0.00	ns
BD	16 (80.0)	38 (43.2)	8.84	.003
Depressive Bip I	5 (25.0)	10 (11.2)	1.03	ns
Mixed/Manic	8 (40.0)	15 (16.9)	3.29	.027
Depressive Bip II	3 (15.0)	13 (14.6)	.01	ns
Psiychotic symptoms				
Congruent	0 (0.0)	3 (3.4)	0.00	ns
Incongruent	2 (10.0)	3 (3.4)	3.19	ns
Rapyd Cycling	1 (5.0)	2 (2.2)	0.46	ns
Panic Disorder	8 (40.0)	23 (25.0)	1.91	ns
Social Phobia	1 (5.0)	2 (2.3)	2.29	ns
DOC	2 (10.0)	0 (0.0)	7.90	ns
Generalized Anxiety	0 (0.0)	2 (2.3)	0.00	ns
Hympulsive Control Disorder	0 (0.0)	2 (2.3)	0.00	ns
GAF. mean (sd)	56.8 (13.9)	60.4 (17.8)	.99	ns
Sheehan Disability Scale. mean (sd):				
Work	4.80 (2.78)	4.78 (2.14)	1.01	ns
Family	4.35 (2.52)	4.56 (1.88)	.95	ns
Social	4.20 (2.35)	4.64 (1.98)	.90	ns
CGI-Bipolare Severity				
Manic	0.95 (1.43)	0.52 (0.91)	1.42	.097
Depressive	2.10 (1.65)	1.46 (1.62)	1.26	ns
Mixt	1.40 (2.01)	0.69 (1.42)	1.23	.071
Anxiety	2.00 (1.69)	1.76 (1.75)	1.08	ns
Himpulsivity	2.05 (1.93)	1.80 (1.84)	1.08	ns
Psychosis	0.20 (0.41)	0.26 (0.08)	.87	ns

Table 10. Response to antidepressive treatment in patient affected by a Substance Use Disorder, with ADHD (ADHD) or without ADHD (noADHD).

	ADHD N=20	noADHD N=89	t or c2(df=1)	p
Response to antidepressive treatment, n (%)				
Viraggio Ipomaniacale	2 (10.0)	7 (7.9)	.098	ns
Instabilità Umore	6 (30.0)	13 (14.6)	2.69	ns
Resistenza	3 (15.0)	3 (3.4)	4.25	.039
Irritabilità	7 (35.0)	14 (15.7)	3.90	.048

Table 11. Factor analisys of ASRS items in 109 patients with Substance Use Disorder

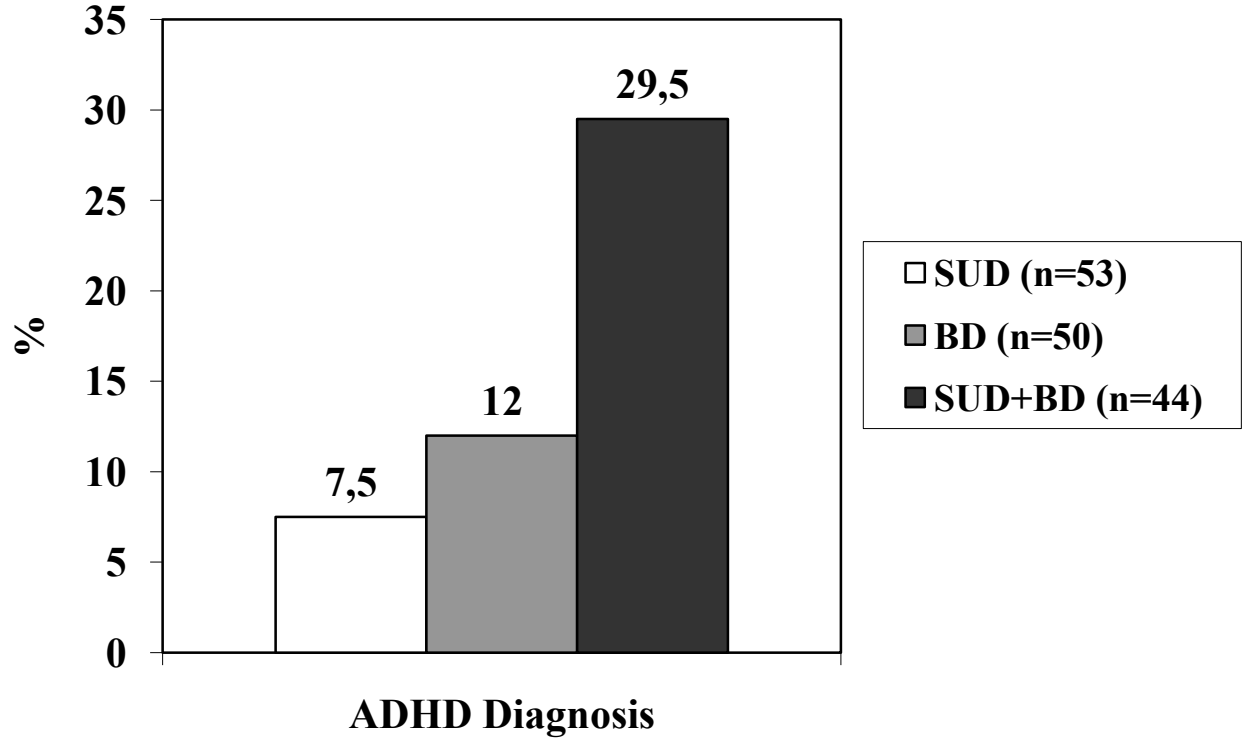
Item ASRS	Factor 1 Hyperactivity/ Hympulsivity	Factor 2 Inattention	Factor 3 Disorganization
1- Having difficulty in focusing and developing details of any a project.	-.043	,150	.722
2- Having difficulty in arranging objects while performing a task that requires organization.	.343	-.039	.692
3- Having trouble remembering appointments and deadlines	,451	-,033	,290
4- To avoid or delay the execution of a task that requires reasoning.	,590	,061	,527
5- Shaking hands or feet when the subject has to sit for a long time.	.406	,576	.079
6- Feeling overly active or constraint to do something as if driven by a motor	,067	,429	,473
7- Making errors due to distraction while performing a difficult or tedious project.	,722	,181	,005
8- Having difficulty to sustain attention during a tedious or repetitive job.	,682	,336	-,336

9- Having difficulty concentrating on what is being said by the interlocutor	,534	,046	,583
10- Loosing things, or having difficulty finding them	,715	-,002	,061
11- Being distract from surround environment: noises and activities	,473	,501	,186
12- Needing to get away from a situation in which one must be present.	,484	,277	,159
13- Feeling non-rested or agitated.	,043	.287	,514
14- Having difficulty to relax	,052	,331	,466
15- Talking too much in social situations.	,097	,695	,061
16- Breaking-off a conversation when the other person has yet to finish talking.	-,129	,771	,118
17- Difficulty to wait your turn	,170	,415	,244
18- Interrupt others when they are very busy	,283	,570	,171
Eingenvalue	3,2	2,8	2,6
% of Variance	17,9	15,5	14,3

Table 12. Demographic aspects in patient with Sustance Use Disorder (SUD), Bipolar Disorder (BD), and dual diagnosis (SUD+BD)

	SUD N= 53	BD N=50	SUD+BD N=44	f or □2	p
Age, mean (sd)	24.8 (9.6)	42.9 (15)	34.9 (6.8)	8.6	<.0001
Gender, male, n (%)	38 (71.7)	23 (46)	34 (77.3)	11.8	.003
Civil status, n (%)					
Unmarried	34 (64.2)	21 (42)	35 (79.5)		
Married	9 (17)	24 (48)	4 (9.1)		
Separated/divorced	10 (18.9)	5 (10)	5 (11.4)	23.5	.0001
Work, n (%)					
Student	7 (13.21)	8 (16)	5 (11.36)		
Disoccupied	12 (22.64)	14 (28)	10 (22.73)		
Worker	23 (43.4)	18 (36)	22 (50)		
Employed	11 (20.75)	10 (20)	7 (15.91)	2.2	ns
Education, n (%)					
University	1 (1.9)	7 (14)	1 (2.3)		
High school	20 (37.7)	19 (38)	11 (25)		
Low school	32 (60.4)	24 (48)	32 (72.7)	11.6	.02

Figure 1. ADHD diagnosis in patient with Sustance Use Disorder (SUD), Bipolar Disorder (BD), and dual diagnosis (SUD+BD)



Chi-quadro= 9.6, p=.008

Table 13. Diagnostic and clinical aspects in patient with Sustance Use Disorder (SUD), Bipolar Disorder (BD), and dual diagnosis (SUD+BD)

	SUD	BD	SUD+BD		
	N= 53	N=50	N=44	f or □2(df)	p
Psychiatric Disorder, n (%):					
BD. I (MDD)	--	8 (16)	12 (27.3)	1.8(2)	ns
BD I (Mixed states)	--	12 (24)	18 (40.9)	3.8(2)	.08
BD I (Mania)	--	9 (18)	0 (0.0)	8.8(2)	.003
BD II (MDD)	--	12 (24)	13 (29.5)	0.4(2)	ns
BD in remission	--	9 (18)	1 (2.3)	6.1(2)	.01
Psychotic congruent	--	3 (6)	1 (2.3)	0.8(2)	ns
Psychotic incongruent	2 (3.8)	5 (10)	3 (6.8)	1.0(3)	ns
Substance, n(%):					
Alcol	17 (32.1)	--	7 (15.9)	3.4(2)	.07
THC	7 (13.2)	--	4 (9.1)	0.4(2)	ns
Cocaine and stimulants	13 (24.5)	--	17 (38.6)	2.2(2)	ns
Heroine	16 (30.2)	--	16 (36.4)	0.4(2)	ns
Comorbidity Lifetime, n (%)					
Major Depressive Disorder	2 (3.8)	--	--		
Panic Disorder	5 (9.4)	3 (6.0)	7 (15.9)	2.6(3)	ns
PD-Agoraphobia	2 (3.8)	7 (14.0)	5 (11.4)	3.4(3)	ns
GAD	1 (1.9)	5 (10.0)	1 (2.3)	4.6(3)	ns
Social Phobia	1 (1.9)	1 (2.0)	1 (2.3)	0.2(3)	ns
DOC	0 (0.0)	2 (4.0)	1 (2.3)	0.8(3)	ns
Alcol	3 (5.7)	4 (8.0)	9 (20.5)	6.1(3)	.05
Heroine	1 (1.9)	1 (2.0)	1 (2.3)	0.2(3)	ns
Cocaine and Stimulants	4 (7.8)	1 (2.0)	9 (20.5)	6.0(3)	.05
Poliabuse	7 (13.2)	0 (0.0)	18 (40.9)	9.6(3)	.002

GAF, mean (sd)	61.8 (20)	52.4 (22.4)	55.7 (12.2)	3.3	.04
Sheehan Disability Scale, media(sd):					
Work	4.6 (2.3)	4.4 (2.3)	5.2 (2.1)	1.4	ns
Family	4.4 (2.1)	3.8 (2.0)	4.6 (1.9)	2.1	ns
Social	4.4 (2.1)	4.5 (2.1)	5 (29)	1.1	ns
CGI-Bipolare, severity:					
Manic	0.3 (0.7)	1.9 (1.8)	0.5 (1.0)	23.8	<.0001
Depressive	0.9 (1.3)	2.4 (1.6)	2.2 (1.8)	13.4	<.0001
Mixed	0.2 (0.8)	1.2 (1.7)	1.1 (1.9)	5.7	.004
Anxiety	1.8 (1.7)	1.9 (1.7)	1.5 (1.8)	0.4	ns
Hympulsity	1.7 /(1.8)	0.9 (1.4)	1.9 (2.1)	4.3	.01
Psychosis	0.1 (0.5)	0.8 (1.6)	0.07 (0.2)	8.1	<.0001

Table 14. ASRS scores comparison in patient with Sustance Use Disorder (SUD), Bipolar Disorder (BD), and dual diagnosis (SUD+BD)

	SUD	BD	SUD+BD		
	N= 53	N=50	N=44	F	p
Items, mean (sd):					
1- Having difficulty in focusing and developing details of any a project.	0.9 (0.9)	1.2 (1.1)	1.3 (1)	1.9	ns
2- Having difficulty in arranging objects while performing a task that requires organization.	1 (1.1)	1.2 (1.2)	1.6 (1.3)	3	0.05a
3- Having trouble remembering appointments and deadlines	1.4 (1.2)	1.3 (1.3)	1.7 (1.3)	1.2	ns
4- To avoid or delay the execution of a task that requires reasoning.	1.5 (1.1)	1.5 (1.2)	1.9 (1.3)	2.1	ns
5- Shaking hands or feet when the subject has to sit for a long time.	1.6 (1.3)	1.5 (1.3)	1.7 (1.3)	0.4	ns
6- Feeling overly active or constraint to do something as if driven by a motor	1.3 (1.3)	1.3 (1.3)	1.4 (1.4)	0.6	ns
7- Making errors due to distraction while performing a difficult or tedious project.	1.6 (0.9)	1.6 (1)	1.7 (0.9)	0.5	ns
8- Having difficulty to sustain attention during a tedious or repetitive job	1.7 (0.9)	1.8 (1.1)	1.7 (1.2)	0.2	ns
9- Having difficulty concentrating on what is being said by the interlocutor	1.4 (1)	1.3 (1.1)	1.5 (1.2)	0.5	ns
10-- Loosing things, or having					

difficulty finding them					
	1.5 (1.1)	1.6 (1.1)	1.5 (1.4)	0.2	ns
11- Being distract from surround environment: noises and activities					
	1.7 (0.9)	1.6 (1)	1.8 (1.2)	0.5	ns
12- Needing to get away from a situation in which one must be present.					
	1 (1)	1 (1.2)	1.3 (1.2)	1.2	ns
13- Feeling non-rested or agitated.					
	1.9 (1)	2.2 (1)	2.2 (1)	1.7	ns
14- Having difficulty to relax					
	1.3 (1.2)	1.7 (1.2)	2.1 (1.3)	5.0	.008b
15- Talking too much in social situations.					
	1.4 (1)	1.7 (1.4)	1.5 (1.3)	0.5	ns
16- Breaking-off a conversation when the other person has yet to finish talking.					
	1.7 (1)	1.7 (1.1)	1.6 (1.2)	0.1	ns
17-- Difficulty to wait your turn					
	1.2 (1.2)	1 (1.1)	1.6 (1.1)	3.5	.03
18- Interrupt others when they are very busy					
	1.1 (0.9)	0.9 (1)	1.2 (1.1)	1.3	ns
Total Scores (first 6 Items)					
	7.9 (3.8)	7.9 (4.1)	9.6 (5.3)	3.7	.05a
Total Scores (18 Items)	25.3 (9.0)	25.9 (9.5)	29.4 (13.2)	3.8	.05a

Bonferroni Analysis Post Hoc: aSUD+BD>BD,SUD; bSUD+BD>SUD